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Predictors and Molecular Epidemiology of Community-Onset Extended-Spectrum β -Lactamase–Producing *Escherichia coli* Infection in a Midwestern Community

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Abstract

OBJECTIVE—To identify predictors of community-onset extended-spectrum β -lactamase (ESBL)–producing *Escherichia coli* infection.

DESIGN—Prospective case-control study.

SETTING—Acute care hospitals and ambulatory clinics in the Chicago, Illinois, region.

PATIENTS—Adults with *E. coli* clinical isolates cultured in ambulatory settings or within 48 hours of hospital admission.

METHODS—Cases were patients with ESBL-producing *E. coli* clinical isolates cultured in ambulatory settings or within 48 hours of admission, and controls were patients with non-ESBL-producing *E. coli* isolates, matched to cases by specimen, location, and date. Clinical variables were ascertained through interviews and medical record review. Molecular methods were used to identify ESBL types, sequence type ST131, and *aac(6′)-Ib-cr*.

RESULTS—We enrolled 94 cases and 158 controls. Multivariate risk factors for ESBL-producing *E. coli* infection included travel to India in the past year (odds ratio [OR], 14.40 [95% confidence interval (CI), 2.92–70.95]), ciprofloxacin use (OR, 3.92 [95% CI, 1.90–8.1]), and age (OR, 1.04 [95% CI, 1.02–1.06]). Case isolates exhibited high prevalence of CTX-M-15 (78%), ST131 (50%), and *aac(6′)-Ib-cr* (66% of isolates with CTX-M-15).

CONCLUSIONS—Providers should be aware of the increased risk of ESBL-producing *E. coli* infection among returned travelers, especially those from India.

The increasing prevalence of antimicrobial-resistant *Escherichia coli* is a public health threat associated with significant morbidity, mortality, and cost.^{1–3} The prevalence of *E. coli* strains expressing extended-spectrum β -lactamases (ESBLs) has increased worldwide.⁴ Furthermore, although antimicrobial-resistant gram-negative infections have been regarded

primarily as causes of healthcare-associated infections, ESBL-producing *E. coli* now commonly cause community-onset infections in previously healthy individuals.⁵⁻⁸

ESBL genes are encoded on transmissible plasmids, facilitating their spread across healthcare and community settings. CTX-M enzymes have replaced TEM and SHV as the most common ESBLs,^{4,9} with CTX-M-15 being especially prevalent⁴ and found in domestic animals,¹⁰ food,¹¹ sewage,¹² and stool from healthy people.¹³ Alarming, there is evidence for co-transmission of genes encoding ESBLs as well as fluoroquinolone and aminoglycoside resistance.¹⁴

The multidrug-resistant phenotypes of ESBL-producing *E. coli* make them particularly challenging to treat, since often few or no oral options exist for outpatient management. Ineffective empiric antibiotics likely contribute to the poor outcomes associated with ESBL-producing *E. coli* infections.^{1,15,16} A better understanding of risk factors for infection with ESBL-producing *E. coli* would lead to more timely identification and treatment of patients and limit the spread of these resistant strains.

Few studies have evaluated risk factors for community-onset ESBL infections. Male sex; age more than 65 years; recent use of a cephalosporin,^{17,18} fluoroquinolone, or aminopenicillin;^{19,20} a variety of comorbidities;^{19,21} and international travel²¹ have been identified as important predictors of community-onset ESBL infections. However, these studies may not be applicable to the United States in the current era of community-wide multidrug-resistant *E. coli*, since none were performed in the United States, and several were conducted prior to the emergence of the highly resistant clonal group sequence type ST131.^{5,22-24} Other studies relied on subgroup analyses of community-onset cases²⁵ or omitted important variables, such as antimicrobial use.²¹

We therefore conducted a case-control study to identify risk factors associated with recent community-onset ESBL-producing *E. coli* infections in suburban Chicago, Illinois, where the prevalence of these strains has been increasing (A. Robicsek, unpublished data). In addition, we performed molecular analyses to determine the prevalence of CTX-M-type ESBLs, ST131, and *aac(6)-Ib-cr*.

METHODS

Study Design and Definitions

We conducted a prospective case-control study, seeking to define risk factors for ESBL presence among community-onset clinical *E. coli* isolates. The study period was from July 11, 2007, through July 26, 2010. Cases and controls were identified through the NorthShore University HealthSystem clinical laboratory, which serves 4 acute care hospitals and 70 ambulatory care sites in the Chicago region. Cases were defined as adults with ESBL-producing *E. coli* cultured from any specimen source either in ambulatory settings or within 48 hours of hospital admission. Controls were defined as the next available 1 or 2 patients with non-ESBL-producing *E. coli* isolates identified just subsequent to the case isolate and cultured in ambulatory settings or within 48 hours of hospital admission. To minimize disturbance to patients, we contacted no more than 3 individuals in an attempt to recruit 2 controls. If the first 3 individuals declined participation, we contacted additional patients until 1 control had been recruited. Using this strategy, we were unable to match 2 controls to every case. As the prevalence of ESBL-producing *E. coli* and risk factors can vary by specimen type and geography, controls were matched to cases by specimen type and clinic location of presentation. All case and control patients provided verbal consent and were interviewed by telephone or in person regarding demographics and clinical and social/travel history. Interviewers were unaware of the hypothesis that international travel is a potential

risk factor for ESBL-producing *E. coli* infection. Race, date of birth, and antimicrobial history were obtained through electronic records, which provide complete capture of all prescriptions within the healthcare system. Isolates that were resistant or intermediate to a given antimicrobial were considered nonsusceptible.

Molecular Analyses

ESBL testing was performed by disk diffusion according to guidelines of the Clinical and Laboratory Standards Institute.²⁶ Major CTX-M groups were identified using multiplex polymerase chain reaction (PCR).²⁷ Reverse-transcription PCR was used to further discriminate among group 1 CTX-M-type ESBLs, but group 9 CTX-M-type ESBLs were not further evaluated. Isolates melting at the temperature corresponding to either CTX-M-15 or CTX-M-3 were presumed to be CTX-M-15 due to its much greater prevalence. ST131 isolates were identified using PCR-based detection of ST131-specific single-nucleotide polymorphisms in *gyrB* and *mdh*.²⁸ All case-control sets collected from July 11, 2007, through May 31, 2009, were assessed for *aac(6)-Ib-cr* variants using a gap ligase chain reaction.²⁹ This study was approved by the NorthShore Institutional Review Board.

Statistical Analysis

To demonstrate an odds ratio (OR) for ESBL-producing *E. coli* of 2.5 among exposed relative to unexposed subjects, assuming the probability of exposure among controls is 0.15, we estimated that 90 case patients and 180 control patients would be needed to reject the null hypothesis with a power of 0.8 and an α of .05. A conditional logit (fixed-effects) model was applied for the study design of case-control matching to generate more precise estimates as well as to eliminate unwanted parameters during the regression procedure. Univariable and multivariable analyses were performed to identify risk factors for ESBL-producing *E. coli* infection. Variables with a univariable *P* value less than .25 were included as candidate risk factors in the multivariable model and were removed by backward selection. The significance criterion was *P* less than .05 (2-sided). The goodness of fit of the model was assessed using the procedure of computing score statistics.^{30,31}

RESULTS

We enrolled 94 of 254 prospective cases with ESBL-producing *E. coli* isolates. We approached 327 patients with non-ESBL-producing *E. coli* isolates in order to recruit 158 control subjects. The majority of nonparticipants could not be reached by telephone despite multiple attempts. Among the cases, participants and nonparticipants did not differ in sex (74% vs 76% female; *P* = .88) or specimen type (91% urine in both groups), although participants were slightly younger than nonparticipants (mean age, 63.8 vs 68.8 years; *P* = .03). Among controls, there were no significant differences between participants and nonparticipants in sex (87% vs 83% female; *P* = .35), specimen type (94% vs 91% urine; *P* = .31), or mean age (54.6 vs 57.6 years; *P* = .19). Urine was the most common source of isolates among both cases (*n* = 89; 95%) and controls (*n* = 152; 96%). Approximately one-third of both cases and controls had been hospitalized or had surgery in the prior 1 year. The proportion of subjects without any comorbidities or history of surgery or hospitalization was similar among cases and controls (Table 1).

Risk Factors for ESBL-Producing *E. coli* Infection

Univariable analysis identified several variables significantly associated with ESBL-producing *E. coli* infection among patients with an *E. coli* infection, including age, male sex, travel to India, and history in the prior year of severe gastroenteritis, intensive care unit admission, visiting a physician, positive urine culture, and use of any antimicrobial (Table 1). When antimicrobials were separated by class, prior use of aminoglycosides, extended-

spectrum cephalosporins, and ciprofloxacin were associated with ESBL-producing *E. coli* cases. In multivariable analysis, 3 variables were identified as statistically significant predictors of ESBL-producing *E. coli*, including age (OR, 1.04 [95% confidence interval (CI), 1.02–1.06]), travel to India in the past year (OR, 14.40 [95% CI, 2.92–70.95]), and use of ciprofloxacin (OR, 3.92 [95% CI 1.90–8.1]; Table 2). Of note, prior use of fluoroquinolones other than ciprofloxacin did not significantly predict ESBL-producing *E. coli* infection.

Resistance and Molecular Epidemiology

Case isolates, compared with control isolates, had a higher prevalence of resistance to a variety of antimicrobials, including ampicillin (100% vs 46%), ceftriaxone (98% vs 0.6%), gentamicin (48% vs 7%), ciprofloxacin (96% vs 15%), and trimethoprim-sulfamethoxazole (65% vs 18%; $P < .001$ for all comparisons). All case isolates were analyzed for CTX-M type. Of 94 isolates, 73 (78%) had CTX-M-15, 11 (12%) had CTX-M-group 9 type ESBLs, and 10 (11%) did not have CTX-M genes. International travel was associated with 35 (48%) of 73 isolates containing CTX-M-15, 5 (45%) of 11 isolates containing CTX-M-group 9 type ESBLs, and 1 (10%) of 10 isolates lacking CTX-M ($P = .078$).

The finding that receipt of ciprofloxacin but not other fluoroquinolones was an independent risk factor for ESBL-producing *E. coli* led us to evaluate a subset of case and control isolates for the presence of an *aac(6′)-Ib* variant, called *aac(6′)-Ib-cr*, that confers reduced susceptibility to ciprofloxacin but not other fluoroquinolones. *aac(6′)-Ib-cr* was found in 21 (66%) of the 32 case isolates that contained CTX-M-15 but in no other case or control isolates. *aac(6′)-Ib-cr* was significantly associated with gentamicin resistance, being identified in 13 (48%) of 27 gentamicin-resistant versus 7 (8%) of 92 gentamicin-susceptible isolates ($P < .001$). *aac(6′)-Ib-cr* was also significantly associated with ciprofloxacin use, which was reported in 11 (52%) of 21 patients with *aac(6′)-Ib-cr*-containing isolates, compared with 14 (14%) of 99 patients with *aac(6′)-Ib-cr*-negative isolates ($P < .001$).

All case and control isolates also were assessed for ST131 status. ST131 was much more prevalent among cases (47/94 [50%]) than controls (21/158 [13%]; $P < .001$). Among case isolates, CTX-M-15 was significantly more common among ST131 (41/47 [87%]) than non-ST131 (32/47 [68%]) isolates ($P = .024$), as was *aac(6′)-Ib-cr* (13/21 [62%] for ST131 vs 8/22 [36%] for non-ST131 isolates; $P = .09$), although this association was not statistically significant.

DISCUSSION

We describe the only case-control study to date from the United States to investigate risk factors for community-onset ESBL-producing *E. coli* infections in the current era of pandemic multidrug-resistant *E. coli* ST131. We identified travel to India, ciprofloxacin use, and age as risk factors for infection with ESBL-producing *E. coli*. Additionally, we found that *E. coli* ST131 accounted for 50% of case isolates (compared with only 13% of control isolates).

This is the second study—and the first from the United States—to quantify the risk of ESBL-producing *E. coli* infection associated with international travel. Although several reports have noted an association between international travel and ESBL-producing *E. coli* infection^{32,33} or colonization,³⁴ Laupland et al²¹ were the first to quantify the much higher risk among travelers returning to the Calgary region from India versus other countries, a finding supported by our results. We speculate that international travelers acquire ESBL-producing *E. coli* strains through ingestion of contaminated food or water or via person-to-person spread³⁵ and that this occurs frequently in India because of the high prevalence there

of ESBL-containing organisms in environmental sources³⁶ and asymptomatic carriers,^{13,37} plus overcrowding and poor sanitation. Supporting this, among previously reported returned travelers who either were asymptomatic or had travelers' diarrhea, fecal colonization with ESBL-producing *E. coli* was highest (nearly 80%) among those returning from India compared with other parts of the world.^{38,39} Likewise, a study from the United Kingdom of fecal isolates from returned travelers found diverse genetic elements not usually seen in the United Kingdom flanking CTX-M-15, suggesting overseas acquisition of ESBLs.⁴⁰ Only one small study has attempted to define travel-related exposures (other than destination country) associated with ESBL-producing *E. coli* colonization; it identified gastroenteritis, staying with family and friends, and taking ciprofloxacin while traveling as significant correlates.³⁸ More research is needed to characterize travel-associated factors associated with ESBL-producing *E. coli* colonization to guide development of strategies to prevent acquisition and transmission of these strains.

Unlike previous studies, we identified receipt specifically of ciprofloxacin, but not other fluoroquinolones, as an important independent risk factor for ESBL-producing *E. coli* infection. It is possible that this specificity of effect for ciprofloxacin was not noted in other studies because they typically grouped all fluoroquinolones as a class rather than analyzing each agent separately.^{17,19,25} Alternatively, our study may have been underpowered to detect statistically significant differences in exposure to fluoroquinolones other than ciprofloxacin. Also in contrast to previous findings,^{17,18,25} we did not find prior cephalosporin use or healthcare exposure to be associated with ESBL infections. Reasons for these discrepancies are not clear but may include differences in patient populations, circulating *E. coli* sequence types, prevalence of ESBL-producing *E. coli* in the community, and antimicrobial prescribing practices.

The association of ciprofloxacin but not newer fluoroquinolones with ESBL-producing *E. coli* prompted us to evaluate case isolates for the presence of *aac(6')-Ib-cr*. This variant aminoglycoside-modifying enzyme acetylates ciprofloxacin and norfloxacin but not the other fluoroquinolones, which are structurally different. *aac(6')-Ib-cr* confers reduced susceptibility to ciprofloxacin⁴¹ and also significantly increases the mutant prevention concentration (the lowest concentration at which no mutations are detected) for ciprofloxacin. Increasing the mutant prevention concentration potentially allows for survival of strains in low concentrations of ciprofloxacin, thereby permitting accumulation of chromosomal mutations that confer higher-level fluoroquinolone resistance. Because two-thirds of tested isolates with CTX-M-15 (but no control isolates) also carried *aac(6')-Ib-cr*, it is possible that these genes are linked and were coselected. Indeed, *aac(6')-Ib-cr* is often found on IncFII plasmids coexpressing CTX-M-15.^{41,42} The extensive use of fluoroquinolones—especially ciprofloxacin—and cephalosporins in clinical practice likely continues to select for plasmids containing both *aac(6')-Ib-cr* and *bla*_{CTX-M-15}.

We found that, as in other parts of the world, the majority of ESBL-producing *E. coli* in our region expressed CTX-M-15. In addition, half of the ESBL isolates were *E. coli* ST131, a widely disseminated virulent clonal group that often harbors CTX-M-15 and *aac(6')-Ib-cr*.^{5,22,24} Our results support the association among CTX-M-15, ST131, and *aac(6')-Ib-cr*, as demonstrated by Pitout et al.⁴³

Study limitations include that we did not use a case-case-control study design that included patients without infection as a control group, as recommended by some.^{44,45} Although we recognize that not including infection-free controls could lead to inflated estimates of relative risk associated with prior antimicrobial exposure, we attempted to minimize this by considering antimicrobial exposure in the past year (rather than only recent exposure). Furthermore, this potential source of bias should not have affected the finding that travel to

India was associated with ESBL infection. Other limitations are that we did not distinguish infection from colonization, did not collect information about antibiotics received abroad or about duration and purpose of international travel, and did not collect data on presence of indwelling devices, although we did collect information about several other risk factors for healthcare-associated infection. Our method of recruiting patients by telephone may have led to selection bias, although baseline characteristics of participants and nonparticipants were not different. Last, we relied on patient self-report of some variables, making our study subject to possible recall bias. Study strengths include that we were able to obtain detailed clinical and social histories, including a comprehensive history of prior antimicrobial use, in a non-selected, largely ambulatory population. This study represents, to our knowledge, one of the largest case-control studies of community-onset ESBL-producing *E. coli* infections in the United States.

Our findings have several important clinical implications. First, providers should be aware of the increased risk of ESBL infection among returned international travelers, especially those from India. The high proportion of travelers who return with fecal colonization with ESBL-producing Enterobacteriaceae is currently underrecognized by clinicians, potentially leading to ineffective empiric treatment of infections in this patient group.³² Second, returned travelers likely act as reservoirs for further dissemination of ST131 and ESBL-expressing plasmids. Third, antimicrobial stewardship, especially more judicious use of ciprofloxacin, may reduce selection pressure for dissemination of ESBL-containing plasmids or strains. Last, there clearly is a need for further research to elucidate additional risk factors among patients with ESBL infections who do not have a history of travel to India or risk factors for healthcare-associated infection, to evaluate the role of ciprofloxacin in propagating ESBLs, and to identify travel-related exposures associated with ESBL acquisition overseas and importation into the United States.

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TABLE 1

Univariable Analysis of 94 Patients with Extended-Spectrum β -Lactamase (ESBL)-Producing *Escherichia coli* Isolates (Cases) and 158 Patients with Non-ESBL-Producing *E. coli* Isolates (Controls)

Category, variable	Prevalence of variable, no. (column %)			P
	Cases (n = 94)	Controls (n = 158)	OR (95% CI)	
Demographic				
Age >65 years	47 (50)	53 (33)	2.44 (1.33–4.48)	.004
Male sex	21 (22.3)	21 (13.2)	2.14 (1.01–4.53)	.05
Caucasian	67 (71.3)	128 (80.5)	0.58 (0.31–1.10)	.10
Group living	9 (9.6)	6 (3.8)	2.90 (0.95–8.8)	.06
Children in household	22 (23.4)	39 (24.5)	0.88 (0.47–1.63)	.68
Pets	38 (40.4)	70 (44.0)	0.88 (0.52–1.48)	.63
Public swimming/bathing	32 (34.0)	53 (33.3)	1.07 (0.61–1.91)	.81
Currently employed	37 (39.4)	76 (47.8)	0.70 (0.40–1.22)	.21
Travel ^a				
India	13 (13.8)	2 (1.3)	10.7 (2.4–47.83)	.002
Mexico	8 (8.5)	12 (7.6)	1.16 (0.47–2.85)	.76
Africa	4 (4.3)	1 (0.6)	6.28 (0.69–57.17)	.10
Europe	10 (10.6)	12 (7.6)	1.45 (0.61–3.46)	.41
Central/South America	3 (3.2)	4 (2.5)	1.36 (0.3–6.13)	.69
China	5 (5.3)	5 (3.1)	2.03 (0.53–7.78)	.30
Other ^b	8 (8.5)	11 (6.9)	1.22 (0.47–3.15)	.68
Comorbidities				
Heart ^c	15 (16)	23 (14.5)	1.09 (0.49–2.41)	.84
Lung ^d	12 (12.8)	16 (10.1)	1.32 (0.54–3.18)	.54
Stroke	4 (4.3)	5 (3.1)	1.17 (0.31–4.44)	.82
Stomach ^e	31 (33)	42 (26.4)	1.35 (0.76–2.38)	.31
Kidney ^f	12 (12.8)	24 (15.1)	0.93 (0.43–1.99)	.85
Cancer	18 (19.2)	25 (15.7)	1.32 (0.60–2.93)	.50
Diabetes ^g	11 (11.7)	15 (9.4)	1.21 (0.48–3.04)	.69
Surgery ^a	29 (30.9)	47 (29.6)	1.09 (0.58–2.04)	.79
Organ transplant	2 (2.1)	3 (1.9)	1.20 (0.16–9.2)	.86
Gastric acid reducers	31 (33)	37 (23.3)	1.60 (0.91–2.83)	.10
Gastroenteritis ^a	26 (27.7)	26 (16.4)	2.00 (1.05–3.8)	.04
Hospitalization ^a	31 (33)	42 (26.4)	1.40 (0.75–2.6)	.29
ICU admission ^a	13 (13.8)	7 (4.4)	3.75 (1.3–10.8)	.01
MD visit ^a	78 (83)	112 (70.4)	2.03 (1.06–3.9)	.03
Positive urine culture ^a	31 (33)	34 (21.4)	1.98 (1.08–3.63)	.03
None	21 (21)	38 (24)	0.91 (0.50–1.67)	.88
Diet				

Category, variable	Prevalence of variable, no. (column %)			P
	Cases (n = 94)	Controls (n = 158)	OR (95% CI)	
Chicken ^h	80 (85.1)	146 (91.8)	0.54 (0.24–1.23)	.14
Beef ^h	69 (73.4)	123 (77.4)	0.79 (0.42–1.47)	.45
Pork ^h	53 (56.4)	93 (58.5)	0.95 (0.54–1.67)	.85
Vegetables ^h	86 (91.5)	153 (96.2)	0.43 (0.15–1.26)	.12
Eat out >2 times per week	26 (27.7)	46 (28.9)	0.94 (0.53–1.68)	.85
Antimicrobials ⁱ				
Any antimicrobial	60 (63.8)	74 (46.5)	1.97 (1.16–3.34)	.01
Penicillin	12 (12.8)	13 (8.2)	1.65 (0.73–3.71)	.23
Aminoglycoside	8 (8.5)	2 (1.3)	8.00 (1.7–37.7)	.009
BL-BLI combination	16 (17)	16 (10.1)	2.05 (0.89–4.72)	.09
First or second cephalosporin	16 (17)	24 (15.1)	1.16 (0.55–2.43)	.70
Third cephalosporin/aztreonam	13 (13.8)	7 (4.4)	2.87 (1.13–7.27)	.03
Carbapenem	1 (1.1)	2 (1.3)	0.78 (.07–8.88)	.84
Moxifloxacin or levofloxacin	22 (23.4)	22 (13.8)	1.88 (0.98–3.63)	.06
Ciprofloxacin	30 (31.9)	21 (13.2)	3.40 (1.74–6.64)	<.001
Macrolide	15 (16)	14 (8.8)	1.92 (.88–4.16)	.10
Clindamycin or metronidazole	9 (9.6)	16 (10.1)	0.96 (0.38–2.43)	.94
Daptomycin, vancomycin, or linezolid	9 (9.6)	10 (6.3)	1.56 (0.63–3.87)	.34
Antifungal	8 (8.5)	8 (5)	1.76 (0.62–4.94)	.29

NOTE. BL-BLI, β -lactam/ β -lactamase inhibitor; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

^aIn the past 1 year.

^bLocation other than India, China, Africa, South or Central America, Mexico, and Europe.

^cIncludes angina, prior myocardial infarction, and coronary artery surgery.

^dIncludes asthma, emphysema, and chronic bronchitis.

^eIncludes gastroesophageal reflux disease, ulcers, diverticulitis, and swallowing difficulties.

^fIncludes kidney stones, kidney transplant, and chronic kidney disease.

^gRequiring insulin.

^hRegular consumption of indicated foods.

ⁱPrescribed in the past 1 year.

TABLE 2

Multivariable Analysis of Risk Factors for Community-Onset Extended-Spectrum β -Lactamase–Producing *Escherichia coli* Infection

Characteristic	OR (95% CI)	P
Age (per year)	1.04 (1.02–1.06)	<.001
Travel to India in past year	14.40 (2.92–70.95)	.001
Ciprofloxacin use in past year	3.92 (1.90–8.1)	<.001

NOTE. CI, confidence interval; OR, odds ratio.