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ORIGINAL ARTICLE

Outcomes of Carbapenem-Resistant *Klebsiella pneumoniae* Infection and the Impact of Antimicrobial and Adjunctive Therapies

Gopi Patel, MD; Shirish Huprikar, MD; Stephanie H. Factor, MD, MPH; Stephen G. Jenkins, PhD; David P. Calfee, MD, MS

(See the commentary by Srinivasan and Patel on pages 1107–1109)

BACKGROUND. Carbapenem-resistant *Klebsiella pneumoniae* is an emerging healthcare-associated pathogen.

OBJECTIVE. To describe the epidemiology of and clinical outcomes associated with carbapenem-resistant *K. pneumoniae* infection and to identify risk factors associated with mortality among patients with this type of infection.

SETTING. Mount Sinai Hospital, a 1,171-bed tertiary care teaching hospital in New York City.

DESIGN. Two matched case-control studies.

METHODS. In the first matched case-control study, case patients with carbapenem-resistant *K. pneumoniae* infection were compared with control patients with carbapenem-susceptible *K. pneumoniae* infection. In the second case-control study, patients who survived carbapenem-resistant *K. pneumoniae* infection were compared with those who did not survive, to identify risk factors associated with mortality among patients with carbapenem-resistant *K. pneumoniae* infection.

RESULTS. There were 99 case patients and 99 control patients identified. Carbapenem-resistant *K. pneumoniae* infection was independently associated with recent organ or stem-cell transplantation ($P = .008$), receipt of mechanical ventilation ($P = .04$), longer length of stay before infection ($P = .01$), and exposure to cephalosporins ($P = .02$) and carbapenems ($P < .001$). Case patients were more likely than control patients to die during hospitalization (48% vs 20%; $P < .001$) and to die from infection (38% vs 12%; $P < .001$). Removal of the focus of infection (ie, debridement) was independently associated with patient survival ($P = .002$). The timely administration of antibiotics with in vitro activity against carbapenem-resistant *K. pneumoniae* was not associated with patient survival.

CONCLUSIONS. Carbapenem-resistant *K. pneumoniae* infection is associated with numerous healthcare-related risk factors and with high mortality. The mortality rate associated with carbapenem-resistant *K. pneumoniae* infection and the limited antimicrobial options for treatment of carbapenem-resistant *K. pneumoniae* infection highlight the need for improved detection of carbapenem-resistant *K. pneumoniae* infection, identification of effective preventive measures, and development of novel agents with reliable clinical efficacy against carbapenem-resistant *K. pneumoniae.*

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The proportion of healthcare-associated infections caused by multidrug-resistant pathogens is increasing.[1] This epidemiological and microbiological phenomenon poses an infection-control challenge and is a significant threat to patient safety. Compared with infections caused by susceptible strains of the same organism, infections caused by several antibiotic-resistant bacteria have been associated with worse outcomes, including longer hospitalizations, higher mortality rates, and greater healthcare expenditures.[2-7] These poor outcomes are likely multifactorial in etiology, including greater severity of underlying illness, delays in initiation of effective therapy, and, in some cases, a lack of effective antimicrobial therapy.

Much attention has focused on antibiotic-resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus,* but the increase in antibiotic resistance among gram-negative pathogens is also of great concern.[8] In 2003, the National Nosocomial Infections Surveillance system reported a 47% increase in resistance to third-generation cephalosporins among *Klebsiella pneumoniae* isolates recovered from patients in intensive care units (ICUs), compared with the mean rate of resistance over the previous 5 years.[1]

Carbapenem-resistant Enterobacteriaceae were first described in the early 1990s,[9] and the isolation of carbapenem-resistant *K. pneumoniae* strains occurred sporadically throughout that decade.[10,11] Over the past few years, however, the recovery of carbapenem-resistant *K. pneumoniae* strains

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from clinical specimens has increased at an alarming rate.[12] A surveillance study in Brooklyn, New York, demonstrated that over one-third of *K. pneumoniae* isolates collected in 2004 carried bla_{KPC}, the gene encoding the carbapenem-hydrolyzing enzyme KPC.[13] Approximately one-quarter of these isolates demonstrated resistance to fluoroquinolones and aminoglycosides, as well as to carbapenems and β-lactams. The limited number of antimicrobials available to treat carbapenem-resistant *K. pneumoniae* infection may adversely affect patient outcomes. A recent study from Israel demonstrated an independent association between the acquisition of carbapenem-resistant *K. pneumoniae* and in-hospital mortality, even after adjustment for underlying severity of illness.[14]

The escalating prevalence of carbapenem-resistant *K. pneumoniae* infection in the northeastern United States, especially New York City,[15] and the increasing incidence of this pathogen in other areas of the United States and worldwide mandate further investigation into the epidemiology of and clinical outcomes associated with carbapenem-resistant *K. pneumoniae* infection.[14,16] Identification of risk factors associated with carbapenem-resistant *K. pneumoniae* infection may assist in the empiric therapeutic decision-making process and may allow for early implementation of appropriate infection-control measures. In our study, we describe the epidemiology of and clinical outcomes associated with carbapenem-resistant *K. pneumoniae* infection, as well as the risk factors associated with in-hospital mortality among patients with carbapenem-resistant *K. pneumoniae* infection.

METHODS

Study Participants

Participants in our study were selected from adult inpatients at the Mount Sinai Hospital, a 1,171-bed tertiary care teaching hospital in New York City. Potential participants were patients with invasive *K. pneumoniae* infection during the period from July 1, 2004, through June 30, 2006, as identified in the clinical microbiology laboratory database. A patient was considered to have invasive *K. pneumoniae* infection if a *K. pneumoniae* isolate was recovered from a specimen obtained from a normally sterile site. Urine, sputum, and rectal specimens were excluded because of the investigator's inability to retrospectively determine whether isolates recovered from these specimens represented colonization or true infection. Clinical syndromes were determined using definitions outlined by the Centers for Disease Control and Prevention.[17]

Study Design and Procedures

The medical records of all patients who received a diagnosis of any type of invasive *K. pneumoniae* infection during the period from July 1, 2004, to June 30, 2006, were reviewed. A logistic regression model that controlled for patient age and sex was used to determine whether carbapenem-resistant *K. pneumoniae* infection was associated with in-hospital mortality.

A matched case-control study was performed to identify risk factors associated with invasive carbapenem-resistant *K. pneumoniae* infection. Case patients were selected from among patients whose infection was caused by carbapenem-resistant *K. pneumoniae*. Control patients were selected from among patients whose infection was caused by carbapenem-susceptible *K. pneumoniae*. Matching was performed at a ratio of 1 : 1 according to the anatomic site of infection. If there were several potential matching control patients, the control patient closest to the case patient in age and date of isolation of *K. pneumoniae* was selected. Each patient was included only once. If *K. pneumoniae* was isolated from multiple clinical cultures, only the first occurrence of invasive infection was included.

To assess the risk factors associated with in-hospital mortality among patients with carbapenem-resistant *K. pneumoniae* infection, a second case-control study was performed. In this study, the case patients were all those patients with carbapenem-resistant *K. pneumoniae* infection from our first case-control study who died from their infections, and the control patients were all those with carbapenem-resistant *K. pneumoniae* infection from our first case-control study who survived. Patients with carbapenem-susceptible *K. pneumoniae* infection from our first case-control study were also divided into case and control patients in the same way.

For descriptive analysis, mortality attributable to infection was defined as the death of a patient with clinical evidence (eg, persistent leukocytosis or leukopenia, persistent fever or hypothermia, and/or failure or compromise of organ systems) that suggested ongoing infection despite administration of antimicrobials demonstrating in vitro activity and/or a positive clinical culture result from a normally sterile anatomic site within 24 hours prior to death. Our study was approved by the institutional review board of the Mount Sinai School of Medicine.

Data Collection

Data were ascertained by review of medical, laboratory, and pharmacy records. Abstracted data included patient's age, sex, and length of stay before infection. Also obtained were data on the presence of comorbidities and healthcare exposures before infection, including diabetes mellitus, renal insufficiency (with a serum creatinine concentration of 2 mg/dL or more or the need for dialysis), chronic heart disease, liver disease (cirrhosis or acute hepatitis), solid-organ or stem-cell transplantation within the previous 6 months, human immunodeficiency virus infection, use of a central venous catheter, receipt of mechanical ventilation for more than 24 hours, and stay in an ICU for more than 48 hours.

Data were collected on all antibiotics with gram-negative activity that were administered during hospitalization or

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TABLE 1. Demographic and Clinical Characteristics of Patients With Carbapenem-Resistant *Klebsiella pneumoniae* Infection (Case) and Patients With Carbapenem-Susceptible *K. pneumoniae* Infection (Control), From July 1, 2004, to June 30, 2006

Charactristic	Case patients (n = 99)	Control patients (n = 99)
Demographic		
Age, mean ± SD, years	60.67 ± 14.95	59.39 ± 13.34
Sex		
Male	58 (59)	58 (59)
Female	41 (41)	41 (41)
Clinical		
Bacteremia	56 (57)	56 (57)
Catheter-associated bacteremia[a]	27/56 (48)	29/56 (52)
Intra-abdominal infection[b]	34 (34)	34 (34)
Intra-abdominal infection with secondary bacteremia	15/34 (44)	8/34 (24)
Urosepsis[c]	2 (2)	2 (2)
Ventriculitis	2 (2)	2 (2)
Osteomyelitis	2 (2)	2 (2)
Empyema	2 (2)	2 (2)
Deep sinus infection	1 (1)	1 (1)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Positive blood culture result was not related to infection at another body site that occurred in a patient with a central venous catheter.

[b] Includes intra-abdominal abscesses, spontaneous bacterial peritonitis, and secondary peritonitis.

[c] Positive urine culture result with concomitant bacteremia.

within 3 months prior to the diagnosis of invasive *K. pneumoniae* infection. Data were also collected on the antibiotics administered after isolation of *K. pneumoniae,* the time to administration of antibiotics with in vitro activity (ie, an antibiotic to which the patient's *K. pneumoniae* isolate was susceptible in vitro), and the use of adjunctive therapy in the treatment of infection. Adjunctive therapy was defined as a procedure employed to remove the probable focus of the infection (eg, debridement, drainage, or catheter removal). Polymyxin B was available for use throughout the study period. Tigecycline became available for use in July 2005. In-hospital mortality and mortality attributable to infection were assessed retrospectively.

Laboratory Methods

An automated broth microdilution system (MicroScan; Dade Behring) was used for identification and initial susceptibility testing of *K. pneumoniae* isolates. Carbapenem resistance was confirmed by the Etest (AB Biodisk) with imipenem. Susceptibility to antimicrobials other than tigecycline was determined according to the criteria of the Clinical Laboratory Standards Institute.[18] Testing for tigecycline and polymyxin B susceptibility among multidrug-resistant isolates of *K. pneumoniae* was performed routinely beginning August 31, 2005. Prior to this date, susceptibility testing for polymyxin B was performed on request. The interpretive criteria for polymyxin B were extrapolated from data on its in vitro activity against strains of *Acinetobacter baumannii,* as published by the Clinical Laboratory Standards Institute.[18] Tigecycline susceptibility was determined by the use of minimum inhibitory concentration breakpoints approved by the US Food and Drug Administration.[19]

Statistical Analyses

All statistical analyses were adjusted for patient age. Multivariable logistic regression was used to determine risk factors independently associated with in-hospital mortality for the entire cohort of 198 patients with invasive *K. pneumoniae* infection. In the first case-control study, conditional logistic regression was used to identify individual variables associated with carbapenem-resistant *K. pneumoniae* infection. Both computer-assisted and manual forward, backward, and stepwise conditional logistic regression models were used to identify risk factors independently associated with carbapenem-resistant *K. pneumoniae* infection. In the second case-control study, the χ^2 test, the Fisher exact test, the Wilcoxon rank-sum test, and the Student t test all were used to identify variables associated with in-hospital mortality among patients with *K. pneumoniae* infection. In univariable analysis, variables achieving a P value of .02 or less were included in a multivariable logistic regression model, to determine inde-

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TABLE 2. Clinical Risk Factors Associated With Carbapenem-Resistant and Carbapenem-Susceptible *Klebsiella pneumoniae* Infections, From July 1, 2004, to June 30, 2006

Risk factor	Case patients ($n = 99$)	Control patients ($n = 99$)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Patient-specific risk factor						
Diabetes	27 (27)	20 (20)	1.45 (0.75–2.82)	.27		
HIV infection	2 (2)	5 (5)	0.40 (0.08–2.14)	.29		
Heart disease	23 (23)	16 (16)	1.52 (0.72–3.20)	.27		
Liver disease	39 (39)	29 (29)	1.67 (0.90–3.08)	.10	1.64 (0.57–4.74)	.36
Renal insufficiency	34 (34)	23 (23)	1.75 (0.94–3.27)	.08	1.46 (0.56–3.81)	.44
Transplant recipient	41 (41)	14 (14)	5.70 (2.65–12.16)	<.001	3.71 (1.41–9.73)	.008
Healthcare-associated factors						
Use of CVC	90 (91)	55 (56)	8.32 (3.74–18.53)	<.001	1.96 (0.58–6.70)	.28
Receipt of mechanical ventilation	65 (66)	22 (22)	6.62 (3.53–12.43)	<.001	2.44 (1.06–5.61)	.04
ICU stay	68 (69)	33 (33)	4.45 (2.45–8.11)	<.001	0.51 (0.12–2.10)	.35
Length of stay before infection, days						
Mean ± SD	25.19 ± 24.9	6.44 ± 10.1				
Median	21	1	1.09 (1.06–1.12)	<.001	1.05 (1.01–1.08)	.01
Prior antibiotic therapy with anti–gram negative activity	98 (99)	55 (56)	78.17 (10.48–583.10)	<.001		
Class of antibiotic used						
Cephalosporin	63 (64)	31 (31)	3.82 (2.11–6.91)	<.001	2.65 (1.45–6.12)	.02
β-lactam and/or β-lactamase inhibitor	54 (55)	33 (33)	2.30 (1.30–4.10)	<.005	1.07 (0.44–2.60)	.88
Fluoroquinolone	36 (36)	23 (23)	1.87 (1.00–3.48)	.05	0.78 (0.3–2.02)	.60
Carbapenem	54 (55)	6 (6)	19.25 (7.61–48.70)	<.001	14.97 (5.29–42.35)	<.001
Monobactam	6 (6)	1 (1)	7.04 (0.82–60.68)	.08	1.64 (0.03–85.17)	.81
Aminoglycoside	14 (14)	3 (3)	5.44 (1.49–19.85)	.01	2.95 (0.57–15.28)	.19

NOTE. Data are no. (%) of patients, unless otherwise indicated. Case patients are patients with carbapenem-resistant *K. pneumoniae* infection, and control patients are patients with carbapenem-susceptible *K. pneumoniae* infection. Univariable and multivariable analyses were performed by conditional logistic regression. Only those variables that achieved a *P* value of .02 or less in the univariable analysis were included in the multivariable analysis. CI, confidence interval; CVC, central venous catheter; HIV, human immunodeficiency virus; ICU, intensive care unit; OR, odds ratio; SD, standard deviation.

pendent predictors of mortality. All statistical analyses were performed using SAS, version 9.1 (SAS Institute).

RESULTS

During the study period, there were 375 patients who had an episode of invasive *K. pneumoniae* infection. Ninety-nine (26%) of these episodes were caused by carbapenem-resistant *K. pneumoniae.* There were no significant differences in age ($P = .70$) or sex ($P = .51$) between patients with carbapenem-resistant *K. pneumoniae* infection and those with carbapenem-susceptible *K. pneumoniae* infection. Among the 99 case patients with carbapenem-resistant *K. pneumoniae* infection, 48 (48%) died during hospitalization, compared with 73 (26%) of the 276 patients with carbapenem-susceptible *K. pneumoniae* infection ($P < .001$).

The 99 case patients were matched to the 99 control patients by anatomic site of infection (Table 1). The most common types of identified infection were primary bacteremia (approximately one-half of these cases were associated with catheter use) and intra-abdominal infection.

Each of the 99 case patients had an isolate of carbapenem-resistant *K. pneumoniae* recovered; of these 99 isolates, 58 (59%) demonstrated in vitro susceptibility to gentamicin, 14 (14%) to amikacin, and 51 (52%) to tetracycline. Susceptibility testing for polymyxin B and tigecycline was performed on only 80 (81%) of the 99 isolates during the study period. Of these 80 isolates, 72 (90%) demonstrated in vitro susceptibility to polymyxin B, and 74 (92%) demonstrated in vitro susceptibility to tigecycline. Preliminary investigations into the resistance mechanisms in specific isolates suggested that two-thirds of the tested isolates expressed KPC-2 and that close to one-third expressed KPC-3. A small number of isolates did not appear to express either KPC subtype, and further evaluation is ongoing (J. Lee, personal communication, May 14, 2008).

Comparison of Case and Control Patients

In univariable analysis (Table 2), carbapenem-resistant *K. pneumoniae* infection was associated with recent solid-organ or stem-cell transplantation (odds ratio [OR], 5.70 [95% confidence interval {CI}, 2.65–12.16]), a longer length of stay before infection (OR, 1.09 [95% CI, 1.06–1.12]), central venous catheterization (OR, 8.32 [95% CI, 3.74–18.53]), receipt of mechanical ventilation (OR, 6.62 [95% CI, 3.53–12.43]), stay in an ICU (OR, 4.45 [95% CI, 2.45–8.11]), and exposure to all major classes of antibiotics with gram-negative activity

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TABLE 3. Clinical Risk Factors Associated With Mortality Among Patients With Carbapenem-Resistant *Klebsiella pneumoniae* Infection, From July 1, 2004, to June 30, 2006

Risk factor	Patients who died ($n = 48$)	Patients who survived ($n = 51$)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Patient-specific risk factor						
Age, mean ± SD, years	62.5 ± 18.2	58.9 ± 11.7	1.02 (0.99–1.05)	.24		
Diabetes	13 (27)	14 (27)	0.98 (0.41–2.38)	.97		
HIV infection	1 (2)	1 (2)	1.06 (0.06–17.80)	.99		
Heart disease	16 (33)	7 (14)	3.14 (1.16–8.53)	.02	4.56 (1.26–16.55)	.02
Liver disease	22 (46)	17 (33)	1.69 (0.75–3.82)	.20	2.36 (0.80–6.91)	.12
Renal insufficiency	22 (45)	12 (24)	2.75 (1.16–6.50)	.02	2.75 (0.93–8.17)	.07
Transplant recipient	20 (42)	21 (41)	1.02 (0.46–2.27)	.96		
Healthcare-associated risk factor						
Length of stay before infection, mean ± SD, days	24.8 ± 24.9	25.6 ± 26.7	1.00 (0.98–1.02)	.35		
Use of CVC	46 (96)	44 (86)	3.66 (0.72–18.58)	.10	2.41 (0.26–17.43)	.50
Receipt of mechanical ventilation	36 (75)	29 (57)	2.28 (0.97–5.36)	.06	0.51 (0.10–2.66)	.15
ICU stay	39 (81)	29 (57)	3.29 (1.32–8.19)	.009	11.10 (1.85–66.95)	.009
Therapeutic intervention						
Use of antibiotics with in vitro activity	35 (73)	31 (61)	1.74 (0.74–4.06)	.20	2.30 (0.73–7.24)	.15
Delay in antibiotic therapy with in vitro activity, mean ± SD, days	3.2 ± 2.3	3.2 ± 2.2	1.00 (0.81–1.24)	.98		
Adjunctive therapy[a]	29 (60)	44 (86)	0.24 (0.09–0.65)	.004	0.14 (0.04–0.49)	.002

NOTE. Data are no. (%) of patients, unless otherwise indicated. Univariable and multivariable analyses were performed by conditional logistic regression. Only those variables that achieved a *P* value of .02 or less in the univariable analysis were included in the multivariable analysis. CI, confidence interval; CVC, central venous catheter; HIV, human immunodeficiency virus; ICU, intensive care unit; OR, odds ratio; SD, standard deviation.

[a] Procedure employed to treat the infection by removing the probable focus of the infection (eg, debridement, drainage, or catheter removal).

(OR, 78.17 [95% CI, 10.48–583.10]). Of the 54 patients with carbapenem-resistant *K. pneumoniae* infection who had received carbapenems during hospitalization or within the 30 days prior to the recovery of a carbapenem-resistant *K. pneumoniae* isolate, 26 (48%) were receiving the antibiotic at the time an isolate of carbapenem-resistant *K. pneumoniae* was recovered. In multivariable analysis, recent organ or stem-cell transplantation (OR, 3.71 [95% CI, 1.41–9.73]; $P = .008$), receipt of mechanical ventilation (OR, 2.44 [95% CI, 1.06–5.61]; $P = .04$), a longer length of stay before infection (OR, 1.05 [95% CI, 1.01–1.08]; $P = .01$), cephalosporin exposure (OR, 2.65 [95% CI, 1.45–6.12]; $P = .02$), and carbapenem exposure (OR, 14.97 [95% CI, 5.29–42.35]; $P < .001$) were independently associated with carbapenem-resistant *K. pneumoniae* infection.

Of the 99 patients in each group, 66 case patients (67%) and 95 control patients (96%) received antimicrobial therapy ($P < .001$). The mean interval between specimen collection and the initiation of antibiotics with in vitro activity against carbapenem-resistant *K. pneumoniae* was 3.2 days for case patients and 0.8 days for control patients ($P < .001$). Compared with control patients, case patients were more than 3 times more likely to die during hospitalization (20% vs 48%; OR, 3.71 [95% CI, 1.97–7.01]; $P < .001$) and were more than 4 times more likely to die from their *K. pneumoniae* infection (12% vs 38%; OR, 4.50 [95% CI, 2.16–9.35]; $P < .001$).

Predictors of Mortality Among Patients With K. pneumoniae Infection

The risk factors independently associated with in-hospital mortality for the cohort of 198 patients with invasive *K. pneumoniae* infection were as follows: heart disease (OR, 3.40 [95% CI, 1.31–8.84]; $P = .012$), liver disease (OR, 2.90 [95% CI, 1.15–7.35]; $P = .024$), stay in an ICU (OR, 5.16 [95% CI, 1.43–18.64]; $P = .012$), and infection with carbapenem-resistant *K. pneumoniae* (OR, 4.69 [95% CI, 1.9–11.58]; $P = .001$). For the full cohort of patients, use of adjunctive therapy was independently associated with survival during hospitalization (OR, 0.15 [95% CI, 0.06–0.37]; $P < .001$).

Predictors of Mortality Among Case Patients

In univariable analysis, a clinical history of heart disease (OR, 3.14 [95% CI, 1.16–8.53]; $P = .02$), renal insufficiency (OR, 2.75 [95% 1.16–6.50]; $P = .02$), and an ICU stay (OR, 3.29 [95% CI, 1.32–8.19]; $P = .009$) were associated with in-hospital mortality among case patients. The use of adjunctive therapy was associated with survival (OR, 0.24 [95% CI, 0.09–0.65]; $P = .004$). Heart disease and an ICU stay prior to diagnosis of infection were independently associated with mortality in case patients (Table 3). Receipt of antibiotics for which the patient-specific *K. pneumoniae* isolate was susceptible in vitro was not associated with patient survival. Inclu-

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sion of an adjunctive procedure in the treatment regimen was independently associated with patient survival (OR, 0.14 [95% CI, 0.04–0.49]; $P = .002$). Only 5 (36%) of the 14 case patient who received antibiotics without an adjunctive therapeutic procedure survived during hospitalization. Although the administration of antibiotics with in vitro activity was delayed for case patients, there was no difference in the time to initiation between those who died and those who survived. In fact, 12 (80%) of 15 case patients who received an antibiotic with in vitro activity within 48 hours of specimen collection died.

Predictors of Mortality Among Control Patients

Similar predictors of mortality were observed among control patients (data not shown). Heart disease was independently associated with mortality (OR, 4.98 [95% CI, 1.08–22.93]; $P = .04$), and the use of an adjunctive therapeutic procedure was associated with patient survival (OR, 0.13 [95% CI, 0.03–0.48]; $P = .003$). Although 27 (71%) of the 38 control patients who received antibiotics with in vitro activity but no adjunctive therapeutic procedure survived during hospitalization, use of an antibiotic with in vitro activity was not an independent predictor of survival (OR, 0.183 [95% CI, 0.014–2.43]; $P = .198$) for this group of control patients.

DISCUSSION

Carbapenem-resistant *K. pneumoniae* is an emerging pathogen that is associated with several healthcare-associated risk factors, including recent solid-organ or stem-cell transplantation, receipt of mechanical ventilation, prolonged hospitalization, and prior treatment with cephalosporins and/or carbapenems. The in-hospital mortality rate associated with carbapenem-resistant *K. pneumoniae* infection, even among case patients who received antibiotics demonstrating in vitro activity against the infecting organism, was relatively high. These findings have important implications for the prevention, detection, and treatment of carbapenem-resistant *K. pneumoniae* infection and strengthen recent findings from other institutions.[14]

Of the 375 patients patients who had an episode of invasive *K. pneumoniae* infection during the 2-year study period, 99 (26%) of these episodes were caused by carbapenem-resistant *K. pneumoniae.* The 99 isolates recovered were multidrug resistant and demonstrated resistance to β-lactams, fluoroquinolones, and sulfonamides and variable susceptibility to aminoglycosides, polymyxin B, tetracycline, and tigecycline. This observed prevalence of carbapenem resistance among *K. pneumoniae* isolates was similar to that reported in another study from New York City[13] that suggested that carbapenem-resistant *K. pneumoniae* has become endemic in this region.

In our study, patients with carbapenem-resistant *K. pneumoniae* infection were extremely ill prior to the onset of infection. They were more likely to have required mechanical ventilation, to have had exposure to broad-spectrum antibiotics, and to have had prolonged hospitalization. Smaller studies have reported similar risk factors for carbapenem-resistant *K. pneumoniae* infection. These studies demonstrated associations between carbapenem-resistant *K. pneumoniae* infection and length of stay, use of central venous catheter, stay in an ICU, and exposure to specific broad-spectrum antimicrobial agents, such as carbapenems, cephalosporins, fluoroquinolones, and antipseudomonal penicillins.[14-16,20-22] These risk factors likely represent severe underlying illness, susceptibility to infection, and antibiotic selection pressure leading to increased risk of infection with multidrug-resistant organisms.

The group of patients that is perhaps unique to our study is the population of patients who have had solid-organ or stem-cell transplantation. Recent solid-organ or stem-cell transplantation was independently associated with invasive carbapenem-resistant *K. pneumoniae* infection. This population of patients with immunosuppressed status had 2 other simultaneous risk factors: previous antibiotic exposure and frequent, prolonged hospitalization. Prior studies have shown *K. pneumoniae* infection to be increasing in prevalence as a cause of bloodstream infections in liver transplant recipients.[23] To our knowledge, our study is the first to show an association between solid-organ or stem-cell transplantation and carbapenem-resistant *K. pneumoniae* infection.

To further explore the increased mortality associated with carbapenem-resistant *K. pneumoniae* infection, we evaluated the impact of patient characteristics and therapeutic interventions on mortality. Compared with control patients, there was a delay in the administration of antibiotics with in vitro activity to case patients. The cause of this was likely multifactorial. Control patients often received antibiotics with in vitro activity as part of an empirical regimen. A lack of knowledge of the epidemiology and prevalence of carbapenem-resistant *K. pneumoniae* infection, the relatively low rate of occurrence of this type of infection, and the hesitancy to use treatment with polymyxins, aminoglycosides, and tigecycline empirically may have been impediments to the inclusion of an antibiotic with in vitro activity in initial regimens. Inherent delays in the availability of comprehensive antimicrobial susceptibility data (because of the manual testing that is required for polymyxin B and tigecycline susceptibility), as well as the absence of a predictable susceptibility pattern among carbapenem-resistant *K. pneumoniae* isolates, may have also contributed to the delayed administration of active agents, even when carbapenem-resistant *K. pneumoniae* was suspected at the time of initiation of an empirical regimen.

Unexpectedly, treatment with 1 or more antibiotics to which the patient-specific carbapenem-resistant *K. pneumoniae* isolate was susceptible in vitro was not associated with patient survival, even with early initiation of active agents. Therefore, the poor outcomes observed in the case group did not seem to be explained completely by the delay in the initiation of antimicrobial therapy with in vitro activity. There is evidence that polymyxins, tigecycline, and aminoglycosides

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have activity against many carbapenem-resistant *K. pneumoniae* isolates in vitro,[24] and there have been reported cases of successful treatment of carbapenem-resistant *K. pneumoniae* infection with polymyxins and with tigecycline.[25-27] Most of these anecdotal successes also involved adjunctive procedures (eg, catheter removal, drainage, or debridement). Our study suggests that these particular antibiotics, alone or in combination, may not be reliably effective in the treatment of carbapenem-resistant *K. pneumoniae* infection and that newer antimicrobial agents with improved clinical activity against carbapenem-resistant *K. pneumoniae* are needed. Because of the retrospective and nonrandomized design of our study, however, we cannot comment on the effectiveness of specific antimicrobials or combinations of those antimicrobials among patients with carbapenem-resistant *K. pneumoniae* infection. This is an important area for future study.

Our study suggests that removal of the focus of infection is currently the most effective means of improving survival among patients with carbapenem-resistant *K. pneumoniae* infection. Survival rates were substantially lower among patients with carbapenem-resistant *K. pneumoniae* infection who were treated with antibiotics alone.

There were limitations to our study. Ideally, case and control patients should be similar in every way except their disease.[28] This may not have been true of our case and control patients. Specifically, in our study, the case patients may have been sicker than the control patients. Although we included such variables as length of stay before infection, stay in an ICU, use of a central venous catheter, and receipt of mechanical ventilation in multivariable analysis, to control for these possible confounders, it is possible that the adverse outcomes that we saw in the case group were the result of a sicker population and not of carbapenem-resistant *K. pneumoniae* infection. Because of our reliance on previously collected data, a standardized severity-of-illness scoring system could not be used because the required information was not available for all patients.

We were not able to include prior colonization with carbapenem-resistant *K. pneumoniae* in our analysis of risk factors for invasive carbapenem-resistant *K. pneumoniae* infection, because the colonization status of each patient was not known. It should be noted, however, that 26 (26%) of the 99 case patients and 4 (4%) of the 99 control patients showed evidence of colonization with carbapenem-resistant *K. pneumoniae* prior to the diagnosis of invasive *K. pneumoniae* infection ($P < .001$). The colonization status of these 30 patients had been identified by either a prior clinical culture result or a surveillance specimen.

We excluded patients from whom *K. pneumoniae* was isolated from only sputum, urine, or superficial wound culture specimens, because of our inability to differentiate reliably between colonization and active infection and to avoid misclassification bias. Therefore, these results may not be generalizable to patients with pneumonia, urinary tract infection, or superficial wound infection due to carbapenem-resistant *K. pneumoniae.*

To determine the impact of carbapenem resistance on outcomes associated with invasive *K. pneumoniae* infection, we selected our control patients from a group of patients infected with carbapenem-susceptible *K. pneumoniae.* Although the use of these control patients to examine risk factors for carbapenem-resistant *K. pneumoniae* infection may have led to an overestimation of the association between carbapenem exposure and carbapenem-resistant *K. pneumoniae* infection,[28] we believe that it was the appropriate control group to elucidate the impact of carbapenem resistance on the outcomes of *K. pneumoniae* infection.

Inaccuracies in automated susceptibility testing may have led to the misclassification of some case patients as potential control patients. Current automated susceptibility testing modalities have failed to reliably detect carbapenem resistance among *K. pneumoniae* isolates. A study of several automated systems found that failure to detect carbapenem resistance occurred in 6%–87% of known resistant isolates.[29] Recommendations to prevent this problem include increasing inoculum size and using ertapenem to assess for resistance to this class of antimicrobials.[13] Use of either strategy may reduce the delay in the administration of appropriate antibiotics and in the use of an adjunctive therapeutic procedure.

Carbapenem-resistant *K. pneumoniae* is emerging as a significant healthcare-associated pathogen. The mortality associated with and the apparent lack of effective antimicrobial treatment options for invasive carbapenem-resistant *K. pneumoniae* infection highlight the critical need for improved clinical and laboratory detection of carbapenem-resistant *K. pneumoniae,* identification of effective preventive measures, and development of new antibiotic agents with reliable clinical activity against carbapenem-resistant Enterobacteriaceae.

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