Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections

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Abstract

The aim of this study was to evaluate the impact of carbapenem-resistant *K. pneumoniae* bloodstream infections on mortality. During the study period 42, 68 and 120 patients were identified with carbapenem-resistant, extended-spectrum β-lactamase producers (ESBL) and susceptible *K. pneumoniae* bloodstream infections, respectively. Patients with carbapenem-resistant *K. pneumoniae* had higher rates of prior antimicrobial exposure, other nosocomial infections, and use of invasive devices. Infection-related mortality was 48% for carbapenem-resistant, 22% for ESBL producers and 17% for susceptible *K. pneumoniae*. Independent risk factors for infection-related mortality were Pitt bacteraemia score, Charlson score and carbapenem resistance.

Keywords: Bloodstream infection, carbapenem resistance, *Klebsiella pneumoniae*, outcome
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Introduction

Klebsiella pneumoniae is one of the most common hospital-acquired Gram-negative pathogens [1]. During the last decade, the spread of extended-spectrum β-lactamase (ESBL)-producing enterobacteriacae has resulted in limited treatment options and increased use of carbapenem antibiotics [2]. Carbapenem-resistant *K. pneumoniae* (CRKP) was first reported in 1996, and is now found worldwide [3–5]. In recent years, CRKP strains have been described in several outbreaks of nosocomial infections and are increasingly prevalent in parts of the US and Israel [6,7].

While previous studies have focused on the epidemiology, laboratory detection methods and molecular characterization of carbapenemase-producing bacteria [8,9], only a few studies have assessed the significance of carbepenem resistance on clinical outcomes [10–12].

During 2006 we have noticed a marked increase in the number of CRKP isolates in our medical centre. We have conducted the current study to describe the epidemiology of *K. pneumoniae* bloodstream infection (BSI) and to determine whether carbapenem resistance has an impact on mortality.

Methods

Setting and participants

This study was approved by the Institutional Review Board of Sheba Medical Center, a 1600-bed tertiary care university teaching hospital in central Israel.

We conducted a retrospective cohort study of hospitalized patients with *K. pneumoniae* BSI between January and December 2006. The patients were identified through records of the clinical microbiology laboratory. Only the first episode of multiple *K. pneumoniae* isolations was included, and patients with polymicrobial BSI were excluded. Patients' data were obtained from the medical records, and included demographic characteristics, comorbid conditions and Charlson Comorbidity Index [13]. Events during hospitalization included duration of hospital stay prior to infection, previous intensive care unit (ICU) stay, use of invasive devices, mechanical ventilation, presence of other nosocomial infections, and antimicrobial therapy administrated during the 30 days prior to the onset of BSI.

To estimate the impact of colonization pressure, the number of CRKP acquisitions during the 30 days preceding the

infection was documented for all hospital wards. Nosocomial infections were determined according to the CDC definitions [14]. Severity of illness during the onset of BSI was calculated by the means of the Pitt bacteraemia score [15]. Antimicrobial therapies were classified as empiric or definite depending on whether they were administered before the results of blood culture became known or after the antibiotic susceptibilities were determined. Antimicrobial therapy was considered appropriate if the treatment regimen included antibiotics that were active *in vitro*.

Outcome

The effect of carbapenem resistance on clinical outcomes was evaluated by the assessment of in-hospital mortality and infection-related mortality. Mortality attributable to BSI was defined by clinical evidence of active infection and positive cultures, or when death occurred as the result of organ failure that developed or deteriorated during the onset of infection.

Microbiological methods

Clinical isolates were identified by standard laboratory methods using an automated Bactec 9240 system (Becton, Dickinson and Company, Sparks, MD, USA). Susceptibility testing was performed according to the Clinical and Laboratory Standards Institute guidelines [16]. For identifying ESBL production, disks were routinely placed with the cephalosporins on either side of the amoxicillin/clavulanic acid for screening by the disk approximation method. Isolates were confirmed as ESBL producers using the double-disk synergy test [17]. Carbapenem resistance was confirmed by the Kirby–Bauer disk-diffusion method on Mueller Hinton plates (BD Diagnostics, Heidelberg, Germany) using ertapenem (10 μg), meropenem (10 μg) and imipenem (10 μg) (Oxoid, Basingstoke UK), and by Etest (AB Biodisk, Solna, Sweden).

Isolates were screened for bla_{KPC} by PCR as described recently [18]. We have developed and validated a real-time PCR assay for detecting bla_{KPC} genes. Briefly, bacterial DNA was extracted from vortexed perianal swabs. TaqMan technology was used for detecting bla_{KPC}, using primer sequences that were designed in-house. Sensitivity and specificity of the real-time PCR were 100% and 95%, respectively. The genetic relatedness of both CRKP and ESBL strains was determined by pulsed-field gel electrophoresis (PFGE) analysis. DNA was prepared as described previously [18], and chromosomal restriction fragments obtained after *Xba*I and *Spe*I cleavage were documented and compared.

Statistical analysis

The data were analysed with the SPSS version 12.0. Normally distributed continuous variables were compared with the Student *t*-test, and non-normally distributed continuous variables by the Wilcoxon rank sum test. The chi-square test or the Fisher exact test was used to compare categorical variables. Multivariable regression models were constructed stepwise. For model building, parameters with p values $\leq$0.1 between groups in the univariate analysis were entered into the model. In the multivariate analysis, variables with p $\leq$0.05 were considered significant. Kaplan–Meier survival curves were used for survival analysis. All p values were two-tailed, with a p value of <0.05 considered statistically significant. We declare no conflicting or dual interests.

Results

During 2006, 210 patients hospitalized at Sheba Medical Center had *K. pneumoniae* BSI. Eighteen patients had polymicrobial bacteraemia, and therefore 192 patients were included in the study.

Forty-two patients (22%) developed BSI with CRKP, 65 (34%) with extended-spectrum β-lactamase-producing *K. pneumoniae* (ESBLKP) and 85 (44%) with susceptible *K. pneumoniae* (SKP). Patients' characteristics are shown in Table 1. Among the three groups, there were no significant differences in the demographic parameters, number of hospitalizations within the prior 12 months, or the Charlson co-morbidity score. A significant difference was observed in several hospital events prior to the onset of infection, including length of stay, nosocomial acquisition, ICU stay, use of invasive devices, and exposure to antimicrobial therapy. Patients with CRKP BSI were more likely to be hospitalized in a ward where other cases of CRKP were identified during the preceding 30 days. A significant difference was a noted in the Pitt bacteraemia score. Patients with SKP BSI had a low Pitt bacteraemia score of 2, compared with patients with ESBLKP or CRKP (scoring 3 and 4, respectively; p <0.001). Significant differences were also documented in the proportions of appropriate empirical antimicrobial therapy (79%, 39% and 12%, respectively; p <0.001).

Outcome measures of patients with *K. pneumoniae* BSI are shown in Table 2. Infection-related mortality was significantly higher among patients with CRKP, compared with those with ESBLKP or SKP BSI (48%, 22% and 17%, respectively). Univariate analysis of predictors for infection-related mortality is shown in Table 3. After multivariate analysis, Charlson co-morbidity score, Pitt bacteraemia score and carbapenem resistance remained independent predictors (Table 4). ESBL production was not associated with increased crude mortality or infection-related mortality. Cox regression analysis revealed carbapenem resistance to be a significant factor for

TABLE 1. Demographic and clinical characteristics of patients with *K. pneumoniae* bloodstream infections

	Variable	SKP (*n* = 85)	ESBLKP (*n* = 65)	CRKP (*n* = 42)	p
Demographic characteristics and co-morbidities	Male (%)	48 (57)	35 (54)	28 (67)	0.4
	Age, years, median (IQR)	71 (28)	73 (22)	73 (27)	0.97
	Previous hospitalizations during prior 12 months (%)	40 (47)	39 (60)	23 (55)	0.28
	Charlson score, median (IQR)	3 (4)	3 (4)	3 (3)	0.47
	Co-morbidities (%)				
	Myocardial infarction	13 (17)	6 (11)	8 (19)	0.45
	Chronic heart failure	18 (23)	4 (7)	11 (26)	0.02
	Stroke	16 (20)	19 (33)	7 (17)	0.11
	Dementia	7 (9)	7 (12)	5 (12)	0.79
	Chronic lung disease	7 (9)	11 (19)	6 (14)	0.23
	Peptic ulcer	1 (1)	5 (9)	11 (26)	0.001
	Diabetes mellitus	27 (34)	19 (33)	15 (36)	0.95
	Chronic renal failure	16 (21)	13 (23)	16 (39)	0.07
	Malignancy	35 (42)	21 (33)	8 (19)	0.04
Hospital events prior to onset of infection	LOS before BSI, median days (IQR)	8 (16)	16 (22)	12 (26)	0.019
	Nosocomial acquisition (%)	67 (79)	62 (95)	42 (100)	0.001
	ICU stay (%)	18 (21)	21 (32)	24 (57)	<0.001
	Urinary catheter (%)	34 (40)	41 (63)	31 (74)	<0.001
	Central venous catheter (%)	22 (26)	19 (29)	21 (50)	0.019
	Surgical procedure (%)	24 (28)	24 (37)	17 (41)	0.32
	Dialysis (%)	2 (2)	5 (8)	7 (17)	0.014
	Other patients with CRKP on the ward (%)	37 (44)	23 (35)	31 (74)	<0.001
	Nosocomial pneumonia (%)	11 (13)	18 (28)	16 (38)	0.004
	Surgical site infection (%)	2(2)	5 (8)	5 (12)	0.09
	Prior antimicrobial treatment (%)	27 (32)	45 (70)	38 (91)	<0.001
	Fluoroquinolones	6 (7)	21 (32)	19 (45)	<0.001
	Carbapenem	5 (6)	12 (18)	11 (26)	0.006
	Cephalosporin	8 (9)	13 (20)	21 (50)	<0.001
	Pipril tazobactam	27 (32)	45 (70)	38 (91)	<0.001
Events on the onset of BSI	Pitt bacteraemia score, median (IQR)	2 (4)	3 (5)	4 (5)	0.002
	Appropriate antibiotic empirical therapy (%)	67 (79)	25 (39)	5 (12)	<0.001

BSI, bloodstream infection; CRKP, carbapenem-resistant *K. pneumoniae*; ESBLKP, extended-spectrum beta lactamase-producing *K. pneumoniae*; IQR, interquartile range; LOS, length of stay; SKP, susceptible *K. pneumoniae*.

TABLE 2. Outcome of patients with *K. pneumoniae* bloodstream infections

Variable	S-KP (*n* = 85)	ESBL-KP (*n* = 65)	CRKP (*n* = 42)	p
In-hospital mortality (%)	20 (24)	25 (39)	29 (69)	<0.001
Infection-related mortality (%)	14 (17)	14 (22)	20 (48)	0.001
LOS after infection, median days (IQR)	9 (16)	16 (34)	18 (22)	0.003
Total LOS, median days (IQR)	21 (36)	36 (70)	37 (31)	0.001

CRKP, carbapenem-resistant *K. pneumoniae*; ESBLKP, extended-spectrum beta lactamase-producing *K. pneumoniae*; IQR, interquartile range; LOS, length of stay; SKP, susceptible *K. pneumoniae*.

TABLE 3. Univariate analysis of the impact of cohort characteristics on mortality

Variable	Survivors (*n* = 118)	Deceased (*n* = 74)	p
Male (%)	71 (60)	40 (54)	0.4
Age, years, median ± SD	67 ± 19	70 ± 17	0.34
Chemotherapy (%)	22 (19)	7 (10)	0.08
Charlson co-morbidity score, median (SD)	3.4 (2.9)	4.3 (3.4)	0.04
Myocardial infarction (%)	11 (11)	16 (22)	0.04
Chronic heart failure (%)	17 (16)	16 (22)	0.3
Stroke (%)	26 (25)	16 (22)	0.6
Dementia (%)	13 (13)	6 (8)	0.3
Chronic lung disease (%)	11 (11)	13 (18)	0.16
Diabetes (%)	37 (35)	24 (33)	0.8
Diabetes with end-stage organ failure (%)	6 (6)	10 (14)	0.07
Malignancy (%)	39 (34)	25 (34)	0.98
Renal failure (%)	24 (23)	21 (29)	0.36
Previous hospitalization (%)	57 (48)	45 (61)	0.09
LOS before infection, mean days ± SD	25 ± 81	27 ± 37	0.87
Intensive care unit stay (%)	26 (22)	37 (50)	<0.001
Mechanical ventilation	25 (21)	44 (60)	<0.001
Urinary catheter (%)	49 (42)	57 (77)	<0.001
Surgical procedure (%)	35 (30)	30 (41)	0.12
Central venous catheter (%)	37 (31)	25 (34)	0.73
Dialysis (%)	3 (3)	11 (15)	0.001
Prior antimicrobial therapy (%)	59 (50)	51 (69)	0.01
Other nosocomial infection (%)	41 (35)	51 (69)	<0.001
Pitt bacteraemia score, average ± SD	1.7 ± 2.0	6.3 ± 1.7	<0.001

LOS, length of stay.

mortality (log-rank test: p 0.006). The survival curve for *K. pneumoniae* BSI is shown in Fig. 1.

PFGE analysis of 14 random CRKP isolates demonstrated the same clone (Fig. 2a). PCR revealed the presence of bla_{KPC-3} in all isolates (Fig. 2b). In contrast, PFGE analysis of eight random isolates of KP ESBL demonstrated eight distinct clones. bla_{KPC-3} was not found among all KP ESBL producer isolates.

Discussion

This study was undertaken to evaluate the epidemiology and risk factors for mortality of patients with *K. pneumoniae* BSI. We found that severity of illnesses and carbapenem resistance were strong prognostic factors for mortality.

TABLE 4. Independent risk factors for mortality among patients with *Klebsiella pneumoniae* bloodstream infections

Variable	Adjusted OR (95% CI)	p
All cause mortality		
Charlson co-morbidity score	1.3 (1.09–1.47)	0.01
Pitt bacteraemia score	1.86 (1.54–2.25)	<0.001
Carbapenem resistance	8.17 (2.66–25.12)	<0.001
ESBL production	1.69 (0.63–4.5)	0.23
Infection-related mortality		
Charlson co-morbidity score	1.18 (1.97–22.67)	0.02
Pitt bacteraemia score	1.54 ((1.34–1.77)	<0.001
Carbapenem resistance	3.89 (1.34–11.25)	0.01
ESBL production	1.20 (0.43–3.36)	0.72

CI, confidence interval; ESBL, extended-spectrum β-lactamase; OR, odds ratio.

The impact of antibiotic resistance on the outcome for patients with nosocomial infections is controversial. Although it is generally accepted that drug resistance is associated with increased morbidity and mortality [17,19], some studies found no such relationship [20,21]. Underlying co-morbidities, delay in the initiation of appropriate antimicrobial therapy, and the severity of illness of the patients infected by the multidrug-resistant pathogens, may be important confounders [22,23]. Therefore, appropriate adjustment for these confounding factors is essential in studies that determine the impact of antimicrobial resistance. In the present study, we found that carbepenem resistance was an independent risk factor for mortality among patients with *K. pneumoniae* BSI. Recently, a few studies have demonstrated that carbapenem resistance was associated with increased mortality. Patel *et al.* [12] have included in their study various infections, while Schwaber *et al.* [10] have included patients with clinical isolates that may represent only colonization. In both studies, control patients had a significantly shorter length of hospital stay compared with case patients (a median of 2 days compared with more than 20 days). Therefore, these control infections may represent community-acquired infections that may have different outcomes relative to nosocomial infections [15].

Our study is one of the first to assess the impact of carbapenem resistance on the outcome of *K. pneumoniae* BSI. In contrast to previous studies, we have divided the cohort into three levels of bacterial resistance: susceptible, ESBL and carbapenemase-producing strains. Patients with BSI from the latter two strain types had a longer hospital stay, were admitted to intensive care, acquired the infection in hospital, and had been exposed to invasive procedures and to prior antimicrobial therapy. Nevertheless, only carbapenem resistance was associated with increased mortality. Although some studies have suggested that increased mortality was associated with ESBL producer strains [17,24], this finding was contended by others [20,25]. A recent systematic review showed that although infections caused by ESBL producers were associated with increased mortality, only one of 16 studies was controlled for confounding factors [26].

The clonality of *K. pneumoniae* isolates was analysed by comparing PFGE profiles. The eight ESBL producers were all different; in contrast, all CRKP isolates were found to be

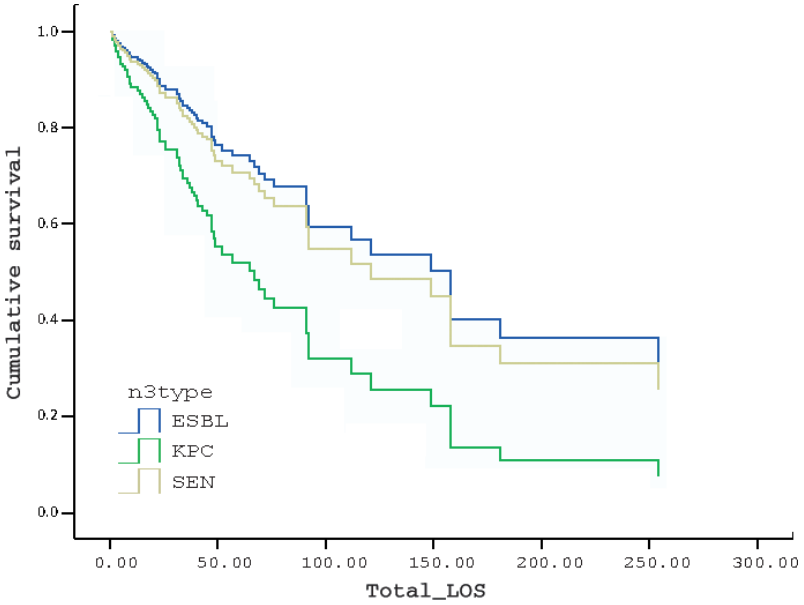

FIG. 1. Survival curve for patients with *K. pneumoniae* bloodstream infections adjusted for Pitt bacteraemia score and Charlson co-morbidity score.

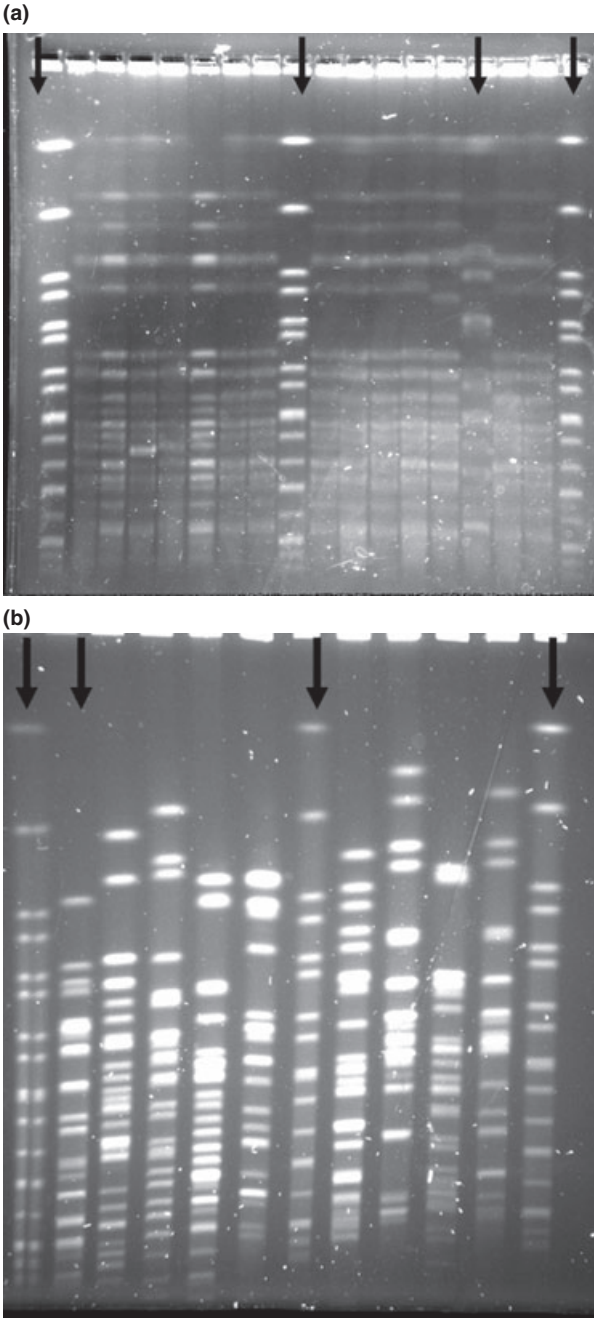

FIG. 2. Pulsed-field gel electrophoresis of 24 isolates of *Klebsiella pneumoniae*. (a) Fourteen isolates of carbapenem-resistant *Klebsiella pneumonia*; (b) eight isolates of ESBL-producing *Klebsiella pneumoniae*. Arrows represent the controls.

identical. Therefore, we cannot determine whether the high mortality rates associated with carbapenem resistance are due to antimicrobial resistance and inappropriate therapy, or alternatively, to a highly virulent clone. All CRKP isolates harboured bla_{KPC}. Recent molecular studies have found that closely related *K. pneumoniae* strains carrying bla_{KPC} have spread in several healthcare facilities in the United States and Israel [27,28]. The occurrence of a dominant clone in two continents demonstrates the potential of a single extensively drug-resistant strain to spread globally. It was suggested that the acquisition of a bla_{KPC} gene may confer on this isolate of *K. pneumoniae* a marked selective advantage that is leading to its successful dissemination [29].

We used Pitt bacteraemia score to assess the severity of illness [15]. This score was shown to predict mortality better than APACHE score among patients with BSI [30,31]. Variables included in the score have occurred on the day of the first positive culture, and therefore we consider this score to represent the true baseline. The effect of different time points of severity score measurement on patients' outcome has been recently assessed, and it was suggested that severity of illness should be measured close to the onset of infection [32]. Of note, Pitt bacteraemia score and appropriate antimicrobial therapy represent variables that occurred at the time of the first positive blood culture, and therefore may be intermediate variables and not confounders. Adjustment for intermediate variables could underestimate the magnitude of the relationship between exposure and outcome. However, our results did not change when the logistic regression for mortality was performed with or without the Pitt bacteraemia score or appropriate antimicrobial therapy.

The observed increased mortality among patients with CRKP BSI may be the result of ineffective antimicrobial therapy. There was a significant difference in the proportion of patients who received appropriate empirical therapy among patients with susceptible KP, KP ESBL producers and CRKP infections: 79%, 39% and 12%, respectively. However, gentamicin, colistin and tigercycline have been considered last-resort treatment against these extremely drug-resistant microorganisms. Although few reports have described favourable outcomes [33,34], no controlled studies have assessed the efficacy of these drugs in serious nosocomial infections. In a recent report, appropriate empirical treatment was not associated with improved survival among patients with CRKP infections [12].

Our study has several limitations. Firstly, clinical data were obtained retrospectively from medical records. There may be differences in physician practices or accuracy of information. Our retrospective design makes our results susceptible to the limitations and potential biases of studies of similar design. Secondly, patients with various admission diagnoses were included in the cohort. As the number of patients in each admission diagnosis category was small, we could not assess the impact of different admission diagnoses on

outcome. In addition, follow-up was limited to the hospitalization period. Therefore, we were able to analyse only in-hospital mortality.

In conclusion, we found that carbapenem resistance in *K. pneumoniae* was associated with increased mortality. Our findings reinforce the urgent efforts needed to prevent the spread of carbapenemases producing Enterobacteriaceae.

Transparency Declaration

All authors declare that there are no conflicts of interest.

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