Review

Use of newer and repurposed antibiotics against Gram-negative bacteria in neonates

Angeliki Kontou[1], Maria Kourti[2], Elias Iosifidis[2,3], Kosmas Sarafidis[1] and Emmanuel Roilides [2,3]*

[1] 1st Department of Neonatology and Neonatal Intensive Care Unit, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, and Hippokration General Hospital, Thessaloniki Greece
[2]Infectious Diseases Unit, 3rd Department of Pediatrics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, and Hippokration General Hospital, Thessaloniki, Greece
[3]Basic and Translational Research Unit, Special Unit for Biomedical Research and Education, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
* Correspondence: Emmanuel Roilides, MD, PhD
3rd Department of Pediatrics, Hippokration Hospital
Konstantinoupoleos 49, GR-54642, Thessaloniki, Greece
Tel: +30-2310-892444 e-mail: roilides@auth.gr

Abstract: Antimicrobial resistance has become a significant public health problem globally with multidrug resistant Gram negative (MDR-GN) bacteria being the main representatives. The emergence of these pathogens in neonatal settings threatens the well-being of vulnerable neonatal population given the dearth of safe and effective therapeutic options. Evidence from studies mainly in adults is now available for several novel antimicrobial compounds, such as new β-lactam/β-lactamase inhibitors (e.g. ceftazidime-avibactam, meropenem-vaborbactam, imipenem/cilastatin-relebactam), although old antibiotics such as colistin, tigecyclin and fosfomycin are also encombassed in the fight against MDR-GN infections that remain challenging. Data in the neonatal population are scarse, with few clinical trials enrolling neonates for the evaluation of efficacy, safety and dosing of new antibiotics, while the majority of old antibiotics are used off-label. In this article we review data about some novel and old antibiotics that are active against MDR-GN bacteria causing sepsis and are of interest to be used in the neonatal population.

Keywords: neonates; ceftazidime-avibactam; ceftolozane/tazobactam; imipenem/ cilastatin-relabactam; meropenem-vaborbactam; colistin; tigecycline; fosfomycin

1. Introduction

Neonatal bacterial sepsis remains one of the major culprits of neonatal morbidity and mortality especially in hospitalized term and preterm neonates all around the world and especially in low- and middle-income countries. An estimated 1.3 million episodes of neonatal sepsis occur annually with 200,000 sepsis-attributable deaths each year worldwide, while severe bacterial infections are responsible for approximately 3% of disability adjusted life years (DALYs) in neonates (1–3).

Antimicrobial resistance (AMR) is a global public health threat; almost 5 million deaths in 2019 were associated with AMR affecting both high-income and low-middle income countries with the three most common pathogens with AMR being *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumoniae* (3). According to World Health Organization (WHO) priority list of non-mycobacterial antibiotic-resistant bacteria, carbapenem-resistant *Enterobacterales* (CRE) and 3rd generation cephalosporin-resistant *Enterobacterales* (3GCRE) are of critical priority; whereas, methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* are of high priority (4). In several countries in the European region, with a north-to-south and west-to-east gradient, high percentages of resistance to third-generation cephalosporins and carbapenems in *K. pneumoniae* and high percentages of carbapenem-resistant *Acinetobacter* species and *Pseudomonas aeruginosa* are of significant concern (5). A population-based modelling analysis using data from point prevalence

European Centre for Disease Prevention and Control (ECDC) studies and surveillance data on AMR, found an estimation of 33,110 attributable deaths and 874,541 DALYs due to healthcare associated infections caused by antibiotic-resistant bacteria whose burden was highest in infants (<1 year old) and people older than 65 years; CREs as well as other multidrug resistant organisms (MDROs) such as 3GCRE, MRSA and VRE were most frequent in infants (6).

Antimicrobial resistance for *Enterobacterales* is primarily based on production of extended-spectrum β-lactamases and carbapenemases. Production of these enzymes renders the current β-lactams ineffective against resistant Gram-negative bacteria. Resistance to carbapenems may develop through carbapenem efflux mechanisms including porin loss or through production of three classes of carbapanemases. Class A consists of serine carbapenemases mainly of *K. pneumoniae*-producing carbapenemase (KPC) type. Class B are metallo-β-lactamases mainly of New Delhi metallo-β-lactamase (NDM) type and of Verona Integrated metallo-β-lactamase (VIM) type. Class D comprises oxacillinase-type carbapenemases, where OXA-48-like enzymes predominate.

The burden of neonatal late onset sepsis (LOS) due to MDR bacteria is exceptionally high in many regions of the world. AMR increase in the last decade has rendered most antibiotics of no utility. Resistance to even "WHO reserve" antibiotics has dramatically increased with 50-70% of the common Gram-negative clinical isolates being now MDR (7). A large, multinational observational study showed that *K. pneumoniae*, *E. coli* and *Enterobacter* spp. are the main Gram-negative bacteria responsible for neonatal sepsis with more than half of isolates being resistant to at least one antibiotic within four to six classes of antibiotics (8). Data from positive blood cultures of hospitalized neonates in NICUs participating in the Neonatal AMR research network revealed carbapenem resistance rates up to 84% (9). Colonization rates with MDR are variable among NICUs; in a NICU in Equador more than half of the neonates were colonized with ESBL-producing *Enterobacterales*, while colonization rate with CRO ranges from 1%-25% (10–12). Whether previous colonization with MDR is a significant risk factor for subsequent infection and the prognostic value of neonatal screening for the development of LOS needs further clarification (10,13). Moreover, higher mortality and morbidity is attributed to neonatal sepsis due to MDROs compared to non-MDROs, with case fatality rate of neonatal and pediatric sepsis due to CRO reaching 36% (14,15).

The limited therapeutic options against antimicrobial drug-resistant Gram-negative bacteria have led to the development and study of several novel antibacterial agents including β-lactam/β-lactamase inhibitor combinations (BLBLIs) and use of old or repurposed antibiotics. A framework for selecting appropriate therapy for children infected with CRE based on expert opinion has been proposed (16). Infectious Diseases Society of America (IDSA) updates annually "suggested approaches" on the treatment of infections caused by extended-spectrum β-lactamase and AmpC β-lactamase producing *Enterobacterales* (ESBL-E), carbapenem-resistant *Enterobacterales* (CRE) and *Acinetobacter baumannii*, *P. aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*) and *Stenotrophomonas maltophilia.* These suggested approaches apply to both adult and pediatric populations, although there is a clear paucity of data on the treatment of such infections in children (15,17,18). Not surprisingly, the above guidance reports are not addressed to neonates. According to recent systematic reviews about therapeutic options in neonates, the limited number of published articles, the low quality of evidence (retrospective data, heterogenous study design and outcome definition, case series or reports) and the very small sample size not permiting any statistical analysis further suggest that neonates remain "therapeutic orphans" in the fight against AMR (15,19). In this article we review data about some novel or repurposed antibiotics that are active against MDR Gram-negative (MDR-GN) bacteria causing sepsis and are of interest to be used in the neonatal population.

NOVEL β-LACTAM- β-LACTAMASE INHIBITOR AGENTS

Ceftazidime-avibactam

Ceftazidime–avibactam (CAZ-AVI) is a newly developed antibiotic, one of the novel β-lactam agents combined with a β-lactamase inhibitor. Ceftazidime, a well-known broad spectrum 3rd

generation cephalosporin with antipseudomonal activity is combined to avibactam, which is a new non- β -lactam β-lactamase inhibitor, able to inactivate several β-lactamases, by forming a covalent adduct with the enzyme that is stable to hydrolysis. In this way, avibactam protects the degradation of ceftazidime allowing it to act against bacteria that would otherwise be resistant. In particular, avibactam inhibits Ambler class A (e.g. TEM- 1, CTX-M-15, KPC-2, KPC-3), class C (e.g. AmpC) and certain class D β-lactamases (e.g. OXA-10, OXA-48), whereas it is inactive against metallo–β–lactamases (class B enzymes e.g. NDM, VIM, IMP) (20,21). Thus, CAZ-AVI is effective for the treatment of infections due to XDR *Enterobacterales* and *P. aeruginosa* when β-lactam resistance is due to production of such β-lactamases. There are reports that the co-administration of CAZ-AVI and aztreonam can overcome resistance conferred by metallo–β–lactamases producing *Enterobacterales* and *P. aeruginosa* (22,23).

Before CAZ-AVI, the primary drug of choice for KPC infection was colistin, which has been known to have a severe side effect profile. Currently, CAZ-AVI is authorized in Europe for the treatment of complicated intra-abdominal infections, complicated urinary tract infections including pyelonephritis, hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP), and infections due to aerobic MDR-GN bacteria susceptible to CAZ-AVI with limited or no other available therapeutic options in adults and children ≥3 months to <18 years old (24). On the contrary, in the United States CAZ-AVI has no approval for the treatment of HAP/VAP in pediatric patients ≥3 months to <18 years old (25,26). Meanwhile, in real clinical practice CAZ-AVI is used off-label in the treatment of bloodstream infections (BSI), catheter-related bacteremia (CLABSI), endocarditis, osteomyelitis, ventriculitis, mediastinitis, and both observational and comparative studies focused on infections in adults due to KPC and OXA-48-producing *Enterobacterales* have shown promising results (27). On the contrary, there is a paucity of data regarding treatment in pediatric patients with infections other than those approved, especially BSI in critically ill children of all ages.

In healthy adult studies both substances (ceftazidime and avibactam) show linear PK and share similar PK parameters allowing their combined dosing. After intravenous administration, both agents have half-life of nearly 2 h, exhibit poor plasma protein binding (5–22.8% and 5–8.2%, respectively) and are not metabolized (27,28). Renal clearance is the main route of elimination and dose adjustment of CAZ-AVI is required in patients with moderate and severe renal impairment (24,29). In pediatric patients of 4 age groups (≥12 to <18 years, ≥6 to <12 years, ≥2 to <6 years, ≥3 months to <2 years) who received a single-dose of i.v. CAZ-AVI, PK profiles of both ceftazidime and avibactam were comparable across the 4 age groups and broadly similar to those observed in adults (30). Furthermore, updated combined adult and pediatric population PK models supported the approval of currently recommended pediatric dosage regimens for children with cIAI or cUTI and normal or mildly impaired renal function (creatinine clearance >50 mL/min/1.73 m^2): ≥6 months to <18 years: 50/12.5 mg/kg; ≥3 to <6 months old: 40/10 mg/kg (every 8 hours by 2-hour intravenous infusion), which achieved exposures and probability of target attainment comparable to those in adults (31). Moreover, the administration of the same dosing regimens to children with HAP/VAP is supported (31).

At present, there are no PK data for neonates and infants <3 months, whereas there are scarce case reports on the safety and efficacy of CAZ-AVI in neonatal patients (32–36). To the best of our knowledge, in the largest case series of 8 pediatric patients, Iosifidis et al. reported the use of CAZ-AVI in 5 NICU preterm (GA: 25^{+5d}-32^{+4d} weeks, PNA: 6-134 days, BW: 0.9-2 kg) and 1 early term neonate (GA: 37^{+3d} weeks, PNA: 21 d, BW: 2.4 kg) as empirically (2/6) or targeted (4/6) salvage therapy in combination with other antimicrobials, for probable or proven sepsis due to carbapenem resistant *Klebsiella pneumoniae*; 2 preterm neonates were on septic shock. CAZ-AVI was administered intravenously (4-21 days) at 62.5 (50/12.5) mg/kg every 8 hours, which are higher than the currently approved doses for infants 3 months of age. During CAZ-AVI therapy, 2 neonates developed hypomagnesemia, managed with increased magnesium supplement in TPN, and one of them direct bilirubinemia, resolved 15 days later without significant intervention. As other antibiotics including colistin, fosfomycin, aminoglycosides, glycopeptides and liposomal amphotericin B were co-

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administered no clear causality to the drug could be attributed. No severe adverse events were reported and the outcome at 30 days was cure without relapse (36).

Similar increased doses were administered by Asfour et al. in 2 preterm neonates. The first case (BW: 920 gr, GA: 27 wk, PNA: 3 wk) was treated with CAZ-AVI (21d) combined to colistin (14d) for *K. pneumoniae* BSI and meningitis, the second case was treated with CAZ-AVI (5d) and amikacin (21d) for *K. pneumoniae* BSI and despite microbiological cure the patient died at the 5th day of CAZ-AVI therapy probably due to sepsis on the ground of prematurity and chronic lung disease (33). No other serious adverse events were observed, except a significant increase in creatinine of the 2nd patient and, as dose adjustment is required in patients with renal impairment, CAZ-AVI frequency changed to every 24 hours although drug PK in neonates, especially in those with acute kidney injury is unknown (33). A 25-d old preemie (GA 27 wk) was successfully treated with lower dose at 40/10 mg/kg/dose every 8 hours as targeted therapy for UTI due to PDR *K. pneumoniae*. Glycosuria, presented during treatment and spontaneously disappeared 5 days after the end of therapy, was referred as the only adverse event possibly related to the drug, due to reversible impairment of renal tubular function (35). In an ELBW (GA: 29wks, BW: 890gr) neonate, successfully treated for MDR *K. pneumoniae* bacteremia and AKI on peritoneal dialysis, the initial dose of 50 (40/10) mg/kg IV q8h was adjusted to 23.75 mg/kg i.v. q48h for 3 days returning to the initial dose on the 5th day until the completion of a 14-day therapy, without reporting adverse events (34).

Off-label use of CAZ/AVI in a large number of neonates has been recently reported (37). In this cohort, 21 neonates received 31 CAZ-AVI courses. The median gestational age at birth was 29 weeks and had a median weight of 1170g, and according to APGAR, CRIB II and SNAPPE scores they had a medium/severe clinical status. The median post-natal age during the initiation of CAZ/AVI administration was 44 days. CAZ/AVI use was started empirically in more than half of cases at a dose of 20-50mg/kg of ceftazidime every 8 hours. The median treatment duration was 10 days but in most cases CAZ/AVI was co-administered with other antimicrobials (i.e colistin, tigecycline, fosfomycin, amikacin). KPC producing *K. pneumoniae* was the most frequently isolated pathogen. However, there were 3 bloodstream infections due to XDR *A. baumannii*. Overall, clinical response was very good on day 15 and 30 (>74%). Five deaths were reported. However, all these neonates were critically ill, had sepsis and treatment included antimicrobials with little or without safety data for neonates (i.e. colistin, tigecycline, fosfomycin and daptomycin) and therefore potential adverse events associated to the use of CAZ/AVI cannot be drawn. For this reason, clinical trials of CAZ/AVI in premature neonates are warranted.

As CAZ-AVI may have a role in the treatment of neonates with serious infections due to XDR/MDR-GN bacteria, more clinical data on the use of the drug is an unmet need. A phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose trial (ClinicalTrials.gov Identifier: NCT04126031) just completed recruiting pediatric patients aiming to evaluate pharmacokinetics, safety and tolerability of single and multiple doses of intravenous CAZ/AVI in hospitalized infants and neonates from 26 weeks gestation to 3 months of age with suspected or confirmed Gram-negative BSI (38). According to study protocol, CAZ/AVI is administered as a 2-hour intravenous infusion at the following dosing regimens based on gestational, corrected and postnatal age and on current weight of the enrolled neonates: i) 30/7.5 mg/kg/dose q12 (ceftazidime and avibactam, respectively) in the group of term infants (GA ≥37 weeks) with postnatal age >28 days and preterm infants with corrected age >28 days to <3 months old, ii) 20/5 mg/kg/dose q12 in term neonates (GA ≥37 weeks) from birth to ≤28 days old, iii) 20/5 mg/kg/dose q12 in the preterm neonates with GA ≥26 weeks to <37 weeks from birth to ≤28 days old (38).

Several reports have addressed the emergence of resistance to CAZ/AVI beyond the intrinsic resistance of Gram-negative bacteria that harbor Ambler class B (metallo-β-lactamases) or some of the class D β-lactamases. In KPC-producing *K. pneumoniae* isolates there have been several mutations (within or outside the omega loop region), which are associated with in vitro resistance to CAZ/AVI in patients with or without previous antimicrobial exposure (39). In addition, (over)expression of KPC in conjunction with other mechanisms of resistance such as porin mutations and other β-lactamases (VEB-25) have been documented in CAZ/AVI resistant bacteria (40). In a recent systematic

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review of clinical cases, CAZ/AVI resistant isolates were infrequently isolated all over the world, but their high fatality rate as well as rising rates are of concern (41).

Ceftolozane/tazobactam

Ceftolozane/tazobactam (C/T) is a combination of a semisynthetic, bactericidal, antipseudomonal, fifth generation cephalosporin, ceftolozane, with the known β-lactamase inhibitor tazobactam. Ceftolozane inhibits bacterial cell wall biosynthesis through penicillin-binding proteins (PBPs), it has enhanced affinity for the PBPs of *P. aeruginosa*, high stability against Amp-C type β-lactamases, frequently present in *P. aeruginosa,* and it is significantly less affected by the changes in the porin permeability or efflux pumps of the external membrane of Gram-negative bacteria (42–44). C/T has a broad coverage against Gram-negative organisms, particularly MDR and XDR *P. aeruginosa*, ESBL-producing *Enterobacterales* and some anaerobes (*Bacteroides fragilis* and non-*Bacteroides* Gram-negatives) and some *Streptococcus* spp. (excluding Enterococcus), while it shows limited activity against ESBL-producing *K. pneumoniae*, carbapenemase-producing *Enterobacterales* and anaerobic Gram-positive cocci (45).

C/T is approved by FDA since 2014 for complicated intraabdominal infections (IAIs) combined with metronidazole and for complicated urinary tract infections (cUTIs) in adults (>18 years old) (46). The indication was extended to HAP/VAP in 2019 (47). On the other hand, in Europe, the drug is currently indicated for the treatment of cIAIs and cUTIs in pediatric patients and neonates of GA >32 wks from the 7th day of life up to 18 years old, at 20 mg/kg ceftolozane/10 mg/kg tazobactam (up to a maximum dose of 1 g ceftolozane / 0.5 g tazobactam) (48).

In a phase 1 open-label, single dose, multicenter study, 7 neonates and young infants of GA >32 wks and PNA 7 d to <3 months, and 6 neonates, of GA ≤32 weeks and PNA 7 days to <3 months, with suspected/proven Gram-negative infection received 20/10 mg/kg and 20/10 mg/kg if estimated glomerular filtration rate (eGFR) >50 mL/min/1.73m^2 or 12/6 mg/kg if eGFR < 50 mL/min/1.73m^2, respectively. PK profiles were generally comparable to those of older children but not surprisingly with greater interindividual variability, higher terminal half-lives probably due to increase of volume of distribution and decreased clearance, that are typical of neonates compared to older patients. The drug was well tolerated without any serious adverse event (49).

A more recent phase 2, randomized trial studied the safety and efficacy of C/T vs. meropenem in 20 full-term neonates and young infants <3 months of age with pyelonephritis. C/T had a favorable safety profile in these patients, and rates of clinical cure and microbiologic eradication were similar to meropenem (50). More data on efficacy in premature neonates are needed.

Imipenem/Cilastatin-Relabactam

The increasing global trend of MDR bacteria colonizing neonates across NICU and causing difficult to treat infections necessitated the development of newer promising agents. In an effort to restore the clinical activity of imipenem, relebactam, which is a novel β-lactamase inhibitor, was combined with imipenem/cilastatin, (an established anti-pseudomonal carbapenem). Relebactam exhibits a dual Ambler class A/C activity but confers no activity against class D OXA-48 and class B MBL producing *Enterobacterales* and carbapenem-resistant *A. baumannii*. Imipenem/cilastatin-relebactam (IMI-REL) is indicated for patients over 18 years of age for the treatment of HABP/VABP due to susceptible Gram-negative bacteria and for complicated cUTIs and cIAIs with limited or no alternative treatment options. In adults, phase 2 clinical trials have shown that IMI-REL is noninferior to imipenem/cilastatin in the treatment of cUTIs, including pyelonephritis, and cIAIs with comparable adverse reactions. The ongoing MK-7655A-016 phase 3 multinational randomized clinical study (NCT03583333) is designed to evaluate the safety, tolerability, and efficacy of IMI-REL versus piperacillin/tazobactam in adult participants with HABP or VABP. Another small phase 3 clinical trial has shown that IMI-REL is an efficacious and well-tolerated option compared to imipenem/cilastatin plus colistin for the treatment of HABP/VABP, cIAIs, and cUTIs caused by imipenem-non susceptible (but IMI-REL- and colistin- susceptible) Gram-negative organisms with

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significantly reduced nephrotoxicity than imipenem/cilastatin plus colistin (51). A recently completed pediatric clinical study (MK-7655A-020) showed that IMI-REL exhibited approximately dose-proportional PK and a single dose was generally well tolerated (52). The ongoing MK-7655A-021 phase 2/3 open-label, randomized clinical study (NCT03969901) will provide valuable information for the pediatric and neonatal population with confirmed or suspected Gram-negative bacterial infection involving 1 of 3 primary infection types (HABP/VABP, cIAI or cUTI).

Meropenem-Vaborbactam

Meropenem-vaborbactam (M/V) is a carbapenem β-lactamase inhibitor combination with activity against broad-spectrum β–lactamases in CRE infections. Vaborbactam, a cyclic boronic acid derivative, is a β-lactamase inhibitor with no antibacterial activity (53). It prevents β-lactamases from hydrolyzing meropenem, which can then exert her action by disrupting bacterial cell-wall synthesis resulting in cell death. M/V shows a potent activity against class A carbapenemases (e.g., KPC-2, KPC-3, KPC-4, BKC-1, FRI-1, SME-2, NMC-A), class A ESBLs (CTX-M, TEM, SHV) and class C β-lactamases (CMY, P99, MIR, FOX) but not against metallo-β-lactamases (e.g. NDM, VIM and IMP) and some class D carbapenemases (OXA-49-like) (53–55). So, M/V is mainly active against *Enterobacterales* with a KPC-mediated mechanism, but it has been shown that its activity is attenuated in isolates with lack of ompK35 and ompK36 genes responsible for the encoding of outer membrane porins K35 and K36 respectively (53). Moreover, M/V has been found to be active against strains producing KPC mutants with resistance to ceftazidime-avibactam (e.g. KPC-8, KPC-31), whereas vaborbactam does not protect meropenem hydrolysis against CR *Acinetobacter* spp. and *P. aeruginosa*, as meropenem resistance is largely attributed to mechanisms unrelated to the vaborbactam mode of action, such as outer-membrane impermeability, upregulation of efflux systems and production of class B or class D β-lactamases (55–57). The drug was first approved in USA (FDA, August 2017) for the treatment of cUTI including pyelonephritis caused by susceptible *Escherichia coli, K. pneumoniae, and Enterobacter cloacae* species complex, while in Europe (EMA approval, November 2018) is also indicated for the treatment of cIAI, hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) only in adult patients (≥18 years), at a dose regimen of 2g/2g every 8 hours, as a 3-hour intravenous infusion, for patients with normal renal function (58,59). EUCAST provided a susceptibility clinical breakpoint of 8 mg/L for *Enterobacterales* and *P. aeruginosa*, while CLSI provided a susceptibility clinical breakpoint of 4 mg/L only for *Enterobacterales* (60).

Until now, PK, safety and efficacy data derive from studies only in adults. To our knowledge, pediatric experience is limited to 2 case reports. Based on pharmacokinetic data of meropenem in critically ill children, Harnetty et al. administered meropenem component of M/V at the dose of 40 mg/kg/dose every 6 hours infused over 3 hours, in a 4-year-old child with KPC *K. pneumoniae* bacteremia, which was successfully treated for 14 days. The dosing regimen provided a target attainment of 100% for meropenem serum concentrations above the minimum inhibitory concentration (MIC) for at least 40% of the dosing interval and was well tolerated (61). In a 10-year-old cystic fibrosis female patient, infected with a PDR *Achromobacter* spp., meropenem-vaborbactam was co-administered (2 g, every 8 hours, infused over 3 hour) with cefiderocol and bacteriophage for 14 days; the combination was reported to be safe, effective and well-tolerated (62). An open label, phase 1 study evaluating dosing, pharmacokinetics, safety and tolerability of a single dose infusion of meropenem-vaborbactam in pediatric patients, from birth to less than 18 years of age with serious bacterial infections in stable condition c (TANGOKIDS, ClinicalTrials.gov Identifier: NCT02687906) is currently conducted and is still recruiting patients (63). According to study protocol enrolled children of 12 to < 18 years old received 40 mg/kg meropenem - 40 mg/kg vaborbactam (2 g meropenem - 2 g vaborbactam for subjects ≥50kg), while after the analysis of the PK, safety and tolerability data in this age group, the dose for ages 2 to <6 years was modified to be 60 mg/kg (2 g meropenem - 2 g vaborbactam for children weighting >33kg) (63).

There is no published experience on meropenem-vaborbactam use in neonates. On the contrary, meropenem, was approved by FDA in infants <3 months with complicated intra-abdominal

infections since 2014, has been studied in both ill hospitalized term and preterm neonates with LOS in a large multicenter phase III superiority RCT (64,65). In terms of efficacy, Neomero-1 trial showed that meropenem was not superior to SOC (ampicillin + gentamycin or cefuroxime + gentamycin), but the drug should be preferred in NICUs where LOS by ESBL and AmpC type beta-lactamases producing gram-negative bacteria are common (65). Neomero PK data and simulations showed that in cases of increased MIC (up to 4 mg/L), doses should be increased to 40 mg/kg every 8 hours to achieve therapeutic targets and that longer infusions (up to continuous infusion) may increase plasma concentrations improving %T>MIC, but worsen CSF penetration decreasing CSF %T>MIC (66). In a recently published PBPK study, using the target of 50% T>MIC for pathogens with MIC of 4 mg/L or 75% T>MIC for MIC of 2 mg/L, favorable target attainment was achieved across all dosing groups further supporting the dosing regimen currently recommended by FDA (67).

OTHER NOVEL OR REPURPOSED ANTIBACTERIAL AGENTS

Colistin

Colistin is among the very few agents still effective against carbapenem-resistant Gram-negative bacteria. It has been introduced for clinical use since the late 1950s, but was substituted some decades later by newer antimicrobials owing to reported neurotoxicity and nephrotoxicity. Recently, due to the stagnation of antibiotic development, colistin was re-evaluated as a last resort. It is a concentration-dependent antibiotic of the polymyxin class that is administered as the inactive form of colistimethate sodium (CMS), which is subsequently converted to the active form by hydrolysis of methane sulphonate radicals (68). Colistin also binds to endotoxins, thus reducing the release of inflammatory cytokines and blocking some of their biologic activity (69). There is a paucity of PK data in pediatrics and neonates due to complicated pharmacokinetics, high interpatient variability, and narrow therapeutic index. Therefore, recommendations for dosage in neonates are challenging. According to a PK study in neonates with normal renal function, the daily dose of CMS should be >150,000 IU/kg/day to achieve average steady-state plasma colistin concentration (Css,avg) of >1 μg/mL, with close monitoring of renal function (70). In addition, a recent PK study in critically ill children including infants aged at least 1 month, found that colistin doses higher than those recommended by both EMA and FDA were associated with better antimicrobial exposure and without any additional safety concern (71). On the other hand, real life data from two global network databases that collected antibiotic prescribing data in children and neonates from hospitals around the world, showed that almost 60% of neonates received colistin doses that were lower than those recommended by both FDA and EMA (72).

In neonates, the inhalational route is also used for the treatment of pneumonia and was first reported in 2010. Nebulized colistin as monotherapy was successfully administered and reported in neonates, but studies are scarce to support this as routine practice (73). Moreover, it is suggested to use it in combination with intravenous colistin, since nebulized colistin alone might not reach the lung segments with pneumonia and parenchymal loss of aeration. Intraventricular (IVT) CMS is used, and microbiological cure is reported in neonates and infants with meningitis in a dose ranging from 20,000-125,000 IU/kg/day. CMS and colistin cross the blood-brain barrier poorly despite the inflammation of meninges. Therefore, it is suggested to treat cerebrospinal infections with combination of intravenous colistin with IVT or intrathecal CMS (74).

Colistin has been recommended by the Infectious Diseases Society of America (IDSA) 2021 guidance for treatment of MDR-GN bacteria only as an alternate strategy when first-line options are not available or tolerated (mainly combination beta-lactamase inhibitors, carbapenems or monobactam). Nevertheless, these recommendations are tailored for adults and high-income settings (75). In low middle-income countries (LMICs) colistin is the most prevalent antimicrobial and most studies come from these countries. Because of the concomitant use of other antimicrobials with colistin, the severity of the clinical condition in neonates, the lack of case control studies in neonates and infants and the retrospective character of studies reported, it is difficult to draw conclusions on

the efficacy and safety of colistin in neonates. Renal impairment and electrolyte deficiencies, such as magnesium and potassium possibly related to renal tubulopathy, have been reported in a review for colistin use in neonates (76). However, concomitant nephrotoxic agents and clinical comorbidities contribute to nephrotoxicity and renal injury. Moreover, evidence of neurotoxicity related to colistin use is rare in neonates. Nevertheless, prospective studies to evaluate the effect of colistin to the developing brain would be useful.

In conclusion, colistin appears to be a last resort agent in the fight against MDR-GN infections and its rational use is essential. It is suggested that the combination of colistin with other antibiotics can minimize the potential for emergence of resistance with colistin monotherapy against *A. baumannii.* However, the optimal combination remains to be elucidated.

Tigecycline

Tigecycline is a bacteriostatic antimicrobial agent of the class of glycylcyclines (semi synthetic derivative of minocycline) with similarities to the structure and mechanism of action of tetracyclines (77). It exerts its action by binding to the bacterial 30S ribosome, blocking the entry of transfer RNA, which inhibits protein synthesis and bacterial growth, against a broad spectrum of Gram-positive and Gram-negative, anaerobic and atypical pathogens, including MDR and extensive drug-resistant (XDR) microbes, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp., *A. baumannii* and Gram-negative bacterial strains that produce extended spectrum β-lactamases (ESBL) and carbapenemases, with the exception of *Pseudomonas* spp. (78–80). In the era of carbapenem-resistant *Enterobacterales* (CRE), tigecycline is one of the last therapeutic options against infections due to such bacteria and its use in pediatric and neonatal population is challenging as it is off-label (81–83).

Tigecycline is approved by FDA for intravenous treatment of cIAI, complicated skin and skin structure infections (cSSTI) and community acquired pneumonia (CAP). However, it is frequently used off-label for the treatment of hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP), rescue therapy for infections due to MDR bacteria, nosocomial urinary tract infections (UTIs) and refractory *Clostridium difficile* infection (77,84,85). FDA has approved its use only in ≥18 years old patients, at a loading dose of 100 mg and maintenance dose of 50 mg twice daily, and warns that tigecycline should be preserved only if alternative antibacterial drugs are no available because of an observed increase of all-cause mortality in tigecycline-treated adult patients in a meta-analysis of 13 phase 3 and 4 clinical trials (85). Meanwhile, EMA has approved its use to ≥8 years old patients for treatment of cIAI and cSSTI in situations where other alternative antibiotics are not suitable, providing the consultation with an infectious diseases expert, at 1.2 mg/kg q12h to a maximum dose of 50 mg q12h for 8–11 years old children, and at 50 mg q12h, for 12–17 years old adolescents without the use of a loading dose (84). Tigecycline pharmacokinetic (PK) properties, optimal dosing regimens, efficacy and safety data comes mainly from studies in adults; published data for the pediatric population are limited to case series, case reports and 1 open-label, phase 2, multiple ascending dose study, whereas for neonates are scarce (81,86–89). The drug exhibits linear pharmacokinetics and its major routes of elimination include: excretion of unchanged drug into feces (through bile, 59%) and urine (renal, 33%), metabolic elimination (through glucuronidation and amide hydrolysis) and non-enzymatic degradation (90). It has a long elimination $t_{1/2}$ 37±12 hours and a large volume of distribution (9-10 L/kg) at steady state, while it is bound to plasma protein to a significant degree (71-87%) showing an atypical nonlinear protein binding (90,91). Because of the high volume of distribution, the drug is rapidly accumulated in the various tissue compartments, with higher degree penetration in bile, gallbladder, colon, to a lesser degree in lungs (even lesser in cerebral spinal fluid, synovial fluid and bone), resulting in low bactericidal concentrations in serum and epithelial lining fluid (92). The latter findings offer a plausible explanation to the reported failures in tigecycline treated adult patients with bloodstream infections and VAP at standard doses (93). Several studies and expert opinion support the use of higher doses of tigecycline (100 mg twice daily) in adults and 2–3.2 mg/kg/dose q12 (after a loading dose) in children for treating CRE infections (e.g.

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HAP/VAP), especially from MBL-producing isolates, while combination therapy with other antibiotics is also suggested for bloodstream infections in severely ill patients (94–97). These peculiar PK characteristics make the off-label use of tigecycline in neonates quite intimidating given the unique physiological and maturational characteristics of the neonatal population and the fact that bacteremia is the predominant type of neonatal infections.

To our knowledge, there are no PK data at all for infants or children <8 years old, whereas in older children doses higher than the currently proposed have not been studied in RCTs (88). There are reports for the off-label use of loading dose (1.8 mg/kg - 6.5 mg/kg) and higher maintenance doses (1.25 mg/kg - 3.2 mg/kg) in children (2.5 months to 14 years old), which were considered tolerable without serious adverse events (87,88,98). Findings regarding efficacy and safety were similar to those observed in adults, although as tigecycline was administered in combination with other antibiotics, definite conclusions on efficacy and safety of the drug in severe MDR/XDR infections in children cannot be drawn. There are scarce reports for the use of tigecycline in neonates (99–101). Due to unavailable alternative treatments, Ipek et al. administered tigecycline to 4 critically ill preterm neonates as salvage combination therapy for the treatment of XDR *K. pneumoniae* BSI. Standard doses were administered, while in one neonate the dose was increased to 2mg/kg q12 due to persistence of bacteremia after 96 hours of therapy. The outcome of all patients was favorable without serious adverse events. Interestingly, after the first week of treatment all neonates presented with thrombocytopenia related to the drug, with PLT gradually returning to normal values after the end of therapy (102).

Liver function, hematology and coagulation parameters, amylase and lipase should be monitored prior to start and regularly during therapy (84). It is generally considered that its use in children <8 years old should be avoided due to the lack of safety data and to the potential adverse event of permanent tooth discoloration, hitherto inadequately studied and confirmed. In a case-series of pediatric patients <8 years old, yellow staining of permanent teeth was presented in 2 out of 12 (17%) children, having received tigecycline at doses close to the recommended regimen for 8-11 years old for at least 19 days (103). To clarify the efficacy, safety and optimal dosing regimen of tigecycline in neonates, well designed studies adjusted to their unique developmental physiological characteristics are needed.

Fosfomycin

Fosfomycin, a phosphoenolpyruvate (PEP) analogue, has recently been identified by WHO as "critically important antimicrobial" (104). It possesses a distinctive mechanism of bactericidal action by permanently inhibiting the primary step in the biosynthesis of peptidoglycan for bacterial wall synthesis (105). It exhibits bactericidal activity against Gram-positive and Gram-negative pathogens including Methicillin-Resistant Staphylococcus (MRSA), Vancomycin-Resistant Enterococcus (VRE), CPE and *P. aeruginosa* and may also penetrate biofilms (106). Nevertheless, species naturally resistant to fosfomycin include *A. baumannii*, *Stenotrophomonas maltophilia*, *Staphylococcus capitis*, *Staphylococcus saprophyticus*, *Mycobacterium tuberculosis*, *Vibrio sheri* and *Chlamydia trachomatis* (107). Fosfomycin's unique mechanism of action permits synergy with other antibiotics (carbapenems and aminoglycosides), as it has been demonstrated in vitro. Resistance to fosfomycin can develop rapidly when it is used as monotherapy and can be either chromosomal or plasmid-mediated (107).

Clinical efficacy of fosfomycin is well-documented in adults especially for MDR urinary tract infections. Moreover, fosfomycin has been administered as a last-resort antibiotic choice for MDR pathogens in critically ill patients, especially in combination with other antibiotics with high clinical cure rates (108). In pediatric population, it is rarely administered and only occasionally prescribed for empirical use. There is limited existing literature describing the use of fosfomycin in neonatal sepsis. A series of studies have recently been published, which acknowledge its promising in vitro activity (109). The potential utility of the combination of fosfomycin and amikacin for neonatal sepsis has been studied by assessing in vitro activity and the nature and extent of any PD interactions and defined a candidate combination regimen suitable for further clinical study. According to an analysis

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of 247 Gram-negative bacteremia isolates from children revealed a high susceptibility rate among both *Enterobacterales* and *Pseudomonas* spp., including MDR and ESBL-producing organisms, in both community- and hospital-acquired infections and across both neonates and older children, rendering fosfomycin combined with aminoglycosides a new carbapenem-sparing regimen to treat antimicrobial-resistant neonatal and pediatric sepsis (110). The recently published results of the NeoFosfo study [a single-centre open-label randomized controlled trial of 120 neonates aged ≤28 days treated with standard-of- care (SOC) antibiotics for sepsis: ampicillin and gentamicin and half the participants randomly assigned to receive additional intravenous then oral fosfomycin at 100 mg/kg two times per day for up to 7 days (SOC-F) and followed up for 28 days] suggest that an intravenous dose of 150 mg/kg two times per day is required for pharmacodynamic target attainment in most children, reduced to 100 mg/kg two times per day in neonates aged <7 days or weighing <1500 g (111). Furthermore, intravenous and oral fosfomycin showed no evidence of impact on serum sodium or gastrointestinal side effects at 100 mg/kg two times per day, respectively (111). Therefore, emerging evidence supports the validity of combination fosfomycin therapy as a promising life-saving last-resort antibacterial option for the treatment of neonatal sepsis caused by MDR bacteria. More solid data on dosing regimens, safety profile and appropriate combinations are needed before clear conclusions are reached. Fosfomycin future place is still under evaluation, probably as companion drug to other IV antibiotics for difficult to treat infections, in variant dosing regimens.

Conclusions

Unfortunately, multidrug resistant organisms, especially Gram-negative bacteria, have entered NICUs and remain there threatening well-being of the most vulnerable neonatal population. In real practice there is a great variability of antibiotic regimens used in neonates with clinicians preferring often the administration of combined regimens of 2 or more antibiotics (15). Colistin in combination with meropenem, amikacin, ciprofloxacin or tigecycline is used for CRE neonatal infections, whereas in association with other antimicrobials such as ciprofloxacin it is prescribed for DTR and XDR *P. aeruginosa.* The most active antimicrobial for XDR *A. baumannii* seems to be colistin, whereas novel antimicrobials such as ceftazidime-avibactam have been infrequently used as salvage therapy (19). Novel antimicrobials seem to be promising based on experience from studies in adults and lately from a very small but increasing number of trials including neonates. Neonatologists face the problem of using many off-label antimicrobial agents and receive a high volume of information regarding newer data of PK and safety even for old antibiotics. Moreover, pharmacologists or infectious diseases experts are not available in many NICUs. These problems turn decision-making difficult. Treatment of neonatal sepsis due to MDR-GN bacteria is complex and challenging. Ideally, therapeutic decisions require expert consultation and individualized approach until more evidence is available.

Future Directions

The battle against MDROs has to focus on two major fields: prevention and management. Prevention is mostly achieved by good infection control pracices. However, as many times this is not perfect and MDR GN bacteria cause infections in the NICU, off label use of newly developed antimicrobials as well as use of old antibiotics (not adequately studied and with dosing and safety concerns in the neonatal population) is a common practice in the NICU. Initiatives for participation of neonates in clinical trials find major challenges due to ethical and physiological difficulties; however, dose-finding PK and safety studies are more than ever necessary. The concept of extrapolation of efficacy data from studies in other populations (e.g adults) is part of the pediatric study decision tree (112). As it is reasonable to assume that there is a similar bacteriologic response to that in adults, PK studies, adapted to the unique physiological and maturational characteristics of different neonatal subpopulations (e.g. extremely preterm, preterm, term, those with *intrauterine growth restriction*), will determine the optimal dose required for targeted exposure and achieve levels

similar to adults, although such an approach has its limitations (113). Undoubtedly, safe and effective use and evaluation in neonates have many challenges (114). Developmental pharmacology research, which describes the impact of maturation on drug disposition (PK) and drug effects (pharmacodynamics, PD) throughout the neonatal and paediatric age range, is rapidly expanding; drug development needs to incorporate innovative techniques such as preclinical models to study therapeutic strategies, and shift from sequential enrolment of subgroups, to more rational designs (115).

On the other hand, epidemiological surveillance and prevention of colonization and infections by MDR-GN bacteria should be priority in every NICU. Strict policies regarding the management of colonized neonates (physical cohorting and staff cohorting), antibiotic stewardship for reducing antibiotic overuse, infection and control practices and re-education of the staff should be implemented. Key prevention strategies for AMR in neonates target four major pillars a) surveillance of healthcare associated infections, feedback and education, b) maintenance of skin integrity, c) promotion of colonization with normal flora, and d) prevention of colonization with pathogens. However, the research on the process of colonization with AMR in neonates and the association to a subsequent infection or other neonatal adverse outcomes has many gaps. Collaboration between NICUs and international networks for the conduction of high quality studies will help on better understanding the circulation and the effect of these pathogens in hospitalized neonates and find effective tools for their prevention.

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