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

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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 bla_{SHV} 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 cephamycins

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

Table 1. Classification Schema of β-Lactamase Genes

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

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.

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-15 [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 bla_{AmpC} (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 bla_{CTX-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

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 (eg, 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 septicemia, 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 bla_{TEM}-type ESBLs, 13 (33%) had bla_{CTX-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

Region/Country	Study	Study Years	Mode of Acquisition	Demographics: Clinical Unit, % Female	Source of Isolate	No. of ESBL-Producing Isolates[a]	Dominant ESBL Genotype (% of Isolates)	Predominant ESBL Enzyme[b] (% of Isolates)
North America								
United States	Qin et al (2008) [49]	1999–2007	CA, HA	All, NS	NS	39 [36]	bla_{CMY} (38.7), bla_{TEM} (34.7)	NS
United States	Weissman et al (2013) [14]	1999–2007	CA, HA	All, 75	NS	22 [21]	bla_{CMY} (38.8), bla_{CTX-M} (34.7)	CMY-2 (38.8), CTX-M-15 (20.4)
United States	Chandramohan et al (2012) [50]	2010–2011	NS	All, NS	Urine, blood, wound, sputum	94	bla_{CTX-M} (74.5), bla_{TEM} (27.7)	CTX-M-15 (59.6), CTX-M-14 (12.8)
Europe								
Croatia	Bedenic et al (2012) [51]	2002–2003	NS	All, 66.6	Urine	77	bla_{SHV} (74), bla_{TEM} (28.6)	SHV-5 (66.2), SHV-2 (3.9)
France	Morgand et al (2014) [52]	2008–2012	CA, HA	All, 65.5	Urine, blood, CSF, sputum, peritoneal fluid	57	bla_{CTX-M} (89.5), bla_{TEM} (8.8)	CTX-M-15 (38.6), CTX-M-14 (24.6)
Hungary	Kristóf et al (2007) [53]	2001–2005	HA	NICU, 51.3	Blood, urine, CSF, sputum	39	bla_{SHV} (100)	SHV-5 (76.9), SHV-12 (23.1)
Poland	Wójkowska-Mach et al (2013) [54]	2009	HA	NICU, 46.9	Sputum, blood, urine, peritoneal fluid, amniotic fluid	47	bla_{CTX-M} (89.4), bla_{SHV} (8.5)	CTX-M-3 (48.9), CTX-M-15 (27.6)
South/Central America								
Brazil	Pereira et al (2013) [55]	2007–2010	HA	All, 48.5	Blood	11	bla_{CTX-M} (63.6), bla_{SHV} (45.4)	NS
Uruguay	García-Fulgueiras et al (2011) [56]	2009	CA, HA	All, NS	Urine, blood, feces, wound	20	bla_{CTX-M} (65), bla_{SHV} (35)	CTX-M-2 (35), SHV-5 (25)
Asia								
South Korea	Kim et al (2002) [47]	1993–1998	HA	All, 44.9	Blood	52	bla_{TEM} (57.7), bla_{SHV} (46.2)	TEM-52 (46.2), SHV-2a (40.4)
Africa/Middle East								
Tanzania	Blomberg et al (2005) [28]	2001–2002	NS	All, NS	Blood	19	bla_{TEM} (36.8), bla_{CTX-M} (31.6)	TEM-63 (36.8), CTX-M-15 (31.6)
Tunisia	Réjiba et al (2011) [57]	2006	NS	All, NS	Urine, feces, sputum, pus, wound, peritoneal fluid	32	bla_{CTX-M} (96.9), bla_{SHV} (6.3)	CTX-M-15 (96.9), SHV-12 (6.3)

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 time 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 near-ly 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 phylogroup strains 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

24 hours. A single cause for the increase was not identified, although 33% of children reported receiving antibiotics within 2 weeks of the study [66]. In contrast, a prospective surveillance study of *E. coli* and *K. pneumoniae* rectal carriage in an Ecuadorian NICU over a 3-month period in 2011 suggests that there remains significant geographic variation in circulating strains, as CTX-M group 1 with 2 distinct genetic clusters was responsible for dissemination in this region [68].

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* sepsis, 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 renutrition 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. Carbapenems 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

References

1. Bush K. Proliferation and significance of clinically relevant beta-lactamases. Ann N Y Acad Sci **2013**; 1277:84–90.
2. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother **2010**; 54:969–76.
3. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev **2005**; 18:657–86.
4. Bush K. Beta-lactamases: ubiquitous and formidable. In: Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, **2014**.
5. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother **2007**; 60:913–20.
6. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum-β-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother **2010**; 54:4085–91.
7. Hsu AJ, Tamma PD. Treatment of multidrug-resistant gram-negative infections in children. Clin Infect Dis **2014**; 58:1439–48.
8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 20th informational supplement. M100-S20. Wayne, PA: CLSI, **2010**.
9. Bush K. Extended-spectrum beta-lactamases in North America, 1987–2006. Clin Microbiol Infect **2008**; 14(suppl 1):134–43.
10. Canton R, Gonzalez-Alba JM, Galan JC. CTX-M enzymes: origin and diffusion. Front Microbiol **2012**; 3:110.
11. Canton R, Coque TM. The CTX-M beta-lactamase pandemic. Curr Opin Microbiol **2006**; 9:466–75.
12. Maiden MCJ, Bygraves JA, Feil E, et al. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. Proc Natl Acad Sci U S A **1998**; 95:3140–5.
13. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev **2009**; 22: 161–82.
14. Weissman SJ, Adler A, Qin X, Zerr DM. Emergence of extended-spectrum beta-lactam resistance among *Escherichia coli* at a US academic children's hospital is clonal at the sequence type level for CTX-M-15, but not for CMY-2. Int J Antimicrob Agents **2013**; 41:414–20.
15. Fedler KA, Biedenbach DJ, Jones RN. Assessment of pathogen frequency and resistance patterns among pediatric patient isolates: report from the 2004 SENTRY Antimicrobial Surveillance Program on 3 continents. Diagn Microbiol Infect Dis **2006**; 56:427–36.
16. Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel) **2013**; 6:1335–46.
17. Gales AC, Castanheira M, Jones RN, Sader HS. Antimicrobial resistance among gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008–2010). Diagn Microbiol Infect Dis **2012**; 73:354–60.
18. Goossens H, Grabein B. Prevalence and antimicrobial susceptibility data for extended-spectrum beta-lactamase- and AmpC-producing Enterobacteriaceae from the MYSTIC Program in Europe and the United States (1997–2004). Diagn Microbiol Infect Dis **2005**; 53:257–64.
19. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother **2014**; 58:833–8.
20. Badal RE, Bouchillon SK, Lob SH, Hackel MA, Hawser SP, Hoban DJ. Etiology, extended-spectrum beta-lactamase rates and antimicrobial susceptibility of gram-negative bacilli causing intra-abdominal infections in patients in general pediatric and pediatric intensive care units–global data from the Study for Monitoring Antimicrobial Resistance Trends 2008 to 2010. Pediatr Infect Dis J **2013**; 32:636–40.
21. Lascols C, Hackel M, Hujer AM, et al. Using nucleic acid microarrays to perform molecular epidemiology and detect novel beta-lactamases: a snapshot of extended-spectrum beta-lactamases throughout the world. J Clin Microbiol **2012**; 50:1632–9.
22. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis **2008**; 8:159–66.
23. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev **2013**; 26: 744–58.

24. Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect 2011; 17:873–80.

25. Laupland KB, Church DL, Vidakovich J, Mucenski M, Pitout JD. Community-onset extended-spectrum beta-lactamase (ESBL) producing Escherichia coli: importance of international travel. J Infect 2008; 57:441–8.

26. Tande D, Boisrame-Gastrin S, Munck MR, et al. Intrafamilial transmission of extended-spectrum-beta-lactamase-producing Escherichia coli and Salmonella enterica Babelsberg among the families of internationally adopted children. J Antimicrob Chemother 2010; 65:859–65.

27. Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum beta-lactamase-producing and nonproducing bacteria: a comparative study. J Pediatr 2013; 163:1417–21.

28. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. J Clin Microbiol 2005; 43:745–9.

29. Knudsen JD, Andersen SE, Bispebjerg Intervention Group. A multidisciplinary intervention to reduce infections of ESBL- and AmpC-producing, gram-negative bacteria at a university hospital. PLoS One 2014; 9:e86457.

30. Oteo J, Cercenado E, Fernandez-Romero S, et al. Extended-spectrum-beta-lactamase-producing Escherichia coli as a cause of pediatric infections: report of a neonatal intensive care unit outbreak due to a CTX-M-14-producing strain. Antimicrob Agents Chemother 2012; 56:54–8.

31. Oteo J, Cercenado E, Vindel A, et al. Outbreak of multidrug-resistant CTX-M-15-producing Enterobacter cloacae in a neonatal intensive care unit. J Med Microbiol 2013; 62:571–5.

32. Cotton MF, Wasserman E, Pieper CH, et al. Invasive disease due to extended spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal unit: the possible role of cockroaches. J Hosp Infect 2000; 44: 13–7.

33. Gupta A, Della-Latta P, Todd B, et al. Outbreak of extended-spectrum beta-lactamase–producing Klebsiella pneumoniae in a neonatal intensive care unit linked to artificial nails. Infect Control Hosp Epidemiol 2004; 25:210–5.

34. Crivaro V, Bagattini M, Salza MF, et al. Risk factors for extended-spectrum beta-lactamase-producing Serratia marcescens and Klebsiella pneumoniae acquisition in a neonatal intensive care unit. J Hosp Infect 2007; 67:135–41.

35. Rettedal S, Hoyland Lohr I, Natas O, Sundsfjord A, Oymar K. Risk factors for acquisition of CTX-M-15 extended-spectrum beta-lactamase-producing Klebsiella pneumoniae during an outbreak in a neonatal intensive care unit in Norway. Scand J Infect Dis 2013; 45:54–8.

36. Shakil S, Akram M, Ali SM, Khan AU. Acquisition of extended-spectrum beta-lactamase producing Escherichia coli strains in male and female infants admitted to a neonatal intensive care unit: molecular epidemiology and analysis of risk factors. J Med Microbiol 2010; 59 (pt 8):948–54.

37. Vijayakanthi N, Bahl D, Kaur N, Maria A, Dubey NK. Frequency and characteristics of infections caused by extended-spectrum beta-lactamase-producing organisms in neonates: a prospective cohort study. Biomed Res Int 2013; 2013:756209.

38. Denkel LA, Schwab F, Kola A, et al. The mother as most important risk factor for colonization of very low birth weight (VLBW) infants with extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E). J Antimicrob Chemother 2014; 69:2230–7.

39. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. Pediatrics 2005; 115:942–9.

40. Jhaveri R, Bronstein D, Sollod J, Kitchen C, Krogstad P. Outcome of infections with extended spectrum beta-lactamase producing organisms in children. J Pediatr Infect Dis 2008; 3:229–33.

41. Blaschke AJ, Korgenski EK, Daly JA, LaFleur B, Pavia AT, Byington CL. Extended-spectrum beta-lactamase-producing pathogens in a children's hospital: a 5-year experience. Am J Infect Control 2009; 37:435–41.

42. Logan LK, Meltzer LA, McAuley JB, et al. Extended-spectrum β-lactamase-producing Enterobacteriaceae infections in children: a two-center case-case-control study of risk factors and outcomes in Chicago, Illinois. J Pediatr Infect Dis Soc 2014; 3:312–9.

43. Fan NC, Chen HH, Chen CL, et al. Rise of community-onset urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli in children. J Microbiol Immunol Infect 2014; 47: 399–405.

44. Topaloglu R, Er I, Dogan BG, et al. Risk factors in community-acquired urinary tract infections caused by ESBL-producing bacteria in children. Pediatr Nephrol 2010; 25:919–25.

45. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2003; 24:601–6.

46. Pitout JDD, Laupland KB, Church DL, Menard ML, Johnson JR. Virulence factors of Escherichia coli isolates that produce CTX-M-type extended-spectrum ß-lactamases. Antimicrob Agents Chemother 2005; 49:4667–70.

47. Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. Antimicrob Agents Chemother 2002; 46:1481–91.

48. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R. Extended-spectrum beta-lactamase-producing and third-generation cephalosporin-resistant Enterobacteriaceae in children: trends in the United States, 1999–2011. J Pediatr Infect Dis Soc 2014; 3:320–8.

49. Qin X, Zerr DM, Weissman SJ, et al. Prevalence and mechanisms of broad-spectrum beta-lactam resistance in Enterobacteriaceae: a children's hospital experience. Antimicrob Agents Chemother 2008; 52:3909–14.

50. Chandramohan L, Revell PA. Prevalence and molecular characterization of extended-spectrum-beta-lactamase-producing Enterobacteriaceae in a pediatric patient population. Antimicrob Agents Chemother 2012; 56:4765–70.

51. Bedenic B, Vranes J, Hofmann-Thiel S, et al. Characterization of the extended-spectrum beta-lactamases and determination of the virulence factors of uropathogenic Escherichia coli strains isolated from children. Wien Klin Wochenschr 2012; 124:504–15.

52. Morgand M, Vimont S, Bleibtreu A, et al. Extended-spectrum beta-lactamase-producing Escherichia coli infections in children: are community-acquired strains different from nosocomial strains? Int J Med Microbiol 2014; 304:970–6.

53. Kristóf K, Szabo D, Marsh JW, et al. Extended-spectrum beta-lactamase-producing Klebsiella spp. in a neonatal intensive care unit: risk factors for the infection and the dynamics of the molecular epidemiology. Eur J Clin Microbiol Infect Dis 2007; 26:563–70.

54. Wójkowska-Mach J, Chmielarczyk A, Borszewska-Kornacka M, et al. Enterobacteriaceae infections of very low birth weight infants in Polish neonatal intensive care units: resistance and cross-transmission. Pediatr Infect Dis J 2013; 32:594–8.

55. Pereira CA, Marra AR, Camargo LF, et al. Nosocomial bloodstream infections in Brazilian pediatric patients: microbiology, epidemiology, and clinical features. PLoS One 2013; 8:e68144.

56. García-Fulgueiras V, Bado I, Mota MI, et al. Extended-spectrum beta-lactamases and plasmid-mediated quinolone resistance in enterobacterial clinical isolates in the paediatric hospital of Uruguay. J Antimicrob Chemother 2011; 66:1725–9.

57. Réjiba S, Mercuri PS, Power P, Kechrid A. Emergence and dominance of CTX-M-15 extended spectrum beta-lactamase among Escherichia coli isolates from children. Microb Drug Resist 2011; 17:135–40.

58. Zerr DM, Qin X, Oron AP, et al. Pediatric infection and intestinal carriage due to extended-spectrum-cephalosporin-resistant Enterobacteriaceae. Antimicrob Agents Chemother 2014; 58:3997–4004.

59. Raymond J, Nordmann P, Doit C, et al. Multidrug-resistant bacteria in hospitalized children: a 5-year multicenter study. Pediatrics **2007**; 119: e798–803.

60. Dotis J, Printza N, Marneri A, Gidaris D, Papachristou F. Urinary tract infections caused by extended-spectrum beta lactamase-producing bacteria in children: a matched case-control study. Turk J Pediatr **2013**; 55:571–4.

61. Kizilca O, Siraneci R, Yilmaz A, et al. Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. Pediatr Int **2012**; 54:858–62.

62. Birgy A, Cohen R, Levy C, et al. Community faecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in French children. BMC Infect Dis **2012**; 12:315.

63. Blanc V, Leflon-Guibout V, Blanco J, et al. Prevalence of day-care centre children (France) with faecal CTX-M-producing *Escherichia coli* comprising O25b:H4 and O16:H5 ST131 strains. J Antimicrob Chemother **2014**; 69:1231–7.

64. Kaarme J, Molin Y, Olsen B, Melhus A. Prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae in healthy Swedish preschool children. Acta Paediatr **2013**; 102:655–60.

65. Fernandez-Reyes M, Vicente D, Gomariz M, et al. High rate of fecal carriage of extended-spectrum-beta-lactamase-producing *Escherichia coli* in healthy children in Gipuzkoa, northern Spain. Antimicrob Agents Chemother **2014**; 58:1822–4.

66. Bartoloni A, Pallecchi L, Riccobono E, et al. Relentless increase of resistance to fluoroquinolones and expanded-spectrum cephalosporins in *Escherichia coli*: 20 years of surveillance in resource-limited settings from Latin America. Clin Microbiol Infect **2013**; 19:356–61.

67. Pallecchi L, Bartoloni A, Fiorelli C, et al. Rapid dissemination and diversity of CTX-M extended-spectrum beta-lactamase genes in commensal *Escherichia coli* isolates from healthy children from low-resource settings in Latin America. Antimicrob Agents Chemother **2007**; 51:2720–5.

68. Nordberg V, Quizhpe Peralta A, Galindo T, et al. High proportion of intestinal colonization with successful epidemic clones of ESBL-producing Enterobacteriaceae in a neonatal intensive care unit in Ecuador. PLoS One **2013**; 8:e76597.

69. Lee CY, Chen PY, Huang FL, Lin CF. Microbiologic spectrum and susceptibility pattern of clinical isolates from the pediatric intensive care unit in a single medical center—6 years' experience. J Microbiol Immunol Infect **2009**; 42:160–5.

70. Sehgal R, Gaind R, Chellani H, Agarwal P. Extended-spectrum beta lactamase-producing gram-negative bacteria: clinical profile and outcome in a neonatal intensive care unit. Ann Trop Paediatr **2007**; 27: 45–54.

71. Ho WS, Balan G, Puthucheary S, et al. Prevalence and characterization of multidrug-resistant and extended-spectrum beta-lactamase-producing *Escherichia coli* from pediatric wards of a Malaysian hospital. Microb Drug Resist **2012**; 18:408–16.

72. Woerther PL, Angebault C, Jacquier H, et al. Massive increase, spread, and exchange of extended spectrum beta-lactamase-encoding genes among intestinal Enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. Clin Infect Dis **2011**; 53:677–85.

73. Megged O. Extended-spectrum beta-lactamase-producing bacteria causing community-acquired urinary tract infections in children. Pediatr Nephrol **2014**; 29:1583–7.

74. Lee J, Pai H, Kim YK, et al. Control of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a children's hospital by changing antimicrobial agent usage policy. J Antimicrob Chemother **2007**; 60:629–37.

75. Rettedal S, Lohr IH, Natas O, Giske CG, Sundsfjord A, Oymar K. First outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a Norwegian neonatal intensive care unit; associated with contaminated breast milk and resolved by strict cohorting. APMIS **2012**; 120:612–21.

76. Benenson S, Levin PD, Block C, et al. Continuous surveillance to reduce extended-spectrum beta-lactamase *Klebsiella pneumoniae* colonization in the neonatal intensive care unit. Neonatology **2013**; 103:155–60.

77. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. Clin Microbiol Rev **2011**; 24:718–33.

78. Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. Pediatrics **2011**; 128: 1062–70.