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# Predictors of Carbapenem-Resistant *Klebsiella pneumoniae* Acquisition among Hospitalized Adults and Effect of Acquisition on Mortality▽

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**Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an emerging nosocomial pathogen. Little is known about its risk factors or mortality. We performed a case-case-control study to assess the risks for CRKP isolation and a retrospective cohort study to assess mortality in three groups of hospitalized adults: (i) patients from whom CRKP was isolated, (ii) patients from whom carbapenem-susceptible *Klebsiella* spp. (CSKS) were isolated, and (iii) controls from whom no *Klebsiella* spp. were isolated. After adjustment for length of stay (LOS), the demographics, comorbidities, and exposures of each case group were compared with those of the controls. Significant covariates were incorporated into LOS-adjusted multivariable models. In the mortality study, we evaluated the effect of CRKP on in-hospital death. There were 48 patients with CRKP isolation (21 died [44%]), 56 patients with CSKS isolation (7 died [12.5%]), and 59 controls (1 died [2%]). Independent risk factors for CRKP isolation were poor functional status (odds ratio [OR], 15.4; 95% confidence interval [CI], 4.0 to 58.6; $P < 0.001$); intensive care unit (ICU) stay (OR, 17.4; 95% CI, 1.5 to 201.9; $P = 0.02$); and receipt of antibiotics (OR, 4.4; 95% CI, 1.0 to 19.2; $P = 0.05$), particularly fluoroquinolones (OR, 7.2; 95% CI, 1.1 to 49.4; $P = 0.04$). CRKP was independently associated with death when patients with CRKP were compared with patients with CSKS (OR, 5.4; 95% CI, 1.7 to 17.1; $P = 0.005$) and with controls (OR, 6.7; 95% CI, 2.4 to 18.8; $P < 0.001$). After adjustment for the severity of illness, CRKP isolation remained predictive of death, albeit with a lower OR (for the CRKP group versus the CSKS group, OR, 3.9; 95% CI, 1.1 to 13.6; and $P = 0.03$; for the CRKP group versus the controls, OR, 5.0; 95% CI, 1.7 to 14.8; and $P = 0.004$). CRKP affects patients with poor functional status, an ICU stay, and antibiotic exposure and is an independent predictor of death.**

Carbapenem resistance in *Klebsiella pneumoniae* is a relatively recent phenomenon that was first reported a decade ago (17) and that is a rare phenotype in most geographical areas. Initial isolates expressed their resistance phenotype by a number of mechanisms, including the loss of outer membrane proteins and the production of an extended-spectrum β-lactamase (ESBL) (17). Subsequently, carbapenemase-producing strains of *K. pneumoniae* emerged: some, reported primarily from Greece, produced metallo-β-lactamases (10, 11), while, in addition, a novel enzyme family, KPC, was described in the United States and caused outbreaks, primarily in New York (4, 6, 26–28).

Carbapenamase-associated resistance is alarming for a number of reasons. The presence of these enzymes, in addition to signifying resistance to carbapenems, the antibiotic class of last resort for the treatment of infections caused by resistant gram-negative pathogens, is also associated with additional mechanisms of resistance to other antibiotic classes that together result in microbes that are highly multidrug resistant and in some cases panresistant. Moreover, both metallo-β-lactamases and KPC enzymes have been implicated in the epidemic spread of carbapenem-resistant *Klebsiella*, and the bacteria producing these enzymes have been isolated extensively from the environment in intensive care units (ICUs) where outbreaks have occurred (6, 7, 26). In addition, the KPC gene is plasmid associated and has been implicated in outbreaks caused by other members of the family *Enterobacteriaceae*, in addition to *K. pneumoniae* (5, 19). Finally, the ability of widely used automated susceptibility testing systems to detect KPC-mediated resistance in *K. pneumoniae* is limited (25).

We have recently described the emergence of KPC-producing carbapenem-resistant *K. pneumoniae* (CRKP) strains at our institution (15). Similar phenomena have been observed elsewhere in Israel (23). Little has been reported, however, regarding the risk factors for the acquisition of CRKP (1, 9, 14), and no studies have investigated its effect on mortality. In the study described in this paper we attempted to determine the factors predictive of CRKP isolation from hospitalized adults and its attributable mortality.

## MATERIALS AND METHODS

**Study setting and patient population.** The Tel Aviv Sourasky Medical Center is a 1,200-bed, tertiary-care teaching hospital with approximately 100,000 annual admissions and 95,000 clinical microbiological cultures processed annually. The study population included adults hospitalized at the medical center from 2003 through 2006. Three study groups were defined: the case 1 group consisted of patients from whom a CRKP strain was isolated during hospitalization, the case 2 group consisted of patients from whom carbapenem-susceptible *Klebsiella* spp. (CSKS) were isolated, and the control group consisted of patients with no clinical cultures positive for *K. pneumoniae* during their hospitalization. We studied the attainable records of all patients meeting the criteria for the case 1 group, while

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an approximately equal number of patients were then selected to comprise both the case 2 group and the controls, chosen at random from lists of patients meeting the criteria for each group.

**Microbiologic methods.** Identification and antimicrobial susceptibility testing were performed by the clinical microbiology laboratory using the Vitek 2 system (bioMérieux, St. Louis, MO). Carbapenem (imipenem and/or meropenem) resistance was confirmed by disk diffusion, according to established methods and breakpoints (8), or by the Etest method, according to the manufacturer's instructions (AB Biodisk, Solna, Sweden).

**Study design.** We conducted a two-part analysis: a retrospective case-case-control study (13) in which the CRKP group and the CSKS group were compared to the controls to determine the factors associated with the isolation of CRKP and CSKS, respectively, and a retrospective cohort study to determine the in-hospital mortality associated with the isolation of CRKP. For the latter analysis we compared the patients with CRKP with the patients in the two reference groups: those with CSKS and those from whom *K. pneumoniae* was not isolated. This method of analysis allowed us to compare the mortality associated with CRKP isolates to that associated with carbapenem-susceptible isolates, assessing the effect of replacing infections with susceptible strains by those with resistant strains; it also allowed us to compare the mortality associated with CRKP isolates to that of the controls from whom *K. pneumoniae* was not isolated, assessing the effect of the addition of infections that would not have occurred otherwise (12). Finally, we evaluated the effect of confounding by the severity of illness on the mortality analysis.

**Data abstraction.** Data were extracted from the patients' medical records and from hospital computerized databases according to a preprepared questionnaire. Cases and controls were compared regarding demographics (age and sex), comorbid conditions (diabetes mellitus, cardiovascular disease, pulmonary disease, renal disease, hepatic disease, central nervous system disease, malignancy, receipt of an organ transplantation, and the overall number of comorbid conditions), treatments and procedures prior to a positive culture (immunosuppressive therapy, placement of a central venous or a urinary catheter, stay in an ICU, dialysis, instrumentation [including cardiovascular and endovascular catheterization, endoscopic procedures, and tracheostomy], surgery, and mechanical ventilation), admission from home versus from an institution, the source of a sample positive by culture, functional status on admission (requiring assistance in activities of daily living or fully independent, as determined by the chart reviewer), the recent receipt of antibiotics (received on admission and/or after admission, before a positive culture was obtained), the classes of antibiotics received before a positive culture was obtained, and the level of underlying comorbidity (as indicated by the Charlson weighted index of comorbidity) (16). The Charlson index was dichotomized into high (>3, indicating a high degree of underlying comorbidity) and low (≤2, indicating a lower degree of underlying comorbidity) (16). Patients were assigned a "high invasive device score" if they were mechanically ventilated or if they had both a Foley catheter and a central venous line. The date of study enrollment for the case patients was the date that *Klebsiella* was first obtained by culture, and for the controls it was a date during their hospitalization which was determined at random. To control for the severity of illness at the time of admission, patients were assigned a score by using a modified McCabe scale (1, expected to live more than 2 years; 2, expected to die within 2 years; 3, expected to die within 2 months) (18).

**Statistical analysis. (i) Case-case-control study.** In order to control for differences in the length of stay prior to enrollment between the case groups and the controls, all analyses were performed with adjustment for time. We compared each case group to the control group using bivariable logistic regression models adjusted for time at risk (length of stay prior to a positive culture for the case groups and time before entry into the study for the controls). Variables with a $P$ value of ≤0.1 in the bivariate model were then incorporated into a multivariable logistic regression model, which also controlled for length of stay prior to a positive culture and which was built by the stepwise selection procedure. Variables with a $P$ value of ≤0.05 were retained in the final model.

**(ii) Outcome study.** In order to determine the risk factors for in-hospital mortality, we compared patients who died in the hospital with those who lived to discharge for the variables listed above. Continuous variables were compared by the Wilcoxon rank-sum test. Dichotomous variables were compared by Fisher's exact test. A multivariable regression model was constructed by using a stepwise selection procedure, incorporating variables with a $P$ value of ≤0.1 on univariate analysis. Covariates significant in this model were incorporated into two separate additional multivariable models to assess the effect of case status on mortality. In the first model the patients with CRKP were included along with those with CSKS, with "carbapenem-resistant *Klebsiella*" included as a covariate. In the second model the patients with CRKP were compared with the controls, again with "carbapenem-resistant *Klebsiella*" included as a covariate. Variables with a $P$ value of ≤0.05 were retained in the final models.

Last, in order to assess for confounding by severity of illness on admission, we incorporated the McCabe score variable into each of the final mortality models obtained and recorded the effect of CRKP isolation on the odds ratio (OR).

TABLE 1. Sources of samples for culture[a]

| Source | % of patients | |
|---|---|---|
| | CSKS | CRKP |
| Unknown or other | 0 | 6 |
| Blood/intravenous line | 15 | 13 |
| Respiratory | 9 | 8 |
| Urine | 55 | 40 |
| Wound/skin/soft tissue | 15 | 19 |
| Abdomen | 7 | 15 |

[a] $P = 0.58$ by Kruskall-Wallis test.

## RESULTS

The records of 48 adult patients from whom CRKP was obtained from clinical cultures between September 2003 and December 2006 were reviewed and analyzed as part of the CRKP group. For 35 of these patients the index sample positive by culture was obtained in 2006. Fifty-six patients from whom CSKS were obtained from cultures of clinical samples (54 patients with *K. pneumoniae*, 2 patients with *K. oxytoca*) were enrolled and are referred to as the CSKS group. Fifty-nine patients with no cultures that grew *Klebsiella* spp. were enrolled as controls. The predominant site of *K. pneumoniae* isolation in both case groups was urine ($P = 0.59$ between groups) (Table 1). The demographic and clinical characteristics of the patients enrolled in the study are summarized in Table 2. The McCabe score was assigned to all but seven patients, whose records were no longer available at the time of subsequent chart review.

**Risk factor analysis. (i) Case-control study 1: CRKP group versus controls.** The length of stay prior to study enrollment was significantly higher for the cases (median, 19.5 days; interquartile range [IQR], 8.5 to 37.5 days) than for the controls (median, 2 days; IQR, 1 to 4 days; $P < 0.001$). All comparisons were therefore time adjusted. The median age was significantly higher among the cases (median age, 77 years; IQR, 63 to 83 years) than among the controls (median age, 68 years; IQR, 53 to 77 years) ($P = 0.02$). There was no difference between the groups in the breakdown by sex. Among the cases there was a greater proportion of patients with neurologic disease (OR, 6.7; 95% confidence interval [CI], 2.1 to 21.4; $P < 0.001$), admission from an institution (OR, 9.9; 95% CI, 2.7 to 36.4; $P < 0.001$), poor functional status (OR, 14.3; 95% CI, 4.2 to 48.5; $P < 0.001$), a high Charlson comorbidity index score (OR, 3.0; 95% CI, 1.0 to 8.9; $P = 0.05$), a high invasive device score (OR, 5.7; 95% CI, 1.5 to 22.1; $P = 0.01$), having been in the ICU (OR, 9.6; 95% CI, 1.0 to 92.8; $P = 0.05$), and having undergone a nonsurgical invasive procedure (OR, 12.5; 95% CI, 1.3 to 124.8; $P = 0.03$). In addition, a greater proportion of cases than controls had received antibiotics prior to a positive culture (OR, 6.2; 95% CI, 1.9 to 20.3; $P = 0.003$). Investigation into the classes of antibiotics received revealed that the cases had received more of each individual class of antibiotic exam-

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TABLE 2. Univariate predictors of *Klebsiella* sp. isolation

| Covariate | No. (%) of patients[a] | | | Time-adjusted comparison of patients with CRKP and controls | | Time-adjusted comparison of patients with CSKS and controls | |
|---|---|---|---|---|---|---|---|
| | *Klebsiella* cases | | | | | | |
| | Carbapenem resistant ($n$ = 48) | Carbapenem susceptible ($n$ = 56) | Controls ($n$ = 59) | OR (95% CI) | $P$ | OR (95% CI) | $P$ |
| Male sex | 23 (48) | 18 (32) | 24 (41) | 0.9 (0.3–2.6) | 0.86 | 0.7 (0.3–1.6) | 0.38 |
| Diabetes mellitus | 15 (31) | 15 (27) | 18 (31) | 1.1 (0.4–3.2) | 0.87 | 0.9 (0.4–2.2) | 0.87 |
| Cardiovascular disease | 29 (60) | 35 (64) | 64 (64) | 1.3 (0.4–3.6) | 0.68 | 0.9 (0.4–1.9) | 0.72 |
| Pulmonary disease | 9 (19) | 9 (16) | 14 (24) | 0.2 (0.1–1.1) | 0.07 | 0.6 (0.2–1.5) | 0.28 |
| Renal disease | 15 (31) | 10 (18) | 12 (20) | 1.1 (0.4–3.6) | 0.82 | 0.9 (0.4–2.4) | 0.86 |
| Liver disease | 2 (4) | 4 (7) | 3 (5) | 0.2 (0.02–3.0) | 0.25 | 1.3 (0.3–6.4) | 0.75 |
| Neurologic disease | 20 (42) | 16 (29) | 10 (17) | 6.7 (2.1–21.4) | 0.001 | 2.4 (1.0–6.0) | 0.06 |
| Malignancy | 15 (31) | 19 (35) | 9 (15) | 1.7 (0.5–5.7) | 0.37 | 3.1 (1.3–7.9) | 0.02 |
| Immunosuppression | 11 (23) | 8 (15) | 4 (7) | 1.9 (0.4–8.0) | 0.40 | 2.3 (0.6–8.2) | 0.21 |
| High no. of comorbidities | 19 (40) | 20 (36) | 19 (32) | 1.3 (0.4–3.5) | 0.68 | 1.3 (0.6–3.0) | 0.48 |
| Admission from institution | 15 (31) | 9 (16) | 6 (10) | 9.9 (2.7–36.4) | <0.001 | 1.7 (0.5–5.4) | 0.37 |
| Transplantation | 2 (4) | 0 (0) | 0 (0) | | | | |
| Poor functional status | 29 (62) | 23 (41) | 8 (14) | 14.3 (4.2–48.5) | <0.001 | 4.6 (1.8–11.8) | 0.001 |
| High Charlson comorbdity index score | 19 (40) | 23 (41) | 11 (19) | 3.0 (1.0–8.9) | 0.05 | 3.5 (1.5–8.3) | 0.005 |
| Presence of central venous line | 20 (44) | 10 (19) | 2 (4) | 5.6 (1.0–32.7) | 0.06 | 4.5 (0.9–22.5) | 0.07 |
| Presence of Foley catheter | 38 (83) | 28 (52) | 16 (28) | 6.0 (2.0–18.2) | 0.002 | 2.2 (1.0–5.0) | 0.06 |
| Surgery | 18 (38) | 13 (23) | 8 (14) | 0.8 (0.2–3.2) | 0.76 | 1.1 (0.4–3.4) | 0.86 |
| Nonsurgical procedure | 18 (38) | 10 (18) | 1 (2) | 12.5 (1.3–124.8) | 0.03 | 8.0 (0.9–69.3) | 0.06 |
| ICU stay | 18 (38) | 10 (18) | 1 (2) | 9.6 (1.0–92.8) | 0.05 | 7.5 (0.8–68.1) | 0.07 |
| Mechanical ventilation | 22 (49) | 10 (18) | 2 (4) | 5.2 (0.9–30.7) | 0.07 | 4.2 (0.8–21.2) | 0.09 |
| Dialysis | 4 (9) | 1 (2) | 0 (0) | | | | |
| High invasive device score | 28 (58) | 14 (25) | 4 (7) | 5.7 (1.5–22.1) | 0.01 | 3.3 (1.0–11.4) | 0.06 |
| Receipt of antibiotics | 39 (83) | 19 (34) | 11 (19) | 6.2 (1.9–20.3) | 0.003 | 1.4 (0.5–3.7) | 0.51 |

[a] The median age of the patients with CRKP infection was 77 years (IQR, 63 to 83 years), that of the patients with CSKS infection was 77 years (IQR, 65 to 84 years), and that of the hospitalized controls was 68 years (IQR, 53 to 77 years). In the time-adjusted comparison of patients with CRKP and controls, the OR for the median age was 1.04 (95% CI, 1.01 to 1.08; $P$ = 0.02); and in the time-adjusted comparison of patients with CSKS and controls, the OR for the median age was 1.04 (95% CI, 1.01 to 1.06; $P$ = 0.007).

ined than did the controls (Table 3). A smaller proportion of cases than controls had pulmonary disease (OR, 0.2; 95% CI, 0.1 to 1.1; $P$ = 0.07).

In time-adjusted multivariable analysis (Table 4), the following factors were found to be predictive of CRKP isolation: poor functional status (OR, 15.4; 95% CI, 4.0 to 58.6; $P$ < 0.001), ICU stay (OR, 17.4; 95% CI, 1.5 to 201.9; $P$ = 0.02), and the receipt of antibiotics (OR, 4.4; 95% CI, 1.0 to 19.2; $P$ = 0.05). Substitution of individual antibiotic classes for the covariate "antibiotics" in the model revealed that the receipt of fluoroquinolones was an independent predictor of CRKP isolation as well (OR, 7.2; 95% CI, 1.1 to 49.4; $P$ = 0.04). The receipt of carbapenems could not be included in the multivariable model, as none of the controls received antibiotics from this class. Nevertheless, 31% of the patients in the CRKP group received carbapenems prior to a positive culture ($P$ < 0.001 by Fisher's exact test), indicating that this class of antibiotic is associated with CRKP isolation.

**(ii) Case-control study 2: CSKS group versus controls.** In contrast to the CRKP group-control group comparison, there was no difference in the length of stay prior to enrollment between the CSKS group (median, 1 day; IQR, 1 to 8 days) and the controls (median, 2 days; IQR, 1 to 4 days) ($P$ = 0.50). Still,

TABLE 3. Case-control comparison of antibiotic use by class[a]

| Antibiotic class | No. (%) of patients | | $P$ |
|---|---|---|---|
| | CRKP | Controls | |
| β-Lactams | 28 (58) | 12 (20) | <0.001 |
| β-Lactam–β-lactamase inhibitor combinations | 7 (15) | 1 (2) | 0.02 |
| Aminoglycosides | 13 (27) | 2 (3) | <0.001 |
| Fluoroquinolones | 13 (27) | 4 (7) | 0.007 |
| Carbapenems | 15 (31) | 0 (0) | <0.001 |
| Other antibiotic classes | 31 (65) | 4 (7) | <0.001 |

[a] A similar comparison between the CSKS group and the controls revealed no results with $P$ values of ≤0.05.

TABLE 4. Multivariable model of risk factors for *Klebsiella* sp. isolation

| Covariate | Time-adjusted comparison of patients with CRKP and controls | | Time-adjusted comparison of patients with CSKS and controls | |
|---|---|---|---|---|
| | OR (95% CI) | $P$ | OR (95% CI) | $P$ |
| Malignancy | | | 3.2 (1.2–9.0) | 0.02 |
| Poor functional status | 15.4 (4.0–58.6) | <0.001 | 6.3 (2.3–17.2) | <0.001 |
| Nonsurgical procedure | | | 9.4 (1.0–92.6) | 0.05 |
| ICU stay | 17.4 (1.5–201.9) | 0.02 | 12.5 (1.3–125.4) | 0.03 |
| Receipt of antibiotics[a] | 4.4 (1.0–19.2) | 0.05 | | |
| Receipt of a fluoroquinolone | 7.2 (1.1–49.4) | 0.04 | | |
| Length of stay prior to enrollment | 1.08 (1.00–1.17) | 0.06 | 1.02 (0.96–1.08) | 0.61 |

[a] Carbapenems could not be entered independently into the model, as no members of the control group received antibiotics from this class.

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TABLE 5. Univariate predictors of mortality for entire cohort

| Covariate | No. (%) of patients[a] who: | | *P* |
|---|---|---|---|
| | Died ($n$ = 29) | Lived ($n$ = 134) | |
| Male sex | 14 (48) | 51 (38) | 0.40 |
| Diabetes mellitus | 10 (36) | 38 (28) | 0.50 |
| Cardiovascular disease | 14 (50) | 88 (66) | 0.14 |
| Pulmonary disease | 8 (29) | 24 (18) | 0.20 |
| Renal disease | 10 (36) | 27 (20) | 0.09 |
| Liver disease | 4 (14) | 5 (4) | 0.05 |
| Neurologic disease | 8 (29) | 38 (28) | 1.00 |
| Malignancy | 13 (46) | 30 (22) | 0.02 |
| Immunosuppression | 8 (29) | 15 (11) | 0.03 |
| High no. of comorbidities | 13 (45) | 45 (34) | 0.29 |
| Admission from an institution | 6 (21) | 24 (18) | 0.61 |
| Transplantation | 1 (4) | 1 (1) | 0.32 |
| Poor functional status | 17 (59) | 43 (32) | 0.01 |
| High Charlson cormobidity index score | 14 (48) | 39 (29) | 0.05 |
| Presence of central venous line | 13 (48) | 19 (15) | <0.001 |
| Presence of Foley catheter | 24 (83) | 58 (45) | <0.001 |
| Surgery | 9 (31) | 30 (22) | 0.34 |
| Nonsurgical procedure | 9 (31) | 20 (15) | 0.06 |
| ICU stay | 12 (41) | 17 (13) | <0.001 |
| Mechanical ventilation | 17 (61) | 17 (13) | <0.001 |
| Dialysis | 3 (10) | 2 (2) | 0.04 |
| Receipt of antibiotics | 22 (79) | 47 (35) | <0.001 |
| Isolation of *Klebsiella* | 28 (97) | 76 (57) | <0.001 |
| Carbapenem resistant | 21 (72) | 27 (20) | |
| Carbapenem susceptible | 7 (24) | 49 (37) | |

[a] The median age for the patients who died was 75 years (IQR, 65 to 84 years), and that of the patients who lived was 73 years (IQR, 60 to 81 years) ($P$ = 0.43). The median length of stay for the patients who died was 19 days (IQR, 10 to 30 days), and that of the patients who lived was 2 days (IQR, 1 to 8 days) ($P$ < 0.001).

TABLE 6. Multivariable risk factors for mortality

| Covariate | Patients with CRKP vs patients with CSKS | | Patients with CRKP vs hospitalized controls | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Carbapenem-resistant *Klebsiella*[a] | 5.4 (1.7–17.1) | 0.005 | 6.7 (2.4–18.8) | <0.001 |
| Mechanical ventilation | 4.9 (1.6–14.7) | 0.005 | | NS[b] |
| Malignancy | 3.9 (1.2–12.2) | 0.02 | | NS |

[a] After introduction of the McCabe score variable into the models, the isolation of CRKP remained an independent predictor of in-hospital mortality, albeit with a lower OR (for patients with CRKP versus those with CSKS, OR, 3.9; 95% CI, 1.1 to 13.6; $P$ = 0.03; for patients with CRKP versus controls, OR, 5.0; 95% CI, 1.7 to 14.8; $P$ = 0.004).
[b] NS, not significant.

for the sake of consistency and the comparability of the results, the case-control comparisons in this portion of the study were also time adjusted. Here, too, the median age was greater among the cases (median age, 77 years; IQR, 65 to 84 years) than among the controls (median age, 68 years; IQR, 53 to 77 years) ($P$ = 0.007), and there was no difference between the two groups in the distribution of the patients by sex. Among the cases there was a greater proportion of patients with neurologic disease (OR, 2.4; 95% CI, 1.0 to 6.0; $P$ = 0.06), malignancy (OR, 3.1; 95% CI, 1.3 to 7.9; $P$ = 0.02), poor functional status (OR, 4.6; 95% CI, 1.8 to 11.8; $P$ = 0.001), a high Charlson comorbidity index score (OR, 3.5; 95% CI, 1.5 to 8.3; $P$ = 0.005), a high invasive device score (OR, 3.3; 95% CI, 1.0 to 11.4; $P$ = 0.06), having been in the ICU (OR, 7.5; 95% CI, 0.8 to 68.1; $P$ = 0.07), and having undergone a nonsurgical invasive procedure (OR, 8.0; 95% CI, 0.9 to 69.3; $P$ = 0.06).

In time-adjusted multivariable analysis (Table 4), independent predictors of CSKS isolation included malignancy (OR, 3.2; 95% CI, 1.2 to 9.0; $P$ = 0.02), poor functional status (OR, 6.3; 95% CI, 2.3 to 17.2; $P$ < 0.001), having undergone a nonsurgical invasive procedure (OR, 9.4; 95% CI, 1.0 to 92.6; $P$ = 0.05), and ICU stay (OR, 12.5; 95% CI, 1.3 to 125.4; $P$ = 0.03).

**Contrasting risk factors for CRKP and CSKS.** When the models examining the risk factors for the recovery of CRKP and CSKS were compared, the prior receipt of antibiotics (in particular, fluoroquinolones and carbapenems) was the only risk factor unique to the CRKP group, while having a malignancy and having undergone an invasive procedure were the risk factors unique to the CSKS group.

**Outcome study: in-hospital mortality.** Twenty-one patients in the CRKP group died (44%), whereas 7 patients in the CSKS group (12.5%) and one of the controls (2%) died. Table 5 summarizes the univariate predictors of in-hospital mortality for the entire cohort of patients included in the study. Crude predictors of mortality included renal disease ($P$ = 0.09), liver disease ($P$ = 0.05), malignancy ($P$ = 0.02), immunosuppression ($P$ = 0.03), poor functional status ($P$ = 0.01), a high Charlson comorbidity index score ($P$ = 0.05), a longer median length of stay before culture ($P$ < 0.001), having a central venous catheter ($P$ < 0.001), having a Foley catheter ($P$ < 0.001), having been in the ICU ($P$ < 0.001), having undergone mechanical ventilation ($P$ < 0.001), having undergone a nonsurgical invasive procedure ($P$ = 0.06), having undergone dialysis ($P$ = 0.04), having received antibiotics ($P$ < 0.001), and the growth of *Klebsiella* in the culture of a clinical sample ($P$ < 0.001).

In the multivariable analysis of mortality predictors for the entire cohort, irrespective of the growth of *Klebsiella*, the following covariates were significant: malignancy (OR, 4.7; 95% CI, 1.5 to 14.5; $P$ = 0.007), mechanical ventilation (OR, 7.8; 95% CI, 2.4 to 25.3; $P$ < 0.001), and the receipt of antibiotics (OR, 3.5; 95% CI, 1.0 to 12.0; $P$ = 0.05). When we added the covariate "isolation of CRKP" to the model for the cohort of patients with CRKP isolation and those with CSKS isolation (Table 6), the isolation of CRKP remained an independent predictor of mortality (OR, 5.4; 95% CI, 1.7 to 17.1; $P$ = 0.005), in addition to mechanical ventilation (OR, 4.9; 95% CI, 1.6 to 14.7; $P$ = 0.005) and malignancy (OR, 3.9; 95% CI, 1.2 to 12.2; $P$ = 0.02); for the cohort of patients with CRKP isolation and the controls (Table 6), the isolation of CRKP was the only independent predictor of in-hospital mortality (OR, 6.7; 95% CI, 2.4 to 18.8; $P$ < 0.001).

After controlling for confounding by the severity of illness by the introduction of the McCabe score variable into the final mortality models, the isolation of CRKP remained an independent predictor of in-hospital mortality, albeit with a lower OR (for the CRKP group versus the CSKS group, OR, 3.9; 95% CI, 1.1 to 13.6; $P$ = 0.03; for the CRKP group versus the controls, OR, 5.0; 95% CI, 1.7 to 14.8; $P$ = 0.004).

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## DISCUSSION

Carbapenem resistance in *K. pneumoniae* is an emerging phenomenon posing a threat to public health. As carbapenems have long been considered the antibiotic class of last resort in the treatment of infections caused by multidrug-resistant gram-negative organisms, the dissemination of carbapenem resistance among pathogenic bacteria has been declared a "global sentinel event" (21).

While little has been reported regarding the risk factors for and the outcomes of carbapenem resistance in the *Enterobacteriaceae*, much is known regarding the risks for and outcomes of other, less extreme variations of multidrug resistance in gram-negative enteric organisms. Risk factors for the isolation of ESBL-producing organisms include severe underlying illness, prolonged hospital stay, the presence of invasive medical devices, and antibiotic use (20). ESBL production has been associated with severe adverse clinical and economic outcomes, including increased mortality, increased length of stay, delay in the institution of effective therapy, decreased functional status on discharge, and increased cost of care (24). In the first of two earlier studies of the risk factors for CRKP isolation, Kwak et al. evaluated 30 patients with nosocomial CRKP isolation in South Korea and found that previous exposure to carbapenem and cephalosporin antibiotics was associated with CRKP acquisition, while fluoroquinolone exposure was protective (14). In a more recent risk factor study, Falagas et al. compared 53 patients with CRKP isolation with 53 matched controls with carbapenem-susceptible *K. pneumoniae* isolation and found that prior exposure to fluoroquinolones and antipseudomonal penicillins were independent risk factors for CRKP infection (9).

In our study, independent predictors of CRKP isolation, after adjustment for the length of stay, were poor functional status, ICU stay, and the receipt of antibiotics. Like Falagas et al. (9) and unlike Kwak et al. (14), we found that exposure to a fluoroquinolone was independently predictive of CRKP isolation. While we did not obtain similar findings with the other antibiotic classes tested, we were unable to evaluate carbapenems in the multivariable model, as no members of the control group received carbapenems. In univariate analysis, carbapenem use was strongly predictive of CRKP isolation.

The CSKS case-control model differs from the CRKP case-control model, in that antibiotics did not play a role in the former; i.e., antibiotic use was associated with carbapenem-resistant but not carbapenem-susceptible *Klebsiella* isolation. Malignancy was a risk factor only for CSKS isolation, an observation consistent with the finding that malignancy is protective against the nosocomial acquisition of certain resistant organisms, perhaps because cancer patients are often hospitalized under conditions of protective isolation (2).

Not surprisingly, CRKP isolation was independently associated with in-hospital mortality in the cohort of CRKP patients and controls. CRKP isolation, however, was associated with increased mortality even in comparison with CSKS isolation, a finding even more noteworthy when we consider the high proportion of ESBL-associated multidrug-resistant isolates among the carbapenem-susceptible *Enterobacteriaceae* found at our institution (3). In the present study, fully 54% of the CSKS isolates were ESBL producers.

There are a number of limitations to our study: as the isolation of CRKP is a relatively new phenomenon in our institution, the sample size of the index group was relatively small. As a result, the powers of both the risk factor and the outcome studies were limited. Moreover, the mechanisms of resistance differed among the CRKP isolates. The most dominant mechanism among isolates in our institution is the production of KPC-2 and KPC-3 (15); however, other mechanisms may also exist among isolates harbored by our study patients, including a combination of the production of an ESBL and porin loss (15a). While resistant isolates may be phenotypically similar, risk factors and outcomes may differ according to the mechanism of resistance.

Although we chose our case and control groups according to established epidemiological principles (22), the age discrepancy between the CRKP and the CSKS groups on the one hand and the control group on the other, as well as the profound difference in the median lengths of stay prior to enrollment between the CRKP group and the two other groups, make comparisons between the study groups difficult. We controlled for these discrepancies using accepted statistical methods. We incorporated age into the multivariable model-building process (it was not an independent predictor of either CRKP or CSKS isolation). Regarding the discrepancy in the length of stay, we went a step further and adjusted for this variable even in our individual analyses of risk factors and, in addition, "forced" it into the multivariable models. Given the available study cohort, we have controlled for confounding by length of stay to the fullest extent possible. Finally, for the mortality study we evaluated our model for confounding by severity of illness and found that despite the presence of confounding, CRKP isolation remained an independent predictor of death.

Our efforts to control for differences in patient populations notwithstanding, the question as to the extent to which the variables that we identified in the risk factor study are "true" risk factors for CRKP isolation rather than merely a function of prolonged length of stay remains not fully answered. We recommend that further studies with other designs specifically aimed at answering this question be performed. Our case-case-control study is limited in its ability to determine the level of causality attributable to the factors identified as being associated with CRKP isolation. Future studies involving larger cohorts and perhaps designed specifically to control for differences in age and length of stay will be required to achieve this goal. In addition, further studies with larger cohorts will be required to determine the effect of CRKP on additional outcomes, such as the length of stay subsequent to a positive culture, discharge disposition, and cost of care.

We have provided an analysis of the factors associated with CRKP isolation among hospitalized adults, the importance of antibiotic exposure to this isolation, and the significant mortality associated with CRKP isolation even compared to that associated with CSKS isolation. Our findings justify the concern raised by the spread of carbapenem resistance among members of the family *Enterobacteriaceae*; provide impetus for further study; and should cause us to redouble our efforts at infection control, formulary interventions, and the containment of spread.

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