Eur J Clin Microbiol Infect Dis (2017) 36:1965–1970
DOI 10.1007/s10096-017-3020-x

ORIGINAL ARTICLE

Risk factors for recurrent carbapenem resistant *Klebsiella pneumoniae* bloodstream infection: a prospective cohort study

Maddalena Giannella[1] · Elena Graziano[1] · Lorenzo Marconi[1] · Nicolo Girometti[1] · Michele Bartoletti[1] · Sara Tedeschi[1] · Fabio Tumietto[1] · Francesco Cristini[1] · Simone Ambretti[2] · Andrea Berlingeri[2] · Russell E. Lewis[1] · Pierluigi Viale[1]

Received: 27 March 2017 / Accepted: 15 May 2017 / Published online: 1 June 2017

Abstract To assess risk factors for recurrent carbapenem-resistant *Klebsiella pneumoniae* bloodstream-infection (CR-KP BSI), we performed a prospective observational cohort study of all consecutive adult patients cured of a CR-KP BSI at our hospital over a six-year period (June 2010 to June 2016). Maximum follow-up per patient was 180 days from the index blood cultures (BCs). Recurrent CR-KP BSI was defined as new evidence of positive BCs in patients with documented clinical response after completing a course of anti-CR-KP therapy. Univariate and multivariate cause-specific Cox proportional hazards analysis were performed. During the study period 249 patients were diagnosed with a CR-KP BSI, 193 were deemed as cured within 14 days after index BCs and were analysed. Recurrence occurred in 32/193 patients (16.6%) within a median of 35 (IQR 25–45) days after index BCs. All but one of the recurrences occurred within 60 days after the index BCs. Comparison of recurrent and non-recurrent cases showed significant differences for colistin use (84.4% vs. 62.2%, $p = 0.01$), meropenem-colistin-tigecycline regimen (43.8% vs. 24.8%, $p = 0.03$) and length of therapy for the index BSI episode (median 18 vs. 14 days, $p = 0.004$). All-cause 180-day mortality (34.4% vs. 16.1%, $p = 0.02$) was higher in recurrent cases. In the multivariate analysis, the only independent variable was source control as a protective factor for recurrence. Recurrence is frequent among patients cured of a CR-KP BSI and is associated with higher long-term mortality. When feasible, source control is mandatory to avoid recurrence. The role of antibiotic treatment should be further investigated in large multicentre studies.

✉ Maddalena Giannella
maddalena.giannella@unibo.it

[1] Infectious Diseases Unit, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital, via Massarenti 11, 40138 Bologna, Italy

[2] Operative Unit of Microbiology, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

Introduction

Bacteraemia due to carbapenem resistant *Klebsiella pneumoniae* (CR-KP) is associated with high morbidity and mortality [1]. Most studies on CR-KP bloodstream infection (BSI) have focused on the risk factors for all-cause mortality [2, 3].

In the clinical practice, recurrence after surviving the primary episode of CR-KP BSI is another important outcome that affects length of stay, need for readmission, and long-term mortality [4]. The knowledge of the risk factors for the recurrence of CR-KP BSI may be useful for treatment decisions.

The aim of our study was to determine how often patients cured of a first episode of CR-KP BSI developed a new episode, and to analyse the risk factors for recurrence.

Material and methods

Study design We performed a prospective observational cohort study of all consecutive adult (≥18 years) patients cured of a first CR-KP BSI at our hospital over six-year period (June 2010–June 2016). The maximum follow-up period per patient was 180 days after the index blood cultures (BCs).

Setting The setting was a 1,420-bed tertiary teaching hospital with approximately 72,000 yearly admissions. Performance of BCs was at the discretion of the attending physician and was

not dictated by study protocol. Standard approach to the therapeutic management of CR-KP BSI consisted of source control when feasible and antibiotic therapy including high-dose (HD) meropenem (6 g/day) administered by extended infusion [5] plus at least one in vitro active drug depending on the infection source, as previously reported [6].

The institutional review board of the hospital approved the study.

Definitions CR-KP BSI was defined as one or more BCs yielding CR-KP obtained from a patient with symptoms and/or signs of systemic inflammatory response syndrome [7]. Patients were considered only once at the time of first episode (index BCs). Subsequent positive BCs were defined as: (i) persistent CR-KP BSI, BCs persistently positive despite initiation of anti-CR-KP antibiotic treatment; (ii) breakthrough CR-KP BSI, new evidence of positive BCs after their clearance during an ongoing antibiotic course; or (iii) recurrent CR-KP BSI, new evidence of positive BCs in patients with documented clinical response after completing a course of anti-CR-KP therapy.

Polymicrobial BSI was defined as the growth of more than one microorganism, excluding potential contaminants (i.e. coagulase-negative staphylococci, Corynebacterium spp., Propionibacterium spp.) isolated in only one set of BCs.

BSI sources were established according to the Centres for Disease Control and Prevention criteria [8]. In the absence of a recognized source, BSI was considered as primary.

Clinical cure was defined as the resolution of all signs and symptoms of infection and was prospectively assessed according to vital signs, laboratory and imaging data at 14 days after index BCs by a trained clinical investigator.

Active empiric therapy was defined as at least one antibiotic with in vitro activity, based on susceptibility results, administered within 24 h from drawing the index BCs. Active directed therapy was defined as at least 1 antibiotic with in vitro activity administered after susceptibility results were available for at least 7 days. The length of antibiotic therapy was defined as the time period form the first to the last day of an active therapy.

Source control was defined as the removal of infection source, including the performance of nonsurgical or surgical procedures to treat an obstructive focus or abscess, and the removal of any device deemed as the source of BSI. In addition, removal of intravascular devices, foreign bodies and urinary catheters was recorded irrespectively of the BSI source.

Data Variables were collected using a standardized case report form including demographic data (age and sex), admission and discharge dates, underlying diseases according to Charlson's index score, solid organ transplantation, ward of admission at the time of index BCs, CR-KP rectal carriage at the time of index BCs, clinical severity at BSI onset according to the sepsis grading [9] and the APACHE II score, polymicrobial BSI, persistent and/or breakthrough BSI, the presumed source of BSI, source control, removal of central venous catheter (CVC), administered drugs with the relative start and end dates, all-cause mortality and date of death, recurrence and date of recurrence, as well as number of recurrences.

Microbiology BCs were incubated using the BACTEC FX Automated Blood Culture System (Becton Dickinson, Franklin Lakes, NJ). All positive BCs were processed with MALDI-TOF for the rapid identification of the microorganism. Identification and susceptibility testing of strains were performed using the Vitek 2 automated system (bioMerieux, Marcy l'Etoile, France). Enterobacteriaceae MICs were interpreted using EUCAST clinical breakpoints for all tested antimicrobials. Carbapenemase production was confirmed by disc-diffusion synergy test (Rosco Diagnostica, Taastrup, Denmark).

Statistical analysis Comparison between recurrent and non-recurrent cases was performed. Categorical variables were compared using Pearson chi-square or Fisher's exact test when appropriate. Continuous variables were compared using Mann–Whitney U test.

To investigate risk factors for recurrence, univariate and multivariate cause-specific Cox proportional hazards analysis were performed. Patients were observed from the index BCs up to recurrence, death or 180 days. The variables with a p value ≤ 0.10 at univariate analysis were entered into the multivariate model. As the correlation test for source control and CVC removal was significant (0.673, $p < 0.001$), only source control was maintained into the final model. Statistical significance was set for p value <0.05. The analysis was performed with SPSS 21.00 software package.

Results

During the study period 249 patients were diagnosed with CR-KP BSI at our hospital. According to study criteria, 193 patients were deemed as cured within 14 days after index BCs and were analysed.

All patients received a combination therapy; the most frequent administered individual antibiotics and combination regimens are shown in Table 1.

Recurrence occurred in 32 out of 193 patients (16.6%) within a median of 35 (IQR 25–45) days after index BCs. All but one of the recurrences occurred within 60 days after index BCs. Five patients developed more than one recurrent CR-KP BSI: three patients developed two episodes, one patient developed three episodes, and one patient developed four episodes. Susceptibility of recurrent strains to the antibiotics

Table 1 General characteristics of patients cured of a first CR-KP BSI episode, and comparison between recurrent and non-recurrent cases

Characteristic	Total $N = 193$ (%)	Recurrent cases $N = 32$ (%)	Non-recurrent cases $N = 161$ (%)	p-value
Demographic variables				
Age (years) (median, IQR)	65 (55–74)	61.5 (55.2–69.7)	65 (55–75)	0.24
Male sex	119 (61.7)	19 (59.4)	100 (62)	0.84
Underlying diseases				
Chronic heart failure	19 (9.8)	3 (9.4)	6 (9.9)	1
Cerebrovascular disease	22 (11.4)	3 (9.4)	19 (11.8)	0.77
COPD	29 (15)	7 (21.9)	22 (13.7)	0.27
Moderate/severe liver failure	37 (19.2)	5 (15.6)	32 (19.9)	0.63
Chronic kidney failure	53 (27.5)	10 (31.3)	43 (26.7)	0.66
Metastatic solid tumour	24 (12.4)	4 (12.5)	20 (12.4)	1
Hematologic malignancy	16 (8.3)	5 (15.6)	11 (6.8)	0.15
Solid organ transplantation	27 (14)	4 (12.5)	23 (14.3)	1
Charlson index (median, IQR)	7 (5–10)	6 (4–9)	7 (5–10)	0.37
Ward of stay at BSI onset				0.87
Surgical ward	44 (22.8)	7 (21.9)	37 (23)	
Medical ward	90 (46.6)	14 (43.8)	76 (47.2)	
ICU	59 (30.6)	11 (34.4)	48 (29.8)	
Characteristics of BSI				
Polymicrobial BSI	33 (17.1)	4 (12.5)	29 (18)	0.61
Persistent BSI	29 (15)	8 (25)	21 (13)	0.10
Breakthrough BSI	3 (1.6)	0 (0)	3 (1.9)	1.00
Infection source				
Primary BSI	39 (20.2)	10 (31.3)	29 (18)	0.09
LRTI	38 (19.7)	10 (31.3)	28 (17.4)	0.08
IAI	63 (32.6)	8 (25)	55 (34.2)	0.41
UTI	24 (12.4)	6 (18.8)	18 (11.2)	0.24
CVC-related	41 (21.2)	5 (15.6)	36 (22.4)	0.48
Severity at BSI onset				
APACHE II score	13 (10–16)	14 (11–16)	13 (9–16)	0.26
Severe sepsis/septic shock	72 (37.3)	15 (46.9)	57 (35.4)	0.23
Rectal colonization at BSI onset	44 (22.8)	8 (25)	36 (22.4)	0.78
Antibiotic resistance				
Meropenem MIC ≥16 mcg/mL	177 (91.7)	29 (90.6)	148 (91.5)	1.00
Colistin	37 (19.2)	5 (15.6)	32 (19.9)	0.75
Tigecycline	182 (94.3)	31 (96.9)	151 (93.8)	0.83
Gentamicin	32 (16.6)	5 (15.6)	32 (19.9)	0.75
Therapeutic management				
Source control	92 (47.7)	11 (34.4)	81 (50.3)	0.12
CVC removal	59 (30.6)	6 (18.8)	53 (32.9)	0.14
Active empiric therapy	73 (37.8)	14 (43.8)	59 (36.6)	0.55
Active definitive therapy	155 (80.3)	28 (87.5)	127 (78.9)	0.33
Administered antibiotics				
Meropenem	177 (91.7)	31 (96.9)	146 (90.7)	0.32
Colistin	128 (66.3)	27 (84.4)	101 (62.7)	0.02
Tigecycline	102 (52.8)	19 (59.4)	83 (51.6)	0.44
Gentamicin	40 (20.7)	8 (25)	32 (19.9)	0.63
Administered regimens				
Meropenem-colistin-tigecycline	54 (28)	14 (43.8)	40 (24.8)	0.03

Table 1 (continued)

Characteristic	Total $N = 193$ (%)	Recurrent cases $N = 32$ (%)	Non-recurrent cases $N = 161$ (%)	p-value
Meropenem-colistin	65 (33.7)	12 (37.5)	53 (32.9)	0.68
Meropenem-tigecycline	34 (17.6)	4 (12.5)	30 (18.6)	0.46
Meropenem-gentamicin	14 (7.3)	1 (3.1)	13 (8.1)	0.47
Number of in vitro active drugs[a]				0.51
0	38 (19.7)	4 (12.5)	34 (21.1)	
1	143 (74.1)	26 (81.3)	117 (72.7)	
2	12 (6.2)	2 (6.3)	10 (6.2)	
Days of active therapy (median, IQR)	15 (11–22)	18 (14–29)	14 (10–21)	0.004
Outcome				
28-day mortality	15 (7.8)	0	15 (9.3)	0.14
180-day mortality	37 (19.2)	11 (34.4)	26 (16.1)	0.02

APACHE acute physiology and chronic health evaluation, *BSI* bloodstream infection, *CCI* Charlson comorbidity index, *COPD* chronic obstructive pulmonary disease, *CVC* central venous catheter, *IAI* intra-abdominal infection, *ICU* intensive care unit, *IQR* interquartile range, *LRTI* lower respiratory tract infection, *UTI* urinary tract infection

[a] This variable refers to drugs administered as definitive therapy

administered during the index CR-KP BSI was analysed. Increase in the MICs of colistin, tigecycline and gentamicin was observed in 37%, 36.8% and 50% of exposed cases, respectively. Meropenem MIC of the initial strain was ≥16 mcg/mL in all but three of the 31 recurrent cases treated with a meropenem-based combination regimen. In two of them the subsequent isolate showed an increase in MIC.

Comparison of recurrent and non-recurrent cases is shown in Table 1. Significant differences were found for colistin use (84.4% vs. 62.2%, $p = 0.01$), meropenem-colistin-tigecycline regimen (43.8% vs. 24.8%, $p = 0.03$) and length of therapy (median 18 vs. 14 days, $p = 0.004$).

All-cause 180-day mortality was significantly higher in recurrent cases (34.4% vs. 16.1%, $p = 0.02$).

The analysis of risk factors for recurrence is shown in Table 2. At the multivariate analysis the only variable that remained significantly associated with recurrent CR-KP BSI as a protective factor was source control.

Discussion

We observed that recurrent CR-KP BSI among patients cured of the first episode is frequent and associated with higher long-term mortality. Source control was the only protective factor associated with recurrent CR-KP BSI at multivariate analysis.

Messina and colleagues recently investigated how often patients colonized or infected with CR-KP were readmitted with repeat positive cultures for CR-KP [4]. CR-KP readmission was observed in 20% of cases, a figure similar to that of our study. In addition, the authors examined the impact of treatment on the risk for CR-KP readmission [4]. Independent risk factors for 90-day CR-KP readmission were: malignant tumour, tigecycline regimen, and receipt >1 in vitro active antibiotic [4]. We observed in the univariate analysis that colistin use, meropenem-colistin-tigecycline regimen, and longer duration of antibiotic therapy during the index BSI were risk factors for recurrent CR-KP BSI. However, at the multivariate model the only variable associated with recurrence as a protective factor was source control. In our opinion, the impact of antibiotic treatment on CR-KP recurrence should be further investigated in larger multicentre studies.

It is unknown whether the introduction of the new active drugs against CR-KP, such as ceftazidime-avibactam, will reduce the rate of recurrence. Unfortunately, in a recent series on the use of ceftazidime-avibactam for treating 37 patients with CR-KP infection, the recurrence rate was 23% [10].

Our study has limitations. First, the single centre design with limited sample size hampers the generalizability of our results and the statistical power of our analysis. Second, genotyping of the strains was not performed thus we were not able to differentiate recurrences between relapses and re-infections [11]. The fact that all but one of the recurrences occurred within 60 days after the index episode may suggest that most episodes were relapses [12]. Third, follow-up blood cultures were drawn at the discretion of attending physicians, thus in several cases the microbiological clearance was presumed on the basis of the good clinical, laboratory and imaging response as normally performed with Gramme negative BSI. Finally, the impact of resistance to the administered antibiotics was analysed using the susceptibility

Table 2 Univariate and multivariate analysis of risk factors for recurrence in patients cured of a first CR-KP BSI episode

Risk factors	Unadjusted HR (95%CI)	*p*-value	Adjusted HR (95%CI)	*p*-value
Age (years) (median, IQR)	0.98 (0.96–1.01)	0.36		
Male sex	1.12 (0.55–2.28)	0.74		
Hematologic malignancy	2.27 (0.87–5.90)	0.09	2.06 (0.69–6.12)	0.19
Charlson index (median, IQR)	0.95 (0.86–1.07)	0.42		
ICU stay at BSI onset	1.13 (0.52–2.44)	0.75		
APACHE II score	1.03 (0.97–1.09)	0.29		
Persistent BSI	1.95 (0.87–4.35)	0.10	1.12 (0.43–2.88)	0.80
Primary BSI	1.87 (0.89–3.96)	0.09	2.40 (0.95–6.09)	0.06
LRTI	2.26 (1.06–4.77)	0.03	2.30 (0.94–5.61)	0.06
Severe sepsis/septic shock	1.61 (0.80–3.22)	0.17		
Source control	**0.47 (0.23–0.99)**	**0.04**	**0.45 (0.21–0.99)**	**0.04**
CVC removal	0.44 (0.18–1.08)	0.07		
Active empiric therapy	1.28 (0.64–2.59)	0.47		
Active definitive therapy	1.70 (0.59–4.86)	0.32		
Meropenem use	3.04 (0.41–22.26)	0.27		
Colistin use	3.00 (1.15–7.81)	0.02	2.11 (0.76–6.35)	0.21
Tigecycline use	1.43 (0.71–2.91)	0.31		
Gentamicin use	1.22 (0.54–2.71)	0.62		
Meropenem-colistin-tigecycline	2.12 (1.05–4.26)	0.03	1.68 (0.74–3.83)	0.21
Meropenem-colistin	1.23 (0.59–2.51)	0.58		
Meropenem-tigecycline	0.69 (0.24–1.98)	0.49		
Meropenem-gentamicin	0.34 (0.05–2.51)	0.29		
Days of therapy	1.02 (1.00–1.05)	0.01	1.03 (0.99–1.05)	0.06

APACHE acute physiology and chronic health evaluation, *BSI* bloodstream infection, *CI* confidence interval, *CVC* central venous catheter, *HR* hazard ratio, *ICU* intensive care unit, *IQR* interquartile range, *LRTI* lower respiratory tract infection

The values shown in bold for the variable 'source control' indicate it was found to be statistically significant at both univariate and multivariate analysis

results obtained with the Vitek 2 automated system. Although there are more accurate methods, this is one of the most common systems used.

To conclude, recurrence is frequent among patients cured of CR-KP BSI and it is associated with higher long-term mortality. When feasible, source control is mandatory to avoid recurrence. The impact of antibiotic therapy should be further investigated in large multicentre studies.

Compliance with ethical standards

Funding No specific funding has been received for this study.

Conflict of interest The authors have no conflicts of interest to declare regarding this study.

Ethical approval The study was approved by the ethics committee of the Sant'Orsola Malpighi Hospital.

Informed consent Waiver of informed consent was obtained due to observational design of the study.

References

1. Munoz-Price LS, Poirel L, Bonomo RA et al (2013) Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis 13:785–796
2. Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M (2013) Predictors of mortality in multidrug-resistant *Klebsiella pneumoniae* bloodstream infections. Expert Rev Anti-Infect Ther 11:1053–1063
3. Girometti N, Lewis RE, Giannella M et al (2014) *Klebsiella pneumoniae* Bloodstream infection: epidemiology and impact of inappropriate empirical therapy. Medicine 93:298–309
4. Messina JA, Cober E, Richter SS et al (2016) Hospital readmissions in patients with carbapenem-resistant *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol 37:281–288
5. Pea F, Viale P, Cojutti P, Furlanut M (2012) Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. Antimicrob Agents Chemother 56:6343–6348
6. Petrosillo N, Giannella M, Lewis R, Viale P (2013) Treatment of carbapenem-resistant *Klebsiella pneumoniae*: the state of the art. Expert Rev Anti-Infect Ther 11:159–177
7. Giannella M, Trecarichi EM, De Rosa FG et al (2014) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream

infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect 20:1357–1362

8. Horan TC, Andrus M, Dudeck MA (2008) Cdc/nhsn surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36:309–332
9. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637
10. Shields RK, Potoski BA, Haidar G et al (2016) Clinical outcomes, drug toxicity and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant enterobacteriaceae infections. Clin Infect Dis 63(12):1615–1618
11. Lai CC, Hsu HL, Tan CK et al (2012) Recurrent bacteremia caused by the acinetobacter calcoaceticus-acinetobacter baumannii complex. J Clin Microbiol 50:2982–2986
12. Wendt C, Messer SA, Hollis RJ, Pfaller MA, Wenzel RP, Herwaldt LA (1999) Recurrent gram-negative bacteremia: incidence and clinical patterns. Clin Infect Dis 28:611–617