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Neonatal infections due to multi-resistant strains: Epidemiology, current treatment, emerging therapeutic approaches and prevention

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ABSTRACT

Severe infections represent the main cause of neonatal mortality accounting for more than one million neonatal deaths worldwide every year. Antibiotics are the most commonly prescribed medications in neonatal intensive care units. The benefits of antibiotic therapy when indicated are clearly enormous, but the continued and widespread use of antibiotics has generated over the years a strong selective pressure on microorganisms, favoring the emergence of resistant strains. Health agencies worldwide are galvanizing attention toward antibiotic resistance in gram-positive and gram-negative bacteria. Infections in neonatal units due to multidrug and extensively multidrug resistant bacteria are rising and are already seriously challenging antibiotic treatment options. While there is a growing choice of agents against multi-resistant gram-positive bacteria, new options for multi-resistant gram-negative bacteria in the clinical practice have decreased significantly in the last 20 years making the treatment of infections caused by multidrug-resistant pathogens challenging mostly in neonates. Treatment options are currently limited and will be some years before any new treatment for neonates become available for clinical use, if ever.

The aim of the review is to highlight the current knowledge on antibiotic resistance in the neonatal population, the possible therapeutic choices, and the prevention strategies to adopt in order to reduce the emergency and spread of resistant strains.

1. Introduction

Neonatal sepsis represents the main cause of neonatal mortality accounting for more than one million neonatal deaths worldwide every year, and antibiotics are the most commonly prescribed medications in neonatal intensive care units (NICU) [1,2]. The development of antibiotic resistance (resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it), on the other hand, is rising among many microorganisms in healthcare settings as well as in community and is associated with increased morbidity and mortality [3]. The risks of antibiotic resistance have been recognized as a nations' security matter at the sixty-sixth World Health Assembly on 2013 [4] and the Institute of Medicine suggests that the control and reduction of infections caused by antibiotic-resistant pathogens is one of the most important issues that medical community must approach [5].

Data from the Centers for Disease Control and Prevention of Atlanta (CDC) report 2 million cases of infection with resistant bacteria in the United States (US) every year with at least 23,000 deaths as direct result and the cost to the US health system has been estimated to be $21–34 billion dollars yearly [6]. European Medicines Agency (EMA) and European Centre for Disease Prevention and Control (ECDC) estimates that 25,000 deaths per year are direct consequence of a multidrug resistance infection [7] and World Health Organization (WHO) report 3.7% of new cases worldwide [3]. A national survey of infectious diseases specialists conducted on 2011 by the Emerging Infectious Network report that more than 60% of specialists had seen an untreatable infection due to a pan-resistant pathogen within the prior year [8].

Recently the most common resistant bacteria have been reported as the "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*,

Abbreviations: ASP, antimicrobial stewardship programs; CA-MRSA, community-associated MRSA; CDC, Centers for Disease Control and Prevention of Atlanta; CONS, coagulase-negative Staphylococcus; CPE, carbapenemase-producing *Enterobacteriaceae*; CSF, cerebrospinal fluid; ECDC, European Centre for Disease Prevention and Control; EMA, European Medicines Agency; EOS, early-onset sepsis; ESBL, extended spectrum β-lactamase; FDA, the Food and Drug Administration; GBS, group B streptococcus; GNB, gram-negative bacteria; GPB, gram-positive bacteria; HA-MRSA, hospital-associated MRSA; IDSA, Infectious Diseases Society of America; KCP, *Klebsiella pneumoniae* carbapenemase; KCP-Kp, KCP K. *pneumonia*; LOS, late-onset sepsis; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of flight mass spectrometry; MRSA, Methicillin-resistant *Staphylococcus aureus*; MDR, multi-drug resistant; NICU, Neonatal intensive care unit; PCR, polymerase chain reaction; PVL, Panton-Valentine leukocidin; VISA, vancomycin-intermediate S. aureus; VLBW, very low birth weight infants; VRE, vancomycin-resistant enterococci; VRSA, vancomycin-resistant S. aureus; WHO, World Health Organization; XDR, extensively drug-resistant.

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Klebsiella pneumonia, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* species) to highlight that they "escape" the effects of antibacterial drugs [9].

2. Epidemiology of resistant pathogens in the NICU

Neonatal sepsis are distinct in early-onset (EOS) due to vertical transmission and late-onset (LOS) usually hospital acquired. Even if the risk to develop an infection due to resistant pathogens is usually related with late-onset nosocomial infections, since hospitalized neonates are frequently exposed to wide-broad antibiotics, there are potential risks also around early-onset infections.

EOS is most often caused by group B streptococcus (GBS) (43%), followed by *Escherichia coli* (15.5–29%) [10]. LOS is caused by Gram-positive bacteria (GPB) (70–81%), most often coagulase-negative Staphylococcus (CONS) (42–45%), followed by *S. aureus* (10–13%). Gram-negative bacteria (GNB) cause 19%–25% of all LOS in the NICU and they are associated with greater mortality (19–36%). Of Gram-negative isolates *Enterobacteriacae* (9–10%) were the most common followed by *E. coli* (7–8%), *Pseudomonas* spp (2–3%) and other organisms (1–4%) [11,12].

2.1. Gram positive bacteria

GBS remains sensitive to penicillin, ampicillin, and the first generation cephalosporins. However there have been described cases of increase in the MIC of penicillin and ampicillin for some strains. The proportion of GBS strains showing in vitro resistance to clindamycin or erythromycin has increased over the last 20 years. In studies published between 2006 and 2009, the prevalence of resistance among invasive strains of GBS isolates in the United States ranges from 25 to 32% for erythromycin and 13–20% for clindamycin [13].

Dual resistance of isolates to both drugs was also very high, with 94.3% of clindamycin-resistant isolates being also resistant to erythromycin and 71.5% of erythromycin-resistant isolates exhibiting co-resistance to clindamycin [13,14].

Enterococci are uncommon pathogens in neonatal settings, even though, ampicillin-resistant, and more recently, an increasing rate of infections due to VRE has been described in children and neonates [15–17]. In particular in the US the rate of vancomycin resistance among Enetrococcus *faecium* isolates is estimated around 60% [9].

Most hospital acquired CONS have widespread resistance to many usually prescribed antibiotics on the neonatal units, including penicillin, synthetic penicillins and gentamicin. In addition they could be multidrug-resistant, for example resistant to gentamicin, rifampin, erythromycin, and clindamycin [16–18].

Methicillin-resistant *S. aureus* (MRSA) has become a frequent source of infection affecting premature and critically ill neonates in NICUs with a wide variability of infection rates from institution to institution. Data from different studies in NICU population report, despite variations in prevalence measurements, a rate of colonized or infected neonates with MRSA between 0.6% and 8.4% [19]. The epidemiology of MRSA is changing from being exclusively a hospital acquired pathogen to a pathogen with widespread distribution in the community [20,21]. This MRSA strains are genotypically and phenotypically distinct [19]. Recently a vertical transmission of MRSA from mother to infants has been described. Similarly, the dominant MRSA clones in the NICU have been changing from hospital-associated (HA) to community-associated (CA) clones [16,19–21].

By definition MRSA is resistant to methicillin and all β-lactam antibiotics. HA strains are more often resistant to multiple types of antibiotics; by contrast CA strains are often susceptible to different non-β-lactam antibiotics [19]. CA-MRSA strains are more often associated with expression of Panton-Valentine leukocidin (PVL) that cause the production of cytoxins [20].

Even though an increase in vancomycin MIC values, within the susceptible range, has been registered among isolates of MRSA, CONS or *S. aureus* strains vancomycin-intermediate or vancomycin-resistant haven't been documented in the NICU population [16,17].

2.2. Gram negative bacteria

Gram-negative bacteria are often resistant to at least one class of antibiotics usually used in health care settings, and bacteria multi- or extensively-resistant to conventional antibiotics are frequently isolated. Pan-resistant pathogens are rarely isolated in the NICUs [16,22] and the most frequent resistance has been described against piperacillin-tazobactam, ceftazidime, and/or gentamicin [17].

Gentamicin resistance (antibiotic widely used for empiric therapy in NICU due to aminoglycoside-converting enzymes) is increasing among *Enterobacteriaceae*. Since the enzyme that confers resistance to gentamicin may not include other agents of antimicrobial category the gentamicin-resistant bacteria could be still susceptible to tobramycin or amikacin [22].

The emergence of ESBL-producing *Enterobacteriaceae* resistant to penicillins and cephalosporins, and often to other antibiotic classes (i.e. fluoroquinolones and aminoglycosides) has become a problem threatening health. ESBL-producing bacteria are found frequently in the community meaning that they are possible causes of an EOS due to a vertical transmission [16,17,22]. *E. coli* and *K. pneumonia* are probable to acquire ESBLs, even if these enzymes are also noted in other species [16].

Even more threatening, is the increasing in the community as well as in the hospital of carbapenemase-producing *Enterobacteriaceae* (CPE) that are no susceptible to carbapenems. The European antimicrobial resistance surveillance network report increasing percentages of *K. pneumoniae* carbapenemase (KPC)-producing isolates between 2005 and 2010 in Europe even if these bacteria are not yet common in neonatal population [9,16,17,22,23].

Failure to start early treatment with antibiotics active against resistant strains is linked with poorer prognosis [16,17].

A recent study conducted by Giuffrè et al. [24] in a NICU shows the colonization by KCP-*K. pneumoniae* (KCP-Kp), in 10 out of 54 neonates admitted in the NICU in the period between September 18 and November 14, 2012, without occurs however, cases of infection. According to the authors this is the first report of a KCP-Kp colonization outbreak in a NICU.

Rates of infection due to resistant *P. aeruginosa* and MDR *Acinetobacter* spp continue to increase in US and globally. *P. aeruginosa* is intrinsically resistant to many commonly used antibiotics. Resistance to both quinolones and carbapenems is increasing among *P. aeruginosa* isolates and recent reports document resistance to polymyxins [9]. However, resistance to multiple antibiotics is rare in neonates. Some strains of MDR *Acinetobacter baumannii* exhibit discordant resistance to carbapenems, being susceptible to impenem but resistant to meropenem and doripenem due to increased expression of naturally occurring carbapenemases [17].

3. Antibiotic use and emergence of resistant strains

The extensive and indiscriminate use of antibiotics over several decades in hospitals, outpatient regime in the territory and outside the health care settings, to the farms to promote growth in food-producing animals, has generated over the years a strong selective pressure on microorganisms, favoring the emergence of resistant strains [25].

The development of resistance is a normal evolutionary process for microorganisms, but it is accelerated by the selective pressure exerted by widespread use of antibacterial drugs.

Already in his Nobel Prize speech in 1945, Alexander Fleming, who discovered penicillin, warned that bacteria could become resistant to these remarkable drugs and that it was appropriate to reduce the use of penicillin to slow the development of resistance [26].