ORIGINAL ARTICLE

# Prevalence and Risk Factors for Acquisition of Carbapenem-Resistant Enterobacteriaceae in the Setting of Endemicity

Mahesh Swaminathan, MD;[1,a] Saarika Sharma, MD;[2,a] Stephanie Poliansky Blash, MPH;[1] Gopi Patel, MD, MS;[1] David B. Banach, MD, MPH;[1,a] Michael Phillips, MD;[2] Vincent LaBombardi, PhD;[3,a] Karen F. Anderson;[4] Brandon Kitchel, MS;[4] Arjun Srinivasan, MD;[4] David P. Calfee, MD, MS[1,5]

OBJECTIVE. To describe the epidemiology of carbapenem-resistant Enterobacteriaceae (CRE) carriage and acquisition among hospitalized patients in an area of CRE endemicity.

DESIGN. Cohort study with a nested case-control study.

SETTING. Two acute care, academic hospitals in New York City.

PARTICIPANTS. All patients admitted to 7 study units, including intensive care, medical-surgical, and acute rehabilitation units.

METHOD. Perianal samples were collected from patients at admission and weekly thereafter to detect asymptomatic gastrointestinal carriage of CRE. A nested case-control study was performed to identify factors associated with CRE acquisition. Case patients were those who acquired CRE during a single hospitalization. Control subjects had no microbiologic evidence of CRE and at least 1 negative surveillance sample. Clinical data were abstracted from the medical record.

RESULTS. The prevalence of CRE in the study population was 5.4% (306 of 5,676 patients), and 104 patients met the case definition of acquisition during a single hospital stay. Mechanical ventilation (odds ratio [OR], 11.5), pulmonary disease (OR, 5.2), days of antibiotic therapy (OR, 1.04), and CRE colonization pressure (OR, 1.15) were independently associated with CRE acquisition. Pulsed-field gel electrophoresis analysis identified 87% of tested *Klebsiella pneumoniae* isolates as sharing related patterns (greater than 78% similarity), which suggests clonal transmission within and between the study hospitals.

CONCLUSIONS. Critical illness and underlying medical conditions, CRE colonization pressure, and antimicrobial exposure are important risk factors for CRE acquisition. Adherence to infection control practices and antimicrobial stewardship appear to be critical components of a CRE control program.

*Infect Control Hosp Epidemiol* 2013;34(8):809-817

Carbapenem-resistant Enterobacteriaceae (CRE), particularly *Klebsiella pneumoniae*, have emerged as an important cause of healthcare-associated infections. *K. pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae have been identified in at least 40 US states and in more than 25 countries on 5 continents. CRE are typically resistant to all β-lactam antibiotics and frequently possess resistance determinants for many other antibiotic classes, which severely limits antimicrobial treatment options. Earlier studies have reported mortality rates associated with carbapenem-resistant *K. pneumoniae* (CRKP) infections that are 3.7–6.5 times greater than those associated with infections caused by carbapenem-susceptible *K. pneumoniae*.[1,2]

Studies conducted in settings of endemic disease or outbreaks and using active surveillance testing (AST) to identify gastrointestinal CRE carriage have reported carriage rates of 2%–39% among intensive care unit (ICU) patients,[3,4] 9% in a non-ICU hospital outbreak,[5] and 2.1%–49% in post–acute care facilities.[6,7] These studies also reported that 37%–87% of CRE carriers detected by AST had not been previously identified by clinical cultures and that many would have remained undetected without AST.[3-5] Asymptomatic carriers may serve as sources of transmission within healthcare facilities[6,8] and are at relatively high risk of subsequent CRE infection.[3,7] Factors associated with CRE infection and/or carriage include duration of hospital stay, antibiotic exposure, and severity of underlying disease.[1,2,6,9,10] Recent studies found an association between CRE prevalence and the incidence of new cases of CRE.[6,8]

The aim of this study was to characterize the epidemiology

Affiliations: 1. Department of Medicine, Mount Sinai School of Medicine, New York, New York; 2. Department of Medicine, New York University Langone Medical Center, New York, New York; 3. Department of Pathology, Mount Sinai School of Medicine, New York, New York; 4. Centers for Disease Control and Prevention, Atlanta, Georgia; 5. Department of Medicine, Weill Cornell Medical College, New York, New York.

Received November 20, 2012; accepted March 5, 2013; electronically published June 11, 2013.

 0899-823X/2013/3408-0007$15.00. DOI: 10.1086/671270

of CRE carriage and acquisition in acute care hospitals in New York City, a geographic region in which CRE have become endemic in many healthcare facilities.[11] Specific objectives were to determine the prevalence of gastrointestinal carriage of CRE among hospitalized patients, to quantify the CRE colonization pressure in high-risk hospital units, and to identify factors associated with CRE acquisition.

## METHODS

### Patients and Setting

The study was conducted in 2 tertiary care hospitals in New York City. Subjects were patients admitted to 7 inpatient units (3 adult ICUs, 2 adult medical-surgical wards, and 2 acute rehabilitation wards) between February 1, 2009, and January 31, 2010. Study units were selected from among those with a relatively high prevalence of patients with risk factors previously associated with CRE colonization or infection.[1,2,6,9,10] The institutional review boards of both institutions and the Centers for Disease Control and Prevention (CDC) approved the study.

### AST Program

AST was performed as part of the study facilities' routine CRE control programs. Nursing staff used dry, sterile, cotton-tipped swabs to obtain a perianal sample from all patients within 2 days of admission to the hospital and weekly thereafter until discharge from the hospital or transfer from the unit. Clinical cultures were collected at the discretion of treating clinicians. Patients identified as CRE carriers were placed under contact precautions, and this information was conveyed to receiving healthcare facilities if patients were subsequently transferred to another facility. CRE acquisition was defined as isolation of CRE from a surveillance or clinical specimen obtained from a subject who had no history of CRE and had at least 1 previous negative surveillance culture at any time during the study period. Among subjects who acquired CRE, we identified a subset in whom acquisition was documented during the course of a single hospital admission (eg, a subject had at least 1 negative surveillance culture followed by a subsequent positive culture from any source during the same hospital admission). The daily colonization pressure on study units was defined as the number of CRE-positive patients divided by the total number of patients on the unit. The monthly colonization pressure was calculated by dividing the number of CRE patient-days by the number of patient-days per month.

### Microbiologic Methods

Surveillance specimens were processed at each study hospital using previously described methods.[12] Initial species identification and susceptibilities were determined using automated systems. Ertapenem was used to determine carbapenem susceptibility. Hospital A also used the modified Hodge test (MHT) to detect carbapenemase production. Clinical specimens were processed using standard protocols. Subjects' first clinical and surveillance CRE isolates were frozen at −70°C and transported to the CDC. Testing performed at the CDC included organism identification, susceptibility testing, and MHT. Pulsed-field gel electrophoresis (PFGE) was performed on *Xba*I-digested DNA as described for *Escherichia coli* (http://www.cdc.gov/pulsenet/protocols.htm) using the CHEF mapper electrophoresis system (Bio-Rad). PFGE patterns were compared using the Dice coefficient and clustering by the unweighted-pair group method using mean linkages (UPGMA; Bionumerics 5.10; Applied Maths). Real-time polymerase chain reaction (PCR) testing for the presence of the $bla_{KPC}$ gene was performed on a select number of MHT-positive isolates using a previously described method.[13] Isolates were confirmed as CRE if MHT or antibiotic susceptibility testing performed at the CDC confirmed carbapenemase production or carbapenem resistance, respectively, or if PCR detected the $bla_{KPC}$ gene.

### Case-Control Study

A nested case-control study was performed to identify factors associated with CRE acquisition. Case patients were subjects who acquired CRE during a single hospital admission. Control subjects were subjects with no evidence of current or previous CRE infection or colonization and at least 1 negative surveillance culture. Control subjects were matched 1 : 1 to cases by sex and were restricted on the basis of the study unit. Control subjects were selected from among potential control subjects using a random number generator. Demographic information, medical history, and healthcare exposures, including invasive devices, procedures, gastric acid suppressants, and antibiotics, were abstracted from the inpatient medical record. For case patients, exposures before the first CRE-positive culture were recorded. For control subjects, exposures before the last negative surveillance culture were included. One day of antibiotic therapy was defined as administration of a single antibiotic agent on a given day regardless of the number or strength of doses prescribed.[14] The total number of days of antibiotic therapy was calculated for each subject. The mean colonization pressure to which each subject had been exposed was the mean of the daily colonization pressures for each day that the subject spent on any study unit.

### Statistical Analysis

Conditional logistic regression was used to identify factors associated with CRE acquisition and was performed separately for each of the candidate risk factors. Variables with a *P* value of less than or equal to .2 in univariable analysis were included in multivariable analyses. Multivariable analyses were adjusted for age, and computer-assisted and manual forward, backward, and stepwise conditional logistic regres-

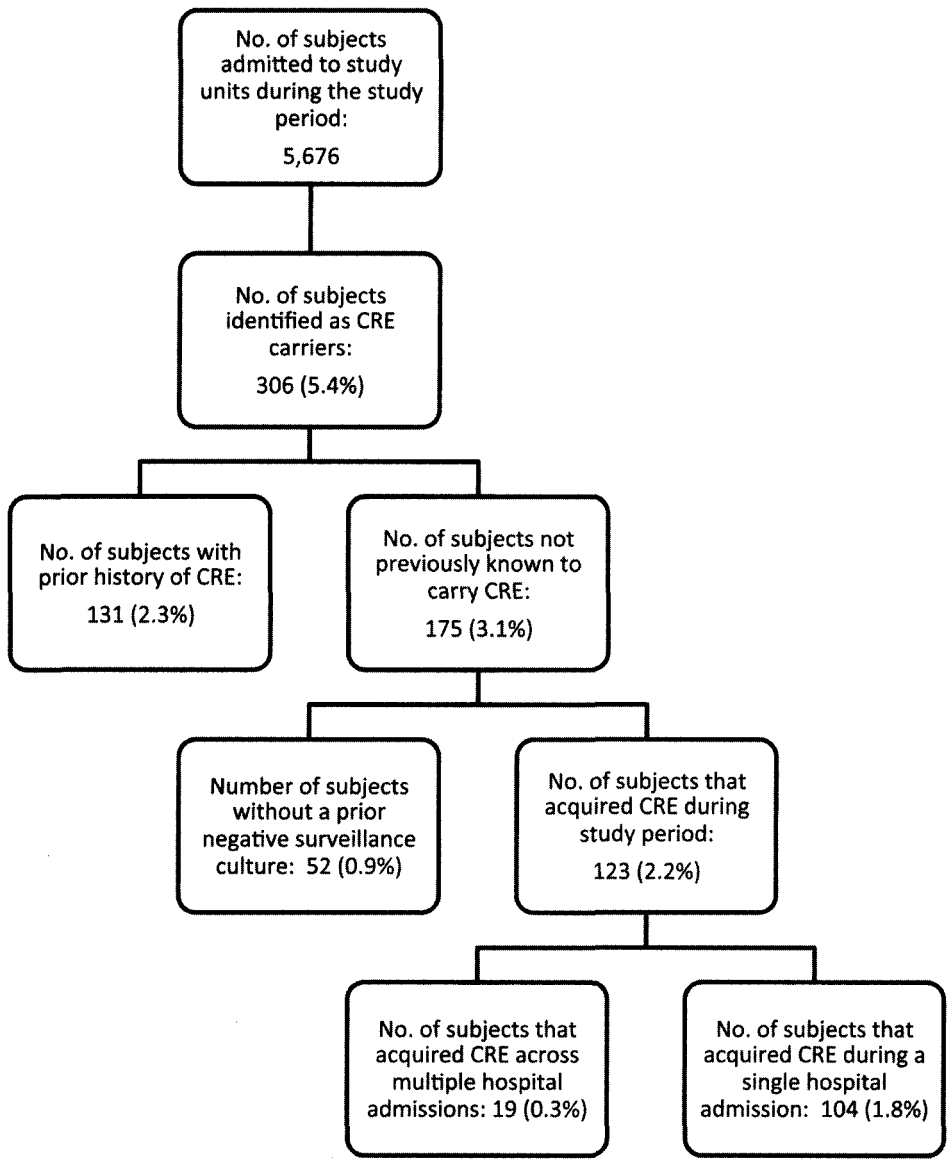


FIGURE 1. Study flow. CRE, carbapenem-resistant Enterobacteriaceae.

sion models were used. Statistical analyses were performed using SPSS, version 19 (SPSS Institute).

## RESULTS

The overall prevalence of CRE was 5.4% (hospital A, 5.8%; hospital B, 4.9%; $P = .15$) among the 5,676 patients admitted to study units (Figure 1). Among the 306 CRE carriers, 175 (57%) were not previously known to be carriers. New acquisition of CRE was documented in 123 (70%), and 104 (84.6%) of these acquired CRE during a single hospitalization. The most common species among newly identified carriers was *K. pneumoniae* (84.7%), followed by *Enterobacter cloacae* (5.7%), *Escherichia coli* (4.6%), *Enterobacter aerogenes* (2.8%), *Klebsiella oxytoca* (1.7%), and *Serratia marcescens* (0.6%). Isolates from 152 (87%) of the 175 newly identified carriers were available for additional testing, and carbapenem resistance was confirmed in 137 (90%). Among the newly identified carriers, 144 (82%) were identified by AST, and 31 (18%) were identified by clinical culture. CRE was isolated from at least 1 subsequent clinical culture in 25 (17%) of the cases detected by AST. The most common source of the first subsequent clinical isolate was blood (44%), followed by urine (36%), other body fluids or tissues (16%), and sputum (4%).

### CRE Colonization Pressure on Study Units

The mean monthly colonization pressure among the study units was 7.3%. At hospital A, the colonization pressure on study units ranged from 0% to 26.5% (Figure 2*A*) with a

https://doi.org/10.1086/671270 Published online by Cambridge University Press

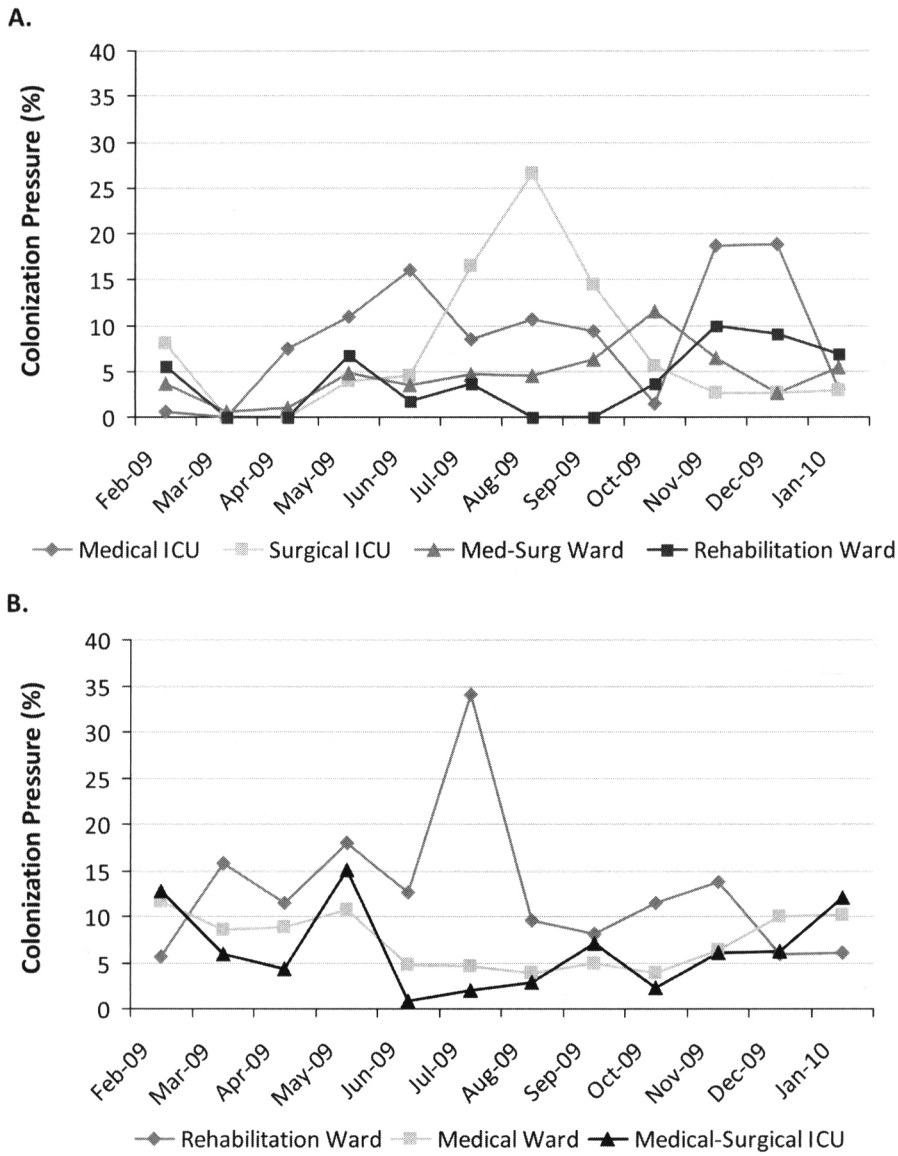


FIGURE 2. Monthly carbapenem-resistant Enterobacteriaceae colonization pressure in hospital A (*A*) and hospital B (*B*) study units. ICU, intensive care unit; Med-Surg, medical surgical.

mean of 5.7% (3.9% in the rehabilitation unit, 4.6% in the medical-surgical ward, and 7.3% and 8.8% in the ICUs). At hospital B, the monthly colonization pressure ranged from 0.9% to 34% with a mean of 8.1% (6.5% in the ICU, 7.4% in the medical ward, and 12.7% in the rehabilitation unit; Figure 2*B*).

### Risk Factors for Acquisition of CRE during a Single Hospital Admission

CRE was confirmed in 86 (92%) of the 93 isolates available for additional testing. The mean time between the first negative surveillance culture and the first CRE-positive culture was 19.5 days (median, 11 days; range, 1–140 days). For the case-control study, the 104 case patients were matched to 104 control subjects (Table 1). The majority of case patients (62%) were male. The mean age of case patients and control subjects was 62.7 and 63.6 years, respectively ($P = .71$). Twenty-four case patients and 16 control subjects died during the index hospitalization ($P = .16$). In univariable analysis, case patients were more likely to require dialysis and to have gastrointestinal disease. Several healthcare-related exposures were associated with acquisition of CRE (Table 2). Case patients had longer hospital stays; spent more time on study units; and were more likely to have had a central venous or urinary catheter, to have required mechanical ventilation, and to have received acid-suppressive medications. Case patients

https://doi.org/10.1086/671270 Published online by Cambridge University Press

TABLE 1. Characteristics of Case-Control Study Population

| Characteristic | Case patients ($n$ = 104) | Control subjects ($n$ = 104) | Univariable analysis OR (95% CI) | Univariable analysis $P$ | Multivariable analysis OR (95% CI) | Multivariable analysis $P$ |
|---|---|---|---|---|---|---|
| Study facility | | | ... | >.99 | ... | |
| Hospital A | 64 (62) | 64 (62) | | | | |
| Hospital B | 40 (38) | 40 (38) | | | | |
| Age at admission, years | | | 1.00 (0.98–1.01) | .71 | 1.00 (0.96–1.04) | .93 |
| Mean ± SD | 62.7 ± 15.2 | 63.6 ± 17.8 | | | | |
| Median | 64 | 66 | | | | |
| Range | 25–94 | 20–95 | | | | |
| Male sex | 64 (62) | 64 (62) | ... | >.99 | ... | |
| Race/ethnicity | | | | | | |
| White | 54 (52) | 62 (60) | ... | | ... | |
| Black | 22 (21) | 14 (13) | ... | | ... | |
| Hispanic/Latino | 14 (13) | 19 (18) | ... | | ... | |
| Asian/Pacific Islander | 4 (4) | 7 (7) | ... | | ... | |
| American Indian/Alaska native | 1 (1) | 0 (0) | ... | | ... | |
| Other/unknown | 9 (9) | 2 (2) | 0.98 (0.77–1.24) | .86 | ... | |
| Underlying medical condition | | | | | | |
| Dialysis | 18 (17) | 8 (8) | 2.67 (1.04–6.82) | .04 | 2.00 (0.33–12.24) | .45 |
| Malignancy | 27 (26) | 39 (38) | 0.63 (0.36–1.09) | .10 | 0.82 (0.28–2.42) | .72 |
| Diabetes | 31 (30) | 21 (20) | 1.67 (0.88–3.16) | .12 | 1.31 (0.34–4.98) | .70 |
| Cardiovascular disease[a] | 63 (61) | 54 (52) | 1.6 (0.84–3.05) | .15 | 1.13 (0.33–3.90) | .85 |
| Pulmonary disease[b] | 27 (26) | 17 (16) | 1.71 (0.89–3.31) | .11 | 5.19 (1.07–25.31) | .04 |
| Gastrointestinal disease[c] | 26 (25) | 13 (13) | 2.44 (1.13–5.31) | .02 | 3.34 (0.71–15.71) | .13 |
| Solid-organ or hematopoietic stem cell transplantation | 11 (11) | 8 (8) | 1.6 (0.52–4.89) | .41 | ... | |
| Hepatobiliary disease[d] | 23 (22) | 17 (16) | 1.86 (0.74–4.65) | .19 | 2.61 (0.41–16.52) | .31 |
| Neurologic disease[e] | 31 (30) | 33 (32) | 0.9 (0.47–1.72) | .74 | ... | |
| Autoimmune disease[f] | 6 (6) | 7 (7) | 0.86 (0.29–2.55) | .78 | ... | |

NOTE. Data are no. (%) of patients, unless otherwise indicated. CI, confidence interval; OR, odds ratio; SD, standard deviation.

[a] Cerebrovascular accident, coronary artery disease, congestive heart failure, cardiomyopathy, peripheral vascular disease.

[b] Chronic obstructive pulmonary disease, asthma, primary pulmonary hypertension, interstitial lung disease.

[c] Chronic or recurrent pancreatitis, inflammatory bowel disease, active gastrointestinal bleed not secondary to portal hypertension.

[d] Cirrhosis, chronic liver disease (including autoimmune hepatitis), chronic viral hepatitis.

[e] Multiple sclerosis, epilepsy, dementia, paralysis, spinal cord trauma.

[f] Systemic lupus erythematosis, rheumatoid arthritis, vasculitis.

were also more likely to have received antibiotics (96 case patients vs 71 control subjects; $P < .001$) and had received more days of antibiotic therapy (mean duration of antibiotic therapy, 53.9 vs 14.4 days; $P < .001$). Case patients were more likely to have received nearly all classes of antibiotics. Finally, case patients were exposed to higher CRE colonization pressure (mean colonization pressure, 8.9% vs 6.4%; $P = .02$). Because of the limited sample size and the expected collinearity between many antibiotics, we used days of antibiotic therapy as the single variable to represent antibiotic exposure in multivariable analysis. Factors independently associated with acquisition of CRE included pulmonary disease (odds ratio [OR], 11.53), mechanical ventilation (OR, 5.19), days of antibiotic therapy (OR, 1.04), and mean colonization pressure (OR, 1.15).

### PFGE Analysis

PFGE was performed on 182 MHT-positive *K. pneumoniae* isolates from 145 subjects. Thirty-seven subjects had surveillance and clinical isolates included in the analysis. A dominant pattern accounted for 159 isolates (87%) and could be subdivided into 3 closely related clonal groups (ie, clusters of isolates with more than 80% similarity in PFGE pattern). The other 23 isolates were unrelated to this dominant pattern and to each other, and they only shared 50%–76% similarity by PFGE. All 3 closely related subgroups included isolates from both study facilities. When compared with the CDC *K. pneumoniae* PFGE database, representative isolates of each subgroup were observed to share indistinguishable PFGE patterns with isolates known to be ST258, the dominant strain

https://doi.org/10.1086/671270 Published online by Cambridge University Press

TABLE 2. Healthcare-Related Exposures among Case-Control Study Subjects

| Healthcare-related exposure | Case patients ($n$ = 104) | Control subjects ($n$ = 104) | Univariable analysis OR (95% CI) | Univariable analysis $P$ | Multivariable analysis OR (95% CI) | Multivariable analysis $P$ |
|---|---|---|---|---|---|---|
| Length of hospital stay, days | | | 1.034 (1.01–1.06) | .001 | 0.94 (0.86–1.01) | .09 |
| Mean | 25.6 ± 28.1 | 11.4 ± 20.14 | | | | |
| Median | 15.5 | 3.0 | | | | |
| Range | 1–184 | 1–150 | | | | |
| Length of stay on study unit(s), days | | | 1.08 (1.04–1.12) | <.001 | 1.08 (0.98–1.2) | .12 |
| Mean | 19.8 ± 23.2 | 6.8 ± 11.1 | | | | |
| Median | 12 | 2 | | | | |
| Range | 1–138 | 0–59 | | | | |
| Previous acute care hospitalization in study facility[a] | 52 (50) | 45 (43) | 1.33 (0.76–2.35) | .32 | ... | |
| Previous admission to study rehabilitation unit[a] | 6 (6) | 8 (8) | 0.71 (0.23–2.25) | .57 | ... | |
| Invasive interventions | | | | | | |
| Central venous catheter | 47 (45) | 19 (18) | 6.6 (2.57–16.91) | <.001 | 0.77 (0.12–5.08) | .79 |
| Urinary catheter | 50 (48) | 30 (29) | 2.82 (1.42–5.61) | .003 | 1.6 (0.44–5.73) | .47 |
| Mechanical ventilation | 48 (46) | 15 (14) | 9.25 (3.3–25.95) | <.001 | 11.53 (1.59–83.88) | .02 |
| Surgical procedure within 6 months | 51 (49) | 47 (45) | 1.21 (0.66–2.22) | .538 | ... | |
| Acid-suppressive medication | 83 (80) | 68 (65) | 2.5 (1.2–5.21) | .01 | 1.59 (0.46–5.53) | .466 |
| Antibiotic exposures[a] | | | | | | |
| Receipt of any antibiotic | 96 (92) | 71 (68) | 7.25 (2.55–20.62) | <.001 | ... | |
| Days of antibiotic therapy | | | | | | |
| Mean | 53.9 ± 52.4 | 14.4 ± 30.5 | 1.03 (1.02–1.05) | <.001 | 1.04 (1.01–1.06) | .003 |
| Median | 37 | 3 | | | | |
| Range | 0–247 | 0–227 | | | | |
| $\beta$-lactam plus $\beta$-lactamase inhibitor combination | 48 (46) | 19 (18) | 3.23 (1.73–6.02) | <.001 | | |
| First- and third-generation cephalosporin | 39 (38) | 35 (34) | 1.25 (0.65–2.41) | .51 | | |
| Cefepime | 42 (40) | 16 (15) | 6.2 (2.41–15.94) | <.001 | | |
| Carbapenem | 44 (42) | 10 (10) | 6.67 (2.83–15.72) | <.001 | | |
| Fluoroquinolone | 53 (51) | 28 (27) | 3.27 (1.67–6.43) | .001 | | |
| Tigecycline | 28 (27) | 4 (4) | 13 (3.09–54.77) | <.001 | | |
| Aminoglycoside | 10 (10) | 5 (5) | 2.25 (0.69–7.31) | .18 | | |
| Polymyxin (IV) | 4 (4) | 1 (1) | 4 (0.45–35.79) | .22 | | |
| Macrolide | 16 (15) | 9 (9) | 2 (0.81–4.96) | .13 | | |
| Vancomycin (IV) | 72 (69) | 31 (30) | 6.86 (3.10–15.15) | <.001 | | |
| Vancomycin (oral) | 18 (17) | 6 (6) | 3.4 (1.25–9.22) | .02 | | |
| Sulfonamide | 21 (20) | 14 (13) | 1.58 (0.77–3.26) | .21 | | |
| Metronidazole | 42 (40) | 20 (19) | 3.44 ((1.64–7.24) | .001 | | |
| Daptomycin | 6 (6) | 2 (2) | 5 (0.58–42.79) | .14 | | |
| Linezolid | 14 (13) | 2 (2) | 7 (1.59–30.8) | .01 | | |
| Rifamycin | 12 (12) | 3 (3) | 4 (1.13–14.18) | .03 | | |
| Colonization pressure, % | | | 1.06 (1.01–1.11) | .02 | 1.15 (1.03–1.28) | .01 |
| Mean | 8.9 ± 7.7 | 6.4 ± 7.6 | | | | |
| Median | 7.9 | 5.7 | | | | |
| Range | 0–44 | 0–38 | | | | |

NOTE. Unless otherwise specified, data represent exposures that occurred during the index hospitalization before first carbapenem-resistant Enterobacteriaceae–positive culture (case patients) or last negative surveillance culture (control subjects). CI, confidence interval; IV, intravenous; OR, odds ratio.

[a] During the 6-month period before the first carbapenem-resistant Enterobacteriaceae–positive culture (case patients) or last negative surveillance culture (control subjects).

of KPC-producing *K. pneumoniae* in the United States.[15] This suggests that the dominant strain in this study is likely to be ST258, with observed variability in PFGE patterns (sharing more than 80% similarity) that has been previously characterized.

## DISCUSSION

To our knowledge, this is the first US study to use AST to characterize the epidemiology of CRE in acute care hospitals in a region where CRE are endemic. As in earlier studies, *K. pneumoniae* was the most commonly identified organism, and most isolates belonged to a related national outbreak strain with a similar PFGE pattern. The overall prevalence of CRE in the study population was 5.4%, and the mean colonization pressure on the studied hospital units was 7.3%. We also demonstrated that the burden of CRE would have been substantially underappreciated had only clinical cultures been used to identify carriers. In fact, 68% of CRE carriers would have remained undetected in the absence of AST.

Although earlier studies have identified risk factors for CRE infection and carriage, identification of patients who converted from culture negative to culture positive during a single hospitalization allowed us to identify factors associated with CRE acquisition. Acquisition was independently associated with pulmonary disease, receipt of mechanical ventilation, the number of days of antibiotic therapy, and the mean daily CRE colonization pressure to which a subject was exposed. Although the first 2 factors may be markers of chronic disease and critical illness, respectively, the latter 2 factors are noteworthy because they are potentially modifiable. In this study, the odds of acquiring CRE increased by 4% per day of antibiotic therapy and by 15% for every 1% increase in the colonization pressure to which a subject was exposed. This association between colonization pressure and acquisition is supported by the findings of another recent study.[8] Furthermore, colonization pressure has been associated with acquisition of other healthcare-associated pathogens.[16-18]

These findings have implications for CRE control programs. In the absence of AST, 68% of CRE carriers would have gone undetected, resulting in the inability to implement recommended infection control measures for the majority of the reservoir for transmission. Although this study was not designed to assess outcomes (eg, reduction in CRE transmission) associated with identifying these asymptomatic carriers, quantification of the burden of unrecognized carriers provides supportive evidence for recommendations for the use of AST in a multifaceted CRE control program.[8,19,20] Similarly, the association between colonization pressure and CRE acquisition and the molecular evidence of patient-to-patient transmission demonstrates the importance of adherence to recommended infection control interventions, such as hand hygiene, contact precautions, and environmental cleaning and disinfection. Although we did not perform environmental sampling, earlier studies have demonstrated that CRE contaminate the healthcare environment,[4,21] and others have associated environmental contamination with acquisition of multidrug-resistant gram-negative bacilli.[22] This suggests that the association between colonization pressure and CRE acquisition is attributable, at least in part, to more frequent direct contact with a contaminated environment, healthcare worker hands, or equipment as the burden of CRE increases. Of note, a recent study found that the correlation between CRE prevalence and incidence was reduced when adherence to CRE-specific infection-prevention measures increased.[8] Another contemporary study suggested that, even with strict adherence to isolation recommendations, CRE exhibits environmental resilience, and augmented infection control measures may be necessary.[23] We have also demonstrated that the risk of acquiring CRE is associated with overall antibiotic exposure. Given that a considerable proportion of antibiotic therapy in hospitals is broader in spectrum or longer in duration than necessary,[24,25] antimicrobial stewardship programs could play a critical role in CRE control by reducing antibiotic selection pressure.

Our study does have limitations. The findings may not reflect the epidemiology of CRE in regions with a lower prevalence of CRE or in lower-risk populations. Because perianal swabs may not detect all gastrointestinal carriers of multidrug-resistant Enterobacteriaceae,[26,27] some CRE carriers may have been misclassified as control subjects, and our definition of CRE acquisition may have included case patients for whom CRE was not newly acquired (eg, a person with low-level colonization in whom the density of organisms increased to a detectable level during antibiotic therapy). We were unable to obtain reliable information on exposures outside of the study institutions, such as outpatient antibiotic therapy, and were unable to measure some factors, such as adherence to hand hygiene, that likely play an important role in CRE transmission. Many subjects spent time on nonstudy units for which we did not have colonization pressure data, and this limited our ability to fully assess the association between colonization pressure and CRE acquisition. Finally, there may have been insufficient statistical power to detect associations between CRE acquisition and some important risk factors.

In conclusion, this study suggests that, in regions where CRE is endemic, asymptomatic gastrointestinal carriage of CRE is relatively common and frequently unrecognized. CRE colonization pressure and antimicrobial exposure play important roles in the acquisition of CRE in such facilities. In 2012, the CDC issued updated guidance for controlling the transmission of CRE in healthcare facilities.[19] Our findings support the control measures outlined in that document, including adherence to infection-control practices, antimicrobial stewardship, and AST.

## ACKNOWLEDGMENTS

We thank the nursing staff on the study units of the Mount Sinai Hospital and New York University Langone Medical Center for their efforts and dedication.

*Financial support.* This study was funded by the Association of American Medical Colleges and the Centers for Disease Control and Prevention (cooperative agreement MM-1085-09/09 to D.P.C.). Salary support for M.S. was provided by the New York State Department of Health Empire Clinical Research Investigator Program.

*Potential conflicts of interest.* All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to David P. Calfee, MD, MS, Associate Professor of Medicine and Public Health, Weill Cornell Medical College, 525 East 68th Street, Box 265, New York, NY 10065 (dpc9003@med.cornell.edu).

Presented in part: 2011 Annual Scientific Meeting of the Society for Healthcare Epidemiology of America; Dallas, TX; April 1–4, 2011.

[a] Present affiliations: Mahesh Swaminathan, Centers for Disease Control and Prevention, Atlanta, Georgia; Saarika Sharma, Permanente Medical Group, Vacaville, California; David B. Banach, Department of Medicine, Yale School of Medicine, New Haven, Connecticut; Vincent LaBombardi, New York Hospital Queens, New York, New York.

## REFERENCES

1. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008;29:1099–1106.
2. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother* 2008;52:1028–1033.
3. Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant *Klebsiella pneumoniae* in intensive care unit patients. *Infect Control Hosp Epidemiol* 2008;29:966–968.
4. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med* 2005;165: 1430–1435.
5. Ben-David D, Maor Y, Keller N, et al. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* infection. *Infect Control Hosp Epidemiol* 2010;31:620–626.
6. Ben-David D, Masarwa S, Navon-Venezia S, et al. Carbapenem-resistant *Klebsiella pneumoniae* in post-acute-care facilities in Israel. *Infect Control Hosp Epidemiol* 2011;32:845–853.
7. Chitnis AS, Caruthers PS, Rao AK, et al. Outbreak of carbapenem-resistant Enterobacteriaceae at a long-term acute care hospital: sustained reductions in transmission through active surveillance and targeted interventions. *Infect Control Hosp Epidemiol* 2012;33:984–992.
8. Schwaber M, Lev B, Israeli A, et al. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011;52:1–8.
9. Marchaim D, Chopra T, Bhargava A, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. *Infect Control Hosp Epidemiol* 2012;33:817–830.
10. Gasink LB, Edelstein PH, Lautenbach E, Synnestvedt M, Fishman NO. Risk factors and clinical impact of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. *Infect Control Hosp Epidemiol* 2009;30:1180–1185.
11. Landman D, Babu E, Shah N, et al. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. *J Antimicrob Chemother* 2012;67:1427–1431.
12. Landman D, Salvani JK, Bratu S, Quale J. Evaluation of techniques for detection of carbapenem-resistant *Klebsiella pneumoniae* in stool surveillance cultures. *J Clin Microbiol* 2005;43:5639–5641.
13. Kitchel B, Lonsway D, Wong B, Rasheed J. Detection of the $bla_{KPC}$ gene encoding *Klebsiella pneumoniae* carbapenemase (KPC) by real-time PCR. In: *Clinical Microbiology Procedures Handbook*. 3rd ed. Washington, DC: ASM, 2010:2041–2050.
14. Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. *Clin Infect Dis* 2007;44:664–670.
15. Kitchel B, Rasheed JK, Patel JB, et al. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258. *Antimicrob Agents Chemother* 2009;53:3365–3370.
16. Merrer J, Santoli F, Appéré de Vecchi C, Tran B, De Jonghe B, Outin H. "Colonization pressure" and risk of acquisition of methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit. *Infect Control Hosp Epidemiol* 2000;21:718–723.
17. Bonten MJ, Slaughter S, Ambergen AW, et al. The role of "colonization pressure" in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch Intern Med* 1998;158:1127–1132.
18. Lawrence SJ, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. *Clostridium difficile* in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol* 2007;28:123–130.
19. Centers for Disease Control and Prevention. Guidance for control of carbapenem-resistant Enterobacteriaceae (CRE). 2012 CRE Toolkit. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion, 2012. http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf. Accessed February 22, 2013.
20. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in healthcare settings, 2006. Centers for Disease Control and Prevention, 2006. http://www.cdc.gov/ncidod/dhqp/pdf/ar/MDROGuideline2006.pdf. Accessed February 22, 2013.
21. Munoz-Price LS, De La Cuesta C, Adams S, et al. Successful eradication of a monoclonal strain of *Klebsiella pneumoniae* during a *K. pneumoniae* carbapenemase-producing *K. pneumoniae* outbreak in a surgical intensive care unit in Miami, Florida. *Infect Control Hosp Epidemiol* 2010;31:1074–1077.
22. Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A. Risk of acquiring multidrug-resistant gram-negative bacilli from prior room occupants in the intensive care unit. *Clin Microbiol Infect* 2011;17:1201–1208.
23. Snitkin ES, Zelazny AM, Thomas PJ, et al. Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genome sequencing. *Sci Transl Med* 2012;4:148ra116.
24. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: cur-

rent patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med* 2003;163:972–978.
25. Shaughnessy MK, Amundson WH, Kuskowski MA, DeCarolis DD, Johnson JR, Drekonja DM. Unnecessary antimicrobial use in patients with current or recent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2013;34:109–116.
26. Weintrob AC, Roediger MP, Barber M, et al. Natural history of colonization with gram-negative multidrug-resistant organisms among hospitalized patients. *Infect Control Hosp Epidemiol* 2010; 31:330–337.
27. Wiener-Well Y, Rudensky B, Yinnon AM, et al. Carriage rate of carbapenem-resistant *Klebsiella pneumoniae* in hospitalised patients during a national outbreak. *J Hosp Infect* 2010;74:344–349.