ORIGINAL ARTICLE

Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship

Dror Marchaim, MD;[1] Teena Chopra, MD;[1] Ashish Bhargava, MD;[1] Christopher Bogan, BS;[1] Sorabh Dhar, MD;[1] Kayoko Hayakawa, MD, PhD;[1] Jason M. Pogue, PharmD;[2] Suchitha Bheemreddy, MD;[1] Christopher Blunden, BS;[1] Maryann Shango, MD;[1] Jessie Swan, BS;[1] Paul R. Lephart, PhD;[3] Federico Perez, MD;[4,5] Robert A. Bonomo, MD;[4,5,6,7,8] Keith S. Kaye, MD, MPH[1]

BACKGROUND. Carbapenem-resistant Enterobacteriaceae (CRE) are rapidly emerging worldwide. Control group selection is critically important when analyzing predictors of antimicrobial resistance. Focusing on modifiable risk factors can optimize prevention and resource expenditures. To identify specific predictors of CRE, patients with CRE were compared with 3 control groups: (1) patients with extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, (2) patients with non-ESBL-containing Enterobacteriaceae, and (3) uninfected controls.

DESIGN. Matched multivariable analyses.

PATIENTS AND SETTING. Patients possessing CRE that were isolated at Detroit Medical Center from September 1, 2008, to August 31, 2009.

METHODS. Patients were matched (1 : 1 ratio) to the 3 sets of controls. Matching parameters included (1) bacteria type, (2) hospital/facility, (3) unit/clinic, (4) calendar year, and (5) time at risk (ie, from admission to culture). Matched multivariable analyses were conducted between uninfected controls and patients with CRE, ESBL, and non-ESBL Enterobacteriaceae. Models were also designed comparing patients with CRE to patients with ESBL, patients with non-ESBL Enterobacteriaceae, and all 3 non-CRE groups combined.

RESULTS. Ninety-one unique patients with CRE were identified, and 6 matched models were constructed. Recent (less than 3 months) exposure to antibiotics was the only parameter that was consistently associated with CRE, regardless of the group to which CRE was compared, and was not independently associated with isolation of ESBL or non-ESBL Enterobacteriaceae.

CONCLUSIONS. Exposure to antibiotics within 3 months was an independent predictor that characterized patients with CRE isolation. As a result, antimicrobial stewardship efforts need to become a major focus of preventive interventions. Regulatory focus regarding appropriate antimicrobial use might decrease the detrimental effects of antibiotic misuse and spread of CRE.

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The prevalence of carbapenem-resistant Enterobacteriaceae (CRE) is rising in healthcare delivery systems worldwide.[1-5] In 2007, among the bacteria causing healthcare-associated infections reported to the Centers for Disease Control and Prevention (CDC), 8% of *Klebsiella* isolates were resistant to carbapenems, compared with fewer than 1% in 2000.[6] Current estimates are even greater (http://www.cdc.gov). In southeast Michigan, CRE has become endemic in the past 3 years, causing outbreaks in various types of healthcare settings.[7,8] To apply preventive measures and interventions throughout the continuum of modern health care and effectively direct healthcare and public health resources, a detailed epidemiological investigation of predictors of CRE isolation is warranted.

Predictors of isolation of CRE have been reported in the literature and include advanced age, reduced functional status, residency in a long-term care facility (LTCF), invasive procedures, and recent use of antibiotics.[2-5,9-16] These risk factor studies used various types of control groups. Control group selection plays a critically important role in determining which forecasters are identified in case-control studies pertaining to antimicrobial-resistant organisms. Controls should reflect the

Affiliations: 1. Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Detroit, Michigan; 2. Department of Pharmacy Services, Detroit Medical Center, Wayne State University, Detroit, Michigan; 3. Department of Clinical Microbiology, Detroit Medical Center, Wayne State University, Detroit, Michigan; 4. Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio; 5. Department of Medicine, Case Western Reserve University, Cleveland, Ohio; 6. Veterans Integrated Service Network 10 Geriatric Research, Education, and Clinical Centers at Veterans Affairs Medical Center, Cleveland, Ohio; 7. Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio; 8. Department of Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, Ohio.

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background population from which the patients with the resistant organisms (ie, cases) have arisen.[17-19] The case-case-control study design has become a standard approach for accurately identifying risk factors that are uniquely associated with isolation of an antimicrobial-resistant pathogen. In the case-case-control study design, comparisons are made between 3 groups of patients: patients with isolation of an antimicrobial-resistant pathogen, patients with isolation of a more susceptible phenotype of the pathogen, and patients without isolation of the study pathogen (uninfected controls).

Several of the previous CRE studies considered patients with carbapenem-susceptible Enterobacteriaceae as controls, without using a group of patients who did not have Enterobacteriaceae isolated (uninfected controls), and others did not appropriately match uninfected controls to cases.[3,15,16] Some studies employed a case-case-control study design using 2 types of control groups, one including patients with isolation of carbapenem-susceptible Enterobacteriaceae and another including uninfected controls. However, the carbapenem-susceptible Enterobacteriaceae group included both extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and non-ESBL-containing Enterobacteriaceae.[14] This raises critical questions since patients with ESBL-producing organisms share at least some of the same risk factors for isolation as do those with CRE.[20] Therefore, by comparing patients with CRE to patients with carbapenem-susceptible Enterobacteriaceae that included both ESBL-producing and non-ESBL-producing Enterobacteriaceae, data pertaining to CRE predictors might have been biased.[18,21,22]

The aim of this study was to investigate predictors of CRE throughout the continuum of medical care (including LTCFs and outpatient clinics) by using 3 types of comparison groups: (1) patients with carbapenem-susceptible, ESBL-producing Enterobaceriaceae; (2) patients with carbapenem-susceptible, non-ESBL-producing Enterobacteriaceae; and (3) patients who did not have isolation of Enterobacteriaceae (ie, uninfected controls) during the study period. Analyzing predictors by using various combinations of comparison groups can help identify predictors that are unique or specific to CRE carriers and can help direct and prioritize interventions and measures to contain the spread of CRE.

METHODS

Study Settings and Design

The Detroit Medical Center (DMC) healthcare system consists of 8 hospitals, has more than 2,200 inpatient beds, and serves as a tertiary referral facility for metropolitan Detroit and southeastern Michigan. DMC has a single centralized Clinical Microbiology Laboratory (DMC-CML), which processes approximately 500,000 samples annually. Multiple outpatient facilities in southeastern Michigan use these laboratory services on a routine basis. Patient data at DMC are stored and managed through electronic medical records.

Patients possessing CRE that were isolated from September 1, 2008, to August 31, 2009, were matched and compared at a 1 : 1 ratio to 3 groups: (1) patients with ESBL-producing Enterobacteriaceae, (2) patients with susceptible non-ESBL-producing Enterobacteriaceae, and (3) uninfected control patients who did not have Enterobacteriaceae isolated. Matching parameters included (1) type of Enterobacteriaceae (for groups 1 and 2), (2) hospital or outpatient facility, (3) unit or clinic, (4) calendar year, and (5) time at risk (ie, time from admission to culture for patients with Enterobacteriaceae). For uninfected controls, the total duration of hospital stay had to be at least as long as the time at risk of their matched case. Eligible patients in the comparison groups were randomly selected using the randomization function in Excel (Microsoft). Institutional review boards at Wayne State University and DMC approved the study before its initiation.

Patients and Clinical Variables

CRE cases consisted of all patients who had CRE discovered in a clinical sample sent from all inpatient and outpatient facilities that submit specimens to DMC-CML. Active surveillance screening cultures were not performed routinely during the study period and were excluded from the analysis. Cultures from all anatomic sites were collected, and both infected and colonized patients were included (categorized according to presence of systemic inflammatory response syndrome and according to criteria established by the CDC[23,24]). For patients who had more than 1 CRE isolate during the study period, only the first episode of CRE isolation was analyzed (ie, only unique patients were included).

Parameters retrieved from patient charts included (1) patient demographics; (2) background and comorbid conditions before bacteria isolation (or during hospital admission for uninfected controls; these included functional status, Charlson scores,[25] and immunosuppressive conditions); (3) recent healthcare-associated exposures, including invasive procedures and devices; (4) acute severity of illness indices, including McCabe score;[26] (5) exposures to antimicrobials in the 3-month period before culture (and prior to admission for uninfected controls); and (6) isolation in the previous 6 months of any multidrug-resistant (MDR) pathogen, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

Microbiology

Bacteria were identified to the species level, and susceptibilities were determined to predefined antimicrobials on the basis of an automated broth microdilution system (MicroScan; Siemens) and in accordance with Clinical and Laboratory Standards Institute (CLSI) criteria.[27] Susceptibilities to colistin and tigecycline were determined by Etest (bioMérieux). ESBLs, after being identified in the automated system, were confirmed with a disc diffusion test.[27] All Enterobacteriaceae that were resistant to 1 or more extended-

spectrum (or third-generation) cephalosporin and had a minimum inhibitory concentration of 2 mg/L or greater to ertapenem were screened for carbapenemase production by the modified Hodge test, conducted according to CLSI criteria.[27] Subsequently, CRE were tested for the presence of bla_{KPC} by polymerase chain reaction (PCR),[2] with previously characterized KPC-producing *Klebsiella pneumoniae* isolates used as controls.[2,28]

Statistical Analysis

All analyses were performed using SPSS 19 (2011; IBM). To identify risk factors, univariate matched analyses were done by comparing groups for each variable of interest, and crude matched odds ratio and their 95% confidence intervals along with *P* values were calculated. Matched multivariable models were constructed using Cox regression. All variables with a *P* value less than .1 in the univariate matched analyses were considered for inclusion in the multivariable matched analyses. A stepwise selection procedure was used to select variables for inclusion in the final model. The final selected model was tested for confounding. If a covariate affected the β coefficient of a variable in the model by more than 10%, then the confounding variable was maintained in the multivariable model. All *P* values were 2-sided. In addition to examining statistical significance and confounding, effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. When effect modification was detected, subgroup analyses were performed.

Matched multivariable models were conducted comparing uninfected controls and patients with CRE, ESBL-producing Enterobacteriaceae, and non-ESBL-containing Enterobacteriaceae. Models were also designed comparing patients with CRE to patients with ESBL-producing Enterobacteriaceae, patients with non-ESBL-containing Enterobacteriaceae, and all 3 comparison groups combined.

RESULTS

Ninety-one unique patients with CRE were included in the study cohort, including 54 patients from tertiary care hospitals, 3 from a community hospital, 23 from long-term acute care facilities (LTACs), 2 from nursing homes, 1 from a rehabilitation center, and 8 from outpatient clinics. Of the CRE isolates, 74 were *K. pneumoniae*, 1 was *Klebsiella oxytoca*, 2 were *Escherichia coli*, and 14 were *Enterobacter* species. All CRE isolates that were included in this study contained bla_{KPC} identified by PCR using appropriate laboratory controls. Controls and the comparison Enterobacteriaceae groups were successfully matched to CRE cases at a 1 : 1 ratio. Thus, a total of 364 subjects were included in the final study cohort.

The mean age of patients included in the final cohort was 62 ± 19 years, and 176 (48%) were elderly (65 years or older). One-hundred ninety-four were female (53%), and 289 (81%) were African American. Forty-one percent of the cohort (n = 144) resided in institutions, 244 (71%) had deteriorated functional status in at least 1 activity of daily living, and 127 (37%) had a permanent indwelling medical device in place. Most Enterobacteriaceae were from a urinary source (111/273 [41%]), and 52 (19%) represented a colonization (patients were not infected per the definition used above).

Table 1 summarizes the univariate analyses of the 6 separate investigations conducted. Demographics (age, sex, and race) were not significantly different between the groups of patients with Enterobacteriaceae isolates and uninfected controls. Patients with CRE had frequent exposures to long-term acute and nonacute facilities, whereas other measures of healthcare exposure (such as recent surgery or invasive devices) were similarly frequent in patients with ESBLs. Although Charlson score and different comorbidities were frequent in patients with Enterobacteriaceae in general, diabetes and neurological impairment (ie, hemiplegia) appeared more frequently in patients with CRE.

Table 2 displays the multivariable matched models. Permanent residency in LTCFs captured patients residing in skilled nursing facilities as well as those residing in LTACs. Because many parts of the world do not have LTACs, utilizing a single variable to capture all types of LTCFs would make the multivariable results more applicable and generalizable to areas that do not have LTACs. In multivariable analysis, when compared with uninfected matched controls, CRE was associated with several independent predictors, including recent exposure to antibiotics, recent isolation of an MDR bacterium, recent invasive procedures (include percutaneous interventions, endoscopies, biopsies, and surgeries), and recent stay in an intensive care unit. However, many of these predictors were also indicative of isolation of other Enterobacteriaceae—that is, they were recognized as independent predictors of isolation of ESBL-producing Enterobacteriaceae and/or non-ESBL-containing Enterobacteriaceae.

In contrast, in this case-case-control analysis exposure to antimicrobial agents was consistently associated with CRE (Table 2). In comparisons between CRE and uninfected controls, CRE and ESBL, CRE and non-ESBL-containing Enterobacteriaceae, and CRE and all 3 comparison groups combined, antimicrobial exposure proved to be a consistent, independent predictor of CRE isolation. Additionally, antibiotic exposure was not an independent predictor of isolation of ESBLs or susceptible Enterobacteriaceae compared with uninfected controls in multivariable analysis (Table 2). Multivariable analyses for recent exposure to specific classes of antibiotic were conducted, but low numbers limited their significance (data not shown). It should be noted, however (Table 1), that previous treatment with fluoroquinolones and carbapenems (30% and 20%, respectively), was more common in patients with CRE than in the other groups. Interestingly, up to 85% of patients with CRE were previously treated with a cephalosporin, higher than the percentage of patients with ESBLs (69%).

TABLE 1. Univariate Analyses of Risk Factors for Isolation of Enterobacteriaceae with Various Levels of Antimicrobial Resistance, Detroit Medical Center, September 1, 2008, to August 31, 2009

	No. (%)[a]				OR[c] (95% CI) [*P* value]					
Variable	CRE	ESBL	Susceptibles[b]	Controls	CRE vs controls	CRE vs susceptibles[b]	CRE vs ESBL	CRE vs all 3 non-CRE groups combined	ESBL vs controls	Susceptibles[b] vs controls
Demographics										
Age, years, mean ± SD	63.4 ± 18.5	63.5 ± 19.4	59.5 ± 20.4	60.8 ± 19.6	*P* = .36	*P* = .17	*P* > .99	*P* = .34	*P* = .37	*P* = .65
Age >65 years	53 (58.2)	45 (49.5)	37 (40.7)	41 (45.1)	1.7 (0.9–3) [.07]	2.0 (1.1–3.8) [.02]	1.4 (0.8–2.6) [.23]	1.7 (1.02–2.8) [.03]	1.2 (0.7–2.1) [.55]	0.8 (0.5–1.5) [.55]
Female sex	46 (50.5)	47 (51.6)	47 (51.6)	47 (51.6)	1.04 (0.55–1.87) [>.99]	0.9 (0.5–1.8) [.9]	1.05 (0.6–1.9) [1]	1.2 (0.7–1.9) [.7]	1 (0.6–1.8) [>.99]	1.4 (0.8–2.6) [.3]
African American race	71 (79.8)	75 (83.3)	68 (74.7)	75 (86.2)	0.6 (0.3–1.4) [.3]	1.3 (0.7–2.7) [.42]	0.8 (0.4–1.7) [.54]	1.1 (0.6–2) [.74]	0.8 (0.4–1.8) [.6]	0.5 (0.2–1) [.54]
Recent healthcare exposures										
LTCF permanent residence	59 (67.8)	41 (46.6)	18 (20)	26 (29.5)	5.0 (2.6–9.1) [<.001]	8.3 (5–16.7) [<.001]	2.5 (1.25–5) [.01]	5.0 (2.5–10) [<.001]	2.0 (1.1–3.3) [.03]	0.6 (0.3–1.2) [.17]
LTAC permanent residence	35 (59.3)	2 (4.8)	0	4 (13.3)	9.5 (2.9–30.7) [<.001]	1.7 (1.3–2.2) [<.001]	29.2 (6.4–132.3) [<.001]	0.05 (0.02–0.13) [<.001]	0.3 (0.1–1.9) [.2]	1.7 (1.3–2.1) [.1]
Transfer from another hospital	1 (1.7)	5 (11.9)	6 (35.3)	17 (56.7)	0.01 (0.002–0.1) [<.001]	0.03 (0.003–0.3) [<.001]	0.13 (0.01–1.1) [.08]	26.6 (3.5–202.1) [<.001]	0.10 (0.03–0.34) [<.001]	0.42 (0.12–1.43) [.2]
Direct admission from LTAC	37 (44.6)	2 (2.2)	0	2 (2.2)	35.0 (8–151.7) [<.001]	1.8 (1.5–2.2) [<.001]	35.0 (8.1–151) [<.001]	52.5 (17.9–154.3) [<.001]	1.0 (0.1–7.3) [>.99]	0.98 (0.95–1.01) [.5]
LTAC stay in past 6 months	48 (56.5)	12 (15.4)	2 (2.2)	2 (2.2)	57.1 (13.2–247.2) [<.001]	57.1 (13.2–247.2) [<.001]	7.1 (3.4–15.1) [<.001]	19.6 (10.1–38.1) [<.001]	8.0 (1.7–37) [.004]	1 (0.1–7.3) [>.99]
Hemodialysis	15 (17.4)	15 (16.7)	11 (12.1)	8 (9.3)	2.1 (0.8–5.2) [.2]	1.54 (0.7–3.6) [.4]	1.1 (0.5–2.3) [>.99]	1.5 (0.8–2.8) [.28]	2.0 (0.8–4.9) [.18]	1.3 (0.5–3.5) [.63]
Hospitalization in past 3 months	65 (76.5)	61 (69.3)	48 (53.3)	49 (55.7)	2.6 (1.4–5) [<.001]	2.8 (1.5–5.5) [.002]	1.4 (0.7–2.8) [.31]	2.2 (1.3–3.88) [.004]	1.8 (0.97–3.3) [.09]	0.9 (0.5–1.6) [.8]
Days from last hospitalization[d]	50.5 ± 121.1; 18 (0–900)	75.6 ± 153.1; 22 (0–1,095)	110.1 ± 168.8; 26.7 (0–730)	97.8 ± 166.6; 29.3 (0–910)	*P* = .06	*P* = .02	*P* = .27	*P* = .04	*P* = .4	*P* = .7
ICU stay in past 3 months	45 (63.4)	52 (59.1)	36 (41.9)	18 (21.7)	6.3 (3.1–12.7) [<.001]	2.4 (1.3–4.6) [.01]	1.2 (0.6–2.3) [.63]	2.5 (1.4–4.2) [.001]	5.2 (2.7–10.2) [<.001]	2.6 (1.3–5.1) [.01]

Regular outpatient clinic visits	37 (42.5)	12 (14)	28 (30.8)	12 (14.1)	4.5 (2.1–9.5) [<.001]	1.7 (0.9–3.1) [.12]	4.6 (2.2–9.6) [<.001]	3.0 (1.8–5) [<.001]	1 (0.4–2.3) [>.99]	2.7 (1.3–5.8) [.01]
Invasive procedure in past 6 months[e]	73 (88)	59 (67)	62 (70.5)	31 (36.9)	12.5 (5.6–27.7) [<.001]	3.1 (1.4–6.8) [.01]	3.6 (1.6–8) [.002]	5.2 (2.6–10.5) [<.001]	3.5 (1.9–6.5) [<.001]	4.1 (2.2–7.7) [<.001]
Surgery in past 6 months[f]	67 (80.7)	52 (58.4)	51 (58.6)	22 (26.2)	11.8 (5.7–24.5) [<.001]	3.0 (1.5–5.9) [.003]	3 (1.5–5.9) [.002]	4.5 (2.5–8.2) [<.001]	4 (2.1–7.5) [<.001]	4.0 (2.1–7.6) [<.001]
Permanent foreign devices[g]	71 (86.6)	65 (72.2)	53 (60.9)	26 (31.3)	14.2 (6.5–31.1) [<.001]	4.1 (1.9–8.9) [<.001]	2.5 (1.1–5.4) [.03]	5.2 (2.6–10.3) [<.001]	5.7 (3–11) [<.001]	3.4 (1.8–6.4) [<.001]
Comorbidities										
Myocardial infarction	25 (29.1)	18 (19.8)	14 (15.4)	5 (5.7)	6.8 (2.5–18.7) [<.001]	2.25 (1.1–4.7) [.03]	1.7 (0.8–3.3) [.16]	2.6 (1.4–4.8) [.004]	4.1 (1.5–11.6) [.007]	3.02 (1.04–8.8) [.05]
Congestive heart failure	36 (41.9)	36 (39.6)	25 (27.5)	25 (28.4)	1.8 (0.9–3.4) [.08]	1.9 (1.01–3.6) [.05]	1.1 (0.6–2) [.76]	1.5 (0.94–2.5) [.09]	1.6 (0.9–3.1) [.16]	0.96 (0.5–1.8) [>.99]
Peripheral vascular disease	16 (18.6)	15 (16.5)	13 (14.3)	7 (8)	2.7 (1.03–6.8) [.45]	1.4 (0.6–3.1) [.54]	1.2 (0.5–2.5) [.8]	1.5 (0.8–2.9) [.2]	2.3 (0.9–5.9) [0.1]	1.9 (0.7–5.1) [.2]
Diabetes mellitus	58 (67.4)	39 (42.9)	32 (35.2)	37 (42)	2.9 (1.5–5.3) [<.001]	3.8 (2.1–7.1) [<.001]	2.8 (1.5–5.1) [.001]	3.1 (1.9–5.2) [<.001]	1.03 (0.6–1.9) [1]	0.75 (0.4–1.4) [.36]
Chronic renal disease[h]	45 (50)	46 (51)	32 (35)	26 (29)	2.5 (1.4–4.7) [.005]	2.0 (1.1–3.7) [.02]	1.1 (0.6–1.9) [.8]	1.7 (1.03–2.9) [.02]	2.4 (1.3–4.4) [.009]	1.3 (0.7–2.4) [.5]
Lung disease[i]	45 (50)	38 (42)	29 (32)	30 (33)	2.2 (1.2–4) [.015]	2.3 (1.3–4.3) [.006]	1.5 (0.8–2.7) [.2]	2 (1.2–3.3) [.006]	1.5 (0.8–2.7) [.3]	0.9 (0.5–1.7) [.9]
Peptic ulcer disease	8 (9.3)	7 (7.7)	13 (14.3)	8 (9.1)	1.3 (0.4–2.9) [>.99]	0.6 (0.2–1.6) [.36]	1.2 (0.4–3.6) [.8]	0.9 (0.4–2) [>.99]	0.8 (0.3–2.4) [.8]	1.7 (0.7–4.2) [.4]
Liver disease	15 (16)	20 (22)	15 (16)	12 (13)	1.4 (0.6–3.1) [.5]	1.1 (0.5–2.4) [.8]	0.8 (0.4–1.6) [.6]	1 (0.5–2) [.96]	1.8 (0.8–3.9) [.2]	1.3 (0.5–2.8) [.7]
Any neurologic disease	53 (61.6)	45 (50.6)	32 (35.2)	26 (29.5)	3.8 (2–7.2) [<.001]	3.0 (1.6–5.5) [.001]	1.6 (0.9–2.9) [.17]	2.6 (1.6–4.2) [<.001]	2.4 (1.3–4.5) [.01]	1.3 (0.7–2.4) [.43]
Cerebrovascular disease	37 (43)	30 (33)	20 (22)	16 (18.2)	3.4 (1.7–6.8) [<.001]	2.7 (1.4–5.2) [.004]	1.5 (0.8–2.8) [.22]	2.3 (1.4–3.9) [.002]	2.2 (1.1–4.4) [.03]	1.3 (0.6–2.6) [.58]
Hemiplegia	31 (36)	16 (17.6)	13 (14.3)	9 (10.2)	4.9 (2.2–11.2) [<.001]	3.4 (1.6–7) [.001]	2.6 (1.3–5.3) [.01]	3.4 (2–6) [<.001]	1.9 (0.8–4.5) [.2]	1.5 (0.6–3.6) [.5]

TABLE 1 (*Continued*)

Variable	No. (%)[a]				OR[c] (95% CI) [*P* value]					
	CRE	ESBL	Susceptibles[b]	Controls	CRE vs controls	CRE vs susceptibles[b]	CRE vs ESBL	CRE vs all 3 non-CRE groups combined	ESBL vs controls	Susceptibles[b] vs controls
Dementia	27 (31.4)	27 (29.7)	13 (14.3)	12 (13.6)	2.9 (1.4–6.2) [.01]	2.8 (1.3–5.8) [.01]	1.1 (0.6–2.1) [.87]	1.9 (1.1–3.3) [.03]	2.7 (1.3–5.7) [.01]	1.1 (0.5–2.5) [>.99]
Malignancy (present or past)	14 (15)	17 (19)	15 (16)	19 (21)	0.7 (0.3–1.5) [.4]	0.5 (0.2–1.1) [.1]	0.8 (0.4–1.7) [.6]	0.7 (0.3–1.3) [.2]	0.9 (0.4–1.8) [.85]	1.4 (0.7–2.7) [.4]
Leukemia	0	1 (1.1)	0	0			0.99 (0.97–1.01) [>.99]	1 (1–0.01) [.6]	1.01 (0.9–1.03) [>.99]	
Lymphoma	1 (1.2)	0	0	1 (1.1)	1.02 (0.1–16.6) [>.99]	*P* = .49	*P* = .49	3.2 (0.2–51) [.4]	*P* = .49	*P* = .31
Solid tumor (present or past)	12 (13)	16 (18)	28 (32)	13 (14)	0.9 (0.4–2.2) [1]	0.4 (0.2–0.8) [.01]	0.8 (0.4–1.7) [.5]	0.6 (0.3–1.2) [.14]	1.2 (0.6–2.7) [.7]	2.6 (1.2–5.4) [.01]
AIDS	0	0	2 (2.2)	1 (1.1)	1.01 (0.99–1.03) [>.99]	0.98 (0.95–1.01) [.5]		1.0 (1–1.02) [.3]	0.99 (0.97–1.01) [.49]	1.96 (0.17–22) [>.99]
Chronic skin ulcer	45 (52.9)	37 (41.6)	8 (8.8)	12 (13.8)	7.0 (3.3–15) [<.001]	11.7 (5–27) [<.001]	1.6 (0.9–2.9) [.17]	4.1 (2.4–7.2) [<.001]	4.4 (2.1–9.3) [<.001]	0.6 (0.2–1.6) [.34]
Charlson weighted index comorbidity[d]	5.3 ± 2.7; 5.1 (1–12)	4.1 ± 2.7; 3.8 (0–10)	3.6 ± 3.2; 2.7 (0–12)	2.8 ± 2.4; 2.6 (0–10)	*P* < .001	*P* < .001	*P* = .01	*P* < .001	*P* = .001	*P* = .08
Charlson combined condition score[d]	7.5 ± 3.3; 7.4 (1–14)	6.3 ± 3.6; 6.4 (0–14)	5.4 ± 3.7; 5.21 (0–15)	4.7 ± 3.1; 4.7 (0–13)	*P* < .001	*P* < .001	*P* = .02	*P* < .001	*P* = .002	*P* = .18
Charlson 10-year survival probability, %[d]	16.9 ± 30.1; 1.1 (0–95)	27.91 ± 37.7; 1.7 (0–98)	37.3 ± 40.6; 17 (0–98)	41.5 ± 40.4; 31.2 (0–98)	*P* < .001	*P* < .001	*P* = .04	*P* < .001	*P* = .02	*P* = .5
Immunosuppressive states										
Neutropenia at culture date	0	0	7 (8)	2 (2.3)	1.0 (0.99–1.1) [.5]	0.92 (0.86–0.98) [.01]		0 (0–1.8) [.12]	0.98 (0.95–1.01) [.24]	3.7 (0.8–18.4) [.17]
Steroid use in past month	20 (23.3)	16 (18.2)	25 (29.4)	15 (17.2)	1.5 (0.7–3.1) [.35]	0.7 (0.4–1.4) [.39]	1.4 (0.7–2.9) [.46]	1.1 (0.6–2) [.77]	1.1 (0.5–2.3) [>.99]	2.0 (0.97–4.1) [.07]
Chemotherapy in past 3 months	2 (2.3)	0	5 (5.5)	6 (6.9)	0.3 (0.1–1.6) [.28]	0.4 (0.1–2.2) [.45]	1.02 (0.99–1.06) [.24]	0.55 (0.1–2.5) [.74]	1.1 (1.01–1.1) [.01]	0.8 (0.2–2.7) [.76]

Radiotherapy in past 3 months	2 (2.3)	1 (1.1)	5 (5.5)	3 (3.4)	0.7 (0.1–4) [>.99]	0.4 (0.1–2.2) [.45]	2.1 (0.2–23.5) [.62]	0.7 (0.2–3.2) [>.99]	0.3 (0.03–3.1) [.4]	1.6 (0.4–7) [.72]
HIV	1 (1.2)	0	3 (3.3)	1 (1.1)	1.0 (0.1–16) [>.99]	0.4 (0.04–3.4) [.62]	1.01 (0.99–1.03) [.49]	0.8 (0.1–7) [>.99]	0.99 (0.97–1.01) [.5]	2.9 (0.3–28.7) [.6]
Posttransplantation	3 (3.5)	1 (1.1)	2 (2.2)	2 (2.3)	1.6 (0.3–9.6) [.7]	1.6 (0.3–10) [.67]	3.26 (0.33–31.93) [.36]	1.92 (0.45–8.23) [.41]	0.48 (0.04–5.36) [.62]	0.96 (0.13–6.93) [>.99]
Anti-TNF in past 3 months	0	0	0	1 (1.1)	0 (0–18) [>.99]			0 (0–54) [>.99]	0.99 (0.97–1.01) [.5]	0.99 (0.97–1.01) [.5]
Microbiology										
Body site of isolation										
Blood	17 (18.7)	17 (18.7)	18 (20.0)			0.9 (0.4–1.9) [.82]	1.0 (0.5–2.1) [>.99]	1.04 (0.5–2) [.9]		
Sputum	23 (25.3)	22 (24.2)	21 (23.3)			1.1 (0.6–2.2) [.76]	1.06 (0.5–2) [.86]	0.9 (0.5–1.7) [.78]		
Urine	36 (39.6)	39 (42.9)	36 (40)			1.0 (0.5–1.8) [.95]	0.9 (0.5–1.6) [.65]	1.1 (0.7–1.8) [.8]		
Wound	13 (14.3)	13 (14.3)	15 (16.7)			0.8 (0.4–1.9) [.66]	1.0 (0.4–2.3) [>.99]	1.1 (0.5–2.3) [.8]		
Resistant bacteria[j] in past 3 months	58 (70.7)	41 (45.6)	29 (31.9)	6 (7.5)	30.0 (11–78) [<.001]	5.2 (2.7–10) [<.001]	2.9 (1.5–5.4) [.001]	5.9 (3.4–10.2) [<.001]	10.3 (4.1–26.2) [<.001]	5.8 (2.3–14.8) [<.001]
Status at admission										
Independent functional status	13 (14.3)	14 (15.6)	27 (31.4)	46 (52.3)	0.2 (0.1–0.4) [<.001]	0.4 (0.2–0.9) [.03]	1.05 (0.5–2.4) [.9]	2.5 (1.3–4.8) [<.001]	0.2 (0.08–0.3) [<.001]	0.4 (0.2–0.8) [<.001]
Alert/nondeteriorated consciousness level	42 (52.5)	39 (43.3)	63 (69.2)	66 (75)	0.4 (0.2–0.7) [<.001]	0.5 (0.3–0.9) [.03]	1.5 (0.8–2.6) [.23]	1.5 (0.9–2.5) [.11]	0.3 (0.1–0.5) [<.001]	0.75 (0.4–1.45) [.4]
Acute illness indices										
Rapidly fatal McCabe score	14 (16.7)	12 (13.2)	9 (9.9)	4 (4.4)	4.3 (1.4–13.7) [.01]	1.8 (0.7–4.5) [.26]	1.3 (0.6–3) [.5]	2.0 (0.9–4.2) [.055]	3.3 (1.01–10.5) [.05]	2.4 (0.7–8) [.07]
Clinical syndrome										
Colonization	20 (28.2)	11 (12.2)	24 (27)			1.1 (0.5–2.1) [.87]	2.8 (1.3–6.4) [.02]	0.6 (0.3–1.2) [.14]		
Central line	8 (11.3)	3 (3.3)	5 (5.6)			2.1 (0.7–6.8) [.19]	3.7 (0.99–14.43) [.06]	2.9 (0.9–9.3) [.07]		

TABLE 1 (*Continued*)

	No. (%)[a]				OR[c] (95% CI) [*P* value]					
Variable	CRE	ESBL	Susceptibles[b]	Controls	CRE vs controls	CRE vs susceptibles[b]	CRE vs ESBL	CRE vs all 3 non-CRE groups combined	ESBL vs controls	Susceptibles[b] vs controls
Pneumonia	14 (19.7)	24 (26.7)	16 (18)			1.1 (0.5–2.5) [.8]	0.7 (0.3–1.4) [.3]	1.2 (0.6–2.3) [.7]		
UTI	14 (19.7)	35 (38.9)	23 (25.8)			0.7 (0.3–1.5) [.36]	0.4 (0.2–0.8) [.01]	0.45 (0.2–0.99) [.04]		
SSTI	11 (15.5)	10 (11.1)	11 (12.4)			1.3 (0.5–3.2) [.6]	1.5 (0.6–3.7) [.41]	0.7 (0.3–1.6) [.4]		
Bone or joint	1 (1.4)	0	0			2.3 (1.9–2.7) [.26]	2.3 (1.9–2.7) [.26]	3.6 (2.9–4.3) [.11]		
Intra-abdominal	0	2 (2.2)	3 (3.4)			1.8 (1.6–2.1) [.12]	1.8 (1.6–2.1) [.2]	1.4 (1.3–1.5) [.2]		
CNS	1 (1.4)	0	0			2.3 (1.9–2.7) [.26]	2.3 (1.9–2.7) [.26]	3.6 (2.9–4.3) [.11]		
Eye	1 (1.4)	0	0			2.3 (1.9–2.7) [.26]	2.3 (1.9–2.7) [.26]	3.6 (2.9–4.3) [.11]		
Bacteremia without focus	2 (2.8)	5 (5.6)	7 (7.9)			0.3 (0.1–1.7) [.17]	0.5 (0.1–2.6) [.4]	2.5 (0.5–11.4) [.2]		
Severe levels of sepsis[k]	11 (18)	19 (23.7)	13 (23.6)			0.7 (0.3–1.8) [.5]	0.7 (0.3–1.6) [.5]	1.4 (0.7–3) [.5]		
On vasopressors at culture date	7 (11.5)	23 (27.7)	14 (17.5)			0.6 (0.2–1.6) [.35]	0.3 (0.1–0.9) [.02]	0.4 (0.2–1.05) [.06]		
Necessitates transfer to ICU	10 (14.1)	12 (20.3)	13 (19.4)			0.7 (0.3–1.7) [.5]	0.6 (0.3–1.6) [.4]	0.7 (0.3–1.5) [.3]		
Necessitates intubation	10 (16.7)	9 (15.3)	9 (12.5)			1.4 (0.5–3.7) [.6]	1.1 (0.4–3) [>.99]	1.3 (0.5–2.9) [.7]		
Necessitates CVC insertion	11 (26.3)	10 (23.3)	9 (18.4)			1.6 (0.6–4.3) [.45]	1.2 (0.4–3.1) [.81]	1.4 (0.6–3.2) [.5]		

Necessitates urinary catheter insertion	11 (30.6)	9 (23.1)	17 (35.4)			0.8 (0.3–2) [.8]	1.5 (0.5–4) [.6]	1.0 (0.4–2.4) [>.99]		
Acute renal failure[l]	17 (20.5)	30 (33)	28 (31.8)			0.55 (0.3–1.1) [.12]	0.5 (0.3–1.04) [.09]	0.5 (0.3–1) [.06]		
Acute liver injury[m]	2 (2.6)	0	3 (3.4)			0.8 (0.1–4.7) [>.99]	1.02 (0.99–1.06) [.21]	1.6 (0.3–9.6) [.6]		
Antibiotics										
Overall antibiotic exposure in past 3 months	70 (95.9)	65 (76.5)	48 (56.5)	36 (41.9)	32 (9–111) [<.001]	18.0 (5.2–62) [<.001]	7.2 (2–25.3) [.001]	16.8 (5.1–55) [<.001]	4.5 (2.3–8.7) [<.001]	1.8 (0.99–3.3) [.06]
Time from last antibiotics, days[d]	8.6 ± 15.9; 0.9 (0–77)	9.7 ± 25.5; 1.2 (0–150)	14.2 ± 19.8; 6.5 (0–95)	15.5 ± 23.6; 0.7 (0–77)	$P = .13$	$P = .13$	$P = .77$	$P = .18$	$P = .27$	$P = .79$
Penicillin in past 3 months	35 (50.7)	26 (31)	14 (16.3)	12 (14)	6.3 (2.9–13.7) [<.001]	5.3 (2.5–11.1) [<.001]	2.3 (1.2–4.5) [.2]	4.0 (2.2–7.3) [<.001]	2.8 (1.3–5.9) [.02]	1.2 (0.5–2.8) [.56]
Cephalosporin in past 3 months	60 (85.7)	58 (69)	23 (26.7)	18 (20.9)	23.0 (10–53) [<.001]	16.4 (7.2–37) [<.001]	2.7 (1.2–6.1) [.02]	9.5 (4.4–21) [<.001]	8.4 (4.2–16.9) [<.001]	1.4 (0.7–2.8) [.42]
Monobactam in past 3 months	2 (2.9)	5 (6)	2 (2.3)	0	1.03 (0.99–1.07) [.2]	1.3 (0.2–9.1) [>.99]	0.5 (0.1–2.5) [.5]	1.06 (0.5–5) [.9]	1.06 (1.01–1.1) [.03]	1.02 (0.99–1.06) [.22]
Carbapenem in past 3 months	15 (21.7)	8 (9.5)	2 (2.3)	2 (2.3)	11.7 (2.6–53) [<.001]	11.7 (2.6–53) [<.001]	2.6 (1.1–6.7) [.04]	5.6 (2.3–15.7) [<.001]	4.4 (0.9–21.5) [.06]	1.0 (0.1–7.3) [.61]
Fluoroquinolone in past 3 months	21 (30.4)	10 (11.9)	5 (5.8)	18 (20.9)	1.65 (0.8–3.4) [.2]	7.1 (2.5–20) [<.001]	3.2 (1.4–7.5) [.01]	3.0 (1.6–5.6) [.002]	0.5 (0.2–1.2) [.15]	0.2 (0.1–0.7) [.01]
Glycopeptide in past 3 months	45 (63.4)	46 (54.1)	21 (24.4)	20 (23.3)	5.7 (2.9–11.4) [<.001]	5.4 (2.7–10.7) [<.001]	1.5 (0.8–2.8) [.3]	3.4 (1.9–6) [<.001]	3.9 (2–7.5) [<.001]	1.07 (0.5–2.2) [.6]
Tetracycline[n] in past 3 months	7 (10.1)	7 (8.3)	1 (1.2)	0	1.1 (1.03–1.2) [.003]	9.6 (1.2–80) [.02]	1.2 (0.4–3.7) [.8]	3.5 (1.1–11.1) [.04]	1.09 (1.02–1.16) [.006]	1.01 (0.99–1.03) [.37]
Colistin in past 3 months	4 (5.9)	6 (7.1)	1 (1.2)	1 (1.2)	5.3 (0.6–49) [.18]	5.3 (0.6–48.7) [.2]	0.8 (0.2–3) [>.99]	1.9 (0.5–7.4) [.3]	6.5 (0.8–55.5) [.06]	1.0 (0.6–16.3) [.61]
Aminoglycoside in past 3 months	9 (13)	8 (9.4)	9 (10.5)	2 (2.3)	6.3 (1.3–30) [.01]	1.3 (0.5–3.4) [.63]	1.4 (0.5–4) [.6]	1.9 (0.7–4.6) [.2]	4.4 (0.9–21.2) [.06]	4.9 (1–23.4) [.06]
TMP-SMX in past 3 months	4 (5.9)	6 (7.1)	4 (4.7)	2 (2.3)	2.6 (0.5–14.8) [.41]	1.3 (0.3–5.3) [.73]	0.8 (0.2–3) [>.99]	1.3 (0.4–4.1) [.75]	3.2 (0.6–16.5) [.17]	2.1 (0.4–11.5) [.7]

TABLE 1 (*Continued*)

Variable	No. (%)[a]				OR[c] (95% CI) [*P* value]					
	CRE	ESBL	Susceptibles[b]	Controls	CRE vs controls	CRE vs susceptibles[b]	CRE vs ESBL	CRE vs all 3 non-CRE groups combined	ESBL vs controls	Susceptibles[b] vs controls
Daptomycin in past 3 months	3 (4.4)	2 (2.4)	4 (4.7)	0	1.1 (0.99–1.2) [.08]	1.0 (0.2–4.4) [>.99]	1.9 (0.3–11.7) [.66]	1.9 (0.4–8.9) [.4]	1.02 (0.99–1.06) [.2]	1.05 (1.01–1.1) [.1]
Linezolid in past 3 months	11 (16.2)	9 (10.7)	2 (2.3)	3 (3.5)	5.3 (1.4–20) [.009]	8.1 (1.7–38) [.003]	1.6 (0.6–4.1) [.34]	3.3 (1.3–8.3) [.003]	3.3 (0.9–12.7) [.08]	0.7 (0.1–4) [.54]
Macrolides in past 3 months	6 (8.8)	7 (8.3)	4 (4.7)	3 (3.5)	2.7 (0.6–11) [.18]	2.0 (0.5–7.3) [.3]	1.1 (0.3–3.3) [>.99]	1.7 (0.6–4.9) [.4]	2.5 (0.6–10) [.2]	1.4 (0.3–6.2) [.57]
Clindamycin in past 3 months	13 (18.8)	10 (11.9)	7 (8.1)	1 (1.2)	19.5 (2.5–153) [<.001]	2.6 (0.98–7) [.06]	1.7 (0.7–4.2) [.26]	3.0 (1.3–7) [.003]	11.4 (1.4–90.8) [.005]	7.4 (0.9–62) [.06]
Metronidazole in past 3 months	13 (18.8)	14 (16.7)	4 (4.7)	4 (4.7)	4.8 (1.5–15.3) [.08]	4.8 (1.5–15.4) [.01]	1.2 (0.5–2.7) [.83]	2.5 (1.1–5.5) [.02]	4.1 (1.3–13) [.01]	1.0 (0.2–4.1) [.61]
Rifampin in past 3 months	2 (2.9)	5 (6)	2 (2.3)	1 (1.2)	2.6 (0.3–29) [.6]	1.3 (0.2–9.3) [>.99]	0.5 (0.1–2.6) [.5]	0.9 (0.2–4.3) [>.99]	5.4 (0.6–47.1) [0.1]	2.0 (0.2–23) [.5]
No. of antibiotic courses in past 3 months[d]	3.56 ± 1.94; 3.37 (0–10)	2.73 ± 1.96; 2.55 (0–8)	1.22 ± 1.5; 0.84 (0–7)	1.1 ± 1.69; 0.61 (0–8)	*P* < .001	*P* < .001	*P* = .01	*P* < .001	*P* < .001	*P* = .63

NOTE. CI, confidence interval; CNS, central nervous system; CRE, carbapenem-resistant Enterobacteriaceae; CVC, central venous catheter; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; HIV, human immunodeficiency virus; ICU, intensive care unit; LTAC, long-term acute care facility; LTCF, long-term care facility; OR, odds ratio; SD, standard deviation; SSTI, skin and soft-tissue infection; TMP-SMX, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor; UTI, urinary tract infection.

[a] The percentages displayed throughout the table are out of the patients for whom data were available (eg, excluding the missing cases). Data that are not no. (%) are indicated.

[b] Non-ESBL and non-CRE susceptible Enterobacteriaceae.

[c] Whenever the OR could not be calculated, the relative risk is provided.

[d] Mean ± SD; median (range).

[e] Any type of invasive procedure, including endoscopies, any percutaneous intervention, biopsies, and any type of surgery.

[f] Any type of surgery, from minor to major, the whole spectrum—from gastric tube insertion and opening an abscess to major surgeries.

[g] Tracheotomies, permanent central venous lines, permanent urinary catheters, orthopedic external fixators, gastrostomies, and drains.

[h] Serum creatinine >1.5 mg/dL.

[i] Includes asthma, chronic obstructive pulmonary diseases, interstitial lung disease, and bronchiectasis.

[j] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

[k] Severe sepsis/septic shock/multiorgan failure.

[l] Elevation of serum creatinine to 50% or more above baseline.

[m] Transaminases double the baseline value, international normalized ratio >1.5 without anticoagulants, and total bilirubin triple the baseline value.

[n] Including tigecycline.

TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

	CRE vs uninfected[b]		ESBL vs uninfected[b]		Susceptible vs uninfected[b]		CRE vs ESBL		CRE vs susceptible		CRE vs all controls combined	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any antibiotic exposure in previous 3 months	11.4 (2–64.3)	.006	1.7 (0.7–4.1)	.24			5.2 (1.4–19.4)	.015	12.3 (3.3–45)	<.001	7.1 (1.9–25.8)	.003
Permanent residency in institution	1.04 (0.2–4.5)	.96	1.3 (0.5–3.6)	.56	0.15 (0.05–0.5)	.002	2.1 (1–4.2)	.05	5.3 (2.1–12.9)	<.001	2.6 (1.3–5.3)	.01
Isolation of resistant bacteria in previous 6 months[c]	15.3 (4.2–55.6)	<.001	8.25 (2.7–25.7)	<.001	6.6 (1.9–23.3)	.003	1.7 (0.76–3.7)	.2	1.8 (0.7–4.7)	.23	2.9 (1.4–5.7)	.003
Dependent functional status in background	1.4 (0.5–4.4)	.55	5.6 (2.1–14.7)	.001	2.6 (1.1–6.4)	.03			2.0 (0.7–6.2)	.2	1.6 (0.6–4)	.33
ICU stay in previous 3 months	3.9 (1.3–12.4)	.02	5.2 (2.1–13.2)	.001	3.0 (1.2–7.2)	.02			1.6 (0.6–4)	.34	1.36 (0.7–2.7)	.37
Recent (6 months) invasive procedure	4.2 (1.2–15)	.03	1.2 (0.4–3.4)	.76	3.2 (1.3–8)	.01	2.8 (1.1–7.6)	.04			2.7 (1.1–7.1)	.04
Charlson weighted index comorbidity ≥3	3.1 (0.8–11.8)	.1	1.1 (0.4–2.7)	.87	2.2 (0.94–5)	.07	2.4 (1.03–5.6)	.04	4.8 (1.9–12.5)	.001	3.1 (1.4–7)	.006

NOTE. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

[a] If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

[b] Part of the case-case-control analysis.

[c] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*.

DISCUSSION

Our study represents an extensive epidemiological investigation that used 3 matched comparison groups to ascertain specific and unique predictors of isolation of CRE. The case-case-case-control study design allowed us to differentiate between predictors of CRE isolation and predictors of isolation of any Enterobacteriaceae. We believe the most striking finding from this analysis was that antimicrobial exposures were strong predictors of isolation of CRE but not of isolation of carbapenem-susceptible ESBL-producing Enterobacteriaceae or carbapenem-susceptible non-ESBL-producing Enterobacteriaceae. This important result suggests that limiting excessive antimicrobial use can help prevent the spread of CRE and places great importance on antimicrobial stewardship and other processes that aim to optimize and limit unnecessary antimicrobial use.

Recent exposure to antibiotics has been reported as a predictor of CRE by other investigators,[14] although this study is the first to report that antimicrobial exposures were the only specific predictor of CRE. Our analyses did not permit identification of which classes of antibiotics were risk factors for CRE colonization or infection. Recently, a mouse model of intestinal colonization found that CRE is promoted by antibiotics that lack significant activity against it and disturb the intestinal anaerobic flora.[29] Interestingly, recent courses of antibiotic treatment were not independent predictors of isolation of ESBL-producing Enterobacteriaceae, although other investigators have reported antibiotic exposures as being associated with ESBL isolation.[30,31] One potential explanation for the differences between the findings of our study and those of other investigations pertains to the rigorous criteria by which control patients were selected in the study at DMC, including matching on several variables, which led to the inclusion of uninfected controls with a relatively high severity of illness and extensive healthcare exposure. Additionally, our investigation was not designed to isolate predictors of ESBLs, and therefore the selected ESBL "controls" might not necessarily reflect the source population from which patients with ESBL-producing Enterobacteriaceae arose. A prospective study would have been a better design to analyze recent antimicrobial use. However, conducting a prospective study was beyond the scope of this project. To address this limitation, all pharmacy records and electronic medical record notes were reviewed to capture antimicrobial exposures.

Recently, emergence of a new carbapenem-resistant Enterobacteriaceae producing New Delhi metallo-β-lactamase was reported from the Indian subcontinent, where antibiotics are frequently consumed without a prescription from a trained practitioner.[32] Antimicrobial misuse that leads to antimicrobial resistance is an urgent global hazard,[32,33] and antimicrobial stewardship should be increasingly recognized as a pivotal intervention in controlling resistance. Contemporary studies indicate that antimicrobial stewardship is becoming increasingly important, as new antimicrobial agents are not being developed by the pharmaceutical industry fast enough.[34] In 2007, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America issued guidelines for developing institutional programs to enhance antimicrobial stewardship.[35] However, success (performance) measurements that quantify adherence to these guidelines are sometimes difficult to report and analyze. Every licensed physician can prescribe antibiotics; unfortunately, the decision to do so has major long-term clinical consequences, as seen herein. On the basis of the findings presented here, we urge that new and strict guidelines be implemented that consider the period of time when antibiotics were last used (3 months or less) to assist clinicians in appropriate decision making. Our findings resonate with recent guidelines from the Infectious Diseases Society of America in the consideration of antibiotic choices for community-acquired pneumonia.[36]

Because of mandatory reporting of hospital-acquired infection (HAI) rates and decreased reimbursement associated with acquirement of some HAIs, there is increased motivation for hospitals to reduce the rates of HAIs in an effort to improve patient safety and clinical care as well as reduce hospital costs while improving their reputation.[37] Senior administrators have become increasingly involved in HAI reduction efforts, and acknowledgment of the importance and role of infection preventionists is increasing. The same rationale that led to these types of initiatives might also be applied to MDR organisms such as CRE in the hospital. Acquisition of CRE within a facility should be perceived as a major threat to patient safety. If it became mandatory to report hospital-acquired CRE rates, the motivation to enhance and focus on stewardship efforts (as well as infection control efforts) might increase dramatically. Such initiatives might inspire hospitals to reduce unnecessary antimicrobial use in healthcare settings and would improve the surveillance and monitoring of MDR organisms such as CRE in facilities, which might also decrease CRE spread. Facilities will frequently screen patients on admission to avoid the false association of the possible future CRE isolation with their institution. CRE screening is simple to perform, is sensitive, and is not associated with extensive burden in terms of technician labor.[38,39] A major advantage of surveillance for MDR organisms is that acquisition of an MDR organism, unlike HAI, is an event that adheres to a simple, objective definition, and rates would not be subjected to misinterpretation or manipulation, as is sometimes the case with HAI rates.[40]

This comprehensive analysis demonstrates that antimicrobial consumption is a specific risk factor for CRE isolation. Nevertheless, compelling questions still remain. What are the genetic platforms harboring bla_{KPC}, and are they related among different genera that are spreading in DMC? Are there other mechanisms of resistance to carbapenems that coexist with bla_{KPC}? What were the transmission dynamics of the 8 CRE isolated outside of hospital settings? Because CRE are also MDR (and sometimes even extensively drug resistant or

pandrug resistant) and are virulent pathogens, substantial measures are needed to prevent continued spread of these pathogens. One option might be to establish administrative, regulatory, and fiscal pressure related to healthcare acquisition of CRE, as is currently applied to certain types of HAI. Such initiatives and pressure would probably improve adherence to appropriate antimicrobial stewardship and infection control practices and improve the safety of hospitalized patients.

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Address correspondence to Dror Marchaim, MD, Division of Infectious Diseases, 5 Hudson, Harper University Hospital, 3990 John R. Street, Detroit, MI 48201 (drormc@hotmail.com).

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