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REVIEW

Neonatal sepsis: A review of the literature

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Abstract: Neonatal sepsis contributes significantly to neonatal morbidity and mortality and is a major public health challenge around the world. Depending on the mode of occurrence, a distinction is made between maternal-transmitted infection and that acquired in the postnatal period. Although the etiologies maternally transmitted diseases are well understood, those of postnatal acquired infections are variable depending on the epidemiology of each hospital environment. On the one hand, risk factors for maternal-transmitted infections are maternal sepsis, prolonged premature rupture of membranes, chorioamnionitis, and bacteriuria in the mother during pregnancy. On the other hand, risk factors for postnatal acquired infections are prematurity, low birth weight, lack of hygiene, and invasive therapeutic interventions. The diagnosis is based on a series of anamnestic, clinical and biological features. Although the positive diagnosis is based on the isolation of the germ by culture on a body sample (blood, cerebrospinal fluid, urine, *etc*.); its low sensitivity leads to the use of markers of the acute phase of inflammation such as C-reactive protein, procalcitonin and interleukins. New molecular biology techniques are promising and offer precise diagnosis with rapid results. Empirical management is a function of microbial ecology while definitive treatment is guided by the results of microbial culture. This article presents the essential elements for understanding neonatal sepsis and discusses new diagnosis and therapeutic management. It offers a thorough reading based on the issue of infections in newborns.

Keywords: neonatal sepsis, early onset sepsis, late onset sepsis, risk factors

1 Introduction

Neonatal sepsis (NS) is defined as a systemic inflammatory response syndrome in the presence or following a suspected or established infection with or without associated bacteremia, documented by a positive blood culture during the first 28 days of life [1, 2].

The term 'neonatal sepsis' is used to denote a condition of bacterial, viral or fungal origin associated with hemodynamic changes and other clinical manifestations [3]. Despite several years of expertise, many challenges remain in the diagnostic approach to newborns suspected of having NS. These include the lack of a consensual definition of NS in everyday practice.

Traditionally, the definition of sepsis has included the isolation of a pathogen from a normally sterile body fluid such as blood or cerebrospinal fluid (CSF) [4, 5]. However, given the understanding of the role of potent pro-inflammatory cytokines in the clinical characterization of sepsis, the term 'Systemic Inflammatory Response Syndrome (SIRS)' has also been used to define sepsis in neonates [2, 4]. NS can be caused by bacterial, viral, and fungal microorganisms. Although the current description is clear on bacterial causes, the share of other microorganisms is no less important in the hospital environment. These include Candida and Enteroviruses responsible for severe pictures of NS [6–9].

Two categories are to be distinguished according to the mode of occurrence:

(1) Early onset sepsis (EONS): these are infections of the newborn resulting from vertical mother to infant transmission which occurs in the perinatal period (before or soon after delivery) and which can appear within the first week of postnatal life [3, 10, 11]. In this context, infection occurs in utero from transplacental transmission or more commonly vertically (ascending) from the vaginal environment after rupture of membranes. In addition, the newborn can become infected when exposed to pathogenic bacteria, viruses or fungi as they pass through the birth canal [12–15].

(2) Postnatal acquired infections (late onset sepsis [LONS]): contamination occurs after delivery following interactions with the hospital or community environment. It usually starts after 72 hours of age. The source of contamination is either nosocomial or community [4, 14–16].

2 Epidemiology

Analysis of several studies reports an estimate of NS of 2,202 (95% CI: 1,099 - 4,360) per 100,000 live births, with mortality between 11% and 19% in high- and middle-income countries [17]. However, the burden of NS varies greatly from one setting to another, depending on the level of organization of the health system and socio-demographic characteristics of the populations.

The reported incidence of NS ranges from 7.1 to 38 per 1,000 live births in Asia, 6.5 to 23 per 1,000 live births in Africa, and 3.5 to 8.9 per 1,000 live births in America South and the Caribbean. By comparison, reported rates in the United States and Australia vary from 1.5 to 3.5 per 1,000 for EONS and up to 6 per 1,000 live births for LONS, for a total of 6-9 per 1,000 for NS [18–22].

In the world, NS contributes significantly to neonatal morbidity and mortality; it constitutes a major public health challenge. The most common causes of death in the neonatal period are infections (35%), followed by prematurity (28%), intrapartum complications (24%), and asphyxia (23%) [2, 23, 24]. NS is responsible for 26% of deaths in children under-5, with the highest death rates in sub-Saharan Africa [25]. The data available is a mixture of official sources and studies both hospital and community [18].

In developing countries, statistics may be underestimated due to high rate of home deliveries and low percentage of attendance by skilled health workers. Establishing numbers and causes of neonatal deaths is therefore difficult given that a large number of newborns die at home without ever being in contact with health workers and without ever integrating the statistics.

Nonetheless, many studies report infections as one of the 3 leading causes of death both in the world and in Africa [26–31].

3 Risk factors and etiologies

3.1 Risk factors for EONS

Anamnestic risk factors for EONS [11] are classified into two groups in decreasing order of risk (although this classification does not prejudge a systematic therapeutic approach).

(1) Major criteria (strongly linked to NS): chorioamnionitis, twin with mother to infant infection, maternal temperature before or during labor $> 38^{\circ}$C, spontaneous prematurity $<$ 35 weeks, prolonged rupture of membranes (PROM) more than 18 h, premature rupture of membranes before 37 weeks, and maternal group B streptococcus infections (GBS) colonization / GBS bacteriuria (during index pregnancy).

(2) Minor criteria (little related to NS): rupture of membranes more than 12 hours but less than 18 hours, spontaneous prematurity less than 37 weeks and more than 35 weeks, abnormal fetal heartbeat or unexplained fetal asphyxia, and tinted or meconium amniotic fluid.

The existence of one of these criteria requires clinical monitoring, particularly close during the first 24 hours of postnatal life. Infection and mortality are inversely related to birth weight and gestational age [3, 10].

Microorganisms most implicated in EONS are those found in maternal urogenital and digestive tracts. These are *Streptococcus agalactiae* (Group B *streptococcus*) and *Escherichia coli*. Secondarily, *Monocytogenic listeria*, *Nontypeable Haemophilus influenzae*, and Gram-negative *Enterobacteriaceae* other than *Escherichia coli* are also implicated [3, 10, 11, 19].

However, the application of a routine maternal screening program and intrapartum antibiotic prophylaxis in some countries has significantly reduced Streptococcus agalactiae in maternally transmitted NS [19, 32].

3.2 Risk factors for LONS

In the hospital environment, several factors predispose to an increased risk of NS. These include stay in intensive care, prematurity, low birth weight, invasive medical procedures, mechanical ventilation, and use of parenteral fluid. Poorly disinfected hands and equipment are important vectors of germs [33, 34].

In the community, the risk of NS is determined by poor hygiene in general (of the hands, bottle-feeding and poor umbilical cord care practices) [33, 35, 36].

Nevertheless, the important role of breastfeeding in preventing postnatal infection is proven [37–40]. Breast milk is believed to be an important vector of exchange between the maternal immune system and the newborn's body. The practice of breastfeeding actively regulates immune and metabolic systems and the microflora in the newborn while providing multiple means of protection against various pathogens [40, 41].

Bacterial aetiologies of LONS are very varied and depend on one setting to another. Coagulase-negative *Staphylococci* are the most reported in neonatal intensive care units [42, 43]. Other germs such as *methicillin-resistant Staphylococcus aureus* and multidrug-resistant Gram-negative bacteria (*Pseudomonas* and *Klebsiella*) are still common in developing countries unlike developed countries [44]. Some Gram-positive germs classically responsible for EONS (*e.g.* Group B streptococcus) can be found in LONS in the community or due to manual transmission or by contaminated equipment in a hospital environment [3, 45, 46].

The over and inappropriate use of antibiotics has favored the emergence of unusual germs and the emergence of multi-resistance to common antimicrobials [47, 48]. Viruses are also a major cause of nosocomial infections, but most of the time they are underestimated. These include, in particular, Enteroviruses and Rotaviruses. Systemic fungal infections are increasingly reported, with *Candida albicans* leading the way [7, 48, 49].

4 Clinical features

Clinical features of NS are vague and ill-defined. Altered feeding behavior (refusal to breast-feed) is a common and early symptom, but not specific. Other signs are thermal disturbances (hypothermia or fever), lethargy, incessant crying, hypotonia, peripheral perfusion disorder (prolonged hair recoloration time), blunt neonatal archaic reflexes, cardiac arrhythmias (bradycardia or tachycardia), metabolic disorders such as hypoglycemia or hyperglycemia, and metabolic acidosis.

In the advanced-stage, signs of organ failure determine the severity of NS [1,3,10]. Symptoms specific to each system are:

(1) Central nervous system: these are a bulging of the anterior fontanel, a blank stare, a sharp and excessive cry, irritability, a coma, convulsions, and a retraction of the neck. The presence of these signs suggests the hypothesis of meningitis.

(2) Cardiac system: mainly hypotension and poor perfusion. Studies have emphasized the value of early diagnosis of NS using characteristic heart rate analysis over electrocardiographic monitoring. Griffin *et al*. [50] found that characteristic abnormal heart rate such as reduced variability and transient decelerations occurred 24 hours before symptoms appeared in NS. Another group experienced an asymmetric increase in the RR interval in 3-4 days preceding sepsis with a greater increase in the last 24 hours [50, 51]. These tests may be useful for early indication of therapeutic management.

(3) Gastrointestinal system: These include vomiting, diarrhea, abdominal distension, paralytic ileus and ulcerative necrotizing enterocolitis.

(4) Hepatic system: Common hepatic signs are hepatomegaly and direct hyperbilirubinemia. A newborn with jaundice or direct bilirubinemia after 8 days of postnatal life is more likely to have a urinary tract infection [52, 53].

(5) Renal system: acute renal failure may be noted.

(6) Haematological system: bleeding and petechiae or purpura may be observed.

(7) Skin system: Multiple pustule-like rashes, sclerema, mottling and oozing umbilicus have been reported. De Felice et al. used colorimetric analysis of skin color to assess the severity of sepsis [52, 54].

5 Diagnostic approach of NS

The diagnosis of NS is based on a host of anamnestic, clinical, and biological arguments. History-taking information helps assess risk factors for sepsis in the newborn and in the mother. There is a significant correlation between some factors (maternal, environmental, and neonatal) and the occurrence of sepsis [55–57].

Prediction algorithms and scores have been developed to assess the risk of NS and thereby reduce exposure to empiric antibiotics. In addition, a good number of the cases of sepsis presented a poor clinical practice even asymptomatic in the immediate postnatal period [58–60]. Clinical signs of sepsis in the newborn are nonspecific. Several non-infectious clinical pictures can constitute differential diagnoses. Likewise, features relating to the immaturity of some functions, in this case in prematurity, may coexist with an infectious process whose demarcation will not be easy in clinical practice. Nevertheless, a careful clinical examination makes it possible to formulate the diagnostic hypothesis and thus guide paraclinical investigations [3].

Several biological approaches are being studied in the development of NS. However, many of them do not have sufficient sensitivity and specificity to be used in isolation [61]. Isolation of the pathogen in a normally aseptic body sample (blood, cerebrospinal fluid, urine, *etc*.) is the gold standard in the diagnosis of sepsis [4, 62]. However, the low sensitivity and the waiting time for

results, especially for blood culture, limit its effectiveness in deciding whether to start treatment. Therefore, the use of biomarkers of the host's response to infection, especially those of the acute phase of inflammation, is of great utility in clinical practice. The most widely used are white blood cell count, C-reactive protein, procalcitonin and interleukins. Understanding the kinetics of inflammatory markers during the infectious process as well as the significant thresholds is essential for a good interpretation. In addition, a combination of different biomarkers can increase sensitivity and specificity in the diagnosis of sepsis [61–63].

High sensitivity molecular diagnostic techniques are developed to overcome the limitations of microbial cultures. These new techniques target the early detection of the pathogen-specific nucleic acid. These are real-time Polymerase Chain Reaction (PCR), PCR followed by post-PCR treatment (matrix hybridization or mass spectroscopy), and Fluorescence In Situ Hybridization (FISH). These techniques have the advantage of being quick and requiring small amounts of blood sample. However, although promising, the cost and complexity of molecular biology analyzes do not currently allow their use in current practice and on a large scale [61, 64].

6 Treatment of NS

Given the etiological diversity of sepsis in newborns, several cases can be envisaged in antimicrobial management. On the one hand, the antimicrobial therapeutic approach of NS can be distinguished according to whether they are suspected cases (empiric treatment) or cases with a pathogen well identified by culture (definitive treatment). On the other hand, the clinical picture and the mode of occurrence (EONS or LONS) must be taken into account in the choice of antibiotics.

To do this, a good anamnestic investigation and a careful clinical examination are essential. Under ideal conditions, a positive bacterial culture before starting treatment is an asset that would effectively and efficiently guide the choice of antibiotic. However, given the prognosis of NS, specimen collection and culture results should not delay initiation of treatment in symptomatic newborns.

6.1 Empirical treatment

By consensus, the empirical approach should be guided by data from antibiograms on bacteria commonly isolated in the neonatal care unit or in the community. Empiric treatment for EONS should consist of administration of Ampicillin and an aminoglycoside (most commonly Gentamicin) with a third or fourth generation cephalosporin. Piperacillin-Tazobactan and Ampicillin-Sulbactan are increasingly used in patients admitted to neonatal intensive care. However, given the low penetration of Tazobactan into the blood-brain barrier, its indication is limited in meningitis, whereas the combination of Sulbactam (beta-lactamase inhibitor) with ampicillin seems to have a good diffusion in the central nervous system [3, 65, 66]. In the case of nosocomial infections, the most susceptible germs are of the group of coagulase negative *Staphylococci* compared to *Staphylococcus aureus* and Gram-negative bacteria. In order to reduce the use of Vancomycin (due to the emergence of resistance), an empirical treatment made of an antistaphylcoccal beta-lactam such as Nafcillin combined with an aminoglycoside is proposed before the results of bacterial cultures [67, 68].

6.2 Definitive treatment

The definitive antimicrobial treatment will be chosen based on the germ identified (by the culture), its sensitivity (antibiogram) and its bioavailability at the main site (s) of infection. In general, the antibiotic of choice should have better systemic availability and good diffusion through the blood-brain barrier.

Ampicillin or any other antibiotic from the penicillin group is generally effective against group B *streptococcus*. Gentamycin is often used in common practice for a synergistic effect with ampicillin; whereas ampicillin alone has excellent efficacy against *monocytogenic Listeria* [10, 69]. The third generation cephalosporins seem to be well indicated in the treatment of enterobacterial septicemia, especially if a meningeal transplant is suspected [3, 70].

Inappropriate use of antibiotics has favored the emergence of strains resistant to several common antibiotics, especially from the beta-lactam class. This explains the increasingly frequent use of vancomycin, carbapenemes and combinations with sulbactan [47, 48, 71].

7 Prevention

Preventive measures focus on the asepsis of the newborn. The hygiene of hands and equipment used, the reduction of manipulations and invasive procedures as well as early enteral

feeding are important pillars [72]. Newborns at risk should be given special surveillance. Breastfeeding is the ideal natural way to help impart anti-infective, anti-inflammatory and immunomodulatory properties to the newborn. Breast milk contains many bioactive molecules that protect against infection and inflammation in the form of cytokines, nucleotides, hormones, and growth factors. The anti-infective properties of breast milk are based on both soluble factors (immunoglobulins) and cellular elements [37, 39]. Sound antimicrobial management and surveillance of antimicrobial resistance would improve the prognosis of NS.

8 Long-term prognosis

In the long term, newborns with sepsis are prone to growth deficits and neurodevelopmental disorders. In the event of NS, newborns with low birth weight are at greater risk of developing cerebral palsy and neurodevelopmental delay [10, 73].

On the one hand, sepsis affects the long-term neurodevelopmental prognosis, either by directly affecting the central nervous system or by causing severe systemic inflammatory lesion responsible for bronchopulmonary dysplasia, retinopathy of prematurity, and cerebral hemorrhages [74]. On the other hand, an association between the development of atopic diseases in childhood and a history of NS has been reported [75, 76].

Abbreviations

CSF: Cerebrospinal fluid
EONS: Early onset sepsis
LONS: Late onset sepsis
NS: Neonatal sepsis
PCR: Polymerase Chain Reaction
SIRS: Systemic Inflammatory Response Syndrome

Conflicts of Interest

No conflict of interest to disclose.

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