

LETTERS TO THE EDITOR

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

To the Editor—The incidence of infections due to extended-spectrum β -lactamase (ESBL)-producing organisms is increasing in both children and adults.¹ This increase is particularly concerning because 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 is important because 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 45-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- μ g ceftriaxone disk and incubated at 37°C. Within 48 hours of inoculation, 100- μ L broth samples with visible turbidity were plated on MacConkey agar with a 30- μ g 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 (Becton Dickinson Diagnostics, Sparks, MD).

Genomic DNA was extracted from isolates with ceftriaxone minimum inhibitory concentrations (MICs) of ≥ 2 μ g/mL using the DNeasy Blood and Tissue Kit (Qiagen, Germantown, MD) and identification of β -lactamase-encoding genes was assessed using the Check-MDR CT103XL kit microarray-based assay (Check-Points, Wageningen, the Netherlands). Multi-locus sequence typing (MLST) was used for amplification and sequencing of 8 housekeeping genes for *E. coli* and 7 housekeeping genes of *K. pneumoniae* (<http://www.pasteur.fr/mlst>).

Case patients were defined as children whose admission surveillance culture grew an ESBL-producing organism. Each

case patient was matched to 3 control patients 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. The Johns Hopkins University School of Medicine Institutional Review Board approved this study with a waiver of informed consent.

Baseline characteristics of cases and controls were compared using a χ^2 or Fisher exact test for categorical variables and the Wilcoxon rank-sum test or Student t test for continuous variables. *P* values $\leq .05$ were considered significant. All analyses were performed using Stata, version 13 (StataCorp, College Station, TX).

In total, 854 rectal swabs from unique patients were obtained over the study period; 24 children were found to be colonized with ESBLs (2.8%). *bla*_{CTX-M} genes were identified in all 21 *E. coli* isolates, in 1 of 2 *K. pneumoniae* isolates, and in 1 of 1 *E. cloacae* isolates. A *bla*_{SHV-12} gene was identified in the second *K. pneumoniae* isolate. Of the 24 ESBLs, 17 (71%) contained *bla*_{CTX-M-15-like} genes. The predominant circulating clonal strain was ESBL-producing *E. coli* ST131, which was identified in 63% of isolates.

The 24 ESBL-positive case patients were matched to 72 ESBL-negative control patients (Table 1). Within the previous 6 months, case patients were more likely to have had previous ESBL colonization or infection (17% vs 1%; *P* = .01) or to have been hospitalized in a high-ESBL-burden foreign country (17% vs 1%; *P* = .01), including China (*n* = 1), India (*n* = 1), Qatar (*n* = 1), and Saudi Arabia (*n* = 2). Case patients were more likely to have received recently chemotherapy (odds ratio [OR], 4.6; 95% confidence interval [CI], 0.9–22.3) or a hematopoietic stem cell transplantation (OR, 10.1; 95% CI, 1.0–102.7). Furthermore, 9 case patients (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 because 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

TABLE 1. Comparison of Children Colonized and Not Colonized With ESBL-Producing *Enterobacteriaceae* on Admission to a Pediatric Intensive Care Unit

Characteristic	ESBL Positive (n = 24), No. (%) ^a	ESBL Negative (n = 72), No. (%) ^a	OR (95% CI)	P Value
Age, median y (IQR)	6.0 (3.0–18.0)	8.0 (3.0–15.0)	1.0 (1.0–1.1)	.40
Male	14 (58.3)	50 (69.4)	0.6 (0.2–1.8)	.32
Race				
White	16 (66.7)	37 (51.3)	0.8 (0.3–2.2)	.24
Black	4 (16.7)	24 (33.3)	0.4 (0.09–1.4)	.19
Asian	2 (8.3)	2 (2.8)	3.2 (0.2–45.6)	.26
Latino	2 (8.3)	4 (5.6)	1.5 (0.1–11.6)	.64
PRISM score, median (IQR)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	1.0 (0.9–1.2)	.80
Days from hospital admission to PICU admission, median d (IQR)	0.0 (0.0–4.0)	0.0 (0.0–17.0)	1.4 (1.0–2.0)	.11
Reason for PICU admission				
Planned surgical procedure	11 (45.8)	32 (44.4)	1.1 (0.4–2.9)	.90
Respiratory failure	2 (8.3)	12 (16.7)	0.4 (0.05–2.3)	.51
Trauma	0 (0.0)	13 (18.0)02
Sepsis	5 (20.8)	2 (2.8)	9.2 (1.3–100.8)	.01
Metabolic derangements	1 (4.2)	4 (5.6)	0.7 (0.01–8.0)	1.00
Other ^b	5 (20.8)	8 (11.1)	2.1 (0.5–8.3)	.23
Pre-existing conditions				
Previously healthy	3 (12.5)	28 (38.9)	0.2 (0.04–0.9)	.02
Congenital heart disease	1 (4.2)	9 (12.5)	0.3 (0.01–2.4)	.44
Chemotherapy within the previous 6 mo ^c	4 (16.7)	3 (4.2)	4.6 (0.95–22.3)	.05
HSCT within the previous 12 mo	3 (12.5)	1 (1.4)	10.1 (1.00–102.6)	.03
Chronic steroid use or immunotherapy ^d	1 (4.2)	2 (2.8)	1.5 (0.02–30.4)	1.00
Other ^e	0 (0.0)	2 (2.8)41
Healthcare exposures in the 6 mo prior to PICU admission				
Hospital admission	12 (50.0)	29 (40.3)	1.5 (0.5–4.2)	.40
PICU admission	2 (8.3)	2 (2.8)	3.2 (0.2–45.6)	.26
Hospitalization in a foreign country	4 (16.7)	1 (1.4)	14.2 (1.3–708.6)	.01
ESBL colonization or infection	4 (16.7)	1 (1.4)	14.2 (1.3–708.6)	.01
No. of hospital days, mean (±SD) ^f	11.8 (±19.5)	11.3 (±20.9)	1.0 (1.0–1.0)	.78
No. of antibiotic days, mean (±SD) ^f	4.5 (±7.2)	11.0 (±34.7)	1.0 (1.0–1.0)	.47
Antibiotic use in the 6 mo prior to PICU admission				
Any antibiotic	9 (37.5)	24 (33.3)	1.2 (0.4–3.4)	.71
Penicillin	6 (25.0)	12 (16.7)	1.7 (0.4–5.6)	.36
Cephalosporins	6 (25.0)	17 (23.6)	1.1 (0.3–3.4)	.89
Carbapenems	3 (12.5)	1 (1.4)	10.1 (0.7–539.6)	.05
Fluoroquinolones	2 (8.3)	1 (1.4)	6.4 (0.3–385.9)	.15
Aminoglycosides	3 (12.5)	5 (6.9)	1.9 (0.3–10.7)	.39

NOTE. ESBL, extended-spectrum β -lactamase-producing; OR, odds ratio; CI, confidence interval; IQR, interquartile range; PRISM, pediatric risk of mortality; PICU, pediatric intensive care unit; SD, standard deviation; HSCT, hematopoietic stem-cell transplantation; SOT, solid organ transplant.

^aUnless otherwise noted.

^bOther reasons for PICU admission included intractable seizures (n = 3), altered mental status (n = 2), burns (n = 2), myocarditis (n = 1), chemotherapy induction (n = 1), anemia (n = 1), cardiac arrest (n = 1), and allergic reactions (n = 2).

^cPatients who received both chemotherapy and HSCT were only categorized as HSCT.

^dExcludes patients receiving immunotherapy for SOT, HSCT, or chemotherapy.

^eOther pre-existing conditions include end-stage renal disease on hemodialysis (n = 1) and solid organ transplantation (n = 1).

^fCalculation of the mean included only patients with the specific exposure.

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 is 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 study has several limitations. This is a single-center study, and 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 several healthcare facilities in Maryland, data may have been missing. However, this factor is expected to have been similar for both cases and controls.

As the incidence of ESBLs 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.

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Colistin-Resistant *Klebsiella* Infections Among Pediatric Oncology and Hematopoietic Stem Cell Transplantation Patients in Eastern India

To the Editor—The epidemiology and clinical outcome of extremely drug-resistant (XDR) gram-negative bacterial (GNB) infections in the hemato-oncologic pediatric population is not well documented. Colistin-resistant *Klebsiella* (CRK) is one such XDR infection; it is resistant to most classes of antibiotics except 1 or 2 classes, and it is one of the most difficult pathogens to treat. These infections are increasingly common in settings with high XDR prevalence, and they are increasing globally because of travel, movement of food items, use in livestock, and widespread use of antibiotics (in patients and food animals).^{1–5} In the last 3 years, the trend in colistin resistance has increased among the commonly encountered GNB in our hospital (ie, for adults and pediatrics combined). From 2014 to 2016, the resistance to colistin in *Klebsiella* increased from 1.98% to 3.12%; in *Escherichia coli*, colistin resistance increased from 0.14% to 0.24%; in *Pseudomonas*, colistin resistance increased from 0% to 0.87%; and in *Acinetobacter*, colistin resistance increased from 0% to 4.49% (see the Figure online). In this retrospective study, we investigated the incidence, clinical presentation, and outcomes of CRK infection among pediatric oncology/transplantation patients (0–18 years old) in a cancer hospital in India between May 2011 and April 2017.