HHS Public Access

Author manuscript

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2018 October 17.

Published in final edited form as:

Infect Control Hosp Epidemiol. 2018 January ; 39(1): 116–118. doi:10.1017/ice.2017.246.

Risk Factors for Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* Carriage upon Pediatric Intensive Care Unit Admission

David X. Li[1], **Anna S. Sick-Samuels**[2], **Nuntra Suwantarat**[3], **Rebecca G. Same**[2], **Patricia J. Simner**[3], and **Pranita D. Tamma**[2]

[1]Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases, Baltimore, Maryland [2]Johns Hopkins University School of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Baltimore, Maryland [3]Johns Hopkins University School of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Baltimore, Maryland

To the Editor:

The incidence of infections due to ESBL-producing organisms is increasing in both children and adults [1]. This increase is particularly concerning as ESBL-producing organisms are frequently resistant to antibiotics used in empiric sepsis regimens, such as ceftriaxone, cefepime, and piperacillin-tazobactam [2]. Additionally, plasmids carrying genes encoding ESBLs often harbor additional resistance mechanisms reducing the activity of aminoglycosides and fluoroquinolones [1,2]. Thus, children with signs and symptoms of severe infections ultimately found to have infections with ESBL-producing organisms may not receive the most appropriate empiric therapy, increasing the likelihood of poor outcomes [3].

Early recognition of ESBL colonization may be important as colonization with ESBLs has been associated with subsequent, invasive infections [4]. Children warranting pediatric intensive care unit (PICU) admission are at particularly high risk for serious infections. An understanding of carriers of ESBL-producing organisms may play an important role in guiding appropriate empiric treatment.

We characterized risk factors for ESBL colonization among children admitted to the PICU by conducting a case-control study among patients admitted to The Johns Hopkins Hospital 40-bed tertiary care PICU in Baltimore, Maryland. Rectal swabs were obtained from all children admitted to the unit between July 2014 and January 2015. Rectal swabs were inoculated into T-soy broth containing a 30 μg ceftriaxone disk and incubated at 37°C. Within 48 hours of inoculation, 100 μL broth samples with visible turbidity were plated on

Corresponding author: Pranita D. Tamma, MD, MHS. The Johns Hopkins University School of Medicine, 200 North Wolfe St., Suite 3149, Baltimore, MD 21287 (ptamma1@jhmi.edu).

None of the authors report any conflicts of interest.

MacConkey agar with a 30 μg ceftriaxone disk and incubated at 37°C overnight. All recovered isolates within the zone of inhibition (Inhibition zone < 23 mm) underwent routine identification and antimicrobial susceptibility testing using the BD Phoenix™ Automated System (BD Diagnostics, Sparks, Maryland).

Genomic DNA was extracted from isolates with ceftriaxone MICs of ≥2 μg/mL using the DNeasy Blood & Tissue Kit (Qiagen, Germantown, Maryland) and identification of β-lactamase-encoding genes was assessed utilizing the Check-MDR CT103XL kit microarray-based assay (Check-Points, Wageningen, Netherlands). Multilocus Sequence Typing (MLST) was used for amplification and sequencing of eight housekeeping genes for *E. coli* and seven housekeeping genes of *K. pneumoniae* (http://www.pasteur.fr/mlst).

Cases were defined as children whose admission surveillance culture grew an ESBL-producing organism. Each case was matched to three controls using a random number generator.Potential risk factors for colonization were collected on all patients. Data were extracted from all available inpatient and outpatient medical records from facilities within the Johns Hopkins Health System, and from medical records of children who received care at institutions within the Epic Care Everywhere Network, a secure exchange that contains patient medical information from a large number of inpatient and outpatient healthcare networks throughout the United States. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board with a waiver of informed consent.

Baseline characteristics of cases and controls were compared using Chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test or Student's t-test for continuous variables. P-values ≤0.05 were considered significant. All analyses were performed using Stata, version 13 (StataCorp, College Station, Texas).

Eight hundred fifty-four rectal swabs from unique patients were obtained over the study period. Twenty-four children were colonized with ESBLs (2.8%). $bla_{\text{CTX-M}}$ genes were identified in all 21 *E. coli* isolates, 1 of 2 *K. pneumoniae* isolates, and 1 of 1 *E. cloacae* isolates. A $bla_{\text{SHV-12}}$ gene was identified in the second *K. pneumoniae* isolate. 17 of the 24 (71%) ESBLs contained $bla_{\text{CTX-M-15-like}}$ genes. The predominant circulating clonal strain was ESBL-producing *E. coli* ST131, identified in 63% of isolates.

The 24 ESBL-positive cases were matched to 72 ESBL-negative controls (Table). Within the previous six months, cases were more likely to have had previous ESBL colonization or infection (17% vs. 1%; p=0.01) or to have been hospitalized in a high ESBL burden foreign country (17% vs. 1%; p=0.01), including China (1), India (1), Qatar (1), and Saudi Arabia (2). Cases were more likely to have received recently chemotherapy (OR = 4.6; 95% CI 0.9 – 22.3) or a hematopoietic stem cell transplantation (OR=10.1; 95% CI 1.0 – 102.7). Nine cases (38%) developed invasive infections with ESBL-producing organisms on a subsequent clinical culture (4 during the hospital admission and 5 within the subsequent 6 months). No control patients developed subsequent ESBL infections.

Our findings suggest that targeted screening of high-risk patients may be a reasonable consideration to identify ESBL colonization. Identifying children colonized with ESBL-

producing organisms may be particularly relevant to help guide empiric antibiotic therapy as 40% of children colonized with ESBL-producing organisms at the time of PICU admission went on to develop invasive ESBL infections.

ESBL-producing bacteria have increasingly been identified in the community, which appears to be driven by clonal expansion of *E. coli* ST131 and person-to-person transmission, sometimes in the absence of significant health care exposure [5-8], Our results indicate that previously healthy children are still at low risk for ESBL colonization. However, hospitalization in a foreign country was a strong predictor of ESBL colonization. This finding reflects that there are significant regional differences in ESBL prevalence, with a disproportionate burden in India, East and Southeast Asia, and the Middle East [9-10].

This is a single-center study. Our findings must be repeated in a larger and more diverse setting. Additionally, although we completed a thorough review of inpatient and outpatient records from a number of health care facilities in the state of Maryland, there may still have been missing data. However, this is expected to be similar for both cases and controls.

As the incidence of ESBL increases and they contribute to considerable morbidity and mortality, it is imperative to develop systems to identify children who are most at risk of infections caused by ESBL-producing organisms. Our findings suggest that in addition to reviewing prior culture histories to identify children with previous ESBL colonization or infection, targeted screening of children who received medical care abroad in high risk countries, who recently received chemotherapy, or who recently underwent hematopoietic stem cell transplantations may be another strategy to help identify those most at risk for ESBL colonization.

Acknowledgments

Funding

The work was supported by funding the National Institutes of Health (K23-AI127935) awarded to PDT.

References

1. Murray TS, Peaper DR. The contribution of extended-spectrum beta-lactamases to multidrug-resistant infections in children. Curr Opin Pediatr. 2015;27(1): 124–31. PubMed PMID:. [PubMed: 25565574]
2. Chandramohan L, Revell PA. Prevalence and molecular characterization of extended-spectrum-beta-lactamase-producing Enterobacteriaceae in a pediatric patient population. Antimicrobial agents and chemotherapy. 2012;56(9):4765–70. PubMed PMID: . Pubmed Central PMCID: PMC3421901. [PubMed: 22733062]
3. Sick AC, Tschudin-Sutter S, Turnbull AE, Weissman SJ, Tamma PD. Empiric Combination Therapy for Gram-Negative Bacteremia. Pediatrics 2014; 133:e1148–55.40. [PubMed: 24709936]
4. Goodman K, Lessler J, Cosgrove SE, Harris AD, Lautenbach E, Han JH, Milstone AM, Masey C, Tamma PD. A Clinical Decision Tree to Predict Whether a Bacteremic Patient is Infected With an ESBL-Producing Organism. Clin Infect Dis 2016; 63:896–903. [PubMed: 27358356]
5. Suwantarat N, Logan LK, Carroll KC, Bonomo RA, Simner PJ, Rudin SD, Milstone AM, Tekle T, Ross T, Tamma PD. The Prevalence and Molecular Epidemiology of Multidrug-Resistant Enterobacteriaceae Colonization in a Pediatric Intensive Care Unit. Infect Control Hosp Epidemiol 2016; 9:1–9.

6. Madigan T, Johnson JR, Clabots C, Johnston BD, Porter SB, Slater BS, Banerjee R.Extensive Household Outbreak of Urinary Tract Infection and Intestinal Colonization due to Extended-Spectrum beta-Lactamase-Producing Escherichia coli Sequence Type 131. Clin Infect Dis 2015;61:e5–e12. [PubMed: 25828998]
7. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R; 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 Pediatric Infect Dis Soc 2014 12;3(4):320–8. [PubMed: 26625452]
8. Logan LK, Meltzer LA, McAuley JB, Hayden MK, Beck T, Braykov NP, Laxminarayan R, Weinstein RA; CDC Epicenters Prevention Program. Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae Infections in Children: A Two-Center Case-Case-Control Study of Risk Factors and Outcomes in Chicago, Illinois. J Pediatric Infect Dis Soc 2014 12;3(4):312–9. [PubMed: 26625451]
9. Mathai D, Rhomberg PR, Biedenbach DJ, Jones RN, India Antimicrobial Resistance Study G. Evaluation of the in vitro activity of six broad-spectrum beta-lactam antimicrobial agents tested against recent clinical isolates from India: a survey of ten medical center laboratories. Diagnostic microbiology and infectious disease. 2002;44(4):367–77. [PubMed: 12543543]
10. Tawfik AF, Alswailem AM, Shibl AM, Al-Agamy MH. Prevalence and genetic characteristics of TEM, SHV, and CTX-M in clinical Klebsiella pneumoniae isolates from Saudi Arabia. Microbial drug resistance. 2011;17(3):383–8. [PubMed: 21612509]

Table.

Comparison of children colonized and not colonized with ESBL-producing *Enterobacteriaceae* on admission to a pediatric intensive care unit.

	ESBL-positive (n=24)	ESBL-negative (n=72)	OR (95% CI)	p-value
Age, years (median, interquartile range)	6.0 (3.0–18.0)	8.0 (3.0–15.0)	1.0 (1.0– 1.1)	0.40
Male	14 (58.3)	50 (69.4)	0.6 (0.2 – 1.8)	0.32
Race				
White	16 (66.7)	37 (51.3)	0.8 (0.3 – 2.2)	0.24
Black	4 (16.7)	24 (33.3)	0.4 (0.09 – 1.4)	0.19
Asian	2 (8.3)	2 (2.8)	3.2 (0.2 – 45.6)	0.26
Latino	2 (8.3)	4 (5.6)	1.5 (0.1 – 11.6)	0.64
PRISM score (median, IQR)	4.0 (2.0 – 7.0)	4.0 (2.0 – 7.0)	1.0 (0.9 – 1.2)	0.80
Days from hospital admission to PICU admission (median, IQR)	0.0 (0.0 – 4.0)	0.0 (0.0 – 17.0)	1.4 (1.0 – 2.0)	0.11
Reason for PICU admission				
Planned surgical procedure	11 (45.8)	32 (44.4)	1.1 (0.4 – 2.9)	0.90
Respiratory failure	2 (8.3)	12 (16.7)	0.4 (0.05 – 2.3)	0.51
Trauma	0 (0.0)	13 (18.0)	--	0.02
Sepsis	5 (20.8)	2 (2.8)	9.2 (1.3 – 100.8)	0.01
Metabolic derangements	1 (4.2)	4 (5.6)	0.7 (0.01 – 8.0)	1.00
Other[1]	5 (20.8)	8(11.1)	2.1 (0.5 – 8.3)	0.23
Pre-existing conditions				
Previously healthy	3 (12.5)	28 (38.9)	0.2 (0.04 – 0.9)	0.02
Congenital heart disease	1 (4.2)	9 (12.5)	0.3 (0.01 – 2.4)	0.44
Chemotherapy within the previous 6 months[2]	4 (16.7)	3 (4.2)	4.6 (0.95 – 22.3)	0.05
Hematopoietic stem-cell transplantation (HSCT) within the previous 12 months	3 (12.5)	1 (1.4)	10.1 (1.00 – 102.6)	0.03
Chronic steroid use or immunotherapy	1 (4.2)	2 (2.8)	1.5 (0.02 – 30.4)	1.00
Other[3]	0 (0.0)	2 (2.8)	--	0.41
Healthcare exposures in the 6 months prior to current PICU admission				
Hospital admission	12 (50.0)	29 (40.3)	1.5 (0.5 – 4.2)	0.40

	ESBL-positive (n=24)	ESBL-negative (n=72)	OR (95% CI)	p-value
PICU admission	2 (8.3)	2 (2.8)	3.2	0.26
			(0.2 – 45.6)	
Hospitalization in a foreign country	4 (16.7)	1 (1.4)	14.2 (1.3 – 708.6)	0.01
ESBL colonization or infection	4 (16.7)	1 (1.4)	14.2 (1.3 – 708.6)	0.01
Number of hospital days[4], mean (SD)	11.8 (19.5)	11.3 (20.9)	1.0 (1.0 – 1.0)	0.78
Number of antibiotic days[4], mean (SD)	4.5 (7.2)	11.0 (34.7)	1.0 (1.0 – 1.0)	0.47
Antibiotic use in the 6 months prior to current PICU admission				
Any antibiotic	9 (37.5)	24 (33.3)	1.2 (0.4 – 3.4)	0.71
Penicillin	6 (25.0)	12 (16.7)	1.7 (0.4 – 5.6)	0.36
Cephalosporins	6 (25.0)	17 (23.6)	1.1 (0.3 – 3.4)	0.89
Carbapenems	3 (12.5)	1 (1.4)	10.1 (0.7 – 539.6)	0.05
Fluoroquinolones	2 (8.3)	1 (1.4)	6.4 (0.3 – 385.9)	0.15
Aminoglycosides	3 (12.5)	5 (6.9)	1.9 (0.3 – 10.7)	0.39

All values represent n (%), unless otherwise noted.

[1]Other reasons for PICU admission included: intractable seizures (3), altered mental status (2), burns (2), myocarditis (1), chemotherapy induction (1), anemia (1), cardiac arrest (1), allergic reactions (2)

[2]Patients who received both chemotherapy and HSCT only categorized as HSCT; [3]Excludes patients receiving immunotherapy for SOT, HSCT, or chemotherapy

[3]Other pre-existing conditions include end-stage renal disease on hemodialysis (1) and solid organ transplantation (1)

[4]Calculation of the mean included only patients with the specific exposure.