Kalam, Neonat Pediatr Med 2023, 9:7

Neonatal and Pediatric Medicine

ISSN: 2572-4983

Review Article Open Access

Antibiotic-Resistant Bacteria are treated with Modern and Enhanced Medications in Neonates

Asfaq-ul Kalam*

Department of Pediatric, University of Rajshahi, Bangladesh

Abstract

Multidrug-resistant Gram-negative (MDR-GN) bacteria are the primary culprits of the global public health issue of antimicrobial resistance. Given the lack of safe and effective therapeutic alternatives, the appearance of these infections in neonatal settings poses a hazard to the health of the community of vulnerable neonates. New -lactam/-lactamase inhibitors, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam, have evidence from studies primarily in adults, but older antibiotics like colistin, tigecycline, and fosfomycin are also included in the fight against MDR-GN infections, which continue to be difficult to treat. Few clinical studies recruit newborns for the evaluation of the effectiveness, safety, and dosage of new antibiotics, while the bulk of these trials enroll neonates for the evaluation of existing antibiotics. As a result, data in the neonatal population are sparse are utilized erratically. This article reviews information on several new and old antibiotics that are effective against MDR-GN bacteria that cause sepsis and may be useful for use in the newborn population.

Keywords: Neonates; Ceftazidime–avibactam; Ceftolozane/tazobactam

Introduction

One of the main causes of newborn morbidity and mortality, particularly in hospitalized term and preterm neonates globally and particularly in low- and middle-income countries, continues to be neonatal bacterial sepsis. Severe bacterial infections cause about 3% of neonatal disability-adjusted life years (DALYs), and there are an estimated 1.3 million bouts of neonatal sepsis each year, with 200,000 sepsis-related deaths worldwide [1].

Almost 5 million deaths worldwide in 2019 were attributed to antimicrobial resistance (AMR), which affects both high-income and low-middle-income countries. Escherichia coli, Staphylococcus aureus, and Klebsiella pneumoniae are the three pathogens most frequently associated with AMR [2]. The non-mycobacterial antibiotic-resistant bacteria priority list published by the World Health Organization (WHO) states that Methicillin-resistant S. aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) are of high priority, whereas carbapenem-resistant Enterobacterales (CRE) and third generation cephalosporin-resistant Enterobacterales (3GCRE) are of critical importance [3]. High percentages of third-generation cephalosporin and carbapenem resistance in K. pneumoniae, as well as high percentages of carbapenem-resistant Acinetobacter species and Pseudomonas aeruginosa, are of serious concern in a number of countries in the European region, with a north-to-south and west-to-east gradient. An estimation of 33,110 attributable deaths and 874,541 DALYs due to healthcare-associated infections caused by antibiotic-resistant bacteria were discovered by population-based modelling analysis using data from point prevalence European Centre for Disease Prevention and Control (ECDC) studies and surveillance data on AMR. The burden of these infections was highest in infants (1 year old) and people over 65 years old; CREs, as well as CREs, and other healthcare-associated infections were found to be particularly problematic. The majority of other multidrug resistant organisms (MDROs), including 3GCRE, MRSA, and VRE, were found in young children. Extended-spectrum -lactamases (ESBLs) and carbapenemase synthesis are the main drivers of antimicrobial resistance for Enterobacterales [4]. The present -lactams are ineffective against resistant Gram-negative bacteria (GNB) due to the synthesis of these enzymes. Two key processes contribute to the complexity of carbapenems resistance: (a) -lactamase activity in conjunction with structural alterations, and (b) carbapenemase enzymes, which hydrolyze carbapenem antibiotics. ESBLs, which are typically encoded by plasmids, and AmpC cephalosporinases (AmpC), whose expression in Enterobacterales is most frequently linked to hyperproduction from inducible or derepressed chromosomal genes, are non-carbapenemase –lactamases [5]. The mutation of porins, a family of proteins found in the outer membrane of Gram-negative bacteria that, when altered or lost, slow down the absorption of antibiotics, together with ESBLs and AmpC, confers carbapenem resistance. At a rate that permits the ESBL and AmpC enzymes to function more efficiently across the bacterial membrane. AmpC, for example, can bind carbapenems in the periplasm and prevent them from reaching their targets since the enzymes are produced in huge amounts and the loss of porins decreases the permeability of the outer membrane. Carbapenemases are categorized into classes A, B, and D using the Ambler classification system based on their molecular makeup [6]. Class A consists of serine carbapenemases, mainly of the K. pneumoniae-producing carbapenemase (KPC) type. Verona Integrated Metallo-Lactamase (VIM) and New Delhi Metallo-Lactamase (NDM) types make up the majority of class B metallo-lactamases. OXA-48-like enzymes are the most common in Class D, which also includes carbapenemases of the oxacillinase type [7].

Ceftazidime–avibactam

A novel -lactam agent coupled with a -lactamase inhibitor, ceftazidime-avibactam (CAZ-AVI) is a recently created antibiotic. Avibactam, a novel non-lactam -lactamase inhibitor, is coupled with ceftazidime, a well-known broad range third generation cephalosporin

***Corresponding author:** Asfaq-ul Kalam, Department of Pediatric, University of Rajshahi, Bangladesh, E-mail: kalamul@gmail.com

Received: 01-July-2023, Manuscript No: nnp-23-107922; **Editor assigned:** 07-July-2023, Pre-QCNo: nnp-23-107922 (PQ); **Reviewed:** 21-July-2023, QCNo: nnp-23-107922; **Revised:** 24-July-2023, Manuscript No: nnp-23-107922(R); **Published:** 31-July-2023, DOI: 10.4172/2572-4983.1000333

Citation: Kalam A (2023) Antibiotic-Resistant Bacteria are treated with Modern and Enhanced Medications in Neonates. Neonat Pediatr Med 9: 333.

with antipseudomonal activity, to inactivate multiple -lactamases by generating a covalent adduct with the enzyme that is stable against hydrolysis. By preventing ceftazidime's breakdown, avibactam enables it to combat germs that would be resistant to it otherwise [8]. Avibactam specifically inhibits Ambler class A (TEM-1, CTX-M-15, KPC-2, KPC-3), class C (AmpC), and some class D -lactamases (e.g., OXA-10, OXA-48), but it has no effect on metallo--lactamases (class B enzymes such as NDM, VIM, and IMP). Thus, when -lactam resistance is brought on by the synthesis of such -lactamases, CAZ-AVI is useful for the treatment of infections caused by XDR Enterobacterales and P. aeruginosa. According to certain findings, the co-administration of CAZ-AVI and aztreonam can overcome the resistance exhibited by Enterobacterales and P. aeruginosa that produce metallo—lactamases [9].

Meropenem–vaborbactam

A carbapenem -lactamase inhibitor combination with broad-spectrum activity against -lactamases in CRE infections is meropenem-vaborbactam (M/V). A -lactamase inhibitor with no antibacterial action, vaborbactam is a derivative of cyclic boronic acid. It stops -lactamases from hydrolyzing meropenem, which would allow them to disrupt the formation of bacterial cell walls and cause 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). As a result, M/V mostly inhibits Enterobacterales through a KPC-mediated mechanism. However, it has been demonstrated that in isolates lacking the ompK35 and ompK36 genes, which encode the outer membrane porins K35 and K36, respectively, their activity is reduced [10]. Vaborbactam does not prevent meropenem hydrolysis against CR Acinetobacter spp. and P. aeruginosa because meropenem resistance is largely attributed to mechanisms unrelated to the vaborbactam mode of action, such as outer-membrane impermeability, the upregulation of efflux systems, and the production of class B or class D -l. Furthermore, M/V has been found to be effective against strains producing KPC.

Additional new or modified antibacterial agents

One of the few substances remaining capable of killing Gram-negative bacteria resistant to carbapenem is colistin. It has been utilised in clinical settings since the late 1950s, but newer antimicrobials have since taken its place due to documented neurotoxicity and nephrotoxicity. Colistin has recently undergone a re-evaluation as a last option because antibiotic development has stalled. The inactive form of colistimethate sodium (CMS), a concentration-dependent antibiotic of the polymyxin class, is supplied before being changed into the active form by the hydrolysis of methane sulphate radicals. Colistin also binds to endotoxins, which inhibits some of their biological action and lessens the release of inflammatory cytokines. Due to complex pharmacokinetics, there are few PK data in paediatrics and neonates. Limited therapeutic indices and substantial interpatient variability. As a result, dose recommendations for neonates are difficult. In order to obtain an average steady-state plasma colistin concentration (Css, avg) of >1 g/mL while closely monitoring renal function, the daily dose of CMS should be >150,000 IU/kg/day, according to a PK investigation in neonates with normal renal function. Additionally, a recent PK research in critically ill children, including newborns aged at least one month, discovered that colistin doses higher than those advised by the EMA and FDA were linked to improved antimicrobial exposure and without raising any extra safety issues. However, actual data from two global network databases that gathered information on the prescription of antibiotics in children and neonates from hospitals around the world revealed that approximately 60% of neonates were given colistin doses that were lower than those advised by the FDA and EMA.

The inhalational method is also utilised to treat neonatal pneumonia, according to a 2010 report. Although nebulized colistin as monotherapy has been delivered and shown to be successful in neonates, there are few studies that support this as standard practice. Additionally, since nebulized colistin alone might not reach the lung segments with pneumonia and a parenchymal loss of aeration; it is advised to use it in conjunction with intravenous colistin. In neonates and babies with meningitis, intraventricular (IVT) CMS is utilised, and microbiological cure is documented at doses between 20,000 and 125,000 IU/kg/day. Despite the meningeal inflammation, CMS and colistin have poor blood-brain barrier penetration. In order to treat cerebrospinal infections, it is advised to use a combination of intravenous using intrathecal CMS or IVT and colistin.

In conclusion, our results support the use of NMR-based urine metabolomics for better understanding the relationship between mild preterm, neonatal illnesses, integrated metabolism, nutrition, and medical conditions. The study of newborn metabolic maturation and the discovery of early biomarkers helpful for diagnosis, specialised care of neonatal illnesses, and early outcome prediction may be improved by knowledge about the metabolic status of LP infants

Conclusion

Unfortunately, Gram-negative bacteria in particular are antibiotic resistant organisms that have made their way into NICUs and are still there, posing a threat to the health of the most fragile neonatal population. Neonatal antibiotic regimens used in real-world practise vary greatly, with doctors frequently favouring the administration of combination regimens of two or more antibiotics. Colistin is used for CRE neonatal infections when combined with meropenem, amikacin, ciprofloxacin, or tigecycline, while it is prescribed for DTR and XDR P. aeruginosa when combined with other antimicrobials like ciprofloxacin, according to a recent systematic review that sought to identify the current antimicrobial treatment options for MDR and XDR GNB infections in the neonatal population. Colistin appears to be the most effective antibiotic for XDR A. baumannii, although new antibiotics like ceftazidime-avibactam are rarely utilised as salvage therapy. Based on results from adult research and recently from a relatively small but growing number of trials involving newborns, novel antimicrobials appear to be promising. The use of several antimicrobials off-label by neonatologists and the abundance of information they get regarding newer PK and safety data, even for outdated antibiotics, provide challenges. Moreover, a lot of NICUs lack access to pharmacologists or experts in infectious diseases. These issues make making decisions challenging. The management of MDR-GN-caused newborn sepsis is difficult and complex. Until further information is available, therapy decisions should ideally involve expert advice and an individualised strategy.

References

1. Goligher, Ewan C (2012) Ventilator-Induced Diaphragm Dysfunction. Anesth 117: 463–464.
2. Stein H (2013) Electrical Activity of the Diaphragm [Edi] Values and Edi Catheter Placement in Non-Ventilated Preterm Neonates. Am J Perinatol 33: 707–711.
3. Chiew Yeong Shiong (2013) Effects of Neurally Adjusted Ventilatory Assist [NAVA] Levels in Non-Invasive Ventilated Patients: Titrating NAVA Levels with Electric Diaphragmatic Activity and Tidal Volume Matching. BioMed Eng 2: 12-61.

4. Beck Jennifer (2009) Patient-Ventilator Interaction during Neurally Adjusted Ventilatory Assist in Low Birth Weight Infants. Pedia Res 65: 663–668.

5. Stein, Howard (2012) Synchronized Mechanical Ventilation Using Electrical Activity of the Diaphragm in Neonates. Cli Peri 39: 525–542.

6. Kallio Merja (2012) Electrical Activity of the Diaphragm during Neurally Adjusted Ventilatory Assist in Pediatric Patients. Pedia Pulmo 50: 925–931.

7. Rahmani A (2012) Neurally Adjusted Ventilatory Assist in the Neonatal Period: Applications and Limitations. J Neo-Peri Med 5: 205–212.

8. Shilpi M, Kumar KS, Kumar D (2020) Ayurvedic Approach Of Treatment Of Recurrent/ Chronic Cough In Children With Special Reference To Pancha Vidha Kasa. Ind J of App Res 10: 51-52.

9. Nelaturi P, Nagarajan P, Sabapathy SK, Sambandam R (2021) Swarna Bindu Prashana—an Ancient Approach to Improve the Infant's Immunity. Bio Tra Ele Res 199: 2145-2148.

10. Asai T, Nagata A, Shingu K (2008) Awake tracheal intubation through the laryngeal mask in neonates with upper airway obstruction. Paediatr Anaesth 18: 77-80.