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A Multi-Centered Study of the Clinical and Molecular Epidemiology of TEM- and SHV-type Extended- Spectrum Beta-Lactamase producing Enterobacterales Infections in Children

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Abstract

Background: Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales-(Ent) infections are increasing in pediatrics. Before CTX-M ESBL emerged, the most common infection-associated ESBL genes were TEM and SHV-type ESBLs. We sought to define the current epidemiology of Ent infections in children due to bla_{TEM} and bla_{SHV} (TEM-SHV-Ent).

Methods: A retrospective case-control analysis of children with TEM-SHV-Ent infections at three Chicago-area hospitals was performed. Cases had extended-spectrum-cephalosporin (ESC)-resistant infections due to bla_{TEM} or bla_{SHV}. DNA analysis assessed beta-lactamase (*bla*) genes, multi-locus sequence types (MLST) and *E. coli* phylogenetic grouping. Controls had ESC-susceptible Ent infections, matched 3:1 to cases by age, source, and hospital. Clinical-epidemiologic infection predictors were assessed.

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Results: Of 356 ESC-R-Ent isolates from children (median 4.3 years), 38 (10.7%) were positive solely for *bla*$_{\text{TEM-ESBL}}$ (26%) or *bla*$_{\text{SHV-ESBL}}$ genes (74%). Predominant organisms were *Klebsiella* (34.2%) and *E. coli* (31.6%); 67% of *E. coli* were phylogroup B2. MLST revealed multiple strains, 58% resistant to ≥3 antibiotic classes. On multivariable analysis, children with TEM-SHV-Ent infections more often had recent inpatient care (OR 8.2), yet were diagnosed mostly as outpatients (OR 25.6) and less in NICUs (OR 0.036) than controls. TEM-SHV-Ent patients had more gastrointestinal (OR 23.7) and renal comorbidities (OR 4.2). Differences in demographics, antibiotic exposure, and foreign bodies were not found.

Conclusion: TEM-SHV-Ent are commonly linked to inpatient exposures in children with chronic conditions but most often present in outpatient settings. Clinicians should be aware of the potential increased risk for TEM-SHV-Ent infections in outpatients with gastrointestinal and renal comorbidities and histories of prolonged hospital stays.

Keywords

Epidemiology; Gram-negative bacteria; *Enterobacterales* infections; drug resistance; children

Introduction

Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales continue to increase in the U.S. and globally[1, 2]. In Enterobacterales, β-lactamase (*bla*) genes on mobile genetic elements encode for a rapidly growing list of β-lactam hydrolyzing enzymes including ESBLs. Much of the increase in ESBL producing organisms has been attributed to the global expansion of community-acquired CTX-M-type ESBL-producing *Escherichia coli* beginning in the 1990s, and in particular due to the emergence of ST131-H30 strains of *bla*$_{\text{CTX-M-15}}$ *E. coli*[3]. Before the emergence of *bla*$_{\text{CTX-M}}$ in *E. coli*, ESBL-producing Enterobacterales associated infections were relatively few, occurred mostly in healthcare settings, and were primarily due to *E. coli* and *Klebsiella pneumoniae* that harbored *bla*$_{\text{TEM-ESBL}}$ and *bla*$_{\text{SHV-ESBL}}$[3, 4]. Despite these differences in epidemiology, the majority of *bla*-harboring Enterobacterales today are known to carry additional plasmid-borne genes rendering them multi-drug resistant (MDR) and leaving few treatment options for clinicians[4, 5].

In children, ESBL-producing Enterobacterales also have continued to increase, though this increase was not recognized until the last few years and the epidemiology relatively unknown[6, 7]. While *bla*$_{\text{CTX-M}}$ are the most commonly reported genes associated with ESBL infections in children[8], we found in a multicentered study of children located in the greater Chicago area that mechanisms and strain types accounting for extended-spectrum cephalosporin β-lactam resistance in children are complex and diverse[9].

The current epidemiology of TEM- and SHV-type ESBL infections is unknown. In this study, we sought to characterize the molecular epidemiology of TEM- and SHV-type ESBL Enterobacterales strains and to identify factors associated with TEM- and SHV-type ESBL Enterobacterales (TEM-SHV Ent) infections in children. Understanding the clinical and molecular epidemiology of pediatric TEM-SHV Ent infections will have a significant effect

on clinical practice, infection control and prevention measures, and public health policies in our most vulnerable population.

Methods

Study Setting

Hospitals A and B are 115-bed and 125-bed children's hospitals, respectively, located within tertiary care academic medical centers, and contain general pediatrics and newborn infant wards and neonatal, and pediatric intensive care units. Hospital C has 288 beds and is a free-standing children's academic medical center that provides complex quaternary services, such as pediatric organ and bone marrow transplantation. All of the participating centers are located within metropolitan Chicago.

Study Population

This study included patients up to 17.99 years of age found to have a positive culture for Enterobacterales with resistance to an extended-spectrum cephalosporin (ceftriaxone, ceftazidime, cefotaxime) due to a suspected *bla* gene. Infections were diagnosed between January 1, 2011 and December 31, 2016, and only one infection per patient was included. The study was approved by the institutional review boards of the three participating institutions and need for informed consent was waived.

Bacterial isolates and antibiotic susceptibility testing

The microbiology laboratories of Hospitals A-C phenotypically characterized presumed ESBL Ent isolates via the MicroScan WalkAway system (Siemens Healthcare Diagnostics, Tarrytown, NY) or by the Vitek 2 microbial identification system (bioMérieux, Athens, GA). Screening for ESBL production was based on guidelines of the Clinical and Laboratory Standards Institute (CLSI) and involved testing with one or more of the following agents: aztreonam, ceftazidime, ceftriaxone, cefotaxime or cefpodoxime[10]. ESBL production was confirmed on the automated instruments; by determining minimum inhibitory concentrations (MICs) of ceftazidime and cefotaxime in the presence and absence of clavulanic acid; or by disk diffusion assays (BBL; Becton, Dickinson and Company, Sparks, MD). A measurement of a 4-fold reduction in the MIC of ceftazidime or cefotaxime in the presence of clavulanic acid or an increase in disk zone diameter of > 5 mm served as confirmation of the ESBL phenotype[10].

Molecular Analysis

Beta-Lactam Resistance Determinants—Genomic DNA was purified from Enterobacterales isolates identified with an ESBL phenotype (DNeasy blood and tissue kit, Qiagen, Inc. Valencia, CA). Polymerase chain reaction (PCR) or DNA Microarray (Check-MDR CT101 and CT103XL; Check-Points, Wageningen, Netherlands) was performed to assess and confirm the presence of *bla* genes in isolates according to the manufacturer's protocol and as previously described[9, 11]. Enterobacterales isolates confirmed to be positive solely for *bla* genes belonging to either TEM or SHV ESBL families were included in the study.

Nomenclature and Characterization—A well-established multiplex PCR-based technique was used to assign *E. coli* to one of four phylogenetic groups (A, B1, B2 and D)[12]. Multi-locus sequence typing (MLST) using the Pasteur scheme [Pasteur website (http://www.pasteur.fr/recherche/genopole/PF8/mlst/)] identified sequence types of the ESBL-producing strains of *E. coli* and *Klebsiella pneumoniae*, while the Oxford scheme [PubMLST website (https://pubmlst.org/ecloacae/)] was similarly used on *Enterobacter cloacae* isolates as previously described[9, 13–15].

Analytic Study Design

A retrospective case–control study design was used to assess factors associated with infection due to isolates in which we detected a $bla_{\text{TEM-ESBL}}$ or $bla_{SHV\text{-}ESBL}$ gene. Hospital electronic laboratory records were used to identify control subjects. Children diagnosed with clinical infections due to Enterobacterales susceptible to extended-spectrum cephalosporins (ESC-S) were included as controls, as determined upon case review by study investigators and/or using standard criteria for infection as defined by the CDC National Healthcare Safety Network[16]. Controls were matched 3:1 to the cases by age range and hospital, as performed in previously published studies[17–19].

Covariates

A number of variables were analyzed as potential factors associated with TEM-SHV Ent infection based on known associations for ESBL-producing Enterobacterales acquisition in adults and children including (1) demographics (age, gender, race/ethnicity); (2) recent inpatient and outpatient healthcare exposures, including hospitalization and/or procedures in the previous 30 days; (3) comorbid conditions (as defined by ICD-9/ICD-10 codes); (4) antibiotic exposures in the 40 days before culture[17, 18]; (5) presence, number, and type of invasive medical devices; and (6) patient residence in Chicago and its suburbs[18, 19].

Statistical Analysis

First, case and control groups were evaluated for differences using parametric or non-parametric tests as appropriate for categorical and continuous variables; $P \leq 0.05$ was considered statistically significant unless otherwise specified. Next, variables with $p \leq 0.1$ on bivariate analysis were included in multivariable analysis. Finally, stepwise multiple logistic regression was performed to examine the multivariable relationship between the covariates and the groups. The final multivariable logistic regression model included the parsimonious model with significant covariates ($p < 0.05$) from the stepwise selection process, with TEM-SHV Ent infection as the dichotomous outcome variable. We did not find evidence of significant confounding during the model building stages nor did we find evidence of significant effect modification; therefore, the simplest model was selected as the final model based on a relatively small sample size and the effect of variables in the model. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

We analyzed 356 pediatric Enterobacterales isolates collected during 2011 – 2016. The isolates harbored 350 *bla* genes, of which 67.9% of all isolates carried $bla_{\text{CTX-M-ESBL}}$

genes[9, 18, 19] and 38 (10.7%) were positive solely for *bla*$_{\text{TEM-ESBL}}$ (26%) or *bla*$_{\text{SHV-ESBL}}$ genes (74%). The median age of children with TEM-SHV Ent infections was 4.3 years. The most common organisms (Table 1) were *Klebsiella* spp. (34.2%) and *E. coli* (31.6%), and the predominant *E. coli* phylogenetic group was B2 (67%). The urinary tract was the most common source of infection (52.6%) followed by the respiratory tract (26.3%). Co-resistance to non-beta-lactam antibiotics was present in 84.2% of isolates and 57.9% were multidrug-resistant, defined as resistant to 3 or more antibiotic classes (Table 1). The highest retained susceptibility (100%) was to amikacin.

Molecular analysis

Of *E. coli*, 67% belonged to phylogenetic group B2; 17% belonged to D and 8% belonged to A. Both B2 and D are virulent phylogroups associated with extra-intestinal pathogenic *E. coli* infections. Of *bla*$_{\text{SHV-ESBL}}$ genes detected by DNA microarray, the most common variants were SHV 238S/240K and SHV 238S, and for *bla*$_{\text{TEM-ESBL}}$, TEM 164S, TEM 238S and TEM 104K. The most common organisms harboring *bla*$_{\text{SHV-ESBL}}$ were *Klebsiella* spp. (46.4%) and *E. coli* (25%). For *bla*$_{\text{TEM-ESBL}}$, 50% were carried by *E. coli* and 40% by *Proteus mirabilis*. *Proteus mirabilis* was found to specifically carry *bla*$_{\text{TEM-ESBL}}$ and *Klebsiella* spp. and *Serratia marcescens* were specific carriers of *bla*$_{\text{SHV-ESBL}}$. *E. coli* and *E. cloacae* harbored both *bla*$_{\text{TEM-ESBL}}$ and *bla*$_{\text{SHV-ESBL}}$.

MLST of twenty-one *E. coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* revealed diverse strain types. Eighteen strains from the three genera were matched to ST types in the Institut Pasteur MLST database (http://bigsdb.web.pasteur.fr/) or Oxford MLST database (https://pubmlst.org/ecloacae/) and three strains were associated with novel MLST types. Of nine *E. coli*, 33% were ST43 (ST131 Achtman scheme) and strains carried *bla*$_{\text{TEM-ESBL}}$ and *bla*$_{\text{SHV-ESBL}}$; ST506 was the next most common (22%) and strains carried *bla*$_{\text{TEM}}$. Of nine *K. pneumoniae*, seven (78%) had differing ST types and two (22%) had a novel ST type. For *E. cloacae*, similar to *K. pneumoniae* of the three strains characterized, there were no matching ST types and one strain had a novel ST type.

Analysis of Factors Associated with TEM-SHV Ent Infection

The 38 cases of TEM-SHV Ent infection were matched by age range, hospital to 114 controls with antibiotic-sensitive Ent infections. Significant factors positively associated with TEM-SHV Ent infection on bivariate analysis included: infection with *Klebsiella spp.*, healthcare-associated infection, male gender, exposure to fluoroquinolone or extended-spectrum cephalosporin antibiotics; gastrointestinal, pulmonary, renal, or multiple comorbidities; gastrointestinal, respiratory, genitourinary or multiple indwelling devices; and length of stay ≥ 7 days before infection onset (Table 2). Cases with TEM-SHV Ent infection were less likely than controls to have a urinary tract infection, infection with *E. coli* or be located on the inpatient ward at the time of infection.

The mean length of stay of before infection onset for TEM-SHV cases was 32.7 days compared to 11.6 days for controls ($p=0.01$) and mean length of stay after infection onset was 34.9 days for cases and 14.2 days for controls ($p<0.001$). There were no differences in mortality.

On multivariable analysis (Table 3), children with TEM-SHV Ent infections were more likely to have had recent inpatient healthcare before infection onset (OR 8.2), yet were often diagnosed in the outpatient clinic setting (OR 25.6). Having a gastrointestinal comorbid condition (OR 23.7) or renal comorbid condition (OR 4.2) also were associated with TEM-SHV Ent infection. Children with TEM-SHV Ent infections were less likely to be located in the NICU at the time of infection onset (OR 0.036). There were no differences in race, gender, residential neighborhood, antibiotic exposure, or indwelling devices after controlling for other factors.

DISCUSSION

In the current study, we used a case-control study design to identify factors associated with TEM- and SHV-type ESBL-producing Enterobacterales (TEM-SHV Ent) infections in children and further describe outcomes associated with these multi-drug resistant infections in pediatric patients cared for in three medical centers in Chicago. We additionally linked resistance phenotypes with the genetic determinants of extended-spectrum cephalosporin resistance and assessed strain relatedness. Our analysis allowed for an important update on the clinical and molecular epidemiology of TEM-SHV Ent, because little is known about the current status.

The dramatic rise in ESBL-producing Enterobacterales is primarily due to the global expansion of community-acquired CTX-M-type ESBL-producing *E. coli* which began in the 1990s, and was mainly due to the emergence of ST131-H30 strains of $bla_{\text{CTX-M-15}}$ *E. coli*[3]. Prior to the emergence of $bla_{\text{CTX-M}}$ in the U.S., infections with ESBL-producing bacteria were due primarily to $bla_{\text{TEM-ESBL}}$ and $bla_{\text{SHV-ESBL}}$ in *E. coli* and *K. pneumoniae*, the majority of which were healthcare-associated[7]. After the emergence of $bla_{\text{CTX-M}}$, co-existence of these bla_{ESBL} genes led to even higher levels of resistance, and an increase in the circulation of Enterobacterales harboring mobile genetic elements associated with multiple antibiotic resistance genes and virulence factors causing invasive infections in community and healthcare settings[20–22].

As seen in adults, there is now a predominance of ST131 *E. coli* harboring $bla_{\text{CTX-M}}$ among children with ESBL-producing Enterobacterales infection[9, 23]. In comparison, in our previous studies of MDR Enterobacterales in children, we found significant diversity in the genetic determinants associated with antibiotic resistance in clinical isolates[9]. Our analyses of host factors and exposures (associated with $bla_{\text{CTX-M-9}}$ producing Ent and plasmid-mediated fluoroquinolone-resistant Ent infections) revealed that there are genetic and geospatial links to MDR in this pediatric population[18, 19, 24].

In the current study, we similarly found diversity in genera and strain types associated with TEM-SHV Ent infections and we hypothesize that there is significant horizontal gene transfer occurring among the Ent genera. Intriguingly, we found that the widely circulating ST131 *E. coli* known for carriage of $bla_{\text{CTX-M}}$ also solely harbor $bla_{\text{TEM-ESBL}}$ and $bla_{\text{SHV-ESBL}}$, which account for a subset ESBL-producing *E. coli* infections in children. However, the clinical epidemiology of TEM-SHV Ent suggests that overall, these infections continue to be associated with exposure to inpatient healthcare settings and occur in patients

with chronic conditions, in particular those with gastrointestinal or renal comorbidities. We did not find any differences in race, gender, residential neighborhood, antibiotic exposure or indwelling devices after controlling for other factors.

Interestingly, pediatric patients commonly presented in outpatient settings at the time of infection onset suggesting prolonged colonization with TEM-SHV Ent. Prolonged colonization with MDR Ent is a finding noted in previous pediatric studies, where children once colonized with MDR Ent were colonized for months to years[25]. This is worrisome from a public health perspective, as children may be serving as silent reservoirs for dissemination of MDROs. Transmission of MDROs in family and outpatient clinical settings is an area that needs further study.

Additionally, often as in the case of other MDROs, TEM-SHV Ent infections were associated significantly with worse outcomes in children, e.g. extended hospital stays compared to controls (34.9 days versus 14.2 days), which is in turn associated with increased healthcare costs[26]. However, we did not find any significant differences in mortality between cases and controls.

We acknowledge that our study has limitations. This is a retrospective study design with a relatively small sample size in a single metropolitan area, selection bias and lack of impact generalizability may be present. However, this bias is potentially lessened by the pooling of data from three centers which serve diverse populations and environments throughout the 3rd largest metropolitan area in the U.S. Additionally, the smaller sample sizes in pediatric ESBL Ent studies are related to the overall low prevalence of these organisms in children in most U.S. areas (1–3%), including in the Chicago and the Midwest region[25, 27, 28]. Nevertheless, the U.S. Centers for Disease Control and Prevention (CDC) 2019 Antibiotic Resistance Threats in the U.S. Report and national studies of ESBL Ent indicate an increase in prevalence of these menacing organisms in adults and children during the last decade. ESBL Ent are a growing threat that requires further evaluation[1, 6, 7, 24].

Conclusion

TEM-SHV Ent are a diverse group of organisms associated with infection in children and most commonly are linked with exposure to inpatient healthcare settings and occur principally in children with chronic conditions. However, children may present with these infections initially in outpatient clinical settings. Clinicians should be aware of the potential increased risk for TEM-SHV Ent infections in children with gastrointestinal and renal comorbid conditions and the association with prolonged hospital stays.

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TABLE 1

CHARACTERISTICS OF ENTEROBACTERALES HARBORING TEM- and SHV-type ESBL GENES

Variable[a]	TEMSHV Ent
Patient	n=38
Organism[b]	
Klebsiella spp.	13 (34.2)
Escherichia coli	12 (31.6)
Serratia marcescens	5 (13.2)
Proteus mirabilis	4 (10.5)
Enterobacter spp.	4 (10.5)
Source	
Urine	20 (52.6)
Respiratory	10 (26.3)
Other[c]	5 (13.2)
Blood	3 (7.9)
Co-Antibiotic Resistance	
Trimethoprim/Sulfamethoxazole	17 (44.7)
Gentamicin	17 (44.7)
Tobramycin	20 (52.6)
Amikacin	0 (0)
Tetracycline[d]	12 (60.0)
Nitrofurantoin[e]	9 (47.4)
Fluoroquinolone	13 (34.2)
Resistant to 3 or more antibiotic classes	22 (57.9)
Phylogenetic group of *E. coli*	n=12
B2	8 (67)
D	2 (17)
A	1 (8)
Indeterminate	1 (8)

[a] Values represent n (%). Abbreviations: Ent, Enterobacterales, TEMSHV, TEM and SHV-type ESBLs

[b] One isolate studied per patient; *Klebsiella* spp. were *K. pneumoniae* (9) and *K. oxytoca* (4); *Enterobacter* spp. were *E. cloacae* (3) and *E. vulneris* (1)

[c] Other sources include: abscess, wound, peritoneal, and abdominal sources

[d] Tetracycline, n-tested = 20

[e] Nitrofurantoin, n-tested = 19

TABLE 2

BIVARIATE ANALYSIS OF DEMOGRAPHICS AND FACTORS ASSOCIATED WITH TEM-SHV ENTEROBACTERALES INFECTION

Characteristic[a]	TEM-SHV[b] Infection	Non-TEM-SHV Infection[c]	p value
Patient	n=38	n=114	
Male Gender	20 (52.6)	39 (34.2)	0.04
Organism[b]			
Klebsiella sp.	13 (34.2)	20 (17.5)	0.03
E. coli	12 (31.6)	68 (59.6)	0.003
Serratia marcescens	5 (13.2)	5 (4.4)	0.07
Proteus sp.	4 (10.5)	3 (2.6)	0.08
Enterobacter sp.	4 (10.5)	18 (15.8)	0.14
Source			
Urine	20 (52.6)	83 (72.8)	0.01
Respiratory	10 (26.3)	18 (15.8)	0.12
Other[c]	5 (13.2)	6 (5.3)	0.14
Blood	3 (7.9)	7 (6.1)	0.70
Location at Diagnosis			
Inpatient, non ICU	6 (15.8)	40 (35.1)	0.03
Outpatient Clinic	9 (23.7)	7 (6.1)	0.001
Emergency Room	6 (15.8)	21 (18.4)	0.68
Pediatric ICU	16 (42.1)	31 (27.2)	0.09
Neonatal ICU	1 (2.6)	15 (13.2)	0.08
Region of Residence[d]			0.08
Recent Health Care			
Inpatient Care	23 (60.5)	25 (21.9)	<0.0001
Outpatient Care[e]	7 (18.4)	54 (47.4)	0.002
No Recent Care	8 (21.1)	35 (30.7)	0.19
Recent Antibiotics			
Cephalosporins[f]	16 (42.1)	27 (23.7)	0.048
Fluoroquinolones[g]	6 (15.8)	3 (2.6)	0.003
TMP/SMX[h]	4 (10.5)	15 (13.2)	0.68
Indwelling Devices			
Central venous line	16 (42.1)	37 (32.5)	0.16
Gastrointestinal	21 (55.3)	38 (33.3)	0.02
Genitourinary	18 (47.4)	31 (27.2)	0.02
Respiratory	20 (52.6)	31 (27.2)	0.005

Characteristic[a]	TEM-SHV[b] Infection	Non-TEM-SHV Infection[c]	p value
Multiple (≥3)	23 (60.5)	42 (36.8)	0.006
Comorbid Conditions			
Gastrointestinal	31 (81.6)	28 (24.6)	<0.001
Neurologic	25 (65.8)	40 (35.1)	0.001
Pulmonary	22 (57.9)	37 (32.5)	0.003
Renal	19 (50)	36 (31.6)	0.03
Cardiovascular	11 (28.9)	25 (21.9)	0.22
Hematologic/Oncologic	8 (21.1)	18 (15.8)	0.21
Multiple (≥3)	31 (81.6)	53 (46.5)	0.002

[a] Values represent n (%) unless otherwise indicated.

[b] Abbreviation TEM-SHV, TEM- or SHV-type extended-spectrum beta-lactamase Enterobacterales infection

[c] Non-TEM-SHV Infection were children with infections due to Enterobacterales sensitive to extended spectrum cephalosporin antibiotics.

[d] Region of residence includes city region and neighboring suburbs

[e] Outpatient care includes care outside of routine child care visits and outpatient procedures.

[f] Includes previous exposure to extended-spectrum cephalosporins (ceftriaxone, ceftazidime, cefotaxime)

[g] Includes previous exposure to ciprofloxacin and levofloxacin

[h] Includes previous exposure to TMP-SMX, Trimethoprim-Sulfamethoxazole

TABLE 3

MULTIVARIABLE ANALYSIS OF FACTORS ASSOCIATED WITH TEM-SHV ENTEROBACTERALES INFECTIONS IN CHILDREN

Associated Factor with TEM-SHV Ent infection[a]	OR	95% CI	p-value
Outpatient Clinic Location at time of infection diagnosis	25.6	4.6, 142.1	0.0002
Gastrointestinal comorbid condition	23.7	6.9, 80.8	<0.001
Recent inpatient healthcare prior to infection onset	8.2	2.7, 25.3	0.0002
Renal comorbid condition	4.2	1.4, 12.6	0.01
NICU Location at time of infection diagnosis	0.036	0.003, 0.378	0.006

[a]Abbreviations, TEM-SHV, TEM- or SHV-type extended-spectrum beta-lactamase; Ent, Enterobacterales; NICU, Neonatal Intensive Care Unit