

Treatment of Multidrug-Resistant Gram-Negative Infections in Children

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Antibiotic resistance in conjunction with the erosion of the drug development pipeline may lead us into a bleak future, a “post-antibiotic era.” Because of a shortage of studies addressing treatment options for multidrug-resistant Gram-negative (MDRGN) infections in children, data must be extrapolated from the adult literature. However, even adult studies are limited by significant methodological flaws. We are in urgent need of pediatric specific pharmacokinetic/pharmacodynamic data for agents with activity against MDRGN infections as well as improved clinical outcomes studies. For the time being, we must rely on in vitro studies, observational data, and clinical experience to guide our therapeutic decisions. In this review, we discuss treatment considerations for infections caused by extended-spectrum β -lactamase-producing organisms, AmpC β -lactamase-producing organisms, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* in the pediatric population.

Keywords. extended-spectrum β -lactamases; carbapenemases; AmpC β -lactamases; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*.

Since the 1990s, the rise of multidrug-resistant Gram-negative (MDRGN) infections has posed a major clinical problem worldwide. MDRGN infections result in significant morbidity and mortality and have now made their way to infants and children [1]. Equally concerning is the withdrawal of several large pharmaceutical companies from antibacterial research and the limited development of novel agents for the treatment of MDRGN infections [2]. A 2013 report from the Infectious Diseases Society of America identified 7 drugs in development for the treatment of MDRGN infections in at least phase 2 of clinical development; however, only 1 of these agents (ceftazidime-avibactam) is currently being investigated in the pediatric population (NCT01893346) [3]. All of these agents have activity against extended-spectrum β -lactamases (ESBLs), and

some have activity against carbapenem-resistant Enterobacteriaceae (CRE), but none of these agents appear to have sufficient activity against carbapenem-resistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. In this review, we focus on treatment considerations for infections caused by ESBLs, AmpC β -lactamases (AmpCs), CREs, carbapenem-resistant *P. aeruginosa*, and carbapenem-resistant *A. baumannii* for the pediatric population.

EXTENDED-SPECTRUM β -LACTAMASES

ESBLs hydrolyze a broad range of β -lactams including penicillins, cephalosporins, and aztreonam, but not carbapenems [4] (Table 1). They are generally inhibited by β -lactamase inhibitors (eg, tazobactam, clavulanate), distinguishing them from AmpCs [4]. Although present in a number of Enterobacteriaceae, they have been of greatest clinical significance in *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis*, perhaps because phenotypic methods of ESBL identification are established for these organisms. Clinical detection of ESBL-producing Enterobacteriaceae is challenging, as the Clinical and Laboratory Standards Institute (CLSI) no longer recommends confirmatory phenotypic testing of

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Table 1. Summary of Clinically Important β -Lactamases Produced by Select Gram-Negative Organisms

Classification	Representative Enzymes	Some Notable Organisms
Class A	ESBLs (TEM, SHV, CTX-M-type groups)	<i>Escherichia coli</i> , <i>Klebsiella</i> spp, <i>Proteus mirabilis</i>
	Carbapenemases (KPC ^a)	<i>Klebsiella pneumoniae</i> , <i>E. coli</i> , <i>Klebsiella oxytoca</i> , <i>Serratia marcescens</i> , <i>Enterobacter</i> spp, <i>Citrobacter freundii</i>
Class B	Carbapenemases; metallo- β -lactamases (VIM, IMP, NDM-1)	<i>K. pneumoniae</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>S. marcescens</i> , <i>Enterobacter</i> spp, <i>C. freundii</i>
Class C	Cephalosporinases (AmpC)	Inducible chromosomal AmpCs: <i>Enterobacter</i> spp, <i>C. freundii</i> , <i>S. marcescens</i> , <i>Morganella morganii</i> , <i>Providencia stuartii</i>
		Plasmid-mediated AmpCs: <i>K. pneumoniae</i> , <i>E. coli</i> , <i>Salmonella enteritidis</i>
Class D	Carbapenemases (OXA)	<i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>C. freundii</i>

Abbreviations: AmpC, AmpC β -lactamase; ESBL, extended-spectrum β -lactamase.

^a Although *Klebsiella pneumoniae* carbapenemases are the most commonly described carbapenem-resistant Enterobacteriaceae in the United States, this resistance mechanism is found in a number of other Enterobacteriaceae.

E. coli, *Klebsiella* species, or *P. mirabilis* for organisms with characteristic susceptibility patterns [5]. This may be problematic as ESBL-producing organisms may appear susceptible in vitro to piperacillin-tazobactam and cefepime [6], even though treatment failures have been reported with these agents as described below.

Piperacillin-Tazobactam

The use of β -lactam- β -lactamase inhibitors (β L- β LI) for the treatment of ESBL infections is controversial. β LIs generally have in vitro activity against organisms possessing a single ESBL [4]. However, many organisms now produce multiple ESBLs simultaneously, reducing the effectiveness of the β LI, resulting in in vitro resistance [4]. Additionally, in vitro and case report data suggest that therapeutic failure with β L- β LIs may occur in high-inoculum infections [7, 8].

A meta-analysis of 21 observational studies of primarily adults with bacteremia due to ESBL-producing organisms comparing carbapenems and β L- β LIs found no difference in 30-day all-cause mortality [9]. Significant heterogeneity related to source of infection, discrepancies between empiric and definitive regimens, variability in dosing, interval, and duration of therapy, and confounding by indication due to the observational nature of the included studies limits applicability of these findings. A post hoc analysis of 192 adult patients with ESBL *E. coli* bacteremia from 6 prospective Spanish studies (included in the aforementioned meta-analysis) found no difference in 30-day all-cause mortality among patients receiving β L- β LIs vs carbapenems as either empiric or definitive therapy [10]. However, important limitations exist with this study. Approximately 44% of patients included in the β L- β LI empiric therapy arm had treatment broadened to a carbapenem agent after susceptibility data were available. Patients receiving definitive

carbapenem therapy had higher severity of illness scores. Additionally, approximately 70% of patients had urinary or biliary sources for their bacteremia, with a trend toward more urinary or biliary sources in the β L- β LI arm.

The pediatric literature is confined to small observational studies of neonates infected with ESBL-producing organisms with no difference in outcomes of neonates receiving β L- β LIs or carbapenems [11, 12]. However, these studies had insufficient power to detect a difference, if one exists. Existing data suggest that piperacillin-tazobactam may be a reasonable treatment option for ESBL-producing Enterobacteriaceae from a urinary source when appropriate dosing is used (Table 2); however, we prefer carbapenem therapy for invasive ESBL infections until a more rigorous study comparing β L- β LIs and carbapenems is performed.

Cefepime

Different ESBLs hydrolyze cephalosporins to various extents, and controversy exists whether cefepime remains a reliable option (Table 3). A retrospective, propensity score-matched study of 34 adults with ESBL bacteremia found increased clinical failure, microbiological failure, and 30-day mortality with cefepime compared with carbapenem therapy [13]. A randomized trial of cefepime vs imipenem-cilastatin for the treatment of 23 adult intensive care unit (ICU) patients with nosocomial pneumonia found a 69% clinical cure rate for patients receiving cefepime, compared with a 100% clinical cure for patients receiving imipenem-cilastatin [14]. Because of the lack of robust clinical data supporting cefepime for the treatment of ESBL infections, we do not recommend cefepime for this indication.

Carbapenems

Carbapenems demonstrate excellent in vitro activity against ESBL-producing organisms [15] and are considered the

Table 2. Suggested Antimicrobial Agents for the Treatment of Multidrug-Resistant Gram-Negative Infections in Children

	First-Line Agents	Second-Line Agents
Extended-spectrum β -lactamase-producing organisms	Meropenem 20–40 mg/kg/dose IV q8h; max 2 g per dose	Ciprofloxacin 10 mg/kg/dose IV q8h; max 400 mg IV per dose OR 20 mg/kg/dose PO q12h; max 750 mg PO per dose
	Imipenem-cilastatin 15–25 mg/kg/dose IV q6h; max 1 g per dose	Trimethoprim-sulfamethoxazole 5 mg/kg/dose of TMP IV/PO every 6–8 h
Urinary tract infections	Ertapenem 3 mo to 12 y: 15 mg/kg/dose IV q12h; max 500 mg per dose >12 y: 1 g IV q24h	Urinary tract infections Piperacillin-tazobactam 100 mg of piperacillin/kg/dose IV q6h; max 4 g of piperacillin per dose
		Nitrofurantoin ^a (cystitis) <12 y: 1.75 mg/kg/dose PO q6h; max 100 mg per dose \geq 12 y: macrocrystal/monohydrate (Macrobid) 100 mg PO q12h
		Oral fosfomycin (cystitis) <18 y: 2 g PO \times 1 dose \geq 18 y: 3 g PO \times 1 dose
		Aminoglycosides (cystitis) Gentamicin 2.5 mg/kg/dose IV q8h Amikacin 7.5 mg/kg/dose IV q8h
AmpC β -lactamase ^b -producing organisms	Meropenem (dosed as above)	Trimethoprim-sulfamethoxazole (dosed as above)
	Imipenem-cilastatin (dosed as above)	Ciprofloxacin (dosed as above)
	Adequate source control Cefepime 50 mg/kg/dose IV q8h; max 2 g per dose	
Carbapenem-resistant Enterobacteriaceae	Prolonged infusion meropenem 40 mg/kg/dose IV q8h, infused over 3 h; max 2 g per dose)	Tigecycline 8–11 y: 1.2 mg/kg/dose IV q12h; max dose 50 mg per dose 12 to <18 y: 50 mg IV q12h \geq 18 y: 100 mg IV loading dose, followed by 50 mg IV q12h
	PLUS Aminoglycoside (dosed as above)	
	OR Fluoroquinolone (dosed as above)	Intravenous fosfomycin (limited availability) 200 mg/kg/day IV divided q6-8h, up to 400 mg/kg/day; max of 16 g per day
	OR Colistin 5 mg/kg/dose IV loading dose of CBA, followed by 2.5 mg/kg/dose IV q12h of CBA	Oral fosfomycin (cystitis); (dosed as above)
Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	Prolonged infusion meropenem PLUS aminoglycoside OR fluoroquinolone OR colistin (dosed as above)	Fosfomycin (dosed as above)
Carbapenem-resistant <i>Acinetobacter baumannii</i>	Prolonged infusion meropenem PLUS aminoglycoside OR fluoroquinolone OR colistin (dosed as above)	Ampicillin-sulbactam 400 mg of ampicillin/kg/day IV divided every 4–6 h; max 2 g of ampicillin per dose
		Tigecycline (dosed as above)

Drug dosages and intervals assume normal renal function.

Abbreviations: AmpC, AmpC β -lactamase; CBA, colistin base activity; IV, intravenous; PO, oral; q, every; TMP, trimethoprim.

^a The use of nitrofurantoin should be limited to cystitis as treatment failures have been observed when prescribed for pyelonephritis.

^b Treatment suggestions are for *Enterobacter* species. For other organisms with chromosomally mediated inducible AmpC β -lactamase resistance (eg, *Citrobacter* species, *Serratia marcescens*), we suggest following in vitro susceptibilities, with the exception of central nervous system infections.

treatment of choice for invasive ESBL infections [9, 16]. Most of the experience treating ESBL infections lays with meropenem and imipenem-cilastatin; however, recent publications in

adults and children highlight the utility of ertapenem, particularly in urinary tract infections (UTIs) [17–19]. Because of limited clinical data evaluating the role of ertapenem for

Table 3. Anticipated In Vitro Susceptibility Pattern for *Klebsiella pneumoniae* Based on Type of β -Lactamase Production, Assuming Multiple Mechanisms of Resistance Not Present^a

Drug	Wild Type	Plasmid-Mediated			
		AmpC	ESBL	KPC	NDM-1
Piperacillin-tazobactam	S	R	S/R ^b	R	R
Ceftriaxone	S	R	R	R	R
Cefepime	S	S	S/R ^b	R	R
Aztreonam	S	R	R	R	S
Meropenem	S	S	S	S/R	R

Abbreviations: AmpC, AmpC β -lactamase; ESBL, extended-spectrum β -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo- β -lactamase; R, resistant in vitro; S, susceptible in vitro.

^a Based on current Clinical and Laboratory Standards Institute breakpoints.

^b Although may be susceptible in vitro, clinical failures have been observed. Some clinical microbiology laboratories always report ESBLs as resistant to piperacillin-tazobactam and cefepime even if susceptible in vitro.

invasive ESBL infections [20], we prefer meropenem or imipenem-cilastatin as first-line therapy for children with invasive ESBL infections. Ertapenem can be considered for infections with urinary sources or soft tissue infections when adequate source control has been achieved (Table 2).

Additional Options

Existing data suggest that fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), fosfomycin, and nitrofurantoin can be considered as alternative therapeutic options for ESBLs [9, 21, 22]. We believe ciprofloxacin or TMP-SMX can be prescribed (if susceptible in vitro) as first-line therapy for infections with a urinary source and after clinical improvement is demonstrated and adequate source control is achieved for other sources (Table 2). Caution should be used when prescribing fluoroquinolones to children owing to osteoarticular side effects observed in juvenile animals [23]. Although rapid emergence of resistance has been observed when aminoglycosides are used as single agents for bacteremia [24], we believe aminoglycoside monotherapy is sufficient therapy for uncomplicated ESBL UTIs, as aminoglycosides can achieve high concentrations in the urine.

The oral formulation of fosfomycin for the treatment of ESBL UTIs is particularly appealing because it is rapidly absorbed following a standard single 3-g oral dose [25]. High urinary concentrations are observed in approximately 4 hours and persist for several days [26]. The experience with oral fosfomycin in pediatrics is limited to a few published studies using a single 2-g dose for cystitis in children and adolescents [27]. Minimal renal parenchymal penetration and insufficient serum levels preclude the use of nitrofurantoin for upper urinary tract disease, although it remains an option for ESBL cystitis [28].

Table 4. Anticipated In Vitro Susceptibility Pattern for *Enterobacter* Species

Drug	AmpC β -Lactamase Encoded on Chromosome (Repressed State)	AmpC β -Lactamase Encoded on Chromosome (Derepressed State)
Piperacillin-tazobactam	S	R
Ceftriaxone	S	R
Cefepime	S	S
Aztreonam	S	R
Meropenem	S	S

Abbreviations: AmpC, AmpC β -lactamase; R, resistant in vitro; S, susceptible in vitro.

AmpC β -LACTAMASES

Enterobacteriaceae with chromosomally mediated inducible AmpCs are challenging, as isolates may initially appear susceptible in vitro but can develop resistance upon exposure to β -lactam therapy, a phenomenon most recognizable for third-generation cephalosporins [29]. Two mechanisms exist by which chromosomally mediated expression occurs: (1) induction in the presence of specific β -lactams or (2) selection of mutants with “de-repressed” AmpC production [29]. Plasmid-mediated AmpCs are not inducible and are emerging worldwide, most notably in *K. pneumoniae*, *E. coli*, and *Salmonella enteritidis* (Table 1). Currently, testing for AmpC expression is limited to the research setting.

Ceftriaxone

AmpC production is typically low (“repressed state”) for *Enterobacter* species, *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, and *Providencia stuartii*; however, derepression can occur (Table 4). *Enterobacter* species has been identified as the most problematic of these organisms [30–32]. At our institution, evaluating almost 400 clinical isolates of *Enterobacter* species, *S. marcescens*, and *Citrobacter* species, 38%, 15%, and 1% of these organisms, respectively, expressed AmpC production in a mixed population of adults and children [33]. Because of growing clinical data demonstrating therapeutic failure with the use of third-generation cephalosporins for *Enterobacter* species, we do not recommend these agents for invasive *Enterobacter* species infections [30, 31, 34–38]. However, we recommend ceftriaxone, if susceptible in vitro, for children infected with *S. marcescens*, *C. freundii*, *M. morganii*, and *P. stuartii* (without meningitis) because of the relatively low likelihood of AmpC derepression in these organisms.

Cefepime

Cefepime, a fourth-generation cephalosporin, is not typically hydrolyzed by AmpCs [29]. Cefepime demonstrates excellent

activity against a conventional Enterobacteriaceae inoculum, but dramatic increases in cefepime minimum inhibitory concentrations (MICs) occur when a 100-fold higher inoculum is present, making it a less reliable option for infections with a high bacterial burden such as undrained fluid collections or persistent hardware infections [39–41]. Emergence of resistance on cefepime therapy appears uncommon and is limited to case reports [42, 43]. Cefepime 2 g intravenously administered every 8 hours (in adults) has been shown to maintain serum concentrations sufficient to suppress emergence of derepressed AmpC mutants in vitro [44]. Observational studies, including approximately 50 mostly adult patients with *Enterobacter cloacae* bacteremia, found no emergence of resistance to cefepime therapy [32, 45, 46]. In a retrospective, propensity-score matched study of 78 predominantly adult patients, we found no difference in 30-day mortality or hospital length of stay comparing patients receiving cefepime compared with meropenem with confirmed AmpC-producing Enterobacteriaceae bacteremia, hospital-acquired pneumonia, or intra-abdominal infections [33]. However, virtually all included patients had adequate source control. Cefepime is an efficacious and a well-tolerated antibiotic in children [47]. We believe cefepime is a reasonable treatment option for children with invasive *Enterobacter* species infections in the setting of adequate source control (Table 2).

Carbapenems

Carbapenems are not susceptible to hydrolysis by AmpCs [29] and exhibit excellent in vitro activity against Enterobacteriaceae [39, 40], making them the treatment of choice for AmpC producing Enterobacteriaceae infections [36, 48]. However, widespread use of carbapenems is not without consequence, particularly in the era of carbapenem-resistant Gram-negative organisms. We reserve carbapenems for high-inoculum infections due to *Enterobacter* species (eg, meningitis, undrained intra-abdominal abscesses, osteomyelitis, endocarditis, presence of prosthetic material).

Additional Options

Literature supporting the use of TMP-SMX for the treatment of AmpC-producing Enterobacteriaceae are limited to case series [49, 50]. We believe TMP-SMX and fluoroquinolones are potential options if β -lactams cannot be tolerated or oral therapy is preferred. The role of piperacillin-tazobactam or aztreonam for the treatment of AmpC-producing bacteria has not been well studied.

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

Clinically important carbapenemases consist of 3 groups of enzymes as described in Table 1. Importantly, carbapenemase production does not always translate to clinical failure with carbapenems clinical failure with carbapenems [51].

Therapeutic efficacy has been reported at approximately 70% for MICs of 4 μ g/mL (reported as resistant according to current CLSI guidelines), no different from MICs ≤ 2 μ g/mL [52]. The mainstay of treatment for CRE is combination therapy of at least 2 agents with in vitro activity, which has been found in multiple observational studies to be more efficacious than monotherapeutic options (Figure 1) [52, 55–59].

Prolonged Infusion Carbapenem Therapy

Bacterial killing is enhanced when the nonprotein-bound β -lactam concentration exceeds the MIC ($f_T > \text{MIC}$) of the organism at least 40% of the time for carbapenems [60]. Intermittent dosing can lead to precipitous drops in serum drug concentrations as meropenem is rapidly cleared through the kidneys. Prolonging the infusion leads to a higher probability of achieving target $f_T > \text{MIC}$ [61]. In children, a meropenem dose of 40 mg/kg/dose intravenously every 8 hours reliably achieves this target for MICs ≤ 2 μ g/mL. For MICs of 4–8 μ g/mL, a prolonged infusion of meropenem over 3 hours can be employed for target attainment [54]. Although clinical data are lacking, in children with CRE infections due to isolates with meropenem MICs of up to 8 μ g/mL, we employ prolonged infusion meropenem therapy in combination with another active agent such as an aminoglycoside, fluoroquinolone, or colistin [54] (Figure 1). Although adult data regarding the pharmacokinetics and efficacy of prolonged-infusion doripenem exists [62–64], there is limited published experience on its use in patients aged <18 years [65].

Polymyxins

Previously retired agents such as polymyxins are being increasingly prescribed for the treatment of CRE. Unfortunately, these second-line agents are often more toxic than β -lactams and appear prone to the emergence of resistance, making the addition of a second agent standard practice [66]. Two polymyxins are commercially available, polymyxin B and polymyxin E (colistin), with similar antibacterial spectra of activity and bactericidal activity. Because polymyxins became clinically available before the advent of contemporary drug-development procedures, there are substantial gaps in knowledge regarding their pharmacokinetics and pharmacodynamics. Recent clinical reports have demonstrated a more favorable tolerability and safety profile of polymyxins compared with reports from several decades ago with nephrotoxicity and neurotoxicity reported in up to 22% and 4% of children, respectively [67].

Colistin is administered parenterally in the form of its inactive prodrug colistin methanesulfonate (CMS), which is slowly and incompletely converted to colistin [68]. Even after administering a loading dose, several hours of delay occurs before achievement of the maximum serum concentration of colistin. Rapid clearance of CMS may reduce the systemic availability of colistin to levels insufficient to overcome infections [68].

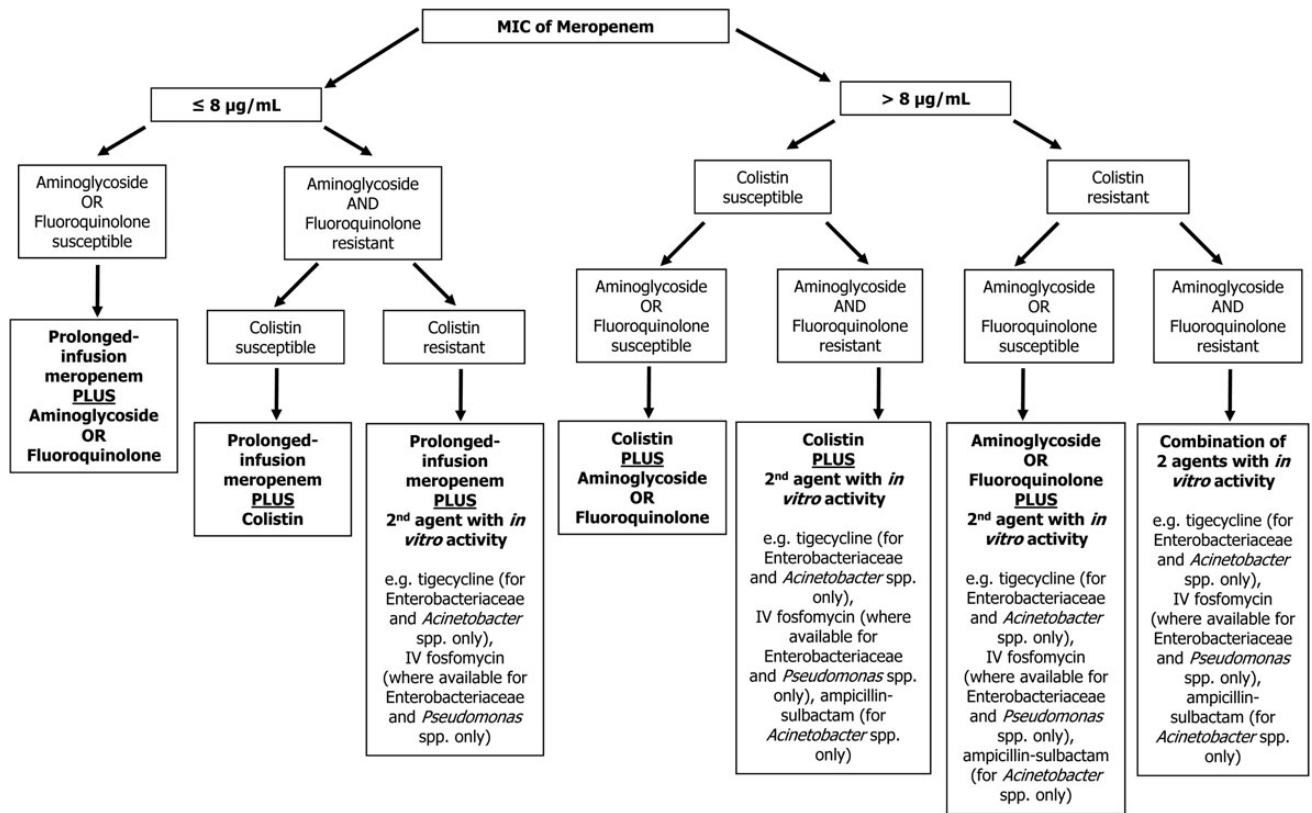


Figure 1. Proposed treatment algorithm for carbapenem-resistant Gram-negative organisms. Adapted with permission from George L. Daikos [53]. Although published clinical data in adults suggest that treatment outcomes with meropenem are less favorable with minimum inhibitory concentrations (MICs) >4 µg/mL, pediatric pharmacokinetic studies suggest that the nonprotein bound meropenem serum concentration exceeds the MIC for 40% of the time for organisms with MICs as high as 8 µg/mL when prolonged infusion strategies are utilized [54]. Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration.

Differences in dosing and conversions between formulations of colistin impede cross-study comparisons [69, 70]. One million units (MU) of CMS is equivalent to approximately 30 mg of colistin base activity (CBA), which corresponds to approximately 80 mg of the chemical CMS [71]. Recent adult pharmacokinetic studies suggest a loading dose of 9 MU of CMS intravenously (ie, 270 mg CBA or approximately 3.9 mg/kg/dose for a 70-kg adult), followed by 4.5 MU of CMS intravenously every 12 hours (ie, 135 mg CBA every 12 hours or approximately 1.9 mg/kg/dose for a 70-kg adult) [71–73]. The typical dose of colistin in children is 2.5 mg/kg/dose of CBA intravenously every 12 hours [67]. Although the utility of a loading dose has not yet been evaluated in children, the concept of achieving desired serum drug concentrations faster makes loading doses a logical approach. We suggest an intravenous loading dose of 5 mg/kg/dose of CBA.

Adult pharmacokinetic data suggest that colistin serum concentrations may be inadequate with CMS monotherapy in patients with normal or near-normal renal function or organisms with colistin MICs ≥1 µg/mL [74]. A multicenter, randomized,

controlled trial is currently under way in the adult population to evaluate the role of colistin in combination with imipenem-cilastatin vs colistin alone for the treatment of bacteremia and/or pneumonia due to carbapenem-resistant Gram-negative organisms (NCT01597973).

Polymyxin B does not have a prodrug and is administered in the form of its active microbiological agent. Adult data suggest that nephrotoxicity is less concerning with this agent compared with colistin as urinary excretion is minimal [75]. Pharmacokinetic studies have not been conducted in children, and published clinical experience in the pediatric population is limited [76].

Tigecycline

Tigecycline is a broad-spectrum, intravenous, bacteriostatic agent designed to be a poor substrate for tetracycline-specific efflux pumps [77]. Tigecycline monotherapy was associated with increased mortality compared with other regimens in a meta-analysis of randomized trials [78], possibly attributable to unfavorable pharmacokinetics, where serum concentrations peak at <1 µg/mL and promptly decline due to rapid tissue

distribution [79]. Limited renal excretion makes it an undesirable choice for UTIs [79]. The US Food and Drug Administration discourages the routine use of tigecycline [80]. However, its use in combination with other active agents may be considered when alternative treatment options are exhausted [55, 56, 58, 59]. Experience with tigecycline in pediatrics is limited [76, 81–83]. Tigecycline may cause permanent teeth discoloration and enamel hypoplasia in children aged <8 years [77]. Tigecycline should not be prescribed if other effective antibiotic choices with activity against CRE are available.

Fosfomycin

Fosfomycin remains active against the majority of CRE isolates with the ability to achieve adequate concentrations in urine, plasma, bronchoalveolar lavage fluid, and cerebrospinal fluid when the intravenous formulation is used [84]. In regions where intravenous formulations are available (Japan and a few European countries), suggested pediatric dosages are available (Table 2) [85]. Resistance to fosfomycin can develop rapidly when used as monotherapy [86]; therefore, although clinical data are limited [87], most experts agree that intravenous fosfomycin should be combined with other active agents if prescribed for the treatment of CRE infections (Figure 1). As with ESBLs, oral fosfomycin remains an option for CRE cystitis in older children and adolescents (Table 2).

CARBAPENEM-RESISTANT *PSEUDOMONAS AERUGINOSA*

Acquired resistance of *P. aeruginosa* to normally active β -lactams, quinolones, and aminoglycosides can be mediated by a number of mechanisms, including degrading enzymes, loss of porins, and active efflux pumps [88]. Isolates resistant to imipenem-cilastatin may be susceptible to meropenem, and vice versa. Susceptibility to specific carbapenems should be confirmed prior to their use.

Prolonged Infusion of Carbapenems, Polymyxins, and Fosfomycin

When MICs are elevated to all available β -lactams, prolonging the infusion of meropenem with the addition of an aminoglycoside, fluoroquinolone, or colistin can be considered (Figure 1). Although tigecycline is not active against *P. aeruginosa*, polymyxins and fosfomycin remain viable options. Susceptibility testing for these agents should be performed prior to use.

Inhaled Polymyxins

Because *P. aeruginosa* is often the culprit in hospital-acquired pneumonia, the role of inhaled colistin in combination with intravenous colistin has been explored. Efficacy data are conflicting [89–91]. Although these agents have the theoretical advantage of increasing drug levels in bronchial secretions

while reducing systemic side effects, they have been associated with bronchospasm [90]. The extent to which CMS is converted to colistin in infected lung tissue after nebulization is unknown. Pending more data on inhaled colistin, we do not routinely recommend inhaled colistin as adjunctive therapy for patients with carbapenem-resistant pneumonia.

CARBAPENEM-RESISTANT *ACINETOBACTER BAUMANNII*

Acinetobacter species have emerged as important nosocomial pathogens worldwide, capable of accumulating multiple antibiotic resistance genes, including β -lactamases, alterations in membrane permeability, and efflux pumps, leading to the emergence of strains resistant to all commercially available antibiotics [92]. As with other carbapenem-resistant organisms, prolonged infusion carbapenem therapy in combination with a second agent is a reasonable therapeutic approach (Figure 1).

Ampicillin-Sulbactam, Polymyxins, and Tigecycline

The sulbactam component of ampicillin-sulbactam may retain activity against highly drug-resistant *A. baumannii* [93] and remains a treatment option for carbapenem-resistant *Acinetobacter* species when susceptible in vitro (Table 2). Although combination therapy with ampicillin-sulbactam is not well studied, we would suggest using it with a second active agent (Figure 1). Polymyxins have been used with variable success for the treatment of *A. baumannii* pneumonia, bacteremia, and meningitis [94–96]. Despite the limitations of existing data, we believe intravenous polymyxins remain an option for patients infected with *Acinetobacter* species resistant to β -lactam agents. When no other options are available, tigecycline should be considered (Table 2).

Rifampin

Rifampin has the unique capacity to penetrate intracellular sites and biofilms [97]. Its use has been explored for the treatment of carbapenem-resistant infections, but clinical data appear inconclusive [97–99]. A multicenter randomized study compared colistin vs colistin and rifampin in 210 adult Italian ICU patients infected with carbapenem-resistant *A. baumannii* [100]. Attributable mortality, hospital length of stay, and development of colistin resistance were equivalent between the 2 groups. However, imbalances between additional active antimicrobials in the 2 arms may have confounded results. If rifampin is prescribed, concomitant medications such as immunosuppressive agents, warfarin, chemotherapy, and azoles should be carefully reviewed as rifampin puts the host at risk for a number of clinically significant drug–drug interactions.

CONCLUSIONS

MDRGN infections continue to be a growing problem in the pediatric population. There are virtually no studies with rigorous methods to direct therapeutic options in children, and data must be extrapolated from the adult literature. However, even adult studies are limited by significant methodological flaws. Well-designed clinical outcomes studies are needed. Additionally, pediatric-specific pharmacokinetic/pharmacodynamic data for agents with activity against MDRGNs are necessary. Regardless of the therapy selected, the fundamental concepts of effective antimicrobial therapy in critically ill children remain: proper culture techniques, timely initiation of therapy, selection of agents with a high likelihood of susceptibility and sufficient penetration to the site of infection, adequate doses and intervals to enhance bactericidal activity, and prompt removal or drainage of infected sources.

Notes

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