ORIGINAL ARTICLE

Clinical and Molecular Characterization of Community-Onset Urinary Tract Infections Due to Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae

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OBJECTIVE. To evaluate risk factors for and molecular characteristics of community-onset extended-spectrum cephalosporin-resistant (ESC-R) Enterobacteriaceae (EB) urinary tract infections (UTIs) in a US health system.

DESIGN. Case-control study.

PARTICIPANTS. All patients presenting to the emergency department or outpatient practices with EB UTIs from December 21, 2010, through April 22, 2013, were included. Case patients had ESC-R EB UTIs. Control patients had ESC-susceptible EB UTIs and were matched 1:1 on study year.

METHODS. Risk factors for ESC-R EB UTI were assessed using multivariable conditional logistic regression. A subset of case isolates was evaluated for extended-spectrum beta-lactamases.

RESULTS. A total of 302 patients with community-onset EB UTI were included, of which 151 were cases. On multivariable analysis, risk factors for ESC-R EB UTI included trimethoprim-sulfamethoxazole use in the prior 6 months (odds ratio, 2.40 [95% CI, 1.22–4.70]; $P = .01$), older age (1.03 [1.01–1.04]; $P < .001$), diabetes (2.91 [1.32–6.41]; $P = .008$), and presentation to the emergency department (2.42 [1.31–4.46]; $P = .005$). The prevalence of extended-spectrum beta-lactamases among 120 case isolates was 52% CTX-M, 29% TEM, 20% OXA, and 13% SHV. The prevalence of AmpC was 25%. Pulsed-field gel electrophoresis of the CTX-M *Escherichia coli* isolates showed no distinct clusters.

CONCLUSIONS. Use of trimethoprim-sulfamethoxazole, older age, diabetes, and presentation to the emergency department were associated with community-onset ESC-R EB UTI. There was a high prevalence of CTX-M among our community isolates. Further studies are needed to determine strategies to limit emergence of these organisms in the community.

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Antibiotic resistance continues to emerge and threaten our antibiotic arsenal.[1] Of particular concern has been the emergence of extended-spectrum cephalosporin-resistant (ESC-R) bacteria, particularly among Enterobacteriaceae (EB) species. Several studies have shown that ESC-R EB infections are associated with increased morbidity, mortality, and healthcare costs.[2,3] The primary mechanisms causing ESC-R among EB species include production of extended-spectrum beta-lactamases (ESBLs) or an AmpC beta-lactamase.[4] ESBLs are typically plasmid-mediated, while production of AmpC can result from overexpression of the chromosomal AmpC gene or from acquisition of a plasmid-mediated AmpC determinant.[5]

Urinary tract infections (UTIs) are the most common bacterial infection among adults in the community setting,[6] and recent data have demonstrated marked increases in bacterial resistance to first-line antibiotics used to treat UTIs in ambulatory settings.[7] Resistance has been associated with increased microbiologic and clinical failure.[8]

Although ESC-R EB infections in healthcare settings have been highlighted as an important issue for many years, the emergence of ESC-R EB infections in the community has only recently been recognized. Since its initial description, the incidence of community-onset ESC-R EB infections has increased significantly.[9–13] One study performed in

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Switzerland reported an increase in ESC-R EB prevalence among outpatients from 0.9% in 2004 to 5.3% in 2011.[14]

Prior studies have sought to investigate risk factors for ESC-R EB infections in the community setting.[10,11,13,15–22] Identified risk factors have varied significantly across studies and have included advanced age,[11,16,17,19,21] diabetes mellitus,[11,23–25] prostatic disease,[16] antibiotic use in the prior 3 months,[11,13,16,18,19,21,22] and prior UTIs.[16,22] However, these studies have had significant limitations, including small sample sizes, focus on only bloodstream infections, which are generally less common in the community setting, and focus on only one organism. Further, only one prior study evaluating risk factors for community-onset UTI with an ESC-R EB organism was conducted in the United States; this study included only ESBL-producing *Escherichia coli* isolates, did not differentiate between true infection and colonization, and was performed nearly 10 years ago,[21] raising concerns about generalizability to the present time given marked increases in resistance over the past decade.[14] Given the limitations of the one prior study performed in the United States, and the marked differences in antibiotic use and expected ESC-R EB epidemiology across countries, the generalizability of the prior findings to the current US population is uncertain.

Characterizing the clinical and molecular epidemiology of ESC-R EB UTIs in the community setting is critical for identification of modifiable risk factors to curb further emergence of resistance, as well as for guiding appropriate empirical antibiotic therapy. Therefore, the objective of our study was to evaluate risk factors for community-onset ESC-R EB UTIs among patients cared for in a large academic health system in the United States. We also sought to evaluate the molecular epidemiology of ESC-R EB isolates causing community UTIs, including prevalence and types of ESBLs.

METHODS

Study Design and Setting

A case-control study was performed at 2 emergency departments (EDs) and a network of outpatient practices within the University of Pennsylvania Health System, as follows: (1) the ED at the Hospital of the University of Pennsylvania (HUP), a 776-bed quaternary care medical center; (2) the ED at Penn Presbyterian Medical Center, a 331-bed academic medical center; and (3) the Practice-Based Research Network, which is a collaboration among 246 primary care physicians at community and hospital-based practices.

Study Population

The initial source population comprised all patients presenting to an ED or an outpatient practice with a community-onset urine culture positive for EB from December 21, 2010 through April 22, 2013. Eligible patients were identified through the HUP Clinical Microbiology Laboratory, which processes all cultures from HUP, Penn Presbyterian Medical Center, as well as more than 90% of urine cultures from Practice-Based Research Network practices. A patient was designated as having a community-onset urine culture if it was obtained in the ED, in outpatient practices, or within 72 hours of hospital admission from the ED or an outpatient clinic. Subsequently, only patients with a true UTI were included because we sought to identify risk factors for ESC-R EB UTI rather than urinary colonization. A urine culture was considered indicative of an infection on the basis of Centers for Disease Control and Prevention definitions,[26] with medical record review performed by an infectious diseases-trained physician (J.H.H.).

Case patients were defined as those with an EB UTI demonstrating resistance to an ESC (ie, ceftriaxone or cefotaxime minimum inhibitory concentration >1 μg/mL) in accordance with recent Clinical and Laboratory Standards Institute criteria.[27] Control patients were those who had a UTI with ESC-susceptible EB during the study period (ie, ceftriaxone and cefotaxime minimum inhibitory concentrations ≤ 1 μg/mL). Control patients were randomly selected from the source population using a computerized random number generator and were matched with case patients on study year in a 1:1 ratio.

Each patient was included as a subject only once. If an ESC-R EB was isolated on multiple occasions in the same patient, only the first episode of infection was considered. The study was approved by the institutional review board of the University of Pennsylvania.

Data Collection

Data on case and control patients were abstracted from the University of Pennsylvania Health System electronic medical records. Information was collected on demographic characteristics (eg, age, gender, race), comorbidities (eg, diabetes, malignant tumor, hemodialysis), urologic disorders (eg, prior UTIs, urinary catheters, prostate disease within the previous 6 months), recent skilled nursing facility or hospital stay, and culture location (ED versus outpatient practice).

All inpatient and outpatient antibiotic therapy in the preceding 6 months was documented. Antibiotics were classified for the purposes of analysis, as follows: penicillins (ie, ampicillin, amoxicillin, nafcillin); extended-spectrum penicillins (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam); first-generation cephalosporins (ie, cefadroxil, cefazolin, cephalexin); extended-spectrum cephalosporins (ie, ceftriaxone, ceftazidime, cefpodoxime, cefepime); aminoglycosides; macrolides; fluoroquinolones; carbapenems; metronidazole; intravenous vancomycin; clindamycin; trimethoprim-sulfamethoxazole; nitrofurantoin; and fosfomycin.

Susceptibility and Molecular Testing of EB Isolates

Susceptibility testing of EB isolates was performed at the HUP Clinical Microbiology Laboratory. All isolates identified from

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study subjects were tested as part of routine care for susceptibility to antibiotics using the semi-automated Vitek 2 identification and susceptibility system (bioMérieux). Updated minimum inhibitory concentration breakpoints for ceftriaxone and cefotaxime were used without confirmatory ESBL testing in accordance with Clinical and Laboratory Standards Institute guidelines.[27]

One hundred twenty (79.5%) of the 151 ESC-R EB isolates were available for further microbiologic testing. These isolates underwent confirmatory ESBL testing using the double disk method, using both cefotaxime and ceftazidime.[27] Real-time polymerase chain reaction (PCR) using SYBR dye for qualitative detection of TEM, SHV, OXA-1, and CTX-M type beta-lactamase genes, followed by gel confirmation of the band sizes, was performed and grouped as previously described by the investigators.[28] All strains with detectable TEM/SHV genes were further confirmed by Sanger sequencing. In addition, multiplex PCR for plasmid-mediated AmpC enzymes was performed as previously described.[29] Finally, the ESC-R EB isolates were screened for the presence of *Klebsiella pneumoniae* carbapenemase, using ertapenem susceptibility screening.[30] Isolates with elevated ertapenem minimum inhibitory concentrations were tested for the presence of *K. pneumoniae* carbapenemase by PCR.[30]

Molecular Typing by Pulsed-Field Gel Electrophoresis (PFGE)

The genetic relatedness of isolates was determined by molecular typing using PFGE as described previously.[31] *E. coli* isolates that were positive for CTX-M ESBL were included in PFGE analysis. XbaI was used to prepare chromosomal digests.[32] All results were analyzed using the Fingerprinting II Informatix Software, version 3.0 (Bio-Rad), and interpreted according to established criteria.[33]

Statistical Analysis

Case and control patients were characterized by potential risk factors, including demographic details, comorbidities, and prior antibiotic use. Continuous variables were compared using the *t* test or Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 or Fisher exact test. Conditional bivariable logistic regression was used to examine the relationship between each potential risk factor and ESC-R EB UTI. An odds ratio (OR) and 95% CI were calculated to evaluate the strength of any association. Multivariable conditional logistic regression was then performed, with variables from bivariable analyses with $P < .20$ considered for inclusion in the final multivariable model. Backward stepwise selection was performed for selection of variables in the final explanatory model, with results confirmed using likelihood ratio testing.[34] All analyses were performed using Stata, version 13.0 (StataCorp).

RESULTS

Study Population

A total of 574 patients had a community-onset urine culture with EB during the study period. Of these, 258 were excluded as they did not represent true UTI. Among the 316 community-onset UTIs, 151 were due to ESC-R EB and 165 were due to ESC-susceptible EB. One hundred fifty-one of the 165 potential control patients with community-onset UTI due to an ESC-susceptible EB were included and matched to case patients on the basis of study year.

Among the entire study cohort of 302 patients, the median age was 56 years (interquartile range, 37–68 years), and 62 (21%) were men. With regard to racial classification, 143 patients (47%) were categorized as white. Eighty-five patients (28%) presented to the ED, while 217 (72%) presented to an outpatient practice. The most common pathogens isolated were *E. coli* (76%), *Klebsiella* species (13%), and *Enterobacter* species (9%). Forty-three patients (14%) required admission to a hospital (HUP or Penn Presbyterian Medical Center).

Risk Factors for Community-Onset UTI Due to ESC-R EB

On bivariable analysis (Table 1), several variables were noted to be significantly associated with community-onset UTI due to ESC-R EB, including older age ($P < .001$), male gender (OR, 2.71 [95% CI, 1.47–5.01]; $P = .001$), presentation to the ED (2.39 [1.38–4.14]; $P = .002$), surgery in the prior 6 months (1.79 [1.02–3.14]; $P = .042$), hospitalization in the prior 6 months (2.55 [1.52–4.28]; $P < .001$), diabetes mellitus (2.70 [1.31–5.58]; $P = .007$), malignant tumor (3.50 [1.73–7.07]; $P < .001$), liver disease (3.67 [1.02–13.14]; $P = .046$), and receipt within the prior 6 months of a first-generation cephalosporin (2.42 [1.01–5.86]; $P = .048$), extended-spectrum cephalosporin (4.75 [1.62–13.96]; $P = .005$), trimethoprim-sulfamethoxazole (2.06 [1.14–3.75]; $P = .017$), and intravenous vancomycin (10.0 [1.28–78.12]; $P = .028$).

On subsequent multivariable analysis (Table 2), receipt of TMP-SMX within the prior 6 months was significantly associated with ESC-R EB UTI (OR, 2.40 [95% CI, 1.22–4.70]; $P = .011$). Other independent risk factors associated with an ESC-R EB UTI were older age (1.03 [1.01–1.04]; $P < .001$), diabetes mellitus (2.91 [1.32–6.41]; $P = .008$), and presentation to the ED (2.42 [1.31–4.46]; $P = .005$).

Susceptibility Testing

Susceptibility testing was performed on all of the EB isolates. Among the 151 ESC-R isolates, most were also resistant to fluoroquinolones (67%) and TMP-SMX (57%). In addition, 20% were resistant to aminoglycosides, and 18% were resistant to nitrofurantoin (18%). Two percent were resistant to meropenem.

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TABLE 1. Bivariable Conditional Logistic Regression of Risk Factors for Community-Onset UTI Due to Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae

Variable	Cases (n = 151)	Controls (n = 151)	OR (95% CI)	*P* value
Age, median (IQR), y	60 (46–70)	49 (27–64)	…	<.001
Male sex	43 (28)	19 (13)	2.71 (1.47–5.01)	.001
Emergency department	55 (36)	30 (20)	2.39 (1.38–4.14)	.002
Surgery in prior 6 months	36 (24)	21 (14)	1.79 (1.02–3.14)	.042
Hospitalization in prior 6 months	66 (44)	35 (23)	2.55 (1.52–4.28)	<.001
Non-white race	78 (52)	81 (54)	0.92 (0.59–1.45)	.729
UTI in prior 6 months	65 (43)	57 (38)	1.22 (0.79–1.90)	.372
Urinary catheter	14 (9)	8 (5)	1.86 (0.74–4.65)	.187
Rehabilitation or SNF stay in prior 6 months	9 (6)	3 (2)	4.00 (0.85–18.84)	.080
Prostate disease (if male)	20 (47)	6 (32)	1.00 (0.06–15.99)	>.999
Comorbidities				
Diabetes mellitus	31 (21)	14 (9)	2.70 (1.31–5.58)	.007
Malignant tumor	39 (26)	14 (9)	3.50 (1.73–7.07)	<.001
Hemodialysis	5 (3)	1 (1)	5.00 (0.58–42.80)	.142
Solid organ transplant	13 (9)	6 (4)	2.17 (0.82–5.70)	.117
Respiratory disease[a]	29 (19)	17 (11)	1.80 (0.96–3.38)	.068
Liver disease[b]	11 (7)	3 (2)	3.67 (1.02–13.14)	.046
Medications[c]				
Penicillins	8 (5)	4 (3)	2.33 (0.60–9.02)	.220
Extended-spectrum penicillins	12 (8)	5 (3)	2.75 (0.88–8.64)	.083
First-generation cephalosporins	18 (12)	8 (5)	2.42 (1.01–5.86)	.048
Extended-spectrum cephalosporins	19 (13)	4 (3)	4.75 (1.62–13.96)	.005
Fluoroquinolones	97 (64)	94 (62)	1.08 (0.69–1.69)	.733
SXT	36 (24)	19 (13)	2.06 (1.14–3.75)	.017
Nitrofurantoin	28 (19)	26 (17)	1.09 (0.62–1.91)	.773
Fosfomycin	2 (1)	1 (1)	2.00 (0.18–22.06)	.571
Vancomycin	10 (7)	1 (1)	10.0 (1.28–78.12)	.028
Aminoglycosides	3 (2)	1 (1)	3.00 (0.31–28.84)	.341
Macrolides	2 (1)	4 (3)	0.50 (0.09–2.73)	.423
Clindamycin	4 (3)	5 (3)	0.80 (0.21–2.98)	.739
Doxycycline	5 (3)	3 (2)	1.67 (0.40–6.97)	.484
Carbapenems	5 (3)	1 (1)	5.00 (0.58–42.80)	.142
Metronidazole	6 (4)	3 (2)	2.00 (0.50–7.97)	.327

NOTE. Data are number (percentage) except where noted. IQR, interquartile range; OR, odds ratio; SNF, skilled nursing facility; SXT, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.
[a]Chronic obstructive pulmonary disease or chronic bronchitis.
[b]Hepatitis or cirrhosis.
[c]Receipt in the prior 6 months.

Microbiologic Characterization

One hundred twenty (79.5%) of the 151 ESC-R EB case isolates were available for further microbiologic testing. Seventy-five (62.5%) of these isolates were positive on double disk testing. Among the isolates that were negative on double disk testing, 31% had at least one ESBL present on PCR testing and 45% were positive for AmpC. Among the isolates that were positive on double disk testing, 4% did not have an ESBL present on follow-up PCR testing. The prevalence of ESBLs among the ESC-R isolates was as follows (Table 3): 52% CTX-M, 29% TEM, 20% OXA, and 13% SHV. The number of ESBLs present in each ESC-R isolate varied: 28.3% had no ESBLs (specifically, no CTX-M, TEM, OXA, or SHV ESBLs), 34.2% had 1 ESBL, 34.2% had 2 ESBLs, 2.5% had 3 ESBLs, and 0.8% (1 patient) had 4 ESBLs. Of the 28.3% of ESC-R isolates that did not have an ESBL, most (19 [56%]) were positive for AmpC.

Thirty (25%) of the 120 characterized isolates were positive for AmpC, and 5 isolates (4%) were positive for *K. pneumoniae* carbapenemase. Among the 120 ESC-R EB isolates, there were 57 *E. coli* isolates that were positive for CTX-M. There were no distinct clusters among the 57 CTX-M *E. coli* isolates on PFGE analysis (Online Supplementary Figure 1). CTX-M groups among these 57 isolates were as follows: 34 (59.6%) were CTX-M-1, 22 (38.6%) were CTX-M-4, and 1 (1.8%) was ungrouped.

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TABLE 2. Multivariable Conditional Logistic Regression Model of Risk Factors for Community-Onset UTI Due to Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae

Variable	OR (95% CI)	*P* value
Age	1.03 (1.01–1.04)	<.001
Presentation to ED	2.42 (1.31–4.46)	.005
Diabetes mellitus	2.91 (1.32–6.41)	.008
SXT receipt within prior 6 months	2.40 (1.22–4.70)	.011

NOTE. ED, emergency department; OR, odds ratio; SXT, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

TABLE 3. Prevalence of ESBLs, AmpC, and KPC Among Cases

ESBLs	Prevalence[a] N (%)
CTX-M (CTX-M-1, CTX-M-4)	62 (52)
TEM (TEM-1, TEM-12)	35 (29)
OXA (OXA-1)	24 (20)
SHV (SHV 1, 11, 12, 28)	15 (13)
AmpC (CIT, FOX, DHA)	30 (25)
KPC (KPC-1)	5 (4)

NOTE. ESBL, extended-spectrum beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase.
[a]For 120 case isolates. The presence of an ESBL is not mutually exclusive (eg, SHV and TEM can co-occur), so the total prevalence will be greater than 100%.

DISCUSSION

In this case-control study, we found that recent use of TMP-SMX, older age, diabetes mellitus, and presentation to the ED (as opposed to an outpatient practice) were significant risk factors for community-onset ESC-R EB UTI in a US health system. Furthermore, we identified a high prevalence of CTX-M-producing EB causing UTIs in the community setting, with more than half of characterized ESC-R isolates positive for CTX-M. The results of our study are strengthened by a large sample size including patients who presented to 2 EDs and a large network of primary care practices in the United States; focus on UTI, which is the most common bacterial infection among adults in the community setting; and inclusion of all EB species that were resistant to extended-spectrum cephalosporins. This is only the second study to date to determine risk factors for community-onset ESC-R EB UTI in the United States and is the larger of the studies.[21]

Our study showed that receipt of TMP-SMX during the prior 6 months was associated with the development of ESC-R EB UTI. Prior studies have found that antibiotic exposure is associated with development of ESC-R EB UTIs, including receipt of penicillins, fluoroquinolones, second- and third-generation cephalosporins, or any beta-lactam antibiotic.[11,13,16,18,19,21] Only one prior study has shown a specific association between TMP-SMX and ESC-R EB infection.[22] This association between TMP-SMX use and ESC-R EB UTI is likely due to TMP-SMX exerting broad selection pressure on gastrointestinal flora and promoting the development of resistance. This association is particularly significant because TMP-SMX is a commonly prescribed antibiotic in the community setting; given the high prevalence of ESBL EB organisms in the community, this suggests that TMP-SMX should be used cautiously in the community and that agents with the narrowest possible spectrum, such as nitrofurantoin, should be used when appropriate. This finding also underscores the importance of effective antibiotic stewardship measures in the community setting to limit the subsequent emergence of antibiotic-resistant organisms. Further study is indicated to assess whether decreased use of TMP-SMX can decrease the incidence of community ESC-R EB UTIs.

Similar to previous studies,[11,16,17,19] we found that older age was also a significant risk factor for development of an ESC-R EB UTI in the community setting. UTIs are one of the most common infections in community-dwelling older adults owing to a number of age-related risk factors, including increased rates of neurogenic bladder, increased use of urinary catheters, benign prostatic hypertrophy in men, and vaginal atrophy and increased incontinence in women.[35] Furthermore, older adults may be at higher risk for colonization and subsequent infection with antibiotic-resistant organisms, including ESC-R EB, as a result of chronic comorbidities and aging-related immunosenescence.

Comorbid diabetes mellitus was also associated with the development of community-onset ESC-R EB UTI in our study. The presence of diabetes mellitus is a well-described risk factor for infections due to ESC-R organisms (eg, UTI, bacteremia).[11,23–25] This elevated risk is likely related to the hyperglycemia-related impairment of immune responses in diabetes mellitus as well as increased prescription of antibiotics for conditions such as asymptomatic bacteriuria.[36]

The results of this study also showed that presentation to the ED (as opposed to an outpatient practice) was significantly associated with development of an ESC-R EB UTI in the community setting. Medically complex patients with greater healthcare and antibiotic exposures are more likely to present to the hospital ED, rather than an outpatient clinic, for presumed infection. It is also possible that patients with ESC-R EB UTIs were more symptomatic than those with an ESC-susceptible EB UTI and were thus more likely to present to an ED. Of note, in contrast to prior studies, our study did not show any significant association between recent hospitalization or stay in a long-term care facility and acquisition of an ESC-R EB UTI in the community.[15,20]

Finally, we found that there was a high prevalence (52%) of CTX-M ESBLs among the community ESC-R EB isolates that we evaluated, as well as a high prevalence of AmpC (25%). This is consistent with prior reports that have found an increasing prevalence of CTX-M in the community.[10,37–39] This high prevalence of CTX-M is concerning, given the association between CTX-M and multidrug resistance, particularly to oral agents that are typically prescribed for community-onset UTIs. High rates of resistance to these oral

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agents were confirmed in our study, with a resistance rate of 72% to both fluoroquinolones and TMP-SMX in CTX-M-positive isolates.

There are potential limitations of our study. Misclassification is a concern in case-control studies. However, the outcome of community-onset ESC-R EB UTI was validated through medical record review by an infectious diseases-trained physician, rather than relying on diagnostic or billing codes. The assessment of recent antibiotic use was limited to prescriptions in the University of Pennsylvania Health System; antibiotics prescribed by outside providers would not have been captured, though the impact should be nondifferential between cases and controls. Although we evaluated 80% of the 151 ESC-R EB isolates, lack of characterization of the entire group may have impacted estimates of ESBL prevalence and antibiotic susceptibility profiles. Finally, the present study was conducted in a single healthcare system, and the results may not be generalizable to other dissimilar institutions.

In conclusion, the results of our study demonstrated that recent use of TMP-SMX, older age, diabetes mellitus, and presentation to the ED were significant risk factors for the development of a community-onset UTI with an ESC-R EB organism in a US health system. Further studies are needed to evaluate the clinical impact of these ESC-R EB infections, as well as to determine optimal infection control strategies to limit the spread of these highly resistant and increasingly common organisms in the community.

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SUPPLEMENTARY MATERIAL

For supplementary material/s referred to in this article, please visit http://dx.doi.org/10.1017/ice.2016.225.

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