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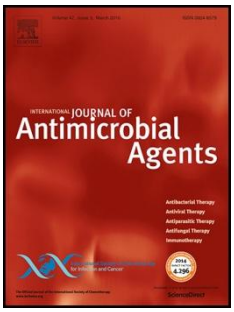

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Effect of combination therapy containing a high dose carbapenem on mortality in patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection

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35 Highlights

36 Bloodstream infection (BSI) due to carbapenem resistant Klebsiella pneumoniae (CR-KP) is associated with
37 high mortality.

38 Combination therapy seems to be better than monotherapy for more severely ill patients. However which
39 combination is optimal is far from being clear.

40 Regimens based on the use of high-dose (HD) carbapenem have been associated with survival by some
41 authors, but they have been criticized from others.

42 Here we analysed the impact on mortality of the HD carbapenem use in patients treated with combination
43 regimens for CR-KP BSI.

44 Our results suggest a benefit of HD carbapenem-based combinations in a cohort of patients with high
45 percentage (77%) of high level (MIC ≥16mcg/L) carbapenem resistance.

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ABSTRACT

Objectives. To evaluate the impact of high-dose (HD) carbapenem-based combination therapy on clinical outcome in patients with monomicrobial carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) bloodstream-infection (BSI).

Methods. *Post hoc* analysis of all adult patients with CR-KP BSI who were treated with combination antibiotic regimen, collected over 6-year period in 6 large teaching Italian hospitals. To control for confounding effects of HD carbapenem combination on 14-day mortality, a multivariate Cox regression analysis was performed. Due to imbalances between patients, a propensity score for receiving HD carbapenem was added to the model.

Results. 595 patients with CR-KP BSI were analysed, 77% of isolates showed a carbapenem MIC ≥16mg/L, 428 (71.9%) received a HD carbapenem-based combination therapy. Overall, 127 patients (21.3%) died within 14 days after BSI onset. The multivariate analysis showed Charlson (HR 1.31, 95%CI 1.20-1.43, p<0.001), septic shock at BSI onset (HR 3.14, 95%CI 2.19-4.50, p<0.001), and colistin resistant strain (HR 1.52, 95%CI 1.02-2.24, p=0.03) were independently associated with 14-day mortality, while admission to surgical ward (HR 0.44, 95%CI 0.25-0.78, p=0.005) and HD carbapenem use (HR 0.69, 95%CI 0.47-1.00, p=0.05) were protective factors. When adjusted for the propensity score, HD carbapenem use showed a greater protective effect (HR 0.64, 95%CI 0.43-0.95, p=0.03). Stratifying the model for carbapenem MIC, the benefit of HD carbapenem was observed also for strains with carbapenem MIC ≥16mg/L.

Conclusions. In patients receiving combination therapy for CR-KP BSI, the use of HD carbapenem seems to be associated with better outcome also in presence of high level of carbapenem resistance.

INTRODUCTION

Over the last decade, the prevalence of carbapenem resistant *Klebsiella pneumoniae* (CR-KP) infections has increased worldwide with associated high morbidity and mortality, especially among patients with bloodstream infection (BSI) [1].

Given the limited number of effective and safe agents, several strategies have been proposed to treat CR-KP infections. One of the most supported strategy is combination antibiotic regimen in order to improve bactericidal activity, suppress the emergence of resistance, and overcome the pharmacokinetic weaknesses of individual agents. Indeed, several studies have reported lower mortality rates (0-40%) among patients who received combination therapy versus patients receiving monotherapy (40-80%) [2-7]. Recently, the positive impact of combination therapy has been shown to be significant, primarily in patients at high risk of dying [8].

Unfortunately, the question of which combination is superior remains unresolved [9]. Among the different combinations, those that included a carbapenem were associated with better outcome in some studies [4-7]. In an Italian multicenter study including 661 patients with CR-KP infection [7], the protective role of carbapenems was confirmed essentially for strains with MIC values ≤8mg/L, which represented around 30% of isolates in that cohort. On the other hand, carbapenem-sparing regimens are advocated by some authors for reducing the carbapenem use in the context of infection control and antimicrobial stewardship programs aimed to contain the high endemicity of CR-KP [10].

To assess the impact on 14-day mortality of a combination therapy containing or not a high dose carbapenem in a cohort of CR-KP BSI patients with high level of carbapenem resistance, we performed a post *hoc* analysis of the Italian cohort of patients with CR-KP infection, selecting those with BSI who received a combination therapy. A propensity score for receiving a carbapenem containing combination was used to adjust the survival analysis.

MATERIAL AND METHODS

Study design, setting and population

We performed a post *hoc* analysis of a multicentre, observational cohort study of all adult (≥18 years) patients with CR-KP infection, hospitalized in six large tertiary-care teaching hospitals in Italy, from January 1st 2010 to December 31st 2015. Thus, with respect to the prior report [7], the current cohort includes patients hospitalized during a larger period (6 instead of 4 years) and in a higher number of centers (6 instead of 5 hospitals). For the purpose of this study, patients with

monomicrobial CR-KP BSI who were treated with a combination regimen were selected. Each patient was included only once at the time of the first positive blood cultures (BCs, index culture), even if more than one CR-KP BSI was reported.

Definitions

CR-KP BSI was defined as isolation of a CR-KP strain in the BCs obtained from a patient with clinical symptoms and/or signs of the systemic inflammatory response syndrome [4]. BSI onset was considered as the date of the index BCs collection (the first BCs yielding the study isolate). BSIs were classified as low-risk or high-risk depending on the source of the bacteraemia (urinary tract versus all other identified and unidentified sources, respectively) [11]. BSIs were further considered as hospital-acquired, healthcare-associated or community-acquired according with Friedman's criteria [12].

Septic shock was defined as sepsis associated with organ dysfunction and persistent hypotension despite volume replacement [13].

Combination therapy was defined as a regimen including two or more antibiotics, with at least one agent showing *in vitro* activity against the CR-KP isolate from BCs. Appropriate empirical antibiotic therapy was defined as treatment with at least one drug that had *in vitro* activity against the infecting organism, initiated within 48 h of the index BCs, and given in adequate dosage [14].

Data

Data were collected in a standardized case report form. Underlying diseases were recorded according with the Charlson's score. Invasive abdominal procedures included open abdominal surgery, endoscopic abdominal surgery and percutaneous drainage. Corticosteroid therapy was defined by 16 mg prednisone-equivalent per day for >15 days; neutropenia was defined as <500 neutrophil cells per microliter of blood for ≥7 days. Clinical severity at BSI onset was assessed according to APACHE III score and septic shock criteria [13]. Therapeutic variables included: administered antibiotics with their dosage, schedule, and duration. As for outcome all cause 14-day mortality was collected. Patients were followed until hospital discharge or in-hospital mortality.

Microbiological study

Isolates were identified with the Vitek 2 system (bioMérieux, Marcy l'Etoile, France) and/or by matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) mass spectrometry (MALDI Biotyper, Bruker Daltonics GmbH, Leipzig, Germany, or Vitek-MS, bioMérieux). The *in vitro*

susceptibility of the isolates was assessed with the Vitek 2 system (bioMérieux) or the Sensititre broth microdilution method (Trek Diagnostic Systems, Cleveland, OH). Results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.

Statistical analysis

Categorical variables were expressed as absolute numbers and their relative frequencies. Continuous variables were expressed as mean ± standard deviation (SD) is normally distributed, or as median and interquartile range (IQR) if non-normally distributed.

To analyse risk factors for 14-day mortality, non-survivors and survivors were compared. All the variables with a p value ≤ 0.1 at the univariate analysis were entered into a multivariate Cox backward regression model after assuming for proportional hazards. Patients were considered from the date of index BCs to death or until 14 days. Combination therapy with or without a carbapenem was introduced as the explanatory variable of interest. A propensity score for receiving carbapenem combination therapy was further added to the model.

The propensity score—the probability of receiving a carbapenem combination therapy—was calculated using a non-parsimonious multivariate logistic regression model in which the outcome variable was the use of carbapenem. The following variables were introduced into the model: age, sex, chronic renal failure, chronic liver failure, chemotherapy, corticosteroid treatment, abdominal invasive procedure, Charlson score, healthcare associated BSI, colistin resistant strain, septic shock at BSI onset, carbapenem MIC, combination therapy containing gentamicin, combination therapy containing tigecycline. The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test (69%) and the ROC curve analysis with an area under the curve of 0.75 (95%CI 0.71-0.79).

Statistical significance was considered for p values <0.05. The software used for the analysis was SPSS (SPSS; version 21.0).

RESULTS

According to the study criteria, 595 patients were analyzed. All strains were *K. pneumoniae* carbapenemase (KPC) producers, mostly KPC-3, 77% of them showed a carbapenem MIC ≥16mg/L.

Overall, 428 (71.9%) patients received a combination therapy containing a carbapenem. This consisted of meropenem administered at high doses (6 g per day) and by extended infusion (each

infusion lasted 3 hours) in all the cases. The remaining 167 (29.1%) patients received a combination therapy without carbapenems. Comparison of the two groups is shown in Table 1.

Overall, 127 patients (21.3%) died within 14 days after BSI onset. Comparison of non-survivor and survivor patients showed significant differences for Charlson's index (median 4 vs 2, p<0.001), APACHE III score at BSI onset (median 27 vs 19, p<0.001), underlying chronic renal failure (26% vs 15.4%, p=0.002), admission to a surgical ward (10.2% vs 22.4%, p=0.002), septic shock at BSI onset (40.9% vs 12.8%, p<0.001), and colistin resistance (27.6% vs 20.5%, p=0.09) (see Table 2). The multivariate Cox regression analysis showed that Charlson's index (HR 1.31, 95%CI 1.20-1.43, p<0.001), septic shock at BSI onset (HR 3.14, 95%CI 2.19-4.50, p<0.001), and isolation of a colistin resistant strain (HR 1.52, 95%CI 1.02-2.24, p<0.001) were independently associated with 14-day mortality, while admission to a surgical ward (HR 0.44, 95%CI 0.25-0.78, p=0.005) was a protective factor, the carbapenem containing combination (HR 0.69, 95%0.47-1.00, p=0.05) remained also in the final model as a protective factor but with borderline significance (see appendix Table). When adjusted for the propensity score the variables that remained into the model were Charlson index (HR 1.65, 95%CI 1.10-2.46, <0.001), corticosteroid therapy (HR 1.93, 95%CI 1.22-3.04, p=0.005), admission to a surgical ward (HR 0.44, 95%CI 0.24-0.78, p=0.005), septic shock at BSI onset (HR 4.70, 95%CI 3.03-7.27, p<0.001), colistin resistant strain (HR 1.65, 95%CI 1.10-2.46, p=0.005), and carbapenem containing combination (HR 0.64, 95%CI 0.43-0.95, p=0.03) (appendix Table). Stratifying the model for the carbapenem MIC, the benefit of combination therapy with a HD carbapenem was observed also for strains with a carbapenem MIC ≥16mg/L (see Figure 1).

DISCUSSION

This is the first study that analyses the outcome of patients with CR-KP BSI treated with a combination therapy containing or not a high dose meropenem using the propensity score for accounting of population imbalances. Our results confirm previous data about the benefit of using a high dose carbapenem as backbone in the combination regimens for CR-KP BSI.

The definition of combination therapy for carbapenem resistant infection is a matter of debate [15]. Some experts define as combination therapy any regimen including more than one antibiotic with activity against Gram negative bacteria (regardless of their *in vitro* activity against the infecting organism) [16], and others consider as combination therapy only regimens including two or more *in vitro* active drugs [6]. Since our objective was to assess the impact on outcome of the meropenem use in carbapenem resistant infections we choosed combinations with at least one *in vitro* active

drug as clinicians usually choose the meropenem' companion on the basis of the *in vitro* susceptibility tests.

In a retrospective study of 141 CR-KP BSIs collected at two New York City hospitals from 2006-2013, the aim of the authors was to assess the patient outcome according to the number of *in vitro* active drugs used and whether an extended-spectrum beta-lactam (meropenem or extended-spectrum cephalosporin) was administered [15]. Of the 111 isolates for which meropenem MICs were available, 90% had a meropenem MIC ≥16 mg/L. A lower proportion of patients treated with meropenem died (24% vs. 37%), but difference was not statistically significant, also after adjusting for meropenem MIC (≤8 mg/L or ≥16 mg/L) or meropenem dosing category (conventional, or high dose administered by extended infusion). There was also no difference between single and multiple *in vitro* active drug used [15].

We reached different results analysing a larger number of patients, investigating only the role of high dose meropenem administered by extended infusion among patients treated with a combination regimen, and using the propensity score for accounting of possible imbalances. Indeed, also in our univariate analysis, the 14-day mortality rate was not significantly different between patients treated with and without HD meropenem (19.9% vs. 25.1%, p=0.18). However, the use of meropenem remained as a protective factor in the multivariate model and the level of significance increased after adjusting the analysis for the propensity score. Finally, we stratified our multivariate model for the meropenem MIC, observing a benefit of HD meropenem combination also for strains with meropenem MIC ≥16 mg/L that represented 77% of overall strains. This could be explained by recent observation that high-dose/prolonged-infusion regimens of meropenem can reach the pharmacokinetic/pharmacodynamics target in patients with BSI caused by CR-KP with meropenem MICs up to 32-64 mg/L, but not for higher values [17, 18]. Unfortunately, the lack of a punctual meropenem MIC in our strains with meropenem MIC ≥ 16 mg/L hindered us to establish for which level of carbapenem resistance the use of carbapenems is still useful. Thus, we deem that the impact of carbapenem MIC on outcome in patients treated with carbapenems for CR-KP BSI should be further investigated in deep assessing together the carbapenem punctual MICs and the therapeutic drug levels.

Our study has some limitations. First the study was not originally designed for the analysis of the impact of treatment on outcome but just to create an observational registry of severe infections with CR-KP. The adjustment of multivariate analysis for the most important confounding factors and for the propensity score should minimize this limitation. However, we have to acknowledge that the propensity score inclusion still leads to residual confounding. Finally, although our paper suffers of some methodological drawbacks as well as some prior reports (retrospective

observational study, lack of punctual meropenem MIC) it has some strengths that we would like to underline: i) it is focused only on patients receiving carbapenem vs non carbapenem combination treatments; ii) it comprises a large number of patients with true CR-KP infection as we selected only those with BSI; iii) meropenem administration schedule was homogeneous (use of high doses by extended infusion); iv) being an observational study it reflects what happens in real life.

To conclude, in a population of patients receiving combination therapy for CR-KP BSI, with 77% of isolates showing a carbapenem MIC ≥16mg/dl, the use of carbapenem seems to be still associated with better outcome. Further studies, in particular clinical trials, should be performed to assess the punctual level of carbapenem resistance for which the use of carbapenems is still useful.

Declarations

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Competing Interests: None

Ethical Approval: Ethical approval was given by the IRB of the coordinator center (Institute of Infectious Diseases, Catholic University of the Sacred Heart, A. Gemelli Hospital, Rome).

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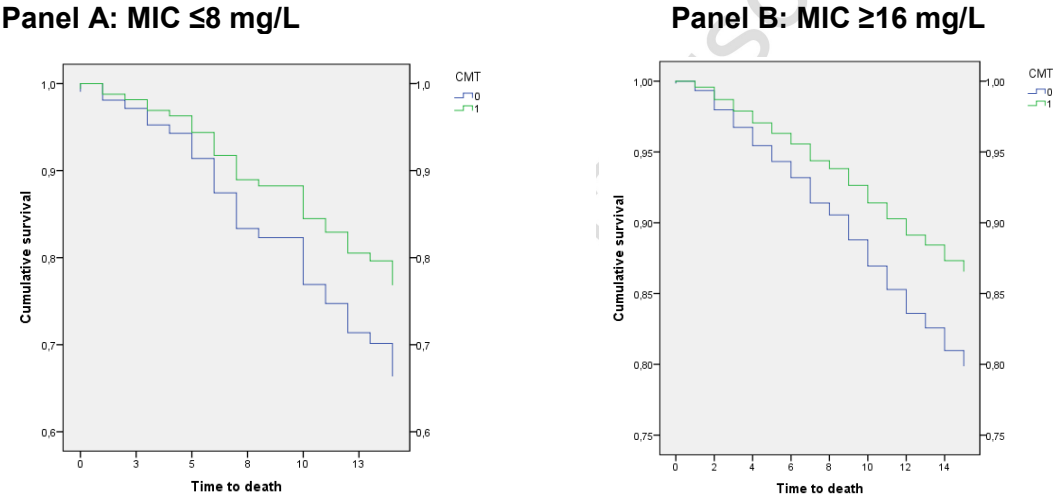
Figure 1. Cox regression analysis of survival stratified for carbapenem MIC



CMT: combination with meropenem treatment: 0 no, 1 yes.

Panel A and Panel B show cumulative survival at 14 days from CR-KP BSI onset for patients receiving or not carbapenem combination therapy, it was adjusted for all the covariates included into the Cox regression model and the propensity score. The model was further stratified according with the meropenem MIC ≤8 mg/L (Panel A), MIC ≥16 mg/L (Panel B), the overall aHR for the variable carbapenem combination therapy (CMT) was: 0.63, 95%CI 0.41-0.96, p=0.03.

Appendix Table. Cox proportional hazards regression analysis of risk factors for 14-day mortality

	Without propensity score adjustment		Adjusted for the propensity score for combination with carbapenem	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Charlson comorbidity index	1.31 (1.20-1.43)	<0.001	1.65 (1.10-2.46)	<0.001
Surgical ward admission	0.44 (0.25-0.78)	0.005	0.44 (0.24-0.78)	0.005
Septic shock at BSI onset	3.14 (2.19-4.50)	<0.001	4.70 (3.03-7.27)	<0.001
Colistin resistant strain	1.52 (1.02-2.24)	<0.001	1.65 (1.10-2.46)	0.005
Combination including carbapenem	0.69 (0.47-1.00)	0.05	0.64 (0.43-0.95)	0.03
Corticosteroid therapy			1.93 (1.22-3.04)	0.005

Abbreviations: BSI bloodstream infection

Table 1. Comparison of patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection who received combination therapy with and without a high dose carbapenem

	Combination with carbapenem N=428 (%)	Combination without carbapenem N=167 (%)	*p*
Demographic variables			
Male sex	269 (62.9)	97 (58.1)	0.30
Age (years) (median, IQR)	66, 54-76	65, 54-76	0.67
Underlying conditions			
Charlson score (median, IQR)	3, 2-6	3, 1-4	0.007
APACHE III score (median, IQR)	21, 13-36	19.5, 15-38.5	0.64
Chronic renal failure	83 (19.4)	22 (13.2)	0.09
Haemodyalisis	59 (13.8)	14 (8.4)	0.09
Chronic liver disease	46 (10.7)	8 (4.8)	0.02
Neutropenia	55 (12.9)	26 (15.6)	0.42
Corticosteroid therapy	79 (18.5)	42 (25.1)	0.07
Chemotherapy	59 (13.8)	35 (21)	0.03
Abdominal invasive procedures	193 (45.1)	88 (52.7)	0.10
Transferred from a LTCF	20 (4.7)	14 (8.4)	0.11
Admission ward at BSI onset			
Medical ward	176 (41.1)	70 (41.9)	0.93
Surgical ward	78 (18.2)	40 (24)	0.13
Intensive care unit	169 (39.5)	56 (33.5)	0.19
Days of hospital stay before BSI (median, IQR)	50, 29-77	42, 27.2-76.5	0.19
Characteristics of BSI			
Low risk source	87 (20.3)	38 (22.8)	0.57
High risk source	341 (79.7)	129 (77.2)	0.57
Septic shock	71 (16.6)	41 (24.6)	0.02
Healthcare associated	28 (6.5)	20 (12)	0.03
Hospital acquired	385 (90)	146 (87.4)	0.37
Characteristics of the strain			
Meropenem MIC ≤ 8 mg/L	103 (24.1)	64 (38.3)	0.001
Meropenem MIC ≥ 16 mg/L	325 (75.9)	103 (61.7)	
Colistin resistant	97 (22.7)	34 (20.4)	0.58
Therapeutic management			
Colistin containing regimen	286 (66.8)	122 (73.1)	0.17
Tigecycline containg regimen	320 (74.8)	143 (85.7)	0.004
Gentamicin containing regimen	170 (39.7)	113 (67.7)	<0.001
Outcome			
14-day mortality	85 (19.9)	42 (25.1)	0.18

In-hospital mortality	122 (28.5)	54 (32.3)	0.36

333 **Abbreviations: BSI** bloodstream infection**; IQR** interquartile range**; LTCF** long term care facility.

334 **Table 2. Comparison of patients with CR-KP BSI who died within 14 days after infection**
335 **onset (date of positive index blood cultures) and survivors**

	Non-survivors N=127 (%)	Survivors N=468 (%)	*p*
Demographic variables			
Male sex	77 (60.6)	289 (61.8)	0.84
Age (years) (median, IQR)	66, 57-77	66, 53-76	0.18
Underlying conditions			
Charlson score (median, IQR)	4, 3-6	2, 2-4	<0.001
APACHE III score (median, IQR)	27, 17-41	19, 13-35	<0.001
Chronic renal failure	33 (26)	72 (15.4)	0.002
Haemodyalisis	20 (15.7)	53 (11.3)	0.22
Chronic liver disease	16 (12.6)	38 (8.1)	0.16
Neutropenia	17 (13.4)	64 (13.7)	1
Corticosteroid therapy	34 (26.8)	87 (18.6)	0.05
Chemotherapy	18 (14.2)	76 (16.2)	0.58
Abdominal invasive procedures	60 (47.2)	221 (47.2)	1
Transferred from a LTCF	10 (7.9)	24 (5.1)	0.27
Admission ward at BSI onset			
Medical ward	59 (46.5)	187 (40)	0.22
Surgical ward	13 (10.2)	105 (22.4)	0.002
Intensive care unit	55 (43.2)	170 (36.3)	0.18
Characteristics of BSI			
Low risk source	25 (19.7)	100 (21.4)	0.71
High risk source	102 (80.3)	368 (78.6)	
Septic shock	52 (40.9)	60 (12.8)	<0.001
Characteristics of the strain			
Meropenem MIC ≤ 8 mg/L	32 (25.2)	135 (28.8)	0.44
Meropenem MIC ≥ 16 mg/L	95 (74.8)	333 (71.2)	
Colistin resistant	35 (27.6)	96 (20.5)	0.09
Antibiotic management			
Inadequate empirical treatment	76 (59.8)	291 (62.2)	0.68
Carbapenem containing combination	85 (66.9)	343 (73.3)	0.18
Meropenem MIC ≤ 8 mg/L	15/85 (17.6)	88/343 (25.7)	0.15
Meropenem MIC ≥ 16 mg/L	70/85 (82.4)	255/343 (74.3)	0.15
Combination without carbapenem	42 (33.1)	125 (26.7)	0.18
1 active drug	28/42 (66.7)	90/125 (72)	0.56
> 1 active drug	14/42 (33.3)	35/127 (28)	0.56

336 **Abbreviations: BSI** bloodstream infection**; IQR** interquartile range**; LTCF** long term care facility.

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