Epidemiology and Clinical Outcomes of Patients with Carbapenem-Resistant *Klebsiella pneumoniae* Bacteriuria

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Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria is a frequently encountered clinical condition, but its clinical impact is unknown. We conducted a retrospective cohort study to define the epidemiology and outcomes for patients with CRKP bacteriuria. Patients with positive urine cultures for CRKP were classified as having asymptomatic bacteriuria (ASB) or symptomatic urinary tract infection (UTI). Among 105 patients with CRKP bacteriuria, 80% (84/105 patients) and 20% (21/105 patients) had ASB and UTI, respectively. Older age ($P = 0.002$) and higher Charlson's comorbidity index scores ($P = 0.001$) were associated with ASB. The median duration of hospitalization prior to CRKP bacteriuria was significantly longer for patients with ASB versus UTI (8.5 versus 2 days; $P = 0.05$). In multivariate analysis, male sex (odds ratio [OR], 4.69 [95% confidence interval (CI), 1.44 to 15.26]; $P = 0.01$), solid-organ transplantation (OR, 4.50 [95% CI, 1.39 to 14.52]; $P = 0.01$), and neurogenic bladder (OR, 18.62 [95% CI, 1.75 to 197.52]; $P = 0.01$) were independently associated with UTI. Ten percent (8/84) of the patients with ASB received antimicrobial therapy. The treatment success rate for patients with UTIs was 90% (19/21 patients), including all patients who received doxycycline ($n = 9$). The overall 30-day mortality rate was 6% (6/105 patients); the deaths were unrelated to CRKP infections. Secondary CRKP infections, including UTIs, were notably absent among patients with ASB who were followed for 90 days. In conclusion, identification of CRKP in the urine was most commonly associated with ASB and did not lead to subsequent infections or death among asymptomatic patients. Factors associated with UTIs included male sex, solid-organ transplantation, and neurogenic bladder. Doxycycline may be an effective therapy for CRKP UTIs.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a major nosocomial pathogen in the United States and worldwide (1). Carbapenem resistance is typically mediated by production of carbapenem-hydrolyzing enzymes, with *Klebsiella pneumoniae* carbapenemases (KPCs) being the most common (2). Few antimicrobial agents retain *in vitro* activity against CRKP, and optimal treatment strategies are thus poorly defined. As a result, health care-associated infections due to CRKP are associated with poor patient outcomes (3). Urinary tract infections (UTIs) are the most common health care-associated infections in the United States (4), and the prevalence of UTIs due to antimicrobial-resistant Gram-negative pathogens has increased precipitously over the past decade (5).

Indeed, *K. pneumoniae* is the second leading cause of health care-associated UTIs, and CRKP is increasingly implicated (5). Nevertheless, the clinical importance of and the need for antimicrobial therapy against CRKP isolated from urine cultures from asymptomatic patients are unknown. In this setting, judicious use of a dwindling antibiotic armamentarium is balanced with the risks of disseminated infections caused by these extensively drug-resistant (XDR) bacteria (6). To date, clinical reports of successful treatment approaches have not differentiated outcomes among patients with asymptomatic bacteriuria (ASB) and symptomatic UTIs (7, 8). Therefore, rates of urinary colonization and long-term outcomes for patients with CRKP bacteriuria are undefined. To address these shortcomings and to improve management strategies against CRKP, we aimed to define the epidemiology and long-term clinical outcomes for patients with CRKP bacteriuria. Moreover, we sought to identify factors associated with CRKP UTIs among patients with bacteriuria.

MATERIALS AND METHODS

Study design and patients. We conducted a retrospective cohort study of patients with CRKP bacteriuria. Adult subjects with bacteriuria involving ertapenem-nonsusceptible *K. pneumoniae* were identified from the microbiology records at a tertiary medical center in Pittsburgh, Pennsylvania, between January 2009 and October 2012 (3). The first urine culture yielding CRKP was considered the index culture for each patient. Patients with CRKP isolated from a nonurinary site within 30 days before or 5 days after the index culture were excluded. The study was approved by the institutional review board at the University of Pittsburgh.

Definitions. UTI was defined as patients having a positive urine culture growing $\geq 1,000$ CFU/ml of CRKP and having ≥ 1 of the following symptoms documented: dysuria, increased urinary frequency, flank pain or tenderness, fevers, and/or altered mental status without an alternative etiology. Presentations with a positive urine culture with CRKP without evidence of symptoms were classified as ASB. Positive cultures were classified as hospital-acquired, health care-associated, or community-acquired cases by using standard definitions previously reported (9).

Outcome measures. The primary clinical outcome of the study was the development of secondary health care-associated infections due to CRKP within 90 days after the index urine culture. Healthcare-associated infections were defined according to standardized definitions from the Centers for Disease Control and Prevention/National Healthcare Safety Network (10). Secondary outcomes included death, microbiological eradication.

Received 7 November 2013 Returned for modification 8 December 2013

Accepted 9 March 2014

Published ahead of print 17 March 2014

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doi:10.1128/AAC.02445-13

ication, and hospital readmission within 30 days. For patients discharged from the hospital prior to 30 days, subsequent hospital records and the Social Security Death Index were assessed to determine patient survival. For patients with UTIs, clinical responses to antimicrobial therapy were defined as (i) cure, i.e., resolution of clinical signs and symptoms of UTI and a negative urine culture, (ii) presumed cure, i.e., resolution of clinical signs and symptoms of UTI without repeat urine cultures, or (iii) failure, i.e., persistent growth of CRKP in urine cultures, no improvement in signs and symptoms of infection, or recurrence of UTI with CRKP within 30 days after the initial resolution.

Statistical analyses. Statistical analyses were performed with SPSS statistical software (version 19; SPSS Inc., Chicago, IL). Categorical variables were evaluated by using the χ^2 test or Fisher's exact test, as appropriate. The Mann-Whitney *U* test was used to compare continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined by logistic regression analysis. Variables associated with UTI with *P* values of ≤ 0.15 in univariate analyses were included in a multivariate logistic regression model using backward selection procedures. All *P* values were two-tailed, and *P* values of ≤ 0.05 were considered statistically significant.

RESULTS

A total of 133 patients with CRKP bacteriuria were identified during the study period. Twenty-eight cases were excluded due to concomitant cultures growing CRKP from another site (*n* = 23) or lack of medical records (*n* = 5). Of the cases included, 20% of patients (21/105 patients) and 80% of patients (84/105 patients) were classified as having UTI and ASB, respectively. Fifty percent of cases (53/105 cases) were hospital acquired, and 50% (52/105 cases) were health care associated; no cases were community acquired.

Manifestations of CRKP UTI. Among 21 patients with UTIs, 7 had fever with no other reason for the febrile illness, 5 had fever and altered mental status, 3 had altered mental status with no alternative explanation, 2 had fever and dysuria, 2 had dysuria alone, and 1 patient each had dysuria with flank pain and generalized weakness with fevers. UTIs were considered to be complicated for 14% of patients (3/21 patients) due to pyelonephritis (*n* = 2) or prostatitis (*n* = 1). In urinalyses, patients with UTIs were more likely to have urinary white blood cell (WBC) levels of ≥ 150 cells/ μ l (57% versus 32%; *P* = 0.04), positive leukocyte esterase findings (100% versus 73%; *P* = 0.005), and $\geq 100,000$ CFU/ml CRKP (100% versus 67%; *P* = 0.001). On the other hand, there was no difference in the rates of leukocytosis (serum WBC levels of $\geq 11,000$ cells/ μ l) among patients with UTI (29%) versus ASB (35%; *P* = 0.79).

Factors associated with UTI. Baseline demographic and clinical characteristics are shown in Table 1. In univariate analyses, male sex (*P* = 0.0004), neurogenic bladder (*P* = 0.001), and suprapubic catheter use (*P* = 0.03) were associated with UTI, while older age (*P* = 0.002) and a higher median Charlson's comorbidity index score (*P* = 0.001) were associated with ASB. By multivariate logistic regression, male sex (odds ratio [OR], 4.69 [95% confidence interval (CI), 1.44 to 15.26]; *P* = 0.01), solid-organ transplantation (OR, 4.50 [95% CI, 1.39 to 14.52]; *P* = 0.01), and neurogenic bladder (OR, 18.62 [95% CI, 1.75 to 197.52]; *P* = 0.01) were factors independently associated with UTI. Transplant types among those with UTIs included liver (*n* = 4), kidney (*n* = 3), multivisceral (*n* = 2), lung (*n* = 1), and heart (*n* = 1). The median duration of hospitalization prior to CRKP bacteriuria was shorter for patients with UTI (2 days [range, 1 to 79 days]) than for patients with ASB (8.5 days [range, 1 to 346 days]; *P* = 0.05).

Antimicrobial therapy and outcomes for patients with CRKP UTIs. All patients with UTIs were treated with systemic antimicrobials for a median duration of 13 days (range, 6 to 15 days). The overall rate of cure was 90% (19/21 patients); 48% of patients (10/21 patients) had a presumed cure. Doxycycline was used to treat 9 patients, and all experienced a clinical cure (4 were presumed). The associated isolates were either susceptible (*n* = 6) or intermediately resistant (*n* = 3) to doxycycline by the Kirby-Bauer disc diffusion method. The remaining patients with clinical cures received a carbapenem (*n* = 4), cefepime (*n* = 2), ciprofloxacin (*n* = 2), amikacin (*n* = 1), or piperacillin-tazobactam (*n* = 1). With the exception of one patient receiving piperacillin-tazobactam, the organism tested as susceptible to the given agent based on susceptibility breakpoints at the time of culture. It is notable that, among patients receiving a carbapenem, the associated isolates were susceptible to imipenem-cilastatin but resistant to ertapenem. Failures occurred in one patient with neurogenic bladder who received colistin for 15 days and in another patient with prostatitis who received 3 doses of fosfomycin. Thirty-three percent (8/21) of the patients had an indwelling urinary catheter at the time of UTI, which was managed with catheter exchange (*n* = 4), removal (*n* = 2), or antimicrobial treatment alone (*n* = 2). No secondary infections were observed within 90 days after the index culture, and all patients survived at hospital discharge and at 30 days. The overall median length of stay was 13 days (range, 1 to 143 days). Thirty-eight percent (8/21) of the patients with UTI were readmitted within 30 days for unrelated medical issues.

Clinical management and outcomes for patients with ASB. Therapeutic interventions for patients with ASB primarily included systemic antimicrobial treatment (10% [8/84 patients]) and urinary catheter removal or exchange (67% [26/39 patients]). Microbiological eradication within 30 days was documented for 56% of patients (47/84 patients), and rates did not vary between patients with (65% [22/34 patients]) or without (50% [25/50 patients]) these interventions (*P* = 0.26). Seven percent of patients with ASB (6/84 patients) died within 30 days; all deaths were due to underlying conditions and not infectious causes. Secondary CRKP infections, including UTIs, within 90 days after the index culture were notably absent among surviving patients. Thirty-one percent (26/84) of the patients were readmitted within 30 days for unrelated medical issues.

DISCUSSION

Invasive infections due to CRKP are associated with substantial morbidity and mortality rates, yet the clinical significance of isolating CRKP from the urine is unknown. To our knowledge, this study is the first to describe the epidemiology and long-term clinical outcomes of patients with CRKP bacteriuria. We identified two particularly noteworthy findings. First, isolation of CRKP from the urine was most commonly associated with ASB, not UTIs. In fact, the overwhelming majority of patients (80%) at our center with CRKP bacteriuria did not manifest clinical symptoms consistent with UTIs. Second, patients with CRKP bacteriuria did not develop secondary infections, and CRKP-associated death was notably absent. Even among the 72% (76/105) of the patients managed without antimicrobial therapy, adverse outcomes within the 90-day follow-up period were not present. Taken together, our findings provide new insights into the clinical manifestations of CRKP bacteriuria and are useful for devising management strategies against XDR pathogens.

TABLE 1 Baseline demographic and clinical characteristics of patients with CRKP bacteriuria

	Data for patients with:		Univariate <i>P</i>	Multivariate <i>P</i>	OR (95% CI)
Variable	ASB (<i>n</i> = 84) ^{<i>a</i>}	UTI (<i>n</i> = 21)			
Demographics					
Age (median [range]) (yr)	62 (20–91)	51 (24–67)	0.002	0.01	4.69 (1.44–15.26)
No. (%) of males	24 (28)	15 (71)	0.0004		
No. (%) of patients residing in intensive care unit	14 (17)	0	0.06		
Duration of hospitalization prior to positive urine culture (median [range]) (days)	8.5 (1–346)	2 (1–79)	0.05		
No. (%) of patients with underlying disease/condition ^{<i>b</i>} :					
Surgery within past 30 days	29 (34)	9 (43)	0.61	0.01	4.50 (1.39–14.52)
Myocardial infarction	14 (17)	3 (14)	1.00		
Congestive heart failure	14 (17)	2 (9)	0.51		
Peripheral vascular disease	3 (3)	3 (14)	0.09		
Dementia	7 (8)	1 (5)	0.69		
Chronic obstructive pulmonary disease	18 (21)	2 (9)	0.35		
Renal disease, moderate to severe	17 (20)	0	0.04		
Solid-organ cancer, no metastasis	2 (2)	0	1.00		
Solid-organ cancer, metastasis	7 (8)	0	0.34		
Cerebrovascular accident	11 (13)	3 (14)	1.00		
Liver disease, mild	1 (1)	0	1.00		
Liver disease, moderate to severe	11 (13)	0	0.11		
Diabetes mellitus	38 (45)	9 (43)	1.00		
Diabetes mellitus without complications	27 (32)	3 (14)	0.17		
Diabetes mellitus with end-organ damage	11 (13)	6 (28)	0.10		
Immunosuppression ^{<i>c</i>}	33 (39)	11 (52)	0.32		
Neutropenia	1 (1)	0	1.00		
Transplant recipient	24 (28)	11 (52)	0.06		
Charlson’s comorbidity index score (median [range]) ^{<i>d</i>}	4 (0–13)	2 (0–7)	0.001		
Acquisition type (no. [%] of patients)					
Hospital acquired	45 (53)	8 (38)	0.23		
Health care-associated	39 (46)	11 (52)	0.80		
No. (%) of patients with urological condition/disease:					
Procedure within 180 days	4 (5)	3 (14)	0.41	0.01	18.62 (1.75–197.52)
Neurogenic bladder	1 (1)	5 (24)	0.001		
Indwelling Foley catheter	47 (56)	7 (33)	0.08		
Suprapubic catheter	0	2 (9)	0.03		
Ureteral stent	3 (3)	2 (9)	0.58		
Renal stone	4 (5)	2 (9)	0.59		
Nephrostomy tube	2 (2)	1 (5)	0.99		
Polymicrobial urine culture	34 (40)	5 (24)	0.20		

^a ASB, asymptomatic bacteriuria; OR, odds ratio; CI, confidence interval.^b No patient had connective tissue disease, peptic ulcer disease, hematological malignancy, or HIV infection.^c An immunocompromised state was defined as the presence of neutropenia, HIV infection with CD4⁺ cell counts of ≤200 cells/μl, or receipt of steroids or other immunosuppressive agents in the 30 days prior to the infection.^d Variables were defined according to the standard Charlson's comorbidity index.

UTIs account for up to 45% of nosocomial infections in the United States and are increasingly caused by XDR bacteria (5, 11). Factors associated with CRKP UTIs identified in our study corroborate those reported earlier (12–14) and include male sex, solid-organ transplantation, and neurogenic bladder. These factors are implicated for UTIs caused by other pathogens and are generally considered to be nonmodifiable. Thus, limiting patient exposure to the organisms in the hospital environment through strict infection control measures is of primary importance (15). Through this, rates of ASB also may be reduced. The median duration of hospitalization was significantly longer for patients with

ASB than for those with UTI. Rates of death and hospital readmission did not differ between patients with ASB versus UTI. In fact, our 30-day mortality rate was lower than those reported previously (11, 16), and no patient died due to CRKP infection. These findings emphasize the population most affected by CRKP bacteriuria, i.e., chronically debilitated, hospitalized patients who die of unrelated causes (11). The absence of community-acquired cases of CRKP bacteriuria further supports the contention that this organism is predominantly a nosocomial pathogen; however, continued surveillance efforts are needed, given the proliferation of other drug-resistant pathogens in the community setting (3, 17).

Among patients with CRKP bacteriuria, 3 to 6% develop bacteremia within 30 days (16); however, rates among patients with ASB are unknown. The onset of other secondary infections and the long-term outcomes of patients with CRKP bacteriuria have not been reported. In this regard, our study is unique not only for distinguishing ASB from UTI but also for the insights into the long-term outcomes of patients with CRKP it provides. Interestingly, no patient in our study developed secondary infections due to CRKP. There are several plausible explanations for this finding. First, among patients with UTIs, antimicrobial therapy was effective. The overall rate of treatment success in our study was 90% and, while our small sample precludes us from drawing definitive conclusions, doxycycline may be a viable option for treating CRKP if the organism tests as susceptible. For isolates that are susceptible to the aminoglycosides, the use of gentamicin results in significant *in vitro* killing of CRKP (18) and microbiological clearance from the urine for patients with bacteriuria (16). Fosfomycin, polymyxin B (or colistin), and the β -lactams are second-line alternatives that warrant further investigation (8, 16). In fact, 7 patients in our study were treated successfully with a β -lactam antibiotic, likely owing to the fact that these agents achieve high urinary concentrations that may overcome the underlying mechanisms of drug resistance (19, 20). It should also be noted that the median treatment duration for patients in our study was 13 days. It is conceivable that prolonged therapy contributed to the absence of secondary infections, which merits further investigation.

Next, we excluded patients with concomitant CRKP cultures from nonurinary sites. In doing so, we were able to study CRKP bacteriuria directly among patients at our center. However, patients who are colonized or infected at multiple sites are more likely to develop secondary infections, resulting in worse clinical outcomes (21). This is particularly true among hospitalized patients with asymptomatic CRKP rectal colonization. Borer and colleagues reported a 9% incidence of CRKP infections, occurring a median of 20 days after the identification of rectal colonization (22). The incidence of infection following rectal colonization may be as high as 46% among patients in the intensive care unit (23). Taken in context, the data suggest that urinary colonization represents a unique reservoir for CRKP, and patient management should be tailored accordingly.

Finally, of patients with ASB who had urinary catheters, 55% (26/47 patients) were managed with catheter removal or exchange, which might have directly prevented secondary infections (24). The rates of microbiological eradication were higher among patients with catheter removal or exchange than among those with retained devices (65% versus 50%; $P = 0.26$). Although this was not statistically significant, it may represent a meaningful finding for patient care. Future studies that are designed to assess rates of pathogen eradication and are controlled for sampling biases may provide meaningful conclusions for the management of patients with CRKP bacteriuria. Overall, 72% of patients (34/47 patients) with indwelling catheters had the devices removed in our study. While this is a study limitation, it also emphasizes the likely beneficial role of catheter removal in preventing subsequent infections. Another 8 patients were treated with antimicrobial therapy; however, 59% of subjects (50/84 subjects) in our study were managed without antimicrobials or catheter removal. This suggests that ASB due to CRKP is similar to that of other *Enterobacteriaceae* and, despite high levels of drug resistance, the organism is unlikely to cause infection even if untreated (25).

Taken together, our data suggest a number of key implications for the management of CRKP bacteriuria. Foremost, it is practical to suggest that antimicrobial therapy should be reserved for patients with UTIs, who represent the minority of patients with CRKP bacteriuria. Restricting therapy to such patients has important ramifications for antimicrobial stewardship and may help to preserve the few therapeutic options remaining against CRKP. Patients at highest risk for UTIs are male, are solid-organ transplant recipients, or have neurogenic bladder, for which doxycycline may be a viable treatment if the organism has retained susceptibility to the agent. As in all retrospective studies, our data collection was limited to available data and patient management was not standardized. The classification of UTI and ASB was determined from available data, and the findings may not reflect the epidemiology at other centers or in prospective trials. Nevertheless, the absence of secondary infections among patients with CRKP bacteriuria is encouraging and warrants further investigation.

ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Center for Advanced Translational Sciences of the National Institutes of Health (NIH) under award number KL2 RR024154 (to R.K.S.). Y.D. was supported in part by a research grant from the NIH (grant R21 AI107302).

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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