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Treatment and Outcomes in Carbapenem-resistant *Klebsiella pneumoniae* Bloodstream Infections

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Abstract

Carbapenem-resistant *K. pneumoniae* (CR-Kp) is an emerging multi-drug resistant nosocomial pathogen. This is a retrospective chart review describing the outcomes and treatment of 60 cases of CR-Kp bloodstream infections. All CR-Kp isolated from blood cultures were identified retrospectively from the microbiology laboratory from January 2007 to May 2009. Clinical information was collected from the electronic medical record. Patients with 14 day-hospital mortality were compared to those who survived 14 days. The all-cause in-hospital and 14-day mortality for all 60 CR-Kp bloodstream infections was 58.3% and 41.7%, respectively. In this collection, 98% of tested isolates were susceptible *in vitro* to tigecycline, compared to 86% to colistimethate, 45% to amikacin and 22% to gentamicin. Nine patients died prior to cultures being finalized, and received no therapy active against CR-Kp. In the remaining 51 patients, those who survived to day 14 (n=35) were compared to non-survivor at day 14 (n=16). These patients were

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characterized by both chronic disease and acute illness. The 90-day readmission rate for hospital survivors was 72%. Time to active therapy was not significantly different between survivors and non-survivors, and hospital mortality was also similar regardless of therapy chosen. Pitt bacteremia score was the only significant factor associated with mortality in Cox regression analysis. In summary, CR-Kp bloodstream infections occur in patients who are chronically and acutely ill. They are associated with high 14-day mortality and poor outcomes regardless of tigecycline or other treatment regimens were selected.

Keywords

Klebsiella pneumoniae; carbapenem resistance; multi-drug resistance; mortality; bacteremia

Since the first reported carbapenem-resistant *K. pneumoniae* (CR-Kp) was identified in 1996, the incidence of infections due to this multi-drug resistant (MDR) pathogen has increased dramatically [1–4]. Currently available penicillins, cephalosporins, and carbapenems do not demonstrate *in vitro* activity against this organism. Therefore, very few treatment options remain for CR-Kp bloodstream infections (BSI). Tigecycline and colistimethate (colistin) are two agents with *in vitro* activity against CR-Kp, which are in current clinical use in the United States [5]. However, the low plasma concentrations of tigecycline and the toxicity associated with colistimethate make these less appealing options for use in BSI. In addition to these concerns, the published outcome data for these two agents in the treatment of CR-Kp BSI are limited. The aim of this study was to describe the treatment and outcomes of CR-Kp BSI in a single large tertiary care center.

Methods

Study Location and Design

The study was conducted at Cleveland Clinic, a 1400 bed academic medical center in Cleveland, Ohio. This was a non-interventional, retrospective chart review of CR-Kp BSI from January 2007 to May 2009. This study was approved by the Cleveland Clinic Institutional Review Board.

Microbiologic Methods

Automated systems were used to process blood cultures (BacTAlert®) and for identification of *K. pneumoniae* isolates (Vitek 2). Antimicrobial susceptibility testing (AST) was performed using the automated broth microdilution system (Vitek 2). Before April 2009, AST for tigecycline and colistimethate was not routinely performed. When applicable, broth microdilution methods were used for tigecycline and colistimethate AST. Interpretive criteria for colistimethate were extrapolated from data on its *in vitro* activity against strains of *Acinetobacter baumannii*, as published by the Clinical Laboratory Standards Institute (CLSI) [6]. Tigecycline susceptibility was determined by the use of minimum inhibitory concentration breakpoints approved by the US Food and Drug Administration [7]. A modified Hodge test was performed on all isolates, as described [8]. Testing for the presence of the *bla*_{KPC} gene was performed in a subset of isolates, as previously described [9].

Patients and Data Collection

All adult patients with blood cultures positive for CR-Kp from January 2007 to May 2009 were included in this study. Only the first episode of BSI was included. To evaluate the effect of therapy, only patients who received *in vitro* active therapy for more than 24 hours were included in risk factor analysis. Data, including demographics, co-morbid conditions, source of infection, and treatment were collected retrospectively from the electronic medical

records and microbiology databases. The need for mechanical ventilation or dialysis was assessed at the time of bacteremia and 30 days prior. The source of BSI was determined from Infection Control designation, following Centers of Disease Control guidelines. If Infection Control was not involved with the case, the Infectious Diseases consult note was used for source determination. Comorbid conditions and severity of illness were measured using the Charlson comorbidity index and Pitt bacteremia score, as described [10–12]. 14-day mortality was the primary outcome of interest. Secondary outcomes included discharge destination (home vs. other), readmission within 90 days of discharge, and microbiological cure, which was defined as documented sterile blood cultures following CR-Kp BSI. Initial regimen was defined as any therapy with *in vitro* activity given for more than 24 hours within the first 5 days of positive cultures.

Statistical Analysis

All comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were compared using the Student *t* test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. The chi-squared or Fisher's exact test were used to compare categorical variables. A multivariate logistic regression model was used in which all stable variables were included which were significant on univariate analysis ($p < 0.05$). A statistical software program (SPSS, version 11.5 for Windows; SPSS, Inc; Chicago, IL) was used to perform all analyses.

Results

During the study period, a total of 60 patients were identified with a CR-Kp BSI. The all-cause hospital and 14-day mortality was 58% (35/60 patients) and 42% (25/60), respectively. Median time to death from positive culture was 9 days, ranging from 1 to 105 days. Nine patients died before cultures were finalized and did not receive therapy active against CR-Kp. These patients were not included in further analysis. Of the 51 patients who received treatment, hospital and 14-day mortality was 51% and 31%. In this group, 14-day survivors ($n=35$) were compared to 14-day non-survivors ($n=16$). In non-survivors, 100% (16 of 16) died while receiving CR-Kp-active therapy. Of the patients, who survived their hospitalization 68% (17 of 25) were discharged to a skilled nursing or long-term care facility and only 32% (8 of 25) to home. Readmission within 90 days occurred in 72% (18 of 25) of the hospital survivors.

No significant differences between survivors and non-survivors were observed in baseline characteristics including age, gender, or race (table 1). Comorbid conditions were also similar in survivors vs. non-survivors. The most frequent co-morbid conditions were diabetes mellitus, heart disease, and kidney disease. The Charlson co-morbidity index was not associated with mortality in this cohort – the mean index in 14-day survivors was 3.5 ± 2.1 , compared to 3.1 ± 1.5 in 14-day non-survivors. In contrast, severity of acute illness as measured by the Pitt bacteremia score was significantly higher for 14-day non-survivors compared to 14-day survivors (mean 5.6 ± 3.8 vs. 2.9 ± 2.3 , $p=0.017$ in univariate analysis). More patients in the 14-day non-survivors underwent surgery in the previous 30 days, 44% compared to 14% in the 14-day survivors ($p=0.033$ in univariate analysis). The presence of a central venous catheter was common overall, and there was no difference in removal rates between 14-day survivors and 14-day non-survivors, 89% vs. 75%. Total hospital length of stay was similar between the groups. More 14-day non-survivors were in the ICU at the time of first positive cultures when compared to 14-day survivors (75% versus 40%, $p=0.020$ in univariate analysis).

The majority of patients acquired their CR-Kp during their hospitalization, 60% (21/35) of 14-day survivors and 88% (14/16) of 14-day non-survivors ($p = 0.050$). Of the remaining

patients all had a hospitalization within the previous 90 days and the majority (12/16) were admitted from nursing homes or long-term acute care facilities. More than half of cases (55%) were thought to be primary or intravenous catheter-related (table 2). The other most common sources were urinary (14%), pulmonary (12%) and intra-abdominal (12%). There were no differences between 14-day survivors and non-survivors and source of CR-Kp bloodstream infection.

Antimicrobial susceptibilities of the CR-Kp blood isolates are shown in figure 1. The majority of isolates were susceptible *in vitro* to tigecycline (98%). In one isolate the tigecycline MIC increased from a baseline of 0.25 mg/L to 1 mg/L on therapy. Out of 21 CR-Kp isolates tested, 3 were resistant to colistimethate (MIC of 8 mg/L). *In vitro* susceptibility to aminoglycosides was found in only 45% of isolates for amikacin and 22% for gentamicin. All CR-Kp isolates were modified Hodge test positive, and a random sample of CR-Kp isolates from 10 patients were tested for presence of the *bla*_{KPC} gene, which was found in all isolates tested.

The median number of documented blood cultures positive for CR-Kp per patient was 2 cultures (range 1–11 cultures). Microbiological cure occurred in 74.5% (38 of 51) patients overall, including 7 patients in the 14-day non-survivor group (44%). In the 38 patients with microbiological cure, the median number of days to negative blood culture was 4 days (range 1–18 days). Recurrent CR-Kp BSI (defined as positive CR-Kp blood culture greater than 7 days after documented negative blood culture) was observed in 9 patients.

Treatment in this patient population was characterized by frequent changes and additions to the antibiotic regimen. The mean number of days from time of first positive blood culture to CR-Kp active therapy was 2.5 days (table 3). No difference in time to treatment was seen between 14-day survivors and non-survivors. In this study, 92% of patients received tigecycline at some time during their hospitalization. The total duration of tigecycline therapy was longer in 14-day survivors compared to non-survivors. However, in time-to-event analysis, no difference was seen between patients who received only tigecycline as initial therapy, and all others (figure 2). Initial regimens consisted of tigecycline-based therapies in 71% of 14-day survivors and 56% non-survivors, colistimethate-based for 17% 14-day survivors and 6% non-survivors and tigecycline-colistimethate combinations in 6% 14-day survivors and 25% non-survivors. In univariate survival analysis, differences were not observed between patients who received tigecycline mono-therapy as initial therapy when compared to all others (figure 2). Also, a similar proportion of 14-day survivors and non-survivors were treated with a combination regimen initially (31% versus 56%, $p=0.126$). In multivariate Cox regression analysis (table 4), a higher Pitt bacteremia score was strongly associated with mortality (HR 1.33 per unit increase, $p=0.039$).

Discussion

Carbapenem-resistant *K. pneumoniae* (CR-Kp) isolates are emerging as a cause of MDR gram-negative infections in healthcare settings [2,3]. Clinically, a limited number of antimicrobial options remain for the treatment of CR-Kp infections, especially BSI. Here, we have summarized the largest reported collection of CR-Kp BSI to date.

The optimal treatment of bacteremia with CR-Kp remains unknown [4]. Randomized trials are not available to compare tigecycline versus colistimethate, which represent the two main treatment options currently available in the US. Colistimethate (also known as polymyxin E) has been available for over 50 years. However, colistimethate use became infrequent after the introduction of aminoglycosides, which had a more favorable side effect profile in comparison. Nephrotoxicity is the most common adverse reaction, occurring in an estimated

45% of patients, although recent data on large patient populations are not available. Neurotoxicity is another concerning side effect [13]. The use of tigecycline for the treatment of BSI remains controversial. The low serum concentrations (mean $C_{\max}$ 0.63–0.87 mcg/ml) may be suboptimal in this context. This is especially concerning for organisms with higher MICs at or near the breakpoint [7]. Of note, a breakthrough bloodstream infection with carbapenem-resistant *Acinetobacter baumannii* while on tigecycline therapy has been reported [14]. However, clearance of persistent Cr-KP bacteremia on tigecycline monotherapy has also been reported [15]. Similarly, we observed several patients in whom tigecycline monotherapy resulted in a clinical cure. There are additional reports of outcomes with tigecycline for the treatment of BSI. Eight phase III clinical trials were pooled and analyzed to evaluate tigecycline in the treatment of secondary bacteremias due to skin and skin-structure infections, intra-abdominal infections, and community-acquired pneumonia. Cure rates were similar in patients with BSI with various Gram-negative bacteria in the tigecycline (n=21, cure rate 81%) and the comparator (n=22, cure rate 90.9%) [16]. In addition, there are a few reports on tigecycline for the treatment of BSI due to multi-drug resistant organisms (MDR-O). In a retrospective case series of 12 patients with MDR-O BSI (10 *K. pneumoniae* and 2 *Acinetobacter baumannii*) treated with tigecycline, an overall clinical and microbiological success rate of 80% was reported. However, many patients received combination therapy and one patient was persistently bacteremic for 2 weeks prior to responding [17]. In another series of 7 BSI due to MDR *A. baumannii*, treatment with tigecycline resulted in a positive microbiological outcome in 4 cases. Patients in this series also received concomitant antimicrobials [18]. However, in these small non-randomized studies, as well as in our study, reported outcomes may be unrelated to tigecycline treatment.

Reported risk factors for infection with CR-Kp are similar to risk factors associated with other MDR-O including extended spectrum β -lactamase producing *K. pneumoniae* [19–21]. These risk factors include higher severity of illness, recent solid organ or stem-cell transplant, mechanical ventilation, longer length of stay and prior antimicrobial exposure to cephalosporins, fluoroquinolones and carbapenems. While risk factor analysis for infection with MDR-O was not the focus of our study, we did observe that patients with CR-Kp BSI in our cohort were both chronically ill, as measured by mean Charlson comorbidity index of 3.3 ± 2.0 , and acutely ill, as evident by high Pitt bacteremia scores. The Pitt bacteremia score is a marker of severity of illness in patients with gram-negative BSI and patients with scores > 4 are considered critically ill [11,12]. Similar to previous studies, in our cohort the Pitt bacteremia score was strongly correlated with mortality. Awareness of risk factors for MDR infections, including CR-Kp BSIs, is important in order to reduce time to appropriate treatment. While there was no significant difference in time to active therapy between groups in our study, the delay in appropriate therapy may, in part, explain the high mortality rate.

The *in vitro* susceptibility profile of CR-Kp isolates has been previously reported in the literature. A report from Brooklyn hospitals on 96 clinical isolates of carbapenemase-producing *K. pneumoniae* and a series of 60 carbapenemase-producing *Klebsiella* species from the SENTRY Antimicrobial Surveillance Program showed a susceptibilities of 100% and 100% for tigecycline, 91% and 93% for polymyxin B, and 45% and 53% for amikacin, respectively [5,22]. In contrast, in our isolates, as well as in other more recent studies, the reported percentage of isolates with *in vitro* susceptibility to tigecycline and colistimethate is between 15% to 98%, and 80% to 86%, respectively [23–25]. In addition, reports are emerging on CR-Kp isolates which display *in vitro* resistance to both tigecycline and colistimethate [26]. Per recent reports, around 50% of CR-Kp isolates remain susceptible to fosfomycin, which is not currently available for intravenous use in the United States [23,24]. Recently reported *In vitro* results for combination therapy which includes doripenem,

rifampin, and polymyxin B are promising, but this combination has not been evaluated in clinical settings [27].

CR-Kp infections are associated with both high morbidity and mortality. The overall hospital mortality of 58% reported in our study is consistent with previous reports. The largest series of CR-Kp BSI (n=32) to date is from Borer et al., who reported a crude and attributable mortality rate of 71.9% and 50%, respectively. No comments on treatment were made in that study [25]. In a New York City outbreak of CR-Kp infections, 19 patients with BSI were reported. The 14-day mortality in this cohort was 47% [28]. In reports of KPC-2 carbapenemase-producing *K. pneumoniae* BSI only 2 of 6 patients, and 4 of 14 patients survived [23,29]. In addition to a high mortality rate, we noted a high readmission rate in those patients who were discharged after CR-Kp BSI. This was likely a consequence of severe underlying disease.

The limitations of our study are inherent to its retrospective design and the relatively limited number of occurrences of this disease. Evaluation the relative efficacy of the various regimens is extremely limited, since the choice of treatment in our cohort was not randomly assigned. In addition, the care of these critically ill patients is often characterized by frequent alterations in the antibiotic regimen. Therefore, choice of antibiotic regimen is closely associated with clinical status. Similarly, the observed difference in tigecycline duration between survivors and non-survivors is likely being driven by patients dying prior to completing their course, rather than it being an indication of efficacy of prolonged tigecycline therapy. Consistent with this notion, no significant differences between treatment regimens were observed in time-to-event analyses.

In summary, CR-Kp BSI are an increasingly important threat for severely and chronically ill hospitalized patients. Few antibiotic options remain for these organisms. Overall, regardless of chosen treatment, CR-Kp BSI were associated with high hospital mortality, and high readmission rates in those who survive the initial hospitalization.

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Figure 1.
In vitro susceptibility of carbapenem-resistant *Klebsiella pneumoniae* isolates.

Figure 2. Survival after positive blood culture for carbapenem-resistant *Klebsiella pneumoniae* (n=51). Nine patients who died prior to cultures being finalized and received no CR-Kp-active therapy were excluded. Data is censored at the time of hospital discharge.

Table 1

Patient Characteristics

	Total	Survivors [*]	Non-survivors [*]	p ^{**}
Demographics	n=51	n=35	n=16	
Age, years, mean $\pm$ SD	60.4 $\pm$ 1.8	59.1 $\pm$ 12.7	63.1 $\pm$ 13.8	
Gender, Male, n (%)	32 (63)	21 (60)	11 (69)	
Race, Caucasian, n (%)	31 (61)	23 (66)	8 (50)	
Hospital length of stay, mean $\pm$ SD	31.6 $\pm$ 25.0	34.0 $\pm$ 27.9	26.2 $\pm$ 16.6	
ICU admission [#] , n (%)	26 (51)	14 (40)	12 (75)	0.020
ICU length of stay, mean $\pm$ SD	20.8 $\pm$ 19.1	23.2 $\pm$ 22.2	17.4 $\pm$ 13.4	
Comorbidities, n (%)				
Diabetes mellitus	18 (35)	12 (34)	6 (38)	
CAD	13 (26)	7 (20)	6 (38)	
COPD	6 (12)	2 (6)	4 (25)	.07
Chronic kidney disease	13 (26)	10 (29)	3 (19)	
End-stage liver disease	8 (16)	5 (14)	3 (19)	
Solid organ transplant	8 (16)	5 (14)	3 (19)	
Hematologic disorders	9 (18)	6 (17)	3 (19)	
Bone marrow transplant	3 (6)	3 (9)	0 (0)	
Charlson comorbidity index, mean $\pm$ SD	3.3 $\pm$ 2.0	3.5 $\pm$ 2.1	3.1 $\pm$ 1.5	
Pitt Bacteremia score, mean $\pm$ SD	3.7 $\pm$ 3.1	2.9 $\pm$ 2.3	5.6 $\pm$ 3.8	0.017
Risk Factors, n(%)				
Surgery [§]	12 (24)	5 (14)	7 (44)	0.033
Central venous catheter	47 (92)	31 (89)	16 (100)	
Central venous catheter removal	43 (84)	31 (89)	12 (75)	
Mechanical ventilation	21 (41)	12 (34)	9 (56)	
Dialysis	16 (31)	9 (26)	7 (44)	

* survivors at 14 days, non-survivors at 14 days

** univariate analysis (p-values >0.1 are not listed).

[#] ICU admission at the time of bacteremia.

[§] surgery within 30 days prior to bacteremia

SD: standard deviation, ICU: Intensive Care Unit, CAD: coronary artery disease, COPD: Chronic obstructive pulmonary disease

Table 2

Source of Blood stream infections

	Total n=51	Survivors n=35	Non-survivors n=16	p *
Source, n (%)				
Primary/Line-related	28 (55)	19 (54)	9 (56)	
Secondary	23 (45)	16 (46)	7 (44)	
Urinary	7 (14)	7 (20)	0	
Pulmonary	6 (12)	3 (9)	3 (19)	
Intra-abdominal	6 (12)	4 (11)	2 (13)	
Surgical site	2 (4)	1 (3)	1 (6)	
Bone & joint	1 (2)	0 (0)	1 (6)	
Multiple	1 (2)	1 (3)	0 (0)	

* univariate analysis.

Table 3Treatment^{**}

	Total n=51	Survivors n=35	Non-survivors n=16	p [*]
Time to active therapy, days, mean $\pm$ SD	2.5 $\pm$ 2.2	2.6 $\pm$ 2.2	2.1 $\pm$ 2.1	
Tigecycline, n (%)	47 (92)	33 (94)	14 (88)	
-Duration, days, mean $\pm$ SD	14.8 $\pm$ 11.1	19.0 $\pm$ 10.7	5.6 $\pm$ 10.6	.001
Colistin, n (%)	19 (37)	13 (39)	6 (38)	
-Duration, days, mean $\pm$ SD	3.14 $\pm$ 5.1	3.5 $\pm$ 5.6	2.3 $\pm$ 4.0	
Amikacin, n (%)	24 (47)	14 (40)	10 (63)	
-Duration, days, mean $\pm$ SD	3.7 $\pm$ 7.0	4.2 $\pm$ 8.2	2.5 $\pm$ 3.3	
Gentamicin, n (%)	2 (4)	2 (6)	0 (0)	
-Duration, days, mean $\pm$ SD	0.35 $\pm$ 2.3	0.35 $\pm$ 2.3	-	

^{**} Includes antibiotics given at any time after first positive blood culture.

^{*} univariate analysis.

SD: standard deviation.

Table 4

Cox Regression Analysis

	HR (95% CI)	p
ICU admission [#]	1.46 (0.26–8.10)	.665
Hospital acquired	2.33 (0.46–11.7)	.305
Mechanical ventilation	0.16 (0.02–1.19)	.073
Dialysis	1.02 (0.25–4.13)	.975
COPD	2.02 (0.53–7.64)	.301
Surgery [*]	4.2 (0.77–22.9)	.097
Pitt Bacteremia score ^{**}	1.33 (1.02–1.75)	.039
Primary/line related	1.79 (0.41–7.90)	.441
Tigecycline monotherapy	0.76 (0.19–3.08)	.701

[#] ICU admission at the time of bacteremia,

^{*} surgery within 30 days prior to bacteremia,

^{**} HR per unit change.

HR: hazard ratio, ICU: Intensive Care Unit