ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2006, p. 1715–1720 Vol. 50, No. 5
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.5.1715–1720.2006

Predictors of Mortality in Patients with Bloodstream Infection Due to Ceftazidime-Resistant *Klebsiella pneumoniae*

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Received 24 August 2005/Returned for modification 27 December 2005/Accepted 11 February 2006

Bloodstream infection (BSI) due to multidrug-resistant *Klebsiella* is associated with high rates of morbidity and mortality. The aim of this study was to identify predictors of in-hospital mortality among patients with BSI due to ceftazidime-resistant (CAZ-R) *Klebsiella pneumoniae* at a tertiary care medical center. Patients with CAZ-R *K. pneumoniae* BSI were identified by our microbiology laboratory between January 1995 and June 2003. Clinical data were collected retrospectively. Logistic regression was used to identify independent predictors of all causes of in-hospital mortality. Of 779 patients with *K. pneumoniae* BSI, 60 (7.7%) had BSI due to CAZ-R *K. pneumoniae*; 43 (72%) of these were nosocomial infections. Pulsed-field gel electrophoresis identified a single predominant strain in 17 (28%) patients. The in-hospital mortality rate was 43% ($n = 26$). Among patients with CAZ-R *K. pneumoniae* BSI, those who died were similar to survivors with respect to demographic, clinical, and antimicrobial susceptibility characteristics. Only 43 (72%) patients received effective therapy within 5 days of BSI. In bivariable analysis, delay in initiation of effective therapy for >72 h after diagnosis of BSI was associated with death ($P = 0.03$). Strain genotype was not predictive of outcome. In multivariable analysis, delay in initiation of effective therapy for >72 h after diagnosis of BSI was an independent predictor of death (odds ratio, 3.32; 95% confidence interval, 1.07 to 10.3). Thus, among patients with BSI due to CAZ-R *K. pneumoniae*, a delay in the initiation of effective therapy of greater than 72 h after BSI was associated with a >3-fold increase in mortality risk.

Klebsiella pneumoniae is a common cause of serious nosocomial gram-negative infections, including ventilator-associated pneumonia, urinary tract infection, and bloodstream infection (BSI) (9, 33). Infections due to *K. pneumoniae* occur in both outbreak settings and settings of endemicity (8, 33). Unfortunately, isolates of *K. pneumoniae* are becoming increasingly resistant to antibiotics. For example, 20.6% of *K. pneumoniae* infections in U.S. intensive care units (ICUs) were resistant to expanded-spectrum cephalosporins in 2003 (23). Compared to the mean rate of resistance for the preceding 5 years, resistance to expanded-spectrum cephalosporins among tested *K. pneumoniae* isolates increased 47% in 2003 (23).

Ceftazidime (CAZ) resistance in *K. pneumoniae* is most commonly caused by plasmid-mediated production of extended-spectrum β-lactamases (ESBL) (15, 37). A variety of different ESBL classes have been described, including the TEM, SHV, CTX-M, and OXA classes (3, 6, 12, 27). ESBL production has become relatively common among *K. pneumoniae* in the United States. Over the past two decades, the prevalence of ESBL production in *K. pneumoniae* has increased from 7 to 34%, depending upon geographic location (1, 16, 40). An additional mechanism of CAZ resistance in *K. pneumoniae* occurs via production of plasmid-mediated *ampC* β-lactamases (32).

Infections due to multidrug-resistant *K. pneumoniae* are associated with increased morbidity and mortality compared to susceptible strains (29). To date, studies of CAZ-resistant (CAZ-R) *K. pneumoniae* have been limited by small numbers, inclusion of non-sterile site infections, grouping of *Klebsiella* strains together with *Escherichia coli* strains, and studying only ESBL-producing CAZ-R *K. pneumoniae* strains; in addition, some studies have been limited to strains associated with outbreaks, limiting the generalizability to CAZ-R *K. pneumoniae* in settings of endemicity (16, 18, 20, 24, 28, 29, 31, 34, 36, 41). To our knowledge, no studies to date have identified predictors of mortality among patients with BSI due to ESBL- and non-ESBL-producing CAZ-R *K. pneumoniae*.

Understanding predictors of mortality among patients with CAZ-R *K. pneumoniae* BSI is important. Infections due to CAZ-R *K. pneumoniae* are increasingly common, and strategies to improve clinical outcomes for infected patients are needed. The objective of this study was to identify predictors of in-hospital mortality among consecutive hospitalized patients with BSI due to CAZ-R *K. pneumoniae*. A specific focus was given to analyzing the impact and timing of effective antimicrobial therapy on mortality.

MATERIALS AND METHODS

Study design, setting, and patients. This was a cohort study conducted at Duke University Medical Center (DUMC). DUMC is a 750-bed tertiary care institution in Durham, North Carolina. Between 1 January 1995 and 1 June 2003, the DUMC Clinical Microbiology Laboratory identified all patients with BSI due to *K. pneumoniae* and classified strains as susceptible, resistant, or of intermediate susceptibility to CAZ. Patients with BSI due to *K. pneumoniae* resistant to or of intermediate susceptibility to CAZ were included in the study cohort and were considered to be CAZ resistant.

Study variables and outcomes. We retrospectively collected clinical and microbiologic variables. Data pertaining to patient demographics (age, gender, and race), co-morbid conditions (dementia, coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic renal disease, chronic liver disease, cancer, and immunocompromised status), indwelling devices (Foley catheter and central venous catheter), surgery, antimicrobial therapy, and other hospital risk factors (stay in ICU, length of stay prior to infection, and history of *K. pneumoniae* colonization) were obtained from patient charts. The Charlson

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index was used as a measure of severity of illness (5, 7). The outcome of interest and all causes of in-hospital mortality were additionally collected from the patient charts. Patients discharged to hospice were classified as fatal outcomes on the day of discharge. The study was approved by the Institutional Review Board at DUMC.

Microbiology. *K. pneumoniae* was isolated and identified in the clinical microbiology laboratory using standard methods (21). Susceptibility testing was performed using the MicroScan Neg Combo type 12 dried panel (Dade Behring). Susceptibility results were obtained from the microbiology databases. For all study isolates, ESBL production was confirmed by either the double disk diffusion test, Etest ESBL strip (AB Biodisk) with end-to-end ceftazidime (0.5 to 32 μg/ml)/ceftazidime (0.125 to 8 μg/ml)-clavulanic acid (4 μg/ml) or by the CLSI (formerly NCCLS) ESBL confirmatory disk diffusion test (22). Genotypic analysis of isolates was performed by pulsed-field gel electrophoresis (PFGE) using the Bio-Rad GenePath system with the Bio-Rad Universal Module and GenePath group 6 enzyme reagent kit (XbaI) as specified in the manufacturer's package insert (Bio-Rad Laboratories, Hercules, CA) (38).

Definitions. The acute period of infection was the time period beginning 48 h prior to the initial positive blood culture for CAZ-R *K. pneumoniae* and extending to 5 days after culture positivity. Antimicrobial therapy refers to administration of any of the following antimicrobial agents with potential activity against *K. pneumoniae* for ≥48 h during the acute period of infection: expanded-spectrum cephalosporins (ceftriaxone or ceftazidime), fluoroquinolones (ciprofloxacin or levofloxacin), β-lactam–β-lactam inhibitor combinations (ampicillin-sulbactam, ticarcillin-clavulanate), and carbapenems (imipenem or meropenem). Single doses of antimicrobials were not included except in the setting of renal failure and/or hemodialysis. Combination therapy is the use of two or more antimicrobial agents overlapping for ≥48 h. Definitive therapy is antimicrobial therapy initiated after in vitro antimicrobial susceptibility test results were released by the clinical microbiology laboratory. Typically, the period for definitive therapy began 48 h after the day of infection and spanned until 5 days after the date of the initial positive culture. Effective therapy is antimicrobial therapy active in vitro against the BSI isolate. Empirical therapy is antimicrobial therapy initiated before in vitro antimicrobial susceptibility test results were released by the clinical microbiology laboratory. The empirical therapy time period spanned from 48 h prior to the culture being obtained until 48 h after the culture was obtained. Patients with immunocompromised status are patients with neutropenia (white blood cell count < 3,000) or receiving systemic corticosteroids at the time of infection. The infection date is the date that the initial positive blood culture for CAZ-R *K. pneumoniae* was obtained. Monotherapy is the use of a single antimicrobial for treatment during the acute period of infection. Nosocomial infection is infection occurring greater than 48 h after admission to the hospital (10). The presence of indwelling Foley catheters and central venous catheters in a given patient on the infection date has been noted. Primary infection is BSI associated with an indwelling vascular catheter with no other primary focus of infection. Secondary infection is BSI occurring as a result of an infection at another anatomic site (e.g., BSI arising from an abscess, urinary tract infection, wound infection, or pneumonia).

Statistical analysis. Data were maintained using Microsoft Access (Redmond, WA) and analyzed using SAS, version 8.2 (SAS Institute, Cary, NC) software. Bivariable analysis was performed using standard statistical tests for categorical and continuous variables. Categorical variables were evaluated using the chi-square or two-tailed Fisher's exact test. Continuous variables were evaluated using the Wilcoxon rank sum test.

Multivariable analysis to identify independent predictors of in-hospital mortality was performed using logistic regression. Variables were considered for inclusion in the multivariable model if they were felt to be clinically significant by the study investigators and/or were associated with mortality in bivariable analysis (P value of ≤0.20). The final model was selected using a forward stepwise selection process. Variables were checked for confounding. If a covariate changed the β coefficient of variable in the final model by 10% or more, it was considered to be a confounder. All confounding variables were included in the final model. P values of ≤0.05 were considered significant for all analyses; all tests were two sided.

RESULTS

Collection of isolates. During the study period, 779 patients with BSI due to *K. pneumoniae* were identified; 60 patients (7.7%) had BSI due to CAZ-R *K. pneumoniae*. Of the 60 patients with CAZ-R *K. pneumoniae* BSI, 43 cases (72%) were classified as nosocomial.

Molecular epidemiology. PFGE analysis on all 60 isolates identified six distinct genotypic patterns among 27 patients (A to F). One predominant strain (pattern E) was observed in 17 (28%) patients. This strain was most frequently identified between 1999 and 2001.

In vitro susceptibility results and ESBL confirmation. All isolates (100%) were susceptible to imipenem. The majority of isolates remained susceptible to amikacin (90%) and ciprofloxacin (63%). However, isolates were highly resistant to all other antibiotics tested: only 33% of isolates were susceptible to gentamicin, 29% to tobramycin, 13% to ceftriaxone, and 2% to ampicillin-sulbactam. No isolates were susceptible to ticarcillin-clavulanate. Fifty-one (85%) of the CAZ-R *K. pneumoniae* isolates were confirmed ESBL producers.

Clinical epidemiology. (i) Characteristics of the study population. Study patients had a high frequency of malignancy (n = 30, 50%) and were often immunocompromised (n = 35, 58%). Forty-nine (82%) patients were on antibiotics prior to the acute period of infection. Patients were in the hospital for several days before infection (median, 14 days; range, 0 to 129 days), and 17 (28%) were in the ICU at the time of infection. Patients frequently had indwelling Foley catheters (n = 19, 32%) or central venous catheters (n = 49, 82%) at the time of infection. Patients remained hospitalized for a median of 23 days (interquartile range, 7 to 35 days) after BSI. Eighteen (30%) patients had secondary BSI with a variety of sources including abscesses (n = 7), urinary tract infection (n = 6), and pneumonia (n = 5). The remaining 42 (70%) patients had primary, catheter-associated BSI.

(ii) Empirical antimicrobial therapy. An expanded-spectrum cephalosporin was the most frequent type of antibiotic used empirically (i.e., within the time span from 48 h prior to the day of BSI to 48 h afterwards) and was given to 32 (53%) patients. Aminoglycoside antibiotics were empirically administered to 19 (32%) patients, β-lactam–β-lactamase inhibitor combination antibiotics to 15 (25%) patients, fluoroquinolones to 13 (22%) patients, and carbapenems to 13 (22%) patients. Eighteen (30%) patients received monotherapy as empirical treatment, while 42 (70%) received combination therapy. Twenty-four (40%) patients received effective empirical therapy.

(iii) Definitive antimicrobial therapy. A carbapenem was administered as definitive therapy (therapy provided > 2 days after infection) in 32 (53%) patients. Aminoglycosides were given as definitive therapy to 13 (32%) patients, fluoroquinolones to 13 (22%) patients, and β-lactam–β-lactamase inhibitor combinations to 3 (5%) patients. Surprisingly, expanded-spectrum cephalosporins were used as definitive therapy in 9 (15%) patients. Thirty-nine (65%) patients received combination therapy, while 21 (35%) patients received monotherapy for definitive therapy. Notably, effective definitive therapy was provided to only 43 (72%) patients.

(iv) Predictors of in-hospital mortality. Twenty-six patients (43%) with BSI due to CAZ-R *K. pneumoniae* died during their hospitalizations. Compared to patients with BSI caused by CAZ-susceptible *K. pneumoniae*, patients with CAZ-R *K. pneumoniae* BSI were approximately three times more likely to die in the hospital (P < 0.001; data not shown) at our institution during the study period.

TABLE 1. Predictors of in-hospital death in 60 patients with ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infections

Parameter	Result for patient group[c]		*P* value	OR (95% CI)
	Survived (n = 34) n (%)	Died (n = 26) n (%)		
Patient demographics				
Age (mean ± SD)	45.2 ± 28.0	47.9 ± 28.1	0.71	NA[d]
Gender (male)	23 (68)	15 (58)	0.59	0.65 (0.23–1.88)
Race (Caucasian)	18 (53)	16 (62)	0.45	1.42 (0.50–4.02)
Baseline clinical characteristics				
Transferred to study hospital	8 (24)	9 (35)	0.40	1.72 (0.55–5.34)
Immunocompromised	19 (56)	16 (62)	0.79	1.26 (0.45–3.58)
Transplant recipient	7 (21)	3 (12)	0.49	0.50 (0.12–2.17)
Central venous catheter present	28 (82)	21 (81)	1.00	0.90 (0.24–3.35)
Foley catheter present	8 (24)	11 (42)	0.16	2.38 (0.79–7.24)
Previously colonized with *K. pneumoniae*	3 (9)	5 (19)	0.28	2.46 (0.53–11.4)
In ICU at time of infection	6 (18)	9 (35)	0.15	2.47 (0.75–8.17)
Length of stay prior to infection (median [IQR[a]])	10 (0–24)	14 (7–30)	0.17	NA
Charlson score (median [IQR])	2.5 (2–4)	3.0 (2–5)	0.36	NA
Co-morbid condition[b]				
Dementia	1 (3)	0	1.00	0.42 (0.02–10.8)
Coronary artery disease	8 (24)	5 (19)	0.76	0.77 (0.22–2.72)
Congestive heart failure	2 (6)	5 (19)	0.22	3.81 (0.68–21.5)
Cerebrovascular disease	6 (18)	1 (4)	0.13	0.19 (0.02–1.66)
Diabetes mellitus	9 (26)	5 (19)	0.56	0.66 (0.19–2.28)
Chronic renal disease	8 (24)	6 (23)	1.00	0.98 (0.29–3.26)
Chronic liver disease	1 (3)	0	1.00	0.42 (0.02–10.8)
Cancer	14 (42)	16 (62)	0.19	2.29 (0.80–6.50)
Metastatic cancer	2 (6)	3 (12)	0.64	2.09 (0.32–13.5)
Hematopoietic tumor	9 (26)	10 (38)	0.40	1.74 (0.58–5.20)
Leukemia	8 (24)	8 (31)	0.57	1.44 (0.46–4.56)
Lymphoma	1 (3)	2 (8)	0.57	2.75 (0.24–32.1)
Infection and organism characteristics				
ESBL	29 (85)	22 (85)	1.00	1.05 (0.25–4.39)
E-type PFGE pattern	9 (26)	8 (31)	0.78	1.23 (0.40–3.82)
Nosocomial bloodstream infection	21 (62)	22 (85)	0.08	3.40 (0.96–12.1)
Isolation of a pathogen other than *K. pneumoniae* prior to acute period of infection	10 (29)	8 (31)	1.0	0.96 (0.52–1.80)
Antimicrobial treatment data				
Received effective therapy during acute period of infection	30 (88)	13 (50)	0.002	0.13 (0.04–0.49)
Did not receive effective therapy within 72 h of infection	8 (23)	14 (54)	0.03	3.80 (1.26–11.5)
Empiric antimicrobial therapy				
Expanded spectrum cephalosporin	20 (59)	12 (46)	0.43	0.60 (0.21–1.68)
β-lactam–β-lactamase inhibitor combination	7 (21)	9 (35)	0.25	2.04 (0.64–6.51)
Aminoglycoside	14 (41)	12 (46)	0.79	1.22 (0.44–3.43)
Fluoroquinolone	11 (32)	9 (35)	1.00	1.11 (0.38–3.26)
Carbapenem	21 (62)	12 (46)	0.30	0.53 (0.19–1.50)

[a] Interquartile range.
[b] Diagnosed either before or at the time of infection.
[c] Unless otherwise noted, results are given as numbers of patients, with percentages indicated in parentheses.
[d] NA, not applicable.

Among patients with BSI due to CAZ-R *K. pneumoniae*, predictors of in-hospital mortality are shown in Table 1. Neither the type of antibiotic used as empirical or definitive therapy nor treatment with monotherapy versus combination therapy was associated with mortality. The PFGE genotype of the pathogen was not associated with mortality.

Failure to receive effective antibiotics during the acute period of infection was predictive of increased mortality. Seventeen (28%) of 60 patients did not receive effective therapy during the entire empirical and definitive treatment periods. Among the 17 patients who did not receive effective therapy during the acute period of infection, 13 (76%) died; while among the 43 patients who received effective therapy, only 4 (9%) patients died (odds ratio [OR], 0.03, $P = 0.001$).

Among the 34 survivors, 30 (88%) received effective therapy during the acute period of infection (i.e., 2 days prior to the first positive blood culture to 5 days afterwards), while among the 26 patients who died, 13 (50%) received effective therapy during the acute period of infection (OR, 0.13; $P = 0.002$). Patients who did not receive effective therapy within 24 h or 48 h of infection were not at increased risk for death ($P = 0.79$ and 0.68, respectively). Notably, however, patients who did not receive effective therapy within 72 h after infection were at significantly increased risk for death compared to patients who received effective therapy within 72 h of the date of infection (OR, 3.80; 95% confidence interval [CI], 1.26 to 11.5; $P = 0.03$).

Candidate variables that were considered for inclusion in the final multivariable model included the following: cerebrovascular disease, history of cancer, history of congestive heart

failure, nosocomial infection, length of stay greater than 7 days, presence of a Foley catheter, and delay in initiation of effective antibiotic therapy for >72 h after infection. After forward stepwise selection, the only statistically significant independent predictor of mortality was delay in initiation of effective antibiotic therapy for >72 h after infection (OR, 3.32; 95% CI, 1.07 to 10.3; $P = 0.04$). The final model included this variable in addition to a history of congestive heart failure, which was not predictive of mortality (OR, 2.57; 95% CI, 0.42 to 15.86). When the analysis was restricted exclusively to ESBL-producing strains, results were similar.

DISCUSSION

This study demonstrated that, among patients with BSI due to CAZ-R *K. pneumoniae*, providing effective antibiotic therapy within 72 h of infection was associated with significantly improved patient survival. This finding demonstrates the importance of rapid determination of in vitro antimicrobial susceptibilities and of appropriately adjusting antimicrobial therapy based upon these results.

Paterson and colleagues examined the impact of delayed therapy on mortality among patients with bacteremia due to ESBL-producing *K. pneumoniae* (29). These investigators noted that, in bivariate analysis, failure to provide effective therapy in the first 5 days of bacteremia was associated with increased mortality (29). In contrast, our study included both ESBL- and non-ESBL-producing CAZ-R *K. pneumoniae*, and in multivariable analysis, we analyzed the impact of a delay in implementation of effective therapy on mortality. In addition, we analyzed a range of breakpoints for implementation of appropriate therapy. While patients who did not receive effective therapy within 24 or 48 h after infection were not at an increased risk for death, patients in whom effective therapy was delayed 72 h or more had an almost four-times-increased mortality risk. Thus, as a complementary finding to the Paterson study, we identified the initial 72 h of bacteremia as the critical period during which effective antimicrobial therapy for BSI due to CAZ-R *K. pneumoniae* needs to be implemented to improve survival.

Other investigators have underscored the clinical importance of rapidly implementing effective antibiotic therapy for severely ill patients with BSI (11, 13, 17, 19). In addition, Lautenbach et al. (16) studied the impact of the timing of effective antibiotic therapy on clinical outcomes of patients with both sterile and non-sterile site infections due to ESBL-producing *K. pneumoniae* and *E. coli* isolates. These investigators demonstrated the importance of administering effective therapy within 72 h after infection: among patients with mortality attributable to infection, only 20% received effective therapy within 72 h of infection, compared to 53% of survivors (16). Compared to the study by Lautenbach et al., the current study had several differences. This study included only patients with BSI and excluded patients with infections at nonsterile sites, included only multidrug-resistant *K. pneumoniae* strains (and excluded other types of multidrug-resistant *Enterobacteriaceae*), and included a larger number of ESBL-producing isolates than prior studies. Our results, however, were quite similar to those of Lautenbach et al. In the present study, we demonstrated that a delay in effective antibiotic therapy of >72 h in patients with BSI due to CAZ-R *K. pneumoniae* was associated with a >3-fold increase in mortality compared to patients receiving effective therapy within 72 h of the date of infection.

CAZ-R *K. pneumoniae* is increasing in prevalence, and infections caused by this organism present a therapeutic challenge (23). While expanded-spectrum cephalosporins remain an important choice for the treatment of many gram-negative infections, these agents are not appropriate choices for the treatment of CAZ-R *K. pneumoniae* BSI. Treatment failures with β-lactam–β-lactamase inhibitor combinations for ESBL-producing *Enterobacteriaceae* have been reported, even in the setting of in vitro susceptibility to these agents, thus limiting the utility of these agents (26, 35, 39). Currently, many consider carbapenems to be the treatment of choice for infections due to ESBL-producing CAZ-R *K. pneumoniae* (14, 26). However, widespread empirical use of carbapenems for suspected gram-negative bacteremia is not desirable, as overuse might facilitate the emergence and spread of carbapenem-resistant *Pseudomonas*, *Acinetobacter*, and *Enterobacteriaceae* (12). Our findings suggest that, among patients with BSI due to CAZ-R *K. pneumoniae*, empirical therapy with carbapenems is not necessarily required for a favorable clinical outcome. Adjusting empirical regimens to include carbapenems (or another active antibiotic) within 72 h after CAZ-R *K. pneumoniae* BSI, however, is critical.

Realistically, MICs are often not available within 72 h after culture. Risk-based assessments that utilize risk factors for infection due to multidrug-resistant pathogens can be used to improve the appropriate use of broad-spectrum agents during the early empirical stages of therapy until MICs are available (2). Another concern is that many laboratories still do not routinely test for ESBL production among gram-negative isolates (4, 30). Among laboratories that perform ESBL testing, current methods for detection of multidrug resistance and confirmation of ESBL production often take at least 72 h to complete. Tests that provide more rapid confirmation of cephalosporin resistance and ESBL production are needed, as they will facilitate the rapid administration of effective therapy and will help to limit the overuse of empirical broad-spectrum antibiotics. One example of a rapid ESBL test is the direct ESBL test, in which samples from blood cultures are directly plated onto agar plates containing cefotaxime and ceftazidime disks, with and without clavulanate (25). This test has been demonstrated to have 100% sensitivity, 98% specificity, and 93% positive predictive value for detecting ESBL production in less than 72 h (25).

Our study has several limitations. First, because all study patients were hospitalized at a single tertiary medical center, the results may not be generalizable to other institutions. Second, only 19 (15%) of the study pathogens were non-ESBL producers; thus, we were unable to analyze this non-ESBL group separately. However, since the majority of isolates were ESBL producers, we were able to perform analyses specific to the ESBL group. Third, even though this study is one of the largest reported series of consecutive patients with BSI due to CAZ-R *K. pneumoniae*, our power to detect meaningful associations was limited by small sample size. Finally, selection of and response to individual antimicrobial therapies is likely to be influenced by patient condition, underlying diseases, and

nonantimicrobial supportive therapy, and although attempts were made to account for bias associated with these variables, confounding variables might not have been completely controlled for in the final multivariable model.

BSI due to CAZ-R *K. pneumoniae* was associated with a >40% in-hospital mortality rate at our institution. In the current study, the implementation of effective therapy within 72 h of infection was associated with improved survival. Prompt identification of these multidrug-resistant pathogens and knowledge of both their antimicrobial susceptibility patterns and the presence of ESBL production will help clinicians to optimize antimicrobial therapy and improve patient outcomes. Future studies of BSI due to *K. pneumoniae* should focus on methods for rapid determination of antimicrobial susceptibility and ESBL production, shortening the time to administration of effective therapy, and developing new and effective strategies for treatment.

ACKNOWLEDGMENTS

K.S.K. was supported by grant K23 AG23621-01A1 from the National Institute of Aging. This study was supported by an unrestricted educational grant from Merck.

Y.C. received grants, honoraria, travel support, and other forms of financial support from the following companies: Bayer Corp., Biomedicum Ltd, Bristol-Myers Squibb, Merck & Co., Inc., Neopharm Ltd, Pfizer Pharmaceuticals, Teva Ltd, Vicuron Pharmaceuticals, and XTL Pharmaceuticals Ltd.

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