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INVITED REVIEW

Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections in Children

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Infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) are increasingly prevalent in children and are associated with poor clinical outcomes. Optimal treatment strategies for CRE infections continue to evolve. A lack of pediatric-specific comparative effectiveness data, uncertain pediatric dosing regimens for several agents, and a relative lack of new antibiotics with pediatric indications approved by the US Food and Drug Administration (FDA) collectively present unique challenges for children. In this review, we provide a framework for antibiotic treatment of CRE infections in children, highlighting relevant microbiologic considerations and summarizing available data related to the evaluation of FDA-approved antibiotics (as of September 2019) with CRE activity, including carbapenems, ceftazidime-avibactam, meropenem-vaborbactam, imipenem/cilastatin-relebactam, polymyxins, tigecycline, eravacycline, and plazomicin.

Keywords. *Klebsiella pneumoniae* carbapenemase; pediatrics; multidrug-resistant organism; gram-negative resistance.

Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are increasingly being identified in children and are associated with poor clinical outcomes [1–4]. Therapeutic paradigms for CRE have evolved significantly in recent years with the availability of novel β-lactam-β-lactamase inhibitor (βL-βLI) agents (eg, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam [hereafter referred to as imipenem-relebactam]), which have revolutionized the treatment of CRE infections. However, optimal treatment of CRE infections in children remains challenging given limited pediatric-specific pharmacokinetic and pharmacodynamic (PK-PD) data, limited clinical experience with a number of CRE-active drugs, and few clinical trials evaluating novel antibiotics for use in this population. In this review, we summarize available CRE-active antibiotics approved by the US Food and Drug Administration (FDA) as of September 2019 and provide clinicians a framework for selecting appropriate therapy for children infected with CRE based on clinical and microbiologic characteristics.

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MICROBIOLOGY

CRE are defined by the Centers for Disease Control and Prevention as any *Enterobacteriaceae* exhibiting carbapenem resistance, defined as an imipenem, meropenem, or doripenem minimum inhibitory concentration (MIC) ≥4 μg/mL or ertapenem MIC ≥2 μg/mL [5, 6]. Common CRE in children include *Enterobacter* species, *Klebsiella pneumoniae*, and *Escherichia coli* [1]. Carbapenem resistance in these organisms develops by 1 of 2 general mechanisms: by production of a carbapenemase (CP-CRE), which are encoded by genes generally found on highly transmissible mobile elements that hydrolyze the β-lactam ring of carbapenem antibiotics or by production of extended-spectrum β-lactamases (ESBLs) or AmpC β-lactamases combined with impaired membrane permeability from porin loss/mutations or efflux pumps. These latter groups are termed non–CP-CRE [7]. Several laboratory tests (including the Carba NP assay and modified carbapenem inactivation method) are available to identify the presence or absence of a carbapenemase. Molecular tests can identify specific carbapenemase genes present and are included in some commercially available rapid molecular diagnostic panels [8, 9]. Of note, since these molecular assays are only able to detect specified carbapenemase genes, "negative" results should not be interpreted as synonymous with the absence of carbapenemase genes not included in the assay or carbapenem susceptibility (as the isolate may be a non–CP-CRE).

MOLECULAR EPIDEMIOLOGY

In the United States, between one-third and one-half of CRE isolates from adults are carbapenemase-producing, and

the Ambler class A serine carbapenemase *K. pneumoniae* carbapenemase (KPC) accounts for upwards of 90% of these CP-CRE [10–12]. Epidemiologic studies in children are limited, but available pediatric case series suggest KPC is also the most common carbapenemase identified in CP-CRE isolates infecting US children [13, 14]. The β-lactamase inhibitors avibactam, vaborbactam, and relebactam effectively protect β-lactams from hydrolysis by KPC enzymes [15, 16].

The Ambler class B carbapenemases are referred to as metallo-β-lactamases (MBLs) because they require zinc to be active. MBLs include New Delhi metallo-β-lactamases (NDM), Verona integron-encoded metallo-β-lactamases (VIM), and active on imipenem (IMP) carbapenemases. They are infrequently identified in the United States but are of particular clinical significance as they are not inhibited by avibactam, vaborbactam, or relebactam, severely limiting treatment options for infections due to these organisms [15, 16]. The possibility of an MBL-producing isolate should be considered if carbapenem resistance is detected in isolates from children with epidemiologic links to MBL-endemic regions, such as South Asia, where NDM carbapenemases are highly prevalent or in a child with a known history of infection or colonization with an MBL-producing isolate [7]. Further, there are adult and pediatric reports of sporadic domestic acquisition of VIM-, IMP-, and NDM-producing isolates in the United States [17–19].

The Ambler class D oxacillinases, which include oxacillinase (OXA)-48–like enzymes (eg, OXA-48, OXA-181, OXA-232), are increasingly being identified in Europe and sporadically in the United States [7, 20]. Avibactam and, to a lesser extent, relebactam, but not vaborbactam, inhibit OXA-48-like enzymes (Table 1) [15, 16].

Finally, it is worth noting that carbapenemase enzymes are often coproduced with elements that confer resistance to non-carbapenem antibiotics. This includes other β-lactamases (eg, the $bla_{CTX\text{-}M\text{-}15}$ ESBL gene, the bla_{CMY} *ampC* gene), aminoglycosides (eg, aminoglycoside-modifying enzymes, ribosomal RNA methyltransferases), fluoroquinolones (eg, *gyrA* or *parC* mutations, *qnr* genes), and trimethoprim/sulfamethoxazole (eg, *dfr*, *sul* genes), resulting in a multidrug-resistant phenotype and often significantly limiting the utility of other antibiotic classes for CP-CRE infections [7, 21–24].

Non–CP-CRE accounts for more than half of CRE isolates from adults in the United States [10, 12]. Although no pediatric molecular epidemiologic data are available comparing the prevalence of CP-CRE vs non–CP-CRE in US children, available data suggest that non-carbapenemase–mediated resistance determinants are likely more common in children as well [13, 25]. Non–CP-CRE develop carbapenem resistance through coproduction of either Ambler class A ESBLs (eg, SHV, CTX-M) or Ambler class C cephalosporinases (AmpC enzymes) along with porin mutations (eg, OmpK35 or OmpK36) and/or the presence of efflux pumps (eg, AcrAB-TolC) [26–31].

GENERAL TREATMENT CONSIDERATIONS: CP-CRE VS NON–CP-CRE

In general, antibiotic choice should not be stratified based on the presence or absence of carbapenemase production, and the guidance provided herein should be applied similarly to patients with CP-CRE and non–CP-CRE. While it is possible that optimal treatment strategies may differ based on the presence or absence of carbapenemase production, data are currently insufficient to recommend this type of stratification.

Instead, we suggest using the results of carbapenem susceptibility testing to decide whether or not a patient can be treated with an extended-infusion carbapenem (most commonly extended-infusion meropenem) vs a newer βL-βLI agent (Figure 1). For carbapenem-resistant isolates (eg, those with a meropenem MIC ≥4 μg/mL), use of the novel

Table 1. Characteristics of Common Carbapenemases Produced by the *Enterobacteriaceae*

Ambler Class	Type of Beta-Lactamase	Active Site	Example(s)	Typical β-Lactam Resistance Profile	Inhibited by Avibactam	Inhibited by Vaborbactam	Inhibited by Relebactam	Geographic Distribution
Class A	Penicillinase	Serine	*Klebsiella pneumoniae* carbapenemase	All β-lactams: Carbapenem hydrolysis can vary from low- to high-level, resulting in variable meropenem minimum inhibitory concentration and occasional isolated ertapenem resistance	Yes	Yes	Yes	Global
Class B	MBL	Zinc	NDM, VIM, IMP	All β-lactams: Monobactams spared from MBL hydrolysis, but frequent coproduction of ESBLs and/or AmpCs mediate monobactam resistance	No	No	No	NDM-1: India, Pakistan, Balkan states VIM: Mediterranean basin IMP: Japan, southeast Asia
Class D	Oxacillinase	Serine	OXA-48– like	Penicillins, carbapenems: Cephalosporins spared from OXA hydrolysis, but ESBLs are often coproduced, resulting in cephalosporin resistance	Yes	No	More data are needed	Mediterranean basin, Middle East

Abbreviations: ESBL, extended-spectrum β-lactamase; IMP, active on imipenem; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

βL-βLI (ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-relebactam) should be considered for both CP-CRE and non–CP-CRE, if susceptible in vitro, for US isolates as KPC production remains the predominant carbapenemase-producing enzyme and KPC enzymes are generally inactivated by all three of these agents. If specific carbapenemase testing is available and a carbapenemase is identified, the specific carbapenemase identified can inform selection of a βL-βLI given differential activity based on carbapenemase type. While large molecular epidemiologic studies of non–CP-CRE characterizing novel β-lactamase activity against various combinations of Ambler class A and C β-lactamases, porin mutations, and efflux pumps across *Enterobacteriaceae* species are limited, the available in vitro data demonstrate high rates of susceptibility among non–CP-CRE isolates to the newer βL-βLI [32–36].

Finally, as with other *Enterobacteriaceae* infections, aminoglycoside monotherapy should be reserved for urinary tract infections. If used for invasive infections, aminoglycosides should be a component of combination therapy. No studies have specifically evaluated fluoroquinolone use for CRE, with only sporadic reports of their use for CRE in the literature [2, 37]. However, if fluoroquinolones or trimethoprim-sulfamethoxazole remain active against a CRE in vitro, there is no evidence to indicate that they should be excluded as treatment options.

CARBAPENEMS

Because the diverse resistance mechanisms that result in in vitro carbapenem resistance result in variably elevated meropenem MICs, meropenem has an important role in the treatment of CRE in clinical scenarios where meropenem MICs are ≤2 μg/mL. Bacterial killing by carbapenems is dependent on time of free drug above the MIC, with optimal effect if time above the MIC exceeds 40% [38]. Pediatric PK data demonstrate that in healthy children, an extended infusion of meropenem over 3 hours can achieve this target for isolates with meropenem MICs of up to 8 μg/mL [39]. However, in critically ill children, target serum concentrations are only reliably achieved for isolates with meropenem MICs ≤2 μg/mL due to alterations in the volumes of distribution expected with sepsis [40]. There are limited clinical data related to the effectiveness of carbapenem monotherapy for the treatment of CRE in adults. However, consistent

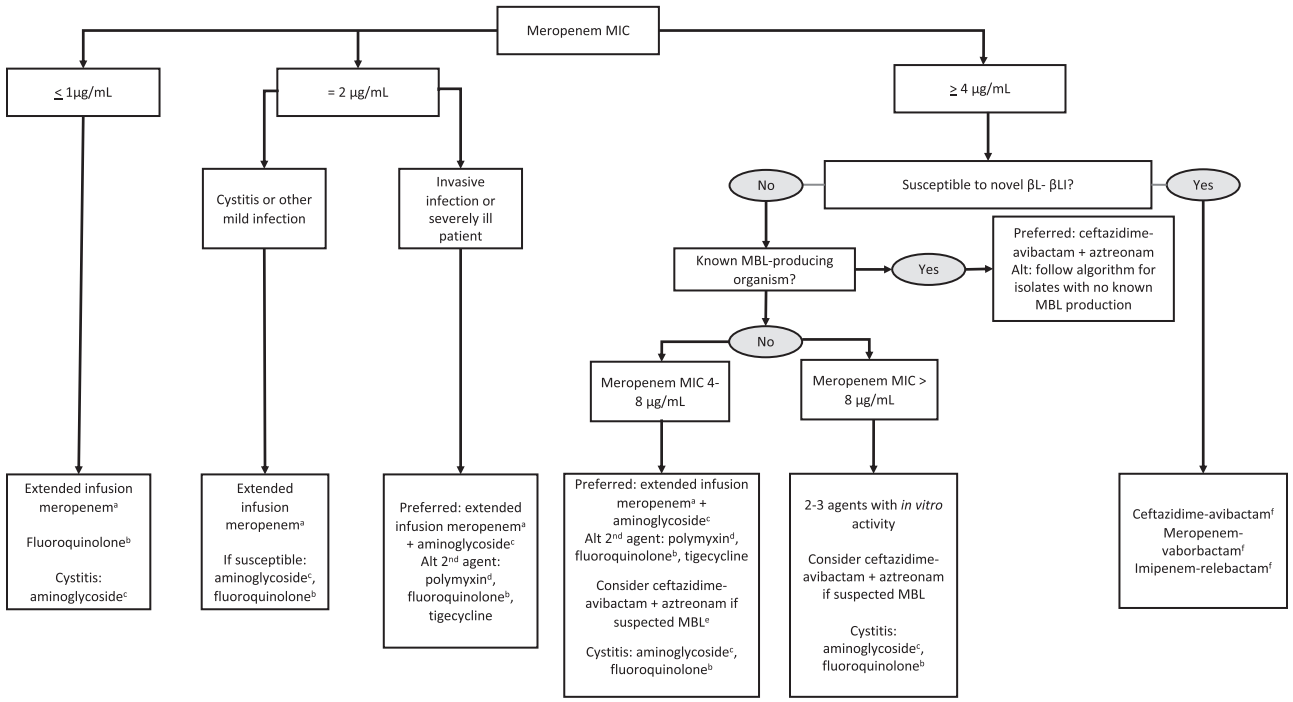

Figure 1. Suggested framework for antibiotic selection for children with carbapenemase–carbapenem-resistant *Enterobacteriaceae* (CP-CRE) and non–CP-CRE. [a]Meropenem administered over 3 hours can achieve target serum concentrations for isolates up to 8 μg/mL in healthy children. [b]Fluoroquinolones are variably active against CRE. If susceptible, these agents can be used as part of combination regimens or as monotherapy for mild to moderate infections. [c]Aminoglycosides are recommended as first-line agents for use in combination for systemic infections given pediatric clinical experience and familiarity with dosing. Aminoglycosides may also be used for cystitis as monotherapy. [d]The polymyxin class includes colistin and polymyxin B. Polymyxin B is preferred given ease of dosing and more reliable pharmacokinetics for nonurinary sources of infection. For urinary tract infections, colistin is preferred. [e]Consider in children with epidemiologic link to a MBL-endemic region (eg, South Asia) or known history of MBL-producing isolate. [f]If the MIC for ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-relebactam is at the breakpoint, addition of a second agent could be considered, with aminoglycosides preferred. Abbreviations: Alt, alternative; βL-βLI, β-lactam/β-lactamase inhibitor; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration. (cUTIs) and (cIAIs;

with available PK data, carbapenems appear most effective for isolates with carbapenem MICs ≤4 μg/mL, with clinical success reported in 69% of patients with carbapenem MICs in this range compared with 29% with carbapenem MICs >8 μg/mL [41, 42].

Based on the PK and limited clinical data, we suggest extended-infusion meropenem for nonsevere infections (eg, infections of the urinary tract) caused by CRE isolates with a meropenem MIC ≤2 μg/mL or invasive infections caused by CRE isolates with a meropenem MIC ≤1 μg/mL (ie, those isolates that met the criteria for CRE because of resistance to another carbapenem; Figure 1 and Table 2). Based on observational studies that indicate improved outcomes for patients with primarily CP-CRE treated with novel βL-βLI agents approved after 2014, these agents should preferentially be considered over carbapenems for infections with meropenem MICs ≥4 μg/mL [43–45].

NOVEL β-LACTAM AGENTS

Ceftazidime-Avibactam

Ceftazidime-avibactam is a βL-βLI combination approved by the FDA in March 2019 for children ages ≥3 months [46–49]. Avibactam is a β-lactamase inhibitor that binds reversibly to serine-β-lactamases and is therefore active against most KPC and OXA-48–like carbapenemases but inactive against MBL producers [50]. However, use of the combination of ceftazidime-avibactam and aztreonam has been reported as salvage therapy for MBL-producing CRE (Figure 1 and Table 1) [51]. The mechanism that underlies this approach is that aztreonam is resistant to degradation by MBLs, but frequent coproduction of Ambler class A and D enzymes (which hydrolyze aztreonam) by most MBL-producing isolates limits use of aztreonam as monotherapy. Avibactam, however, effectively inhibits these serine carbapenemases, thus allowing aztreonam to remain active [52]. In vitro susceptibility to ceftazidime-avibactam among KPC producers is high, with 2 large series reporting approximately 98% of tested isolates susceptible at the current Clinical and Laboratory Standards Institute (CLSI) breakpoint of ≤8/4 μg/mL [6, 35, 53]. While non–CP-CRE susceptibilities were not specifically reported, susceptibility to ceftazidime-avibactam among all meropenem-nonsusceptible *K. pneumoniae* was 99% [35].

Several observational studies and case series have reported on clinical experiences with ceftazidime-avibactam for the treatment of CRE infections in adults, including comparative effectiveness studies that demonstrated improved outcomes with ceftazidime-avibactam compared with other treatment regimens [43–45, 54–56]. The comparator groups used in these studies were variable and heterogeneous, including patients treated with carbapenems, colistin, tigecycline, fosfomycin, and/or aminoglycosides, often in combination [43–45]. A pediatric case series that included 8 children similarly reported successful treatment of invasive CRE infections with ceftazidime-avibactam [57]. Notably, several reports have highlighted the potential for ceftazidime-avibactam

Table 2. Suggested Pediatric Dosing for Antibiotics Used to Treat Carbapenem-Resistant *Enterobacteriaceae* Infections

Antibiotic[a]	Dosing
Meropenem	40 mg/kg/dose IV q8h infused over 3 hours (max 2000 mg/dose)
Meropenem-vaborbactam[b]	40 mg/kg/dose meropenem and 40 mg/kg/dose vaborbactam (max 2000 mg/dose) IV q8h infused over 3 hours
Ceftazidime-avibactam	Aged 3 months to 6 months: 40 mg/kg/dose ceftazidime and 10 mg/kg/dose avibactam IV q8h infused over 2 hours Aged 6 months to <2 years: 50 mg/kg/dose ceftazidime and 12.5 mg/kg/dose avibactam IV q8h infused over 2 hours Aged 2 years to 18 years: 50 mg/kg/dose ceftazidime (max 2000 mg ceftazidime/dose) and 12.5 mg/kg/dose avibactam (max 500 mg avibactam/dose) IV q8h infused over 2 hours
Imipenem-relebactam[c]	Aged 3 months to < 2 years: dose not available as of September 2019 Aged 2 years to <12 years: 15 mg/kg/dose imipenem (max 500 mg) and 7.5 mg/kg/dose relebactam (max 250 mg) IV q6h infused over 30 minutes Aged 12 to <18 years: 500 mg imipenem and 250 mg relebactam IV q6h infused over 30 minutes
Amikacin	7.5 mg/kg/dose IV q8h (no maximum dose[d]) *or* Extended interval: 15 to 20 mg/kg/dose IV q24h (no maximum dose[d])
Gentamicin	2.5 mg/kg/dose IV q8h (no maximum dose[d]) *or* Extended interval: (no maximum dose[d]) Aged ≥3 months to <2 years: 9.5 mg/kg/dose IV q24h Aged 2 to <8 years: 8.5 mg/kg/dose IV q24h Aged ≥8 years and adolescents: 7 mg/kg/dose IV q24h
Tobramycin	2.5 mg/kg/dose IV q8h (no maximum dose[d]) *or* Extended interval: (no maximum dose[d]) Aged ≥3 months to <2 years: 9.5 mg/kg/dose IV q24h Aged 2 to <8 years: 8.5 mg/kg/dose IV q24h Aged ≥8 years and adolescents: 7 mg/kg/dose IV q24h
Ciprofloxacin	10 mg/kg/dose IV q8h (max 400 mg/dose) *or* 20 mg/kg/dose PO q12h (max 1000 mg/dose)
Levofloxacin	Aged 6 months to <5 years: 10 mg/kg/dose IV/PO q12h (max 375 mg/dose) Aged ≥5 years: 10 mg/kg/dose IV/PO q24h (max 750 mg/dose)
Tigecycline	Aged ≥ 8 years: 4 mg/kg/dose IV loading dose × 1 (max 200 mg/dose) followed by 2 to 3.2 mg/kg/dose IV q12h (max 100 mg/dose[e])
Colistin	5 mg/kg dose IV loading dose × 1 (maximum dose 300 mg CBA[f]), followed by 2.5 mg/kg/dose IV q12h (maximum dose 180 mg CBA[f])
Polymyxin B	25 000 units/kg loading dose × 1, followed by 15 000 units/kg/dose IV q12h (maximum dose of 2 000 000 units/day [f])
Aztreonam	>1 month: 120 mg/kg/day IV divided q6 to 8h infused over 3 h (max 8000 mg/day)
Eravacycline	No pediatric dosing available
Plazomicin	No pediatric dosing available

Abbreviations: CBA, colistin-base activity; h, hour; IV, intravenous; PO, per os/by mouth; q, every.

[a] Listed dosing and intervals assume normal renal function and apply to children aged >30 days except as noted.

[b] Dose used in ongoing phase 1 pharmacokinetic study (NCT02687906); interval derived from usual interval for meropenem administration as well as adult dosing interval for meropenem-vaborbactam.

[c] Dose used in planned phase 2/3 trial for children with complicated intraabdominal infections and complicated urinary tract infections (NCT03969901).

[d] Dosing should be based on adjusted body weight when actual body weight is 30% greater than ideal body weight.

[e] Maximum dose of 100 mg 2 times a day is based on the dose used in adult clinical trials. However, the authors have used a dose of up to 150 mg/dose for treatment of carbapenem-resistant infections.

[f] Maximum doses based on adult daily maximum.

resistance to develop following even a short duration of therapy, including 1 report in which resistance developed due to KPC mutations in 3 of 10 microbiologic failures [56, 58]. These findings underscore the importance of ceftazidime-avibactam antibiotic susceptibility testing for CRE isolates, which may not be routinely performed at many institutions, as well as vigilance for emerging resistance while on therapy.

Meropenem-Vaborbactam

Meropenem-vaborbactam is a βL-βLI approved by the FDA in 2017 [59]. Vaborbactam is a cyclic boronic acid–based β-lactamase inhibitor that inhibits serine carbapenemases including KPC, but not MBLs or OXA-type carbapenemases [16]. It has high in vitro activity against KPC-producing CRE [34, 60]. In a study that included 991 KPC-producing isolates, 99% were susceptible using the CLSI breakpoint of ≤4/8 μg/mL [6, 60]. Among non–CP-CRE, the addition of vaborbactam resulted in a 4-fold decrease in the meropenem MIC, with more than 95% of isolates susceptible using the CLSI breakpoint [34].

Although clinical data related to the use of this drug for the treatment of CRE are limited, a phase 3, randomized, controlled trial compared treatment with meropenem-vaborbactam monotherapy (n = 32) with the best available therapy (n = 15) for invasive CRE infections, including bacteremia (44%), (35%) complicated urinary tract infection (cUTI), pneumonia (13%), and complicated intra-abdominal infection (cIAI) (6%). Sixty-six percent of patients treated with meropenem-vaborbactam experienced clinical cure at the end of therapy compared with 33% of patients treated with the best available therapy, achieving statistical significance [61]. Development of resistance during therapy with meropenem-vaborbactam appears infrequent based on in vitro data and was not observed in the previously mentioned phase 3 trial, though 1 isolate out of 32 obtained post-randomization did exhibit a 4-fold increase in the meropenem MIC [61–63]. The extent to which resistance to meropenem-vaborbactam will occur during or following meropenem-vaborbactam therapy is unknown, but vigilance for this phenomenon is required as the drug becomes used more widely.

Pediatric data are limited to a single case report in which a 4-year-old child with KPC-producing *K. pneumoniae* bloodstream infection was treated successfully with meropenem-vaborbactam [64]. A phase 1 study evaluating dosing, PK, and safety of meropenem-vaborbactam in children is underway (NCT02687906) [65].

Imipenem-Relebactam

Imipenem-relebactam is a βL-βLI approved by the FDA in July 2019 [66, 67]. Like avibactam, relebactam is a β-lactamase inhibitor that is highly active against KPC-producing isolates but not MBL-producing isolates [16, 36, 68]. More data are needed for OXA-48–producing isolates. The addition of relebactam also resulted in a dose-dependent reduction in imipenem MICs in 10 non–CP-CRE isolates [36].

Clinical data related to the use of imipenem-relebactam for CRE infections are limited to a phase 3 trial that included 31 patients with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), cIAI, or cUTI caused by imipenem-nonsusceptible *Pseudomonas aeruginosa* (24/31) and *Enterobacteriaceae*. This study compared imipenem-relebactam vs the combination of imipenem and colistin. An overall favorable clinical response was demonstrated in 71% of the imipenem-relebactam group vs 70% of the imipenem-colistin group, and importantly, nephrotoxicity was significantly less frequent in the imipenem-relebactam group than in the imipenem-colistin group (10% vs 56%) [69]. Despite the small number of CRE patients included, these findings are relevant to clinicians given the unfavorable side-effect profile of colistin compared with imipenem-relebactam demonstrated in this study. Finally, a phase 3 study that evaluated imipenem-relebactam vs piperacillin-tazobactam for the treatment of VAP and HAP in adults was recently completed, with results pending [70]. A phase 1 PK study (NCT03230916) and a phase 2/3 treatment study in children with suspected or confirmed gram-negative infections (NCT03969901) are ongoing [71, 72].

Suggested Use of Novel βL-βLI

Novel βL-βLI should be strongly considered as first-line options for susceptible CRE isolates with meropenem MICs ≥4 μg/mL or isolates known to produce KPC based on rapid molecular diagnostic testing. Though pediatric data are limited, extensive clinical experience with the β-lactam component of each of the novel βL-βLI in children, efficacy data from adult studies, and significant challenges associated with other CRE active agents make these preferred agents (Figure 1 and Table 2). Formulary considerations, regional prevalence of KPC vs OXA-48-like enzymes, and the results of antibiotic susceptibility testing should be considered when selecting 1 of these 3 agents.

COMBINATION THERAPY

Because of the historical lack of antibiotics with good in vitro activity against KPC-producing CRE, the possible benefit of combining 2 or more agents (sometimes with limited in vitro activity) has been explored in several observational studies. Most of these studies focused on adults with KPC-producing bloodstream infections and demonstrated a mortality benefit with combination antibiotic therapy, in particular, with carbapenem-containing combinations [73–77]. Other studies have suggested that this benefit is limited to patients at highest risk for mortality (including patients with septic shock, rapidly fatal underlying diseases, and bacteremia from nonurinary/nonbiliary sources) and, specifically, for carbapenem-containing combinations, for isolates with carbapenem MICs ≤8 μg/mL [37, 78,

79]. No published randomized trials have sufficiently compared monotherapy with combination therapy in patients with CRE. One trial enrolled a small number of CRE patients (73/406) and compared the impact of colistin vs colistin plus meropenem in patients with infections due to carbapenem-resistant gram-negative organisms, though the majority of patients included in this study were infected with carbapenem-resistant *Acinetobacter baumannii* (312/406). Although no difference in a composite clinical and microbiological outcome was detected, the trial was not powered to evaluate differences in outcomes among the small number of CRE patients enrolled, limiting the generalizability of these data to patients with CRE infections [80].

As the methodologic quality of many of these studies was relatively low, with significant variation in antibiotics used in combination, varied definitions of carbapenem resistance, lack of sufficient statistical adjustment for confounding factors, and variable timing of exposure and outcome classification, interpretation of their findings is challenging. Perhaps reflecting these methodologic limitations, other studies have failed to demonstrate any benefit with combination therapy [81–83]. Finally, and perhaps most importantly, combination regimens have historically utilized drugs with limited in vitro activity against CRE, a paradigm that has shifted with the availability of newer β-lactam agents with excellent activity against most CRE isolates. The impact of combination therapy when one of the newer agents is utilized has not been formally evaluated, but available data do not support the need for the routine addition of a second agent.

If a second agent is added because the β-lactam prescribed (ie, a carbapenem or one of the novel β-lactams) has an MIC at the breakpoint, we preferentially prescribe an active aminoglycoside over polymixins, whenever susceptible, given availability of pediatric-specific PK-PD data to inform dosing, greater familiarity with therapeutic drug monitoring, more pediatric clinical experience with these agents, and published experience with aminoglycosides for treatment of CRE infections [37, 75–78, 81, 84] (Figure 1).

Finally, a second scenario in which treatment with 2 antibiotics is warranted is in the treatment of MBL-producing CRE, where use of both aztreonam and ceftazidime-avibactam can be considered [51]. However, the need for combination therapy in this scenario is a practical one related to the lack of a commercially available single antibiotic that contains both aztreonam and avibactam as of September 2019.

POLYMIXINS

Colistin

Colistin achieves bactericidal killing by binding to negatively charged phosphate moieties in the lipopolysaccharide layer of the cell membrane, thus disrupting the cell membrane and causing loss of intracellular products [85]. Resistance is reported in up to 27% of CRE, generally due to chromosomally mediated mechanisms [86]. Plasmid-mediated *mcr* genes remain a rare cause of colistin resistance [87].

Challenges to the clinical use of colistin include complex pharmacokinetics that result from colistin being administered as a prodrug (colistimethate [CMS]) with slow, unpredictable, and incomplete conversion to active drug; variable dose unit definitions depending on region (Table 3); nephrotoxicity in approximately 40–60% of adults; and controversy surrounding optimal susceptibility testing methodology [88–90]. Administration of a colistin loading dose results in more rapid serum target attainment and use of doses higher than those currently recommended by the FDA may be needed to achieve adequate serum concentrations, particularly for organisms with colistin MICs ≥1 μg/mL and in patients with normal renal function [91–97].

Observational clinical studies focused on comparing colistin to other CRE-active agents have suggested high mortality rates with use of colistin monotherapy for CRE [73, 74, 76, 83], including a comparative effectiveness study that demonstrated a higher probability of poor outcomes with a colistin-based regimen compared with ceftazidime-avibactam [45].

Pediatric data related to colistin are limited. Like adult studies, pediatric PK data generally suggest that the doses currently recommended by the FDA result in inadequate serum concentrations [98–100]. One report suggested that a loading dose of 150 000 units/kg followed by 75 000 units/kg every 12 hours (slightly higher than the doses recommended in the United States; Tables 2 and 3) achieved target attainment in almost all patients [101]. However, the methodology used in this study has been questioned by experts who recommend caution in interpreting the investigators' conclusions [102]. Clinical data in children are limited to case series and have often included patients with both CRE and other carbapenem-resistant organisms [103–105]. While clinical success rates were generally >70% and nephrotoxicity reported in <20% of children in these studies, an association between colistin monotherapy and mortality has been observed [3, 103–105].

Polymyxin B

Polymyxin B has a spectrum of activity similar to colistin, differing from colistin by only a single amino acid [85].

Table 3. Colistin and Polymyxin B Dosage Conversions

Colistimethate Sodium	Colistimethate Sodium	Colistin-base Activity
30 000 units	2.4 mg	1 mg
1 000 000 units	80 mg	34 mg
4 500 000 units	360 mg	150 mg
9 000 000 units	720 mg	300 mg
Polymyxin B		
10 000 units	1 mg	…

However, unlike colistin, polymyxin B is administered in its active form, which results in more rapid and consistent achievement of therapeutic concentrations in adult PK studies, though a loading dose is still recommended [106–110]. Polymyxin B does not rely on renal excretion, so dose adjustments based on renal impairment are not necessary [106, 110]. Of note, this lack of renal tubular secretion makes polymyxin B a less favorable option for urinary sources. Few clinical studies have compared colistin and polymyxin B, but available data suggest a lower incidence of nephrotoxicity and no difference in clinical outcomes for adults treated with polymyxin B [111]. Pediatric clinical and PK data are limited to case reports and case series [112–114].

Suggested Use of Polymyxins

While newer β-lactams have largely replaced the polymyxins for susceptible CRE isolates, polymyxins remain a consideration for MBL-producing isolates or in situations where alternatives to these agents are sought [115]. We favor polymyxin B over colistin given its more favorable PK characteristics and lower rates of nephrotoxicity for nonurinary sources of infection, with colistin favored for urinary sources [110, 115]. We recommend combination therapy whenever polymixins are prescribed (Figure 1) [110]. Finally, we recommend a loading dose be administered with either polymyxin based on the PK characteristics of these agents (Table 2).

TIGECYCLINE

Tigecycline is a glycylcycline antibiotic that acts on the bacterial ribosome and has excellent in vitro activity against CRE isolates, with 89% reported susceptible [116]. Tigecycline distributes rapidly into most tissues following administration, resulting in poor achievement of bactericidal serum concentrations at standard doses, and does not concentrate well in the lung endothelium or in urine [117]. Clinical data from observational studies suggest poor outcomes when tigecycline is used at standard doses as monotherapy for CRE infections, though this finding is likely dose-dependent as several subsequent studies have demonstrated improved efficacy of tigecycline for the treatment of CRE infections in adults with higher doses of 100 mg twice daily [73, 75, 76, 78, 118–121].

Published pediatric experience with tigecycline is limited to case reports, case series, and a PK study that demonstrated that a dose of 1–1.2 mg/kg of tigecycline every 12 hours achieves a similar area under the curve as standard adult doses [122, 123]. There are no PK data related to higher doses. However, based on improved efficacy observed in adult studies, doses of up to a 4 mg/kg loading dose followed by 2–3.2 mg/kg/dose every 12 hours have been reported [123].

Newer βL-βLI should replace tigecycline in cases of KPC- or OXA-producing CRE, but tigecycline may be an option for MBL-producing isolates. If used, we suggest a loading dose and a higher standing dose of 2–3.2 mg/kg/dose every 12 hours based on published series and our own clinical experience (Table 2). We also suggest combination therapy for bloodstream infections and in severely ill patients, while we suggest monotherapy for noncritically ill children with intraabdominal infections (Figure 1). Finally, tigecycline should generally be avoided for urinary sources when other options are available.

ERAVACYCLINE

The FDA approved eravacycline in 2018 [124]. Eravacycline is a synthetic tetracycline with good in vitro activity against KPC, MBL, and OXA-48–like *Enterobacteriaceae* and exhibits its mechanism of action through binding to the 30S ribosome [125, 126]. No clinical studies have evaluated its use specifically for CRE or other antibiotic-resistant organisms. In 2 trials that evaluated its use for cUTI, eravacycline failed to meet the noninferiority margin when compared with levofloxacin and ertapenem [127]. Despite these findings, eravacycline likely has a role in treatment of nonurinary and nonbacteremic infections due to CRE, including those due to MBL-producing isolates. A phase 1 pediatric study evaluating the PK of eravacycline is currently ongoing (NCT03696550) [128].

PLAZOMICIN

The FDA approved plazomicin in 2018 for adults with cUTIs [129, 130]. Plazomicin is a semisynthetic aminoglycoside resistant to modification by most aminoglycoside-modifying enzymes, which results in increased activity against KPC and OXA-48–like producing CRE compared with other aminoglycosides, as well as some activity against MBL-producing isolates [131, 132]. Clinical data related to its use for CRE are limited. The single phase 3 randomized trial comparing plazomicin-containing combination therapy to colistin-containing combination therapy for CRE bloodstream infections and pneumonia was terminated for low enrollment after randomizing just 39 patients. However, the plazomicin-exposed group had lower mortality (12% vs 40%) and a lower likelihood of acute kidney injury (8% vs 38%), suggesting that plazomicin is preferred over colistin [133, 134]. Use of plazomicin in children with CRE infections is currently limited by lack of pediatric dosing information.

CONCLUSIONS

Treatment of CRE infections in children is complex. Therapeutic decisions require expert consultation and an individualized approach, often based on adult data given the dearth of pediatric studies. The meropenem MIC of the infecting isolate, type of carbapenemase produced, the patient's illness severity, and

source of infection should be considered when selecting antibiotic therapy. Finally, while the treatment recommendations contained herein reflect currently available data, treatment paradigms are likely to evolve over time as agents in the antibiotic pipeline become available and pediatric experience with available agents grows.

Notes

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