Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae in Children: Old Foe, Emerging Threat

Paul J. Lukac,1 Robert A. Bonomo,3,4,5,6 and Latania K. Logan1,2,3

1Department of Pediatrics, and 2Section of Pediatric Infectious Diseases, Rush University Medical Center, Rush Medical College, Chicago, Illinois; 3Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Departments of 4Medicine, 5Pharmacology, and 6Molecular Biology and Microbiology, Case Western Reserve School of Medicine, Cleveland, Ohio

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae present an ever-growing burden in the hospital and community settings, across all ages and demographics. Infections due to ESBL-containing pathogens continue to be associated with significant morbidity and mortality worldwide. With widespread empiric broad-spectrum β-lactam use creating selective pressure, and the resultant emergence of stable, rapidly proliferating ESBL-producing clones with continued horizontal gene transfer across genera, addressing this issue remains imperative. Although well characterized in adults, the epidemiology, risk factors, outcomes, therapies, and control measures for ESBL-producing bacteria are less appreciated in children. This analysis provides a brief summary of ESBL-producing Enterobacteriaceae in children, with a focus on recent clinical and molecular data regarding colonization and infection in nonoutbreak settings.

Keywords. child; β-lactamases; drug resistance; Enterobacteriaceae infections; epidemiology.

Multidrug-resistant (MDR) gram-negative bacterial infections pose one of the most vexing challenges in infectious diseases today. The β-lactamases, a potent family of enzymes that effectively hydrolyze the β-lactam ring, rendering antibiotics ineffective, remain a major factor in the rise of antibiotic resistance in gram-negative bacteria. β-lactamases have existed for millennia as innate defense mechanisms in environmental bacteria [1, 2].

The extended-spectrum β-lactamases (ESBLs), first described in 1983 in Germany, arose from a single-nucleotide polymorphism in the blaSHV gene that resulted in a novel, transferable β-lactamase with an altered substrate specificity to oxyimino-cephalosporins [1–3]. ESBLs confer resistance to penicillins, cephalosporins, and monobactams, but not to cephemycins or carbapenems. ESBLs are inhibited by the commercially available β-lactam inhibitors (clavulanic acid, tazobactam, and sulbactam) [2]. As of this writing, there are >1600 known β-lactamases, a list that is rapidly expanding [4]. The clinical impact of ESBL-producing pathogens on morbidity and mortality in infectious diseases in adults, as well as their economic burden, are well documented [5, 6].

Unfortunately, ESBL-producing bacteria in children have come to the forefront of emerging antibiotic-resistant bacteria. Options for treatment of MDR gram-negative bacterial infections are generally limited, and given that fewer antibiotics are approved for use in children, as well as the perpetual dearth of pediatric drug trials, the problem is critically important to address [7]. This review will explore the global epidemiology, molecular characteristics, treatment, and management of ESBL-producing Enterobacteriaceae in children.

CHARACTERIZATION OF ESBLs

Historically, there are 2 classification systems for β-lactamases, as summarized in Table 1 [2]. Presently, the
Clinical and Laboratory Standards Institute (CLSI) guidelines are used for phenotypic identification of ESBL-producing Enterobacteriaceae [8]. In a 2010 revision, CLSI lowered minimum inhibitory concentration (MIC) breakpoints, with cefotaxime and ceftriaxone reported as resistant at MICs ≥4 µg/mL [8].

In the mid- to late 1980s, TEM- and SHV-type ESBL-producing bacteria were largely responsible for the dissemination of ESBLs and often spread as single clones associated with hospital outbreaks; community-acquired ESBL infections were uncommon [9]. However, the molecular epidemiology of ESBLs in Enterobacteriaceae changed dramatically in the late 1990s with the recognition of community- and hospital-acquired CTX-M–type ESBLs [10,11]. CTX-M–type ESBLs are named for their increased activity against cefotaxime [3]. The advent of next-generation sequencing and precision typing methods expanded our understanding of the molecular epidemiology of ESBL-producing bacteria and revealed widespread dissemination of Escherichia coli sequence type (ST) 131 bearing CTX-M–type ESBLs [11,12]. This clone is the “driving force” behind the current ESBL pandemic, and circulating CTX-M strains often harbor multiple co-resistance genes such as to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, and fluoroquinolones, thus limiting therapeutic options [11].

There are several other types of β-lactamases that confer resistance to expanded-spectrum cephalosporins that are beyond the scope of this review, although plasmid-mediated AmpC cephalosporinases (AmpC) in Enterobacteriaceae bear mention. Plasmid-based blaAmpC (PB AmpC) genes are less commonly described in the literature, but are increasingly found in E. coli and Klebsiella species [13]. PB AmpC can be phenotypically mischaracterized as ESBLs, although, unlike ESBL-producing bacteria, AmpC-producing bacteria are not generally inhibited by β-lactamase inhibitors, are nonsusceptible to cephamycins, and do not confer resistance to cefepime [2,13]. CMY-2 is the most widely distributed PB AmpC and has been recognized as a significant cause of cephalosporin resistance in children [13,14].

### OVERVIEW OF THE EPIDEMIOLOGY OF ESBL INFECTIONS

Multiple global surveillance programs (SMART, The Meropenem Yearly Susceptibility Test Information Collection, SENTRY) document an expanding landscape with increasing ESBL prevalence worldwide [15–20]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) followed resistance patterns of gram-negative bacteria in 92 086 intra-abdominal infections and 24 705 urinary tract infections (UTIs) worldwide from 2002 to 2011 [16]. Significant increases in infections by ESBL-producing bacteria were found across all studied continents, with the exception of Africa. More than 40% of clinical isolates from Asia were ESBL producers in 2011. Additionally, Latin America, the Middle East, Africa, Europe, and the South Pacific displayed a prevalence of ESBL of approximately 10%–35% [16]. SENTRY, a microbial surveillance system, recently reported data from 2012 on ESBL E. coli, Klebsiella species, and Proteus mirabilis collected from 72 hospitals across 9 US census regions and found that 12.2% (701/5739) of clinical isolates displayed an ESBL phenotype [19].

The predominant genotypes in the SENTRY study were CTX-M group 1 (which includes CTX-M-15) and SHV-type enzymes, accounting for 43.2% (303) and 25.1% (176) of all ESBLs, respectively [19]. Additionally, 62.9% of isolates carried ≥2 bla genes. The dissemination of CTX-M within the United States is consistent with worldwide data trends. A detailed analysis of 1093 phenotypic ESBL-producing isolates obtained during the 2008–2009 SMART study confirmed an increasing global trend toward CTX-M dominance with 93.6% (683) and 65.6% (223) of all ESBL E. coli and Klebsiella pneumoniae, respectively, found to carry blaCTX-M [21]. CTX-M-15 accounted for 67% of all CTX-M isolates. The study also noted a large diversity of enzymes, with the emergence of several new variants [21].

### RISK FACTORS FOR ESBL ACQUISITION IN ADULTS

Risk factors for ESBL acquisition in adults are well characterized [3,22]. The increase in community-acquired ESBL infections has led to recognition of concomitant high rates of fecal carriage (colonization) with ESBL-producing organisms. Currently, several countries are documenting ESBL colonization rates of >10% (and as high as 69% in rural Thailand) [23]. Risk factors associated with ESBL fecal carriage are complex and include exposure to farm animals, retail animal products, and companion animals; foreign travel; international adoption; recent UTI; and recent antibiotic treatment [24–27]. Interestingly, intrafamilial transmission of ESBL-producing bacteria between household

---

### Table 1. Classification Schema of β-Lactamase Genes

<table>
<thead>
<tr>
<th>Ambler Classification</th>
<th>Bush/Jacoby Classification</th>
<th>Notable Enzyme Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A 2a, 2b, 2be, 2br, 2ber, 2c, 2ce, 2e, 2f</td>
<td>TEM, SHV, CTX-M, PER</td>
<td>ESBLs—TEM, SHV, CTX-M, PER</td>
</tr>
<tr>
<td>Class B 3a, 3b</td>
<td>Carbapenemases—IMP, VIM, NDM</td>
<td>Carbapenemases—IMP, VIM, NDM</td>
</tr>
<tr>
<td>Class C 1, 1e</td>
<td>Cephalosporinases—AmpC</td>
<td>Cephalosporinases—AmpC</td>
</tr>
<tr>
<td>Class D 2d, 2de, 2df</td>
<td>OXA Carbapenemases—OXA</td>
<td>OXA Carbapenemases—OXA</td>
</tr>
</tbody>
</table>

Source: Bush and Jacoby [2].

Abbreviations: ESBL, extended-spectrum β-lactamase; IMP, active on imipenem metallo-β-lactamase; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.
members is more commonly being described [23, 26]. Despite heightened awareness and various control measures, mortality rates associated with ESBL bacterial infection remain high [5, 6, 28, 29].

RISK FACTORS FOR ESBL ACQUISITION IN CHILDREN

Early reports regarding risk factors for infection or colonization by ESBL-producing bacteria in children were from pediatric intensive care units (PICUs) and neonatal intensive care units (NICUs). These reports have most often described single-unit outbreaks [30, 31] and note various factors contributing to spread, such as bacterial transfer via artificial nails of hospital staff and cockroach infestation as vectors [32, 33]. In nonoutbreak settings, healthcare-related risk factors independently associated with neonatal ESBL colonization and infection include younger gestational age, low birth weight, prolonged mechanical ventilation, length of hospital stay, invasive devices, and antibiotic use [34–37]. Additionally, in a 2-center prospective surveillance study of 209 very low birth weight infants in Germany, the incidence of ESBL colonization (as determined by rectal cultures using chromogenic medium selective for ESBL-producing organisms) was 6-fold higher for infants born to mothers colonized by ESBL-producing E. coli vs noncolonized mothers (P < .001) [38]. Five neonates (including 1 set of triplets) were noted to share identical ESBL-producing strains with their mothers, suggesting that maternal–child transmission may be an underrecognized risk factor for newborn colonization. Most studies of ESBL risk factors in children beyond the neonatal period are case-control, single-center studies, and parallel risk factors in adults [24, 39–41]. However, a 2-center case-control study of ESBL risk factors in children from Chicago, Illinois, identified underlying neurological conditions as a potential risk factor specific to children [42], which was also noted as a risk factor in a case-control study of community-acquired UTI in Taiwanese children [43]. Other associations specific to ESBL UTIs in children include urinary tract anomalies, UTI prophylaxis, and infection with Klebsiella species [27, 43, 44].

OUTCOMES

As with adults, ESBL infections in children are associated with longer hospital stays, frequent complications, and increased mortality, at higher than adult rates in certain regions [28, 39, 40, 45]. The clonal CTX-M E. coli strains belonging to phylogenetic groups (e.g., B2) often express extraintestinal pathogenic E. coli virulence factors that are associated with serious, invasive infections [46]. In a report of 113 Tanzanian children with sepsisemia, the fatality rate in children with ESBL-producing Enterobacteriaceae was 71% vs 39% in those with non-ESBL isolates (P < .039) [28]. In a cohort of Korean children, 26.7% (12/45) of children with ESBL-producing bacteria bloodstream infection died compared with 5.7% (5/87) mortality in cases with non-ESBL-producing bacteria (P < .001) [47]. Inadequate empiric regimens and poor health status of these children likely played a significant role in worse overall study outcomes [47].

PREVALENCE OF COLONIZATION AND INFECTION, AND MOLECULAR CHARACTERIZATION OF ESBL IN CHILDREN BY REGION

North America

Studies in North America describe (compared to adults and other continents) rising rates of ESBL-producing E. coli with late emergence and subsequent predominance of CTX-M-type ESBLs. In 2014, the largest study of ESBL trends among children to date was published [48]. Of 368 398 pediatric clinical isolates characterized in the United States from 1999 to 2011, the number of ESBL-producing Enterobacteriaceae (total 1734) more than tripled, with ESBLs representing only 0.28% of all E. coli, K. pneumoniae, and P. mirabilis in children from 1999 to 2001 and later increasing to 0.92% of all isolates in 2010–2011. Apparently, regional variability, with most ESBL isolates coming from West and South Atlantic regions, is present [48]. This observation is consistent with prevalence data from single-center US studies [14, 41, 42, 49, 50].

A more concerning finding in this study was that 74% of ESBLs in children were MDR pathogens, exhibiting resistance to ≥3 antibiotic classes. Individually, there was 83% resistance to piperacillin-tazobactam, 66% resistance to TMP-SMX, and 54% resistance to fluoroquinolones [48]. In 2008–2010, the SMART study of North American children described the highest rates of pediatric ESBL infections, where ESBL E. coli and K. pneumoniae accounted for 4% (3/80) and 25% (4/16) of intra-abdominal infections, respectively, although a small sample size of K. pneumoniae isolates was noted in North America and across all regions [20].

Regrettably, reports regarding the molecular characterization of ESBLs are mainly single-center experiences (Table 2). In a study conducted at Seattle Children’s Hospital from 1999 to 2007, 86 of 8048 (1.1%) isolates displayed broad-spectrum β-lactam resistance. Of characterized ESBL strains, 26 of 39 (67%) carried blaTEM-type ESBLs, 13 (33%) had blaCTX-M enzymes, and 5 (13%) contained both [49]. An increase in broad-spectrum β-lactam resistance during the study period was due to the emergence of the PB AmpC β-lactamase CMY-2 in 36 of 86 (41.9%) isolates (relative risk, 9.11; P = .001). Community-acquired ESBLs in otherwise healthy children accounted for 22% of infections [49]. A substudy from the same investigators found that 16% (8/49) of isolates were the CTX-M-15–producing...
Table 2. Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae in Children: Epidemiology, Molecular Characterization, bla Genes

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Study</th>
<th>Study Years</th>
<th>Mode of Acquisition</th>
<th>Demographics: Clinical Unit, % Female</th>
<th>Source of Isolate</th>
<th>No. of ESBL-Producing Isolates(a)</th>
<th>Dominant ESBL Genotype (% of Isolates)</th>
<th>Predominant ESBL Enzyme(b) (% of Isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Bedenic et al (2012) [51]</td>
<td>2002–2003</td>
<td>NS</td>
<td>All, 66.6</td>
<td>77</td>
<td>bla(<em>{TEM}) (74), bla(</em>{TEM})</td>
<td>SHV-5 (66.2), SHV-2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Wójkowska-Mach et al (2013) [54]</td>
<td>2009</td>
<td>HA</td>
<td>NICU, 46.9</td>
<td>47</td>
<td>bla(<em>{ETX-M}) (89.4), bla(</em>{SHV})</td>
<td>CTX-M-3 (48.9), CTX-M-15 (27.6)</td>
<td></td>
</tr>
<tr>
<td>South/Central America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>Pereira et al (2013) [55]</td>
<td>2007–2010</td>
<td>HA</td>
<td>All, 48.5</td>
<td>11</td>
<td>bla(<em>{ETX-M}) (63.6), bla(</em>{SHV})</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Korea</td>
<td>Kim et al (2002) [47]</td>
<td>1993–1998</td>
<td>HA</td>
<td>All, 44.9</td>
<td>52</td>
<td>bla(<em>{TEM}) (57.7), bla(</em>{SHV}) (46.2)</td>
<td>TEM-52 (46.2), SHV-2a (40.4)</td>
<td></td>
</tr>
<tr>
<td>Africa/Middle East</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunisia</td>
<td>Réjiba et al (2011) [57]</td>
<td>2006</td>
<td>NS</td>
<td>All, NS</td>
<td>32</td>
<td>bla(<em>{ETX-M}) (96.9), bla(</em>{SHV}) (6.3)</td>
<td>CTX-M-15 (96.9), SHV-12 (6.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: All, pediatric multiunit experience; CA, community acquired; CSF, cerebrospinal fluid; ESBL, extended-spectrum β-lactamase; HA, hospital acquired; NICU, neonatal intensive care unit; NS, not specified.

\(a\) Number of plasmid-AmpC cephalosporinase producing isolates in brackets, when applicable.

\(b\) Plasmid-based AmpC cephalosporinase-producing isolates included, when applicable.
ST131 E. coli clone, suggesting introduction of this highly drug-resistant clone into their pediatric community in 2003 [14].

Similar to the experience in Seattle, a study of children in Texas during 2010–2011 reported that 94 of 1430 (6.6%) Enterobacteriaceae cultures were ESBL producers. CTX-M was documented in 74% (70/94) of the isolates, of which 80% (56/70) were CTX-M-15 and 17.1% (12/70) were CTX-M-14. TEM- and SHV-type ESBLs were found in 26 of 94 (28%) and 23 of 94 (24%) isolates respectively, and 25.5% encoded multiple bla genes. The CTX-M-15 ST131 clone accounted for 12.5% of the CTX-M-15–producing E. coli specimens, which suggests that a diverse mix of strains may account for the rise of ESBLs in children [50].

Increasingly, the association between fecal carriage in children and risk for subsequent infection with an ESBL Enterobacteriaceae is being reported [58]. In a prospective cohort study evaluating children aged 0.8–14.5 years with history of extended-spectrum cephalosporin-resistant Enterobacteriaceae infections, 17 of 27 (63%) children who had stool screening were found to be colonized with ESBL, and 18 of 105 (17%) children in the study developed 37 subsequent ESBL infections. Colonization persisted in some children for up to 4 years (range, 62–1576 days; median, 199 days), highlighting the potential for further community spread via colonization of household members of index cases [58].

Europe

A multicenter Parisian study from 1999 to 2003 provided an early glimpse into the emergence of ESBL-producing organisms in children. Whereas 23.2% of K. pneumoniae strains expressed an ESBL phenotype, only 1.4% of E. coli did likewise [59]. SENTRY data from 2004 described even higher pediatric rates, with ESBL production identified in 5.4% of E. coli and 21.2%–24.7% of Klebsiella isolates [15]. These data were comparable to the 6% prevalence of ESBL-producing E. coli in the more recent 2008–2010 SMART study of European pediatric intra-abdominal infections [20]. Particular to community-acquired ESBLs, UTI rates ranged from 3.8% to as high as 43% in European children with multiple genitourinary comorbidities [27, 44, 60, 61].

European studies of the molecular epidemiology of ESBL-producing isolates in children are primarily small, single-center cohort studies. However, overall trends are consistent with global shift to CTX-M–type ESBL dominance. In the early 2000s, SHV-5 was the most common ESBL in Europe, with SHV-12 predominating in some countries [53]. Data from pediatric studies done in Croatia during this period found that 74% (57/77) of ESBL E. coli UTI isolates carried SHV-type ESBLs (66% were SHV-5, whereas only 2.5% were CTX-M type); in Hungary, 77% (30/39) of pediatric ESBL Klebsiella clinical isolates were SHV-5–type ESBLs with the remaining isolates harboring TEM-1/SHV-12–type ESBLs [51,53]. By 2009, a study performed in a NICU in Poland showed that nearly 90% of all ESBLs were CTX-M producers, with CTX-M-3, CTX-M-15, and CTX-M-9 constituting 48.9%, 27.6%, and 12.7% of ESBLs, respectively [54]. The march of CTX-M into children mirrored the adult experience, although a higher variety of genotypes may account for the CTX-M surge than solely the CTX-M-15 ST131 clone. In a 2008–2012 report of ESBL-producing E. coli infections in French children, 16 of 36 (44%) community-acquired ESBLs were CTX-M-15, although CTX-M-14 was also relatively common, found in 11 of 36 (30.6%) clinical isolates. In healthcare-associated infections, CTX-M-15 accounted for 28.6% (6/21) of ESBLs. More than 60% of the B2 phylogenetic groups in both healthcare- and community-acquired infections belonged to the ST131 clone [52].

Several studies on increasing fecal carriage of ESBLs in healthy European children are published [62–65]. Intestinal carriage by ESBL-producing gram-negative bacteria in healthy French and Swedish children ranged from 2.9% to 6.7%, with CTX-M-15, CTX-M-14, and CTX-M-1 constituting the majority of ESBLs; evidence of transmission occurred between unrelated children in the preschool setting [64]. A much higher rate of colonization was recognized in a prospective cohort study of 125 healthy Spanish children, with 24% (30/125) of children colonized with 34 ESBL-producing strains. CTX-M-1 was the most common (8/19 [42%] CTX-M ESBLs), although significant carriage rates of SHV-12 (32%) and TEM-52 (6%) were noted [65].

South and Central America

The 2004 SENTRY study documented 9% prevalence of ESBL in E. coli and a striking 34.4%–39.8% in Klebsiella species in South American children. TMP-SMX resistance in E. coli was 47.7%, nearly 2-fold greater than any other continent [15]. Ciprofloxacin co-resistance in E. coli was 7.1% [15]. Meanwhile, SMART data from 2008 to 2010 showed ESBLs accounting for 23% of pediatric E. coli intra-abdominal infections [20]. Historically, CTX-M-2 ESBLs have a known niche in South American countries, and data of healthcare-associated and community-acquired ESBL infections in children confirm high prevalence of this enzyme across Enterobacteriaceae, although CTX-M-15 has been increasingly described [55, 66–68].

Community fecal carriage of resistant E. coli in healthy South American children has been described for >20 years, and ESBL-producing E. coli carriage has increased dramatically. In Bolivia, CTX-M–producing E. coli colonization in children increased 120-fold, from 0.1% (2/1594 isolates) in 2002 to 12% (58/482 isolates) by 2011, with a staggering 91% resistance to fluoroquinolones [66]. In contrast to other regions, CTX-M-9 constituted the majority of isolates; this was a radical change of CTX-M groups from prior studies showing CTX-M-2 dominance in Bolivia and Peru [66, 67]. The children were characterized as healthy, aged 6–72 months, with no diarrhea in the previous
Asia
Initially, reports of studies in children were less common. However, once described, it was quickly evident that the endemicity of ESBLs in Asia had not spared children [3]. A 6-year hospital experience (2001–2006) in a Taiwanese PICU found the rates of ESBL-producing *K. pneumoniae* to be ≥20% [69]. India, known for extreme antibiotic resistance, describes some of the highest pediatric ESBL rates in Asia. A retrospective analysis of neonatal gram-negative septicemia from 2002 to 2003 reported that 61% (46/75) of cases were due to ESBL-producing strains [70].

A retrospective study of 157 isolates in a South Korean children's hospital from 1993 to 1998 reflected emerging adult trends [47]. Production of ESBLs by gram-negative bacteria was reported in 17.9% (16/89) of *E. coli* and 52.9% (36/68) of *K. pneumoniae* isolates, with significant genotypic diversity. SHV-2a- and TEM-52-type ESBLs predominated, with only 2 of 157 bloodstream isolates possessing CTX-M (both CTX-M-14) [47]. More recently, a 2009–2010 Malaysian study characterized ESBL *E. coli* colonization trends in hospitalized children [71]. Of 110 distinct isolates, 49% (54/110) carried TEM-1, whereas 11.8% (13/110) were CTX-M producers, with CTX-M-15 (77%) and CTX-M-9 (13%) predominating. The PB AmpC CMY-2 accounted for 6.2% of extended-spectrum cephalosporin resistance, signifying great diversity among β-lactamases affecting Asian children [71].

Africa/Middle East
The first report on emergence of CTX-M-15-type ESBLs in Africa was in Tanzanian children with septicemia in 2001–2002 [28]. Of 113 children with septicemia, 16 (14%) children were found to have 19 ESBL infections. ESBLs accounted for 25% (9/36) of *E. coli*, 17% (9/52) of *Klebsiella* species, and 3% (1/37) of *Salmonella enterica* species, although 15 children had polymicrobial cultures. Of the 20 ESBLs identified, 7 (35%) were TEM-63, whereas 6 (30%) were CTX-M-15 [28]. A 2006 single-center Tunisian study analyzed 32 ESBL *E. coli* isolates in children collected during a 10-month period and reported CTX-M-15 in 97% (31/32) of isolates; 81% (26/32) also harbored TEM-1b [57].

Fecal carriage rates of ESBL-producing *E. coli* appear to be high in certain African communities, despite an overall lower use of broad-spectrum antibiotics compared with other continents. With children often presenting with severe illnesses requiring prolonged hospitalization, this may provide a ripe environment for colonization and subsequent spread of ESBLs into the community. In a 2007–2008 study on intestinal carriage of ESBL-producing *E. coli* in a pediatric nutrition center in Niger (where all children admitted are described as sick and malnourished and all receive antibiotics), 31% (17/55) of children were found to be colonized with ESBL-producing gram-negatives on admission, whereas among previously noncolonized children, the acquisition rate was 94% (15/16) by hospital discharge (median length of stay, 10 days). Almost all strains (>90%) were CTX-M-15. The authors attributed the disturbing spread to extreme antibiotic pressure, poor hygiene, and high patient density in the hospital, commonplace in the developing world [23, 72].

Studies from Israel offer a unique perspective on ESBL-producing infections in children from the Middle East, where a significant uptrend was found in yearly incidence of pediatric ESBL UTI infections, increasing from 1.2% to 5.2% by the end of the study period (2008–2011) [73].

TREATMENT AND MANAGEMENT OF PEDIATRIC ESBL INFECTIONS
Children are particularly vulnerable in the MDR Enterobacteriaceae pandemic due to lack of broad-spectrum antibiotics approved for use in children. A 2014 review of treatment of MDR gram-negative infections in children described that at present, of the 7 drugs in development for use in MDR gram-negative infection, only 1 (ceftazidime-avibactam) was tested in children [7]. ESBL-producing strains frequently harbor co-resistance genes conferring resistance to aminoglycosides, fluoroquinolones, and TMP-SMX, among others, limiting therapeutic options, especially with oral agents [3, 48]. Fosfomycin has oral dosing for older children and is useful in the management of cystitis, whereas optimal pediatric dosing of polymyxins, particularly colistin, remains elusive [7, 48]. The use of β-lactam/β-lactamase inhibitor drugs in the management of infections by ESBL-producing bacteria is still controversial. Carabapenems remain the gold standard of treatment for serious pediatric ESBL infections [3, 7].

ESBL CONTROL MEASURES IN PEDIATRIC SETTINGS
Fastidious hygiene, patient isolation, cohorting, dedicated staff, and alternating antibiotic regimen policies were all employed to control outbreaks of ESBL-producing bacteria with varying degrees of success [35, 45, 74, 75]. The utility of surveillance cultures for control of ESBL spread has been described in NICU settings. In a single-center NICU study, weekly stool cultures for ESBL *K. pneumoniae* reduced neonatal colonization by 52% over a 4-year period. However, the study authors note...
that during periods of peak hospital admissions, increased acquisition of ESBL-producing bacteria was associated with a decrease in surveillance compliance among staff [76]. A steady but escalating concern is the impact of low-dose, prolonged antibiotic use in livestock as an important contributor to the current MDR gram-negative bacteria crisis [77]. Several countries have initiated restrictions on the use of antibiotics in livestock to control this potential source [24, 77]. Finally, antibiotic stewardship programs are becoming more commonplace in pediatric healthcare facilities in an effort to implement appropriate antibiotic usage and reduce antibiotic selection pressure [78].

**CONCLUSIONS**

ESBL-producing Enterobacteriaceae infections are a growing threat to children. The treatment of pediatric MDR Enterobacteriaceae infections, including ESBLs, will undoubtedly become more and more challenging, and heightened awareness of ESBL-producing bacteria in children and the dedication of targeted resources for prevention and management of ESBL infections remain imperative. National and international programs dedicated to the health of children worldwide need to consider the emerging threat of ESBL-producing bacteria in both resource-rich and resource-challenged countries, and research efforts should focus on the molecular characterization of ESBL types as well as additional controlled studies assessing risk factors and outcomes in children.

**Notes**

**Acknowledgments.** We thank Dr Mary Hayden for her thoughtful comments and guidance.

**Financial support.** L. K. L. acknowledges support from the National Institutes of Health (NIH) award number 1K08AI112506-01. This work was also supported by The Children’s Foundation. R. A. B. acknowledges support from the NIH award numbers R01AI072219, R01AI063517, and R01AI005060. This work was also supported by the Louis Stokes Cleveland Department of Veterans Affairs Medical Center and the Veterans Integrated Service Network 10 Geriatric Research, Education and Clinical Care Center of the Department of Veterans Affairs.

**Potential conflicts of interest.** All authors: No reported conflicts.

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**


