Trends in Prevalence of Extended-Spectrum Beta-Lactamase-Producing *Escherichia Coli* Isolated From Patients With Community- And Healthcare-Associated Bacteriuria: Results From 2014 To 2020 In An Urban Safety-Net Healthcare System

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Research

Keywords: extended-spectrum beta-lactamase, Escherichia coli, antimicrobial resistance, bacteriuria, risk factors

Posted Date: January 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-150328/v1

Version of Record: A version of this preprint was published at Antimicrobial Resistance and Infection Control on August 11th, 2021. See the published version at https://doi.org/10.1186/s13756-021-00983-y.

Abstract

Background

The prevalence of infections caused by extended-spectrum beta-lactamase producing *Escherichia coli* (ESBL-*E. coli*) is increasing worldwide, but the setting in which this increase is occurring is not well defined. We compared trends and risk factors for ESBL-*E. coli* bacteriuria in community vs healthcare settings.

Methods

We collected electronic health record data on all patients with *E. coli* isolated from urine cultures in a safety-net public healthcare system from January 2014 to March 2020. All analyses were stratified by healthcare-onset/associated (bacteriuria diagnosed > 48 hours after hospital admission or in an individual hospitalized in the past 90 days or in a skilled nursing facility resident, N=1,277) or community-onset bacteriuria (all other, N=7,751). We estimated marginal trends from logistic regressions to evaluate annual change in prevalence of ESBL-*E. coli* bacteriuria among all bacteriuria. We evaluated risk factors using logistic regression models.

Results

ESBL-*E. coli* prevalence increased in both community-onset (0.91% per year, 95% CI: 0.56%, 1.26%) and healthcare-onset/associated (2.31% per year, CI: 1.01%, 3.62%) bacteriuria. In multivariate analyses, age >65 (RR 1.88, CI: 1.17, 3.05), male gender (RR 2.12, CI: 1.65, 2.73), and Latinx race/ethnicity (RR 1.52, CI: 0.99, 2.33) were associated with community-onset ESBL-*E. coli*. Only male gender (RR 1.53, CI: 1.03, 2.26) was associated with healthcare-onset/associated ESBL-*E. coli*.

Conclusions

ESBL-*E. coli* bacteriuria frequency increased at a faster rate in healthcare-associated settings than in the community between 2004 to 2020. Male gender was associated with ESBL-*E. coli* bacteriuria in both settings, but additional risks—age >65 and Latinx race/ethnicity—were observed only in the community.

Introduction

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are a growing public health threat.[1, 2] In 2019, the Center for Disease Control and Prevention (CDC) designated ESBL-producing Enterobacteriaceae as ”serious threat” pathogens.[2] While the first US cases of infections caused by ESBL-producing *Escherichia coli* (ESBL-*E. coli*) were identified in a skilled nursing facility, it is now a nascent concern in community settings.[3–8] Recent hospitalization and prior antibiotic use are major drivers of ESBL-*E. coli* infections, but factors unrelated to healthcare are increasingly recognized, including international travel and consumption of meat contaminated with ESBL-*E. coli*.[9–14] However, most studies compare infection with ESBL-*E. coli* to infection with drug-

susceptible *E. coli* to assess risk for ESBL-*E. coli* infections.[11] As such, identified risks may determine infection with antimicrobial resistant *E. coli* and not necessarily ESBL-*E. coli*. Furthermore, despite the increasing prevalence of community-onset ESBL-*E. coli* infections, little is known about risk factors for such infections in community settings.

Previously, we found increasing trends in ESBL-*E. coli* bacteriuria in the San Francisco safety-net public healthcare system from 2012 to 2018, but community-onset cases could not be differentiated from those associated with healthcare exposure.[15] Here, we compared community-onset vs healthcare-onset/associated bacteriuria episodes caused by ESBL-*E. coli* in the same public healthcare system from 2014 to 2020. This healthcare system serves a multiethnic, low-income, under-studied population residing in various neighborhoods. Identifying risk factors specific to community-onset bacteriuria caused by ESBL-*E. coli* in this population is paramount to devising effective antibiotic stewardship efforts and targeted interventions to reduce transmission within communities.

Methods

Study design and settings

This is an observational study drawn from electronic medical record (eMR) data at the San Francisco public healthcare system for all patients whose urine culture grew *E. coli* from January 2014 to March 2020. This healthcare system includes 15 primary care outpatient clinics as part of the San Francisco Health Network (SFHN), the San Francisco General Hospital (SFGH), an acute care hospital, and Laguna Honda Hospital (LHH), a skilled nursing facility. SFHN patients and LHH residents are usually hospitalized at SFGH. The SFGH microbiology laboratory processes all laboratory tests for this public healthcare system. Data on all urine cultures were collected, including bacterial species and antimicrobial susceptibility test results. We analyzed bacteriuria episodes, which may represent either urinary tract infection or asymptomatic bacteriuria, caused by *E. coli*. Repeat *E. coli* bacteriuria episodes from the same patient were included.

Exposure and outcome measures

To evaluate prevalence trends, we defined culture date as years since baseline (January 2014). Our primary independent variables were extracted from eMRs: age at time of culture (0–17, 18–34, 35–64, or over 65 years); gender (male or female); race/ethnicity (Asian, Black, Latinx, White, or Other); and preferred language (any Chinese dialect, English, Spanish, or Other).

Community-onset *E. coli* bacteriuria episodes were defined as cases in which a urine culture, obtained in a) an outpatient clinic or emergency department setting, or b) within 48 hours of inpatient admission, grew *E. coli*. Healthcare-onset/associated bacteriuria episodes were defined as cases in which a urine culture, obtained in a) inpatients after at least 48 hours of hospital admission, b) outpatients who had been hospitalized in the 90 days prior to culture, or c) residents of the skilled nursing facility, grew *E. coli*.

Antimicrobial susceptibility testing (AST)

The microbiology laboratory performs AST with Microscan and disk diffusion tests, with reports of resistance based on CLSI breakpoint standards.[16] The microbiology laboratory reports extended-spectrum beta-lactamase producing *E. coli* (ESBL-*E. coli*) as an *E. coli* strain resistant to ceftazidime or cefotaxime and inhibited by clavulanic acid. As of 2016, CLSI no longer requires confirmatory testing for ESBL production.[16] Results reported as “intermediate resistance” were considered resistant in this study (Appendix 1).

Bacteriuria episode caused by ESBL-*E. coli* was the main outcome of interest. Sub-analyses included *E. coli* with resistance to nitrofurantoin, trimethoprim-sulfamethoxazole, ciprofloxacin (most commonly used to treat urinary tract infections), any resistance, and multi-drug resistance.

Statistical data analysis

Descriptive statistics, including frequencies and percentages for categorical data and mean values with standard deviations for continuous data, were used to summarize key exposure and outcome variables. Differences in prevalence of ESBL-*E. coli* and patient characteristics for community-onset versus healthcare-onset/associated bacteriuria were evaluated with chi-squared tests and t-tests. Annual changes in resistance to antimicrobial agents from 2014 to 2020 were fit with logistic regression models and trends were estimated based on marginal effects, separately for community-onset and for healthcare-onset/associated bacteriuria. Unadjusted and covariate adjusted logistic regression models were performed to assess which demographic characteristics of patients with bacteriuria predicted *E. coli* resistant to antimicrobial agents (considering as separate outcomes: ESBL-*E. coli;* resistance to each of 3 antibiotics separately [nitrofurantoin, trimethoprim-sulfamethoxazole, and ciprofloxacin]; any drug resistance; and multidrug resistance). Bootstrap (clustered at the individual level) confidence intervals were reported for adjusted logistic regressions to adjust for repeated measures on unique patients.[17] All analyses were conducted by RStudio4 version 1.3.1073. We report 95% confidence intervals to characterize uncertainty in our effect estimates. Sub-analyses were also performed for place of care: outpatient, inpatient, and skilled nursing facility.

Results

Characteristics of the study samples and patients

From January 2014 to March 2020, 82,800 urine samples were processed at the SFGH clinical microbiology laboratory. Of these, 13,522 urine cultures grew an identifiable organism, of which 9,028 (67%) grew *E. coli* (7,751 community-onset and 1,277 healthcare-onset/associated).

We identified 6,291 unique patients with an *E. coli* bacteriuria episode. Of these, 5,576 patients met the definition of a community-onset *E. coli* bacteriuria and 926 patients had a healthcare-onset/associated bacteriuria; given that a patient may have had multiple bacteriuria episodes, these were not mutually exclusive (Table 1). There were 4,844 outpatients, 1,183 inpatients, and 264 skilled nursing facility residents. Fifteen hundred patients had more than one *E. coli* bacteriuria episode; one patient had as

many as 27 episodes. Patients with community-onset bacteriuria (mean age 46) were younger compared to patients with healthcare-onset/associated bacteriuria (mean age 60). Patients with bacteriuria were predominantly women (85%). The study population was multiethnic, with 40% Latinx, 20% Asian, 18% White, and 14% Black patients. Demographic characteristics of outpatients, inpatients and skilled nursing facility residents can be found in Supplemental table 1.

Table 1
Demographic characteristics of patients with community-onset vs healthcare-onset/associated *E. coli* bacteriuria episodes, San Francisco, 2014–2020

	Number of patients, N (%)		
	Community-onset N = 5576	Healthcare-onset/associated N = 926	Total N = 6291
Age category (years)			
0–17	329 (6)	12 (1)	334 (5)
18–34	1619 (29)	105 (11)	1677 (27)
35–64	2483 (45)	407 (44)	2786 (44)
65+	1145 (21)	402 (43)	1494 (24)
Gender			
Female	4841 (87)	639 (69)	5320 (85)
Male	731 (13)	287 (31)	967 (15)
Unknown	4 (< 1)		4 (< 1)
Race/ethnicity			
Asian	1079 (19)	179 (19)	1231 (20)
Black	746 (13)	175 (19)	896 (14)
Latinx	2335 (42)	254 (27)	2494 (40)
Other	408 (7)	64 (7)	452 (7)
Unknown/Declined	90 (2)	8 (1)	97 (2)
White	918 (16)	246 (27)	1121 (18)
Preferred language			
Chinese dialect	426 (8)	90 (10)	505 (8)
English	3167 (57)	626 (68)	3664 (58)
Unknown	82 (1)	15 (2)	98 (2)
Other	227 (4)	37 (4)	256 (4)
Spanish	1674 (30)	155 (17)	1768 (28)

Note: Data from a public healthcare system including inpatient and outpatient services and a skilled nursing facility.

Prevalence of antimicrobial resistant E. coli

Table 2a shows the overall frequency at which the *E. coli* bacteriuria episodes were resistant to antimicrobial agents. ESBL-*E. coli* bacteriuria frequency was higher in healthcare onset/associated bacteriuria episodes (24%) compared to those of community-onset bacteriuria (8%) (P < .001) (Table 2a and 2b). ESBL-*E. coli* accounted for only 13% of community-onset but 34% of healthcare onset/associated antimicrobial resistant *E. coli* bacteriuria episodes (P < .001). Bacteriuria episodes caused by ESBL-*E. coli* had 4.14 (95% confidence interval [CI] 3.41, 5.02) times the risk of nitrofurantoin resistance, 3.89 (95% CI 3.41, 4.43) times the risk of trimethoprim-sulfamethoxazole resistance, and 12.95 (95% CI 11.15, 15.05) times the risk of ciprofloxacin resistance compared to bacteriuria caused by non-ESBL-*E. coli*. Amongst 14 carbapenem-resistant *E. coli* bacteriuria episodes, 6 were identified as community-onset, of which 2 were caused by non-ESBL-*E. coli*. All eight carbapenem-resistant *E. coli* strains causing healthcare onset/associated bacteriuria were ESBL-*E. coli*. The majority of ESBL-*E. coli* isolates were multidrug resistant (72% of 931) but only a minority (39% of 1707 isolates) of multidrug resistant episodes were due to ESBL-*E. coli*.

Table 2

a. Overall frequency of antimicrobial resistant *E. coli* from community-onset vs healthcare-onset/associated bacteriuria episodes, 2014–2020

	Number of antimicrobial resistant *E. coli* bacteriuria episodes, n (%)					
	NIT	T/S	CIP	ESBL	Any AMR	MDR
Community onset*	129 (2)	2691 (35)	1537 (20)	623 (8)	4719 (61)	1306 (16.85)
Healthcare onset/associated**	42 (3)	544 (43)	496 (39)	308 (24)	911 (71)	401 (31.30)
Note: Data from a public healthcare system including inpatient and outpatient services and a skilled nursing facility; NIT: nitrofurantoin, T/S: trimethoprim/sulfamethoxazole, CIP: ciprofloxacin, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistance, MDR: multidrug resistance. Not all ESBL-*E. coli* samples were tested for NIT, T/S or CIP.						
*7,751 isolates tested for ESBL, Any AMR, or MDR, 7,737 for T/S and CIP, 7,736 tested for NIT						
**1,277 isolates tested for ESBL, Any AMR, or MDR, 1,274 for T/S and CIP, 1,273 for NIT						

Table 2

b. Prevalence of antimicrobial resistance in healthcare-onset/associated *E. coli* bacteriuria episodes compared to those that are community-onset, 2014–2020

	RR (95% CI)					
	NIT	T/S	CIP	ESBL	Any AMR	MDR
Community onset (reference)						
Healthcare onset/associated	1.98 (1.40, 2.79)	1.23 (1.14, 1.32)	1.96 (1.80, 2.13)	3.00 (2.65, 3.39)	1.17 (1.13, 1.22)	1.86 (1.69, 2.05)

Note: Data from a public healthcare system including inpatient and outpatient services and a skilled nursing facility; RR: risk ratio, NIT: nitrofurantoin, T/S: trimethoprim/sulfamethoxazole, CIP: ciprofloxacin, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistance, MDR: multidrug resistance.

Trend over time of bacteriuria episodes caused by drug-resistant E. coli

ESBL-*E. coli* frequency in community-onset bacteriuria episodes increased from 6% in 2014 to 10% in 2020 (although 2020 included only 3 months of data), ranging from 5–10% and increasing an average of 0.91% (95% CI: 0.56%, 1.26%) per year (Table 3 and Fig. 1). ESBL-*E. coli* frequency in healthcare-onset/associated bacteriuria episodes increased from 17% in 2014 to 24% in 2020, ranging from 17–29% and increasing an average of 2.31% (95% CI: 1.01%, 3.62%) per year. ESBL-*E. coli* frequency increased an average of 1.03% (95% CI: 0.67, 1.40) per year in outpatients and an average of 3.51% (95% CI: 1.50, 5.52) per year in skilled nursing facility residents; it did not increase significantly in inpatients (Supplemental table 2). Nitrofurantoin and trimethoprim-sulfamethoxazole resistance and resistance to any antimicrobial agent also increased (Table 3 and Fig. 1).

Table 3
Annual percentage point changes in prevalence of antimicrobial resistant *E. coli* from bacteriuria episodes, 2014–2020

	Annual percent point change (95% CI)					
	NIT	T/S	CIP	ESBL	Any AMR	MDR
Community onset	0.34 (0.16, 0.51)	0.64 (0.04, 1.23)	0.13 (-0.37, 0.62)	0.91 (0.56, 1.26)	1.00 (0.40, 1.61)	0.25 (-0.21, 0.72)
Healthcare onset/associated	1.61 (0.74, 2.47)	0.41 (-1.07, 1.90)	-0.59 (-2.05, 0.87)	2.31 (1.01, 3.62)	-0.18 (-1.54, 1.18)	-0.13 (-1.52, 1.27)

Note: Data from a public healthcare system; CI: confidence interval, NIT: nitrofurantoin, T/S: trimethoprim/sulfamethoxazole, CIP: ciprofloxacin, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistance, MDR: multidrug resistance. Logistic regression are univariate analyses including presence or absence of antimicrobial resistance to antibiotic and year from baseline

*Association between patient demographic characteristics and ESBL-*E. coli *bacteriuria by community-onset and healthcare-onset/associated bacteriuria*

In univariate logistic regression models, among all *E. coli* bacteriuria episodes, community-onset ESBL-*E. coli* was associated with age over 65 years (risk ratio [RR] 1.93, 95% CI: 1.26, 2.94), male gender (RR 2.24, CI: 1.87, 2.69), and Chinese dialect (RR 1.37, CI: 1.03, 1.81) or Spanish (RR 1.25, CI: 1.05, 1.48) as a preferred language (Table 4a). In models comparing ESBL-*E. coli* bacteriuria episodes to episodes caused by non-ESBL drug-resistant *E. coli*, older age, being male, and Chinese dialect as a preferred language, but not Spanish, were significantly associated.

Table 4

a. Association between patient demographic characteristics and ESBL-*E. coli* bacteriuria episode among all *E. coli* bacteriuria episodes or non-ESBL drug-resistant *E. coli* bacteriuria episodes, univariate analyses

	RR (95% CI)			
	Community-onset		Healthcare-onset/associated	
	ESBL-*E. coli* among all *E. coli* episodes	ESBL-*E. coli* among AMR *E. coli* episodes	ESBL-*E. coli* among all *E. coli* episodes	ESBL-*E. coli* among AMR *E. coli* episodes
Age category (years)				
0–17 (reference)				
18–34	0.76 (0.48, 1.19)	0.78 (0.50, 1.22)	1.88 (0.25, 14.08)	1.50 (0.20, 11.24)
35–64	1.44 (0.95, 2.18)	1.33 (0.87, 2.01)	3.97 (0.56, 28.33)	3.23 (0.45, 23.05)
65+	1.93 (1.26, 2.94)	1.70 (1.12, 2.60)	2.66 (0.37, 19.07)	2.46 (0.34, 17.65)
Gender				
Female (reference)				
Male	2.24 (1.87, 2.69)	2.01 (1.67, 2.41)	1.61 (1.29, 2.02)	1.44 (1.50, 1.81)
Race/ethnicity				
Asian	1.07 (0.81, 1.41)	1.10 (0.83, 1.45)	0.74 (0.51, 1.07)	0.84 (0.58, 1.22)
Black	0.75 (0.54, 1.05)	0.80 (0.58, 1.12)	0.83 (0.59, 1.18)	0.77 (0.54, 1.09)
Latinx	1.23 (0.98, 1.55)	1.13 (0.89, 1.42)	1.10 (0.83, 1.46)	0.95 (0.72, 1.26)
Other	1.13 (0.79, 1.61)	1.09 (0.77, 1.56)	0.88 (0.53, 1.46)	0.84 (0.51, 1.40)
White (reference)				
Preferred language				
Chinese dialect	1.37 (1.03, 1.81)	1.36 (1.03, 1.81)	0.76 (0.48, 1.19)	0.89 (0.57, 1.39)
English (reference)				
Other	1.21 (0.81, 1.79)	1.23 (0.83, 1.82)	1.10 (0.63, 1.92)	1.13 (0.65, 1.98)

Note: Univariate logistic regressions. Data from a public healthcare system; RR: risk ratio, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistant.

	RR (95% CI)			
Spanish	1.25 (1.05, 1.48)	1.08 (0.91, 1.29)	1.01 (0.76, 1.31)	0.90 (0.67, 1.20)

Note: Univariate logistic regressions. Data from a public healthcare system; RR: risk ratio, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistant.

Table 4

b. Association between patient demographic characteristics and ESBL-*E. coli* bacteriuria episode among all *E. coli* bacteriuria episodes or non-ESBL drug-resistant *E. coli* bacteriuria episodes, multivariate analyses

	RR (95% CI)			
	Community-onset		Healthcare-onset/associated	
	ESBL-*E. coli* among all *E. coli* episodes	ESBL-*E. coli* among AMR *E. coli* episodes	ESBL-*E. coli* among all *E. coli* episodes	ESBL-*E. coli* among AMR *E. coli* episodes
Age category (years)				
0–17 (reference)				
18–34	0.84 (0.50, 1.41)	0.83 (0.51, 1.35)	1.87 (3.03E-19, 1.15E + 19)	1.37 (3.78E-16, 5.01E + 15)
35–64	1.41 (0.88, 2.26)	1.29 (0.81, 2.05)	3.92 (8.69E-23, 1.76E + 23)	2.90 (4.64E-18, 1.81E + 15)
65+	1.88 (1.17, 3.05)	1.60 (0.98, 2.61)	2.74 (1.99E-22, 3.78E + 22)	2.26 (4.17E-18, 1.23E + 18)
Gender				
Female (reference)				
Male	2.12 (1.65, 2.73)	1.90 (1.50, 2.41)	1.53 (1.03, 2.26)	1.36 (0.96, 1.92)
Race/ethnicity				
Asian	0.96 (0.62, 1.48)	0.94 (0.62, 1.44)	0.78 (0.45, 1.35)	0.88 (0.51, 1.52)
Black	0.83 (0.52, 1.32)	0.83 (0.54, 1.26)	0.85 (0.50, 1.44)	0.79 (0.50, 1.26)
Latinx	1.52 (0.99, 2.33)	1.39 (0.98, 1.98)	1.35 (0.72, 2.54)	1.20 (0.73, 1.97)
Other	1.41 (0.84, 2.35)	1.28 (0.82, 1.99)	0.93 (0.50, 1.73)	0.94 (0.53, 1.66)
White (reference)				
Preferred language				
Chinese dialect	1.36 (0.86, 2.15)	1.39 (0.88, 2.21)	1.15 (0.53, 2.47)	1.12 (0.55, 2.25)

Note: Multivariate logistic regressions including all variables presented above. Cluster bootstrap confidence intervals presented. Data from a public healthcare system; RR: risk ratio, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistant.

	RR (95% CI)			
English (reference)				
Other	1.18 (0.76, 1.83)	1.25 (0.80, 1.94)	1.41 (0.77, 2.56)	1.33 (0.74, 2.39)
Spanish	0.97 (0.73, 1.30)	0.88 (0.67, 1.17)	0.90 (0.50, 1.60)	0.85 (0.53, 1.37)

Note: Multivariate logistic regressions including all variables presented above. Cluster bootstrap confidence intervals presented. Data from a public healthcare system; RR: risk ratio, ESBL: extended-spectrum beta-lactamase, AMR: antimicrobial resistant.

In multivariate logistic regression models adjusted for age category, gender, race/ethnicity and preferred language, community-onset ESBL-*E. coli* bacteriuria was associated with age older than 65 years (RR 1.88, CI: 1.17, 3.05) and male gender (RR 2.12, CI: 1.65, 2.73), among all *E. coli* bacteriuria episodes (Table 4b). Among bacteriuria episodes caused by non-ESBL drug-resistant *E. coli*, ESBL- *E. coli* bacteriuria was associated with male gender (RR 1.90, CI: 1.50, 2.41) as well as age older 65 years (RR 1.60, CI: 0.98, 2.61) although the CI included the null. Association of ESBL- *E. coli* bacteriuria with Latinx race/ethnicity was also observed although the CI included the null among all *E. coli* bacteriuria episodes (RR 1.52, CI: 0.99, 2.33) and among bacteriuria episodes caused by non-ESBL drug-resistant *E. coli* (RR 1.39, CI: 0.98, 1.98).

For healthcare-onset/associated bacteriuria episodes, among all *E. coli* bacteriuria episodes, ESBL-*E. coli* was associated only with male gender in both univariate (RR 1.61, CI: 1.29, 2.02) and multivariate (RR 1.53, CI: 1.03, 2.26) analyses. Among episodes caused by non-ESBL drug-resistant *E. coli*, ESBL-*E. coli* bacteriuria was associated with male gender only in univariate analyses (RR 1.44, CI: 1.50, 1.81).

The results of analysis of association between patient demographic characteristics and other antimicrobial agents are described Supplemental tables 3 and 4.

Association between patient demographic characteristics and ESBL-E. coli bacteriuria episodes by place of care

For inpatients, male gender (RR 1.66, CI: 1.13, 2.43) was significantly associated with ESBL-*E. coli* bacteriuria in multivariate regression models adjusted for age category, gender, race/ethnicity, preferred language, and hospitalization in the 90 days prior to urine culture, among all *E. coli* bacteriuria episodes (Supplemental table 5 and 6). Among bacteriuria episodes caused by non-ESBL drug-resistant *E. coli*, ESBL-*E. coli* bacteriuria was also associated with male gender (RR 1.38, CI: 0.98, 1.93), although the CI included the null. Among all *E. coli* bacteriuria episodes, hospitalization in the 90 days prior to urine culture was associated with ESBL-*E. coli* bacteriuria (RR 2.35, CI: 1.72, 3.20). Among bacteriuria episodes caused by non-ESBL drug-resistant *E. coli*, hospitalization in the 90 days prior to urine culture was also associated with ESBL-*E. coli* bacteriuria (RR 1.97, CI: 1.51, 2.57).

For outpatients, in multivariate regression models, among all *E. coli* bacteriuria episodes, significant predictors of ESBL-*E. coli* bacteriuria were age older than 65 years (RR 1.62, CI: 1.00, 2.62), male gender (RR 2.00, CI: 1.52, 2.64), Latinx race/ethnicity (RR 1.65, CI: 1.04, 2.62), and hospitalization in the 90 days before culture (RR 2.81, CI: 2.04, 3.88). Among episodes caused by non-ESBL drug-resistant *E. coli*, ESBL-*E. coli* bacteriuria was associated with male gender and hospitalization in the 90 days before culture; association with Latinx race/ethnicity was noted, although the CI included the null (RR 1.47, CI: 0.98, 2.22). No associations were found among skilled nursing facility residents (Supplemental tables 5 and 6).

Results of associations between patient demographic characteristics and other antimicrobial agents are described in Supplemental table 5 and 6.

Discussion

In this study of drug-resistant *E. coli* bacteriuria spanning more than 6 years in a safety-net public healthcare system serving a diverse population, we found antimicrobial resistant *E. coli* frequency to increase over time in both community and healthcare settings. The magnitude of the increase was greatest among ESBL-*E. coli* bacteriuria, which doubled in community settings and increased by more than 40% in healthcare settings. Older age, male sex, and Chinese dialect or Spanish as a preferred language (or, in some models, Latinx race/ethnicity) were associated with higher prevalence of ESBL-*E. coli* among all *E. coli* bacteriuria episodes.

Increasing prevalence of ESBL-*E. coli* in community-onset and healthcare onset/associated infections is now observed worldwide.[4, 10, 12, 18–22] A 2019 CDC report showed a 50% increase in hospital- and community-onset infections caused by ESBL-producing Enterobacteriaceae between 2012 and 2017 in the US.[2] A report from the Study for Monitoring Antimicrobial Resistance Trends (SMART) found prevalence of urinary tract infections caused by ESBL-*E. coli* to increase from 7.8–18.3% between 2010 and 2014 in the US, particularly among hospital-associated infections.[23] In contrast, the authors found increasing prevalence in community-onset infections in Canada.[23] Most recently, a report on urinary tract infections in US hospitalized patients found a prevalence of 17.2% for ESBL-producing Enterobacteriaceae.[24] We have previously shown increase in ESBL-*E. coli* bacteriuria cases in the same San Francisco public healthcare system, but were unable to decipher whether this increase occurred in community or healthcare settings.[15] Here, while prevalence and increase per year was greater in healthcare onset/associated ESBL-*E. coli* bacteriuria, we also found a significant increase among community-onset bacteriuria.

We first compared ESBL-*E. coli* bacteriuria to bacteriuria caused by all other *E. coli* strains (non-ESBL drug-resistant and drug-susceptible *E. coli*), which would not necessarily distinguish risk factors associated with ESBL-*E. coli* from those associated with drug-resistant *E. coli*. Therefore, we performed secondary analyses comparing ESBL-*E. coli* bacteriuria to bacteriuria caused by non-ESBL drug-resistant *E. coli*. For community-onset ESBL-*E. coli* bacteriuria, we found older age and male gender to be

associated risk factors. For healthcare-onset/associated bacteriuria, we found male gender to be associated with ESBL-*E. coli*.

The association with older age and male gender may represent complicated urinary tract infections more likely to occur in these populations, which may include catheter-associated infections or prostatitis requiring prolonged treatment with extended-spectrum beta-lactam drugs.[25] Since multidrug resistance is associated with ESBL-*E. coli*, factors contributing to frequent antibiotic exposures among older persons in community settings, such as frequent contact with healthcare, higher likelihood of recurrent urinary tract infection, and urinary retention requiring catheterization, may also contribute to the ESBL-*E. coli* selection.[9, 11, 26–28]

Few studies have found differences in ESBL-*E. coli* infection by race/ethnicity, independent of healthcare exposures. A New York study found that children identified as Asian had greater odds of infection with ESBL-producing Enterobacteriaceae.[13] Studies utilizing genotyping methods have found that the majority of community-onset urinary tract infection caused by ESBL-*E. coli* are caused by major pandemic *E. coli* lineages belonging to specific sequence types, including ST131 and ST69.[9, 10, 29] This may point to common-source exposures in the community. There is mounting evidence that infection with ESBL-*E. coli* is associated with international travel, particularly to South Asian countries, and food habits, including eating meat contaminated with ESBL-*E. coli*.[11–14]

No study to our knowledge has found higher risk of ESBL-*E. coli* in Latinx populations. Our findings may represent increased access to antibiotics by this population in San Francisco, but prior studies from other regions in the US found no difference in access to and use of non-prescribed antibiotics among Latinx compared to non-Latinx individuals.[30] A majority of Latinx patients in this public healthcare system come from Mexico. Travel to Mexico may be a risk factor in our study population. A report from the SMART study showed that Mexico has the highest prevalence of community infections caused by ESBL-*E. coli* in Latin America.[31] Thus, unmeasured risk factors, such as travel and food consumption, may also be driving increasing community-onset bacteriuria caused by ESBL-*E. coli*.

While co-resistance of ESBL-*E. coli* to other antimicrobial agents, specifically fluoroquinolones and trimethoprim-sulfamethoxazole, is very common,[3, 9, 32–34] even more concerning is our finding of phenotypic carbapenem co-resistance amongst ESBL-*E. coli*. We found that 12 (86%) of 14 carbapenem-resistant *E. coli* were ESBL-*E. coli*, although we do not have genetic information to evaluate whether they were carbapenemase-producers. A new report from the CRACKLE2 study found that 20% of non-carbapenemase-producing carbapenem-resistant Enterobacteriales isolated from hospitalized patients produced CTX-M, a common ESBL type.[35]

There are several limitations to our study. First, community-onset cases were defined as cases with no history of hospitalizations in the 90 days at SFGH or LHH prior to urine culture. We did not obtain patient information before 90 days, when such patients could have had other healthcare exposures. Second, it may be that we underestimated hospitalization in the 90 days prior to urine culture if individuals were hospitalized in other healthcare systems. Prior studies, however, have shown high retention rate of

patients within our public healthcare system.[36] Lastly, while our study population is diverse in its racial/ethnic representation and their San Francisco neighborhoods, it is homogenous in that individuals receiving care in this public healthcare system have similar socio-economic circumstances. Thus, findings from our study may not be generalizable to other populations.

Conclusion

Our findings raise concerning trends in both community and healthcare settings of ESBL-*E. coli* bacteriuria among patients examined at a San Francisco safety-net public health system. As bacteriuria, in particular urinary tract infections, often precede complications such as bacteremia and sepsis, this observation has serious implications for the clinical management of many types of infections. These findings also have important public health implications, emphasizing an increasing need for better surveillance and antibiotic stewardship programs for community-onset infections.

Declarations

Ethics approval and consent to participate. This study was approved by institutional review boards from UCSF and SFGH (IRB number 19-27233)

Consent for publication. Not applicable

Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

Funding. ER is supported by a T32HP19025 grant. This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR001872. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Authors' contributions. ER collected, analyzed, and interpreted the data. HC and MG were major contributors in design of the study and guiding analyses. ER drafted the manuscript; HC and MG edited the manuscript for clarity. All authors read and approved the final manuscript.

Acknowledgements. The authors thank the SFGH clinical microbiology laboratory. ER thanks Dr. Lee Riley for his valuable guidance, the UCSF Primary Care Research Fellowship for their valuable input for early drafts of the manuscript, and Sarah Neil for her input in final drafts of the manuscript. ER also thanks the National Institutes of Health Loan Repayment Program.

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Figures

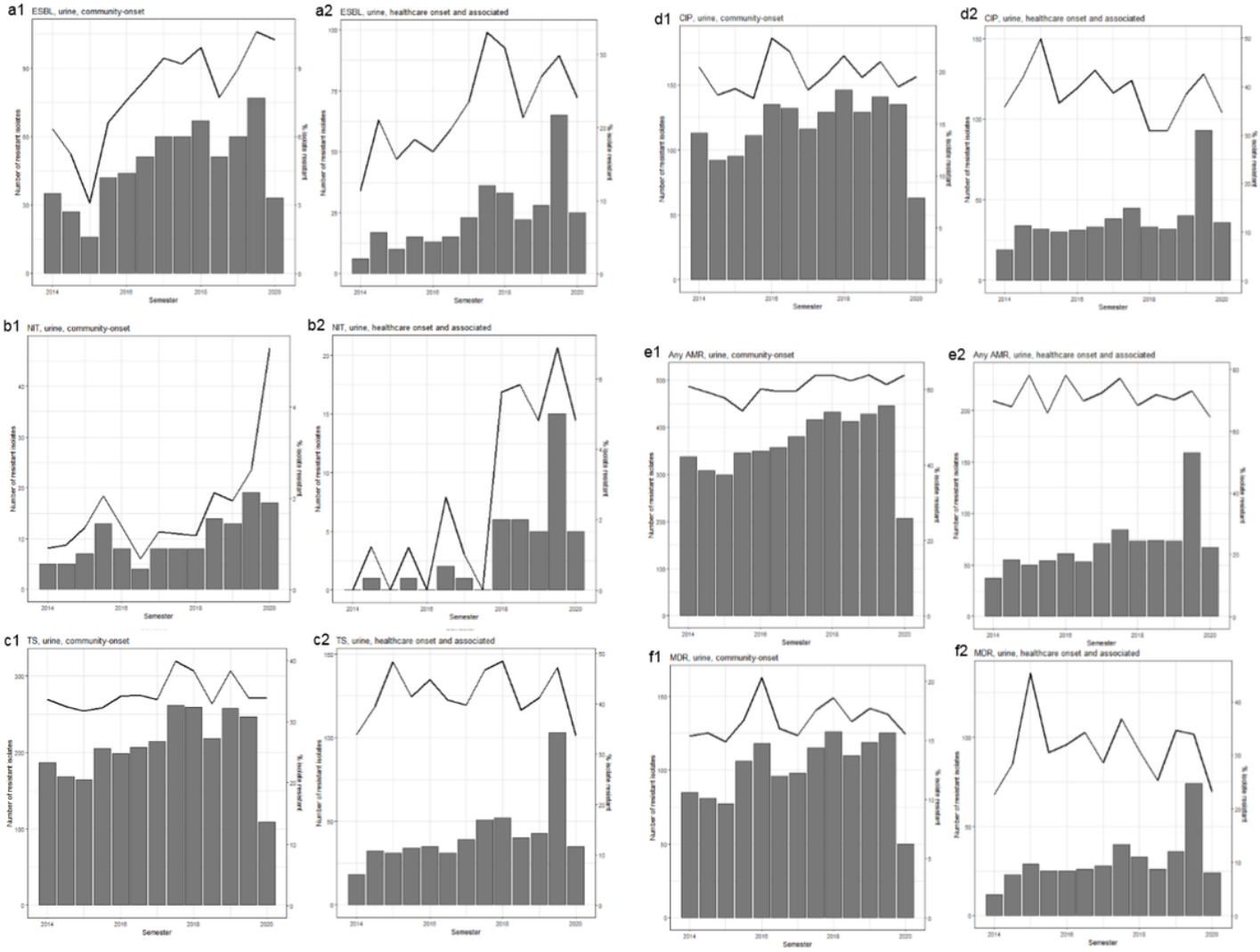

Figure 1

Temporal trend in community-onset vs healthcare-onset/associated bacteriuria caused by antimicrobial resistant E. coli by semester, 2014-2020 Note: bar = number of bacteriuria episodes, line= percent resistance a. ESBL-producing 1. Community-onset 2. Healthcare-onset/associated b. Nitrofurantoin 1. Community-onset 2. Healthcare-onset/associated c. Trimethoprim/sulfamethoxazole 1. Community-onset 2. Healthcare-onset/associated d. Ciprofloxacin 1. Community-onset 2. Healthcare-onset/associated e. Any resistance 1. Community-onset 2. Healthcare-onset/associated f. Multidrug resistance 1. Community-onset 2. Healthcare-onset/associated

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