

## ORIGINAL ARTICLE

# Increasing Incidence of Extended-Spectrum $\beta$ -Lactamase-Producing *Escherichia coli* in Community Hospitals throughout the Southeastern United States

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**OBJECTIVE.** To describe the epidemiology of extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) and *Klebsiella pneumoniae* (ESBL-KP) infections

**DESIGN.** Retrospective cohort

**SETTING.** Inpatient care at community hospitals

**PATIENTS.** All patients with ESBL-EC or ESBL-KP infections

**METHODS.** ESBL-EC and ESBL-KP infections from 26 community hospitals were prospectively entered into a centralized database from January 2009 to December 2014.

**RESULTS.** A total of 925 infections caused by ESBL-EC (10.5 infections per 100,000 patient days) and 463 infections caused by ESBL-KP (5.3 infections per 100,000 patient days) were identified during 8,791,243 patient days of surveillance. The incidence of ESBL-EC infections increased from 5.28 to 10.5 patients per 100,000 patient days during the study period ( $P = .006$ ). The number of community hospitals with ESBL-EC infections increased from 17 (65%) in 2009 to 20 (77%) in 2014. The median ESBL-EC infection rates among individual hospitals with  $\geq 1$  ESBL-EC infection increased from 11.1 infections/100,000 patient days (range, 2.2–33.9 days) in 2009 to 22.1 infections per 100,000 patient days (range, 0.66–134 days) in 2014 ( $P = .05$ ). The incidence of ESBL-KP infections remained constant over the study period ( $P = .14$ ). Community-associated and healthcare-associated ESBL-EC infections trended upward ( $P = .006$  and  $P = .02$ , respectively), while hospital-onset infections remained stable ( $P = .07$ ). ESBL-EC infections were more common in females (54% vs 44%,  $P < .001$ ) and Caucasians (50% vs 40%,  $P < .0001$ ), and were more likely to be isolated from the urinary tract (61% vs 52%,  $P < .0001$ ) than ESBL-KP infections.

**CONCLUSIONS.** The incidence of ESBL-EC infection has increased in community hospitals throughout the southeastern United States, while the incidence of ESBL-KP infection has remained stable. Community- and healthcare-associated ESBL-EC infections are driving the upward trend.

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Infections caused by extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacteriaceae* are increasing worldwide. In some locations, including areas of Latin America, Europe, Asia, and Africa, ESBL-producing *Enterobacteriaceae* are endemic.<sup>1–6</sup> In the United States, the incidence of infection with ESBL-producing *Enterobacteriaceae* at academic medical centers has increased during the past 9 years.<sup>7,8</sup> Community acquisition of ESBL-producing *Enterobacteriaceae* infection appears to be responsible for a proportion of these infections,<sup>8,9</sup> but data from community hospitals verifying this phenomenon are limited. Further data on the epidemiology of ESBL-producing *Enterobacteriaceae* in community hospitals are needed because more than half of the hospital care provided in the United States occurs in small, community hospitals.<sup>10</sup>

We previously reported on the emergence of ESBL-producing *Escherichia coli* (ESBL-EC) in a cohort of 16 community hospitals in North Carolina from 2005 to 2008.<sup>11</sup> In the present study, we sought to understand how the incidence of ESBL-EC and ESBL-producing *K. pneumoniae* (ESBL-KP) infections has changed since 2009 in a larger cohort of community hospitals.

## METHODS

### Participating Hospitals and Study Patients

The Duke Infection Control Outreach Network (DICON) provides infection prevention and surveillance services to 43 community hospitals in the southeastern United States.

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Infection preventionists in DICON-affiliated hospitals routinely collect data on patients with ESBL-producing bacterial isolates. These data are entered into a centralized, standardized database and include basic demographic information, date of hospital admission, previous admissions to the same hospital during the preceding year, specimen collection date and type, dialysis dependence, intensive care unit (ICU) admission, and whether admission is from home or another healthcare facility.

For the present study, we included data from 26 DICON-affiliated community hospitals in North Carolina ( $n=20$ ), Virginia ( $n=3$ ), Georgia ( $n=2$ ), and South Carolina ( $n=1$ ) with complete surveillance data during the 6-year study period.<sup>12</sup> We excluded 17 community hospitals that either joined DICON after January 2009 or left the surveillance network before December 2014. The 26 study hospitals had a mean of 219 beds (range, 102–709 beds) and were located in 25 different counties or independent cities. All patients with ESBL-producing organisms isolated from January 1, 2009 through December 31, 2014 (study period) at these 26 hospitals were included. ESBL status was determined either by methods of the Clinical Laboratory Standards Institute or by automated platforms [ie, Vitek II (bioMérieux, Marcy-l'Étoile, France) or Microscan Walkaway (Dade Behring, Deerfield, IL, USA)] using panels provided by the manufacturer for this purpose. Specimen types were recorded for all patients. All analyses were performed using the first isolate for each patient.

### Definitions

Standard definitions were used at all hospitals. Hospital-onset infection was defined by positive culture results of specimens collected  $>2$  days after hospital admission. Community-onset infection was defined by positive culture results of specimens collected  $\leq 2$  days after hospital admission. Community-onset infections were further classified as either healthcare-associated or community-associated.<sup>11</sup> Patients with healthcare-associated infection had  $\geq 1$  of the following characteristics: home health care, admission from a nursing home or long-term care facility, transfer from another hospital, dependence on dialysis, or admission to a hospital within the previous 12 months. All other community-onset infections were defined as community-associated infections. ICU requirement refers to whether a patient was in the ICU at the time of infection. Dialysis-dependence refers to whether a patient required dialysis at the time of admission. Patients with missing data were excluded from analyses requiring those data.

### Statistical Analyses

We calculated incidence rates (number of new infections per 100,000 patient days per year) of infections due to ESBL-EC and ESBL-KP. Second, we compared the characteristics of patients infected with ESBL-EC with those of patients infected with ESBL-KP. Proportions were compared using the  $\chi^2$  test,

as appropriate. Poisson regression was used to determine trends in the rates of ESBL-EC and ESBL-KP detection and to calculate relative rates and 95% confidence intervals (CI). Overdispersion was observed and corrected using the Pearson  $\chi^2$  as the dispersion parameter. Generalized estimating equation (GEE) regression using a Poisson distribution was used to test for trend while controlling for nonrandom clustering of each outcome. Denominator data were normalized by log transformation. SAS version 9.3 software was used for all calculations (SAS Institute, Cary, NC). A 2-sided  $P$  value of  $\leq 0.05$  was considered significant for all tests.

### RESULTS

We identified a total of 925 patients with ESBL-EC infection and 463 patients with ESBL-KP infection during 8,791,243 patient days of surveillance. The aggregate rate of infection of ESBL-EC at the 26 study hospitals increased from 5.28 to 10.5 patients per 100,000 patient days during the study period ( $P=.006$ ) (Figure 1). In 2009, only 17 study hospitals (65%) had  $\geq 1$  patient with ESBL-EC infection; in 2014, 20 study hospitals (77%) had  $\geq 1$  patient with ESBL-EC. Throughout the study period, 24 study hospitals (92%) had  $\geq 1$  patient with ESBL-EC infection. The median ESBL-EC isolation rates among individual hospitals that had  $\geq 1$  ESBL-EC infection increased from 11.1/100,000 patient days (range, 2.2–33.9) in 2009 to 22.1/100,000 patient days (range, 0.66–134) in 2014 ( $P=.05$ ).

In contrast to the trend observed for ESBL-EC, the aggregate rate of ESBL-KP infection remained constant over the study period ( $P=.14$ ) (Figure 1). In total, 23 study hospitals (88%) had  $\geq 1$  patient with ESBL-KP infection. There was no clear trend in the total number of hospitals with ESBL-KP infections throughout the study period, as 18 study hospitals (69%) had  $\geq 1$  ESBL-KP infection in 2009, and 20 (77%) had  $\geq 1$  ESBL-KP infection in 2014. Of the 23 study hospitals with  $\geq 1$  ESBL-KP infection over the study period, the rate of ESBL-KP isolation decreased or remained constant in 18 hospitals and increased in 5 hospitals.

Patients with ESBL-EC infection were more likely to be female (500 of 925, 54%) than patients with ESBL-KP (203 of 463, 44%;  $P<.001$ ) (Table 1). In addition, a larger percentage of ESBL-EC patients were Caucasian (50% vs 40%) and Hispanic (4% vs  $<1\%$ ). In contrast, a large proportion of ESBL-KP patients were African-American (35% vs 23%) (Table 1).

The overall distributions of hospital-onset, healthcare-associated, and community-associated infections were different between patients with ESBL-EC compared to ESBL-KP ( $P<.0001$ , by 3 by 2  $\chi^2$  test) (Table 1). Patients with ESBL-EC were more likely to have community-associated infection than patients with ESBL-KP (23% vs 10%). In contrast, patients with ESBL-KP were more likely to have hospital-onset infection (17% vs 10%). The incidence of healthcare-associated and community-associated ESBL-EC infections increased significantly over the study period ( $P=.02$  and

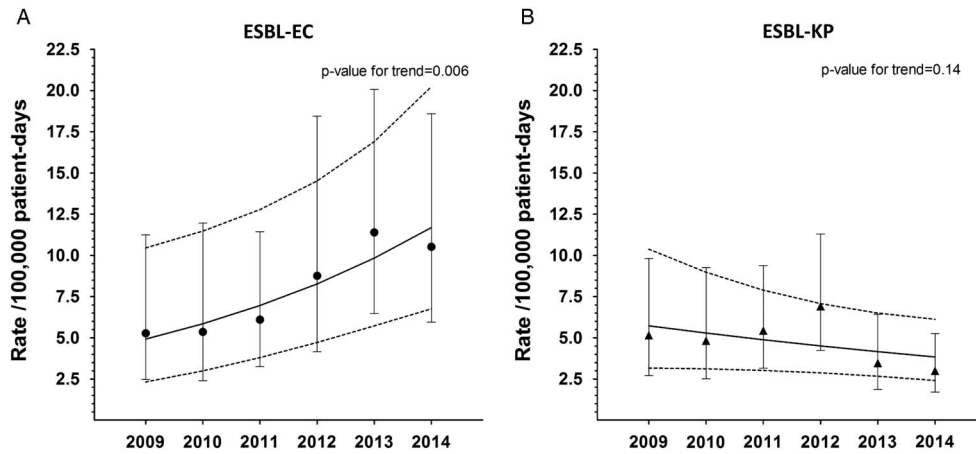


FIGURE 1. Rate of extended-spectrum  $\beta$ -lactamase-producing *E. coli* (ESBL-EC) (A) and extended-spectrum  $\beta$ -lactamase-producing *K. pneumoniae* (ESBL-KP) (B) infections in 26 community hospitals throughout the southeastern United States by year. The mean rate of ESBL-EC and ESBL-KP infections per 100,000 patient days per year, along with the 95% confidence intervals (CI), are noted here. The trend lines and 95% CI were constructed using Poisson regression while controlling for clustering by hospital.

TABLE 1. Characteristics of Patients with ESBL-EC and ESBL-KP Infections in 26 Community Hospitals Throughout the Southeastern United States

	ESBL-EC (N = 925), No. (%)	ESBL-KP (N = 463), No. (%)	P Value
Median age, y	72 (range, 0–100)	70 (range, 0–101)	.96
Female gender	500 (54)	203 (44)	<.001
Ethnicity			
Caucasian	466 (50)	183 (40)	<.0001
African-American	210 (23)	160 (35)	
Asian	10 (1)	1 (<1)	
Hispanic	35 (4)	2 (<1)	
Native American	4 (<1)	7 (2)	
Other/Unknown	200 (22)	110 (24)	
Source			
Urinary tract	560 (61)	240 (52)	<.0001
Blood	150 (16)	70 (15)	
Sputum	36 (4)	47 (10)	
Other	179 (19)	106 (23)	
Admission from			
Home	523 (57)	220 (48)	.003
Nursing home	320 (35)	180 (39)	
Home health	11 (1)	13 (3)	
Another hospital	10 (1)	13 (3)	
Other extended-care facility	33 (4)	26 (6)	
Hospice	4 (<1)	1 (<1)	
Newborn	2 (<1)	0 (0)	
Other/Unknown	22 (2)	10 (2)	
Infection type			
Healthcare associated	610 (66)	333 (72)	<.0001
Community associated	216 (23)	47 (10)	
Hospital onset	94 (10)	80 (17)	
ICU requirement	133 (14)	90 (19)	.02
Dialysis dependent	44 (5)	38 (8)	.01

NOTE. ESBL-EC; extended-spectrum  $\beta$ -lactamase-producing *E. coli*; ESBL-KP, extended-spectrum  $\beta$ -lactamase-producing *K. pneumoniae*; ICU, intensive care unit.

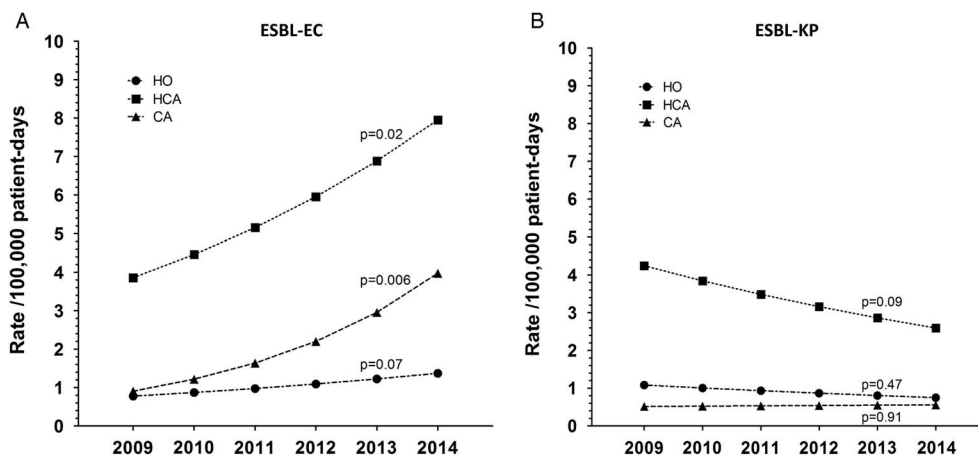


FIGURE 2. Rate of extended-spectrum  $\beta$ -lactamase-producing *E. coli* (ESBL-EC) (A) and extended-spectrum  $\beta$ -lactamase-producing *K. pneumoniae* (ESBL-KP) (B) infections in 26 community hospitals throughout the southeastern United States by year, stratified by infection type. Infection types include hospital onset (HO), healthcare associated (HCA), and community associated (CA). The mean rate of ESBL-EC and ESBL-KP infections per 100,000 patient days per year are noted here. Trend lines were constructed using Poisson regression while controlling for clustering by hospital.

$P = .006$ , respectively), while the upward trend in hospital-onset infections did not reach statistical significance ( $P = .07$ ) (Figure 2A). The incidence of corresponding ESBL-KP infections remained stable (Figure 2B). Consistent with the fact that a greater proportion of ESBL-EC patients had community-associated infections, ESBL-EC patients were more often admitted from home (57% vs 48%). ESBL-KP patients were more often admitted from a nursing home or other extended-care facility (45% vs 39%;  $P = .003$ ;  $8 \times 2 \chi^2$  test) (Table 1).

Patients with ESBL-EC and ESBL-KP infections had significantly different sources for their infections ( $P < .0001$ ;  $4 \times 2 \chi^2$  test) (Table 1). ESBL-EC and ESBL-KP patients were similar in proportion of bloodstream infections (16% vs 15%, respectively), but ESBL-EC were more often isolated from the urinary tract than ESBL-KP (61% vs 52%), and less often isolated from the sputum (4% vs 10%) (Table 1). Interestingly, a high proportion of all study patients were in the intensive care unit at the time of infection (ESBL-EC 14% and ESBL-KP 20%;  $P = .02$ ). Patients with ESBL-KP were more likely to be dialysis dependent (8%) than patients with ESBL-EC infections (5%,  $P = .01$ ).

## DISCUSSION

We previously demonstrated the emergence and rise in ESBL-EC infections in community hospitals from 2005 to 2008 in a cohort of 16 community hospitals in North Carolina.<sup>11</sup> In this study, we described the continued increase in the rate of ESBL-EC infections in 26 DICON community hospitals throughout the southeastern United States from 2009 to 2014 and confirmed that ESBL-EC are more common than ESBL-KP. This increase was likely due to the increasing number of hospitals with ESBL-EC-infected patients and a general rise in the

infection rate among hospitals with ESBL-EC infections throughout the study period. Of note, and importantly for clinicians, ESBL-EC infections were more likely to present as community-onset infections than ESBL-KP infections.

Our findings are consistent with a previous study that demonstrated a rising rate of community-associated ESBL infections in tertiary care hospitals.<sup>8</sup> Our findings are novel, however, because we identified this trend in small, community hospitals. This healthcare setting is particularly important; more than half of the healthcare in the United States is provided in this type of hospital.<sup>10</sup> Given the small size of community hospitals and the generally low (though increasing) prevalence of ESBL-producing bacteria in the community, analysis of data collected in networks of community hospitals, or in large cohorts of hospitals that use similar laboratory and surveillance methods, are needed to fully understand the impact of ESBL-producing bacteria in the community.

Overall, the majority of infections caused by ESBL-EC occurred after healthcare exposure: >75% of ESBL-EC infections were either hospital onset or healthcare associated. Thus, we believe that hospitals, including both tertiary and community, and other healthcare facilities are important foci for ESBL transmission. Hospitalized patients have high<sup>13</sup> and increasing<sup>14</sup> levels of colonization with ESBL-producing bacteria, and patients in long-term care facilities are also frequently colonized.<sup>15</sup> The lack of active screening for ESBL-producing bacteria in the majority of American hospitals means that infection control measures such as contact isolation and patient cohorts are not applied to asymptomatic colonized patients. These “silently” colonized patients in turn increase the risk of transmission of highly resistant bacteria to susceptible patients via the hands of hospital staff or environmental contamination. Such “silent” intrahospital

transmission predisposes hospitalized patients who become exposed and colonized to subsequent infections with ESBL-producing bacteria.<sup>14</sup> The fact that most hospital- or healthcare-associated bacterial transmission events go unnoticed also means that the actual rate of ESBL-producing bacterial acquisition is much higher than our data suggest.

Remarkably, the increased rate of ESBL-EC infections noted in our study cohort occurred without a corresponding similar change in the rate of ESBL-KP infections. Including data from our prior analysis,<sup>11</sup> our data demonstrate that the epidemiology of ESBL-KP remained largely unchanged from 2005 to 2014. Although the rate of ESBL-KP infections has increased in some geographic locations,<sup>16,17</sup> other investigators have also described a trend of stable ESBL-KP infections and rising ESBL-EC infections similar to our findings in this study.<sup>8,18</sup>

The reasons for the disparity in ESBL-EC and ESBL-KP infection trends are unknown. However, this disparity could in part be related to higher rates of transmission of ESBL-EC outside healthcare settings. Only 10% of ESBL-KP infections in patients in our study were community associated. In contrast, 23% of patients with ESBL-EC infections were community associated, and there was a clear increasing trend in community-associated ESBL-EC infections over the study period. Other potential sources of ESBL-producing bacteria outside the healthcare system such as the food supply chain, water treatment and delivery systems, and soil may be responsible for the acquisition of both ESBL-EC and ESBL-KP by the patients in our study. Both ESBL-EC and ESBL-KP infections and colonization have been associated with each of these sources.<sup>19–28</sup>

The Clinical and Laboratory Standards Institute (CLSI) adopted new and lower minimum inhibitory concentration (MIC) breakpoints for aztreonam and several first- and third-generation cephalosporins in 2010.<sup>29</sup> We do not believe that these new breakpoints played a major role in the increased ESBL-EC described here since we contacted all 26 hospitals and found that only 5 (19%) had adopted the lower MIC breakpoints over the study period. Furthermore, the 5 hospitals that did adopt the lower breakpoints made the transition in late 2014 (ie, September–December). Therefore the observed increase in ESBL-EC infection incidence over the study period is not the result of shifting MIC guidelines.

A recent study by Chen et al<sup>30</sup> demonstrated that 84% of ESBL-EC isolates from patients in community hospitals contain a CTX-M  $\beta$ -lactamase. We suspect that propagation of CTX-M  $\beta$ -lactamase genes is responsible in part for the increased rate of ESBL-EC infections we observed in our study population. Chen et al also reported that that 19% of infections by ESBL-producing bacteria were community associated.

We are aware of several limitations pertaining to this study. First, surveillance data were collected by local hospital infection preventionists following their interpretation of complex microbiology data. Despite use of standard protocols and database that serve to limit inter-site variability, subjectivity is inherent in surveillance of this type. Second, all community hospitals in our cohort were located in the

southeastern United States. Further study is needed to establish the generalizability of these findings to other geographic locations. Third, we did not collect data on the presence of particular ESBL enzyme variants; thus, we cannot comment on the molecular epidemiology of genes contributing to the ESBL phenotype in patients in our study. Fourth, we do not have complete data regarding the total number of admissions to participating hospitals over the study period. This information would be useful in further evaluating the incidence of healthcare-associated and community-associated infections in particular. The limited hospital admission data demonstrate no trends toward increasing or decreasing admissions over time, however, which is consistent with the data regarding patient days. Therefore we feel that patient days is an appropriate denominator to evaluate trends in ESBL-EC and ESBL-KP infections. Despite these limitations, we believe our large, multicenter study provides a practical description of the detection rates of ESBL-EC and ESBL-KP in a sample of community hospitals, and highlights important epidemiological factors associated with their acquisition.

Further studies are needed to better understand the sources that are contributing to the growing reservoir of ESBL-EC within our communities. Our network serves as a regional surveillance resource for understanding the epidemiology of antimicrobial resistance in community hospitals that is analogous to the One-Health surveillance strategy recommended in the President's National Action Plan to Combat Antibiotic-Resistant Bacteria, which emphasizes enhancement and expansion of existing surveillance networks in healthcare and community settings.<sup>31</sup> DICON has more than tripled in size since its inception in 1998 to 43 community hospitals throughout the southeastern United States presently; however, aggregated time-trended data from other regional surveillance networks in other geographic areas are needed to confirm these trends and to better understand the extent of ESBL-EC within our communities.

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*Potential conflicts of interest.* All authors report no conflicts relevant to this article.

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