Emergence of Extended-Spectrum β-Lactamase Urinary Tract Infections Among Hospitalized Emergency Department Patients in the United States

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Study objective: Enterobacteriaceae resistant to ceftriaxone, mediated through extended-spectrum β-lactamases (ESBLs), commonly cause urinary tract infections worldwide, but have been less prevalent in North America. Current US rates are unknown. We determine Enterobacteriaceae antimicrobial resistance rates among US emergency department (ED) patients hospitalized for urinary tract infection.

Methods: We prospectively enrolled adults hospitalized for urinary tract infection from 11 geographically diverse university-affiliated hospital EDs during 2018 to 2019. Among participants with culture-confirmed infection, we evaluated prevalence of antimicrobial resistance, including that caused by ESBL-producing Enterobacteriaceae, resistance risk factors, and time to in vitro–active antibiotics.

Results: Of 527 total participants, 444 (84%) had cultures that grew Enterobacteriaceae; 89 of 435 participants (20.5%; 95% confidence interval 16.9% to 24.5%; 4.6% to 45.4% by site) whose isolates had confirmatory testing had bacteria that were ESBL producing. The overall prevalence of ESBL-producing Enterobacteriaceae infection among all participants with urinary tract infection was 17.2% (95% confidence interval 14.0% to 20.7%). ESBL-producing Enterobacteriaceae infection risk factors were hospital, long-term care, antibiotic exposure within 90 days, and a fluoroquinolone- or ceftriaxone-resistant isolate within 1 year. Enterobacteriaceae resistance rates for other antimicrobials were fluoroquinolone 32.3%, gentamicin 13.7%, amikacin 1.3%, and meropenem 0.3%. Ceftriaxone was the most common empirical antibiotic. In vitro–active antibiotics were not administered within 12 hours of presentation to 48 participants (53.9%) with ESBL-producing Enterobacteriaceae infection, including 17 (58.6%) with sepsis. Compared with other Enterobacteriaceae infections, ESBL infections were associated with longer time to in vitro–active treatment (17.3 versus 3.5 hours).

Conclusion: Among adults hospitalized for urinary tract infection in many US locations, ESBL-producing Enterobacteriaceae have emerged as a common cause of infection that is often not initially treated with an in vitro–active antibiotic. [Ann Emerg Med. 2021;77:32-43.]

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INTRODUCTION

Background

Enterobacteriaceae (now order Enterobacterales), which are the most common cause of urinary tract infections, have demonstrated increasing rates of in vitro resistance to commonly used antibiotics. Fluoroquinolone resistance rates now exceed 15% in many US communities.[1] However, resistance is emerging to alternative treatments; specifically, ceftriaxone and related cephalosporins, mediated through bacterial production of extended-spectrum β-lactamases

Editor's Capsule Summary

What is already known on this topic

Emergency physicians widely administer ceftriaxone to patients with urinary tract infections.

What question this study addressed

How often do patients who are hospitalized for urinary tract infections due to Enterobactericaeae have an isolate resistant to ceftriaxone?

What this study adds to our knowledge

In this prospective multicenter analysis of 444 patients with Enterobacteriaceae urinary tract infections, 21% of isolates were resistant, with considerable heterogeneity among sites.

How this is relevant to clinical practice

This large multicenter sample of patients hospitalized for urinary tract infections found ceftriaxone-resistant isolates to be frequent.

(ESBLs).[2] In 2017 in the United States, ESBL-producing Enterobacteriaceae infection caused 197,400 hospitalizations and 9,100 deaths.[3]

Based on surveys of culture specimens submitted to hospital laboratories, rates of ESBL-producing Enterobacteriaceae have generally been below 15% in North American.[4,5] However, in Asia, Latin America, the Middle East, and Europe, rates have been observed in the range of 25% to 45%.[6] Carbapenems retain in vitro activity against ESBL-producing Enterobacteriaceae isolates. Although less prevalent, carbapenem-resistant Enterobacteriaceae have also emerged.[7]

Importance

Guidelines and authoritative reviews recommend that an antibiotic of a different class be chosen for initial empirical treatment of pyelonephritis when the local resistance rate to the antibiotic being considered exceeds 10% (eg, a nonfluoroquinolone, such as ceftriaxone or an aminoglycoside), with a lower threshold for critically ill patients.[8,9] However, basing empirical treatment of urinary tract infection on resistance rate surveillance of submitted specimens, such as informed by local hospital antibiograms, may be misleading because of misclassification (eg, asymptomatic bacteriuria), biases associated with the types and frequency of patients tested (eg, recurrent urinary tract infection), and broad grouping of inpatients and outpatients made up of various subgroups with varied resistance risk.[10] With the potential for rapid changes in antimicrobial resistance patterns, current and accurate surveillance is critical to guide empirical treatment and optimize patient outcomes.

Goals of This Investigation

Our primary aim was to determine the prevalence of Enterobacteriaceae antimicrobial resistance among patients who were hospitalized for urinary tract infection in the United States, and specifically the prevalence of ESBL-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae infections, antimicrobial susceptibility and genetic profiles of these isolates, infection risk factors, time to in vitro–active empirical antibiotic treatment, and 30-day outcomes.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective, observational study at 11 geographically diverse, US, university-affiliated, hospital emergency departments (EDs) that participate in *EMERGE*ncy ID NET, a Centers for Disease Control and Prevention–collaborative emerging infections research network (Appendix E1, available online at http://www.annemergmed.com).[11] All site institutional review boards approved the study.

Selection of Participants

We enrolled consenting English- and Spanish-speaking patients aged 18 years or older who presented to the ED and were hospitalized with a primary diagnosis of urinary tract infection. Eligible patients were identified by their treating physician, a trained research coordinator, or both either during ED care or by daily review of hospital admission logs. Each patient was enrolled only once. All patients were enrolled between February 2018 and February 2019. Periods of site enrollment varied with the times of institutional approval and enrollment of 85 to 90 patients, a maximum established to achieve more balanced site representation (Appendix E1, available online at http://www.annemergmed.com).

We defined the study population as those who had a hospital discharge diagnosis of urinary tract infection and a positive result for initial urine or blood culture (with urine culture showing contamination or no growth associated with antibiotic pretreatment) that grew a uropathogen. A positive urine culture result was defined as follows: if growth of 1 uropathogen, growth of greater than or equal to 10^4 colony-forming units/mL; if growth of 2 or more uropathogens, any with growth of greater than or equal to

10^5 colony-forming units/mL.[12,13] Uropathogenic bacteria are defined in Appendix E1, available online at http://www.annemergmed.com.

Methods of Measurement

During ED care or within 24 hours of hospital admission, research coordinators interviewed participants and treating clinicians to confirm the presumptive diagnosis of urinary tract infection and collect participant demographics, comorbidities, urinary tract infection complicating characteristics (definition in Appendix E1, available online at http://www.annemergmed.com), and antibiotic risk factor history on standardized forms.

We collected urine specimens by using standard techniques (Appendix E1, available online at http://www.annemergmed.com). Site laboratories tested specimens for the presence of uropathogens and conducted antimicrobial susceptibility testing. Laboratories determined minimum inhibitory concentrations by automated susceptibility testing (using VITEK commercial panels [bioMérieux, Durham, NC] at 7 sites, and Phoenix Instrument System [Becton Dickinson, Sparks, MD] at 4 sites) according to the manufacturers' instructions. We based minimum inhibitory concentration break points and quality-control protocols on standards from the Clinical and Laboratory Standards Institute.[14] Site laboratories preserved Enterobacteriaceae isolates that were suspected ESBL producers or carbapenem-resistant Enterobacteriaceae (ie, ceftriaxone minimum inhibitory concentration >1 μg/mL or meropenem minimum inhibitory concentration >1 μg/mL), and nonfermenting Gram-negative bacilli at –70°C (-94°F). We shipped saved isolates to a reference laboratory (IHMA, Schaumburg, IL), where their identities were confirmed with Matrix-Assisted Laser Desorption-Ionisation-Time of Flight spectrometry (Bruker Daltonics, Billerica, MA). The reference laboratory also performed multiplex polymerase chain reaction to characterize genes encoding for β-lactamases, confirmed and characterized ESBL and carbapenem-resistant Enterobacteriaceae genotypes (Appendix E1, available online at http://www.annemergmed.com), and conducted susceptibility testing against a range of antimicrobials, including amikacin, cefepime, ceftriaxone, ciprofloxacin, meropenem, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol. Two hospital laboratories (Valleywise, Phoenix, AZ; and University of New Mexico, Albuquerque, NM) independently performed confirmatory ESBL testing.

One month after enrollment, research coordinators queried participant electronic medical records for additional data, including initial vital signs and laboratory test values, maximum temperature in the ED, presence of pyuria (>5 WBCs/high-power field), hospital bed type, documentation of ESBL-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae infection within 90 days and 1 year of initial presentation, length of stay, ICU transfer and days, imaging findings, antibiotic administration start times in the ED through 4 hospital days, discharge diagnosis, and final disposition (ie, home, hospital transfer, long-term care facility, or death). We calculated Charlson Comorbidity Index[15] and quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) scores[16] at the first ED evaluation. We categorized participants as having sepsis if they had a qSOFA score greater than or equal to 2 or a lactate level of greater than or equal to 2 mmol/L (definitions in Appendix E1, available online at http://www.annemergmed.com). Study coordinators telephoned participants to identify all 30-day readmissions.

During their enrollment period, each site performed a case-finding audit to determine case enrollment sensitivity by reviewing the electronic medical records of patients presenting to their ED with a broad range of hospital UTI and sepsis discharge diagnosis codes (Appendix E1, available online at http://www.annemergmed.com). We assessed the potential for bias among eligible enrolled and nonenrolled patients by comparing differences in age, sex, qSOFA score, ICU admission rate, length of stay, inhospital mortality rate, and uropathogen frequency and antimicrobial susceptibility.

Outcome Measures

Our primary outcome was the prevalence of ESBL-producing Enterobacteriaceae infection; we determined overall prevalence and prevalence by site.

Our secondary outcomes included measures of the prevalence of previously identified risk factors for antibiotic-resistant Enterobacteriaceae infection (ie, long-term care facility residence, hospitalization, prior antimicrobial treatment, travel outside of North America in the prior 90 days, and fluoroquinolone-, ceftriaxone-, or carbapenem-resistant isolate within 90 days and 1 year).[1] We calculated the difference in the prevalence of these risk factors among patients who did and did not have ESBL-producing Enterobacteriaceae infection and determined the sensitivity of any risk factor and specificity of no risk factor in identifying patients with resistant infections. We recorded patient outcomes, including length of stay, ICU

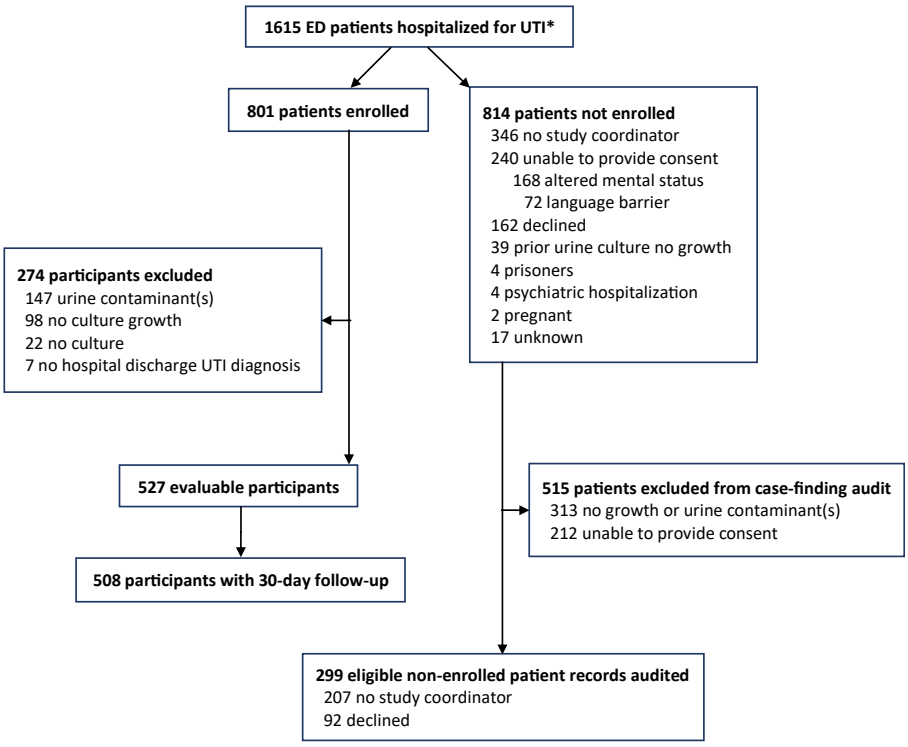

Figure 1. Enrollment, selection of evaluable participants, and case-finding audit of emergency department patients hospitalized for urinary tract infection.

admission, readmission, death, and out-of-hospital days during 30 days and tabulated these findings among participants who were and were not infected with ESBL-producing Enterobacteriaceae.

Finally, we determined how frequently participants with ESBL-producing Enterobacteriaceae infection received treatment with an in vitro–active antibiotic (and for those with sepsis, a carbapenem[17]) within 12 hours of ED presentation, as well as the time until these treatments were started.

Primary Data Analysis

We based our sample size on our desire to estimate the lower limit for the prevalence of ESBL-producing Enterobacteriaceae infection with a precision of 3.0%. Assuming that 15% of our participants would have ESBL-producing Enterobacteriaceae infection, we determined that a sample size of 500 would yield a lower 95% confidence limit of 12%. Anticipating that 20% of our enrolled patients would ultimately meet analysis exclusion criteria resulted in our plan to enroll at least 650 participants.

We used descriptive statistics to summarize participant characteristics and resistance prevalence. We calculated relative risk, differences, and 95% confidence intervals (CIs) to determine associations between categoric variables and median differences and 95% CIs to describe associations between continuous variables for major outcomes of interest. We excluded missing data from relevant analyses and present denominators. To manage study data, we used Research Electronic Data Capture.[18,19] To analyze data, we used SAS (version 9.4; SAS Institute, Inc., Cary, NC) and Microsoft Excel (Microsoft Corporation, Redmond, WA).

RESULTS

Characteristics of Study Subjects

Enrollment, selection of evaluable participants, follow-up, and the case-finding audit are described in Figure 1. Of 801 enrolled patients, we excluded 274 (34.2%); 22 (2.7%) had no urine culture, 98 (12.2%) had cultures with

Table 1. Characteristics of participants hospitalized for urinary tract infection from 11 US EDs, 2018 to 2019.

Characteristic	All Participants (n=527*)	Participants With ESBL-Producing Enterobacteriaceae (n=89)	Participants With Non–ESBL-Producing Enterobacteriaceae (n=346)
Median age (IQR), y	56.0 (41.0–69.0)	58.0 (43.0–69.0)	55.0 (37.0–67.0)
Median Charlson Comorbidity Index score (IQR)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)
Median maximum temperature in ED (IQR), °C	37.8 (37.0–38.9)	37.4 (36.8–38.4)	37.9 (37.0–39.1)
Median days in hospital for index admission through 30 days† (IQR)	3.1 (1.9–5.7)	4.8 (3.1–8)	2.8 (1.8–4.3)
Median days spent home through 30 days (IQR)	26.4 (23.4–28.0)	24.2 (17.8–26.5)	27.1 (25.0–28.2)
		n (%)	
Women	328 (62.2)	52 (58.4)	236 (68.2)
Altered mental status	78 (14.8)	12 (13.5)	49 (14.2)
Sepsis‡	185 (35.1)	29 (32.6)	120 (34.7)
Prior antibiotics			
In prior 90 days	265 (50.4)*	66 (75.0)	143 (41.3)
In prior 48 h	68 (12.9)*	25 (28.4)	29 (8.4)
IV antibiotics in prior 30 days	114 (21.7)*	31 (35.2)	48 (13.9)
LTC facility living			
In prior 90 days	52 (9.9)	19 (21.4)	24 (6.9)
Currently	42 (8.0)	12 (13.5)	20 (5.8)
Admitted to the hospital in prior 90 days	174 (33.0)	39 (43.8)	88 (25.4)
Travel outside US/Canada in prior 90 days	36 (6.8)*	8 (9.0)	26 (7.5)
Urinary tract abnormalities§			
Kidney stone	93 (17.7)	19 (21.4)	45 (13.0)
Genitourinary procedure in last 30 days	30 (5.7)	5 (5.6)	14 (4.1)
Prostatic pathology	50 (9.5)	11 (12.4)	29 (8.4)
Bladder catheter within 30 days	86 (16.3)	20 (22.5)	36 (10.4)
Neurogenic urinary retention	44 (8.4)	7 (7.9)	28 (8.1)
Renal transplant	34 (6.5)	5 (5.6)	24 (6.9)
Nephrostomy tube	36 (6.8)	7 (7.9)	14 (4.1)
Comorbidities§			
Cerebral vascular accident	63 (12.0)*	10 (11.2)	40 (11.6)
Diabetes without chronic complications	102 (19.4)*	20 (22.5)	64 (18.6)
Diabetes with chronic complications	66 (12.6)*	13 (14.6)	47 (13.6)
Paraplegia or hemiplegia	61 (11.6)	17 (19.1)	29 (8.4)
Moderate or severe kidney disease	71 (13.5)	11 (12.4)	45 (13.0)
Any cancer	105 (19.9)	20 (22.5)	60 (17.3)
Complicated UTI‖	385 (73.1)	72 (80.9)	230 (66.5)

Table 1. Continued.

Characteristic	All Participants (n=527*)	Participants With ESBL-Producing Enterobacteriaceae (n=89)	Participants With Non–ESBL-Producing Enterobacteriaceae (n=346)
Critical care intervention during hospitalization			
Any	70 (13.3)*	17 (19.1)	40 (11.6)
Steroids	31 (5.9)	6 (6.7)	22 (6.4)
Ventilatory support	13 (2.5)	2 (2.3)	8 (2.3)
Central venous access	19 (3.6)	6 (6.7)	7 (2.0)
Arterial line	8 (1.5)	2 (2.3)	4 (1.2)
Vasopressors	20 (3.8)	8 (9.0)	9 (2.6)
Final hospital disposition			
Discharged home	432 (82.0)	63 (70.8)	297 (85.8)
Discharged to nursing facility	67 (12.7)	19 (21.4)	33 (9.5)
Transferred to another hospital	5 (1.0)	0	3 (0.9)
Left against medical advice	5 (1.0)	2 (2.3)	2 (0.6)
Died in hospital	2 (0.4)	1 (1.1)	1 (0.3)
Other¶	16 (3.0)	4 (4.5)	10 (2.9)
Final hospital discharge diagnosis#			
Urosepsis	73 (13.9)	11 (12.4)	47 (13.6)
Sepsis	147 (27.9)	23 (25.8)	98 (28.3)
Pyelonephritis	163 (30.9)	29 (32.6)	117 (33.8)
UTI	252 (47.8)	44 (49.4)	164 (47.4)
Urolithiasis	18 (3.4)	2 (2.3)	7 (2.0)
Cystitis	29 (5.5)	3 (3.4)	21 (6.1)
Other	11 (2.1)	2 (2.3)	7 (2.0)
Readmitted in first 30 days**	76 (15.5)*	22 (26.8)	40 (12.4)
Readmission, died, or still in hospital in first 30 days	94 (18.5)*	26 (30.2)	51 (15.2)

IQR, Interquartile range; *IV*, intravenous; *LTC*, long-term care; *US*, United States; *UTI*, urinary tract infection.
*Participants with missing values for a particular variable were excluded from that variable analysis. There were 9 participants with Enterobacteriaceae infection but who did not have ceftriaxone susceptibility results, so these participants were excluded from the second and third columns.
†Because follow-up occurred at 30 days after the ED visit, participants who were still hospitalized at 30 days (2 with ESBLs and 8 without them) were considered to have been hospitalized for 30 days.
‡Sepsis was defined as qSOFA score greater than or equal to 2 or lactate level greater than or equal to 2 mmol/L.
§Data are included for urinary tract abnormalities present in greater than 5% of participants and comorbidities present in greater than 10% of participants.
‖Complicated UTI is defined in Appendix E1, available online at http://www.annemergmed.com.
¶Other final hospital dispositions included discharged to home health (n=5), rehabilitation facility (n=6), cardiology clinic (n=1), swing bed facility (n=1), and homeless shelter (n=2).
#Hospital discharge diagnoses were those listed in the electronic medical record. Other discharge diagnoses included tubule-interstitial nephritis, pyonephrosis, and obstructive nephropathy. Participants could have more than one hospital discharge diagnosis.
**Participants with no follow-up, who died, or who were still in the hospital at 30 days could not be readmitted and so were excluded from this variable analysis.

no growth, 147 (18.4%) had cultures that grew greater than or equal to 1 contaminant, and 7 (0.8%) did not have a hospital discharge diagnosis of urinary tract infection. The remaining 527 participants formed our study population. Of these patients, 441 (83.7%) had cultures that grew 1 uropathogen at greater than or equal to 10^4 colony-forming units/mL, 49 (9.3%) had cultures that grew 2 at greater than or equal to 10^5 colony-forming units/mL, 6 (1.1%) had cultures that grew 3 or more with growth at greater than or equal to 10^5 colony-forming units/mL, and 31 (5.9%) had positive blood culture results for a uropathogen but negative urine culture results or contaminated urine

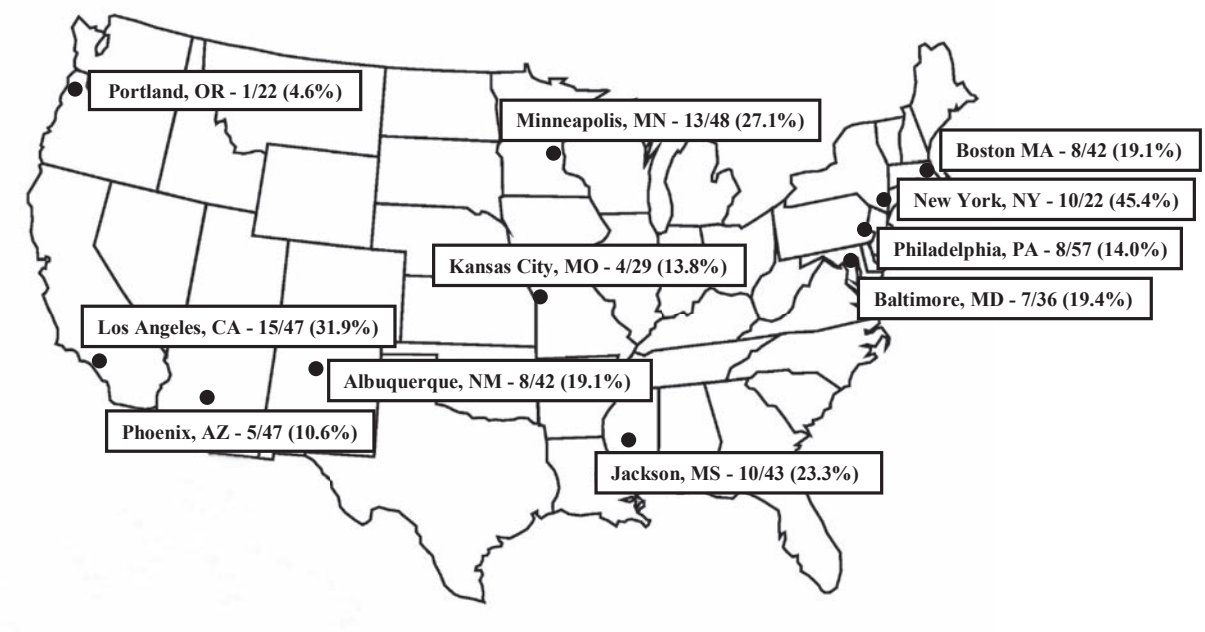

Figure 2. ESBL-producing Enterobacteriaceae prevalence among participants hospitalized with Enterobacteriaceae urinary tract infections during 2018 to 2019 by *EMERGE*ncy ID NET site location.

culture. We were able to assess 30-day outcomes for 508 participants (96.4%). Our case-finding audit by electronic medical records review found that the study population of 527 participants comprised 63.8% of a total of 826 eligible patients for analysis during the enrollment periods at all sites. Clinical characteristics of our enrolled and nonenrolled patients, including for rates of ceftriaxone- and fluoroquinolone-resistant Enterobacteriaceae, were similar (Table S1 in Appendix E1, available online at http://www.annemergmed.com).

Participant median age was 56 years (range 18 to 97 years); 62.2% were women (Table 1; Table S2 in Appendix E1, available online at http://www.annemergmed.com). Infections were community acquired in 57.3% of participants and health care associated in 42.7%. Median Charlson score was 2.0 (range 0.0 to 16.0). The most common comorbidity was cancer, present in 19.9% of participants. A complicating urinary tract abnormality existed in approximately three quarters of all participants, including those with sepsis. Median maximum temperature in the ED was 37.8°C (range 33.8°C to 41.9°C). Pyuria was present in 91.8% of participants. Sepsis criteria were present in 35.1% of participants. Participants were hospitalized for a median 3.1 days (range 0.3 to 30 days). Among participants with 30-day follow-up, 15.0% were rehospitalized, 2.4% were still hospitalized, and 1.6% died.

Main Results

Of 527 total participants, 444 (84%) had cultures that grew Enterobacteriaceae; 89 of 435 participants (20.5%; 95% CI 16.9% to 24.5%; 4.6% to 45.4% by site) (Figure 2) whose isolates had confirmatory testing had bacteria that were ESBL producing. The prevalence among all enrolled participants of ESBL-producing Enterobacteriaceae was 17.2% (95% CI 14.0% to 20.7%).

Among 444 participants with an Enterobacteriaceae isolate, cultures grew *Escherichia coli, Klebsiella* spp., and *Proteus* spp. in 62.4%, 13.5%, and 6.5%, respectively. Complete microbiology results, including tabulations by pyelonephritis, complicated urinary tract infection, and sepsis, are presented in Tables S3 and S4 in Appendix E1, available online at http://www.annemergmed.com. We found nonlactose-fermenting Gram-negative bacteria in 6.6% of participants, including *Pseudomonas aeruginosa* in 5.9%.

Antimicrobial resistance rates determined at site laboratories for all Enterobacteriaceae isolates from all participants, and those with uncomplicated and complicated urinary tract infection, are shown in Table 2. Of 473 Enterobacteriaceae isolates at site laboratories (some participants' cultures grew >1 Enterobacteriaceae isolate) (Table S3 in Appendix E1, available online at http://www.annemergmed.com), 472 (99.8%) had susceptibility testing; 94 of 440 (21.4%) were ceftriaxone resistant and

Table 2. Antimicrobial resistance rates for 473 Enterobacteriaceae urine and blood isolates among 527 participants hospitalized for uncomplicated and complicated urinary tract infection from 11 US EDs, 2018 to 2019.

Antimicrobial	No. Resistant Isolates/Total Tested (%)* Among All Participants	No. Resistant Isolates/Total Tested (%) Among Participants With Uncomplicated UTI†	No. Resistant Isolates/Total Tested (%) Among Participants With Complicated UTI†
Ampicillin	265/423 (62.6)	76/128 (59.4)	189/295 (64.1)
Ampicillin/sulbactam	108/328 (32.9)	27/89 (30.3)	81/239 (33.9)
Amikacin	4/304 (1.3)	0/77 (0.0)	4/227 (1.8)
Piperacillin-tazobactam	11/368 (3.0)	2/99 (2.0)	9/269 (3.3)
Trimethoprim-sulfamethoxazole	163/465 (35.1)	51/132 (38.6)	112/333 (33.6)
Cefazolin	111/407 (27.3)	21/117 (17.9)	90/290 (31.0)
Ceftriaxone	94/440 (21.4)	18/127 (14.2)	76/313 (24.3)
Ciprofloxacin	120/383 (31.3)	25/106 (23.6)	95/277 (34.3)
Levofloxacin	106/339 (31.3)	22/96 (22.9)	84/243 (34.6)
Gentamicin	63/461 (13.7)	17/131 (13.0)	46/330 (13.9)
Ertapenem	4/290 (1.4)	0/79 (0.0)	4/211 (1.9)
Fluoroquinolones‡	151/448 (32.3)	30/133 (22.6)	121/335 (36.1)
Carbapenems‡	7/401 (1.7)	0/106 (0.0)	7/295 (2.4)

*These results are from testing conducted at site hospital laboratories. Not all antimicrobials were tested for each isolate. Denominators with total tested for each antimicrobial are presented.
†Complicated UTI is defined in Appendix E1, available online at http://www.annemergmed.com.
‡For general fluoroquinolones, combined ciprofloxacin and levofloxacin susceptibility results are presented, and for general carbapenems, combined doripenem, ertapenem, imipenem, and meropenem results are presented. In most cases, only one agent from a class of antibiotics was tested. If more than one drug from a class was tested for an isolate and if resistance was found with any, then the isolate was considered resistant.

151 of 448 (32.3%) were fluoroquinolone resistant. Enterobacteriaceae resistance rates for other antimicrobials were gentamicin 14%, amikacin 1.3%, and meropenem 0.3%.

Among 90 confirmed ESBL-producing Enterobacteriaceae isolates (95.7%), antimicrobial susceptibility rates were as follows: ciprofloxacin 11 of 88 (12.5%), trimethoprim-sulfamethoxazole 26 of 90 (28.9%), gentamicin 55 of 89 (61.8%), piperacillin-tazobactam 68 of 83 (81.9%), ceftolozane-tazobactam 65 of 68 (95.6%), amikacin 79 of 82 (96.3%), meropenem 89 of 90 (98.9%), ceftazidime-avibactam 68 of 68 (100%), and cefiderocol 68 of 68 (100%) (Table S5 in Appendix E1, available online at http://www.annemergmed.com). Carbapenem-resistant Enterobacteriaceae was confirmed in 1 of 90 participants (1.1%). *P aeruginosa* and other Gram-negative nonfermenting isolate susceptibility results are shown in Tables S6 and S7 in Appendix E1, available online at http://www.annemergmed.com.

Among all participants, risk factors associated with ESBL-producing Enterobacteriaceae are presented in Table 3. We found that the presence of having any risk factor conveyed a sensitivity of 86.5% in predicting the presence of ESBL-producing Enterobacteriaceae infection, with an accompanying specificity of 42.4%.

For all participants, we found that the most common antibiotics administered parenterally within 12 hours of presentation were: ceftriaxone, 53.9%; piperacillin/tazobactam, 17.1%; cefepime, 14.8%; a carbapenem, 10.2%; and a fluoroquinolone, 8.5% (Table S8 in Appendix E1, avilable online at http://www.annemergmed.com, including by uncomplicated pyelonephritis, complicated UTI, and sepsis).

Among participants with an ESBL-producing Enterobacteriaceae infection, 48 (53.9%) were not treated with an in vitro–active antibiotic within 12 hours of ED presentation. Among participants with an Enterobacteriaceae infection, median time to an in vitro–active antibiotic for those with and without an ESBL-producing Enterobacteriaceae infection was 17.3 and 3.5 hours, respectively. Compared with participants with other Enterobacteriaceae infections, those with ESBL-producing Enterobacteriaceae had longer hospital stays, more frequent arterial line and vasopressor use, and fewer days home, and a higher 30-day readmission rate (Table 1).

Among 29 participants with sepsis and an ESBL-producing Enterobacteriaceae infection, 17 (58.6%) were not treated with an in vitro–active antibiotic within 12 hours. Among these participants, median time to an in vitro–active antibiotic with and without an ESBL-

Table 3. Prevalence of risk factors for ESBL-producing Enterobacteriaceae among 518* participants hospitalized for urinary tract infection from 11 US EDs.

Factor	Prevalence Among Patients With ESBL-Producing Enterobacteriaceae (n=89; No./Total [%])	Prevalence Among Patients Without ESBL-Producing Enterobacteriaceae (n=429; No./Total [%])	Difference in Prevalence (95% CI)
Male sex	37/89 (41.6)	157/429 (36.6)	5.0 (−6.4 to 17.0)
Altered mental status	12/89 (13.5)	64/429 (14.9)	−1.4 (−8.5 to 8.3)
Sepsis†	29/89 (32.6)	152/429 (35.4)	−2.8 (−13.4 to 9.0)
Antibiotics in prior 90 days	66/88 (75.0)	194/429 (45.2)	29.8 (18.1 to 39.4)
IV antibiotics in prior 30 days	31/88 (35.2)	81/428 (18.9)	16.3 (5.7 to 27.7)
Currently living in LTC facility	12/89 (13.5)	29/429 (6.8)	6.7 (−0.1 to 15.2)
Lived in LTC facility in prior 90 days	19/89 (21.4)	32/429 (7.5)	13.9 (5.5 to 23.1)
Admitted to hospital in prior 90 days	39/89 (43.8)	130/429 (30.3)	13.5 (2.0 to 25.4)
Admitted to ICU in prior 90 days	11/89 (12.4)	28/429 (6.5)	7.2 (0.1 to 14.8)
Travel outside of US/Canada in prior 90 days	8/89 (9.0)	28/428 (6.5)	2.4 (−3.1 to 10.4)
History of fluoroquinolone-resistant isolate			
In prior year	37/89 (41.6)	63/429 (14.7)	26.9 (16.0 to 37.9)
In prior 90 days	30/89 (33.7)	31/429 (7.2)	26.5 (16.8 to 36.0)
History of ceftriaxone-resistant isolate			
In prior year	37/89 (41.6)	37/429 (8.6)	32.9 (22.6 to 43.0)
In prior 90 days	29/89 (32.6)	13/429 (3.0)	29.6 (21.0 to 36.5)
History of carbapenem-resistant isolate			
In prior year	4/89 (4.5)	3/429 (0.7)	3.8 (0.3 to 6.7)
In prior 90 days	3/89 (3.4)	2/429 (0.5)	2.9 (0.0 to 5.1)

*There were 9 participants with Enterobacteriaceae infection but who did not have ceftriaxone susceptibility results, so these participants were excluded from the table.
†Sepsis was defined as qSOFA score greater than or equal to 2 or lactate level greater than or equal to 2 mmol/L.

producing Enterobacteriaceae infection was 20.8 and 2.7 hours, respectively. Among all 185 septic participants, 34 (18.5%) were not empirically treated with an in vitro–active antibiotic and 170 (91.9%) with a carbapenem within 12 hours.

Among 83 confirmed ESBL-producing Enterobacteriaceae isolates, 69 (76.7%) were tested by polymerase chain reaction for β-lactamase type, 40 (58.0%) were CTX-M-15 (21 [30.4%] only CTX-M-15); 17 (24.6%) CTX-M-15 and TEM–original-spectrum β-lactamase; 2 (2.9%) CTX-M-15 and SHV–original-spectrum β-lactamase; and 8 (11.6%) CTX-M-15, TEM–original-spectrum β-lactamase, and SHV–original-spectrum β-lactamase. There was one KPC-3 carbapenemase. Among 51 *E coli* isolates tested, 30 (58.8%) were clonal type ST131.

LIMITATIONS

This investigation has limitations. The principal limitation is that our sample of adult hospitalized patients from 11 geographically diverse, urban, university-associated hospital EDs may not be representative of other US populations. Although these were EDs at teaching hospitals, they were different types and there did not appear to be a higher prevalence of ESBL infections at sites that were more specialty referral and transplant centers (eg, Oregon Health & Science University) compared with general public hospitals (eg, Olive View–UCLA Medical Center). We attempted but were unable to enroll all consecutive patients. Using a broad range of urinary tract infection and sepsis diagnostic codes, our electronic medical records audit for eligible patients showed similarity of those enrolled and not enrolled, including for Enterobacteriaceae ceftriaxone and fluoroquinolone resistance rates. Thus, our overall results reflect resistance rates of more than 800 patients, which supports greater confidence in our findings. Site antibiotic resistance prevalences are associated with a greater degree of uncertainty because of smaller samples sizes.

Site laboratories varied in the antibiotics composing their susceptibility panels, so whereas ceftriaxone was tested against almost all Enterobacteriaceae isolates, not all were tested against a specific aminoglycoside, fluoroquinolone, or carbapenem. Therefore, susceptibility rates may not fully

reflect those for all isolates, especially for specific aminoglycosides. Similarly, because of handling errors, approximately half of Gram-negative nonfermenting and some ceftriaxone-resistant and some possible ESBL isolates were not sent to the reference laboratory for susceptibility testing (2%) and typing (17%). Because 96% of Enterobacteriaceae isolates with ceftriaxone minimum inhibitory concentration greater than 1 μg/mL were ESBL producers, we characterized these as "ceftriaxone resistant." However, ceftriaxone may be effective against some of the non–ESBL-producing strains, and rare strains with inducible β-lactamases may be susceptible to cefepime.

Some participants may have wrongly received a diagnosis of urinary tract infection. However, greater than 90% of participants had pyuria, and all had urine or blood culture uropathogen growth and an initial and final urinary tract infection clinical diagnosis. Definitions of uncomplicated and complicated urinary tract infection vary; we used definitions consistent with the Infectious Diseases Society of America's criteria for uncomplicated infection and its complement, which provide clinicians general guidance. qSOFA score and lactate level are recognized markers for sepsis-related poor outcomes that are available at ED care. However, other methods can more accurately predict infection outcomes.[16] Our requirement of consent likely disproportionately excluded patients with central nervous system disease and more severe illness.

Although patients with ESBL infections tended to have worse clinical outcomes, this was not a randomized trial comparing outcomes among patients empirically treated with in vitro–active versus inactive antibiotics. However, the association of in vitro–active empirical antibiotic treatment and improved patient outcomes has been demonstrated in numerous investigations that, unlike ours, were sufficiently large to allow multivariate analyses, including observational studies of patients with sepsis[20] and Enterobacteriaceae bacteremia[21,22] and a case-control study of patients with Enterobacteriaceae urinary tract infection.[23]

DISCUSSION

We found that ESBL-producing Enterobacteriaceae, which demonstrate in vitro resistance to ceftriaxone and other cephalosporins, have now emerged as a frequent cause of urinary tract infections leading to hospitalization in many US locations. Enterobacteriaceae account for greater than 80% of urinary tract infections. Among patients with urinary tract infection requiring hospitalization, at 11 geographically diverse EDs during 2018 to 2019, approximately 17% had an ESBL infection overall, well above the recommended threshold for empirical antibiotic coverage.[8,9] We found that approximately 1 in 5 Enterobacteriaceae infections was caused by an ESBL-producing strain; at one site, almost half of Enterobacteriaceae infections were ESBL producing. Although already prevalent in many parts of the world,[6] emergence of resistance to this level in the United States is new and generally unrecognized as reflected by the finding that in greater than half of participants with ESBL-producing Enterobacteriaceae infection, initial empirical treatment at these university-associated hospitals did not include an in vitro–active antimicrobial. Ceftriaxone was by far the most common initial treatment. Most strains were CTX-M-15, which is the most prevalent genetic resistance type worldwide and portends further increasing ESBL rates.[2] Although the prevalence of infections caused by ESBL-producing Enterobacteriaceae was generally high, resistance rates varied among sites, with some locations still having low rates, emphasizing the need for careful periodic local surveillance to guide empirical approaches. The emergence of ESBL-producing Enterobacteriaceae infection will require revision of empirical treatment guidelines and new approaches where these infections are now common.[24]

The 2010 Infectious Diseases Society of America guidelines address uncomplicated pyelonephritis, defined as occurring in premenopausal nonpregnant women without urologic abnormalities or comorbidities.[8] *E coli* accounts for greater than 90% of these infections.[1] For empirical treatment, these guidelines recommend a fluoroquinolone unless the prevalence of resistance is greater than 10%, in which case for initial intravenous treatment, an antibiotic of another class (eg, ceftriaxone, an aminoglycoside) is recommended. We found that approximately one third of all Enterobacteriaceae isolates and approximately one quarter of those cultured from participants with uncomplicated urinary tract infection were resistant to fluoroquinolones with frequent ceftriaxone resistance. Our results suggest that a carbapenem or amikacin is a better choice than ceftriaxone or gentamicin for empirical intravenous treatment of uncomplicated pyelonephritis. Currently, there are no oral antibiotics with consistent activity against ESBL-producing Enterobacteriaceae that have been demonstrated clinically effective for pyelonephritis, representing a critical need.[20]

Compared with patients with uncomplicated infections, those with complicated urinary tract infection are infected with a broader range of pathogens, including Gram-negative nonlactose fermenting bacteria, such as *P aeruginosa*, which can be multidrug resistant.[21] We found that participants with complicated urinary tract infection also had higher rates of fluoroquinolone- and ceftriaxone-resistant Enterobacteriaceae. For patients with complicated urinary tract infection requiring hospitalization, the 2017

European Association of Urology guidelines recommend a third-generation cephalosporin, extended-spectrum penicillin, or aminoglycoside alone or in combination.[25] In many US locations with high ESBL rates, our results do not support use of cephalosporins alone, including those with activity against *P aeruginosa*. Susceptibility rates of *P aeruginosa* to meropenem, piperacillin-tazobactam, and amikacin ranged from approximately 78% to 95% and were 100% susceptible to ceftolozane-tazobactam, ceftazidime-avibactam, and cefiderocol, these latter agents also having varied activity against carbapenem-resistant Enterobacteriaceae. At the time of this study, carbapenem-resistant Enterobacteriaceae was rarely found but represents another emerging threat.

The Surviving Sepsis Campaign recommends timely sepsis treatment with broad-spectrum antibiotics and advises clinicians to be cognizant of Gram-negative resistance to β-lactams.[26] Initiation of empirical antibiotics lacking in vitro activity against the offending pathogen has been associated with a 5-fold reduction in survival among patients with septic shock.[20] Approximately one third of our participants met sepsis criteria with a qSOFA score greater than or equal to 2 or lactate level greater than or equal to 2 mmol/L. Harris et al[17] recently showed that among patients with ESBL-producing Enterobacteriaceae bacteremia, piperacillin-tazobactam was not noninferior to meropenem and was associated with higher rates of clinical and microbiological failure and death despite rare in vitro resistance. In our study, 15.7% of septic participants were infected with ESBL-producing Enterobacteriaceae, of whom most were not initially treated with an in vitro–active antibiotic or a carbapenem within 12 hours of presentation. Of all septic participants, including those with other infections, approximately 20% were not empirically treated with an in vitro–active antibiotic and almost all were not treated with a carbapenem.

We found that the prevalence of ESBL-producing Enterobacteriaceae infection among patients with urinary tract infection requiring hospitalization exceeded the 10% threshold recommended for empirical treatment in 10 of our 11 US sites, with a rate of greater than 40% at 1 center.[8,9] Empiric antimicrobial regimens active against ESBL-producing Enterobacteriaceae appear warranted in treating patients with urosepsis in many US sites. We actively assessed previously identified antibiotic-resistance risk factors at the time of patient care and found that hospitalization, long-term care residence, and antibiotic exposure within 90 days and a fluoroquinolone- or ceftriaxone-resistant isolate within 1 year were associated with an ESBL-producing Enterobacteriaceae infection.[1] Further evaluation is needed to determine how these risk factors may be used to guide empirical treatment strategies.

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