Research Article
Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1244480

Urinary tract infections caused by carbapenem-resistant Klebsiella pneumonia: monotherapy or combined therapy?

Karbapenem dirençli Klebsiella pneumonia'nın neden olduğu idrar yolu enfeksiyonları: monoterapi ya da kombineterapi?

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Posted date:30.01.2023 Acceptance date:01.03.2023

Abstract

Purpose: In this study, we evaluated healthcare-associated urinary tract infections caused by carbapenem-resistant Klebsiella pneumoniae.

Materials and methods: The study included 134 patients, diagnosed with healthcare-associated urinary tract infection caused by carbapenem-resistant Klebsiella pneumoniae. Demographic features, initial clinical conditions, comorbidities, and Charlson's comorbidity index of the patients were recorded. In addition, the MIC values of meropenem on the CR-Kp isolates, treatment regimens, clinical and microbiological responses to the treatment, as well as 14- and 28-day mortality rates of the patients, were reviewed.

Results: The 14-day mortality rate was 34.3%, and the 28-day mortality rate was 42.5%. The mean age of the patients who died was significantly higher (p=0.03). Similarly, Charlson's comorbidity index (p=0.03) and the qSOFA values (p=0.00) were significantly higher in the patients who died. The microbiological response rate was higher in the patients who survived (p=0.01) with no difference in bacteremia between the groups (p=0.29). It was found that combined antibiotherapy provided significantly better 14- and 28-day mortality rates compared to monotherapy in the group of patients with sepsis (p=0.00 and p=0.04, respectively). However, monotherapy and combination therapy in groups of patients without sepsis were insignificant (p=0.72 and p=0.36, respectively).

Conclusion: Our study supports the use of combination therapy in patients with sepsis, and monotherapy with an in-vitro active agent may be used for patients without sepsis in the treatment of urinary tract infections caused by CR-KP.

Key words: Klebsiella pneumoniae, carbapenem-resistant, healthcare-associated infection, urinary tract infection.

Temocin F, Kayhan SB, Sensoy L, Kuruoglu T, Atilla A, Tanyel E. Urinary tract infections caused by carbapenem-resistant Klebsiella pneumonia: monotherapy or combined therapy? Pam Med J 2023;16:290-297.

Öz

Amaç: Bu çalışmada karbapenem dirençli Klebsiella pneumoniae'nın neden olduğu sağlık hizmeti ilişkili üriner sistem enfeksiyonlarını değerlendirildi.

Gereç yöntem: Çalışmaya karbapenem dirençli Klebsiella pneumoniae'nın (CR-Kp) neden olduğu sağlık hizmeti ilişkili idrar yolu enfeksiyonu tanısı almış 134 hasta dahil edildi. Hastaların demografik özellikleri, başlangıç klinik durumları, komorbiditeleri ve Charlson komorbidite indeksi kaydedildi. Ayrıca meropenemin CR-Kp izolatları üzerindeki MİK değerleri, tedavi rejimleri, tedaviye klinik ve mikrobiyolojik yanıtları ile hastaların 14 ve 28 günlük mortalite oranları incelendi.

Bulgular: 14 günlük mortalite oranı %34,3, 28 günlük mortalite oranı ise %42,5 bulundu. Ölen hastaların yaş ortalaması anlamlı olarak daha yüksekti (p=0,03). Benzer şekilde ölen hastalarda Charlson komorbidite indeksi (p=0,03) ve qSOFA değerleri (p=0,00) anlamlı olarak yüksekti. Yaşayan hastalarda mikrobiyolojik yanıt oranı daha yüksekti (p=0,01) ve bakteriyemi açısından gruplar arasında fark yoktu (p=0,29). Sepsisli hasta grubunda kombine antibiyoterapinin 14 ve 28 günlük mortalite oranlarını monoterapiye göre anlamlı olarak daha üstün olduğu saptandı (sırasıyla p=0,00 ve p=0,04). Ancak sepsis olmayan hasta gruplarında monoterapi ve kombinasyon tedavisi arasında anlamlı fark yoktu (sırasıyla p=0,72 ve p=0,36).

Sonuç: Çalışmamız, CR-Kp'nin neden olduğu üriner sistem enfeksiyonlarının tedavisinde sepsisli hastalarda kombinasyon tedavisinin, sepsis olmayan hastalarda ise in vitro aktif bir ajanla monoterapinin kullanılabileceğini desteklemektedir.

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Anahtar kelimeler: Klebsiella pneumonia, karbapenem dirençli, sağlık hizmetiyle ilişkili enfeksiyon, idrar yolu enfeksiyonu.

Temoçin F, Kayhan ŞB, Şensoy L, Kuruoğlu T, Atilla A, Tanyel E. Karbapenem dirençli Klebsiella pneumonia'nın neden olduğu idrar yolu enfeksiyonları: monoterapi ya da kombineterapi? Pam Tıp Derg 2023;16:290-297.

Introduction

Klebsiella pneumoniae is one of the most common causative bacteria of hospital infections, particularly urinary tract infections (UTI) [1]. Until recently, carbapenems were the last-resort antibiotics used against Enterobacterales, including *K. pneumoniae*; however, the antimicrobial activity decreased considerably with the emergence of carbapenemase-producing isolates [2]. Carbapenem-resistant *K. pneumoniae* (CR-KP) is an important cause of mortality with rising frequency due to limited treatment options and hospital outbreaks. Currently, outbreaks of carbapenem-resistant *Enterobacterales* (CR-E) infections are reported worldwide, particularly CR-KP infections, and this has made the treatment a global priority [3-5]. In 2017, the World Health Organization published for the first time the list of bacteria with the urgent need for new antibiotics and included CR-KPs in the group of bacteria of critical importance [6].

CR-KPs are resistant to first-line antibiotics, including carbapenems [7]. Currently, several alternative antibiotics (e.g., colistin, aminoglycosides, fosfomycin, and tigecycline) are used in the treatment of these infections in a wide geography of the world [8]. However, these antibiotics have several disadvantages, such as low urinary concentrations (tigecycline), nephrotoxicity (colistin, aminoglycosides), and poor efficacy (fosfomycin) [9, 10]. Although new antibiotics in development or recently approved antibiotics are unavailable in many regions of the world, the development of resistance to these new antibiotics is inevitable [11, 12].

In this view, available data should be reviewed to aid the clinicians in planning the treatment of infections associated with resistant bacteria. Thus, we evaluated healthcare-associated urinary tract infections (HA-UTI) caused by CR-KPs belonging to the Enterobacterales family. This study aimed to determine the preferred treatment strategies as well as clinical and microbiological responses to these treatments, 14- and 28-day mortality rates, and factors affecting mortality.

Materials and methods

Design and data collection

The study was conducted by the Infectious Diseases and Clinical Microbiology Department of Ondokuz Mayis University, Medical Faculty Hospital. This regional hospital, situated in the Black Sea Region of Türkiye, has a main building with 1,100 beds, an additional Hematology-Oncology building with 120 beds, and an adult intensive care unit with 100 beds. The study included all patients aged 18 years and older, diagnosed with healthcare-associated urinary tract infection caused by culture-confirmed carbapenem-resistant *Klebsiella pneumoniae* from January 2010 to August 2020. Healthcare-associated UTI (HA-UTI) was defined according to the CDC recommendations.

Patients were included by searching the clinic's archive, hospital digital archive, and the surveillance records of the Infection Control Committee.

Patients were excluded under 18 years of age or if they had bacteria susceptible to any carbapenem antibiotics, lower urinary tract infections, or treatment duration of less than 48 h.

Demographic features, initial clinical conditions, comorbidities, and Charlson's comorbidity indices of the patients were recorded. In addition, the MIC values of meropenem on the CR-KP isolates, antibiotic treatment regimens used, clinical and microbiological responses to the treatment, as well as 14- and 28-day mortality rates of the patients were reviewed and evaluated using statistical analysis. The presence of sepsis at the beginning of the treatment was determined using the quick Sequential Organ Failure Assessment (qSOFA) score. The qSOFA score is a score consisting of three items: respiratory rate (RR) ≥22 breaths per minute, altered mentation (Glasgow Coma

Scale [GCS] <15), and systolic blood pressure (SBP) <100 mmHg.

Microbiological analysis

We performed species-level identification and antibiotic susceptibility testing with automated VITEK® 2 Systems 8.01 (bioMérieux, Inc., Marcy l'Etoile, France). The in-vitro antibiotic susceptibility of the isolates was determined based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Colistin susceptibility testing was performed using 96-well broth microdilution (BMD) panels following the recommendations of EUCAST.

Statistical analysis

Statistical analysis was performed using the SPSS v.21 software (Armonk, NY: IBM Corp., USA). Pearson's Chi-square and Fisher's exact test was used for categorical variables. An independent t-test was used for non-categorical variables with normal distribution, and the results were presented as mean±standard deviation. Mann-Whitney U test was used for the groups without normal distribution, and the results were presented as the median (minimum-maximum). All tests were performed with a confidence interval of 95%, and a *p*-value of <0.05 was considered statistically significant. The study was approved by the Ondokuz Mayis University, Medical Faculty Clinical Research Ethics Committee.

Results

Sixty-eight male (50.7%) and 66 (49.3%) female patients meeting the inclusion criteria and previously diagnosed with healthcare-associated urinary tract infection (HA-UTI) caused by CR-KP were evaluated during the study period. In the study, the 14-day mortality rate was 34.3% (46/134), and the 28-day mortality rate was 42.5% (57/134). The mean age of the patients who died was significantly higher than that of the surviving patients (*p*=0.03). Similarly, Charlson's comorbidity index (*p*=0.03) and the qSOFA values (*p*=0.00) at the start of treatment were significantly higher in the patients who died. The microbiological response rate was higher in the patients who survived (*p*=0.01) with no difference in bacteremia between the groups (*p*=0.29). The distribution and statistical analysis of the surviving and dying patients are tabulated (Table 1).

Table 1. Comparison of surviving and dying patients with urinary tract infections caused by carbapenem-resistant *Klebsiella pneumoniae*

	All patients (n=134)	**Surviving patients (n=77)**	**Dying patients (n=57)**	***p*-value**
Gender (M/F)	68/66	37/40	31/26	0.46
Age (mean ± standard deviation)	64.9±14.2	62.7±13.9	68±14.3	**0.03**
Ward				
Internal medicine ward	75 (56%)	51 (68%)	24 (32%)	**0.01**
Surgery ward	24 (17.9%)	13 (54.2%)	11 (45.8%)	**0.01**
Intensive care unit	35 (26.1%)	13 (37.1%)	22 (62.9%)	**0.01**
Charlson's comorbidity index median (minimum-maximum)	6 (0-13)	5 (0-9)	6 (1-13)	**0.03**
Meropenem MIC <32	68 (50.7%)	39 (57.4%)	29 (42.6%)	0.5
Meropenem MIC <32	66 (49.3%)	38 (57.6%)	28 (42.4%)	0.5
Sepsis at the start of treatment	56 (41.8%)	12 (15.5%)	44 (77.2%)	**0.00**
Bacteremia	36 (26.9%)	18 (23.4%)	18 (31.6%)	0.29
Microbiological cure	98 (73.1%)	63 (81.8%)	35 (61.4%)	**0.01**
Treatment				
Monotherapy	56 (41.8%)	35 (62.5%)	21 (37.5%)	0.31
Combination therapy	78 (58.2%)	42 (54.5%)	36 (46.2%)	0.31

Among the patients, 56 (41.7%) received monotherapy with an in-vitro active agent, while 78 (58.2%) received combination therapy. No difference was found in 14- and 28-day mortality rates between the monotherapy and combination therapy groups (p=0.77 and p=0.31, respectively). During the sub-group analysis of the initial treatment regimens of patients, it was found that combined anti-biotherapy provided significantly better 14- and 28-day mortality rates compared to monotherapy in the group of patients with sepsis (p=0.00 and p=0.04, respectively). However, monotherapy and combination therapy in groups of patients without sepsis at the start of treatment were insignificant (p=0.72 and p=0.36, respectively) (Table 2).

Meropenem and colistin combination was the preferred combination in patients treated with combination therapy, with 34.6% of patients receiving this regimen, followed by a combination of meropenem and aminoglycoside, received by 21.7% patients. No significant difference was found between the preferred combination regimens in terms of mortality and microbiological cure. Conversely, only the combinations containing tigecycline showed a significantly worse microbiological response. Among all combination therapies, meropenem was preferred by 65.3% of the patients. There was no significant difference in 14-day mortality, 28-day mortality, and microbiological response between the patients receiving combination therapy with or without meropenem (Table 3).

The MIC values of meropenem for 68 strains of CR-KPs was ≥16 and ≥32 for 66 strains. Comparison of patients with a meropenem MIC of ≥16 and ≥32 showed no significant difference in terms of 14-day mortality, 28-day mortality, and microbiological cure irrespective of the treatment regimen (Table 4). In addition, no difference was observed in the mortality and microbiological cure that included only the 51 patients receiving meropenem in combination therapy (Table 5). CR-KP strains showed 37.2% colistin resistance, and 55.9% amikacin resistance, presented in Table 6, along with other antibiotic resistance rates.

Table 2. Comparison of treatments of patients with or without sepsis at the start of treatment

	Total	Monotherapy	Combination therapy	*p*-value
All patients	n=134	n=56	n=78	
14-day mortality	46 (34.3%)	20 (35.7%)	26 (33.3%)	0.77
28-day mortality	57 (42.2%)	21 (37.5%)	36 (46.2%)	0.31
Patients with sepsis at the start of treatment	n=56	n=17	n=39	
14-day mortality	37 (66.1%)	16 (94.1%)	21 (53.8%)	**0.00**
28-day mortality	44 (78.6%)	16 (94.1%)	28 (71.8%)	**0.04**
Patients without sepsis at the start of treatment	n=78	n=39	n=39	
14-day mortality	9 (11.5%)	4 (10.3%)	5 (12.8%)	0.72
28-day mortality	13 (16.7%)	5 (12.8%)	8 (20.5%)	0.36

Table 3. Comparison of combination regimens with and without meropenem

	Combination with meropenem n=51	Combination without meropenem n=27	*p*-value
14-day mortality	17 (33.3%)	9 (33.3%)	1
28-day mortality	23 (45.1%)	13 (48.1%)	0.7
Microbiological cure	13 (25.5%)	7 (25.9%)	0.9

Table 4. The 14- and 28-day mortality rates of all patients by meropenem MIC values

	Meropenem MIC ≥16 (n=68)	Meropenem MIC ≥32 (n=66)	*p*-value
14-day mortality	25 (36.8%)	21 (31.8%)	0.5
28-day mortality	29 (42.6%)	28 (42.4%)	0.9
Microbiological cure	22 (32.4%)	14 (21.2%)	0.1

Table 5. The 14- and 28-day mortality rates of the patients receiving meropenem in combination therapy by meropenem MIC values

	Meropenem MIC ≥16 (n=22)	Meropenem MIC ≥32 (n=29)	*p*-value
14-day mortality	8 (36.4%)	9 (31.0%)	0.6
28-day mortality	10 (45.5%)	13 (44.8%)	0.9
Microbiological cure	14 (63.6%)	24 (82.8%)	0.2

Table 6. Rates of resistance against other antibiotics in carbapenem-resistant *Klebsiella pneumoniae* strains

	Amikacin (n=134)	Fosfomycin (n=118)	Colistin (n=51)	Tigecycline (n=47)
Susceptible	59 (44%)	73 (61.8%)	32 (62.7%)	23 (48.9%)
Resistant	75 (55.9%)	45 (38.2%)	19 (37.2%)	24 (50%)

Discussion

In the present study, the 14-day mortality rate was 34.3%, and the 28-day mortality rate was 42.5% in HA-UTIs caused by carbapenem-resistant *Klebsiella pneumoniae*. These high mortality rates are noteworthy and emphasize the significance of HA-UTIs caused by CR-Kp. Thus, these infections should be evaluated carefully. Xu et al. [7] evaluated 62 studies by meta-analysis and reported a 42% mortality rate in infections caused by CR-Kp, with lower mortality in urinary tract infections. The meta-analysis also suggested that older age, the need for intensive care, and the presence of underlying diseases are variables increasing the mortality. Concordant to literature data, our study also found that mortality increased with age. In addition, high Charlson's comorbidity index scores, the presence of sepsis, and the need for intensive care were found to increase mortality. Thus, patients with comorbidities and/or elderly patients should be closely monitored.

It is challenging to define the standard treatment regimens, as the first-line antibiotics are not used in the majority of the cases of CR-Kp infection [7]. Antibiotics, including colistin, aminoglycosides, fosfomycin, and tigecycline, used in monotherapy or combination therapy of these infections, are sometimes associated with side effects, and uncertainty in its efficacy [8]. However, the impact of monotherapy and combination therapies on survival outcomes is still unclear [13, 14]. Paul et al. [15] showed that combination therapy, including at least one *in-vitro* active agent, decreased mortality in patients with sepsis and septic shock in their study on 205 patients with CR-Kp bacteremia. Tumbarello et al. [16] found no difference between monotherapy and combination therapy in urinary tract infections caused by KPC-producing *Klebsiella pneumoniae*. Moreover, they also reported that combination therapy was associated with higher survival compared to monotherapy in patients with septic shock. Combination therapy was found to be significantly superior to monotherapy in urinary tract infections caused by CR-Kp in terms of 14- and 28-day survival in patients with sepsis, similar to the literature. However, no significant differences were found between combination and monotherapy in the group without sepsis.

Thus, monotherapy with an *in-vitro* active agent could be administered to patients without sepsis/septic shock at the start of treatment for urinary tract infections caused by CR-Kp, and combination therapy could be initiated in patients with sepsis.

There is inadequate evidence to propose specific antibiotic combinations for the treatment of CR-Kp infections [17]. Papst et al. [18] reviewed the treatment strategies in a cross-sectional study used for CR-E infections in all hospitals (France, Greece, Israel, Italy, Kosovo, Spain, and Slovenia) and some selected hospitals in the U.S. with more than 800 acute care beds. It was observed that the carbapenem-colistin combination was used in 50.5% of patients with HA-UTI caused by CR-Kp. In our study, the most preferred antibiotic pair was meropenem and colistin, followed by meropenem and aminoglycoside. Although several studies reported that colistin-containing combinations are associated with lower mortality [19, 20], our study showed no significant difference between the combinations.

Despite carbapenem-resistance, adding carbapenem in combination regimens and evaluating meropenem MIC values decreases mortality and speeds up clinical recovery. In a multicenter study assessing the efficacy of different antibiotic combinations on infections caused by CR-Kp, combination regimens containing meropenem provided considerable therapeutic benefits when MIC was ≤8 mg/L while proving ineffective with MIC over 32 mg/L. Thus, emphasizing that further studies are required to define the potential of carbapenem-containing combinations for isolates with a meropenem MIC of 16 [16]. A similar study demonstrated that in septicemia by CR-Kp, the slow addition of infused high-dose meropenem to the combination also decreased mortality in patients with a MIC of ≥16 [21]. Another study reported that combination regimens, including carbapenem with at least one active drug (commonly colistin), provides a significantly higher success rate compared to non-carbapenem-containing regimens [22]. In our present study, meropenem was added to an *in-vitro* active agent in 51 of the 78 patients (65.3%). However, no difference was found in mortality between combinations with and without meropenem. Analysis based on the meropenem MIC against *Klebsiella pneumoniae*, following treatment regimens with or without meropenem, showed insignificant differences between patients with a MIC of ≥16 and ≥32 in terms of mortality and microbiological cure. However, our study did not include strains with lower MIC values, since there were no isolates with MIC values of <16. Moreover, an inadequacy of our study was that meropenem doses and infusion times used in patients were not evaluated. In most studies, meropenem was used in high doses and prolonged infusion regimens proposing its addition to combination regimens on strains with high MIC values in CR-Kp infections. Furthermore, the contribution of high-dose, prolonged infusion of meropenem to the combination regimens in HA-UTIs caused by CR-Kp should be investigated.

The resistance rates of the CR-Kp strains to colistin, aminoglycosides, tigecycline, and fosfomycin were 37.2%, 55.9%, 50%, and 38.2%, respectively. The 37% resistance to colistin is particularly alarming. A joint recommendation by the CLSI and EUCAST released in 2016 recommended the ISO-20776 standard broth microdilution (BMD) method for MIC testing of colistin [23, 24]. Other testing methods, such as agar dilution, disk diffusion, and gradient diffusion, are not currently recommended. Our high colistin resistance rates may be due to the use of disc diffusion for susceptibility testing in the past. But it is a fact that colistin resistance is dramatically increasing over the years [25]. Resistance rates vary depending on regions, similar to the literature. Consequently, we risk losing all these treatment options in the near future until strict policies for antibiotic use and infection control measures are implemented.

In conclusion, our study aimed to contribute by providing an analysis of data on urinary tract infections caused by CR-Kp, and its increasing frequency, which is a significant health problem due to high mortality rates and limited treatment. Our study supports the use of combination therapy in patients with sepsis, and monotherapy with an in-vitro active agent may be used for patients without sepsis in treating urinary tract infections. An additional benefit of adding meropenem to combination therapy was not established. However, it should be kept in mind that meropenem MIC values were ≥16 for 68 strains and ≥32 for 66 isolates.

More studies are needed to evaluate the treatment and follow-up options, considering the high morbidity and mortality rates of carbapenem-resistant *Klebsiella pneumoniae* infections. This can be achieved if each center could contribute by presenting their data. Thus, there is a need for data and recommendations with high-level evidence from randomized controlled studies on this subject.

Conflicts of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: The study was approved by the Ondokuz Mayıs University, Medical Faculty Clinical Research Ethics Committee (reference number: 2020/316).

Author contributions

Concept – F.T., Ş.B.K., L.Ş.; Design – F.T., Ş.B.K., L.Ş., T.K.; Supervision – F.T., T.K., A.A., E.T.; Materials – F.T., T.K., A.A., E.T.; Data Collection and/or Processing – F.T., Ş.B.K., L.Ş., T.K.; Analysis and/or Interpretation – F.T., T.K., A.A., E.T.; Literature Review – F.T., T.K., A.A., E.T., Ş.B.K., L.Ş.; Writing Manuscript – F.T., Ş.B.K., L.Ş., T.K.; Critical Review – F.T., T.K., A.A., E.T. Approval of the final manuscript: all authors.