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The Prevalence and Molecular Epidemiology of Multidrug-Resistant Enterobacteriaceae Colonization in a Pediatric Intensive Care Unit

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Abstract

OBJECTIVE—To determine the prevalence and acquisition of extended-spectrum β -lactamases (ESBLs), plasmid-mediated AmpCs (pAmpCs), and carbapenemases (“MDR Enterobacteriaceae”) colonizing children admitted to a pediatric intensive care unit (PICU).

DESIGN—Prospective study.

SETTING—40-bed PICU.

METHODS—Admission and weekly thereafter rectal surveillance swabs were collected on all pediatric patients during a 6-month study period. Routine phenotypic identification and antibiotic susceptibility testing were performed. Enterobacteriaceae displaying characteristic resistance profiles underwent further molecular characterization to identify genetic determinants of resistance likely to be transmitted on mobile genetic elements and to evaluate relatedness of strains including DNA microarray, multilocus sequence typing, repetitive sequence-based PCR, and *hsp60* sequencing typing.

Results—Evaluating 854 swabs from unique children, the overall prevalence of colonization with an MDR Enterobacteriaceae upon admission to the PICU based on β -lactamase gene identification was 4.3% ($n = 37$), including 2.8% ESBLs ($n = 24$), 1.3% pAmpCs ($n = 11$), and

0.2% carbapenemases (n =2). Among 157 pediatric patients contributing 603 subsequent weekly swabs, 6 children (3.8%) acquired an incident MDR Enterobacteriaceae during their PICU stay. One child acquired a pAmpC (*E. coli* containing *bla*_{DHA}) related to an isolate from another patient.

Conclusions—Approximately 4% of children admitted to a PICU were colonized with MDR Enterobacteriaceae (based on β -lactamase gene identification) and an additional 4% of children who remained in the PICU for at least 1 week acquired 1 of these organisms during their PICU stay. The acquired MDR Enterobacteriaceae were relatively heterogeneous, suggesting that a single source was not responsible for the introduction of these resistance mechanisms into the PICU setting.

The global spread of multidrug-resistant (MDR) Entero-bacteriaceae continues to threaten children worldwide.^{1,2} MDR Enterobacteriaceae can be introduced into the intensive care unit (ICU) environment by colonized children and subsequently spread to other critically ill pediatric patients, resulting in devastating consequences. This is a particular concern with organisms producing extended-spectrum β -lactamases (ESBLs), plasmid-mediated AmpC β -lactamases (pAmpCs), and carbapenemases because genes encoding these enzymes are generally carried on mobile genetic elements, facilitating patient-to-patient transmission. These organisms have been implicated in a number of outbreaks in the ICU setting.^{3–7} Because of frequent transfer to and from acute-care facilities, pediatric patients hospitalized in the ICU may introduce and propagate the spread of resistant pathogens across a variety of healthcare settings.

Most reports regarding the molecular characterization of ESBLs, pAmpCs, and carbapenemases in children in the United States focus on clinical isolates. In a study at Seattle Children's Hospital from 1999 to 2007, 1% of isolates displayed broad-spectrum β -lactamase production, predominantly pAmpCs (*bla*_{CMY}) and ESBLs (*bla*_{TEM}).^{8,9} Similarly, 1% of *Escherichia coli* or *Klebsiella* spp. isolates recovered from children in Utah from 2003 to 2007 were ESBL producers.¹⁰ Investigators at Texas Children's Hospital found that ~ 7% of Enterobacteriaceae clinical isolates from 2010 to 2011 were ESBL producers, with CTX-M variants predominating.¹¹ The burden of colonization of MDR Enterobacteriaceae in US children admitted to critical care units and subsequent acquisition from the ICU environment has not been previously described. Unless colonization prevalence is periodically enumerated and appropriate control measures are implemented when necessary, we may continue to observe an increase in MDR Enterobacteriaceae infections among children, as there will be inadequate "source control." We sought to evaluate the prevalence and molecular characteristics of MDR Enterobacteriaceae (ie, ESBL, pAmpC, and carbapenemase) colonization upon PICU admission and the frequency of new MDR Enterobacteriaceae acquisition during PICU hospitalization in the absence of contact isolation precautions specific for these organisms.

METHODS

Study Setting and Participants

The Johns Hopkins Hospital contains a 40-bed PICU that routinely cares for children in Baltimore, Maryland, as well as the greater mid-Atlantic region hospitalized with life-threatening acute illnesses. Patients recovering from cardiothoracic surgery; solid organ transplant surgery; major neurosurgical; urologic and orthopedic surgeries; and ear, nose and throat surgery also receive their postoperative care in the unit. The Johns Hopkins Hospital PICU is the designated “shock trauma” and burn unit for critically injured children in the state of Maryland.

The unit is comprised entirely of single-patient rooms. Routine surveillance cultures are collected from the nares for methicillin-resistant *Staphylococcus aureus* (MRSA) and the rectal region for vancomycin-resistant *Enterococcus* (VRE) upon admission and weekly thereafter for all children admitted to the PICU. There is no routine surveillance for MDR Enterobacteriaceae in the PICU. Gowns and gloves are worn when entering the rooms of pediatric patients colonized or infected with organisms such as MRSA, VRE, *Clostridium difficile*, MDR Gram-negative organisms (from clinical isolates), and/or respiratory viruses. Hand hygiene and environmental cleaning compliance are monitored and reported to the unit at monthly intervals.

Identification of Multidrug-Resistant Gram-Negative Colonization

Rectal surveillance swabs (BD CultureSwab, Becton Dickinson Diagnostics, Sparks, MD) were obtained upon PICU admission and weekly thereafter until PICU discharge for all children admitted to the Johns Hopkins Hospital PICU between July 16, 2014, and January 15, 2015. The initial rectal swab was obtained on the day of PICU admission and subsequent weekly swabs were obtained every Wednesday for all patients until discharge from the PICU. Each swab was processed in real time and 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 underwent routine identification and antimicrobial susceptibility testing using the Phoenix Automated System (Becton Dickinson Diagnostics). Confirmatory testing of potential ESBLs and AmpCs using the ESBL Etest (bioMérieux, Durham, North Carolina) and AmpC Etest (bioMérieux), respectively occurred for Enterobacteriaceae with ceftriaxone MICs of 2 μ g/mL. Enterobacteriaceae resistant to any carbapenem (eg, ertapenem, meropenem, or imipenemcilastatin) were further characterized using the Modified Hodge Test (MHT) and/or the metallo- β -lactamase Etest (bioMérieux), as appropriate.

Detection of β -lactamase Genes

All MDR Enterobacteriaceae isolates resistant to ceftriaxone were further evaluated using molecular methods. If a child was colonized with an ESBL in addition to an AmpC-producing Enterobacteriaceae, that child was categorized as having an ESBL-producing Enterobacteriaceae. If a child was colonized with carbapenemase-producing

Enterobacteriaceae in addition to an ESBL and/or AmpC-producing Enterobacteriaceae, that child was categorized as having carbapenemase-producing Enterobacteriaceae.

Genomic DNA was extracted from isolates using the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA). The identification of β -lactamase-encoding genes in isolates was assessed utilizing a DNA microarray-based assay Check-MDR CT103XL kit (CheckPoints, Wageningen, Netherlands), according to the manufacturer's protocol.¹² The CheckPoints assay can detect the following β -lactamase genes: (1) ESBLs (CTX-M-1 group, CTX-M-2 group, CTX-M-8 & -25 group, CTX-M-9 group, TEM wild type, TEM-type ESBL, SHV wild type, and SHV-type ESBL and (2) pAmpCs (CMY I/MOX, ACC, DHA, ACT/MIR, CMY II, and FOX); and (3) carbapenemases (KPC, NDM, VIM, IMP, GES, GIM, SPM, and OXA-variants).

Multi-Locus Sequence Typing (MLST)

MLST is a nucleotide sequence-based approach for the characterization of bacteria that provides a highly discriminating typing system particularly for *E. coli* and *K. pneumoniae* associated with clonal outbreaks.^{13,14} Gene amplification and sequencing of 8 housekeeping genes of *E. coli* (*dinB*, *icdA*, *pabB*, *poB*, *putP*, *trpA*, *trpB*, and *uidA*) and 7 housekeeping genes of *K. pneumoniae* (*rpoB*, *gapA*, *mdh*, *pgi*, *phoE*, *infB*, and *tonB*) were performed as previously described,¹³⁻¹⁵ and allele and sequence types were determined according to the MLST database of the Institut Pasteur (<http://www.pasteur.fr/mlst>).

Repetitive Sequence-Based PCR (rep-PCR)

To assess clonal relatedness, rep-PCR was performed on *E. coli*, *K. pneumoniae*, and *Citrobacter* spp. isolates.¹⁶ Genomic DNA was extracted from bacterial isolates using an UltraClean Microbial DNA Isolation Kit (MO BIO Laboratories, Carlsbad, CA). PCR amplification was performed using a Diversi-Lab fingerprinting kit (bioMérieux). Rep-PCR amplicons were then separated by electrophoresis on microfluidic chips and analyzed with an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Resulting band patterns were compared using Pearson's correlation; isolates with >95% similarity were considered to be of the same strain type.

Molecular Typing for *Enterobacter* Species

Because MLST is only recently being used to characterize *Enterobacter* spp. and an accepted universal database does not exist, sequence typing of the highly conserved *hsp60* gene was used to evaluate the genetic relatedness of *Enterobacter* species, as previously described.^{17,18}

Phylogenetic Group Classification

All *E. coli* strains were assigned to 1 of the 4 main phylogenetic groups (A, B1, B2, or D) to illustrate evolutionary relatedness using a previously described multiplex PCR-based method.¹⁹

Protected Health Information

All swabs were given a de-identified number upon collection and were only linked with patient identifiers after the 6-month study period was completed. Neither clinical staff nor patients were aware of swab results; thus, identification of colonization with MDR Enterobacteriaceae did not impact isolation precautions or treatment decisions. Data were stored in a secure REDCap database and all data analysis was descriptive in nature. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, and a waiver of informed consent was granted.

RESULTS

Description of Cohort

A total of 854 admission rectal swabs were obtained from 859 unique children admitted to the PICU during the study period. The median age was 6 years (range, 1 month to 23 years) and 45% of children were female (Table 1). Approximately 27% of children were previously healthy. The median Pediatric Risk of Mortality III Score (PRISM III) upon admission was 5 (range, 1–49). Furthermore, 22% of the cohort was on contact isolation for reasons unrelated to the present study, as healthcare providers and patients were unaware of their MDR Enterobacteriaceae status based on study results. The median duration of the current PICU admission was 4 days (range, 1–143 days).

Overview of Phenotypic Analysis upon PICU Admission

The prevalence of MDR Enterobacteriaceae (based on a positive ESBL Etest, AmpC Etest, MHT, or metallo- β -lactamase Etest) isolated from admission swabs was 7.6% (n=65). ESBLs, AmpCs, and carbapenemases were identified in 2.8% (n=24), 4.4% (n=38), and 0.4% (n=3) of children, respectively (Table 1). The MDR Enterobacteriaceae identified included *E. coli* (n=29), *Enterobacter cloacae* (n=17), and *Citrobacter* species (n=11), *K. pneumoniae* (n=5), *Proteus mirabilis* (n=2), and *Morganella morganii* (n=1).

Overview of Genotypic Analysis upon PICU Admission

All isolates that were resistant to ceftriaxone underwent molecular analysis, regardless of the results of phenotypic testing. The overall prevalence of MDR Enterobacteriaceae colonization on admission based on genotypic testing was 4.3% (n=37). ESBLs, pAmpCs, and carbapenemases were identified in 2.8% (n=24), 1.3% (n=11), and 0.2% (n=2) of children, respectively (Table 2).

Overview of Phenotypic Analysis during the PICU Stay

According to phenotypic testing (eg, ESBL Etest, AmpC Etest, MHT, MBL Etest), from a total of 157 children who received a second rectal swab, 29 children (18.4%) acquired an incident MDR Enterobacteriaceae during their PICU stay with a median time to colonization of 9 days (Table 3).

Overview of Genotypic Analysis during PICU Stay

From 157 children who remained hospitalized in the PICU for at least 7 days, 6 children (3.8%) acquired an incident MDR Enterobacteriaceae during their PICU stay. These 6 children became colonized with the following organisms: (1) 1 *E. cloacae* isolate producing an ESBL (*bla*_{SHV-238}), (2) 1 *E. cloacae* isolate producing a carbapenemase, ESBL, and AmpC (*bla*_{ACT/MIR}), (3) 1 *E. cloacae* producing a carbapenemase (*bla*_{KPC-2}, *bla*_{SHV}, *bla*_{ACT/MIC}), (4) 1 *K. pneumoniae* isolate producing both an ESBL and AmpC (*bla*_{CTX-M-15}, *bla*_{CMY11}), (5) 1 *K. pneumoniae* isolate producing an ESBL (*bla*_{CTX-M-9}), and (6) 1 *E. coli* isolate producing an AmpC (*bla*_{DHA}).

ESBL-Producing Enterobacteriaceae

Figures 1 and 2 depict characteristics of *E. coli* and *K. pneumoniae* isolates producing ESBLs, respectively. Of the 27 ESBL-producing isolates, 25 (93%) carried a *bla*_{CTX-M} gene, with *bla*_{CTX-M-15} being the most commonly detected CTX-M-type gene (68%). All *E. coli* ESBL-producing isolates (n = 1), 3 of the 4 *K. pneumoniae* isolates, and 1 of the 2 *E. cloacae* isolates carried *bla*_{CTX-M} genes. The remaining *K. pneumoniae* and *E. cloacae* isolates contained *bla*_{SHV}-type corresponds to ST131 in Achtman's MLST. Co-expression of genes. The predominant circulating clonal strain was an ESBL and AmpC (*bla*_{CTX-M-15} and *bla*_{CMY II}) occurred in 1 ESBL-producing *E. coli* ST43 (Pasteur MLST scheme), which *E. coli* isolate and 1 *K. pneumoniae* isolate.

During the study period, 1 child acquired an incident ESBL/AmpC. She became colonized with a *K. pneumoniae* isolate carrying both *bla*_{CTX-M-15} and *bla*_{CMY II} genes 6 days after admission. Another patient became colonized with a *K. pneumoniae* carrying a *bla*_{CTX-M-9} 6 days after PICU admission, and a third patient became colonized with an *E. cloacae* harboring a *bla*_{SHV-238} 13 days after admission. All 3 of these children had underlying medical issues and had extensive antibiotic exposure during their time in the PICU. Their ESBL-producing isolates appeared unrelated to those identified in other children during the study period.

AmpC-producing Enterobacteriaceae

Based on the results of the AmpC Etest, 38 children (4.4%) had isolates producing AmpC- β -lactamases upon PICU admission. pAmpC β -lactamase genes were detected in *E. coli* (8 isolates), *M. morgani* (1 isolate), and *P. mirabilis* (2 isolates). Overall, 27 (71%) of these isolates, which included 15 *E. cloacae*, 11 *Citrobacter* spp., and 1 *K. pneumoniae*, were presumed to be chromosomally mediated AmpC-producing Enterobacteriaceae.

Based-on phenotypic characteristics, the majority of children with new MDR Enterobacteriaceae acquisition during their PICU stay became colonized with AmpC-producing organisms (n = 24). Of the 24 isolates, 22 appeared to have chromosomally mediated AmpC β -lactamase resistance (Table 2). Of the presumed chromosomally mediated AmpC hyperproducers detected, 14 (64%) were *E. cloacae*. Results of *hsp60* gene patterns for *Enterobacter* spp. evaluating relatedness of strains suggest that these isolates were not clonal. One child admitted for elective surgery became colonized with an *E. cloacae* producing a pAmpC (*bla*_{ACT/MIR}) on day 8 of his PICU stay. Also on day 8 of his PICU

stay, a different patient became colonized with an *E. coli* containing a *bla*_{DHA} gene that appeared identical to that of another pediatric patient colonized with this organism at the time of PICU admission. Both patients were hospitalized during the same time period and were on contact isolation for the duration of their hospital stays for reasons unrelated to the presence of MDR-Enterobacteriaceae. Neither child developed a clinical infection in the subsequent 12 months with these organisms.

Carbapenemase-Producing Enterobacteriaceae

One child was colonized with a metallo- β -lactamase-producing organism upon PICU admission, and this organism was confirmed to contain a carbapenemase-producing gene using molecular testing. This patient had recently received medical care in Kuwait and was colonized with a metallo- β -lactamase-producing *K. pneumoniae* ST14 that carried *bla*_{VIM-4}, *bla*_{CMY-4} genes, which had previously never been identified in a child hospitalized in the United States. Ultimately, this child succumbed to a ventilator-associated pneumonia from this organism.

Another pediatric patient was colonized with a KPC-3 producing *E. cloacae* identified upon hospital admission. This infant had a previous liver transplant and subsequently died of an intra-abdominal infection caused by this organism. Another 3 children had isolates that were MHT positive. On molecular analysis, 1 isolate carried *bla*_{ACT/MIR}, another carried *bla*_{CTX-M-15}, and a β -lactamase gene was not identified in the third. For the first 2 isolates, we assumed that they may have had a carbapenem-specific porin mutation in addition to their ESBL/AmpC-producing gene as both isolates were resistant to meropenem (minimum inhibitory concentrations of 4 μ g/mL and 8 μ g/mL, respectively). One child acquired a carbapenemase-producing *E. cloacae* after 12 days of hospitalization which carried *bla*_{KPC-2}, *bla*_{SHV} and *bla*_{ACT/MIR} genes. He subsequently died from septicemia related to an intra-abdominal infection from this organism.

DISCUSSION

Our study indicates that approximately 4% of children admitted to the PICU were colonized with MDR Enterobacteriaceae (based on β -lactamase gene identification) and an additional 4% of children who remained in our PICU for at least 1 week became colonized with these organisms during their hospital stay, with a median time to MDR Enterobacteriaceae acquisition of 9 days. This is the first study evaluating the results of active surveillance for MDR Enterobacteriaceae in critically ill children in the United States.

We decided to focus on ESBLs, pAmpCs, and carbapenemases because these β -lactamase mechanisms of resistance are generally carried on mobile genetic elements facilitating their spread in ICUs. These resistance mechanisms have been implicated in a number of outbreaks.³⁻⁷ Interestingly, in our study, only 1 transmission of an MDR Enterobacteriaceae occurred. We believe the low transmission rate may be due to good adherence to standard infection control practices. All of the patients in our study were hospitalized in private rooms. The nurse-to-patient ratio was consistently between one-to-one and one-to-two. There was an average of 91% hand hygiene compliance in the PICU during the study period. The incidences of both central line-associated bloodstream infections and catheter-

associated urinary tract infections in our PICU were well below their national pooled means during the months the study was conducted. There was only one incident infection with *Clostridium difficile* in the PICU during the study period. These data suggest that there may be limited spread of MDR Enterobacteriaceae in the critical care setting with good adherence to appropriate infection control practices.

In our cohort, only about 20% of pediatric patients were on contact isolation during the study period. Others have explored the utility of contact isolation for patients colonized with MDR Enterobacteriaceae in the non-epidemic setting. Tschudin-Sutter et al²⁰ evaluated the spread of ESBL-producing Enterobacteriaceae in a tertiary care institution. All patients hospitalized in the same room as a patient colonized or infected with ESBL-producing Enterobacteriaceae for at least 24 hours were screened for ESBL carriage. Transmission occurred in 1.5% of contact patients. The same group of investigators found that after discontinuing the policy of contact precautions for ESBL *E. coli*, transmissions remained below 3%.²¹ Similarly, Ohmagari et al²² found that the incidence of MDR Enterobacteriaceae did not change after the introduction of strict isolation practices. Han et al²³ evaluated the impact of a urine culture screening strategy for detecting ESBLs. Patients determined to be colonized or infected with ESBLs were placed on contact precautions. These investigators found that contact precautions did not impact nosocomial incidence rates with ESBL-producing pathogens when there was good compliance with standard precautions.

Traditional concerns about transmission of ESBLs focused on the healthcare setting, but more and more reports describe the community as an important reservoir for ESBLs.^{24–27} In our cohort, 24 of the 27 ESBLs (89%) detected were identified from admission rectal swabs. Of these, 41% belonged to ST131, and all admission isolates carrying ESBLs carried a *bla*_{CTX-M-type} gene. The rapid spread of ESBLs appears to be driven largely by the clonal expansion of ST131, with person-to-person transmission in the community being an important mode of spread.²⁸ ST131 appears to be efficiently transmitted in households. Madigan et al described 2 young children who presented to medical care for the treatment of ESBL infections from the same household.²⁹ On further evaluation, all 6 household members were identified as carrying the same *E. coli* ST131 strain. Genetically identical ESBL strains have also been recovered from the diapers of children in common daycare settings.³⁰

Carbapenem-resistant Enterobacteriaceae have been identified throughout the United States but are most prevalent in the mid-Atlantic region,³¹ which includes the state of Maryland where the present study took place. KPCs are the most prevalent carbapenemases identified in the United States, but both metallo- β -lactamases and OXA-types have been identified in a number of states, generally in patients who previously received medical care in foreign countries.³¹ The incidence of CRE among US children remains low. A recent study reported that the proportion of carbapenem resistance in clinical isolates in patients under 18 years of age is under 1%.³² Unlike ESBL-producing organisms, carbapenemase-producing organisms in US children have been limited to those with previous healthcare exposure.^{2,33}

Our study has a number of limitations to consider. First, as this was a single-center study, the prevalence and molecular mechanisms of MDR Enterobacteriaceae in our patient population may not be generalizable to patients hospitalized in other PICUs. Second, we only screened for MDR Enterobacteriaceae carriage in the rectal region, where we believe the largest burden of Enterobacteriaceae exists. We may have underestimated the prevalence of these organisms if some children were colonized with these organisms in other body sites. Third, we did not evaluate for non- β -lactamase mechanisms of resistance such as those that relate to reduced outer membrane permeability, as we preferred to focus on resistance mechanisms with a high predilection for patient-to-patient transmission. Additionally, although the CheckPoints multiplex assay employed in our study includes a comprehensive list of β -lactamases, as with all available microarrays, it can only evaluate for previously characterized β -lactamase-producing genes included in the assay. Finally, as the duration of PICU stay for most children was relatively short, we realize that many children may not have had an “opportunity” to acquire an MDR Enterobacteriaceae. Although this is a limitation, the median PICU stays of our patients is representative of average PICU stays in US hospitals.^{34,35}

Despite these limitations, our study suggests that the transmission of MDR Enterobacteriaceae may be low in an acute care setting with rigorous adherence to standard precautions. A single assay to screen for all β -lactamase genes is not currently available. Even if such an assay existed, it would not detect common mechanisms of resistance seen in non-fermenting Gram-negative organisms (eg, loss or alterations of outer membrane porins, upregulation of efflux pumps, etc.) or resistance mechanisms common to Gram-positive organisms. Because no single, user-friendly, inexpensive, rapid screening method will detect all of the resistance mechanisms found in critical care units, it may be more prudent to focus efforts on reinforcing standard infection control practices.

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FIGURE 1.

Genetic relatedness of *Escherichia coli* isolates from children admitted to a pediatric intensive care unit. For isolates identified as not available (N/A) for multilocus sequence typing (MLST), no match was identified in the MLST database. Phenotype is indicated according to results of ESBL Etest, AmpC Etest, modified Hodge test, or metallo- β -lactamase Etest.

FIGURE 2.

Genetic relatedness of *Klebsiella pneumoniae* isolates from children admitted to a pediatric intensive care unit. For isolates identified as not available (N/A) for multilocus sequence typing (MLST), no match was identified in the MLST database. Phenotype is indicated according to results of ESBL Etest, AmpC Etest, modified Hodge test, or metallo- β -lactamase Etest.

TABLE 1

Characteristics of 854 Children Admitted to the Pediatric Intensive Care Unit (PICU) During a 6-Month Period

Variable	No. (%)
Age, median yr (range)	6 (0.08–23)
Female	379 (44.4)
Race^a	
White	349 (40.9)
Black	337 (39.5)
Asian	45 (5.3)
Latino	64 (7.5)
Middle Eastern	28 (3.3)
PRISM score on day of PICU admission, median (range)	5 (1–49)
Duration of time from hospital admission to PICU admission, median d (range)	0 (0–365)
Reason for current PICU admission^b	
Sepsis	98 (11.5)
Burn	9 (1.1)
Trauma	73 (8.5)
Respiratory failure	129 (15.1)
Cardiac arrest	18 (2.1)
Liver failure	8 (0.9)
Gastrointestinal hemorrhage	6 (0.7)
Metabolic derangements	69 (8.0)
Exchange transfusion	8 (0.9)
General surgical procedure	91 (10.7)
Neurosurgical procedure	54 (6.3)
Ophthalmology or ear, nose, or throat procedure	26 (3.0)
Cardiac procedure	64 (7.5)
Urological procedure	18 (2.1)
Orthopedic procedure	47 (5.5)
Plastic surgery procedure	19 (2.2)
Pre-existing medical conditions prior to PICU admission	
Previously healthy (no previous hospitalizations)	230 (26.9)
Congenital heart disease	54 (6.3)
End-stage renal disease (receiving dialysis)	18 (2.1)
End-stage liver disease	2 (0.2)
Solid organ transplantation	11 (1.3)
Hematopoietic stem-cell transplantation within the previous 12 mo	19 (2.2)
Chemotherapy within the previous 6 mo ^c	32 (3.7)
Chronic steroid use or immunotherapy ^d	26 (3.0)
Previous healthcare exposure within the 6 mo prior to current PICU admission	

Variable	No. (%)
Healthcare in a foreign country	27 (3.2)
Total no. of PICU days, median (range)	0 (0–34)
Total no. of hospital days, median (range)	0 (0–180)
Total antibiotic days, median (range)	0 (0–279)
Multidrug-resistant organism colonization or infections within the 6 months prior to the current PICU admission^e	
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	9 (1.1)
Vancomycin-resistant Enterococcus (VRE)	8 (0.9)
Multidrug-resistant <i>Pseudomonas aeruginosa</i>	8 (0.9)
Multidrug-resistant <i>Acinetobacter baumannii</i>	2 (0.2)
Extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL)	10 (1.2)
Carbapenem-resistant Enterobacteriaceae (CRE)	2 (0.2)

^aRace included only if a single race was identified in the medical records.

^bPatients categorized into a single reason for admission.

^cPatients who received both chemotherapy and hematopoietic stem cell transplantation (HSCT) only categorized as HSCT.

^dExcludes patients receiving immunotherapy for solid organ transplant, HSCT, or chemotherapy.

^eMultidrug-resistant (MDR) *P. aeruginosa* defined as *P. aeruginosa* nonsusceptible to at least 1 drug in at least 3 of the following 5 categories: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin-tazobactam; MDR *A. baumannii* defined as *A. baumannii* nonsusceptible to at least 1 drug in at least 3 of the following 6 categories: Extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin-tazobactam, or ampicillin-sulbactam (http://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf).

Multidrug-Resistant Enterobacteriaceae Recovered Upon Pediatric Intensive Care Unit Admission Among 854 Children During a 6-Month Period

TABLE 2

Organism	Extended-Spectrum β -Lactamases		AmpC β -Lactamases		Carbapenemases	
	ESBL Phenotype ^d	ESBL Encoding Genes Identified	AmpC Phenotype ^b	AmpC Encoding Genes Identified	Carbapenemase Phenotype ^c	Carbapenemase Encoding Genes Identified ^d
<i>Citrobacter</i> spp.	Not applicable	0	11	0	0	0
<i>Enterobacter cloacae</i>	Not applicable	1 ^e	15	0	1	1 ^k
<i>Escherichia coli</i>	21	21 ^f	8	8 ^h	0	0
<i>Klebsiella pneumoniae</i>	2	2 ^g	1	0	2	1 ^l
<i>Morganella morganii</i>	Not applicable	0	1	1 ⁱ	0	0
<i>Proteus mirabilis</i>	0	0	2	2 ^j	0	0
Total	24	24	38	11	3	2

^aExtended-spectrum β -lactamases (ESBLs) Etest positive (only performed on *E. coli*, *Klebsiella* spp., and *P. mirabilis*)^bAmpC Etest positive.^cModified Hodge test or Metallo- β -lactamase Etest positive.^dIf an isolate contained an ESBL gene in addition to an AmpC gene, it was categorized as an ESBL. If an isolate contained an ESBL and/or AmpC gene in addition to a carbapenemase gene, it was categorized as a carbapenemase.^e1 isolate carried blaCTX-M-15.^f12 isolates carried blaCTX-M-15. 2 isolates carried blaCTX-M-15 and blaTEM. 1 isolate carried blaCTX-M-15 and blaCMY II. 1 isolate carried blaCTX-M-2. 3 isolates carried blaCTX-M-9. 2 isolates carried blaCTX-M-32.^g1 isolate carried blaCTX-M-15. 1 isolate carried blaSHV-238s, blaSHV-240k.^h1 isolates carried blaCMY II. 1 isolate carried blaDHA.ⁱ2 isolates carried blaCMY II.^j1 isolate carried blaDHA.^k1 isolate carried a blaKPC-3.^l1 isolate carried blaVIM-4 and blaCMY-4.

TABLE 3

Incident Multidrug-Resistant Enterobacteriaceae Recovered From 157 Children Who Stayed More Than 1 Week in a Pediatric Intensive Care Unit Over a 6-Month Period

Organism	Extended-Spectrum β -Lactamases		AmpC β -Lactamases		Carbapenemases	
	ESBL Phenotype ^a	ESBL Encoding Genes Identified	AmpC Phenotype ^b	AmpC Encoding Genes Identified	Carbapenemase Phenotype ^c	Carbapenemase Encoding Genes Identified ^d
<i>Citrobacter</i> species	Not applicable	0	6	0	0	0
<i>Enterobacter cloacae</i>	Not applicable	1 ^e	15	1 ^g	1	1 ⁱ
<i>Escherichia coli</i>	0	0	2	1 ^h	1	0
<i>Klebsiella pneumoniae</i>	2	2 ^f	0	0	0	0
<i>Morganella morganii</i>	Not applicable	0	0	0	1	0
<i>Serratia marcescens</i>	Not applicable	0	1	0	0	0
Total	2	3	24	2	3	1

^aExtended-spectrum β -lactamases (ESBL) Etest positive (only performed on *E. coli*, *Klebsiella* spp., and *P. mirabilis*).

^bAmpC Etest positive.

^cModified Hodge test or metallo- β -lactamase Etest positive.

^dIf an isolate contained an ESBL gene in addition to an AmpC gene, it was categorized as an ESBL. If an isolate contained an ESBL and/or AmpC gene in addition to a carbapenemase gene, it was categorized as a carbapenemase.

^e1 isolate carried blaSHV-238.

^f1 isolate carried blaCTX-M-15 and blaCMY II and 1 isolate carried blaCTX-M-9.

^g1 isolate carried blaACT/MIR.

^h1 isolate carried blaDHA.

ⁱ1 isolate carried blaKPC-2, blaSHV, and blaACT/MIR.