Infections Due to Antibiotic-resistant Gram-negative Bacteria in Pediatrics

Possible Management Strategies

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Antibiotic-resistant Gram-negative bacteria can cause severe infections in children especially in hemato-oncology, transplant (solid organ or hematopoietic stem cells), neonatal or pediatric intensive care, cystic fibrosis, and urologic settings. Deactivation of antibiotics (hydrolysis or modification), targets modification (mutation or protection) and prevention of intracellular accumulation (decreased uptake or increased efflux) represent resistance mechanisms that can be present individually or simultaneously in the same strain. In the last years, new molecules have been extensively studied and many of them introduced in clinical practice,[1] but unfortunately, only few of them have a pediatric registration by European or North American regulatory agencies, whereas others are under investigation. Table 1 summarizes the presently available antibiotics with their spectrum of activity, with registered or "under study" pediatric dosages. Most new compounds are represented by the combination of a cephalosporin or a carbapenem and a β-lactamase inhibitor, but they are not effective against all resistant strains. Possible exceptions are aztreonam plus avibactam combination (formulation not available, but achievable by concomitant administration of aztreonam with ceftazidime-avibactam) and cefiderocol (a siderophore cephalosporin) for which, however, strains with reduced susceptibility or even resistance have already been observed even in pediatric centers, where this drug has never been used.[2] New drugs of other classes are as follows: eravacycline, a tetracycline derivative with bactericidal activity against *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumoniae*, but not *Pseudomonas aeruginosa*; plazomicin, an aminoglycoside, which retains stability against several aminoglycoside-modifying enzymes, generally efficacious against Gram-negatives, but with variable activity against strains resistant to other antibiotics; and delafloxacin, a fluoroquinolone with activity similar to that of ciprofloxacin against *Enterobacteriales*, *P. aeruginosa* and *A. baumannii*. For some of these compounds, the pediatric registration process has been interrupted, at least in Europe.

Administration of (new and old) antibiotics according to their pharmacokinetics/pharmacodynamics (PK/PD) should be considered to improve effectiveness and reduce the risk of resistance selection,[3,4] especially in presence of few effective alternatives. Beta-lactam antibiotics have a bactericidal activity related to the proportion of time between 2 doses in which the free, unbound drug concentration is greater than minimally inhibitory concentration (MIC). Maximal bactericidal activity is observed when trough (the time just before an administration) is ≥4 MIC, even if a trough ≈6 MIC is required to prevent selection of resistant strains.[4] On the other hand, it should also be noted that trough concentrations >8 × MIC breakpoint for ceftazidime, piperacillin-tazobactam and meropenem have been associated with neurological adverse events in adults, but not in pediatrics. Studies were carried out first in adults and subsequently in children to evaluate the efficacy of prolonged infusions to improve the probability of (trough) target attainment. Piperacillin/tazobactam is one of the most studied drugs in critically ill children, and it has been demonstrated that the licensed dosage for febrile neutropenia (80 mg/kg of piperacillin q6h in 30 minutes of infusion) is unable to achieve a satisfactory trough for most MICs and only with 24-hour continuous infusion (proposed at a

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TABLE 1. Effectiveness of Antibiotics Used for Treatment of Resistant Gram-negative Infections and Pediatric Dosages; in *italics* Are Reported Dosages Currently Studied in Clinical Trials Registered on "clinicaltriasl.gov" (United States) or "clinicaltrialsregister.eu" (European Union)]

	Enzymatic Resistance Mechanisms Typical for *Enterobacteriales*				Carbapenem Nonsusceptible Peculiar Strains		Pediatric Dosages
	ESBL, AmPC	KPC	OXA-48	VIM, NDM (metallo-β lactamases)	*P. aeruginosa*	*A. baumannii*	
Ceftolozane-tazobactam	++	–	–	–	±[(a)]	–	*20 mg/kg, 40 mg/kg in pneumonia, maximum 1000 mg (as ceftolozane) in 1 h, q8h*
Ceftazidime-avibactam	++	++	++	–	+	–	*0–3 mo 30 mg/kg q8h* *3–6 mo: 40 mg/kg (as ceftazidime) in 2 h, q8h* *>6 mo: 50 mg/kg maximum 2000 mg (as ceftazidime) in 2 h, q8h*
Cefiderocol	++	++	++	++	++	++	*60 mg/kg maximum 2000 mg) in 2 h, q8h*
Meropenem-vaborbactam	++	++	–	–	–	–	*40 mg/kg maximum 2000 mg (as meropenem) in 3 h, q8h*
Imipenem-relebactam	++	++	–	–	±	–	*≥2 y: 15 mg/kg maximum 500 mg (as imipenem) in 30', q8h*
Aztreonam-(ceftazidime) avibactam	++	++	++	++	±	–	Aztreonam, >1 mo: 30 mg/kg maximum 2000 in 3 h, q6h
Eravacycline	++	++	++	+	–	++	*Single dose, PK study:* *8 to <12 y 1.5 mg/kg in 1 h* *2 to <18 y 1.75 mg/kg in 1 h*
Plazomicin	++	++	++	±	–	–	No data available
Delafloxacin	+	–	–	–	–	–	*In adolescents for ceftriaxone-resistant gonorrhea 450 mg q12h administered once*
Fosfomycin	++	++	++	++	++	–	Preterm neonate (<40 wks of gestation): 50 mg/kg q12h Neonate (40–44 wks of gestation): 67 mg/kg q12h 1–12 mo (up to 10 kg body weight) 67–100 mg/kg q8h 1–12 y (up to 40 kg body weight) 50–100 mg/kg q6h ≥12 y (40 kg body weight) 3000–6000 mg q6h
Colistin	++	++	++	++	++	++	*As colistimetate: 200,000–300,000 (maximum 9,000,000) IU/kg in 1h (load), then 100,000–150,000 (maximum 4,500,000) IU/kg in 1h, q12h*
Tigecycline	++	++	++	++	–	++	4 mg/kg (maximum 200 mg in 1 h (load), then 2–3.2 mg/kg (maximum 100 mg) in 1h q12h

Proportion of isolate susceptible: ++ >90%; + 70%–90%; ± around 50%, may be susceptible; – probably/definitively not effective.

(a) Effective only in case of elevated efflux, derepressed AmPC or loss of specific porin (OprD).

ESBL indicates extended-spectrum beta-lactamase; KPC, Klebsiella Pneumoniae Carbapenemase; NDM, new dely metallobetalactamase; OXA-48, oxacillinase-48; VIM, Verona-Integron encoded Metallobetalactamase.

dosage of 300 mg/kg/day), it is possible to reach a concentration >MIC for 100% of the time between 2 doses.[5] Similarly, ceftazidime at a starting dose of 60–100 mg/kg infused in 1 hour and immediately followed by a 24-hour maintenance continuous infusion of 200–300 mg/kg (maximum 3000–6000 mg/day), according to glomerular filtration rate and body surface area, can achieve a probability of (trough) target attainment >90% for *P. aeruginosa*.[6] Finally, meropenem administration at a higher than registered dose (eg, 20–30 mg/kg q6h) in prolonged infusion (3 hours) or in a 24-hour continuous infusion with a loading dose, sometimes can allow the achievement of concentrations that can be effective against Gram-negative bacteria with MIC higher than the usually indicated breakpoint.[7] The availability of tools to perform therapeutic drug monitoring of β-lactams could be very useful in these conditions. Another class of antibiotics widely used in pediatrics and for which dosage has been changed to make it more adherent to PK/PD are aminoglycosides. Their effectiveness is proportional to unbound drug maximum concentration (peak or Cmax) and its relationship with MIC (Cmax/MIC). With this type of pharmacokinetic and considering their saturable oto- and nephrotoxicity profile, the best method of administration is once a day, without increased (and maybe with lower) toxicity. PK/PD should be considered also for an effective therapy for localized infections, especially skin and soft tissue, bone, central nervous system, endocardium, or lung in cystic fibrosis, sites where adequate antibiotic concentrations could be difficult to be reached with the risk for treatment failure and resistance selection.

A further therapeutic strategy to cope with the lack of drugs effective against multiresistant Gram-negatives is to combine different antibiotics, both new and old ones.[4,8] However, it must be underlined that many of the possible combinations proposed have been identified in in vitro models and their clinical efficacy could be lower than expected. Anyway, some antibiotics represent elective drugs for combination therapies. Intravenous Fosfomycin is frequently active in vitro and has high tissue (bone, central nervous system) penetration. In adults, highly fractionated or continuous infusion has been documented as effective also in the presence of resistance mechanisms: intermittent administration of 2000 mg q6h for extended-spectrum beta-lactamase-producing *E. coli*; continuous infusion of 8000 mg/day for *K. pneumoniae*, and extended-spectrum beta-lactamase-producing *K. pneumoniae*; continuous infusion of 12,000 mg for *P. aeruginosa*; or 16,000 mg for Klebsiella Pneumoniae Carbapenemase-producing *K. pneumoniae*.[9] No pediatric data are available for these schedules, but it is plausible that a proportionate dosage should be effective also in children. Noteworthy, Fosfomycin has a high risk of resistance selection if used in monotherapy. Moreover, the risk of high Na^+ load (it is a Na^+ salt) or hyperglycemia related with drug dilution must be kept in mind. In patients with normal renal function, high dose intravenous colistin (polymyxin E) administered with a load followed by a q12h maintenance is at present considered the best administration strategy in all ages, even if in children the most correct dose is still under investigation.[10] However, there is an important

and potentially confusing characteristic in colistin's dosage expression since the drug is available in 2 salt forms: colistin sulfate and colistimethate sodium. In Europe, colistimethate sodium (a prodrug of colistin that is slowly metabolized to colistin in plasma) is available, and dosing is expressed usually in international units, and sometimes in milligrams of colistimethate sodium; in the United States, the dosage of US Food and Drug Administration–approved colistimethate sodium is defined in milligrams of colistin base activity. Therefore, particular attention should be paid to avoid dosage errors. Approximate dose conversion: 1,000,000 international units = 80 mg of colistimethate sodium = 30 mg colistin base. In the United States, polymyxin B is also available and it should be administered at 1.25 mg/kg q12h or with a 2 mg/kg load followed by 1.25–1.5 mg/kg q12h maintenance. Continuous infusion has also been proposed for polymyxin B, but no difference in effectiveness has been noted compared with intermittent administration, whereas a risk of acute kidney injury in patients with high body mass index (>25 kg/m^2) has been reported.[3] Beside the risk of polymyxin-induced renal damage, the possibility of neurological toxicity because of Ca^{++} chelation by polymyxin must not be neglected. Tigecycline is a tetracycline approved for pediatric patients ≥8 years old.[11] It is active against carbapenem-resistant *Enterobacteriales*, but not *P. aeruginosa*, and it can be useful for treating resistant *A. baumannii*, especially in combination with colistin or imipenem.[8] Finally, sulbactam is a β-lactamase inhibitor frequently inactive against antibiotic-resistant Gram-negatives, but that could be active against *A. baumannii*.[11] The drug is generally available in combination with ampicillin or cefoperazone, which however are not effective against this pathogen. In adults, the recommended dose is 2000 mg of sulbactam infused in 4 hours q8h. Unfortunately, there are no data in pediatrics for this indication.

At this point, it must be stressed that in case of prolonged and especially in continuous infusion drug stability at room temperature, presence of "dead space" in infusion tubing and the possibility of drug-drug incompatibilities must be kept in mind. Moreover, in the case of continuous infusion a loading dose should be always used to get adequate levels quickly.

Finally, 3 pathophysiological conditions should also be kept in mind in treating an infection caused by resistant pathogens, especially in a critically ill patient: (1) presence of augmented renal clearance (creatinine clearance >130 mL/min/1.73 m^2) that can reduce plasma (and tissues) concentrations of antibiotics with renal elimination, (2) presence of hypoalbuminemia that can increase the amount of free drug of highly bounded antibiotics, increasing their elimination especially in the presence of augmented renal clearance; (3) presence of acute kidney injury often observed at onset of severe infections, that in theory could cause drug accumulation and toxicity. However, this last condition frequently reverses in the first 48 hours. Therefore, antibiotics with high therapeutic index and renal elimination, as β-lactams, should be administered initially at full dosage for the first 48 hours to prevent the risk of suboptimal concentrations in the first hours of treatment of a severe infection.[12] Dose reduction should be performed only if renal compromission persists beyond this time.

In conclusion, treatment of infections resulting from antibiotic-resistant Gram-negatives may be a challenge in pediatrics. New drugs can be useful but not in all situations, and resistance development is around the corner. Combination treatments, with old and new drugs, along with considering PK/PD data and pathophysiological conditions may be pivotal for improving effectiveness and reducing the risk of (further) resistance selection.

REFERENCES

1. Yusuf E, Bax HI, Verkaik NJ, et al. An update on eight "New" antibiotics against multidrug-resistant gram-negative bacteria. *J Clin Med.* 2021;10:1068.
2. Mariani M, Medici C, Ugolotti E, et al. Colonization by Escherichia coli strains with increased minimal inhibitory concentration for cefiderocol: when resistance anticipates drug use. *J Infect Public Health.* 2021;14:749–750.
3. Gustinetti G, Cangemi G, Bandettini R, et al. Pharmacokinetic/pharmacodynamic parameters for treatment optimization of infection due to antibiotic resistant bacteria: a summary for practical purposes in children and adults. *J Chemother.* 2018;30:65–81.
4. Gatti M, Pea F. Continuous versus intermittent infusion of antibiotics in Gram-negative multidrug-resistant infections. *Curr Opin Infect Dis.* 2021;34:737–747.
5. Maarbjerg SF, Thorsted A, Kristoffersson A, et al. Piperacillin pharmacokinetics and target attainment in children with cancer and fever: can we optimize our dosing strategy? *Pediatr Blood Cancer.* 2019;66:e27654.
6. Cojutti PG, Maximova N, Schillani G, et al. Population pharmacokinetics of continuous-infusion ceftazidime in febrile neutropenic children undergoing HSCT: implications for target attainment for empirical treatment against Pseudomonas aeruginosa. *J Antimicrob Chemother.* 2019;74:1648–1655.
7. Cojutti PG, Candoni A, Lazzarotto D, et al. Population pharmacokinetics of continuous-infusion meropenem in Febrile Neutropenic patients with hematologic malignancies: dosing strategies for optimizing empirical treatment against enterobacterales and P. aeruginosa. *Pharmaceutics.* 2020;12:E785.
8. Scudeller L, Righi E, Chiamenti M, et al. Systematic review and meta-analysis of *in vitro* efficacy of antibiotic combination therapy against carbapenem-resistant Gram-negative bacilli. *Int J Antimicrob Agents.* 2021;57:106344.
9. Rinaldi M, Cojutti PG, Zamparini E, et al. Population pharmacokinetics and Monte Carlo simulation for dosage optimization of fosfomycin in the treatment of osteoarticular infections in patients without renal dysfunction. *Antimicrob Agents Chemother.* 2021;65:e02038–20.
10. Antachopoulos C, Geladari A, Landersdorfer CB, et al. Population pharmacokinetics and outcomes of critically ill pediatric patients treated with intravenous colistin at higher than recommended doses. *Antimicrob Agents Chemother.* 2021;65:e00002–e00021.
11. Chiotos K, Hayes M, Gerber JS, et al. Treatment of carbapenem-resistant Enterobacteriaceae in fection in children. *J Pediatr Infect Dis Soc.* 2020;9:56–66.
12. Crass RL, Rodvold KA, Mueller BA, et al. Renal dosing of antibiotics: are we jumping the gun? *Clin Infect Dis.* 2019;68:1596–1602.