Carbapenem-Resistant Enterobacteriaceae: An Emerging Problem in Children

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Antibiotic resistance among gram-negative bacteria has reached critical levels. The rise of carbapenem resistance in Enterobacteriaceae carrying additional resistance genes to multiple antibiotic classes has created a generation of organisms nearly resistant to all available therapy. Carbapenem-resistant Enterobacteriaceae (CRE) infections are known to be associated with significant morbidity and mortality, and these pathogens have now made their way to the most vulnerable populations, including children. This review provides a brief overview of CRE, with a focus on CRE infections in children, and highlights available data on the epidemiology, clinical characteristics, carbapenemase types, risk factors, treatment, and outcomes of these multi-drug resistant infections in the pediatric population.

The war against multidrug-resistant bacteria is challenging and of global concern. Although media attention on antibiotic resistance and drug development have focused in recent years on the gram-positive cocci, such as Staphylococcus aureus and Enterococcus species, the gram-negative bacilli, especially the Enterobacteriaceae, have begun to take center stage clinically as broad-spectrum resistance within this family of organisms has reached critical levels. The Infectious Diseases Society of America brought major attention to this problem and to the need for novel therapeutics with the call-to-action “Bad Bugs No Drugs” campaign, and with the acronym “ESKAPE” pathogens (Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii species, Pseudomonas aeruginosa, and Enterobacter species) [1]; 4 of the 6 “ESKAPE” bacteria are gram-negative bacilli, and 2 are Enterobacteriaceae [1, 2].

Enterobacteriaceae are a major cause of healthcare-associated infection. Recent summary data reported by the National Healthcare Safety Network (NHSN) of the US Centers for Disease Control and Prevention show that ≥21.3% of cases of device-related healthcare-associated infection were due to Enterobacteriaceae, with Escherichia coli representing the most common cause of catheter-related urinary tract infection [3].

Multidrug resistance within Enterobacteriaceae is not a new phenomenon. The rise of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae (resistant to penicillins, cephalosporins, and monobactams) has reached high levels, and the number of unique ESBL protein sequences exceeded 1000 in 2011 [4]. For serious infections, carbapenems have been the preferred, and at times only, treatment [5].

Most recently, the emergence of carbapenemases carried on mobile genetic elements, such as transposons or plasmids that can harbor additional resistance genes affecting multiple classes of antibiotics, has led to high level antibiotic-resistant bacteria, and the mobile resistance elements often have transferred into strains capable of efficient person-to-person spread.

As surveillance and more accurate detection of carbapenem-resistant Enterobacteriaceae (CRE) have improved, the global, rapid spread of these organisms has become increasingly evident. It is now clear that
CRE infections can be associated with significant morbidity and mortality [6]. Among the latest concerns are reports of the spread of these organisms into pediatric populations, where few, if any, therapeutic options exist.

**MECHANISMS OF CARBAPENEM RESISTANCE**

Gram-negative bacteria use 2 main mechanisms to develop phenotypic resistance to carbapenems: the production of carbapenemases or a combination of structural mutations and production of other β-lactamase enzymes (Table 1). Bacteria that produce carbapenemases, enzymes that hydrolyze carbapenems, are also able to break down other β-lactam antibiotics including penicillins, cephalosporins, and monobactams.

ESBLs and AmpC cephalosporinases (AmpCs) confer carbapenem resistance when associated with alterations or loss of porins, a family of proteins on the outer membrane of gram-negative bacteria. Porins allow diffusion of substrate (eg, antibiotics) across the bacterial membrane. Deletions or mutations of porin genes that hinder this diffusion are common resistance mechanisms in gram-negative bacteria [7]. β-lactam resistance by AmpC expression in Enterobacteriaceae is most commonly associated with hyperproduction of enzymes from inducible or derepressed chromosomal genes (though AmpC can also be plasmid based), whereas ESBLs generally are encoded by plasmids [8, 9]. Carbapenemase production can be chromosomal or plasmid based [8]. Molecular structural classifications include Ambler class A, B, and D carbapenemases [10]. These are distinguished by the active site of the hydrolytic mechanism. Class A and D carbapenemases require serine at their active site (serine carbapenemases), whereas class B, the metallo-β-lactamas (MBLs), are zinc dependent. Class A carbapenemases include *K. pneumoniae* carbapenemase (KPC), IMI, SME, GES, and NMC-A enzymes, of which KPC is the most common in the United States [11]. KPC often is carried on a mobile plasmid or transposon with other β-lactamas; plasmid location facilitates dissemination of KPCs among Enterobacteriaceae, although at present *K. pneumoniae* remains the most common KPC-containing CRE [5, 11–13].

Class D OXA carbapenemases, named for their oxacillin-hydrolyzing abilities, have been found in Enterobacteriaceae, but are more commonly seen in *P. aeruginosa* and *Acinetobacter* species [12, 14]. Class B, which includes the plasmid-based Verona integron-encoded MBL (VIM) and IMP genes, has recently gained much attention owing to the addition of the New Delhi MBL (NDM) to the class; the plasmid-mediated NDM has spread with striking rapidity globally and into multiple Enterobacteriaceae species [15, 16].

ESBL and carbapenemase-producing bacteria often carry additional plasmid-borne genes that encode for resistance to aminoglycosides and sulfonamides, as well as high-level resistance to fluoroquinolones due to alterations in target enzymes, making these strains truly multidrug-resistant organisms [5].

**LABORATORY DETECTION OF CRE**

CRE detection can be complex, and suspicion of carbapenemase production by microbiology laboratory personnel often is necessary to initiate testing, because some carbapenemase-producing organisms actually will test as susceptible to carbapenems because of low-level in vitro resistance. This is particularly the case for group 2 carbapenems (meropenem, imipenem), for which CREs may display elevated but not resistance-level minimum inhibitory concentrations (MICs) or Kirby-Bauer testing disk zones. Therefore, the Clinical Laboratory Standards Institute (CLSI) recommends screening

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**Table 1. Carbapenem Resistance Mechanisms in Enterobacteriaceae**

<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>Ambler/Jacoby–Bush Classification</th>
<th>Genetic Basis</th>
<th>Notable Types</th>
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<tr>
<td>Carbapenemases</td>
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<tr>
<td>Serine</td>
<td>A/2f</td>
<td>Plasmid</td>
<td>KPC</td>
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<tr>
<td>Metallo-β-lactamas</td>
<td>D/2df</td>
<td>Plasmid</td>
<td>SME, IMI, NMC-A</td>
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<td></td>
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<td></td>
<td>OXA</td>
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<tr>
<td>Other mechanisms (β-lactamas)</td>
<td>B/3</td>
<td>Plasmid</td>
<td>VIM, IMP, NDM</td>
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<tr>
<td>AmpC hyperproduction plus porin deletion or alteration</td>
<td>C/1</td>
<td>Chromosomal</td>
<td></td>
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<tr>
<td>ESBL production plus porin deletion or alteration</td>
<td>A/2be</td>
<td>Plasmid</td>
<td>CMY, FOX, ACT</td>
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</table>

From references 5, 7, 8, 10–14, and 16.
Abbreviations: AmpC, AmpC cephalosporinase; ESBL, extended-spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; VIM, Verona integron-encoded MBL.
for CREs using very low carbapenem concentrations [17]. Confirmatory testing for carbapenemase production can be done by a modified Hodge test (MHT) [18, 19]. NDMs may demonstrate negative or weakly positive MHT results, further complicating detection [20]. Other testing for MBLs in Enterobacteriaceae include the double-disk synergy test, the combination disk test, and the bioMérieux MBL E-test [21]. Identification of specific enzymes requires molecular characterization of β-lactamase (bla) genes (including serine and MBL carbapenemases, ESBLs, and AmpCs) using polymerase chain reaction (PCR) testing [22].

**OVERVIEW OF EPIDEMIOLOGY OF CRE**

Improvements in laboratory detection of CRE have facilitated identification of the many diverse enzymes belonging to this large group of organisms. Although reporting of CREs is not mandated by most health departments, data from programs such as the SENTRY antimicrobial surveillance program (JMI Laboratories); NHSN reporting of antimicrobial-resistant pathogens associated with healthcare infections; the Merck Study for Monitoring Antimicrobial Resistance Trends (SMART) trial; and the European Centre for Disease Prevention and Control Antimicrobial Resistance and Healthcare-Associated Infections Programme enable global tracking of the spread of CREs.

There are regional differences in predominant carbapenemase types. In the United States, KPC is the primary carbapenemase. Since the first KPC was identified in 1996 in North Carolina, KPC-producing organisms have been reported in 36 states, Washington, DC, and Puerto Rico; have become endemic in the northeastern United States; and are represented by a predominant clone (ST258) of *K. pneumoniae* [13, 23, 24]. Recent 2006–2007 NHSN-reported rates of carbapenem resistance in some device-related infections were as high as 4% in *E. coli* and 10.8% in *K. pneumoniae* [3]. SENTRY data from Europe and the Americas (2007–2009) revealed that KPCs were widespread in most regions (with the highest prevalence in the United States and Israel), OXA and IMP-type enzymes were found in Europe and Latin America, whereas other MBLs were noted mainly in Europe with VIM-type enzymes predominantly found in Greece, Italy, Turkey and Spain [25]. NDM-1 originally identified in India (the major carbapenemase reported in 38.5% of SENTRY Enterobacteriaceae isolates in 2006–2007) has emerged globally, particularly among patients and “medical tourists” receiving medical care on the Indian subcontinent [15, 20].

In the United States, KPC mainly has been found in healthcare settings, with long-term care facilities representing a potential reservoir for interfacility spread of organisms [26]. However, in India, NDM community-onset infection is not uncommon, and NDM-1 was discovered in drinking water and sewage samples, which potentially could result in even more rapid, and community, dissemination [27].

Several studies have evaluated risk factors for CRE colonization and infection in adults. Risk factors include critical illness, exposure to healthcare, recent organ or stem cell transplantation, mechanical ventilation, longer length of stay before infection, and prior exposure to antibiotics, particularly fluoroquinolones, cephalosporins, and carbapenems [6, 28, 29]. CRE infection in adults has been associated with high morbidity and mortality rates, and treatment options have been limited [6, 14].

**CRE IN CHILDREN**

A MEDLINE search (of drug resistance, microbial + Enterobacteriaceae, and/or Enterobacteriaceae infections + child for 1948 through 2012 in the English language) yielded 44 articles, of which 6 studies highlighted children with CRE infections [30–35]. No additional articles meeting review criteria were found in the Scopus or Cochrane Databases. Cases reviewed included demographic information and molecular characterization of isolates and were not attributed to outbreak situations. Study authors were queried for additional unpublished data. Complete data were not available for review in most cases. A surveillance database (SMART program 2011) was queried for pediatric data on CRE (Samuel Bouchillon, personal communication, unpublished data).

**Demographics and Clinical History of Children With CRE Infection**

The 6 studies and the SMART program included 64 isolates from 63 children, cultured between 2002 and 2010. CRE infection was found in a diverse population of children, including newborns (as young as 8 hours) to teenagers, from 5 countries on 4 continents (Table 2). The median age of the 63 children was 1 year (range, 0–17 years); 42 (67%) were male and 21 (33%) were female. As to the regional distribution, 24 (38%) were from India, 18 (29%) from Israel, 12 (19%) from Spain, 7 (11%) from the United States, and 2 (3%) from Greece. The clinical history of children with CRE infection is shown in Table 3. The majority (87%) were hospitalized for >48 hours before their CRE infection, suggesting hospital-acquired infection. Complete admission, discharge and culture dates were available in 5 studies (33 children). The median length of hospitalization before CRE infection was 16 days (range, 1–385 days). Hospital location was available for 60 children; 32 children (53%) were in an ICU (neonatal or pediatric), 11 (18%) in pediatric wards, 9 (15%) in surgical wards, 4 (7%) in a hematology- oncology ward, and 3 (5%) in other specialty wards. One child’s infection in a sixth study was discovered in the emergency department.
Underlying medical conditions were noted in 34 (92%) of 37 children. The most common condition was pulmonary disease (11 children; 30%); 10 (27%) had a history of prematurity, 7 (19%) had an oncologic process (including leukemia or solid tumor), 7 (19%) had cardiac disease, 5 (14%) had necrotizing enterocolitis and/or short-bowel syndrome, and 4 (11%) had a solid-organ or stem-cell transplant. Nineteen children (51%) were receiving immunosuppressants at the time of their infection. A history of surgery was reported in 18 (43%) of 42 children; 12 (67%) of the procedures were gastrointestinal. An indwelling device was reported in 37 (90%) of 41 children. Data on antibiotic regimens and duration of antibiotics before infection were not available; however, excluding the cases in newborn infants, 36 (97%) of 37 children received antibiotics before CRE infection.

Microbiologic and Molecular Characteristics of CRE in Children

Sixty-four isolates thought to represent infection were recovered from 63 children (Table 4). Carbapenemases were found in 6 genera consistent with known ease of dissemination into members of the Enterobacteriaceae family via mobile genetic elements (Supplementary Table 1); 22 CRE strains (34%) were Enterobacter species, 20 (31%) were Klebsiella species, and 18 (28%) were E. coli. CRE were isolated from blood in 19 children (30%), urine in 16 (25%), gastrointestinal tract in 12 (19%) and respiratory tract in 11 (17%). NDM (including NDM-1 and NDM-6) were the most common carbapenemase and were found in CRE from 23 cases (36%); KPC and VIM were found in CRE from 22 (34%) and 15 (23%) children,
respectively. All NDM cases were from India, KPC cases were from the United States or Israel, and all VIM cases were from Europe. Sixty-two organisms were additionally analyzed for the presence of other β-lactam resistance mechanisms (62 and 52 isolates analyzed for ESBL and AmpC, respectively); 47 (76%) carried an additional β-lactamase, of which 37 (71%) possessed an AmpC, 24 (39%) carried an ESBL, and 13 (25%) exhibited both resistance genes. *Enterobacter cloacae* and *Enterobacter aerogenes* were assumed to carry and express chromosomal AmpC [9].

### Antibiotic Susceptibilities of CREs in Children

Phenotypic susceptibility testing by disk diffusion demonstrated known discrepant patterns in carbapenemase-producing organisms (Table 5). Revised CLSI carbapenem break points were used in this review to determine sensitivity or intermediate/resistance where MICs were provided [17]. Imipenem resistance was determined by disk diffusion in 37 (82%) of 45 isolates; however, only 16 (59%) of 27 and 27 (54%) of 50 CRE isolates demonstrated resistance to ertapenem and meropenem, respectively, which could be interpreted in discordant strains as carbapenem susceptibility. This highlights the importance of additional screening tests such as the MHT; however, MBL, present in 40 (63%) of the 64 isolates, may demonstrate negative or weakly positive MHT results, making the diagnosis difficult without *bla* PCR testing.

CRE are known to carry multiple resistance determinants, and multiclass drug resistance was present in the majority of
The most common coreisistances were to ampicillin-sulbactam (15 [100%] of 15 tested isolates), piperacillin-tazobactam (49 [82%] of 60 isolates), trimethoprim-sulfamethoxazole (49 [68%] of 60 isolates), aminoglycosides (42 [66%] of 64 isolates), and fluoroquinolones (11 [23%] of 48 isolates). When aminoglycoside sensitivity was retained it was most often solely due to amikacin susceptibility. Although limited data are available in children, antibiotics known to demonstrate efficacy against CRE infections in adults, such as tigecycline and polymyxin B or E (colistin), were tested in 22 pediatric cases and demonstrated good in vitro susceptibility; that is, only 4 (18%) were resistant to tigecycline and 1 (4.5%) was resistant to polymyxin. However, tigecycline is a member of the tetracycline family, which generally are not recommended in children <8 years of age (median age of children reviewed here, 1 year) because of the risk of dental staining.

**Treatment and Outcomes of Children With CRE Infection**

Antibiotic treatment data were available for 24 cases (Table 6). Aminoglycosides were used in 14 (58%) cases; in 5 of these cases, aminoglycosides were used in combination with a fluoroquinolone (4 cases) or trimethoprim-sulfamethoxazole (1 case). Tigecycline was used as single-drug therapy in 1 case. No children were treated with a fluoroquinolone or trimethoprim-sulfamethoxazole as single-drug therapy. Of note, 9 children (38%) received no therapy thought to be active against CRE; 6 of these children survived and had no reported recurrence of infection. Other potential therapy data, such as removal of infected foci (eg, indwelling devices, surgical procedures) were not available.

The median length of stay after infection was 23 days (range, 0–414 days). Mortality rates were lower than those reported in adults [36], yet 5 (10%) of 52 children died during the study period and 4 (80%) of those deaths were attributed to the CRE infection. Recurrence of infection occurred in 3 (8%) of 37 children, of whom 1 child had 5 additional CRE infections.

**CURRENT AND FUTURE OPTIONS FOR THE TREATMENT AND CONTROL OF SPREAD OF CRE**

Recent pharmacokinetic studies of tigecycline in children aged 8–11 years with serious bacterial infection suggest that a dose of 1.2 mg/kg every 12 hours would produce therapeutic levels, based on target AUC$_{0-24}$/MIC ratios, in 82% of cases; however, phase III clinical trials are necessary [37]. Intravenous colistin has a recommended dosing of 2.5–5 mg/kg/d, divided into 2–4 equal doses; the half-life of colistimethate is...
2–4 hours in children with normal renal function [38]. Older drugs, such as fosfomycin, are being reevaluated for urinary tract infections particularly due to KPC [13, 14]. Fosfomycin dosing in children is variable and based on age and body weight [39].

Several novel agents are in early stages of development, including β-lactamase inhibitors formulated in combination with β-lactams, newer aminoglycosides (neoglycosides), and polymyxin derivatives [14]. Pediatric data are sparse with any of these agents, particularly in the management of CRE [37–41].

Prevention of transmission and determination of patients at highest risk seem to be the most critical pieces in the control of CRE. Nosocomial spread remains the most common risk factor for organism acquisition, although in some regions, the worrisome development of community acquisition, possibly by contaminated public water, adds to the velocity of spread [27, 42]. The global use of known effective multifaceted infection control strategies against CRE, including contact precautions, proper hand hygiene, and cohort nursing care, along with point prevalence surveys, active surveillance cultures, and bundled prevention strategies in high-risk settings (eg, long-term care facilities) will be essential to slow the spread of these organisms [36, 43].

For children, transfer of resistance plasmids from CRE to nonlactose fermenters such as P. aeruginosa and Acinetobacter baumannii [42] adds concern not only for hospitalized and immunocompromised children but also for many others, such as patients with cystic fibrosis, for whom antibiotic-resistant infections and transmission of resistant strains between patients in the outpatient setting is already a vexing problem [44].

CONCLUSIONS

CRE infection remains an uncommon but serious problem in children and may be associated with significant morbidity and mortality and prolonged hospitalization. Children with CRE infection tend to be very young and critically ill, and potential risk factors include comorbid conditions, presence of indwelling devices, history of surgery, receipt of immunosuppressive agents, and prior antibiotic use. Controlled studies are necessary to further assess risk factors and outcomes in children. Effective antibiotic therapy is even more limited than in adult patients, and few new antimicrobials against CRE are near Food and Drug Administration approval. Infection control and bundled prevention strategies are critical to thwart the rapid global spread of these dangerous pathogens.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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