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Outcome of carbapenem or colistin resistant *Klebsiella pneumoniae* bacteremia in the intensive care unit

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Carbapenem-resistant *Klebsiella pneumoniae* (CRKp) infections continue to be an important cause of mortality. In this retrospective study, the effect of carbapenem or colistin resistance on mortality in *Klebsiella pneumoniae* bacteremia and combined meropenem + colistin administration in CRKp bacteremia was evaluated. In addition to that, a mathematical model is applied to explore the relationships between the resistance and mortality. A total of 139 adult patients diagnosed with *K. pneumoniae* bacteremia(73 carbapenem sensitive and 66 carbapenem resistant) between 01/01/2000 and 31/07/2019 were included in the study. The 30-day mortality in entire cohort were 19.4%. 30-day mortality was significantly higher in the carbapenem resistant-colistin sensitive group and in the carbapenem resistant-colistin resistant group compared to the carbapenem susceptible group. Meropenem + colistin combination was administered to 37 (95%) of carbapenem resistant–colistin sensitive ($n = 39$) and 25 (93%) of carbapenem resistant–colistin resistant patients($n = 27$). Notably, mortality was not significantly affected regardless of whether CRKp was colistin sensitive and whether a high dose and prolonged infusion of meropenem was administered. Mortality is higher in carbapenem resistant *Klebsiella pneumoniae* bacteremia compared to carbapenem susceptible group. In cases of combined meropenem and colistin administration, high dose and prolonged infusion of meropenem is not superior to standard dose and infusion in both carbapenem resistant–colistin sensitive and carbapenem resistant–colistin resistant *K. pneumoniae* bacteremia.

Keywords Klebsiella, Bacteremia, Carbapenem resistance, Colistin, Meropenem

Carbapenem-resistant *Klebsiella pneumoniae* (CRKp) infections are an important cause of morbidity and mortality. According to World Health Organization(WHO) GLASS in 2021, the resistance rates of meropenem for *Klebsiella pneumoniae* was 12.34%[1]. The infection prevalence of carbapenemase-producing Enterobacteriaceae was shown to be 1.3 per 10,000 hospital admissions in European Survey[2]. In carbapenem-resistant Enterobacteriaceae bacteremia, 43% mortality rate was reported in 2004–2013 from European Hospitals[3]. Wang et al. reported that 30 day mortality rate for patients with CRKp bacteremia was 34% in a study of 991 patients from 71 hospitals worldwide during 2017–2018[4]. In a meta-analysis evaluating mortality, clinical and microbiological response for CRKp infections, mortality rate was 37.2%, clinical response was 69%, and microbiological response was 63.7%[5].

Paniagua-Garcia et al. reported that the difference in 30-day mortality rates between patients with carbapenem–resistant Enterobacterales(88.5% with *Klebsiella* spp.) infection compared with patients with carbapenem-susceptible(31.4% with *Klebsiella* spp.) infection was 13.2%[6].

Giacobbe et al. reported that crude 30 day mortality rate was 33.8% and 20.7% for CRKp and carbapenem-susceptible *Klebsiella pneumoniae* bloodstream infections, respectively in study which included 426 patients from 16 centers between January and August 2020 and ceftazidime/avibactam was the most frequently(74.7%) used for CRKp bloodstream infection[7].

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There are conflicting results in the carbapenem-resistant group on the effects of the bacteria also being resistant to colistin on mortality[8–12].

Treatment with new antibiotics such as ceftazidime-avibactam was reported to significantly reduce mortality in CRKp infections compared with older antibiotics such as meropenem, polymyxin (polymyxin-B and colistin), tigecycline, fosfomycin, and aminoglycosides[13–16].

However, access to new antibiotics is not always possible owing to economic factors, development of resistance, or intolerance. Therefore, older antibiotics may still be needed from time to time. One of the most commonly used combinations in CRKp infections is meropenem plus colistin[17,18].

Tumbarello et al. showed that even if *K. pneumoniae* is carbapenem resistant, in combinations including meropenem (high dose, prolonged infusion) in the treatment, mortality was significantly lower in the MIC ≤ 8 mg/L group than infections caused by strains with MIC values > 8 mg/L[19]. Similarly, Daikos et al. reported that mortality increased from 19.4 to 35.5% in drug combinations containing meropenem when the meropenem MIC value was > 8 mg/L[20].

In a study by Gomez-Simmonds et al. (meropenem MIC ≥ 16 mg/L in 90% of the isolates), combination therapy (a single effective antibiotic + meropenem or broad-spectrum cephalosporin) was not superior to monotherapy (a single effective antibiotic)[21].

Gianella et al. compared carbapenem-containing combinations with carbapenem-free combinations in bloodstream infections caused by CRKp and reported that meropenem-containing combinations were more effective than meropenem-free combinations in terms of 14-day mortality even if meropenem MIC was ≥ 16 mg/L[22].

In the present study, the primary objective was the effect of carbapenem resistance or carbapenem and colistin resistance on mortality in *Klebsiella pneumoniae* bacteremia. Combined meropenem + colistin administration in CRKp bacteremia was retrospectively evaluated using minimal inhibitory concentration (MIC) and synergy data as a secondary objective.

In addition to that, we study mathematical model by different mathematical tools such as matrices, determinants, eigenvalues, functions, relations, etc. and we comment on the obtained values from this model to obtain the properties of the real life situation. In this study, a mathematical model is introduced to illustrate the relations between the resistance and mortality values to cure a random illness by means of any given number of drugs. Three new parameters are introduced to help us to decide which drug(s) are to be used in the treatment. At the end, the algorithm and model are applied to the main problem of this study.

Methods

A total of 139 patients (age, > 18 years) with *K. pneumoniae* bacteremia who were hospitalized in the Anesthesia and Reanimation Intensive Care Unit of our tertiary care 1000 bed hospital located in Bursa, Türkiye between 01/01/2000 and 31/07/2019 were included in the study. The retrospective study was performed in accordance with relevant guidelines and regulation and approved by the Clinical Research Ethics Committee of Uludağ University Faculty of Medicine (2021-9/3). Due to the retrospective nature of the study, the need of informed consent was waived by the Clinical Research Ethics Committee of Uludağ University Faculty of Medicine. All patient information was retrieved from the electronic file system of our hospital. The following data were recorded for each patient: age, sex, central venous catheter, mechanical ventilation support, urinary catheter, APACHE-II score, SOFA score, Pitt bacteremia score, neutropenia, use of steroids, sepsis according to sepsis-1 criteria, source of bacteremia, use of antibiotics in the last 30 days, use of carbapenems in the last 30 days, meropenem and colistin dose and type of infusion, comorbidities such as chronic obstructive pulmonary disease, congestive heart failure, chronic renal failure, chronic liver disease, diabetes mellitus, solid organ malignancy, hematological malignancy, cerebrovascular events, autoimmune disease and solid organ transplantation.

Bloodstream infection(BSI) was classified as primary, i.e., a laboratory confirmed BSI that is not secondary to another site infection, or secondary that is thought to be seeded from a site-specific infection at another body site[23].

In the presence of a focus of infection, the source of bacteremia was defined according to whether *K. pneumoniae* was isolated in the culture obtained from the focus of infection the day before or the same day after the positive blood culture. Catheter-associated bacteremia was defined as *K. pneumoniae* growth in blood culture from a catheter or in quantitative culture of catheter tip and peripheral blood culture, provided that there was no other active focus of infection[24–27].

All patients were classified as "sepsis," "severe sepsis," or "septic shock" based on consensus conference sepsis-1 criteria[28].

For the diagnosis of nosocomial pneumonia, in addition to the development of pneumonia within at least 48 h after the hospital admission and the presence of new or progressing infiltration on the chest radiography, at least two of the following criteria should be present[29]:

1. Presence of high fever (body temperature > 38 °C).
2. Presence of leukocytosis > 10,000/mm^3 or leukopenia < 4,000/mm^3.
3. Purulent bronchial secretion indicated by the presence of > 25 leukocytes and ≤ 10 epithelial cells in the gram staining examination of the Deep Endotracheal Aspiration (DTA) (10×).
4. Decreased oxygenation.

Diagnostic criteria of the international sepsis group were used for other infection diagnoses[30].

Use of prednisone or an equivalent steroid by the patient at a dose of 20 mg/day for 2 weeks or 30 mg/day for 1 week within the last one month was considered as a risk factor for steroid use[31].

Patients with a neutrophil count < 500/mm^3 at the time of diagnosis were considered neutropenic.

Acute Physiology and Chronic Health Evaluation-II score was calculated within 24 h of admission to the ICU[32]. Pitt Bacteremia scores were calculated at the diagnosis of infection[33].

The 14-day and 30-day mortality values were calculated according to the first 14 days and 30 days from the date of diagnosis. Antibiotics used by the patients before the diagnosis (i.e., used for at least 48 h in the last 30 days) were evaluated[34].

Colistin was administered as a maintenance dose after the standard loading dose in all patients[35]. Meropenem was administered either as standard dose(3 g/d) and infusion or as high dose(6 g/d) and prolonged infusion(4 h)[36].

Identification and antibiotic susceptibility testing of *K. pneumoniae* isolates were performed using a Phoenix 100 (Beckton Dickinson, USA) automated system. In order to confirm ESBL negativity and positivity of *K. pneumoniae* isolates, a combined disk confirmation test was performed as recommended by Clinical Laboratory Standarts Institute(CLSI). Carbapenem resistance was defined as a minimum inhibitory concentration (MIC) to meropenem of greater than 8 mg/L. The MIC of colistin was determined by broth microdilution method, and a strain with MIC $\leq$ 2 mg/L was considered to be susceptible to colistin[37].

For combinations containing colistin, meropenem, tigecycline, or fosfomycin, synergy testing was performed by gradient diffusion method and evaluated according to European Committee on Antimicrobial Susceptibility Testing(EUCAST) criteria. For Colistin, Meropenem, Tigecycline, and Fosfomycin, 0.5 McFarland turbidity bacterial suspensions were spread on 4 MHA plates. If the MIC values of antibiotics A and B, the combination of which was to be tested, were not known beforehand, gradient diffusion method strips containing the antibiotics were placed separately in a petri dish to determine their MICs individually. Strip B was placed in the third petri dish first and incubated for 1 h. Strip B was removed with sterile forceps and strip A was placed on the same place. Strip A was placed in the fourth petri dish and stored for 1 h. Strip A was removed and strip B was placed on the same place. After 24 h of incubation at 35–37 °C, the MIC of A in the presence of B in the third petri dish and the MIC of B in the presence of A in the fourth petri dish were measured and evaluated according to EUCAST recommendations. Interaction in combination tests was determined using fractional inhibition concentration (FIC) index and evaluated as synergistic for FIC $\leq$ 0.5, additive for 0.5 < FIC $\leq$ 1, indifferent for 1 < FIC < 4, and antagonistic for FIC $\geq$ 4[37–39].

Mathematical model

In this section, we introduce a mathematical model for the treatment of an illness by means of several known or prospective drugs using a decision making algorithm by means of two newly introduced mathematical parameters called as the resistance index and mortality index. The model introduced here will then be applied as a special case to the problem considered in this study for the treatment against *Klebsiella pneumoniae* bacteremia.

Let us try to find a treatment against an illness, say I, by means of several known or prospective drugs, say D1, D2, …, Dk. Let us assume that we have information about the recent use of these drugs in either our hospital, or in all hospitals in our town or region, or in all hospitals nationwide or in all hospitals in whole world. Any of these localities give us the number of patients who has been exposed to illness I, the number of patients to whom the drugs D1, D2, …, Dk are administered, the number of patients who have resistance against these drugs, and the number of mortalities in each case. By means of all these, we define the following parameters:

$$m_1 = \frac{the\ number\ of\ mortalities\ amongst\ patients\ to\ whom\ D1\ is\ administered}{the\ number\ of\ patients\ to\ whom\ D1\ is\ administered}$$

and for $i = 2, 3, \ldots, k$,

$$m_i = \frac{the\ number\ of\ mortalities\ amongst\ patients\ to\ whom\ D1\ and\ Di\ are\ administered\ together}{the\ number\ of\ patients\ to\ whom\ D1\ and\ Di\ are\ administered\ together}$$

.

m_1 is called the mortality index for drug D1 and m_i is called the mortality index for drugs D1 and Di used in combination.

Similarly, by means of the above mentioned information, we define the resistance index of drug Di as

$$r_1 = \frac{the\ number\ of\ patients\ who\ have\ resistance\ against\ the\ drug\ D1}{the\ number\ of\ patients\ to\ whom\ D1\ is\ administered}$$

and

$$r_i = \frac{the\ number\ of\ patients\ who\ have\ resistance\ against\ the\ drug\ Di}{the\ number\ of\ patients\ to\ whom\ D1\ and\ Di\ are\ administered\ together}$$

for $i = 2, \ldots, k$. *Note that all these indices takes values between 0 and 1 and the lower their values, the better the outcome.*

Without losing of generality, we can assume $r_1 \leq r_2 \leq r_3 \leq \ldots \leq r_k$. That is, we name the drugs according to their resistance indices and hence, D1 has the least and Dk has the highest resistance amongst all drugs in the list. Lower resistance means the drug under consideration is less virulant. Therefore $m_1 \leq m_2 \leq m_3 \leq \ldots \leq m_k$. At this point, we need the following well-known mathematical inequality called as rearrangement inequality:

Lemma (Rearrangement inequality) If $a_1 \leq a_2 \leq \ldots \leq a_n$ and $b_1 \leq b_2 \leq \ldots \leq b_n$ are real numbers, then.

$a_1b_1 + a_2b_2 + \ldots + a_nb_n \geq c_1b_1 + c_2b_2 + \ldots + c_nb_n \geq a_nb_1 + a_{n-1}b_2 + \ldots + a_1b_n$.
for any permutation $(c_1, c_2, \ldots, c_n)$ of $(a_1, a_2, \ldots, a_n)$.

That is, when multiplying pairs of numbers from two sets and adding the obtained products, the larger value is obtained by multiplying the large one with large one and small one with small one.

Next, we can introduce our algorithm:

STEP 1 Our algorithm starts with the drug D1 having the lowest resistance index.

We check whether the patient has resistance against D1.

If no, the patient is administered by D1 which is the best possible case and the algorithm ends.

STEP 2 If yes, then we administrate the next drug having second lowest resistance index in combination with D1. To make the algorithm stronger, we shall utilize the rearrangement inequality.

The smaller the resistance index r_i and the mortality index m_i, the much more smaller their product r_im_i by a special case of rearrangement inequality using the fact that all these numbers are between 0 and 1 and the product of numbers close to zero is more closer to zero than the numbers themselves.

Using this fact, we define another parameter for a drug Di by

$$\mathrm{rmi} = \mathrm{rimi}$$

which we call as resistance-mortality index of drug Di.

STEP 3 The next step in the algorithm is to calculate the resistance-mortality indices of the remaining drugs D2, D3, …, Dk. By the rearrangement inequality, we shall have.

$rm_2 < rm_3 < \ldots < rm_k$.

STEP 4 Next step in the algorithm is to check whether the patient is resistant to drug D2.

If no, we administrate D2 in combination with D1 and the algorithm ends.

STEP 5 If yes, we continue with D3 and administrate D3 in combination with D1. We repeat Steps 4 and 5 until finding the smallest resistance-mortality index rm_i and the patient has no resistance to the drug Di.

Note that this algorithm must be updated from time to time as the resistance indices and virulance or the recovery potential of the drugs change by the time.

Statistical analysis

The Pearson chi-squared test or Fisher-Freeman-Halton exact test were used. P value of < 0.05 were considered statistically significant.

Results

A total of 139 adult patients diagnosed with *K. pneumoniae* bacteremia between 01/01/2000 and 31/07/2019 were included in the study. The median age was 61 (33–98) years. Antibiotics were used in 58 (41.7%) of the patients in the last 30 days and 36 (25.9%) of these patients used carbapenems, 11 (7.9%) used 3rd generation cephalosporins, 6 (4.3%) used 4th generation cephalosporins, and 3 (2.2%) used tigecyclines.

The median length of stay in the intensive care unit until the diagnosis of *K. pneumoniae* bacteremia was 17[1–42] days. Some demographic characteristics of the patients are shown in Table 1.

A total of 97 (69.7%) patients had various underlying diseases. Among these, 29 (20.8%) had more than one underlying disease (Table 2).

The 14-day mortality was 8.6% ($n = 12$) and 30-day mortality was 19.4% ($n = 27$). No significant difference was noted between the 14- and 30-day mortality rates in terms of the source (Table 3).

14-day mortality was significantly higher in the carbapenem resistant-colistin resistant group compared to the carbapenem sensitive (extended spectrum beta-lactamase-ESBL positive) group and the carbapenem resistant-colistin sensitive group.

30-day mortality was significantly higher in the carbapenem resistant-colistin sensitive group compared to the carbapenem susceptible (ESBL positive) group and in the carbapenem resistant-colistin resistant group compared to the carbapenem susceptible (ESBL positive) group (Table 4).

Meropenem + colistin combination was administered to 37 (95%) of carbapenem resistant–colistin sensitive ($n = 39$) patients. The 30-day mortality rate was 37.8% in 37 patients receiving meropenem + colistin. A high dose and prolonged infusion of meropenem was administered in 19 of 39 patients and as standard dose and infusion in 20 patients; furthermore, no intergroup differences in mortality were noted in terms of mortality (36% vs. 40%, $p = 0.839$). Synergy testing was performed in 14 of 37 patients receiving meropenem + colistin. No synergy or antagonism was detected between meropenem and colistin and was considered as indifferent. Meropenem MIC level was ≥ 32 mg/L in all strains.

Of the 27 carbapenem resistant–colistin resistant patients, 25 (93%) received meropenem + colistin combination. In these 25 patients, the 30-day mortality rate was 40%. In 13 patients, a high dose and prolonged

Demographic Characteristics	Number of Patients (*n*)	Percentage (%)
Sex Male Female	 82 57	 59 41
Age (years) ≥ 65 < 65	 56 83	 40.2 59.8
CVC +	87	62.6
APACHE II ≥ 20	57	41
APACHE II < 20	82	59
PBS ≥ 4	116	83.4
PBS < 4	23	16.6
Neutropenia	27	19.4
Mechanical Ventilation Support	100	71.9
Antibiotic use in the last 30 days	58	41.7
Carbapenem use in the last 30 days	36	25.9
Steroid use	14	10

Table 1. Demographic characteristics of patients. APACHE-II: Acute Physiology and Chronic Health Evaluation-II; CVC: Central Venous Catheter; PBS: Pittsburg bacteremia score.

Underlying disease	Number of patients (*n*)	Percentage (%)
COPD	10	7.1
CRF	29	20.8
DM	43	30.9
SOT	3	2.1
CHF	27	19.4
Other	8	5.7
Total illness	120	
Total patients	97	69.7

Table 2. Underlying diseases of the patients. CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CRF: Chronic Renal Failure, SOT: Solid Organ Transplantation, DM: Diabetes Mellitus.

	14-day mortality			30-day mortality			
Source	**Deceased *n* (%)**	**Survivor *n* (%)**	***P***	**Deceased *n* (%)**	**Survivor *n* (%)**	***P***	**Total *n***
Primary bacteremia	6 (11.3)	47 (88.6)		12 (22.6)	41 (77.3)		53
Catheter-associated bacteremia	4 (6.4)	58 (93.5)	1.000	12 (19.3)	50 (80.6)	0.982	62
Ventilator-associated pneumonia	2 (8.3)	22 (91.6)		3 (12.5)	21 (87.5)		24
Total	12 (8.6)	127 (91.3)		27 (19.4)	112 (80.5)		139

Table 3. Mortality rates by source of bacteremia.

	14-day mortality			30-day mortality		
	Number of patients (*n*)	**Percentage (%)**	***P* value**	**Number of patients (*n*)**	**Percentage (%)**	***P* value**
Carbapenem sensitive-ESBL positive (*n* = 73)*	1	1.3		1	1.3	
Carbapenem resistant-colistin sensitive (*n* = 39)	0	0	1.000	15	38.4	**< 0.001**
Carbapenem sensitive-ESBL positive (*n* = 73)*	1	1.3		1	1.3	
Carbapenem and colistin resistant (*n* = 27)	11	40.7	**< 0.001**	11	40.7	**< 0.001**
Carbapenem resistant-colistin sensitive (*n* = 39)	0	0		15	38.4	
Carbapenem and colistin resistant (*n* = 27)	11	40.7	**< 0.001**	11	40.7	**0.852**

Table 4. Mortality rates according to resistance profile. *All carbapenem-susceptible-ESBL postive patients were treated with carbapenem monotherapy.

infusion of meropenem was administered, whereas 14 patients received a standard dose and infusion. No significant intergroup difference was noted in terms of mortality (38% vs. 42%, $p=0.816$). In this group, synergy testing was performed in 16 of 25 patients receiving meropenem + colistin. No synergy or antagonism was detected between meropenem and colistin and was considered as indifferent. Meropenem MIC level was ≥ 32 mg/L in all strains.

Application of mathematical model to *Klebsiella pneumoniae* bacteremia.

As an application, we apply this algorithm for *Klebsiella pneumoniae* bacteremia as claimed in this paper. Our notations and terminology are adopted as below:

The illness is I = *Klebsiella pneumoniae* bacteremia.

The drugs are antibiotics.

The number of drugs is k = 2.

Drugs are D1 = Carbapenem, and D2 = Colistin.

$m_1 = 1/73 = 0{,}014$.

$m_2 = 15/39 = 0{,}385$.

$r_1 = 66/139 = 0{,}475$.

$r_2 = (27+27)/(39+46) = 0{,}635$.

$rm_1 = 0{,}007$.

$rm_2 = 0{,}244$.

Note that the conditions $m_1 \le m_2$, $r_1 \le r_2$ and $rm_1 \le rm_2$ hold. So for a random patient, we can apply the steps of the algorithm and decide about whether only use Carbapenem (Step 1) or use Carbapenem in combination with colistin (Step 4) for this patient.

Discussion

Many studies have demonstrated that carbapenem resistance significantly increases mortality compared with carbapenem susceptible groups. In a multicenter study, 30-day mortality rate in bloodstream infections caused by CRKp was 44%[40]. In a meta-analysis evaluating CRKp bacteremia, mortality was 42.14% in the carbapenem-resistant group and 21.16% in the carbapenem-sensitive group. Mortality was reported to be 54.30% in bloodstream infections and 13.52% in urinary tract infections[41]. The very low mortality rates in the carbapenem susceptible group in the present study may be explained by the fact that carbapenem was used in all of these cases.

Balkan et al. reported that colistin resistance increased 28-day mortality in bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae*[10]. Menekşe et al. found that increasing MIC of colistin as a independent mortality factor in *Klebsiella pneumoniae* bloodstream infections[11]. On the other hand, Aslan et al. reported that colistin resistance in CRKp had no impact on 30-day mortality[8].

In the present study, we found that the presence of colistin resistance in addition to carbapenem resistance did not affect 30-day mortality. However, we found that significantly increased 14-day mortality. Different colistin susceptibility methods, whether colistin loading dose was given or not, whether meropenem dose and prolonged infusion were used or not, meropenem MIC values, combination or monotherapy and design of studies may have played a role in these different results.

In the present study, meropenem + colistin combination was indifferent (neither synergistic nor antagonistic) by gradient diffusion system.

In vitro synergy studies for carbapenem-resistant Enterobacteriaceae, the combination of polymyxin + carbapenem was generally found to be synergistic[42].

In their study with the time-kill method, Sharma et al. showed that the combination was bactericidal if the MIC of meropenem was ≤ 16 mg/L in colistin-susceptible and meropenem-resistant *K. pneumoniae* strains[43].

Kulegowski et al. also showed that if the MIC of meropenem is ≤ 32 mg/L, the combination of meropenem + polymyxin B generally has a synergistic effect on polymyxin B-susceptible strains[44].

However, in a study involving 19 patients with bloodstream infection caused by *K. pneumoniae*, Bono et al. did not reach the PK/PD targets in cases with MIC values ranging from 256 to 1024 mg/L, although the patients were given high dose and prolonged infusion. Furthermore, in vitro synergy with colistin was not detected. However, measured serum meropenem levels could reach the hypothetically determined T > 40% 1xMIC PK/PD targets of meropenem at a rate of 98% for the MIC value of 8 mg/L, 68% for 16 mg/L, and 32% for 32 mg/L[36]. The lack of synergistic effect in our study may be attributable to meropenem MIC levels of ≥ 32 mg/L.

There was no therapeutic drug monitoring(TDM) for meropenem to evaluate PK/PD parameters in our study. We consider that TDM could be useful for infections caused by CRKp with MIC ≤ 64 mg/L[45,46].

Mathematical models and algorithms are used when we cannot solve a real life problem by classical methods not including mathematical tools. Laboratory experiments are a nice example of this method. A mathematical model can be formed by means of statistics, linear algebra, differential equations or graph theory. We think that such problems can be solved more easily by means of classical graphs where the items are modeled by vertices and the relations between them are modeled by the edges or the directed/weighted graphs. One can try to solve this open problem of forming a graph theoretical model for the problem in this paper.

In the present study, no significant difference in mortality was noted between high dose - prolonged infusion of meropenem and normal dose - standard infusion of meropenem. In the carbapenem resistant-colistin sensitive and carbapenem resistant-colistin resistant groups, no significant difference in mortality was observed between high dose and prolonged infusion of meropenem and normal dose infusion.

It was shown that meropenem MIC is very important in the success of meropenem plus colistin combination in CRKp infections. If meropenem MIC > 8 mg/L, we can expect higher mortality[19,20].

Gianella et al. compared carbapenem-containing combinations with carbapenem-free combinations in bloodstream infections caused by CRKp and reported that meropenem-containing combinations were more

effective than meropenem-free combinations in terms of 14-day mortality even if meropenem MIC was ≥ 16 mg/L[22].

The fact that the synergy test results were indifferent and that there was no mortality difference between high-dose and prolonged infusion of meropenem and standard dose infusion in both groups suggests that high-dose and prolonged infusion meropenem treatment does not provide any benefit compared to standard dose and infusion if the meropenem MIC is ≥ 32 mg/L.

There are certain limitations of this study. The study was conducted retrospectively. The number of cases was relatively small and the study was single centered. Not all carbapenem-resistant strains were tested for synergy. The results were not compared with a group given colistin monotherapy. Lastly, the strains were not epidemiologically analyzed at the molecular level and carbapenemase enzymes were not analyzed.

In conclusion, 30-day mortality was significantly higher in the carbapenem resistant-colistin sensitive group and in the carbapenem resistant-colistin resistant group compared to the carbapenem susceptible (ESBL positive) group. When combined with colistin, if meropenem MIC is ≥ 32 mg/L, meropenem administration with high dose and prolonged infusion is not superior to standard dose and infusion in both carbapenem resistant-colistin sensitive and carbapenem resistant-colistin resistant *K. pneumoniae* bacteremia.

Data availability

The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Bursa Uludag University for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Bursa Uludag University from: halis@uludag.edu.tr.

Received: 14 February 2024; Accepted: 20 September 2024
Published online: 28 October 2024

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Acknowledgements

We would like to thank Prof. Dr. Güven Özkaya for evaluating the statistical analysis of our study. HA is responsible for the content of the manuscript, data analysis and interpretation, study design, writing of the manuscript, and critical review. CS contributed to data collection, data analysis, interpretation of results and the writing of the manuscript. Rİ, NKG and FK are responsible for clinical follow-up, data collection and data interpretation. CS, KE and CÖ contributed substantially to the in vitro study design, data analysis and interpretation, and the writing of the manuscript. Mathematical model is developed by Naci Cangül.

Author contributions

H.A. is responsible for the content of the manuscript, data analysis and interpretation, study design, writing of the manuscript, and critical review. C.S. contributed to data collection, data analysis, interpretation of results and the writing of the manuscript. R.İ., N.K.G. and F.K. are responsible for clinical follow-up, data collection and data interpretation. C.S., K.E. and C.Ö. contributed substantially to the in vitro study design, data analysis and interpretation, and the writing of the manuscript. Naci Cangül is responsible for the mathematical model.

Declarations

Competing interests

The authors declare no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. There is no conflict of interest.

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