Multidrug-Resistant Organisms: Considerations in Antibiotic Selection and Administration

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Abstract

Keywords

- ▶ multidrug-resistant organisms
- ▶ antibiotic selection
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Managing infections caused by multidrug-resistant organisms is a significant clinical challenge. Multidrug-resistant organisms' treatment is complicated in the pediatric population because of the lack of primary data, treatment guidelines, rapidly changing pharmacokinetic/pharmacodynamic parameters, and fewer approved antibiotic indications and dosing guidance. Treatment decisions must incorporate available pediatric data, clinical experience, and careful extrapolation from adult data while considering the unique challenges faced by children with complicated infections.

Introduction

Infections caused by multidrug-resistant organisms (MDROs) have become a major problem worldwide and present significant therapeutic challenges among children. Antibiotic resistance, originally a problem limited to hospitalized patients or those receiving immunosuppressive therapy, has now spread to the community, causing serious infections in previously healthy patients. Antimicrobial resistance mechanisms are the result of different factors that involve the organisms as summarized in ▶ **Table 1**, the host, and previous antibiotic exposure. Host factors include severity of illness, presence of indwelling catheters and other supporting devices, mechanical ventilation, length of hospital and pediatric intensive care unit (PICU) stay, immunosuppressive therapy, and malnutrition. The ease of cross-contamination and antibiotic pressure in the intensive care setting are other factors that contribute to the emergence and spread of drug-resistant organisms.^{1–3}

Antibiotic resistance is independently associated with prolonged hospitalization and death among PICU patients with health care associated infections, and similar worsened

outcomes have been observed among neonates with multidrug-resistant gram-negative bacteremia.^{4,5} These data are particularly concerning in the setting of limited antibiotic development and the suboptimal pharmacokinetic/pharmacodynamic (PK/PD) and toxicity profiles of many existing second- and third-line treatment options. These drugs have similar limitations in the pediatric population, compounded by PK/PD alterations, more contraindications, fewer data, and fewer Food and Drug Administration-approved indications. These considerations are reviewed below for common and challenging infections caused by gram-positive and gram-negative MDRO.

Methicillin-Resistant *Staphylococcus aureus*

Staphylococcus aureus is a common and important pathogen among both children and adults, and invasive infection is associated with poor outcomes. Children with invasive community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been noted to have prolonged PICU lengths of stay and higher mortality than other PICU

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Table 1 Common mechanisms of antibiotic resistance

Drug class	Mechanisms of resistance	Common pathogens
Beta-lactams	Penicillin-binding protein alterations	Methicillin-resistant <i>Staphylococcus aureus</i> , <i>Streptococcus</i> spp.
	Beta-lactamases	Enterobacteriaceae
	Efflux pump overexpression	<i>Pseudomonas aeruginosa</i>
	Porin deficiency	<i>P. aeruginosa</i>
Glycopeptides	Altered glycopeptide precursors	Vancomycin-resistant <i>Enterococcus</i> , Vancomycin-resistant <i>S. aureus</i>
	Peptidoglycan overproduction	Vancomycin-intermediate <i>S. aureus</i>
Protein synthesis inhibitors	Decreased uptake	<i>P. aeruginosa</i>
	Increased efflux	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp.
	Acetyl, adenylyl, phosphoryl transferases	Enterobacteriaceae
	Ribosomal binding site methylation	<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp.

patients.⁶ Additionally, nosocomial acquisition of MRSA colonization is common among both neonatal intensive care unit and PICU patients and is strongly associated with subsequent infection.⁷ Compared with the reported decline in the incidence of invasive hospital-associated MRSA infections in adults, the incidence in the pediatric population appears to be unchanged. Moreover, the incidence of community-acquired MRSA infections is on the rise in the pediatric age group.⁸

Comprehensive guidelines for the treatment of both children and adults infected with MRSA have been established by the Infectious Diseases Society of America.⁹ Vancomycin is the recommended first-line therapy for invasive infections, but in the absence of concomitant bacteremia, clindamycin remains an empiric treatment option in areas with low rates of clindamycin-resistant MRSA (<10%). Clindamycin may be considered for clinically stable patients with skin and soft tissue infections, pneumonia, and osteomyelitis.⁹ Linezolid is another possible alternative for these infections, with an additional potential role in central nervous system (CNS) infections.^{10–13} When appropriate, surgical incision, drainage, and/or debridement are important aspects of treatment.⁹

MRSA bacteremia and endocarditis are severe infections with significant mortality rates ranging from 30 to 37%.^{14,15} Vancomycin is recommended as the first line of therapy, with a 2 to 6 weeks of treatment course depending upon infection source, endovascular involvement, and other complicating factors. Daptomycin is an alternative treatment with clinical data in adult patients describing improved outcomes in the setting of elevated (>1 mg/L) vancomycin minimum inhibitory concentrations (MICs), but data regarding its safety and efficacy in children are limited.^{16,17} Combination of vancomycin with rifampin for the complete course of 6 weeks and with gentamicin for first 2 weeks is recommended for the treatment of prosthetic valve MRSA endocarditis in adults, extrapolated from two small retrospective studies of *Staphylococcus epidermidis*.^{18,19} However, data in children are limited and the decision of combination therapy should be

individualized.⁹ Susceptibility of MRSA isolates to daptomycin should be confirmed, as nonsusceptible isolates have been described.^{9,20,21} Recently approved additional agents with activity against MRSA include ceftaroline, telavancin, oritavancin, dalbavancin, and tedizolid, but pediatric data and experience are currently limited.

Vancomycin-Intermediate *S. aureus* and Vancomycin-Resistant *S. aureus*

Vancomycin overuse has led to the emergence of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains, mediated through cell wall glycopeptide overproduction and precursor alterations.²² VISA isolates have vancomycin MICs between 4 and 8 mg/L, and VRSA is defined as vancomycin MIC ≥ 16 mg/L.²² Emergence of strains with reduced susceptibility to vancomycin is one of the reasons of vancomycin treatment failure.⁹ For patients infected with MRSA with vancomycin MICs equal to 2 mg/L and failing to improve with vancomycin treatment, microbiology laboratory should perform a more sensitive antimicrobial susceptibility testing technique such as an E test to better detect VISA strains.^{9,23} Alternative agents such as those described above for MRSA treatment should be considered.⁹ Use of linezolid for the treatment of endocarditis caused by VISA has been described in a systematic review of literature, with a cure rate of 66% (6/9).²⁴ Use of alternate or combination therapy in pediatric patients should be individualized, as data in this age group are lacking.⁹

Vancomycin-Resistant Enterococci

Enterococcal infections are the second most common cause of health care associated infections after *Staphylococcus* with a reported 1:1.5 prevalence ratio between *Enterococcus faecalis* and *Enterococcus faecium*.²⁵ Vancomycin resistance develops when mutated *Enterococcus* species use alternative glycopeptide precursors like D-ala-D-serine for cell wall formation

instead of the typical D-ala-D-alanine, to which vancomycin binds to exert bactericidal activity.²⁶ Vancomycin-resistant enterococci (VRE) infections have been associated with increased mortality compared with infections caused by vancomycin-susceptible enterococci.²⁷ Infections caused by VRE, especially *E. faecium*, are increasing. A recent study by the Centers of Disease Control and Prevention revealed that 80% ($n = 983$) of *E. faecium* isolates were resistant to vancomycin as compared with 6.9% isolates of *E. faecalis* ($n = 1,542$).²⁵ A recent large retrospective pediatric study of enterococcal bacteremia determined that *E. faecium* caused the majority (31/39, 79%) of VRE bacteremia.²⁸

Daptomycin and linezolid are the main treatment options for VRE bacteremia in adults and appear to be equally effective in retrospective outcome data, but data in pediatrics are limited.^{29,30} In one pediatric prospective study, microbiologic clearance was achieved with linezolid in 5/7 (71%) children with VRE bacteremia.³¹ In the setting of endocarditis, addition of other agents with activity against VRE such as tigecycline, doxycycline with rifampin, quinupristin-dalfopristin, or fluoroquinolone may be considered. High doses of ampicillin combined with aminoglycoside (gentamicin or streptomycin) synergy is recommended for endocarditis caused by vancomycin-resistant *E. faecium* (VREF) without high-level aminoglycoside resistance and ampicillin MIC of ≤ 64 mg/L.³² When the targeted pathogen is susceptible to both gentamicin and streptomycin, gentamicin is generally preferred because it is more readily available and therapeutic drug monitoring is more easily accessible with better-defined target serum concentrations.³³ Alternatively, for isolates that have ampicillin MICs greater than 64 mg/L, the combination of an aminoglycoside with high-dose daptomycin (8–12 mg/kg/day) is recommended.³² High-dose daptomycin plus ampicillin is recommended for ampicillin-susceptible VRE with high-level resistance for aminoglycosides. For endocarditis caused by vancomycin-resistant *E. faecalis* isolates, which are sensitive to β -lactams, the combination of ampicillin with imipenem/ cilastatin or ceftriaxone is recommended.³³ A few reports of successful treatment of VREF-infective endocarditis have been described using daptomycin in combination with tigecycline in adults, and novel combinations between daptomycin and cephalosporins continue to be researched in vitro.^{34–38}

Guidelines for the treatment of VRE infections of CNS in adults and pediatric population have not been established. Linezolid has good CNS penetration with drug concentration in the cerebrospinal fluid (CSF) reaching up to 70% of serum concentration in healthy individuals and 74 to 92% in patients with meningitis, and has been successfully used for the treatment of VRE meningitis in pediatric patients.^{39–43} In a pediatric case report of ventriculitis caused by VRE isolate resistant to linezolid, combination of intraventricular daptomycin and intravenous tigecycline achieved CSF sterility.⁴⁴ Quinupristin-dalfopristin for ventriculitis has been described in adults with varying results, but its CSF penetration is poor and often requires additional VRE agents and/or concomitant intrathecal administration.⁴⁵

Clinical data describing the treatment of urinary tract infection (UTI) caused by VRE in pediatric population are

lacking. In the setting of UTI caused by ampicillin-resistant VRE, nitrofurantoin or doxycycline may be considered for cystitis, reserving doxycycline for children older than 8 years of age. Linezolid and daptomycin should be reserved for multidrug-resistant VRE UTI with bacteremia. The therapy should be continued for 7 to 14 days for severe infections such as urosepsis and pyelonephritis or for patients with delayed clinical response.⁴⁶

Extended-Spectrum β -Lactamases

β -Lactam agents are widely hydrolyzed by plasmid-mediated extended-spectrum β -lactamases (ESBLs) harbored by several Enterobacteriaceae. Carbapenems, which maintain stability and provide excellent activity, have emerged as the standard preferred therapy for infections caused by these pathogens.⁴⁷ As the Clinical and Laboratory Standards Institute no longer recommends confirmatory testing to identify ESBL production among Enterobacteriaceae, ESBL-producing pathogens with low cefepime and piperacillin-tazobactam MICs may still be reported as susceptible, and controversy has emerged regarding whether these agents may be used in the management of such infections.⁴⁸ In vitro studies have identified an inoculum effect wherein cefepime and piperacillin MICs become elevated in the setting of greater concentrations of ESBL-producing bacteria, which may translate to reduced efficacy in serious, high inoculum infections caused by these pathogens.⁴⁹ Retrospective clinical data have described worsened outcomes when cefepime was compared with carbapenems for the treatment of adults with serious infections caused by ESBL-producing pathogens appearing susceptible to cefepime.^{50,51} Conversely, children treated with either a carbapenem or a noncarbapenem, primarily other β -lactams, achieved similar and successful results in a study of UTIs caused by ESBL-producing pathogens.⁵² Of note, 4 of the 23 patients in the noncarbapenem group received treatment to which the causative pathogen was resistant and still achieved clinical resolution, underscoring the importance of the lower bacterial inoculum, as seen in UTIs, for successful use of alternative β -lactams. In terms of treatment with β -lactam/ β -lactamase inhibitor combinations such as piperacillin-tazobactam compared with carbapenems, meta-analyses describing adults with bacteremia due to ESBL-producing organisms did not find any difference in outcome between the two drug classes.^{53,54} However, multiple limitations were noted in these studies restricting broad clinical application. Given limited and conflicting data with other β -lactams, carbapenems remain the preferred agents for the treatment of infections caused by ESBL-producing pathogens, while appropriately dosed piperacillin-tazobactam may be considered as an alternative for UTI treatment.⁵⁵

Trimethoprim-sulfamethoxazole and ciprofloxacin are viable options for the management of UTI if susceptibility report indicates that the ESBL-producing pathogen is sensitive and patient is clinically improving. Aminoglycoside monotherapy has also been described, as these agents can achieve high concentrations in the urine. Alternative options for cystitis may include nitrofurantoin or fosfomycin.

AmpC β -Lactamases

Management of infections caused by pathogens harboring chromosomally mediated AmpC β -lactamases is challenging. Resistance may be present at baseline among stably derepressed isolates with high-level AmpC expression or may develop during treatment through inducible resistance despite initial apparent susceptibility in vitro.⁵⁶ This phenomenon is best described among *Enterobacter* species pluralis (spp.), for which treatment with ceftriaxone or ceftazidime increases the risk of resistance to third-generation cephalosporins, an independent risk factor for increased mortality.^{57,58} Inducible chromosomal AmpC β -lactamases are known to be present in *Citrobacter* spp., *Serratia* spp., *Morganella* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Proteus vulgaris*, and *Providencia stuartii*, but *Enterobacter* is the most notorious for treatment failures with third-generation cephalosporins. Owing to its reduced affinity for AmpC β -lactamases and enhanced bacterial cell-wall permeability, cefepime is the only cephalosporin that remains stable and is a viable treatment option in the setting of pathogens harboring this resistance mechanism.⁵⁹ Similar to ESBL-producing organisms, in vitro data have identified an inoculum effect with cefepime, raising concern for reduced activity in serious, high inoculum infections caused by AmpC-producing organisms.⁶⁰ However, this concern has not been substantiated by multiple recent clinical studies that identified similar outcomes among adult patients treated with either cefepime or carbapenem for invasive infections due to AmpC-producing organisms including *Enterobacter* bacteremia.^{61,62}

Carbapenems are stable and remain highly effective for the treatment for AmpC-producing Enterobacteriaceae infections. However, carbapenems should be reserved for patients with cefepime intolerance or failure, or for critically ill patients with invasive *Enterobacter* infections. Caution must be exercised to avoid unnecessary carbapenem use, which can contribute to the development of carbapenem resistance and create a particularly challenging therapeutic dilemma.⁶³

Carbapenem-Resistant Gram-Negative Organisms

Carbapenem resistance is becoming more prevalent, notably in Enterobacteriaceae, *Acinetobacter* spp., and *Pseudomonas* spp.^{64–66} Selecting appropriate antimicrobials for carbapenem-resistant gram-negative organism (CRGN) infections is challenging because resistance to other antibiotic classes is common (e.g., β -lactams, fluoroquinolones, and aminoglycosides), and the antibiotics most likely to retain activity (e.g., colistin, polymyxin B, rifampin, and tigecycline) are limited by variable PK/PD parameters, toxicities, and the rapid emergence of resistance.^{64,67–71} Combinations of two or more antimicrobials targeting CRGNs are increasingly being used to overcome limitations of monotherapy.^{67,68,70–73} Currently available evidence suggests a benefit to combination therapy; but this evidence is limited and not derived from randomized, controlled trials.^{70,71,74} The optimal combination is unknown

and should be selected based on patient- and organism-specific considerations. This section will refer to CRGNs collectively; in actuality, these organisms should be considered discrete entities and data should not be extrapolated between organisms.

Carbapenems remain an important treatment option even in organisms producing carbapenemases; however, the role of monotherapy is unclear.⁷⁵ Based on available evidence, carbapenems used in combination with aminoglycosides and polymyxins are associated with decreased mortality in carbapenem-resistant Enterobacteriaceae bloodstream infections.^{67,72,76} In vitro studies suggest carbapenems are synergistic with polymyxins or aminoglycosides and prevent emergence of resistance.^{77–81} Carbapenem therapy should be optimized by using high doses and prolonged infusions.^{67,72,75,82}

Colistin is a mainstay of treatment because it remains the most active agent in vitro.^{69,83} Colistin therapy is associated with favorable outcomes for various multidrug-resistant gram-negative infections in critically ill children.^{84–88} A loading dose is necessary to achieve therapeutic concentrations in a timely manner.^{89,90} Secondary to PK limitations inherent to the administration of colistin as a prodrug, patients with normal renal function may achieve subtherapeutic concentrations, while dose adjustments are required in renal dysfunction to prevent accumulation.⁸⁹ Reversible nephrotoxicity occurs in 5 to 20% of critically ill children.^{84–88,91} Resistance may occur during colistin monotherapy; however, combination therapy (e.g., with carbapenems) minimizes the development of resistance.^{77,78,81}

Tigecycline also remains one of the most active agents in vitro against CRGNs, with the important exception of *Pseudomonas* spp.⁹² Tigecycline in combination with carbapenems plus colistin or aminoglycosides was associated with decreased mortality in carbapenem-resistant Enterobacteriaceae infections.^{67,72} There are mixed data regarding the use of tigecycline in carbapenem-resistant *Acinetobacter* spp.^{93,94} Tigecycline should not be used as monotherapy for serious infections because blood, urine, and lung concentrations are often subtherapeutic.^{95–97} Tigecycline resistance and breakthrough bacteremias have been reported during therapy and tigecycline was inferior to comparators in the treatment of ventilator-associated pneumonia.^{66,94,98,99} Use of higher than Food and Drug Administration-approved doses may overcome these limitations.^{96,97,100} Tigecycline is associated with profound, dose-dependent nausea, abdominal pain, and vomiting as well as reports of pancreatitis.⁹⁷ There is limited evidence for the use of tigecycline in pediatric infections caused by CRGNs, and tetracyclines and glycylcyclines are avoided in patients less than 8 years of age because they can cause permanent discoloration of growing teeth.^{101,102}

Aminoglycosides retain variable in vitro activity against CRGNs, are often synergistic with other agents, and are widely used in pediatrics.^{67,94,103,104} Gentamicin or amikacin is generally more active against Enterobacteriaceae (e.g., one- to four-fold lower MICs), and tobramycin is generally more active against *Pseudomonas* spp. and *Acinetobacter* spp.⁷¹ Aminoglycosides have performed favorably when used in

combination with carbapenems in small clinical studies, and monotherapy is an effective treatment option for UTIs caused by CRGNs.^{67,76,105}

Rifampin has been used as adjunct therapy especially for infections caused by *Acinetobacter* spp., due to potent synergistic activity in preclinical studies.^{106–108} However, the largest randomized, controlled trials to date found no significant mortality benefit to rifampin plus colistin combination compared with colistin monotherapy.^{68,109,110} Rifampin is associated with hepatotoxicity, significant drug interactions, and increased risk of nephrotoxicity when combined with colistin.^{68,111}

Fosfomycin is available as an intravenous formulation in select countries, but in the United States it is only available as an oral formulation (fosfomycin tromethamine) approved for lower UTIs. Although highly subject to geographical variation, fosfomycin often has activity against multidrug-resistant *Escherichia coli* and *Klebsiella pneumoniae*, has variable activity against *Pseudomonas* spp., but is rarely active against *Acinetobacter* spp.⁹³ Fosfomycin possesses a unique bactericidal mechanism of action, is well tolerated, is often synergistic in vitro with other antibiotics when given systemically, and achieves high urine concentrations when given orally.^{93,112} Clinical evidence is limited for both intravenous and oral therapy. Oral therapy has been used with variable success to treat lower UTIs caused by CRGNs.^{113,114}

Fluoroquinolones generally do not retain activity against CRGNs, and resistance is easily mediated through multiple mechanisms.^{67,115,116} If pathogens are susceptible, fluoroquinolones are a suitable treatment option in the absence of other active antimicrobials, though doses must be optimized in critically ill patients to achieve PK/PD targets and minimize the development of resistance.^{117,118}

Finally, sulbactam, available in combination with ampicillin, retains substantial activity against *Acinetobacter* spp. and yields outcomes comparable to imipenem or colistin in ventilator-associated pneumonia.^{94,119–121} The optimal treatment of infections caused by CRGNs remains unclear. However, currently available clinical and in vitro evidence suggests a benefit to combination therapy with dose optimization. Therapy should be tailored based on patient and organism-specific considerations. In general, combinations of colistin and aminoglycoside plus a carbapenem or tigecycline appear to be the most beneficial.

Antibiotic Administration Considerations

Pediatric patients present a variety of unique PK/PD considerations that impact drug selection and dosing considerations including high volumes of distribution, rapid drug clearance, and varied time to maturation of different metabolic pathways.¹²² Some of these challenges and management suggestions are summarized in ►Table 2. Dose selection and administration techniques can have an important impact on PD target attainment, which has been correlated with improved clinical outcomes.¹²³ The strategy of prolonged infusion of β -lactam antibiotics has emerged as a means to optimize the percentage of the dosing interval during which

free drug concentration exceeds the MIC (% fT [unbound fraction of the drug] > MIC), the PD parameter best associated with antimicrobial efficacy.^{124,125} While improved clinical outcomes have been achieved with prolonged infusion of piperacillin-tazobactam compared with standard infusions among critically ill adults, most data come from PK modeling simulations used to anticipate PD target attainment. For example, meropenem efficacy is optimized when free drug concentration exceeds the MIC for at least 40% of the dosing interval, and modeling studies are used to determine the likelihood of achieving this goal, or probability of target attainment (PTA).¹²⁴ The common pediatric meropenem dose of 20 mg/kg every 8 hour as a 30-minute infusion has only a 72% PTA when treating a *Pseudomonas aeruginosa* infection with a meropenem MIC of 2 mg/L (the breakpoint for interpretation as susceptible), while giving the same dose with a longer infusion time of 3 hour increases the PTA to 100%.¹²⁵ When considering treatment options for meropenem-resistant *P. aeruginosa* (MIC $\geq$ 8 mg/L), standard doses of 20 mg/kg every 8 hour with a 30-minute infusion time offers only a 3% PTA, but when the dose is doubled to 40 mg/kg and the infusion time prolonged to 3 hours, the PTA is increased to 97% when the MIC is 8 mg/L.¹²⁵ However, PTA quickly falls as MICs reach 16 mg/L and higher, emphasizing the importance of determining exact MIC in the setting of a CRGN infection.

PK/PD optimization strategies may also be employed when using aminoglycosides which achieve maximal bactericidal activity in a dose-dependent manner (i.e., maximum concentration to MIC ratio of 10:1).¹²⁶ “Once daily” or “high peak, extended interval” dosing, serum concentration monitoring, and dose individualization is the most effective way to achieve optimal concentrations and minimize nephrotoxicity risk.¹²⁶ This strategy is recommended by the Cystic Fibrosis Foundation for the management of infectious exacerbations as a means to optimize therapy in this special population with characteristically larger volumes of distribution, more rapid renal clearance, and a viscous mucus barrier to lung penetration.^{127,128}

Neonatal patients represent another special population requiring careful attention to dose selection and adjustment. In general, initial antimicrobial doses are often reduced or given less frequently in the first week of life and then administered more aggressively as renal function matures. Close attention must also be paid to often-rapid increases in weight, which can significantly impact dosage appropriateness and may warrant frequent dose adjustment.¹²²

Vancomycin remains the treatment of choice for invasive MRSA and ampicillin-resistant enterococcal infections; however, ideal dose selection and targeted serum concentrations are not as well established for children as for adults. In the absence of national consensus guidelines, pediatric practitioners often aim for the same vancomycin serum trough concentrations of 15 to 20 mg/L as recommended for adults which, assuming vancomycin MIC = 1, correlate with an area under the concentration–time curve (AUC)-to-MIC ratio of ≥ 400 and improved clinical outcomes in invasive MRSA infections.^{129,130} Attainment of serum vancomycin trough

Table 2 Common challenges and management suggestions for selected antibiotics

Antibiotics	Challenges	Management suggestions
Fluoroquinolones	Musculoskeletal adverse effects limited to animal studies, accumulating data supporting safety in children	Acceptable second-line treatment alternative for children
Tetracyclines, Glycylcyclines	Permanent tooth discoloration	Contraindicated for children aged younger than 8 y
Vancomycin	Difficulty attaining target troughs described for adult patients, unclear clinical impact of target serum concentrations	Maintain serum trough concentrations >10 mg/L
Daptomycin	Lower exposure in children than adults	Higher weight-based doses under investigation

concentrations greater than 15 mg/L is challenging in pediatric practice, and some pediatric PK/PD modeling data indicate that trough concentrations as low as 7 to 10 mg/L are sufficient to attain targeted AUC:MIC ≥ 400 .^{131,132} However, as vancomycin trough concentrations alone are less reflective of total drug exposure than AUC:MIC and because troughs below 10 mg/L may predispose patients to the development of vancomycin resistance, prospective research and clinical outcomes data are needed prior to any major changes in practice.¹³³ In addition to selection of an appropriate maintenance dose, vancomycin loading doses have been described as a means to shorten time to therapeutic concentrations in critically ill adult patients with adequate renal function, as well as those requiring hemodialysis.^{134,135} In contrast, the one randomized study of vancomycin loading doses in children did not find any difference in target serum trough concentration attainment when a single 30 mg/kg dose given prior to initiating maintenance dosing of 20 mg/kg/dose every 8 hour was compared with trough attainment when the same maintenance dose was used without an initial load.¹³⁶

In the setting of multidrug-resistant organisms for which typical first- and second-line antimicrobial agents are ineffective, several treatment options described in the above sections are not approved for use in pediatric patients by the Food and Drug Administration. Thus, risks and benefits of therapy must be carefully considered and discussed with patients and caregivers as appropriate. For example, fluoroquinolones are not approved for use in children due to concerns of musculoskeletal toxicity to growing joints and tendons as observed in animal studies, as reviewed in a clinical report from the American Academy of Pediatrics concluding that fluoroquinolones should be reserved for children only when safer alternatives are unavailable.¹³⁷ A recent 5-year prospective safety follow-up of children who had received levofloxacin did not identify any increased risk of musculoskeletal adverse events, confirming this class to be a reasonable option when typical preferred treatments cannot be used due to resistance or other factors.¹³⁸

Further, a lack of approved pediatric dosing increases health care providers' reliance on primary literature to guide decisions. An important example of this is daptomycin dose selection for the treatment of gram-positive infections among

children intolerant or unresponsive to first-line therapies. As young children appear to have reduced systemic drug exposure compared with older children and adults, the need for a higher weight-based dosing in pediatrics to achieve exposure comparable to adults is becoming well established.¹³⁹ One small PK study concluded that doses of 8 to 10 mg/kg are needed for patients 2 to 6 years of age to achieve drug exposure comparable to adults receiving 4 to 6 mg/kg doses.¹⁴⁰ Pediatric dose selection is further complicated given the frequent approach in adult medicine to administer daptomycin at higher doses than listed in the package insert, that is, 8 to 12 mg/kg/dose.¹⁴¹ Clinical studies of larger daptomycin doses, up to 12 mg/kg in young children are ongoing.¹⁴²

Summary

In conclusion, multidrug resistance is a serious concern, and while infections among children are increasing, available antimicrobial agents and data to guide their use are limited. As pediatric studies and indications continue to lag behind what is available for adult patients, treatment decisions must largely be extrapolated from adult data. When caring for children infected with MDROs, risks and benefits along with unique PK/PD challenges and potential impact of antibiotic selection on further development of resistance must be carefully considered.

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