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REVIEW ARTICLE

Antimicrobial Stewardship in the Neonatal Intensive Care Unit: An Update

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Abstract: Neonates represent a vulnerable population for infections and neonatal sepsis is a major cause of mortality and morbidity worldwide. Therefore, antimicrobials are the most commonly prescribed drugs in the Neonatal Intensive Care Unit Setting but unfortunately are quite often used inappropriately with various short and long-term effects. The rational use of antimicrobials is of paramount importance in this population and structured antimicrobial stewardship interventions should be in place. These interventions are slightly different from those used in adults and older children due to the particularities of the neonatal medicine. The aim of this review is to provide an update in the field and identify areas for further consideration and future research..

Keywords: Antimicrobial stewardship, neonate, interventions, pathogens, *Candida,* therapeutic challenges.

1. INTRODUCTION

Over-consumption of antimicrobials and the subsequent creation of multidrug-resistant pathogens are a major problem for public health worldwide,which , according to the World Health Organization data, threatens the achievements of modern medicine [1, 2]. Antimicrobials are the most commonly prescribed drugs in the Neonatal Intensive Care Units (NICUs) and are often used inappropriately [3, 4]. Prolonged use of broad spectrum antimicrobials in NICUs increases the risk of *Candida* colonization and invasive infection, necrotizing enterocolitis, late onset neonatal sepsis and death [5-10]. Recently published data also suggest long-term effects of the overuse of antimicrobials during the neonatal period through their effect on the intestinal microbiome, including the development of atopic diseases [11]. Neonatal infections from multidrug-resistant strains are associated with increased mortality, excessive cost, prolonged hospitalization and therapeutic challenges [12]. Additionally, the colonization of the newborns with these pathogens makes them the potential source of nosocomial outbreaks [13]. For all the above reasons, the rational use of antimicrobials in NICUs is imperative.

2. CHARACTERISTICS AND PARTICULARITIES OF ANTIMICROBIAL PRESCRIBING IN THE NICU SETTING

There are particular issues in the NICUs that make the use of antimicrobials different from other settings which are as follows:

1. Diagnostic Challenges: Neonatal sepsis can present with non-specific symptoms and signs, which may also be due to non-infectious causes (such as apnoea, congenital heart disease, gastroesophageal reflux disease). The absence of findings from the physical examination of the newborn does not exclude the infection. In addition, there are no laboratory tests to confirm or exclude with certainty a potential bacteraemia in its early stages. Therefore, the empirical antimicrobial use is a common and widely accepted practice in the neonatologist `s daily routine.
2. Culture Negative Neonatal Sepsis: Initial empirical antimicrobial therapy is often continued in neonates despite negative blood cultures due to the clinical picture of the newborn or suggestive laboratory findings. One of the main reasons leading to this is prematurity, which is often characterized by frequent episodes of apnoeas and hypotension, which are findings that could also indicate neonatal septicaemia. Another reason is the perception that the administration of antimicrobials to mothers during labour can mask an episode of neonatal septicaemia by leading to negative blood cultures of the newborn. However, administering this treatment only to high-risk mothers aims at preventing neonatal infection and sterilizing neonatal cultures. Therefore, this approach greatly reduces the risk of neonatal septicaemia.
3. Chorioamnionitis: If the mother of the newborn had chorioamnionitis, there is no consensus in the literature with regard to which, antibiotics are to be administered to neonates that have a good clinical picture (described as asymptomatic). A common practice is the prolonged administration of antimicrobials even

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when the blood cultures are negative. Based on the Centres for Disease Control (CDC) guidance in 2010, newborns of mothers diagnosed with chorioamnionitis are the only asymptomatic infants in whom antimicrobial treatment is warranted without however indicating the duration of this treatment [14, 15]. If there are other risk factors (such as inadequate antibiotic cover for mothers colonised with B-haemolytic streptococci, rupture of membranes≥ 18 hours before delivery) for asymptomatic terms, follow-up for at least 48 hours without treatment is advised, whereas for premature infants in addition to monitoring, limited laboratory work-up (full blood count, blood culture and CRP), is advised. For the asymptomatic infants of mothers who have been diagnosed with chorioamnionitis, the American Committee of Fetus and Newborn in 2014 has proposed the following [15, 16]:

- Discontinuation of the antimicrobials in newborns of mothers with chorioamnionitis that appear clinically well and have normal laboratory investigations 48 hours after their onset (if the blood cultures are negative).
- In preterms or in terms with abnormal laboratory results, the possibility of antimicrobial treatment should be considered for up to 72 hours after their initiation (if the blood cultures are negative).

The philosophy of guidelines in the United Kingdom published in 2012 by the National Institute of Clinical Excellence (NICE) for the treatment of early onset neonatal sepsis (https://www.nice.org.uk/guidance/cg149) is in line with the above mentioned American guidelines. In particular, in neonates with risk factors, antimicrobial therapy should be discontinued 36 hours after its initiation if the following conditions are met: blood cultures are negative, the initial clinical suspicion of infection is not strong, the clinical picture and the levels of CRP are not suggestive of infection. We note here that in these guidelines, the parenteral administration of antimicrobials to mothers with suspected or confirmed septicaemia during labour, 24 hours before or postpartum, is considered as a *red flag* for early neonatal sepsis.

Duration and Type of Antimicrobial Treatment: There is no consensus on the duration and the type of antimicrobial that should be administered. As a result, there is a wide variation in the treatment of both neonatal septicaemias with negative cultures as well as microbiologically confirmed septicaemia [17, 18]. For the duration of treatment, we mention as an example neonatal pneumonia, a disease entity presenting diagnostic difficulties due to overlapping with surfactant deficiency and transient newborn tachypnoea. The duration of treatment varies even when the diagnosis is confirmed, and it has been suggested that neonates that look well 48 hours after initiation of treatment should be given a total of 4 days of treatment course [19].

4. With regard to the types of antimicrobials used, guidelines for the empirical use of antimicrobial guidelines vary particularly for Late-Onset neonatal Sepsis (LOS) at both national and international level. For instance, in a study from Greece involving eleven NICUs, seven different combinations of antimicrobials for empirical treatment of LOS were recorded [20]. In a similar study from Australia, the guidelines for the LOS vary widely, as opposed to Early Onset neonatal Sepsis (EOS) where fewer combinations of antimicrobials are used [21]. Lutsar and colleagues, in a prospective study involving five European countries, also demonstrated that LOS management varies considerably [22]. Similarly, at a wider European level (19 countries), 20 different combinations of antimicrobials were recorded with a more prominent variation in empirical antimicrobial treatment for LOS [16]. All of these observed differences could be partly explained by the different epidemiology of pathogens per country and susceptibility to antimicrobials.
5. Dosage and Levels of Antimicrobials: The ideal dosage and monitoring of the levels of antimicrobial drugs can be challenging in the newborns. The Glomerular Filtration Rate (GFR) and tubular excretion rates are lower, resulting in differences in the pharmacokinetics and pharmacodynamics of drugs and especially aminoglycosides in both term and in preterm infants. In addition, central nervous system infections are common in preterm infants and require higher doses of certain antibiotics for adequate management.
6. Perioperative Chemoprophylaxis: Perioperative chemoprophylaxis should not be administered more than 24 hours in most cases, as adults studies have shown. There are not many studies and guidelines for infants. Therefore, neonates that have undergone surgery continue to receive prolonged treatments with combinations of antimicrobials. A European point prevalence survey in 2008 showed that 67% of children and neonates in the study received surgical prophylaxis for more than a 24-hour period [23]. The above is worrying if we consider that not only does prolong surgical prophylaxis prevent surgical site infections, but, contrary to that, it can increase the risk of infections by multidrug-resistant pathogens [24, 25].

3. ANTIMICROBIAL STEWARDSHIP: DEFINITIONS AND PRINCIPLES

According to the WHO, the judicious use of antimicrobials is recognized as vital for patient safety and quality in medical care, as it prevent the development of multi-drug resistant pathogens and preserves the existing antimicrobials from misuse. Antimicrobial Stewardship (AMS) includes all the coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration [26]. AMS aims to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains [26]. Acknowledging the importance of AMS, the CDC sets up the basic principles that should guide the rational use of antimicrobials in the hospitalized patient (www.cdc.gov/

getsmart/). In 2013, Hyun and colleagues summarize the basic principles of AMS in paediatrics [27] which are listed below:

1. When and to whom antimicrobial treatment should be given (timely and appropriate treatment).
2. Which Antimicrobial (Suitability).
3. How (dose, duration, route).
4. Continuous monitoring of antimicrobial use.
5. Use of resources, human resources and education.

The various strategies for the AMS that have been published and successfully used in NICUs are mainly restriction of the use of antimicrobial (restrictive) limiting use of cephalosporins [28-30]. Several studies [31-35] have shown that for the rational use of antimicrobials biomarker measurement in neonates such as CRP, interleukin 8 or procalcitonin may shorten the duration of treatment. In addition, access to guidelines for neonatal septicaemia at national level [36, 37] is another successful AMS strategy. Fewer strategies have been used to change the behavior of prescribers such as prospective recording and control of prescription with educational intervention and constructive feedback [38]. We mention here that education is the most widely used AMS strategy, but it is often not sufficient to produce results, and is therefore an additional component of other interventions that have been occasionally used. In conclusion, it appears that all of the above interventions as a whole can lead to a reduction in the prescription of antimicrobials and to the administration of shorter treatment courses.

4. ANTIMICROBIAL STEWARDSHIP IMPLEMENTATION IN THE NICU SETTING

Specific interventions may lead to more rational use of antimicrobials in NICUs such as the following:

1. Diagnosis of Neonatal Septicaemia: Due to the diagnostic difficulties, it is important to accurately diagnose neonatal infection and consequently use antibiotics more judiciously. Biomarkers could be useful here. As mentioned above, CRP, procalcitonin and interleukins 6 and 8 have been used with great success to increase the negative prognostic value of a sterile blood culture [31-35]. However, it is crucial to obtain a sufficient amount of blood from the newborn so that potential pathogens can grow in the blood culture. Ideally, two blood cultures (especially when the neonate has a central line in situ) should be obtained to clarify the possibility of contamination when *coagulase-negative staphylococci* are isolated. The probability of isolation of a pathogen increases as the blood volume increases (1-2 ml) [39]. The American Academy of Pediatrics suggests that at least 1 ml of blood should be collected from neonates [40]. This practice does not always appear to be followed in NICUs and in general in pediatrics but can be improved by appropriate training [41].
2. Choice of Empirical Antimicrobial Treatment: The choice of appropriate antimicrobial treatment is important and should be based on the epidemiological and microbiological data of each NICU. At both local and national level continuous epidemiological surveillance of responsible pathogens and their antimicrobial resistant patterns are of paramount importance.

The proposed empirical antimicrobial treatments are based on the distinction between EOS and LOS. For the EOS, different definitions exist. Epidemiologists define the EOS as an infection with a positive culture of blood or cerebrospinal fluid (CSF) during the first 3 days of life [42]. The CDC defines EOS from *beta hemolytic streptococci group B* (GBS) when there is positive blood culture or CSF during the first 7 days of life [14]. *GBS* and *Enterobacteriaceae* are the most common causes of EOS worldwide. Therefore, the most widely used regimes for EOS include a combination of ampicillin and gentamicin. The use of cephalosporins should be avoided when there is no meningitis because it is associated with an increased risk of candidiasis especially in very low birth weight infants [5, 9] and promotes colonization by multidrug-resistant pathogens. For LOS, the use of a semisynthetic penicillin in combination with an aminoglycoside is most widely recommended. Alternatively, piperacillin and tazobactam can be used in the combination of empirical treatment for suspected infections from Gram-negative pathogens, especially in neonates that are already colonized with those. Third-generation cephalosporins should only be administered if there is a suspicion of meningitis.

The main problem with this proposed coverage is that *coagulase-negative staphylococci* are generally resistant to antistaphylococcal penicillins. For this reason, empirical treatment with vancomycin is administered to many NICUs. In order to limit the use of this glycopeptide, some NICUs permit the use of vancomycin only after the isolation of coagulase-negative staphylococci in the blood culture and not as empirical treatment and this restriction had no adverse effect in the neonatal morbidity and mortality [38].

LOS often involves empirical coverage for fungi and especially for *Candida*. We will make a brief reference to the proper use of antifungal agents based on the recent guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of *Candida* infections [43]. Based on these guidelines for the empirical treatment of neonatal candidiasis and meningitis first-line treatment is amphotericin B deoxycholate. Alternatively, fluconazole may be administered provided that the newborn does not already receive fluconazole prophylaxis. Instead of the above, liposomal amphotericin B can also be administered with particular caution when the urinary tract is involved. In general, deoxycholate and not liposomal amphotericin B should be used in neonates whose kidney function is not impaired. In addition, antifungal treatment should be discontinued if the blood cultures do not develop fungi and there are no other risk factors such as fungal colonization. With regard to echinocandins, these should be used with caution and only as a rescue therapy or in

cases where resistance or toxicity excludes the use of first-line antifungal agents.

With regard to antifungal prophylaxis, in NICUs with high incidence of invasive candidiasis (> 10%), fluconazole (intravenous or oral) is recommended twice weekly and for 6 weeks in newborns with birth weight <1000 grams [43]. As an alternative to fluconazole (unavailable or resistance) oral nystamycin can be used for 6 weeks in neonates weighing <1500 grams.

3. Reassessment of the Initial Antimicrobial Treatment When Culture Results are Available: If the pathogen is isolated from areas that are not sterile such as bronchial secretions, it is most likely that we deal with colonization and not true infection especially if the clinical picture of the newborn is good. In addition, the incubation time of blood cultures is important as the results that are positive after 48 hours are most likely to represent contamination with a small number of microbial colonies and not true pathogen growth [44]. In this case and if the newborn remains in good condition it is recommended that the treatment should be stopped immediately. In contrast, when the culture results are available within 48 hours and the pathogen and its sensitivities are reported, immediate adaptation of the antimicrobials should be made. This strategy is sometimes not followed, and this is one of the most important causes of inappropriate use of antibiotics in NICU [4]. For bacteraemias from *methicillin-sensitive staphylococcus aureus* (MSSA), antistaphylococcal penicillins are better than glycopeptides and constitute the treatment of choice and [45]. Moreover, it is worth reminding at this point that vancomycin should be immediately discontinued when there is growth of a Gram-negative pathogen.

4. Dosage and Monitoring of Antimicrobial Levels: Due to the particularities of pharmacokinetics and toxicity of certain antibiotics such as gentamicin in neonates, including reduced renal function and longer half-lives, it is necessary to administer higher doses at longer intervals in preterm infants to achieve similar levels with term infants and older children. Therefore, the clinician should take into account the postmenstrual and chronological age of the infant when prescribing this antibiotic as both the actual dose as well as the recommended dose intervals vary. Monitoring of antimicrobial levels is also of paramount importance, for antibiotics such as gentamicin and vancomycin, in order to detect toxicity (trough levels) and assess the potency (peak levels) of the administered drug. Specifically for vancomycin, in 2009, the Infectious Diseases Society of America (IDSA) published desirable levels of vancomycin 15-20 mg/ l for the treatment of severe staphylococcal infections such as bacteraemia, meningitis, endocarditis, in adults and children [46]. There is not much data on neonatal infections but in practice it seems that trough levels of 10-20 mg/l can be used with concurrent monitoring of renal function [47]. With regards to novel approaches to antimicrobial use, recent data suggest continuous infusion of vancomycin, which is well tolerated by infants and achieves better therapeutic levels [48-49], but more studies are needed before this use is widespread. The antimicrobial activity of vancomycin is dependent on the time that the serum concentration of the drug exceeds the minimum inhibitory concentration (MIC) i.e. the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism. The goal of dosing for vancomycin from a phramakodynamic point of view is not only to maximize the duration of exposure but the concentration of the drug as well (which reflects the actual total exposure of the antibiotic to an organism). Continuous infusion offers the advantages of faster time to achieve target drug concentrations, lower daily dose and reduced therapy costs than intermittent dose regimens [48-49]. As far as the use of meropenem is concerned when dealing with neonatal infections from multidrug-resistant pathogens, it appears that, similarly to adults, extended infusion of meropenem exhibits the potential for improved efficacy and safety of eradicating infections and improving clinical outcomes in neonates [50]. The rationale behind the extended infusion is that meropenem, as a b-lactam antibiotic, has a time-dependent killing pattern and maximizing the duration of exposure is crucial to overcome the high MICs of specific pathogens.

5. Measurement of Antimicrobial Use and Continuous Assessment of its Necessity: In order to evaluate the use of antimicrobials in NICUs and to design relevant interventions, a potential strategy is to record the treatment days with antimicrobials referred to as DOTs (days of therapy). This is a measure that is often used in pediatrics because, unlike the exact dose of the drug, it does not depend on patient weight and renal function [51]. If in DOTs, we use 1000 days of hospitalization as a denominator, the ratio that comes up helps comparing the use of antibiotics among different institutions. For example, the use of third-generation cephalosporins per month can be recorded on a NICU level and compared with previous months or other NICUs. However, in infants and especially early on, there are restrictions on the use of DOTs such as the administration of gentamicin every 36 hours which makes difficult the accurate recording. In addition, many newborns have prolonged hospitalization in NICUs for establishing feeds without taking antibiotics. Therefore, if the ratio of DOTs to 1000 days of hospitalization is used, the actual use of antimicrobials is underestimated.

6. Development of AMS teams consisting of infectious diseases specialists, microbiologists, pharmacists, infection control nurses and representatives of the Intensive Care Units. These teams could perform weekly visits in NICUs where all the antimicrobials administered to the newborns (administration indication, dose, duration of treatment, *etc*.) are checked and suggestions are made for optimal use of these. Also, this group could be responsible for the preauthorization of drugs (such as vancomycin and meropenem), a strategy that has been previously successfully applied to NICUs [36, 38].

CONCLUSION

In conclusion, newborns are often administered prolonged antimicrobial treatments for suspected neonatal sepsis with severe short-term and long-term effects. The judicious use of antimicrobials in NICUs is vital for the protection of this vulnerable population and can be achieved by simple interventions. A necessary component in order to achieve that is the collaboration of neonatologists with healthcare professionals of related specialties. Finally, it is necessary to continuously evaluate these antimicrobial stewardship interventions in order to ensure their uneventful and sustained application.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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