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REVIEW

Optimal Management of Complicated Infections in the Pediatric Patient: The Role and Utility of Ceftazidime/Avibactam

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Abstract: Antimicrobial resistance poses a substantial threat to global public health. The pursuit of new antibiotics has decreased and very few options have been investigated for the treatment of complicated multidrug-resistant Gram-negative (MDR-GN) infections in adult population and even less in pediatric patients. Ceftazidime-avibactam (CAZ-AVI) is novel cephalosporin/β-lactamase inhibitor (BL-BLI) combination with broad antibacterial spectrum. The aim of this review is to describe the current and future role CAZ-AVI in the pediatric population with suspected or confirmed MDR-GN infections.

Keywords: pediatric, infections, multidrug-resistant Gram-negative, ceftazidime/avibactam

Introduction

Over the last years, the prevalence of multidrug-resistant Gram-negative (MDR-GN) pathogens has increased worldwide, both in adults and in children.[1] Antimicrobial resistance poses a substantial threat to global public health concern, since it decreases the probability of effectively treating an infection and increases risk of morbidity and mortality. Nevertheless, the pursuit of new antibiotics has decreased for years and very few options have been investigated for the treatment of complicated MDR-GN infections in adult population and even less in pediatric patients.[2] More recently, new molecules have been proposed for use in clinical practice, such as ceftazidime-avibactam (CAZ-AVI), a novel cephalosporin/β-lactamase inhibitor (BL-BLI) combination with a broad antibacterial spectrum.

CAZ-AVI was first approved in adult population by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015 for adults complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and, in February 2018, it was approved for the treatment of hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[3] Furthermore, CAZ-AVI received approval by EMA for infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. In March 2019, FDA has expanded the approval of CAZ-AVI to include pediatric patients aged ≥3 months for the treatment of cIAI, used in combination with metronidazole, and for cUTI, including pyelonephritis. Safety and effectiveness have not been established in pediatric patients with HAP/VAP (Table 1).

The aim of this review is to describe the current and future role CAZ-AVI in pediatric population with suspected or confirmed MDR-GN infections.

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Table 1 Indication and Usage of CAZ-AVI in Adult and Pediatric Population

Adult Population (18 Years and Older)	Pediatric Population (3 Months and Older)
• cIAI, used in combination with metronidazole • cUTI, including pyelonephritis • HAP, VAP • Infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.	• cIAI, used in combination with metronidazole • cUTI, including pyelonephritis

Abbreviations: cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

Epidemiology and Risk Factors for MDR-GN in Pediatric Population

The number of pediatric patients with severe bacterial infections due to MDR bacteria is increasing and their morbidity and mortality are considerable.[1,4,5] Understanding the epidemiology and the drug resistance patterns of infections in children is crucial to provide appropriate antimicrobial prescription and to guide antimicrobial stewardship programs.

Previous studies have demonstrated that GN infections account for 30–55% of all bloodstream infections (BSIs) detected in children depending on age stratification, type of ward, comorbidity and geographical setting. The most frequent isolated microorganism is *E. coli* and *K. pneumoniae* followed by *P. aeruginosa*.[6] Hospital data from developing countries suggest that pathogens causing neonatal infections (in the first 28 days of life) and in early-onset (likely maternally-acquired neonatal infections) are frequently resistant to first line regimen with ampicillin plus gentamicin.[7]

The most important emerging MDR-GN pathogens in children are extended-spectrum β-lactamases (ESBL), carbapenem-resistant Enterobacteriaceae (CRE), MDR and carbapenem-resistant (CR) *P. aeruginosa*.

Despite the increased global attention to MDR-GN, little research has been conducted on these infections in children, the few available data suggest that MDR-GN epidemiology, risk factors, and outcomes are comparable with those observed in adults.[8] Nosocomial outbreaks have been reported in neonatal and pediatric intensive care units and the geographical distribution was generally consistent with adults patients one.[8]

Bacterial surveillance, strategies for implementing effective infection-prevention, and antimicrobial stewardship programs specifically for children are needed.

ESBL Infections

The isolation of third generation cephalosporin-resistant and ESBL-producing Enterobacteriaceae (ESBL-PE) is becoming more common across pediatric patients, both in the community and in health care settings.[9] These findings are consistent with previous data in adults, which also report an upward trend in EBSL in inpatient and outpatient settings. SENTRY Antimicrobial Surveillance Program in Europe, North and South America (1997–2002) signaled that among <1 and 1±12 years old children, the prevalence of ESBL-producing isolates among *Klebsiella* spp. bloodstream pathogens was 41.7% and 31.3%, respectively.[10] A large national database of antimicrobial susceptibility in the United States has found that the prevalence of third generation cephalosporin-resistant and ESBL phenotypes increased, respectively, from 1.39% and 0.28% in 1999–2001 to 3% and 0.92% in 2010–2011.[11]

A systematic review and meta-analysis reporting the prevalence of ESBL-PE among confirmed BSIs in 3381 pediatric patients from 1996 to 2013 has found that the prevalence of ESBL-PE was 9% with an annual increase of 3.2% (P = 0.04), with higher prevalence rates among neonates (11%) compared to children older than 28 days (5%). The pooled prevalence was higher in Africa (15%), South America (12%), India (11%) and the rest of Asia (7%), compared to Europe (4%) and Oceania (0%). Importantly, these infections appear to be more common among neonates while the mortality rate among neonates with BSI due to ESBL-PE was 36%, significantly higher compared to those infected with other pathogens (18%, p= 0.01).[12]

Clinical risk factors for ESBL colonization and infection for children, besides prematurity and low weight at birth, are quite similar to those described in adults, such as gender, country of birth, travel outside metropolitan area, immunosuppression, underlying chronic disease, urinary tract disease, previous hospitalization, local outbreaks, prolonged length of stay, known ESBL carriage, prior antibiotic use, and indwelling devices.[9,13]

After the development of an algorithm in adult population,[14] a decision tree illustrating the risk of antimicrobial resistance among children with GNB BSI based on individual patient risk factors has been recently proposed for pediatric population, but it needs to be validated more widely before incorporation into clinical practice.[15]

CRE Infections

Despite global attention to CRE, limited data have been published on the epidemiology of these infections in children,[16] CRE in pediatrics are less frequently described compared to ESBL. However, the growing number of infections reports along with an increasingly medically complex pediatric population suggest that CRE could emerge as a significant nosocomial pathogen in pediatric centers over the coming years.[17] A large national database of antimicrobial susceptibility in the United States found that the frequency of carbapenem resistance increased from 0% in 1999–2000, to 0.47% in 2010–2011 among Enterobacteriaceae in children.[18] The frequency of meropenem-resistant *K. pneumoniae* and *E. coli* pediatric isolates has been reported as approximately 4% and <1% worldwide, respectively.[19]

Children with CRE infection tend to be very young and critically ill, and potential risk factors include: age, travel from endemic regions, chronic comorbidity, presence of indwelling devices (including mechanical ventilation), history of surgery, prior colonization, immunosuppressive agents exposure, frequent or prolonged hospitalizations and previous antibiotic use.[17,20] Other identified risk factors include intensive care unit stay, solid organ transplant, renal failure, bedbound status, pediatric long-term care facilities.[16] Mortality rates in children with CRE have been reported as very variable, but neonates seem to be the group with the highest risk.[21]

MDR and CR *P. aeruginosa* Infections

Infections due to *P aeruginosa* in children are reported most often in association with pulmonary disease in patients with cystic fibrosis.[22]

A recent national surveillance network assessed the epidemiology of 300 *P. aeruginosa* isolates from 77,349 children without cystic fibrosis (inpatient, outpatient and long-term care facilities) and analyzed trends in antibiotic resistance.

From 1999 to 2012, the prevalence of MDR isolates increased significantly from 15.4% to 26%, while CR isolates rose significantly from 9.4% to 20%. After adjusting by year, patient and isolate characteristics, the prevalence of MDR and CR *P. aeruginosa* was higher among children aged 13–17 years, in the West North Central region of the US and in respiratory specimens. The highest prevalence of CR *P. aeruginosa* was among patients in ICU, while for MDR prevalence was in children in long-term care facilities.[23]

CAZ-AVI Mechanism of Action and Spectrum of Action

CAZ-AVI is a recently marketed novel agent containing the third-generation cephalosporin, ceftazidime, and avibactam, a newly developed BL-BLI. Ceftazidime inhibits peptidoglycan synthesis by binding to a variety penicillin-binding proteins (PBP), including the PBP3 of Gram-negative bacteria, including *P. aeruginosa*, resulting in cell wall instability and cell death. Avibactam demonstrates excellent in vitro activity against a wide range of bacterial beta-lactamases, including Ambler class A [including ESBL and *Klebsiella pneumoniae* carbapenemase (KPC)], C (AmpC), and some class D serine beta-lactamases [eg, oxacillinase (OXA) 48] (Table 2).[24]

In-vitro studies showed that the combination of CAZ-AVI is highly effective also against d P. *aeruginosa* and demonstrated activity against some MDR and CR *P. aeruginosa* isolates.[25,26] Avibactam has a limited activity against *A. baumannii* and other anaerobic Gram-negative rods[27] (Tables 1 and 2).

Notably, avibactam is not able to inhibit strains producing metallo-β-lactamases (MBL-Class B), such as the New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM) and Imipenmase (IMP), as well as many of the Class D enzymes, including *Acinetobacter* OXA carbapenemases.[28] However, in vitro studies suggested a synergistic effect of aztreonam combined with CAZ-AVI for MDR Enterobacteriaceae MBL producers, but this combination unfortunately is not yet commercialized.[29,30] Interestingly, CAZ-AVI has shown highly bactericidal activity in vitro against *Mycobacterium avium* complex and *Mycobacterium tuberculosis*, including MDR strains[31,32] (Tables 2 and 3).

During treatment of carbapenem-resistant *Klebsiella pneumoniae* infection, the emergence of CAZ-AVI resistance, due to KPC-2- and KPC-3-producing isolates, was noted in approximately 10% of cases. Noteworthy, some of the mutations that confer resistance to ceftazidime-avibactam can reduce the carbapenemase activity of KPC-3, resulting in lower carbapenem MICs and restoring the susceptibility of these isolates to carbapenems, however, this is generally not sustainable.[33]

Table 2 Classification of Most Frequent Extended-Spectrum b-Lactamases and Carpapenemase

Molecular Class	Enzymes	Relevant Organisms	Substrates of Hydrolysis
A	**ESBL (TEM, SHV, CTX-M, others)**	• *E. coli* • *Klebsiella* spp. • *Proteus mirabilis*	Penicillins, cephalosporins (except cefamycins), aztreonam.
A	**KPC**	• *E. coli* • *K. pneumoniae* • *K. oxytoca* • *Serratia marcescens* • *Enterobacter* spp. • *Citrobacter freundii*	Penicillins, cephalosporins, aztreonam, carbapenems.
B	**MBLs (VIM, IMP, NDM, others)**	• *E. coli* • *K. pneumoniae* • *K. oxytoca* • *Serratia marcescens* • *Enterobacter* spp. • *Citrobacter freundii*	Penicillins, cephalosporins and carbapenems. Monobactams are susceptible.
C	**AmpC**	• *K. pneumoniae* • *E. coli* • *Enterobacter* spp. • *Salmonella enteritidis* • *C. freundii* • *S. marcescens*	Cephamycins, 3rd generation cephalosporins
D	**OXA (OXA-48, OXA-23, others)**	• *Acinetobacter baumannii* • *P. aeruginosa* • *E. coli* • *K. pneumoniae* • *P. mirabilis* • *C. freundii*	Penicillin, aztreonam and carbapenems

Abbreviations: ESBL, extended-spectrum b-lactamases; IMP, imipenmase metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-β-lactamases; NDM, New Delhi metallo-beta-lactamase; OXA-48, oxacillinase-48; OXA-23, oxacillinase-23; VIM, Verona integron-encoded metallo-beta-lactamase.

CAZ-AVI Pharmacokinetics/ Pharmacodynamics, Safety, Tolerability and Clinical Effectiveness in the Pediatric Population

Limited reports have been available on CAZ-AVI use in infants, children, and adolescents prior to the FDA approval for pediatric patients.[30,34]

Search for clinical trials on ceftazidime-avibactam in patients ageing < 18 years was performed in European[35] and USA database.[36] A total of 6 clinical trials were retrieved, but two were included in both registries. Only one clinical trial was complete and results were published[37,38] in a peer-reviewed journal.[39] This was a PK/PD and safety clinical trial on a single dose CAZ-AVI, and it involved a total of 32 patients, 8 (25%) aging 28 days–23 months. Patients received a single 2-h intravenous infusion of ceftazidime-avibactam with different dosages based on age and/or body weight. Mean plasma concentration–time curves, geometric mean maximum concentration (Cmax), and area under the concentration–time curve from time zero to infinity were similar across all cohorts for both drugs and comparable between each of the 4 age groups and similar to those previously observed in adults. Overall, proportion of patients experiencing mild to moderate adverse events was about 19%. Another single-dose PK/PD and tolerability study is planned in children from 3 months to less than 18 years of age with nosocomial pneumonia is planned but not still recruiting patients.[40] Age cohorts identified are the same

Table 3 Spectrum of Activity of Ceftadizime/Avibactam

ACTIVE in vitro	NOT ACTIVE in vitro
• *Aeromonas* • *Arcanobacter* • *B. cepacia* • *Capnocytophaga* • *Citrobacter freundii* +*Citrobacter koseri* • *Enterobacter aerogenes* + *Enterobacter cloacae* • *Escherichia coli* • *Hemophilus influenzae* • *Kingella* spp • *Leptospira* spp • *Klebsiella oxytoca* + *Klebsiella pneumoniae* • *Mycobacterium avium* • *Mycobacterium tuberculosis* ° • *Moraxella catarrhalis* • *Morganella* spp. • *Neisseria meningitides* • *Propionibacterium acnes* • *Pseudomonas aeruginosa* • *Proteus mirabilis* + *Proteus vulgaris* • *Peptostreptococci* • *Providencia* spp. • *Salmonella* spp. • *Serratia* spp. • *Shigella* spp. • *Streptococcus agalactiae* (B) • *Streptococcus anginosus* spp • *Streptococcus* gp C, F, G • *Streptococcus pneumoniae* • *Vibrio parahemolyticus* + *Vibrio vulnificus*	• MRSA • Anaerobes • *Enterococcus* spp. • *Stenotrophomonas maltophilia* • *Acinetobacter* spp (limited activity)
SUSCEPTIBLE MDR-GN *	**NOT SUSCEPTIBLE MDR-GN**
• ESBL • CRE-KPC • CRE-OXA48 • MDR *Pseudomonas*	• NDM • VIM • IMP • Most Class D enzymes

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamase; IMP, imipenmase; MBLs, metallo-β-lactamases; MDRGN, multidrug-resistant gram-negatives; MRSA, methicillin-resistant *Staphylococcus aureus*; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase ° including MDR strains; *, in vitro sensitive strains.

of those of PK/PD study already published, but no data on dosages are reported. Finally, 2 clinical studies evaluated CAZ-AVI in urinary tract infections[41,42] (number of patients enrolled 97, 38 [39%] aging 28 days–23 months) and intra-abdominal infections[43] (number of patients enrolled 83, 1 [1.2%] aging 28 days–23 months). Patients' stratifications and dosages were the same used in the other studies. Data from the study in cUTI have been recently published[44] and showed a safety profile consistent with that on adults and of ceftazidime alone, and effectiveness in children with urinary tract infections due to Gram-negative pathogens. In addition, CAZ-AVI plus metronidazole has shown to be well tolerated, with a safety profile similar to ceftazidime alone, and appeared effective in pediatric patients with cIAI due to Gram-negative pathogens, including ceftazidime-non-susceptible strains.[45] Some further data are available from single case reports or small series.[34,46,47]

Caution should exercised if CAZ-AVI is to be administered to a penicillin or other beta-lactam allergic patient. The most common adverse reactions (≥3%) in pediatric patients were vomiting, diarrhea, rash, and infusion site phlebitis. The risk of adverse events includes *C. difficile*-associated diarrhea, which has been reported for nearly all systemic antibacterial drugs, including CAZ-AVI, fungal superinfections and central nervous system events (seizure and other CNS reactions), primarily described in the setting of renal impairment.[48] Monitoring Creatinine Clearance (CrCl) at least daily in adult and pediatric patients with changing renal function and adjust the dose of CAZ-AVI accordingly is recommended.

CAZ-AVI Monotherapy and Combination Therapy in Pediatric Population

Treatment options with ceftazidime-avibactam and combination therapy for MDR-GN infections in pediatrics are summarized in Table 4, according to in vitro activity or case series in adults. Real life use of CAZ-AVI is encouraging, in terms of safety, clinical response. The biggest concern is the emergence of resistance. According to clinical experience, continuous (over 8 hours) or prolonged infusion (over 2–3 hours) is recommended in order to maximize the bactericidal effect of intravenous beta-lactam antibiotics.[44,45,49] Concern for resistance and the need of increasing the bactericidal effect of the treatment during severe infections, probably justifies the combination of CAZ-AVI with other antibiotics (Table 3).[50–52]

In vitro potential advantages were found against *Pseudomonas* spp combining CAZ-AVI with rifampin, fosfomycin or colistin,[53–55] and synergistic activity was observed with carbapenems as meropenem or imipenem against *Klebsiella pneumoniae* KPC[56] and *Serratia marcescens*.[57]

CAZ-AVI plus aztreonam combination has been studied in vitro and *in vivo*.[58,59] Aztreonam is a monobactam with low grade of cross-hypersensitivity reactions in

Table 4 Treatment Options with Ceftazidime-Avibactam and Combo Therapy for MDR-GN Infections. Dose Adjustment Is Recommended Depending on Renal Function and Antimicrobial Susceptibility Tests

Drug	Dosage	Reference
Ceftazidime/ avibactam	According to weight and age-Weight <40 kg≥6 months to <18 year: 50 +12.5 mg/kg every 8 hours-Weight >40 kg≥6 years: 2000 + 500 mg/kg every 8 hoursAccording to age≥3 to <6 months: 40 + 10 mg/kg every 8 hours Observations: EI (over 3 h) every 8 hours is recommended	[44]
Aztreonam	90–120 mg/kg/day divided in 3 dosesIn Cystic fibrosis200 to 300 mg/kg/day divided in 4 doses	[99,100]
Meropenem	60 mg/kg/day divided in 3 dosesIn Cystic fibrosis or onco/hematological patients120 mg/kg/day divided in 3 dosesObservations: CI every 6 h in 6 hours or EI every 8 hours over 3–6 is recommended	[101]
Fosfomycin	According to weight and age-Premature neonates, corrected gestational age <40 weeks: 100 mg/kg divided in 2 doses-Neonates, corrected gestational age *40–44 weeks: 200 mg/kg in 3 divided doses*1 to 12 months (up to 10 kg): 200–300 mg/kg in 3 divided doses*1 to 12 years (10 to 40 kg): 200–400 mg/kg in 3 to 4 divided dosesObservations: Always in combination therapy. Contains high sodium concentrations. Caution is recommended in patients with liver cirrhosis or heart failure	[62,64]
Colistin	**Caution required due to very limited safety data**-Usual adult dose is: 9.000.000 IU as loading dose and then 4.500.00 IU every 12 hours Possible dosage suggested based on available data:200.000 IU/kg loading dose and then 100.000 every 12 hours Observations: High doses are associated with renal toxicity	[69–75,78]
Tigecycline	According to age8 to 11 years: 1.2 mg/kg (max 50 mg) every 12 hours12 to 17 years: 50 mg every 12 hour	[77,102]
Amikacin	15–20 mg/kg/day single doseObservations: High doses are associated with renal toxicity	[83,101]
Gentamicin	7 mg/kg/day single doseObservations: High doses are associated with renal toxicity	[101]
Rifampicin	20 mg/kg/day single doseObservations: Always in combination therapy	[61,78,85]

Notes: The loading dose should be administered in all patients including those with renal dysfunction. Antimicrobial susceptibility test: Colistin: MIC ≤ 2 mg/L continue colistin; MIC >2 mg/L consider alternative in vitro active antimicrobial. Tigecycline: MIC ≤1 mg/L consider tigecycline; MIC >1 mg/L consider alternative in vitro active antimicrobial. Fosfomycin: MIC ≤32 mg/L consider fosfomycin; MIC >32 mg/L consider alternative in vitro active antimicrobial. Aminoglycoside: MIC ≤2 mg/L for gentamicin/ tobramycin or ≤4 mg/L for amikacin consider aminoglycoside; MIC >2 for gentamicin/tobramycin or >4 mg/L for amikacin consider alternative in vitro active antimicrobial.
Abbreviations: CI, continuous infusion; EI, extended infusion; h, hours.

patients allergic to other beta-lactams. The combination could provide coverage against MBLs that are not neutralized by avibactam. Unfortunately, recent data on aztreonam mostly regard its administration by in inhalation (aztreonam lysine in cystic fibrosis) and no clinical experience is available nowadays in pediatrics (Table 4).[50,60-63]

Fosfomycin dose varies widely according to countries, but its best administration is probably based on weight and age, using correct gestational age in pre-term neonates, up to the maximum dose of 400 mg/kg in 4 divided doses in life-threatening infection. The compound contains a high concentrations of sodium that can lead to ion balance alteration with the possibility of severe adverse events, especially in patients with heart diseases[64] and/or cirrhosis.[65] In neonates there is a reduced ability in excreting large amount of Na^+, so they could be at high risk of developing high sodium plasma concentrations following fosfomycin infusion, leading to chronic lung disease.[64,66] Considering the risk of selecting for resistant strains, fosfomycin should be administered in combination with other drugs especially for MDR-GN (Table 4).[67]

Colistin is frequently used for treatment of infections due to MDR-GN.[68] Unfortunately, data on safety and dosage in pediatrics are very limited and still not well defined. This drug seems to be well tolerated even at high dosage and renal adverse events are reversible after drug interruption.[69–73] Plasma concentrations should be monitored to improve its effectiveness and reduce toxicity, but this practice can be challenging due to instrument variability (Table 4).[69,74,75]

The use of tigecycline in children aged >8 years is approved by EMA, when no other options are available,[76] for a maximum of 50 mg/dose, without a loading dose.[77] Data available from adults indicate that a higher dosage could be needed[78] in order to improve plasma concentration and drug effectiveness.[79] It is not known if higher doses should be used also in pediatrics. Availability of therapeutic drug monitoring (TDM) could

be useful to solve this question. Tigecycline is usually well tolerated,[76] but adverse events are reported, especially nausea and vomiting.[80] Substantially, there are no data for patient aged <8 years (Table 4).

Aminoglycosides are concentration-depending bactericidal drug usually administered as part of a combination therapy with notorious oto-and nephro-toxicity[81] that is reduced by a once-daily high dose schedule.[82,83] This schedule of administration can be considered as a standard also in pediatrics.[84]

As for many other molecules, there is a lack of recent data for rifampicin use in pediatric population for non-mycobacterial infection. A single daily-dose is generally suggested, but it must be used in combination with other drugs in order to limit the onset of resistant strains (Table 4).[61,85,86]

Finally, also meropenem can show higher success rate against strains with higher MIC values in children, compared to standard dosage, when administered as extended or continuous infusion,[87–90] in order to provide a pharmacodynamic exposures of 40% T >MIC,[91] or when it is administered at double dosage as in cystic fibrosis.[92] Data in adults in intensive care unit have shown the risk of central nervous system toxicity with high plasma concentrations of meropenem,[93] but this observation has not been confirmed in pediatrics.[94] In this case, the possibility to perform therapeutic drug monitoring of at least some of the drugs indicated for combination therapy[95–98] could further improve effectiveness and reduce the toxicity of these treatments (Table 4).

Conclusions and Future Prospective

In conclusion, CRE may emerge as a significant nosocomial pathogen over the coming years in the pediatric population. CAZ-AVI stands out as one of the most important additions in our armamentarium, as the first marketed fixed combination with activity against KPC and OXA producers. In addition, ceftazidime-avibactam can be used in combination with aztreonam to treat infections caused by a MBL-producing organism. Real life use of CAZ-AVI is encouraging, in terms of safety, clinical response, and survival both in adult and pediatric population. The biggest concern is the emergence of resistance in KPC-producing organisms and an irrational use of this antibiotic should be avoided. In our opinion and based on previous data on CRE infections from observational studies, we believe that PK/PD optimisation with CAZ-AVI extended infusion and combination therapy (with an aminoglycoside, TMP/SMX, fosfomycin, tigecycline, colistin) may be considered as a potential option to avoid the emergence of resistances. Companion drugs of CAZ-AVI can be selected based on susceptibility tests and infection site. The broad spectrum covering also ESBL-PE and significant proportions of *P. aeruginosa*, makes CAZ-AVI an interesting treatment option also for empiric regimens in patients with risk factors for MDR-GN infections and as a target carbapenem saving strategy. High-quality clinical trials on new and old antibiotics are needed to allow the definition of the currently best available empirical and target treatments for MDR-GN infections in the pediatric population.

Disclosure

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