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Escherichia coli ST131 Associated with Increased Mortality in Bloodstream Infections from Urinary Tract Source

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ABSTRACT *Escherichia coli* sequence type 131 (ST131) is a globally dominant multidrug-resistant clone, although its clinical impact on patients with bloodstream infection (BSI) is incompletely understood. This study aims to further define the risk factors, clinical outcomes, and bacterial genetics associated with ST131 BSI. A prospectively enrolled cohort study of adult inpatients with *E. coli* BSI was conducted from 2002 to 2015. Whole-genome sequencing was performed with the *E. coli* isolates. Of the 227 patients with *E. coli* BSI in this study, 88 (39%) were infected with ST131. Patients with *E. coli* ST131 BSI and those with non-ST131 BSI did not differ with respect to in-hospital mortality (17/82 [20%] versus 26/145 [18%]; $P = 0.73$). However, in patients with BSI from a urinary tract source, ST131 was associated with a numerically higher in-hospital mortality than patients with non-ST131 BSI (8/42 [19%] versus 4/63 [6%]; $P = 0.06$) and increased mortality in an adjusted analysis (odds ratio of 5.85; 95% confidence interval of 1.44 to 29.49; $P = 0.02$). Genomic analyses showed that ST131 isolates primarily had an H4:O25 serotype, had a higher number of prophages, and were associated with 11 flexible genomic islands as well as virulence genes involved in adhesion (*papA*, *kpsM*, *yfcV*, and *iha*), iron acquisition (*iucC* and *iutA*), and toxin production (*usp* and *sat*). In patients with *E. coli* BSI from a urinary tract source, ST131 was associated with increased mortality in an adjusted analysis and contained a distinct repertoire of genes influencing pathogenesis. These genes could contribute to the higher mortality observed in patients with ST131 BSI.

KEYWORDS ST131, bacteremia, bloodstream infections, *Escherichia coli*, urinary tract infection

Escherichia coli bloodstream infections (BSI) are associated with increased health care costs, infection recurrence, and increased mortality that is often due to antibacterial resistance (1–3). Much of the increasing *E. coli* antibacterial resistance has been driven by the global spread of the genetic clone sequence type 131 (ST131) (4, 5). *E. coli* ST131 has been the subject of significant research; yet, important questions remained unanswered.

First, the risk factors for *E. coli* ST131 infection are incompletely understood. Previous studies have shown that patients with *E. coli* ST131 and those with non-ST131 BSI have generally similar baseline characteristics, although risk factors for ST131 acquisition have included recent surgery (6, 7), infection source (8–10), and prior antibiotic use (7). One area that has not received significant attention, however, is how geospatial factors influence acquisition of *E. coli* ST131 BSI. For example, it is unclear how a patient's local community (e.g., where the patient lives) influences the bacterium with which they are infected. Second, the

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influence of the ST131 genotype on patient outcomes in *E. coli* BSI is unclear. Prior work has demonstrated an association between ST131 and persistent or recurrent infection (11–13), but no firm association between ST131 and increased mortality has yet been established. One study showed an association between ST131 and mortality in an adjusted analysis (14), while multiple others did not (6, 9–11, 15). Third, we have an incomplete understanding of the virulence genes and flexible genomic islands that distinguish ST131 strains from non-ST131 strains. A better understanding of the genetic factors that have led to the global success of this clone may help to combat its further spread.

In this work, we generated a large cohort of prospectively enrolled patients with *E. coli* BSI at Duke University Medical Center from 2002 to 2015. Detailed clinical data and outcomes were collected from each patient, and the bacterial isolates were sequenced by the J. Craig Venter Institute. This cohort was used to address three hypotheses. First, ST131 isolates would be associated with specific geospatial locations. Second, ST131 would be associated with increased mortality relative to non-ST131 isolates in *E. coli* BSI after adjustment for patient factors. Third, ST131 would be associated with a specific set of virulence genes and flexible genomic islands (fgi) that are differentially present in ST131 isolates. Given that *E. coli* ST131 has been demonstrated to have an association with treatment failure in urinary tract infections (13), we paid particular attention to the subgroup of patients with BSI from a urinary tract source.

MATERIALS AND METHODS

Clinical data. The patient clinical data and bacterial isolates were obtained from the Duke Blood Stream Infection Biorepository (BSIB). The BSIB contains prospectively collected clinical data on greater than 3,500 unique inpatients at Duke University Hospital with monomicrobial Gram-negative bacterial BSI since 2002. Consent was obtained from all study participants, and the study was approved by the Duke University Institutional Review Board. Definitions are outlined in Text S1 in the supplemental material.

Whole-genome sequencing and bioinformatics analyses. The whole-genome sequencing and bioinformatics analyses are detailed in Text S1.

Statistical analysis. In the unadjusted analyses, continuous variables were reported as means with standard deviations (SDs) and compared with *t* tests. Dichotomous variables were reported as counts and percentages and compared with Fisher's exact or chi-square tests as appropriate. In the adjusted analyses, logistic regression models were generated to determine associations. Outcomes of interest in the adjusted models included the presence of ST131 (as opposed to non-ST131 *E. coli* BSI) and in-hospital mortality. Model covariates included age, gender, race, route of infection (e.g., hospital-acquired infection, etc.), source of infection, hematopoietic or solid organ transplant, diabetes mellitus, recent corticosteroid use (within 30 days before BSI), HIV, recent surgery (within 30 days before BSI), days to effective antibiotics, ST131 genotype, and chronic health Acute Physiology and Chronic Health Evaluation II (APACHE-II) score. The chronic health portion of the APACHE-II describes whether a patient has severe organ system insufficiency on hospital admission. These covariates were selected to broadly encompass the clinical factors known or thought to influence BSI outcome. Model covariates with near-significant *P* values ($P \leq 0.15$) in a univariable analysis were included in the final multivariable logistic regression models. In the analysis of virulence genes associated with ST131 compared with non-ST131, we performed a Bonferroni correction to account for multiple comparisons. *P* values less than 0.05 were considered significant. The geospatial analysis is described in Text S1.

Data availability. All of the genomes determined in this study are available at NCBI under BioProject number PRJNA290784.

RESULTS

Patient characteristics. In total, 227 patients with *E. coli* BSI were included in this study. Of these, 88 (39%) were infected with ST131. Patients with ST131 BSI, compared with those with non-ST131 infections, were more likely to have a health care-associated route of infection (either hospital-acquired or healthcare-associated, community-acquired; 80/88 [91%] versus 100/139 [72%]; $P = 0.003$) (Table 1). Otherwise, patients with ST131 and non-ST131 *E. coli* BSI had similar characteristics (Table 1). As expected, ST131 isolates exhibited higher antibiotic resistance to fluoroquinolones (77/88 [88%] versus 31/139 [22%]; $P < 0.0001$) and were more commonly multidrug resistant (77/88 [88%] versus 73/139 [53%]; $P < 0.0001$) (Table 1). Interestingly, however, ST131 and non-ST131 isolates did not differ with respect to ceftriaxone resistance (17/88 [19%] versus 24/139 [19%]; $P = 0.73$). In total, 43 patients (19%) did not survive to discharge. Patients with *E. coli* ST131 BSI, compared with those with non-ST131 BSI, did not differ with respect to in-hospital mortality (17/82 [20%] versus 26/145 [18%]; $P = 0.73$) or in any of the listed

TABLE 1 Characteristics of patients with *E. coli* bloodstream infections and bacteria

Patient/bacterial characteristics[a]	ST131 *N* = 88 *n* (%)	Non-ST131 *N* = 139 *n* (%)	*P* value[d]
Age (mean [SD])	62 (14)	63 (15)	0.34
Male gender	50 (57)	73 (53)	0.59
Race			0.29
White	52 (59)	96 (69)	
Black	28 (32)	32 (23)	
Other	8 (9)	11 (8)	
Hemodialysis dependent	10 (11)	10 (7)	0.34
Diabetes mellitus	36 (41)	41 (29)	0.09
Corticosteroid use within 30 days	21 (24)	29 (21)	0.62
Hematopoietic or solid organ transplant	9 (10)	17 (12)	0.83
HIV	2 (2)	1 (1)	0.56
Surgery within 30 days	24 (27)	30 (22)	0.34
Source			0.24
Urine/pyelonephritis	42 (48)	63 (45)	
Abscess	2 (2)	5 (4)	
Pneumonia	5 (6)	3 (2)	
Skin/soft tissue infection	3 (3)	8 (6)	
Biliary tract	10 (11)	12 (8)	
Line	1 (1)	6 (4)	
Other[b]	13 (15)	13 (9)	
Unidentified source	12 (14)	31 (22)	
Route			**0.003**
Hospital acquired	19 (22)	22 (16)	
Community acquired, healthcare associated	61 (69)	78 (56)	
Community acquired, non-health care associated	8 (9)	39 (28)	
APACHE-II acute physiology score (mean [SD])	8 (6)	8 (6)	0.86
APACHE-II chronic health score (mean [SD])	4 (2)	4 (2)	0.08
Days to effective antibiotic therapy			0.11
0	51 (58)	88 (63)	
1	20 (23)	31 (22)	
2	5 (6)	13 (9)	
≥3	12 (14)	7 (5)	
Antibiotic resistance			
Ceftriaxone-resistant	17 (19)	24 (19)	0.73
Fluoroquinolone-resistant	77 (88)	31 (22)	**<0.0001**
Trimethoprim-sulfamethoxazole resistant	52 (59)	48 (35)	**0.004**
Carbapenem-resistant	0	0	1.00
Multidrug resistant	77 (88)	73 (53)	**<0.0001**
Extensively drug resistant	0	0	1.00
Patient outcomes	**ST131 *N* = 88 *n* (%)**	**Non-ST131 *N* = 139 *n* (%)**	***P* value**
In-hospital mortality	18 (20)	25 (18)	0.73
Recurrent bloodstream infection	2 (2)	0 (0)	0.15
Complications[c]	44 (50)	66 (47)	0.78
Septic shock	20 (22)	33 (24)	1.00
Acute kidney injury	32 (36)	39 (28)	0.24
ALI/ARDS	5 (6)	11 (7.9)	0.60
Disseminated intravascular coagulation	2 (2)	4 (3)	1.00

[a]Patients were stratified by whether they had an infection with *E. coli* sequence type 131 (ST131) or another *E. coli* ST; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation.
[b]The "Other" category includes bloodstream infections from sources such as septic arthritis, sinusitis, etc. that do not fit into the predefined categories.
[c]Defined as present if ≥1 of the below complications were suffered.
[d]*P* values less than 0.05 are in bold.

TABLE 2 Adjusted analysis of factors influencing acquisition of *E. coli* ST131 bloodstream infection

Patient characteristics	Odds ratio	95% CI	*P* value[c]
Race[a]			
Black	1.54	0.80 to 2.97	0.190
Other	1.36	0.47 to 3.81	0.550
Diabetes mellitus	1.50	0.83 to 2.72	0.180
Route of acquisition[b]			
Hospital acquired	4.03	1.52 to 11.49	**0.006**
Community acquired, health care associated	3.58	1.60 to 8.90	**0.003**
Chronic APACHE-II score	1.08	0.94 to 1.24	0.280

[a]Reference is white race.
[b]Reference is community acquired, non-health care associated.
[c]*P* values less than 0.05 are in bold.

complications of BSI (Table 1). The only two cases of recurrent BSI were caused by ST131, although this did not meet statistical significance given the low sample size (2/88 [2%] versus 0/139 [0%]; $P = 0.15$). The first case of *E. coli* ST131 BSI was in 2004, and the number of such infections increased over time (Fig. S1 in the supplemental material).

Risk factors for *E. coli* ST131 BSI. A multivariable logistic regression model revealed that the only risk factor for ST131 BSI, relative to non-ST131 BSI, was health care exposure. Compared to patients with community-acquired, non-health care-associated infections, both hospital-acquired (odds ratio [OR] of 4.03; 95% confidence interval [CI] of 1.52 to 11.49; $P = 0.006$) and community-acquired, health care-associated infections (OR of 3.58; 95% CI of 1.60 to 8.90; $P = 0.003$) were associated with *E. coli* ST131 BSI relative to non-ST131 BSI (Table 2). We did not find a significant association between geography and the odds of ST131 infection ($P = 0.75$ for significance of smoothed coordinate terms), and models incorporating patient geospatial coordinates were not significantly different than aspatial models.

Outcomes in patients with *E. coli* BSI. We generated a multivariable logistic regression model of in-hospital mortality in patients with *E. coli* BSI (Table S1). The covariate of ST131 BSI (relative to patients with non-ST131 BSI) was not included in the final model as it was associated with a *P* value greater than 0.15 in a univariable analysis (OR of 1.17; 95% CI of 0.59 to 2.29; $P = 0.64$). Age (OR of 1.04; 95% CI of 1.01 to 1.07; $P = 0.02$) and unidentified source of BSI (OR of 2.88; 95% CI of 1.09 to 8.20; $P = 0.02$) were independently associated with increased mortality.

Subgroup analysis of patients with BSI from a urinary tract source. Given that *E. coli* ST131 has been demonstrated to have an association with treatment failure in urinary tract infections (13), we performed a subgroup analysis on patients with BSI from a urinary tract source. There were 105 (46%) such patients. Of these 105 patients, 42 (40%) were infected with *E. coli* ST131. Patients with ST131 BSI, compared with those with non-ST131 BSI, more often had either hospital-acquired or community-associated, health care-associated infections (36/42 [86%] versus 37/63 [59%]; $P = 0.001$) and had recent surgery (14/42 [33%] versus 5/63 [8%]; $P = 0.002$) (Table S2). BSI with ST131 was associated with a numerically higher in-hospital mortality than non-ST131 BSI, although this did not meet statistical significance (8/42 [19%] versus 4/63 [6%]; $P = 0.06$). In the adjusted analysis, however, *E. coli* ST131 BSI was associated with increased mortality (OR of 5.85; 95% CI of 1.44 to 29.49; $P = 0.02$) (Table 3). Other factors associated with increased mortality included

TABLE 3 Adjusted analysis of factors influencing in-hospital mortality in patients with *E. coli* bloodstream infections with a urinary tract source

Variable	Odds ratio	95% CI	*P* value[a]
Age	1.08	1.03 to 1.16	**0.007**
Chronic health APACHE-II score	1.59	1.09 to 2.90	**0.040**
ST131	5.85	1.44 to 29.49	**0.020**

[a]*P* values less than 0.05 are in bold.

age (OR of 1.08; 95% CI of 1.03 to 1.16; $P = 0.0007$) and APACHE-II chronic health score (OR of 1.59; 95% CI of 1.09 to 2.90; $P = 0.04$). The final model did not contain the variable for days to effective antibiotic therapy, as this covariate was associated with a P value of 0.38 in a univariable analysis. However, the association of ST131 with increased in-hospital mortality remained significant when days to effective antibiotic therapy was included as an additional covariate in the model.

Comparative genomic analysis of ST131 versus non-ST131 *E. coli* BSI isolates. To further investigate why the ST131 genotype was associated with increased mortality in patients with BSI from a urinary tract source, we used whole-genome sequencing to identify the serotypes, flexible genomic islands (fgis), and virulence genes associated with ST131 relative to non-ST131 strains. This analysis was limited to 193 *E. coli* strains for which we had high quality sequences with adequate coverage (193/227 [85%]). ST131 isolates primarily had an O25:H4 serotype (62/68 [91%]). This serotype was rare among non-ST131 isolates (2/125 [2%]). ST131 primarily contained allele 30 of the type 1 fimbriae adhesin gene *fimH* (i.e., *fimH30*; 56/68 [82%]). ST131 was associated with 11 fgis that contained 255 genes (Table S3). The fgis ranged in size from 1 to 59 genes. The primary putative function of the fgis associated with ST131 was adhesion. One of the fgis ($n = 44$ genes; fgi 33 in Table S3) encodes a second flagellar system (i.e., the FLAG-2 locus), a second fgi ($n = 8$ genes; fgi 335 in Table S3) encodes putative fimbriae-associated genes, and the third adhesion locus encodes a flagellin *fliC* gene ($n = 1$ gene; fgi 5626 in Table S3).

Of the 11 fgis associated with ST131, 4 (36%) were homologous to putative prophages. Genes within these four fgis accounted for 71% (161/227) of all genes in ST131-associated fgis (fgi 22, 27, 59, and 65 in Table S3). Given the high proportion of ST131-associated fgis that contained prophages, we performed a full genomic analysis of prophages in this set of *E. coli* BSI isolates using Phage_Finder. In total, 1,110 prophages greater than 10 kilobases (kb) were identified, and they grouped into 46 clusters by average nucleotide identity. The number of prophages per *E. coli* BSI isolate ranged from 1 to 13 (mean of 5.8 and standard deviation of 2.4; Fig. 1A). ST131 isolates contained a significantly higher number of prophages than non-ST131 isolates (mean of 7.7 [standard deviation of 2.0] versus mean of 4.7 [standard deviation of 1.9], respectively; $P < 0.0001$; Fig. 1B). The numbers of putative prophages identified for each *E. coli* BSI isolate are shown in Fig. S2. We determined if the presence of any specific prophage clusters was associated with patient mortality. We found that presence of prophage cluster 36 was associated with increased patient in-hospital mortality (cluster 36 in-hospital mortality 43% [10/23]; all other in-hospital mortality 18% [30/170]; $P = 0.01$). This association remained significant after adjusting for patient and treatment variables (OR of 4.14; 95% CI of 1.72 to 13.56; $P = 0.009$). However, prophage cluster 36 was not identified in any ST131 *E. coli* isolates. VirulenceFinder (16) was used to identify putative virulence genes within this prophage cluster. Genes *iss* (increased serum survival gene) and putative heat-labile enterotoxin *eltIIAB-c2* were associated with prophage cluster 36. Gene *iss* has been extensively studied and is associated with increased serum survival and pathogenicity in chick sepsis models (17–19). Deletion of *iss* reduces production of the capsule, which in turn increases susceptibility to complement-mediated serum killing (20). The putative heat-labile enterotoxin *eltIIAB-c2*, or LTII-c2, has not been well studied, although it has been associated with increased cytotoxicity (21).

We further examined putative virulence genes in the entire cohort using VirulenceFinder. In total, 6,444 virulence genes were identified in the 193 *E. coli* BSI isolates. The BSI isolates had a mean of 33.4 virulence genes (standard deviation [SD] of 6.6). ST131 isolates, on average, had fewer virulence genes than non-ST131 isolates (mean of 31.3 [SD of 2.9] versus mean of 34.6 [SD of 7.6]; $P < 0.0001$). However, ST131 had a distinct repertoire of virulence genes relative to non-ST131. Ten putative virulence genes were associated with ST131 relative to non-ST131. These 10 genes have diverse roles in pathogenesis, such as adhesion, iron acquisition, and toxin production (Table 4). The adhesion genes included a polysaccharide capsule synthesis gene *kpsM*, an adhesin gene *iha*, and fimbrial genes *papA* and *yfcV*. The iron acquisition genes *iucC* and *iutT* are the synthase and receptor, respectively, for the

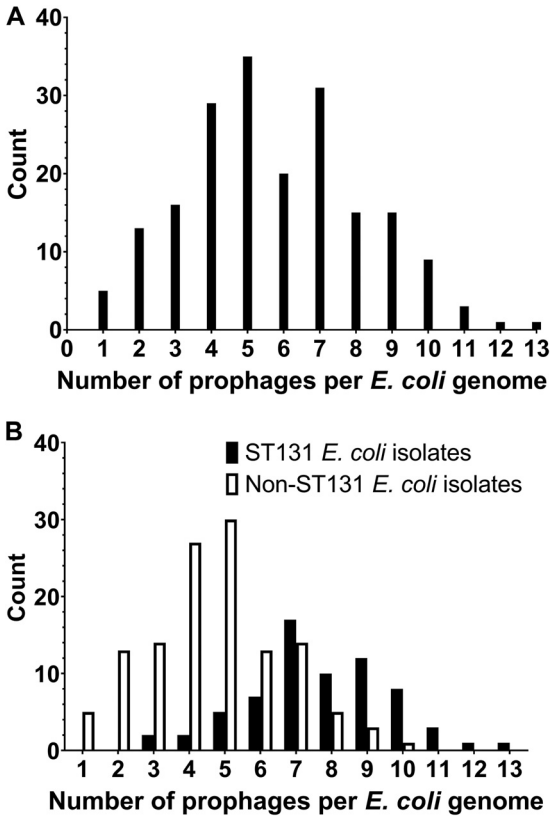

FIG 1 Distribution of number of prophages per *E. coli* BSI isolate. (A) Histograms of all *E. coli* included in this study (n = 193). (B) *E. coli* BSI isolates stratified by sequence type 131 (ST131) or not. *E. coli* ST131 was associated with a higher number of prophage clusters per genome ($P < 0.0001$).

siderophore aerobactin. The toxin genes *usp* and *sat* have been shown to exhibit activity against mammalian cells (22, 23).

DISCUSSION

In this study, we performed a genomic analysis on a large set of clinical *E. coli* BSI isolates that were procured from prospectively enrolled and well-characterized patients at a large US institution from 2002 to 2015. Our aims were to better understand the risk factors for and outcomes associated with *E. coli* ST131 BSI. This study revealed several key findings.

First, we found that ST131 was associated with increased mortality in patients with *E. coli* BSI from a urinary tract source. This is an area of controversy as one study showed an association between ST131 and mortality (14), while multiple others did not (6, 9–11, 15). When *E. coli* BSI from all sources were considered together, no association between ST131

TABLE 4 Virulence genes associated with *E. coli* ST131 bloodstream infection isolates compared with non-ST131 bloodstream infection isolates

Gene	No. (%) of ST131 strains that contain gene N = 68	No. (%) of non-ST131 strains that contain gene N = 125	Annotation	Adjusted P value[a]
hha	67 (99)	75 (60)	Hemolysin expression modulator	1.41E−08
iha	65 (96)	45 (36)	Adherence protein	2.02E−15
iucC	64 (94)	66 (53)	Aerobactin synthetase	8.43E−08
iutA	64 (94)	65 (52)	Ferric aerobactin receptor	3.63E−08
kpsMII K5	43 (68)	16 (13)	Polysialic acid transport protein; group 2 capsule	1.52E−10
ompT	68 (100)	101 (81)	Outer membrane protease	1.80E−03
papA F43	57 (84)	29 (23)	Major pilin subunit F43	2.00E−14
sat	64 (94)	45 (36)	Serine protease autotransporters of *Enterobacteriaceae* (SPATE)	1.71E−14
usp	68 (100)	71 (57)	Uropathogenic specific protein	3.85E−11
yfcV	67 (99)	74 (59)	Fimbrial protein	1.27E−08

[a]Adjusted P value refers to P value after applying a Bonferroni correction to account for multiple comparisons.

and increased mortality was identified, underscoring the importance of stratification by infection source. We performed a subgroup analysis on patients with *E. coli* BSI from a urinary tract source because portal of entry is a well-described factor in BSI outcomes, logistic regression models may not adequately adjust for all covariates such as source of BSI, and ST131 has been demonstrated to be associated with treatment failure in urinary tract infections (13). Interestingly, the association between ST131 and increased mortality remained even after "days to appropriate antibiotic therapy" was added to the model. This suggests that ST131 may be associated with increased virulence or there is a confounding clinical factor that is not represented in the adjusted analysis.

Second, we performed a genomic analysis of *E. coli* BSI isolates to identify genetic factors that may be contributing to the observed increased mortality in patients with *E. coli* ST131. To our knowledge, this is the first study to specifically examine prophage content associated with ST131 isolates, and we identified increased prophage content within ST131 isolates. We also examined the fgis and virulence genes associated with ST131. ST131, compared with non-ST131, contained fgis encoding putative virulence factors, such as a second flagellar system and genes involved in adhesion, iron uptake, and toxin production. While there has been speculation that the second putative flagellar system (i.e., FLAG-2) plays a role in pathogenesis (24), functional studies have not clearly shown such a role (25, 26). However, some of the genes associated with ST131 could impact virulence and mortality in patients with *E. coli* BSI. For example, capsular genes such as *kpsM* could influence capsule production and hence serum survival, iron uptake genes such as *iucC* and *iutA* could influence survival in the blood, and the toxins *usp* and *sat* have been shown to exhibit activity against mammalian cells (22, 23). The virulence genes associated with ST131 in this study have all been identified in at least one prior study (4, 27–29).

This study had several limitations. First, all patients were enrolled from a single institution. Differences in patient population and treatment practices at other institutions may influence the mortality associated with ST131 BSI, and so these results require validation at additional sites. Second, information on detailed management decisions (e.g., timing/volume of intravenous fluids) that could have influenced patient outcomes is not available for each patient. Some such management decisions, such as the use of carbapenems to treat ceftriaxone-resistant *E. coli* BSI (30), have likely changed since this historical cohort was enrolled. However, the number of days to appropriate antibiotic therapy was measured and was similar between groups. Third, the sample size may have limited our ability to identify a relationship between ST131 BSI and a patient's home address. However, the lack of a spatial relationship suggests that factors explaining outcomes are not geographically distributed in this study population.

In conclusion, we show that after adjustment for patient demographics, medical comorbidities, and treatment factors, the mortality associated with *E. coli* ST131 BSI from a urinary tract source is higher than that of non-ST131 BSI from a urinary tract source. This result provides some evidence for increased virulence of the ST131 genotype in *E. coli* urinary tract infections complicated by BSI.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, DOCX file, 0.8 MB.

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