Original Article

Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae* Infections in Children: A Two-Center Case–Case–Control Study of Risk Factors and Outcomes in Chicago, Illinois

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Received November 3, 2013; accepted November 12, 2013; electronically published March 19, 2014.

Background. Extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* infections are an emerging problem in children. We sought to identify risk factors and describe outcomes associated with pediatric ESBL-producing bacterial infections at 2 hospitals in Chicago, IL from 2008 to 2011.
Methods. A case–case–control study of children aged 0–17 years was conducted. Cases of *Escherichia coli, Klebsiella*, and *Proteus* spp. ESBL-producing bacterial infections (n = 30) were compared to uninfected controls and in parallel, cases of non-ESBL–producing bacterial infections (n = 30) were compared to uninfected controls (n = 60). We then qualitatively compared these results.
Results. Median age of cases was 1.06 years; 62% of isolates were from urine, and 60% were *E. coli*. By multivariable analysis, ESBL cases were 5.7 and 3.3 times more likely to have gastrointestinal ($P = .001$; 95% confidence interval [CI] 1.9–17.0) and neurologic ($P = .001$; 95% CI 1.1–3.7) comorbidities, respectively, than controls; non-ESBL cases were also more likely to have gastrointestinal comorbidities than controls ($P = .014$; odds ratio 3.6; 95% CI 1.2–10.1). Study period prevalence remained stable (1.7%). Most (60%) infections occurred in the intensive care unit; however, 30% of children presented in the outpatient setting. Seventy-seven percent of isolates were multidrug resistant (ie, resistant to ≥3 antibiotic classes). Recurrence of infection occurred in 17% of ESBL cases. Crude mortality rates (7%) did not differ between cases and controls.
Conclusions. The incidence of pediatric infection due to ESBL-positive *Enterobacteriaceae* was stable at 2 large tertiary-care medical centers over a 4-year period. Multidrug resistance in pediatric ESBL isolates is common. Risk factors for infection due to ESBL-producing bacteria include neurologic medical conditions.

Key words. antibacterial agents; child; drug resistance; *enterobacteriaceae* infections; epidemiology; β-lactamases.

Antibiotic resistance among the *Enterobacteriaceae* represents an escalating problem in healthcare-associated and community-acquired infections. Resistance among *Enterobacteriaceae* to the broadest-spectrum β-lactam antibiotics, the mainstay of therapy, has reached epidemic proportions [1, 2]. A major component of this growing resistance is due to the production by bacteria of enzymes known as extended-spectrum β-lactamases (ESBL). ESBLs confer resistance to all β-lactam antibiotics except carbapenems and cephamycins, and are best differentiated from

Journal of the Pediatric Infectious Diseases Society, Vol. 3, No. 4, pp. 312–19, 2014. DOI:10.1093/jpids/piu011

AmpC-type β-lactamases by their inhibition by β-lactamase inhibitors such as clavulanic acid [3–5]. β-Lactamase genes in *Enterobacteriaceae* such as those that encode ESBLs are most commonly carried on mobile genetic elements, including transposons or plasmids that can harbor additional resistance genes affecting multiple classes of antibiotics [4, 6, 7]. Risk factors for ESBL infection have been best defined in adult populations and include prior hospitalization, prolonged length of stay, prior antibiotic use, and indwelling devices such as central venous catheters, urinary catheters, tracheostomy, and endotracheal tubes [8–10].

Infection with ESBL-producing *Enterobacteriaceae* has been shown to have a negative impact on patient outcomes, resulting in prolonged hospital stays, higher hospitalization costs, and increased mortality rates [6, 11–13]. Recent data indicate a growing prevalence of ESBLs isolated from U.S. children (Logan et al. [14]). However, there are few studies describing their clinical epidemiology in pediatric populations outside of outbreaks [15–17], and no published studies are multicenter or focused on children in the Midwest. In this study, we conducted a case–case–control analysis of children to assess risk factors for ESBL infection, and determined the prevalence and outcomes of ESBL infections at 2 large acute-care hospitals in Chicago, Illinois.

METHODS

Study Setting

Rush University Medical Center (RUMC) is a tertiary-care, academic medical center that includes Rush Children's Hospital, which comprises 120 pediatric beds (general pediatric and psychiatric wards, neonatal [level III], cardiac surgery, and pediatric intensive-care units) and is located within RUMC. John H. Stroger, Jr. Hospital of Cook County (CCH) is a public, safety-net, teaching hospital housing 98 pediatric beds (general, level III neonatal intensive-care unit [ICU], and pediatric intensive care unit). Together, the 2 institutions serve more than 80,000 children annually (outpatient, inpatient, and emergency department). There is intermixing of adult and pediatric patients within both facilities, primarily through outpatient laboratories and radiology suites. Units for pediatric patients are located on separate floors.

Study Design

We used a retrospective, case–case–control risk-factor study design as previously described [18] in order to avoid limitations of case–control study design and to best assess risk factors specifically related to infection with the ESBL phenotype. Two separate analyses were conducted within the study. The first comparison was between the resistant bacterial phenotype of interest (ESBL) and control patents who were not infected with the target organism and who were representative of the source population. We selected as controls uninfected children who had sterile cultures obtained within the same time period as did cases. The second comparison was between patients with infections due to susceptible species of the organisms of interest and the same control patients. Comparison of the two models allowed identification of specific risk factors for the resistance phenotype of interest (ie, ESBL) [18].

Specifically, the first case group in this study comprised children infected with ESBL-producing organisms from any site. The second case group included children with non-ESBL-producing infections of the same species and site of organism isolation. Control subjects were children identified via electronic laboratory records (ELRs) with sterile cultures during the study time period. Controls were matched 2:1 (similar to other ESBL studies) [19, 20] to each of the 2 cases by age, healthcare setting (inpatient, outpatient, ICU), and specimen source. Control patients were different patients than those included either case group.

We used the ELRs of RUMC and CCH to retrospectively identify all children younger than 18 years with an *Enterobacteriaceae* isolate growing in any culture between January 1, 2008 and December 31, 2011. We then queried the ELR for ESBL-producing *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp. within the same population, which are identified by the laboratory methods described below and captured in the ELR for surveillance of antibiotic resistant organisms. Only 1 isolate per patient per healthcare encounter was included.

Our secondary objectives were to compare outcomes of subjects with ESBL-producing and non-ESBL-producing bacterial infections and controls, and to compare our local demographic, isolate, and prevalence data to a national laboratory surveillance database (Logan et al. [14]).

Laboratory Methods

The laboratories of RUMC and CCH performed species identification and susceptibility testing of ESBL bacterial isolates at the respective institutions using the MicroScan WalkAway system (Siemens Healthcare Diagnostics, Tarrytown, NY). During the study period, screening drugs included any one of cefpodoxime, cefotaxime, ceftazidime, ceftriaxone, or aztreonam [21]. ESBL production was confirmed by disk diffusion (BBL; Becton, Dickinson and Company, Sparks, MD) or on the Microscan instrument by comparing minimum inhibitory concentrations (MICs) of cefotaxime and ceftazidime with and without the addition of clavulanic acid [21]. An increase of >5 mm

in zone diameter or a 4-fold reduction in MIC of cefotaxime or ceftazidime in combination with clavulanic acid compared to the MIC of the antibiotic when tested alone confirmed the ESBL phenotype [21].

Definitions and Data Collection

For cases, only children with infection rather than colonization were included in the analysis. Colonization was defined as detection of a pathogen in culture without the identification of correlating signs or symptoms of infection [22]. We defined infection of the blood, urinary, and respiratory tract using previously published criteria of the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) [23]. Infections at other sites were determined by the study investigators (L.L. and L.M.) and included wound infections, defined by purulent discharge and at least one of either site pain, tenderness, swelling, redness, or warmth. Patient records were fully reviewed to determine whether ESBL infection recorded during the study period was the first infection or a recurrent infection. Recurrent infection was defined as an infection occurring in a previously infected patient during a subsequent encounter. Multidrug resistance was defined as resistance to three or more drug classes [24].

Covariates

We analyzed several variables as potential risk factors including (1) demographics (sex, race); (2) length of hospital stay before culture; (3) comorbid conditions (as defined by ICD-9 codes; a list of ICD-9 codes used to define comorbid conditions is available in Supplementary Materials); (4) prematurity, defined as born at less than 37weeks; (5) recent healthcare exposure, defined as hospitalization or outpatient procedures within 30 days preceding culture; (6) presence, type, and number of invasive medical devices or interventions; (7) all recent antibiotic and extended-spectrum cephalosporin exposures within 40 days before culture (assessed by review of electronic inpatient and outpatient pharmacy and medical records); and (8) receipt of immunosuppressive therapy, defined as any chemotherapy or steroids within the past 30 days. Outcome measures assessed included mortality within the 4-year study period and length of hospital stay after culture.

Statistical Analysis

First, differences between the three groups were assessed using χ^2 tests for categorical, and analysis of variance for continuous variables. If significant differences were found, Fisher's exact test and Wilcoxon rank-sum tests were performed to assess which pairs of groups were different. $P \leq .05$ was considered statistically significant unless otherwise specified. Stepwise multiple logistic regression was used to examine the multivariate relationships between the covariates and each pair of groups. Starting with a null model where each variable was considered univariately, the variable with the smallest P-value was added to the model and the remaining variables were again considered 1 at a time. The stepwise selection of variables continued and the procedure was repeated until there were no more statistically significant covariates ($P \leq .05$). Bonferroni adjustments were made to the P-values in multiple comparisons. All analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

During the study period, we identified 1812 *E. coli*, *Klebsiella* spp., and *Proteus* spp. isolates in cultures from children ages 0–17 years (Table 1). Thirty cases of infections caused by ESBL-producing isolates were identified. The study period prevalence of ESBL infection was 1.7% and did not change significantly over time. Medical records of all 30 ESBL-positive case subjects were reviewed with those of 30 case subjects with antibiotic-susceptible gram-negative (non-ESBL-producing) infection of the same genus and those of 60 culture-negative control subjects. Characteristics of ESBL isolates are shown in Table 1. The majority of cases [18 (60%)] were due to *E. coli*, 10 (33%) were caused by *Klebsiella* spp., and 2 (7%) by *Proteus* species. The largest source of isolates was the urinary tract (63%). Multidrug resistance was found

Table 1. Characteristics of ESBL-Producing Bacterial Isolates

Study Year	ESBL-Producing/Total Isolates n/N (%)
2008	3/385 (0.8)
2009	8/454 (1.8)
2010	9/480 (1.9)
2011	9/493 (1.8)
Total	30/1812 (1.7)
Species	**N (%)**
Escherichia coli	18 (60)
Klebsiella pneumoniae	8 (27)
Klebsiella oxytoca	2 (7)
Proteus mirabilis	2 (7)
Source	
Urine	19 (63)
Respiratory	6 (20)
Blood	2 (7)
Other	3 (10)
Antibiotic resistance	
Piperacillin/tazobactam	5 (17)
Carbapenems	0 (0)
Aminoglycosides	14 (47)
Fluoroquinolones	8 (27)
Trimethoprim/sulfamethoxazole	9 (30)
$\geq$ 3 classes of antibiotics	23 (77)

Abbreviation: ESBL, extended-spectrum β-lactamase–producing *Enterobacteriaceae*.

Table 2. Demographic Information and Outcomes of Children With ESBL and Non-ESBL–Producing Bacterial Infections Compared to Controls

Variable	ESBL (n = 30)[a]	Non-ESBL (n = 30)[a]	Control (n = 60)[b]
Age, median (y) (range)	1.06 (0.008–17.99)	1.33 (0.04–17.83)	0.94 (0.019–17.61)
Male, n (%)	10 (33)	11 (37)	23 (38)
Race			
Black	10 (33)	17 (57)	30 (50)
Hispanic	14 (47)	10 (33)	21 (35)
Prematurity[c]	12 (40)	10 (33)	25 (42)
Hospital setting			
NICU	11 (37)	11 (37)	23 (38)
PICU	7 (23)	7 (23)	12 (20)
Pediatric Ward	3 (10)	3 (10)	7 (12)
Emergency Department	8 (27)	7 (23)	18 (30)
Clinic	1 (3)	2 (7)	0 (0)
LOS, median, after cx, d (range)	8 (0–182)	10 (0–154)	12.5 (0–125)
Died	2 (7)	3 (10)	7 (12)

Abbreviations: Clinic, ambulatory healthcare setting; cx, culture; d, days; ESBL, extended-spectrum β -lactamase–producing *Enterobacteriaceae*; LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; y, years.

Continuous variables reported as median days (range), categorical variables reported as n (%).

[a]Cases and controls were matched by age, healthcare setting, bacterial species, and time period; there were no significant differences in demographics or outcomes (P = NS).

[b]Controls were patients who had cultures taken that were negative during the same time period.

[c]Prematurity defined as less than 37 weeks gestation.

in 23 (77%) ESBL-positive cases; 47% had concomitant resistance to aminoglycosides, 30% to trimethoprim/sulfamethoxazole, and 27% to fluoroquinolones. All were susceptible to carbapenems. The rate of recurrent ESBL infection was 17%. The average number of recurrences per child was two with ≥1 recurrence at a different site than the primary infection in each child.

Local demographic information and outcomes (Table 2) include median age, 1.06 years (range 0–17 years), with the youngest a 3-day-old born at 36 weeks' gestation presenting with poor feeding. The majority were female (67%) and often Hispanic (47%); 12 (40%) were born prematurely. There were no significant demographic differences between the 2 case groups and controls. While most patients (60%) with ESBL-producing bacterial infections were in the ICU at the time of infection, 9 (30%) presented in the outpatient setting, of whom 4 (13%) had no history of hospitalization or invasive procedure, but 6 (67%) had recent antibiotic exposure. Length of stay post culture and crude mortality (7%) did not differ between case groups and controls.

Table 3 shows results of univariate analysis of risk factors for ESBL-producing and non-ESBL-producing bacterial infections in Chicago children. Children with ESBL-producing infection were significantly more likely to have recent healthcare exposure than controls (90% vs. 63%; P = .008) and to have a comorbid gastrointestinal (60% vs. 18.3%, P < .001) or neurologic (53% vs. 20% P = .01) illness. The only significant risk factor for non-ESBL infection was comorbid gastrointestinal illness (43.3% vs. 18.3%, P = .012). In multivariable analysis (Table 4), ESBL cases were more likely to have gastrointestinal (P = .001; OR 5.7; 95% CI 1.9–17.0) or neurologic (P = 0.001; OR 3.3; CI 1.1–3.7) comorbidities than controls were; non-ESBL cases were also more likely to have gastrointestinal comorbidities than controls (P = .014; OR 3.6; CI 1.2–10.1) (Table 4) suggesting that gastrointestinal comorbidities may predispose to *Enterobacteriaceae* infection in general, rather than to the ESBL phenotype.

A descriptive analysis of patients with neurologic comorbidities (n = 16) associated with ESBL infection revealed a diverse group of children. The median age was 8.4 months (range 14 days–16 years), 69% were female, and 62.5% of infecting isolates were *E. coli*. Infection sources were urine (8 [50%]), sputum (5 [31.3%]), blood (2 [12.5%]), and abscess (1 [6.3%]). Multidrug resistance was common (10 [62.5%]). Most infections 12 (75%) were associated with a foreign body; all respiratory infections were associated with a ventilatory device (eg, tracheostomy, endotracheal tube), all blood infections with a central line, and 4 (50%) urinary tract infections were associated with frequent or prolonged urinary tract catheterization. The associated ICD-9 comorbid diagnoses included cerebrovascular disease and/or encephalopathy in 8 (50%), neurogenic bladder in 4 (25%), and cognitive deficits/developmental delay in 4 (25%), of which 3 were trach dependent. One child (6.3%) died: a 3-month-old with severe intraventricular hemorrhage, diffuse encephalopathy, and seizures who developed sepsis from ESBL *E. coli* bloodstream infection and died 5 days later.

Table 3. Univariate Analysis of Risk Factors for ESBL-Producing and Non-ESBL-Producing Bacterial Infection Versus Uninfected Controls

Variable	ESBL N = 30 n (%)	Non-ESBL N = 30 n (%)	Control N = 60 n (%)	ESBL vs. Control *P*-Value	Non-ESBL vs. Control *P*-Value
Black	10 (33.3)	17 (56.7)	30 (50)	0.14	0.55
Hispanic	14 (46.7)	10 (33.3)	21 (35)	0.28	0.88
Prematurity[a]	12 (40)	10 (33.3)	25 (41.7)	0.88	0.45
Recent healthcare[b]	27 (90)	20 (66.7)	38 (63.3)	0.008	0.73
Recent antibiotics	24 (80)	15 (50)	36 (60)	0.058	0.37
Recent 3GCeph	8 (26.7)	8 (26.7)	25 (41.7)	0.16	0.16
Recent FQ	2 (6.7)	0 (0)	0 (0)	0.11	—
Recent steroids	4 (13.3)	6 (20)	15 (25)	0.20	0.60
FB present	22 (73.3)	17 (56.7)	33 (55)	0.09	0.88
FB CVL	14 (46.7)	13 (43.3)	29 (48.3)	0.88	0.65
FB Resp	14 (46.7)	6 (20)	23 (38.3)	0.45	0.08
FB GI	11 (36.7)	11 (36.7)	14 (23.3)	0.18	0.18
FB GU	5 (16.7)	2 (6.7)	5 (8.3)	0.29	1.0
Comorb CV	10 (33.3)	8 (26.7)	14 (23.3)	0.32	0.73
Comorb GI[b]	18 (60)	13 (43.3)	11 (18.3)	<0.001	0.012
Comorb Pulm	18 (60)	12 (40)	32 (53.3)	0.55	0.23
Comorb Neuro[b]	16 (53.3)	8 (26.7)	12 (20)	0.001	0.47
Comorb HO	8 (26.7)	5 (16.7)	9 (15)	0.34	0.77
Comorb Renal	5 (16.7)	5 (16.7)	9 (15)	0.84	0.84
Survived	28 (93.3)	27 (90)	53 (88.3)	0.71	1.0
LOS before cx, mean (SD)	34.2 (48.7)	25.6 (37.6)	26.8 (42.3)	0.83	0.97
LOS post cx, mean (SD)	38.7 (52.9)	27.5 (41.0)	29.1 (34.5)	0.72	0.73

Abbreviations: Comorb, cormorbidity; CV, cardiovascular; CVL, central venous line; cx, culture; ESBL, extended-spectrum β-lactamase–producing *Enterobacteriaceae*; FB, foreign body; FQ, fluoroquinolones; 3GCeph, 3rd-generation cephalosporins; GI, gastrointestinal; GU, genitourinary; HO, hematology–oncology; LOS, length of stay; Pulm, pulmonary; Neuro, neurologic; Resp, respiratory.
Bonferroni adjusted significant *P*-values ($P<0.001$).
[a]Prematurity defined as <37 weeks' gestation.
[b]Corresponds to risk factors with significant *P*-values ($P \leq 0.05$).

Table 4. Multivariate Analysis of Risk Factors for ESBL-Producing Bacterial Infection and Non-ESBL-Producing Bacterial Infection Versus Uninfected Controls

Risk Factor	ESBL vs. Control			Non-ESBL vs. Control		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Gastrointestinal comorbidity	5.7	1.9–17.0	0.001	3.6	1.2–10.1	0.014
Neurologic comorbidity	3.3	1.1–3.7	0.001			

Abbreviations: CI, confidence interval; ESBL, extended-spectrum β-lactamase–producing *Enterobacteriaceae;* OR, odds ratio.

DISCUSSION

In this study, we used a case–case–control study design to identify risk factors and describe outcomes of children with ESBL infections at 2 medical centers in Chicago, Illinois. We found that the main risk factor for ESBL infection in children was having a neurologic comorbidity and that the majority of infections were multidrug resistant. Most infections occurred in children located in the ICU; however, 30% of children presented in the outpatient setting.

Antibiotic resistance in *Enterobacteriaceae* has reached epidemic proportions. The NHSN report of healthcare-associated infections (HAI) found that 4% of antimicrobial-resistant pathogens from all HAIs were extended-spectrum cephalosporin-resistant *E. coli* or *Klebsiella* spp. [2]. ESBL infections are increasing dramatically across the globe. Genes encoding ESBLs are often carried on mobile genetic elements such as plasmids, which are capable of rapid spread and dissemination [3, 4, 6].

Several studies have defined risk factors for ESBL infection in adults, and these include prior hospitalization, prolonged length of stay, prior antibiotic use (including extended-spectrum cephalosporins in some studies), and indwelling devices such as central venous catheters, urinary catheters, tracheostomy, and endotracheal tubes [6, 25–27]. Risk factors for infection in the few case–control studies of U.S. children include chronic medical

conditions, prior immunosuppressive therapy, and similar to adults, prolonged hospital stays and prior antibiotic use (extended-spectrum cephalosporins) [14–16]. ESBL infections also have been found to have a negative impact on patient outcomes such as increasing hospital costs, length of stay, and mortality rates [6, 13, 28].

To our knowledge, our study is among the few to use a case–case–control design in the assessment of risk factors for antibiotic resistance, and the first to do so with regard to ESBL-producing bacteria and infection outcomes in children. This study design is used to differentiate between risk factors specific to the resistant phenotype of interest, risk factors specific to the organism (both the resistant and susceptible phenotype), and risk factors specific to the antibiotic susceptible phenotype [18]. Use of this design allowed us to best identify risk factors specific to ESBL infection.

The number of subjects in our analysis was comparable to those in other pediatric studies [15–17], and we were able to show that children at highest risk for ESBL infection include those with neurologic comorbidities, independent of invasive devices, immunosuppressive therapy, and prior length of hospital stay. Of note, gastrointestinal comorbidity was a risk factor for infection in both the ESBL and the non-ESBL infection group. Interestingly, we did not find that ESBL infection was significantly associated with recent antibiotic (or extended-spectrum cephalosporin) exposure as found in previous studies when ESBL cases were compared to controls (80% vs. 50%, $P = .058$). This may, however, be due to the small sample size. While our study is underpowered for a formal risk assessment specific to the high-risk group of children with neurologic comorbidities, a descriptive analysis of this cohort revealed that ESBL infection was often associated with a foreign body (75%) and that 50% of children had a history of cerebrovascular disease and/or diffuse encephalopathy.

Our results did not suggest worse outcomes in children with ESBL infections, as mortality and length of stay after infection were not different between cases and controls. Reported outcomes in other studies have varied, perhaps due to differences in patient populations [16, 17].

To help assess the generalizability of our 2-center study, we also compared our data to regional and national susceptibility trends, demographic, and isolate characteristics from The Surveillance Network Database-USA (TSN, Eurofins-Medinet, Herndon, VA). The database has approximately 300 participating laboratories and represents the largest ESBL pediatric cohort study to date (Logan et al., [14]). We found that our local population demographics were very similar to the national data. The median age of our children was 1.06 years, which was younger than that found in prior pediatric studies, but consistent with the TSN national data, where the largest increases in ESBLs occurred in the 1–5-year age group between the years of 1999 and 2011. Our local prevalence of ESBL-producing bacterial isolates was stable over time, consistent with the lower prevalence of ESBL phenotypes in children from the East North Central (Midwest) region in TSN data (Logan et al., [14]).

Data from adults suggest that the predominant ESBL genotype in *E. coli* is now the rapidly expanding group of CTX-M enzymes, often referred to as the community-acquired ESBL [2, 6, 29, 30]. Clonal strains such as sequence type (ST) 131 in ESBL *E. coli* are responsible for a significant proportion of the national and global spread of β-lactam-resistant *Enterobacteriaceae*. In Chicago, a recent study of ESBLs found that ST131 composed 53% of all CTX-M ESBL-producing *E. coli* [31]. Very little is known about predominant genotypes in U.S. children; however, 1 recent single-center study suggests that CTX-M may also predominate in this group [32]. In our study, 30% of children presented as outpatients and 13% were considered to have community-onset infection based on previous definitions [12]. We found our study numbers to be comparable to those of other pediatric studies [15–17]; however, they were lower than findings in our national cohort study, where 51.3% of children presented in the outpatient setting (Logan et al., [14]).

The high rates of multidrug resistance (77%) was another concerning finding in our study. This drastically limits therapeutic options, particularly for oral drugs, and most antibiotic clinical trials for ESBL-producing infections are in adult populations.

Our study has limitations. We used a retrospective study design with a relatively small sample size, which might have allowed for selection bias; however, the pooling of data from 2 centers serving diverse populations may have lessened this bias. We also used a case–case–control design in an attempt to overcome known limitations of case–control study design when evaluating risk factors associated with resistant organisms. Additionally, we may not have captured all outpatient antibiotic records, as some were based on patient report. Finally, our study environment represents centers caring for adults and children, and results may not reflect findings of hospitals caring solely for children.

ESBL infections in children are increasing nationally, though our local 2-center prevalence remained stable over a 4-year period. The majority of isolates in our study were multidrug resistant. Children at highest risk of infection included those with neurologic comorbidities. Further studies in children of potential means of acquisition, the molecular

epidemiology of ESBL-producing bacteria, and surveillance, including in outpatient settings, are warranted.

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

We would like to thank Amanda Grasso, Pamela Hagen, and Kelly Hock for their assistance with data retrieval, and Drs. Kenneth Boyer, Norman Jacobs, and Bala Hota for their guidance and input.

Financial support. This work was supported by the Rush University–Stroger Hospital Collaborative Research Award (L. L., J. M.) and The Childrens Foundation (L. L.).

Potential conflicts of interest. All authors: no conflict.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

REFERENCES

1. Braykov NP, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in resistance to carbapenems and third-generation cephalosporins among clinical isolates of *Klebsiella pneumoniae* in the United States, 1999–2010. Infect Control Hosp Epidemiol **2013**; 34:259–68.
2. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol **2013**; 34:1–14.
3. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother **2010**; 54:969–76.
4. Bush K, Fisher J. Epidemiological expansion, structural studies, and clinical challenges of new β-lactamases from gram-negative bacteria. Annu Rev Microbiol **2011**; 65:455–78.
5. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. Infection **1983**; 11:315–7.
6. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: A clinical update. Clin Microbiol Rev **2005**; 18:657–86.
7. Logan LK. Carbapenem-resistant *Enterobacteriaceae*: An emerging problem in children. Clin Infect Dis **2012**; 55:852–9.
8. Stürenburg E, Mack D. Extended-spectrum ß-lactamases: Implications for the clinical microbiology laboratory, therapy, and infection control. J Infect **2003**; 47:273–95.
9. Shah AA, Hasan F, Ahmed S, Hameed A. Characteristics, epidemiology and clinical importance of emerging strains of Gram-negative bacilli producing extended-spectrum ß-lactamases. Res Microbiol **2004**; 155:409–21.
10. Hayakawa K, Gattu S, Marchaim D, et al. Epidemiology and risk factors for isolation of *Escherichia coli* producing CTX-M-type extended-spectrum ß-lactamase in a large U.S. medical center. Antimicrob Agents Chemother **2013**; 57:4010–8.
11. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* outbreak in a neonatal intensive care unit. Infect Control Hosp Epidemiol **2003**; 24:601–6.
12. Apisarnthanarak A, Kiratisin P, Saifon P, et al. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing *Escherichia coli* infections in Thailand: A case–case–control study. Am J Infect Control **2007**; 35:606–12.
13. Ramphal R, Ambrose PG. Extended-spectrum β-lactamases and clinical outcomes: Current data. Clin Infect Dis **2006**; 42(suppl 4):S164–72.
14. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R, for the CDC Epicenters Prevention Program. Extended-spectrum β-lactamase–producing and third-generation cephalosporin-resistant Enterobacteriaceae in children: Trends in the United States, 1999–2011. J Pediatr Infect Dis Soc **2014**; 3:320–8.
15. Blaschke AJ, Korgenski EK, Daly JA, et al. Extended-spectrum beta-lactamase-producing pathogens in a children's hospital: A 5-year experience. Am J Infect Control **2009**; 37:435–41.
16. Jhaveri R, Bronstein D, Sollod J, Kitchen C, Krogstad P. Outcome of infections with extended spectrum beta-lactamase producing organisms in children. J Pediatr Infect Dis **2008**; 3: 229–33.
17. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species in children. Pediatrics **2005**; 115:942–9.
18. Kaye KS, Harris AD, Samore M, Carmeli Y. The case-case-control study design: Addressing the limitations of risk factor studies for antimicrobial resistance. Infect Control Hosp Epidemiol **2005**; 26:346–51.
19. Kotapati S, Kuti JL, Nightingale CH, Nicolau DP. Clinical implications of extended spectrum beta-lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness. J Infect **2005**; 51:211–7.
20. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum ß-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: Risk factors for infection and impact of resistance on outcomes. Clin Infect Dis **2001**; 32:1162–71.
21. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement (June 2010 Update). Wayne, PA: CLSI, December 29, 2011.
22. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
23. Centers for Disease Control and Prevention (CDC). The National Healthcare Safety Network (NHSN) Manual. Patient Safety Component Protocol. **2013**; Available at: http://www.cdc.gov/nhsn/TOC_PSCManual.html (http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf). Accessed September 14, 2013.
24. Magiorakos A, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18: 268–81.
25. Cordery RJ, Roberts CH, Cooper SJ, Bellinghan G, Shetty N. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species in the intensive care unit; antibiotic management and clinical outcome. J Hosp Infect **2008**; 68:108–15.

26. Hyle EP, Lipworth AD, Zaoutis TE, et al. Risk factors for increasing multidrug resistance among extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species. Clin Infect Dis **2005**; 40:1317–24.
27. Bisson G, Fishman NO, Patel JB, Edelstein PH, Lautenbach E. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species: Risk factors for colonization and impact of antimicrobial formulary interventions on colonization prevalence. Infect Control Hosp Epidemiol **2002**; 23:254–60.
28. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. J Clin Microbiol **2005**; 43:745–9.
29. Cantón R, Coque TM. The CTX-M β-lactamase pandemic. Curr Opin Microbiol **2006**; 9:466–75.
30. Munoz-Price LS, Quinn JP. The spread of *Klebsiella pneumoniae* carbapenemases: A tale of strains, plasmids, and transposons. Clin Infect Dis **2009**; 49:1739–41.
31. Peirano G, Costello M, Pitout JD. Molecular characteristics of extended-spectrum beta-lactamase-producing *Escherichia coli* from the Chicago area: High prevalence of ST131 producing CTX-M-15 in community hospitals. Int J Antimicrob Agents **2010**; 36:19–23.
32. Chandramohan L, Revell PA. Prevalence and molecular characterization of extended-spectrum-ß-lactamase-producing *Enterobacteriaceae* in a pediatric patient population. Antimicrob Agents Chemother **2012**; 56:4765–70.