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Epidemiology and Risk Factors for Isolation of *Escherichia coli* Producing CTX-M-Type Extended-Spectrum β-Lactamase in a Large U.S. Medical Center

Kayoko Hayakawa,[a] Sureka Gattu,[b] Dror Marchaim,[a] Ashish Bhargava,[a] Mohan Palla,[a] Khaled Alshabani,[a] Uma Mahesh Gudur,[a] Harish Pulluru,[a] Pradeep Bathina,[a] Pranathi Rao Sundaragiri,[a] Moumita Sarkar,[a] Hari Kakarlapudi,[a] Balaji Ramasamy,[a] Priyanka Nanjireddy,[a] Shah Mohin,[a] Meenakshi Dasagi,[a] Satya Datla,[a] Vamsi Kuchipudi,[a] Swetha Reddy,[a] Shobha Shahani,[a] Vijaya Upputuri,[a] Satya Marrey,[a] Vedavyas Gannamani,[a] Nandhini Madhanagopal,[a] Srinadh Annangi,[a] Busani Sudha,[a] Kalyan Srinivas Muppavarapu,[a] Judy A. Moshos,[a] Paul R. Lephart,[c] Jason M. Pogue,[d] Karen Bush,[b] Keith S. Kaye[a]

Division of Infectious Diseases, Wayne State University, Detroit Medical Center, Detroit, Michigan, USA[a]; Department of Biology, Indiana University, Bloomington, Indiana, USA[b]; Detroit Medical Center University Laboratories, Detroit, Michigan, USA[c]; Department of Pharmacy Services, Detroit Medical Center, Detroit, Michigan, USA[d]

A case-case-control study was conducted to identify independent risk factors for recovery of *Escherichia coli* strains producing CTX-M-type extended-spectrum β-lactamases (CTX-M *E. coli*) within a large Southeastern Michigan medical center. Unique cases with isolation of ESBL-producing *E. coli* from February 2010 through July 2011 were analyzed by PCR for $bla_{\text{CTX-M}}$, bla_{TEM}, and bla_{SHV} genes. Patients with CTX-M *E. coli* were compared to patients with *E. coli* strains not producing CTX-M-type ESBLs (non-CTX-M *E. coli*) and uninfected controls. Of 575 patients with ESBL-producing *E. coli*, 491 (85.4%) isolates contained a CTX-M ESBL gene. A total of 319 (84.6%) patients with CTX-M *E. coli* (282 [74.8%] CTX-M-15 type) were compared to 58 (15.4%) non-CTX-M *E. coli* patients and to uninfected controls. Independent risk factors for CTX-M *E. coli* isolation compared to non-CTX-M *E. coli* included male gender, impaired consciousness, H2 blocker use, immunosuppression, and exposure to penicillins and/or trimethoprim-sulfamethoxazole. Compared to uninfected controls, independent risk factors for isolation of CTX-M *E. coli* included presence of a urinary catheter, previous urinary tract infection, exposure to oxyimino-cephalosporins, dependent functional status, non-home residence, and multiple comorbid conditions. Within 48 h of admission, community-acquired CTX-M *E. coli* ($n = 51$ [16%]) and non-CTX-M *E coli* ($n = 11$ [19%]) strains were isolated from patients with no recent health care contacts. CTX-M *E. coli* strains were more resistant to multiple antibiotics than non-CTX-M *E. coli* strains. CTX-M-encoding genes, especially $bla_{\text{CTX-M-15}}$ type, represented the most common ESBL determinants from ESBL-producing *E. coli*, the majority of which were present upon admission. Septic patients with risk factors for isolation of CTX-M *E. coli* should be empirically treated with appropriate agents. Regional infection control efforts and judicious antibiotic use are needed to control the spread of these organisms.

Extended-spectrum-β-lactamase (ESBL)-producing organisms are increasingly prevalent worldwide and pose a serious public threat (1, 2). Until recently, ESBL-producing organisms were primarily nosocomial, of the TEM and SHV types, and were produced by many enteric bacteria, but most particularly by *Klebsiella pneumoniae*. However, this epidemiology has radically changed globally (3, 4). ESBL-producing *Escherichia coli*, particularly strains producing CTX-M ESBLs, have been increasingly reported around the world (3–5). The epidemiological characteristics of infections caused by CTX-M ESBLs are different from those of TEM or SHV ESBLs. In particular, CTX-M enzymes are frequently isolated from patients with community-onset infections who have no clear health care contact (4–6). CTX-M ESBL-producing *E. coli* (CTX-M *E. coli*) pathogens have become a serious cause of community-onset bloodstream infections and urinary tract infections (UTIs) (7, 8). Isolates harboring CTX-M enzymes frequently display antimicrobial resistance to other classes of antimicrobials, particularly to fluoroquinolones (9–11). Recently, *E. coli* sequence type 131 (ST131), often associated with the CTX-M-15 extended-spectrum β-lactamase, has been recognized as an emerging globally disseminated pathogen that harbors a broad range of virulence and resistance genes, especially to fluoroquinolones (12, 13). The mortality among patients with community-onset bloodstream infection due to *E. coli* strains producing ESBLs (predominantly of the CTX-M family) was reported to be as high as 17% and was even higher among those inappropriately treated with cephalosporins or fluoroquinolones (24% and 29%, respectively) (8). CTX-M-producing organisms have become prevalent in many regions in the world (6–9, 12–17), and the emergence of these isolates has been described in the United States as well (10, 12, 14–16, 18, 19). The MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) surveillance study of 2007 identified CTX-M-encoding genes in 80% of the U.S. medical centers that reported ESBL-producing isolates in their survey (17).

Little is known pertaining to the epidemiology and outcomes associated with CTX-M ESBLs in the United States. To our knowledge, there has been no study that has used a large study cohort to systematically evaluate the risk factors for the isolation of CTX-M *E. coli* using appropriate control populations (18). The case-case-

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Address correspondence to Kayoko Hayakawa, kayokohayakawa@gmail.com.

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TABLE 1 Primers used for ESBL screening of *E. coli* isolates

Gene type or family	Primer direction	Primer (5′→3′)	Amplicon size (bp)
CTX-M-14 type	Forward	ATGGTGACAAAGAGAGTGCA	870
	Reverse	CCCTTCGGCGATGATTCTC	
CTX-M-15 type	Forward	ACGCTGTTGTTAGGAAGTGT	748
	Reverse	TGAAGTAAGTGACCAGAATCAG	
TEM family	Forward	TTCTTGAAGACGAAAGGGC	1,150
	Reverse	ACGCTCAGTGGAACGAAAAC	
SHV family	Forward	GCGTTATATTCGCCTGTGTA	205
	Reverse	TTTAAAGGTGCTCATCATGG	

control study design of this study, which utilizes two separate case-control analyses, has become a standard approach for accurate identification of risk factors that are uniquely associated with isolation of an antimicrobial-resistant pathogen (19). Because of their potential to rapidly spread among healthy individuals in the community, and because of the severity of many infections caused by CTX-M *E. coli*, it is imperative to better characterize and identify the risk factors for invasive infections due to CTX-M *E. coli* in the United States. We conducted the present study on a large cohort of CTX-M *E. coli* strains from southeastern Michigan to evaluate the epidemiology and risk factors for the isolation of CTX-M *E. coli* using two types of control groups—(i) non-CTX-M-type ESBL-producing *E. coli* (non-CTX-M *E. coli*) and (ii) matched uninfected controls.

MATERIALS AND METHODS

Study settings and design. Two retrospective case-control investigations of risk factors for isolation of CTX-M *E. coli* were conducted at the Detroit Medical Center (DMC) and ambulatory clinics located in the Detroit area and southeast Michigan, where microbiological specimens are sent to the DMC clinical microbiology laboratory. The DMC health care system consists of 8 hospitals, representing ~2,200 inpatient beds, and serves as a tertiary referral hospital for metropolitan Detroit and southeast Michigan. Patients with CTX-M *E. coli* were compared to patients with non-CTX-M *E. coli* (study 1) and matched uninfected controls (study 2). Institutional Review Boards at Wayne State University and DMC approved the study before its initiation.

Patients and variables. For study 1, patients who had clinical isolates of ESBL-producing *E. coli* from 1 February 2010 through 31 July 2011 were divided into CTX-M *E. coli* group (cases) and non-CTX-M *E. coli* group (controls) based on molecular detection results. For patients who had >1 strain of ESBL produced by *E. coli* isolated during the study period, only the first episode was analyzed (i.e., the study included only unique patient episodes).

For study 2, patients who had clinical isolates of CTX-M *E. coli* during the study period (from 1 February 2010 through 31 July 2011) were matched in a 1:1 ratio to uninfected controls who did not have *E. coli* isolated during the study period.

For study 2, uninfected controls were matched to cases with CTX-M *E. coli* by the following parameters: (i) hospital where patient was cared for, (ii) unit from which the ESBL-producing *E. coli* was recovered, (iii) calendar year, and (iv) time at risk (i.e., time from admission to day when the culture was obtained that eventually grew ESBL-producing *E. coli*). For uninfected controls, the total duration of hospital stay was considered to be the time at risk. The time at risk for the uninfected controls had to be at least as long as the time at risk of their matched ESBL-producing *E. coli* case. The time at risk for patients with isolates recovered from ambulatory clinics was considered 0, and cases from ambulatory clinics were matched to uninfected controls from ambulatory clinics. Once an eligible pool of controls was identified for each case, controls were randomly selected using the randomization function in Microsoft Excel.

Parameters retrieved from patient record included the following: (i) demographics; (ii) background conditions and comorbid conditions (including Charlson's scores) (20); (iii) recent health care-associated exposures in the past 3 months, such as a stay in a health care facility, invasive procedures, and presence of indwelling devices; (iv) the severity of the underlying disease, including McCabe score (21); (v) exposures to antimicrobials in the 3 months prior to culture (or prior to admission for controls); and (vi) outcomes, including in-hospital and 90-day mortality, length of hospital stay (LOS), functional status deterioration (defined as deterioration from admission to discharge in ≥1 activity of daily living [ADLs] according to Katz criteria [22]), and discharge to a long-term-care facility (LTCF) after being admitted from home.

Infectious clinical syndromes were determined for patients with isolation of ESBL-producing *E. coli* according to Centers for Disease Control and Prevention definitions (23) and, when present, according to consult notes from the Infectious Diseases Consult Service. ESBL-producing *E. coli* isolates were considered to be colonizers if patients did not have any sign of infection based on the above criteria and in cases of asymptomatic bacteriuria.

Microbiology. DMC has a single centralized microbiology laboratory, which processes ~500,000 samples annually. Standard identification and susceptibility testing of *E. coli* were performed and interpreted using an automated broth microdilution system (MicroScan; Siemens AG, Germany) in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria (24). Positive ESBL phenotypic tests per the automated broth microdilution system were confirmed with disc diffusion tests in accordance with 2009 CLSI criteria (25). *E. coli* strains that were resistant to one or multiple agents in the extended-spectrum cephalosporin class (cefotaxime, ceftazidime, and ceftriaxone) and that demonstrated elevated MICs to ertapenem (≥2 μg/ml) underwent modified Hodge testing (MHT) using a meropenem disk according to CLSI criteria (24). MHT-positive isolates were excluded to remove potential carbapenemase-producing strains.

PCR analyses. Phenotypically confirmed ESBL-positive *E. coli* isolates were analyzed at Indiana University by PCR. PCR amplification was performed using GoTaq DNA polymerase (Promega) to determine the presence of the ESBL gene types $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-15}}$, bla_{SHV}, and bla_{TEM} as described elsewhere (26, 27). Forward and reverse primers are shown in Table 1.

Statistical analysis. All analyses were performed using IBM-SPSS statistics 20 (2012) and SAS software, version 9.3 (SAS Institute). For study 1, bivariate analyses were performed using Fisher's exact test or the chi-square test for categorical variables and the *t* test or the Mann-Whitney U test for continuous variables. Multivariable models for risk factors were

TABLE 2 Demographics and types of ESBL genes among *Escherichia coli* isolates from February 2010 through July 2011

ESBL gene	No. (%) of ESBL types detected			*P* value
	Total (n = 575)	Isolates from Detroit Medical Center (n = 377 [65.6%])	Isolates from ambulatory clinic (n = 198 [34.4%])	
Any CTX-M type	491 (85.4)	319 (84.6)	172 (86.9)	0.535
CTX-M-14 type	67 (11.7)	40 (10.6)	27 (13.6)	0.278
CTX-M-15 type	428 (74.4)	282 (74.8)	146 (73.7)	0.841
Both CTX-M-14 and CTX-M-15 types	5 (0.9)	4 (1.1)	1 (0.5)	0.664
TEM type	244 (42.4)	156 (41.4)	88 (44.4)	0.534
SHV type	44 (7.7)	29 (7.7)	15 (7.6)	1
Both CTX-M and TEM types	204 (35.5)	129 (34.2)	75 (37.9)	0.409
Both CTX-M and SHV types	27 (4.7)	17 (4.5)	10 (5.8)	0.527

constructed using logistic regression. For study 2, matched bivariate analyses were conducted using a conditional logistic regression model for categorical variables and the *t* test or the Mann-Whitney U test for continuous variables. Matched multivariable models were constructed using Cox proportional hazards regression, accounting for clustering on matched pairs. All variables with a *P* value of <0.1 in the bivariate analyses were considered for inclusion in the multivariate analysis. 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 >10%, then the confounding variable was maintained in the multivariable model. All *P* values were two sided. Throughout the text, each of the percentages displayed represents the "valid percentage," which indicates the percentage excluding the missing data from the denominator.

RESULTS

A total of 575 patients with ESBL-producing *E. coli* were identified during the study period. A total of 377 (65.6%) patients had the organism cultured while they were being cared for at the DMC, including inpatients and patients who visited emergency departments (including same-day visits). A total of 198 (34.4%) isolates were obtained from patients being cared for in ambulatory clinics in Southeast Michigan and Detroit. The types of ESBL-producing isolates are shown in Table 2. Isolates that tested positive for $bla_{\text{CTX-M}}$ ESBL genes were isolated from 491 (85.4%) of the patients, 67 (11.7%) of which were $bla_{\text{CTX-M-14}}$-type ESBLs and 428 (74.4%) of which were $bla_{\text{CTX-M-15}}$-type ESBLs. Five patients (0.9%) had strains that tested positive for genes encoding both the CTX-M-14 and CTX-M-15 types of ESBLs. Among patients with ESBL-producing *E. coli*, 277 (48.2%) were positive for bla_{CTX}-type genes only; 204 (35.5%) were positive for both bla_{CTX}-type and bla_{TEM}-type genes, and 27 (4.7%) were positive for both bla_{CTX}-type and bla_{SHV}-type genes. Forty-nine (8.5%) patients had non-CTX-M *E. coli* isolation only; 32 (5.6%) of them had bla_{TEM}-type genes, 9 (1.6%) had bla_{SHV}-type genes, and 8 (1.4%) had both bla_{TEM}-type and bla_{SHV}-type signals. No significant differences were noted with regard to the proportions of different types of ESBLs between those recovered from the DMC and those recovered from other ambulatory clinics. A total of 214 (37.3%) patients were male; the mean age of the whole study cohort was 66 ± 18.2 years.

In vitro antimicrobial susceptibility results for 377 patients from DMC are summarized in Table 3. CTX-M *E. coli* strains were frequently resistant to multiple classes of antibiotics, including ciprofloxacin, gentamicin, tobramycin, and trimethoprim-sulfamethoxazole. The resistance to these antibiotics, as well as to tetracycline, ampicillin-sulbactam, and cefepime was more common in CTX-M *E. coli* than non-CTX-M *E. coli*. Of note, the resistance to ciprofloxacin was as high as 94.7% in the CTX-M *E. coli* group. Amikacin and nitrofurantoin retained good activity against CTX-M *E. coli*. Resistance to multiple categories of non-β-lactam classes of antibiotics (aminoglycosides [≥1 agent], ciprofloxacin, nitrofurantoin, trimethoprim-sulfamethoxazole, and tetracycline) was common in this study cohort (for CTX-M *E. coli* versus non-CTX-M *E. coli*, resistance to 5 categories, 13 [4.1%] versus 3 [5.2%], $P = 0722$; resistance to 4 categories, 110 [34.6%] versus 9 [15.5%], $P = 0.003$; resistance to 3 categories, 89 [28.1%] versus 11 [19%], $P = 0.196$; resistance to 2 categories, 73 [23%] versus 12 [20.7%], $P = 0.865$). Resistance to ciprofloxacin and aminoglycosides (≥1 agent) was higher with the CTX-M *E. coli* group than the non-CTX-M *E. coli* group (205 [64.7%] versus 19 [32.8%]; $P < 0.001$), as was resistance to ciprofloxacin and trimethoprim-sulfamethoxazole (189 [59.4%] versus 21 [36.2%]; $P = 0.001$) and resistance to aminoglycosides and trimethoprim-sulfamethoxazole (133 [41.8%] versus 11 [19%]; $P = 0.001$). The antimicrobial susceptibility results of the entire cohort of 575 patients revealed similar results.

Cases from ambulatory clinics had limited medical information available, so further clinical epidemiologic analyses were conducted focusing on the cohort of 377 patients from DMC (319 [84.6%] CTX-M *E. coli*, 58 [15.4%] non-CTX-M *E. coli*) who had detailed medical records available for review.

The results of bivariate analyses comparing patients with CTX-M *E. coli* to patients with non-CTX-M *E. coli* (study 1) and to uninfected controls (study 2) are shown in Table 4. Patients with CTX-M *E. coli* were more likely to be male, have dementia, and/or be dependent in terms of functional status than patients with non-CTX-M *E. coli*. The median Charlson's combined condition score was slightly higher in patients with CTX-M *E. coli* than in those with non-CTX-M *E. coli*. Use of H2 blockers was more common in patients with CTX-M *E. coli*, and pregnancy was less common in patients with CTX-M *E. coli* than patients with non-CTX-M *E. coli*. The frequencies of exposure to health care setting and antibiotics did not differ between the two groups, except that trimethoprim-sulfamethoxazole exposure was more common in the non-CTX-M *E. coli* group. There were trends for increased use of oxyimino-cephalosporins and less β-lactam/β-lactamase inhibitor use in the CTX-M *E. coli* group than in the non-CTX-M *E. coli* group. There was no significant difference in anatomic sites of isolation and infectious clinical syndromes between CTX-M *E.*

TABLE 3 Antibiotic susceptibility and MICs of ESBL-producing *Escherichia coli* isolates from Detroit Medical Center from February 2010 through July 2011[a]

Antibiotic profile parameter	Result for: CTX-M *E. coli* (n = 319)	Non-CTX-M *E. coli* (n = 58)	P value
Ciprofloxacin-resistant isolates, no. (%)[b]	**302 (94.7)**	**35 (60.3)**	**<0.001**
Ciprofloxacin MIC_{50}, MIC_{90} (μg/ml)	>2, >2	>2, >2	NA[c]
Tobramycin-resistant isolates, no. (%)	**206 (64.8)**	**18 (31)**	**<0.001**
Tobramycin MIC_{50}, MIC_{90} (μg/ml)	>8, >8	2, >8	NA
Gentamicin-resistant isolates, no. (%)	**164 (51.4)**	**14 (24.1)**	**<0.001**
Gentamicin MIC_{50}, MIC_{90} (μg/ml)	>8, >8	≤1, >8	NA
Amikacin-resistant isolates, no. (%)	20 (6.4)	3 (5.2)	1.0
Amikacin MIC_{50}, MIC_{90} (μg/ml)	≤4, 16	≤4, 8	NA
Trimethoprim-sulfamethoxazole-resistant isolates, no. (%)	197 (61.8)	28 (48.3)	0.06
Median trimethoprim-sulfamethoxazole MIC (IQR)	>2/38, >2/38	≤2/38, >2/38	NA
Tetracycline-resistant isolates, no. (%)	**200 (62.7)**	**24 (41.4)**	**0.003**
Tetracycline MIC_{50}, MIC_{90} (μg/ml)	>8, >8	≤4, >8	NA
Tigecycline-resistant isolates, no. (%)	0 (0)	0 (0)	NA
Tigecycline MIC_{50}, MIC_{90} (μg/ml)	≤1, ≤1	≤1, ≤1	NA
Nitrofurantoin-resistant isolates, no. (%)	40 (12.7)	11 (19)	0.213
Median nitrofurantoin MIC, IQR (μg/ml)	≤32, 64	≤32, >64	NA
Piperacillin-tazobactam-resistant isolates, no. (%)	30 (9.5)	7 (12.1)	0.631
Median piperacillin-tazobactam MIC, IQR (μg/ml)	≤8/4, 32/4	≤8/4, 32/4	NA
Ampicillin-sulbactam-resistant isolates, no. (%)	262 (83.4)	42 (72.4)	0.063
Median ampicillin-sulbactam MIC, IQR (μg/ml)	>16/8, >16/8	16/8, >16/8	NA
Cefepime-resistant isolates, no. (%)	**296 (92.8)**	**21 (36.2)**	**<0.001**
Cefepime MIC_{50}, MIC_{90} (μg/ml)	>16, >16	≤2, >16	NA

[a] All percentages shown represent patients for whom data were available (i.e., excluding the missing cases). Boldface indicates statistically significant difference between groups (P < 0.05).
[b] Including intermediate and resistant isolates, based on CLSI-approved criteria (approved standard M100-S20 [24]) unless otherwise noted.
[c] NA, data not available.

coli and non-CTX-M *E. coli* groups (colonization, n = 79 [24.8%] versus 11 [19.0%]; respiratory tract infection, 20 [6.3%] versus 5 [8.6%]; urinary tract infection, 178 [55.8%] versus 33 [56.9%]; skin and soft tissue infection, 27 [8.5%] versus 3 [5.2%]; focus unknown/other infection, 12 [3.8%] versus 3 [5.2%]; P > 0.05, respectively). Intra-abdominal infection was common among members of the non-CTX-M *E. coli* group, even though the numbers were limited (3 [0.9%] versus 3 [5.2%]; P = 0.018). As shown in Table 4, there were no differences noted between the 2 groups in terms of the sites of ESBL-producing *E. coli* isolation, and 22 (6.9%) of the CTX-M *E. coli* strains and 6 (10.3%) of the non-CTX-M *E. coli* strains were isolated from blood. The prevalences of polymicrobial culture (i.e., isolation of additional bacteria other than ESBL-producing *E. coli* from the same culture) were similar between the 2 groups (n = 157 [49.2%] versus n = 31 [53.4%]; P > 0.05). A total of 247 (77.4%) cases of CTX-M *E. coli* and 44 (75.9%) cases of non-CTX-M *E. coli* were present at the time of hospital admission (i.e., within 48 h of admission). The prevalence of isolation of ESBL-producing *E. coli* present at the time of hospital admission differed depending on the anatomic sites of isolation in both groups (P < 0.001 for both groups). No difference was noted between CTX-M *E. coli* and non-CTX-M *E. coli* in terms of the prevalence of the isolation of ESBL-producing *E. coli* present at the time of hospital admission from each site: urine (200 [63%] versus 37 [63.8%]; P = 0.873), blood (15 [4.7%] versus 5 [8.6%]; P = 0.221), sputum (10 [3.1%] versus 0 [0%]; P = 0.172), or wound (21 [6.6%] versus 2 [3.4%]; P = 0.359).

In multivariate analysis, male gender, impaired consciousness at the time of hospital admission, use of H2 blockers, immunosuppressive status, and exposure to penicillins and/or trimethoprim-sulfamethoxazole were identified as independent risk factors for the isolation of CTX-M *E. coli* compared to non-CTX-M *E. coli* (Table 5).

Outcomes, including mortality and functional deterioration and hospital length of stay after the isolation of ESBL-producing *E. coli*, were also similar between the two groups (Table 4).

In study 2, patients with CTX-M *E. coli*, compared to uninfected controls, were older and were more likely to reside in a facility and have a higher frequency of comorbid conditions (Table 4). In addition, patients with CTX-M *E. coli* were more likely to have obstructive urinary tract diseases and more likely to be on an H2 blocker and/or proton pump inhibitor (PPI). Exposure to health care settings was more common among patients with CTX-M *E. coli*, including gastrointestinal (GI) tract endoscopy and/or a urological invasive procedure. Indwelling devices, especially urinary catheters, were more common among patients with CTX-M *E. coli* than among uninfected controls. Antimicrobial exposures, including to oxyimino-cephalosporins, ertapenem, fluoroquinolone, tetracycline, aminoglycosides, metronidazole, and vancomycin were more common among the CTX-M *E. coli* group than controls. Three-month mortality was higher in patients with CTX-M *E. coli* than controls (13.7% versus 7.6%; P = 0.017). Patients with CTX-M *E. coli* stayed in the hospital longer than did uninfected controls (median duration of hospitalization [interquartile range; IQR], 7 days [4 to 12 days] versus 4 days [2 to 6 days], respectively; P < 0.001). CTX-M *E. coli* cases were more frequently discharged to long-term-care facilities after being ad-

TABLE 4 Bivariate analysis of risk factors and outcomes for isolation of CTX-M *E. coli* compared to non-CTX-M *E. coli* and uninfected controls from the Detroit Medical Center from February 2010 through July 2011[a]

Parameter	Result for:						
				CTX-M *E. coli* vs non-CTX-M *E. coli*		CTX-M *E. coli* vs uninfected controls	
	CTX-M *E. coli* (n = 319)	Non-CTX-M *E. coli* (n = 58)	Uninfected controls (n = 319)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
General patient demographics							
Age, yr, mean (±SD)	68.2 (17.2)	64.7 (19.1)	59.8 (17.7)	NA	0.209	NA	**<0.001**
Male gender, no. (%)	143 (44.8)	15 (25.9)	162 (50.8)	**2.33 (1.24–4.36)**	**0.009**	0.82 (0.54–1.24)	0.341
African-American, no. (%)	213 (66.8)	35 (60.3)	222 (69.6)	1.32 (0.74–2.35)	0.368		
Non-home residence, no. (%)	169 (53.3)	24 (41.4)	54 (17)	1.62 (0.92–2.85)	0.116	**6.52 (4.12–10.33)**	**<0.001**
Acute and chronic conditions on admission							
Dependent functional status, no. (%)	238 (74.8)	35 (60.3)	123 (38.9)	**1.96 (1.09–3.51)**	**0.026**	**5.35 (3.52–8.12)**	**<0.001**
Impaired consciousness, no. (%)	149 (46.9)	19 (32.8)	62 (19.5)	1.81 (1–3.27)	0.061	**3.9 (2.61–5.82)**	**<0.001**
History of UTI, no. (%)	113 (37.7)	16 (31.4)	24 (7.7)	1.32 (0.7–2.5)	0.435	6 (3.64–9.88)	**<0.001**
Urolithiasis, no. (%)	11 (3.4)	4 (6.9)	3 (0.9)	0.48 (0.15–1.57)	0.263	**3.67 (1.02–13.14)**	**0.046**
Urinary stent, no. (%)	6 (1.9)	3 (5.2)	5 (1.6)	0.35 (0.09–1.45)	0.147	1.2 (0.37–3.93)	0.764
Benign prostate hypertrophy, no. (%)	47 (14.7)	6 (10.3)	17 (5.3)	1.5 (0.61–3.68)	0.537	**3.14 (1.72–5.74)**	**<0.001**
Obstructive urinary tract disease, no. (%)	33 (10.3)	5 (8.6)	5 (1.6)	1.22 (0.46–3.28)	0.816	**6.6 (2.58–16.91)**	**<0.001**
Obstructive biliary tract disease, no. (%)	2 (0.6)	1 (1.7)	2 (0.6)	0.36 (0.03–4.03)	0.345	1 (0.14–7.1)	1
Pregnancy, no. (%)	3 (0.9)	4 (6.9)	0	**0.13 (0.03–4.03)**	**0.013**	9 (0.66–122.79)	0.083
Current use of H2 blocker, no. (%)	72 (22.6)	4 (6.9)	51 (16)	**3.94 (1.38–11.23)**	**0.004**	**1.53 (1.03–2.28)**	**0.044**
Current use of PPI, no. (%)	88 (27.6)	22 (37.9)	61 (19.1)	0.62 (0.53–1.12)	0.118	**1.61 (1.11–2.34)**	**0.015**
Current use of H2 blocker or PPI, no. (%)	158 (49.5)	25 (43.1)	109 (34.2)	1.3 (0.74–2.28)	0.394	**1.96 (1.4–2.75)**	**<0.001**
Rapidly fatal McCabe score, no. (%)	50 (15.7)	6 (10.3)	24 (7.5)	1.61 (0.66–3.95)	0.421	**2.53 (1.44–4.44)**	**0.001**
Cerebrovascular accident, no. (%)	83 (26)	12 (20.7)	60 (18.8)	1.35 (0.68–2.67)	0.511	**1.47 (1.02–2.11)**	**0.038**
Congestive heart failure, no. (%)	94 (29.5)	16 (27.6)	63 (19.7)	NA	0.876	**1.84 (1.23–2.74)**	**0.003**
Dementia, no. (%)	125 (39.2)	13 (22.4)	36 (11.3)	**2.23 (1.16–4.3)**	**0.017**	**5.24 (3.28–8.35)**	**<0.001**
Hemiplegia, no. (%)	50 (15.7)	5 (8.6)	12 (3.8)	1.97 (0.75–5.17)	0.224	**4.45 (2.32–8.57)**	**<0.001**
Peripheral vascular disease, no. (%)	60 (18.8)	9 (15.5)	37 (11.6)	1.26 (0.59–2.71)	0.712	**1.92 (1.18–3.11)**	**0.008**
Peptic ulcer disease, no. (%)	47 (14.7)	8 (13.8)	21 (6.6)	1.08 (0.48–2.42)	1	**2.44 (1.41–4.23)**	**0.001**
Diabetes mellitus, no. (%)	132 (41.4)	21 (36.2)	90 (28.2)	1.24 (0.7–2.22)	0.561	**1.82 (1.3–2.57)**	**0.001**
Any liver disease, no. (%)	18 (5.6)	4 (6.9)	16 (5.1)	0.81 (0.26–2.48)	0.759	1.11 (0.56–2.23)	0.861
Any renal disease, no. (%)	99 (31.1)	12 (20.7)	64 (20.3)	1.73 (0.88–3.41)	0.12	**1.94 (1.3–2.91)**	**0.001**
Active malignant disease, no. (%)	43 (13.5)	6 (10.3)	27 (8.5)	1.35 (0.55–3.34)	0.672	**2 (1.1–3.64)**	**0.024**
Median Charlson combined condition score (IQR)	6 (4–8)	5 (3–7)	4 (1–6)	NA	**0.019**	NA	**<0.001**
Charlson combined condition score of ≥5, no. (%)	224 (70.2)	33 (57.9)	138 (43.3)	1.72 (0.96–3.06)	0.088	**3.09 (2.23–4.29)**	**<0.001**
Chronic skin ulcer, no. (%)	91 (28.5)	11 (19.3)	30 (9.5)	1.67 (0.83–3.37)	0.195	**4.47 (2.64–7.56)**	**<0.001**
Recent steroid use, no. (%)	33 (10.3)	3 (5.3)	18 (5.6)	2.08 (0.62–7.02)	0.328	**1.88 (1.05–3.39)**	**0.035**
Immunosuppressive state, no. (%)[b]	52 (16.3)	5 (8.8)	35 (11)	2.03 (0.77–5.31)	0.165	1.57 (0.99–2.48)	0.055
Exposure to health care settings and environments before isolation of ESBL-producing *E. coli*							
Recent hospitalization in past 3 mo, no. (%)	185 (58.2)	27 (47.4)	129 (41)	1.55 (0.88–2.72)	0.148	**2.08 (1.48–2.93)**	**<0.001**
No recent heath care contact within 3 months, no. (%)[c]	55 (17.4)	15 (26.3)	147(46.1)	0.59 (0.31–1.13)	0.138	**0.23 (0.16–0.35)**	**<0.001**
No recent health care contact or antibiotic exposure within past 3 mo, no. (%)	43 (13.6)	11 (19.3)	137 (42.9)	0.66 (0.32–1.37)	0.304	**0.2 (0.13–0.31)**	**<0.001**
Days from last hospitalization, median no. (IQR)	23 (9–45)	20 (5–41)	20 (6–40)	NA	0.529	NA	0.236
History of outpatient clinic, no. (%)	73 (60.3)	23 (67.6)	120 (45.6)	0.73 (0.33–1.63)	0.55	**2.21 (1.8–4.16)**	**0.014**
History of wound care, no. (%)	20 (16.9)	3 (8.8)	15 (5.7)	2.11 (0.59–7.58)	0.291	NA	0.991
History of nursing care, no. (%)	16 (14.3)	3 (9.1)	6 (2.3)	1.67 (0.45–6.11)	0.565	NA	0.991
History of i.v. therapy, no. (%)	35 (24)	6 (18.2)	23 (8.7)	1.42 (0.54–3.72)	0.647	**3.0 (1.35–6.68)**	**0.007**
Hemodialysis, no. (%)	21 (6.6)	1 (1.7)	23 (7.2)	4.02 (0.53–30.46)	0.223	0.91 (0.49–1.68)	0.752
GI tract endoscopy in past 3 mo, no. (%)	45 (14.1)	10 (17.2)	25 (7.9)	0.79 (0.37–1.67)	0.545	**1.95 (1.15–3.3)**	**0.013**
Recent urological procedure in past 3 mo, no. (%)	22 (6.9)	4 (6.9)	8 (2.5)	1 (0.33–3.02)	1	**3.0 (1.28–7.06)**	**0.012**
Invasive procedure in past 3 mo, no. (%)[d]	69 (21.6)	11 (19)	70 (22)	1.18 (0.58–2.4)	0.729	0.98 (0.67–1.43)	0.923
Surgery in past 3 mo, no. (%)	72 (22.6)	12 (20.7)	54 (17)	1.12 (0.56–2.22)	0.864	1.43 (0.96–2.12)	0.076
Invasive procedure/urological procedure or surgery in past 3 mo, no. (%)	133 (41.7)	26 (44.8)	98 (30.7)	0.88 (0.5–1.55)	0.667	**1.57 (1.14–2.15)**	**0.006**
Central line, no. (%)[e]	67 (21.1)	14 (24.6)	29 (9.1)	0.82 (0.42–1.59)	0.6	**2.58 (1.61–4.14)**	**<0.001**
Urinary catheter, no. (%)[e]	132 (41.5)	20 (35.1)	35 (11)	1.31 (0.73–2.36)	0.384	**6.33 (3.85–10.41)**	**<0.001**
Any permanent device, no. (%)[f]	187 (58.8)	32 (56.1)	106 (33.2)	1.12 (0.63–1.97)	0.771	**2.88 (2.04–4.08)**	**<0.001**
ICU stay in past 3 mo, no. (%)	75 (23.5)	9 (15.8)	49 (15.4)	1.64 (0.77–3.5)	0.23	**1.69 (1.14–2.53)**	**0.012**
Antimicrobial exposure in past 3 mo							
Any antibiotics, no. (%)	144 (45.3)	28 (48.3)	64 (20.1)	0.89 (0.51–1.55)	0.775	**3.67 (2.45–5.49)**	**<0.001**
Penicillins, no. (%)[g]	21 (6.6)	7 (12.1)	21 (6.6)	0.52 (0.21–1.27)	0.17	1.54 (0.77–3.09)	0.227
Oxyimino-cephalosporins, no. (%)[h]	89 (28)	13 (22.4)	25 (7.9)	1.35 (0.69–2.61)	0.426	**5.43 (3.07–9.6)**	**<0.001**
Other cephalosporins, no. (%)	12 (3.8)	4 (6.9)	10 (3.1)	0.53 (0.17–1.7)	0.286	1.22 (0.51–2.95)	0.655
Cephalosporins, no. (%)	91 (28.6)	17 (29.3)	32 (10.1)	0.97 (0.52–1.79)	1	**4.11 (2.49–6.78)**	**<0.001**
Aztreonam, no. (%)	3 (0.9)	1 (1.7)	0	0.54 (0.06–5.31)	0.49	1473121.00	0.984
β-Lactam/β-lactamase inhibitors, no. (%)[i]	19 (6)	5 (8.6)	10 (3.1)	0.67 (0.24–1.88)	0.394	2.13 (0.92–4.92)	0.079
Ertapenem, no. (%)	10 (3.1)	0	1 (0.3)	1.03 (1.01–1.05)	0.372	**10.0 (1.28–78.11)**	**0.028**
Imipenem or meropenem, no. (%)	7 (2.2)	0	3 (0.9)	1.02 (1.01–1.04)	0.601	2.33 (0.6–9.02)	0.22
Carbapenems, no. (%)	16 (5)	0	4 (1.3)	1.05 (1.01–1.08)	0.147	**4 (1.34–11.96)**	**0.013**
β-Lactam antibiotics, no. (%)	104 (32.7)	22 (37.9)	42 (13.2)	0.8 (0.45–1.42)	0.452	**3.3 (2.14–5.07)**	**<0.001**
Fluoroquinolone, no. (%)	36 (11.3)	10 (17.2)	9 (2.8)	0.61 (0.29–1.32)	0.198	**4.38 (2.03–9.43)**	**<0.001**
Tetracyclines, no. (%)	21 (6.6)	4 (6.9)	8 (2.5)	0.96 (0.32–2.89)	1	**2.63 (1.16–5.93)**	**0.02**
Aminoglycosides, no. (%)	7 (2.2)	1 (1.7)	0	1.28 (0.16–10.63)	1	**9 (1.63–49.8)**	**0.008**
Trimethoprim-sulfamethoxazole, no. (%)	5 (1.6)	5 (8.6)	7 (2.2)	**0.17 (0.05–0.61)**	**0.01**	0.71 (0.23–2.25)	0.566
Metronidazole, no. (%)	24 (7.5)	6 (10.3)	9 (2.8)	0.71 (0.28–1.82)	0.436	**2.67 (1.24–5.74)**	**0.012**
Vancomycin, no. (%)	65 (20.4)	11 (19.3)	27 (8.5)	1.07 (0.53–2.19)	1	**3.53 (1.99–6.27)**	**<0.001**

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TABLE 4 (Continued)

Parameter	Result for: CTX-M *E. coli* ($n = 319$)	Non-CTX-M *E. coli* ($n = 58$)	Uninfected controls ($n = 319$)	CTX-M *E. coli* vs non-CTX-M *E. coli* OR (95% CI)	*P* value	CTX-M *E. coli* vs uninfected controls OR (95% CI)	*P* value
Microbiology							
Median length of hospital stay prior to isolation of ESBL-producing *E. coli*, days (IQR)	0 (0–2)	0 (0–2.25)	NA	NA	0.475	NA	NA
ESBL-producing *E. coli* isolated from blood, no. (%)	22 (6.9)	6 (10.3)	NA	0.64 (0.23–1.86)	0.357	NA	NA
ESBL-producing *E. coli* isolated from sputum, no. (%)	22 (6.9)	5 (8.6)	NA	0.79 (0.27–2.48)	0.639	NA	NA
ESBL-producing *E. coli* isolated from wound, no. (%)[j]	32 (10)	4 (6.9)	NA	1.51 (0.48–5.24)	0.455	NA	NA
ESBL-producing *E. coli* isolated from urine, no. (%)	241 (75.5)	43 (74.1)	NA	1.08 (0.54–2.13)	0.819	NA	NA
Outcomes							
In-hospital mortality, no. (%)	18 (5.7)	2 (3.5)	12 (3.8)	1.66 (0.37–7.34)	0.751	2.33 (0.9–6.07)	0.083
3-mo mortality, no. (%)	36 (13.7)	5 (10.2)	22 (7.6)	1.4 (0.52–3.75)	0.647	**2.36 (1.17–4.78)**	**0.017**
Functional status deterioration, no. (%)	21 (7.1)	5 (9.1)	17 (5.6)	0.77 (0.28–2.13)	0.579	1.21 (0.6–2.46)	0.591
Discharge to LTCF after being admitted from home, no. (%)	24 (18.6)	7 (21.9)	9 (3.5)	0.82 (0.32–2.11)	0.627	**8.5 (1.96–36.79)**	**0.004**
Additional hospitalizations within 6 mo following isolation of ESBL-producing *E. coli*, no. (%)[k]	170 (58.6)	27 (50.9)	126 (41.7)	1.36 (0.76–2.45)	0.365	**1.84 (1.33–2.54)**	**<0.001**
Invasive procedure or surgery within 3 mo following isolation of ESBL-producing *E. coli*, no. (%)[k]	122 (40.3)	20 (36.4)	105 (33.8)	1.18 (0.65–2.14)	0.654	1.34 (0.97–1.87)	0.08
Total length of hospital stay excluding death, median days (IQR)[l]	7 (4–12)	7 (3–20)	4 (2–6)	NA	0.571	**NA**	**<0.001**

[a] All percentages shown represent patients for whom data were available (i.e., excluding the missing cases). Boldface indicates statistically significant difference between groups ($P < 0.05$). Abbreviations: CI, confidence interval; ESBL, extended-spectrum β-lactamase; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; i.v., intravenous; LTCF, long-term-care facilities; NA, data not available; OR, odds ratio; SD, standard deviation, UTI, urinary tract infection.
[b] Includes one or more of the following: neutropenia (<500 neutrophils) at time of culture, glucocorticoid/steroid use in the past month, chemotherapy in the past 3 months, radiotherapy in the past 3 months, posttransplantation or anti-tumor necrosis factor alpha therapy in the past 3 months, and HIV infection.
[c] No health care contact includes all of the following: admission from home, no history of surgery or invasive procedures within 3 months, and no recent hospitalization within 3 months.
[d] Includes percutaneous interventions, endoscopies, and biopsies.
[e] At the time of isolation of ESBL-producing *E. coli* (for uninfected controls, on admission).
[f] Indwelling devices (e.g., tracheotomies, central lines, urinary catheters, orthopedic external fixators, percutaneous endoscopic gastrostomy) that were in place at the time of isolation of ESBL-producing *E. coli* (for uninfected controls, on admission).
[g] Penicillins include β-lactam and β-lactamase inhibitor combinations.
[h] Includes ceftriaxone, cefepime, and ceftazidime.
[i] Includes ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate, and amoxicillin-clavulanate.
[j] Includes skin/soft tissue, bone/joint, and surgical site.
[k] For uninfected controls, after admission.
[l] Excluding the patients who died during the hospitalization.

mitted from home (18.6% versus 3.5%; $P < 0.001$) and were more frequently readmitted within 6 months after discharge (58.6% versus 41.7%; $P < 0.001$) than were controls.

Independent risk factors for the isolation of CTX-M *E. coli* were determined as indwelling urinary catheter, history of urinary tract infection (UTI), exposure to oxyimino-cephalosporins, dependent functional status, non-home residence (i.e., nursing home residence or transfers from other hospitals), and multiple comorbid conditions (i.e., Charlson's combined comorbidity score of ≥5) (Table 6).

TABLE 5 Multivariate analysis of risk factors for the isolation of CTX-M *E. coli* compared to non-CTX-M *E. coli*[a]

Variable	Adjusted OR (95% CI)[b]	Adjusted *P* value
Male gender	2.59 (1.30–5.14)	0.007
Impaired consciousness upon admission	2 (1.03–3.79)	0.041
Use of H2 blocker at time of culture	3.59 (1.19–10.77)	0.023
Immunosuppressive status[c]	2.96 (1.02–8.57)	0.046
Use of penicillins in past 3 mo[d]	0.34 (0.12–0.93)	0.036
Use of trimethoprim-sulfamethoxazole in 3 mo prior to culture	0.16 (0.04–0.62)	0.008

[a] Controlled for the confounding effects of use of fluoroquinolones in the past 3 months and recent hospitalization in the past 3 months.
[b] OR, odds ratio; CI, confidence interval.
[c] Includes one or more of the following: neutropenia (<500 neutrophils), steroid use in the past month, chemotherapy in the past 3 months, radiotherapy in the past 3 months, HIV infection, transplantation, or anti-tumor necrosis factor alpha therapy in the past 3 months.
[d] Penicillins include β-lactam or β-lactamase inhibitor combinations.

TABLE 6 Multivariate analysis of risk factors for the isolation of CTX-M *E. coli* compared to uninfected controls[a]

Variable	Hazard ratio (95% CI)[b]	*P* value
Indwelling urinary catheter[c]	4.1 (2.0–8.2)	<0.001
History of urinary tract infection	3.3 (1.7–6.3)	<0.001
Oxyimino-cephalosporins within 3 mo prior to culture[d]	3.2 (1.4–7.4)	0.007
Dependent functional status at time of admission	2.5 (1.4–4.6)	0.002
Non-home residence	2.5 (1.3–4.8)	0.007
Charlson combined comorbidity index of ≥5	2.3 (1.3–3.9)	0.003

[a] Controlled for vancomycin exposure in the past 3 months.
[b] CI, confidence interval.
[c] At the time of isolation of CTX-M *E. coli* (for uninfected controls, on admission).
[d] Includes ceftriaxone, cefepime, and ceftazidime.

DISCUSSION

To our knowledge, this study reports on a large cohort of CTX-M *E. coli* strains recovered in the United States and is the first study to systematically elucidate independent risk factors for the isolation of CTX-M *E. coli* (18). Because this study was not limited in terms of types of infection or populations included, the results are likely more generalizable than prior studies (7, 8, 28, 29).

This study identified several key epidemiological characteristics and risk factors for the isolation of CTX-M *E. coli*. CTX-M *E. coli* strains were found in more than 85% (491 out of 575 cases) of the study subjects with ESBL-producing *E. coli*, confirming that CTX-M *E. coli* strains have been widely spread among ESBL-producing *E. coli* strains in southeast Michigan. The most common *bla* gene detected was associated with production of CTX-M-15-type ESBL, which is similar to other recent reports from the United States (10, 27). Of particular interest and concern, more than 75% of both CTX-M *E. coli* and non-CTX-M *E. coli* strains were isolated within 2 days after admission, most commonly from urine. Sixty-two (16%) of the ESBL-producing *E. coli* strains were present at the time of hospital admission and also were isolated from patients with no identified recent health care contacts, including long-term-care facilities, and thus were truly community acquired (51 cases [16%] of CTX-M *E. coli* and 11 cases [19%] of non-CTX-M *E. coli*). Fifty cases of infection (42 cases [13%] of CTX-M *E. coli* and 8 cases [14%] of non-CTX-M *E. coli*) were in patients who had not had antimicrobial exposure. The high frequency of CTX-M *E. coli* strains that were present at the time of hospital admission is similar to findings reported by other investigators both inside and outside the United States (28, 30, 31). In addition, a majority of ESBL-producing *E. coli* strains were imported to the hospital from health-care-associated settings, including long-term-care facilities. Non-home residence and a history of recent hospitalization were quite common among patients with ESBL-producing *E. coli*. Reports from the United Kingdom reported a high level of (40%) fecal carriage of ESBL-producing *E. coli* strains in nursing home residents (31). A recent multicenter study on ESBL-producing *Enterobacter cloacae* bloodstream infection in the United States also revealed that as many as 56.3% of patients with ESBL-producing *E. cloacae* were admitted from a nursing home and that ESBL production is one of the independent risk factors for ESBL production in their cohort (32). This study identified unique epidemiologic characteristics of patients harboring CTX-M *E. coli* compared to patients with non-CTX-M *E. coli*, including male gender, impaired consciousness, prior use of H2 blockers, immunosuppressive status, and exposure to penicillins and/or trimethoprim-sulfamethoxazole. These findings are in concordance with prior studies that identified male gender as a predictor of ESBL-producing *Enterobacteriaceae*, the majority of which were CTX type (28, 30), and that identified H2 blocker use as predictor of fecal carriage of ESBLs at the time of hospital admission (28).

Compared to uninfected controls, the presence of an indwelling urinary catheter, history of UTI, exposure to oxyimino-cephalosporins, dependent functional status, non-home residence, and multiple comorbid conditions were all independently associated with isolation of CTX-M *E. coli*. Several of these risk factors have been reported previously as risk factors for community-onset ESBL-producing *E. coli* (8, 28, 33) and for CTX-M *E. coli* (9).

In our study, in-hospital mortality and 3-month mortality were similar between the CTX-M *E. coli* group and non-CTX-M *E. coli* group (18 [5.7%] versus 2 [3.5%] and 36 [13.7%] versus 5 [10.2%]). Among the patients with bacteremia, in-hospital mortality and 3-month mortality were also similar between the CTX-M *E. coli* group and non-CTX-M *E. coli* group (in-hospital mortality, 2 [9.1%] versus 1 [16.7%]; 3-month mortality, 3 [13.6%] versus 1 [16.7%]). Mortality associated with CTX-M *E. coli* infection varies in the published literature. Previous reports on nosocomial infection due to ESBL-producing *E. coli* (57% CTX-M *E. coli*) reported a crude mortality rate of 30% and an infection-related mortality rate of 14% (7). Another study reported mortality among patients with community-onset bloodstream infection due to ESBL-producing *E. coli* (predominantly of the CTX-M family) to be 17% (24 to 29% in subjects who were inappropriately treated) (8). A recent report of community-associated bacteremia due to ESBL-producing *E. coli* in the United States included 12 patients with episodes of bacteremia (9 with CTX-M *E. coli*), none of whom died (34). The differences between previously published studies and the present study were likely due in part to diverse patient populations with a variety of different comorbid conditions and differences with regard to receipt and timing of effective antimicrobial therapy. In our study, a relatively high proportion of patients with bacteremia received effective therapy (86.4% of CTX-M *E. coli* patients, and 83.3% of non-CTX-M *E. coli* patients), which might have led to lower rates of mortality.

Patients with infection due to CTX-M *E. coli* were more frequently discharged to long-term-care facilities (after being admitted from home) compared to uninfected controls ($P = 0.004$) and readmitted to the hospital within 6 months compared to uninfected controls ($P < 0.001$). Thus, utilization of health care resources was greater among patients with CTX-M *E. coli.* Patients in the CTX-M *E. coli* group had a high frequency of dementia and were more functionally dependent, which may have predisposed them to these unfortunate outcomes.

A recently described *E. coli* strain, designated ST131, is associated with CTX-M-15 production and is derived from virulence-associated phylogenetic group B2 (35). Thus, there might have been an impact of strain type on the adverse outcomes among patients infected with CTX-M-producing *E. coli*. However, no controlled outcome analyses of ST131 versus other *E. coli* ESBL STs had been conducted prior to this study. The explanation for the association between CTX-M production and certain adverse outcomes is still unclear and deserves further study.

A recent multicenter study in the United States reported frequent community-associated infection (36.8%) among patients with ESBL-producing *E. coli*. More than 80% of study patients had urinary tract infections. Of the community-associated infections, 54.2% were caused by the ST131 strain, and 91.3% of the isolates produced CTX-M-type ESBL. The findings confirm the importance of CTX-M *E. coli* as the primary type of community-associated ESBL-producing pathogen in the United States (34).

In addition to its retrospective nature, there are several limitations of this study. Due to the limited available information, it was necessary to exclude patients with isolates from ambulatory clinics from the detailed epidemiologic analysis. Bivariate analyses on the cohort of ambulatory clinic patients were conducted comparing patients with CTX-M *E. coli* ($n = 172$) to patients with non-CTX-M *E. coli* ($n = 26$). Due to the inability to access complete medical charts in this cohort, much of the data were missing. The results revealed similar characteristics compared to the inpatient cohort, except that patients with CTX-M *E. coli* were older (mean age [standard deviation; SD], 64.5 [18.4] versus 56 [19.5] years; $P = 0.03$), and sicker (median combined Charlson's condition score [IQR], 3.5 [1 to 6] versus 0 [0 to 4.8]; $P = 0.04$) than patients with non-CTX-M *E. coli* in the ambulatory clinic patients' cohort. This study cohort was limited to patients from southeast Michigan, and thus the results might not be generalizable to other geographic regions. We did not attempt to determine the presence of *E. coli* ST131, which is associated with the successful dissemination of CTX-M-15 ESBL in various parts of the world (35). In our study, TEM and SHV enzymes were identified in some isolates, either as the sole ESBL or in concert with a CTX-M-type enzyme, further limiting therapeutic options. For the summary of molecular results, we included only those strains that produced strong PCR responses for the probes tested. We did not identify the ESBL molecular etiologies for the 35 isolates that did not produce strong responses to our probes. The lack of responses might have been due to the loss of plasmidic enzyme during multiple transfers of the isolates, the presence of ESBLs that were not included in the PCRs, or the rare possibility of false-positive phenotypic ESBL test results at the initial laboratory testing at DMC. In this study, molecular analyses for the CTX-M-2 group were not conducted.

CTX-M *E. coli* demonstrated resistance to more classes of antibiotics than did non-CTX-M *E. coli*. Thus, given the likely continued emergence and spread of CTX-M *E. coli* in the United States, it will be important for infectious disease physicians and infection control personnel to be aware of local susceptibility patterns for *E. coli*, so as to afford patients optimal care. In particular, individuals who are septic and possess risk factors for the isolation of CTX-M *E. coli* should be empirically treated with appropriate agents (i.e., carbapenems).

Considering that more than 75% of both CTX-M *E. coli* and non-CTX-M *E. coli* isolates were isolated within 2 days after admission, ESBL *E. coli* should be considered a possible pathogen in community-onset infections, particularly among individuals who have recently been managed in institutional settings, have had recent urinary catheterization or urinary procedures, and have received recent antimicrobials. Regional efforts at infection control and implementation of antimicrobial stewardship practices across the continuum of health care settings will hopefully help to curb the emergence and spread of ESBL-producing *E. coli*.

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