

Neonatal Sepsis: Highlights and Controversies

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ABSTRACT

Sepsis may be defined as a systemic illness caused by microbial invasion of normally sterile parts of the body, inducing a systemic inflammatory response. Such systemic infection occurring in infants within 28 days of life is referred to as "neonatal sepsis". Actually, a consensus over a definite clinical or semiological definition of neonatal sepsis remains controversial. This is partly due to questions of semantics and classification, with a problem of age delimitation, responsible for misuses of the "neonatal sepsis diagnosis". More so, the limitation of neonatal sepsis to bacterial etiology due to its severity has led to an increasing misunderstanding of sepsis, to the detriment of other causative agents such as viruses, fungi, protozoans and mycoplasma. These controversies are further amplified by the diversity of the literature available on the subject, the plurality of language concepts and translation bias. Physicians worldwide may therefore be faced with diagnostic and semantic challenges as far as infections in neonates and slightly beyond the neonatal period are concerned. This indicates a necessity for the re-questioning of past concepts for clarity, or reconsideration if need be. In this paper, we did a succinct review of neonatal sepsis and its highlights, exposing controversies while proposing some adjustments to consider.

Keywords

Neonatal sepsis, Highlights, Controversies, Semantics.

The Highlights of Neonatal Sepsis

Neonatal sepsis is an important cause of morbidity and mortality of newborns and a major cause of prolonged hospitalization, especially in preterm infants and neonates with very low birth weight [1-3]. The incidence of neonatal sepsis in high-income countries is estimated between 1 and 12 per 1000 live births [1]. Whereas the incidence in low and middle-income countries is higher, with about 62.5 % neonatal emergencies being attributed to sepsis in some settings [4]. Mortality rates up to 70% have been observed in some low- and middle-income countries, making the pathology not only an old issue, but an important and persistent concern in pediatrics and public health at large [1,5-7]. Frequently reported risk factors include low birth weight (<2500grams) and preterm, febrile illness in the mother within 2 weeks prior to delivery, Foul smelling amniotic fluid, prolonged rupture of membranes (>18 hours), repetitive vaginal examinations during labor, prolonged and difficult delivery

with instrumentation, as well as difficult resuscitation [1-3]. The source of infection may also be nosocomial or community acquired through admission in the Neonatal Intensive Care Unit (NICU), poor hygiene, poor umbilical cord care, bottle feeding, invasive procedure, superficial infection, non-lacteal feeding, ventilation, and aspiration of feeds [1-3].

The most frequently involved pathogens in bacterial neonatal sepsis of term and preterm infants are the Group B streptococcus (GBS) and Escherichia coli, which account for approximately 70% of sepsis. Group B streptococcus (GBS) is the most common etiologic agent, while Escherichia coli is the most deadly [8-11]. Other bacteria involved are Streptococcus pneumoniae, Staphylococcus aureus, and Enterococcus species. Gram-negative enteric bacilli such as Enterobacter species, Haemophilus and Listeria monocytogenes [8-11]. Similarities of the pathogenic bacterial ecologies and hence the treatment for sepsis in infants within the first three months of life has led to an extrapolated definition of neonatal sepsis, beyond the neonatal period [8-11]. Because of its severity and incidence, there have gradually been

a focalization on bacterial sepsis, and less for others, with non-bacterial pathogens being rarely discussed. Nevertheless, viral infections, including herpes simplex virus (HSV), enteroviruses, and parechoviruses, may also be responsible for neonatal sepsis and need to be differentiated from other causative agents [12,13]. Some viruses such as rubella virus, cytomegalovirus may equally be involved in congenital infections, with an onset which is earlier before the neonatal period. Seasonal viruses including influenza virus, respiratory syncytial virus (RSV), adenoviruses, rhinoviruses, and rotaviruses may sometimes be implicated in neonatal sepsis as well [14]. On the other hand, very few fungal pathogens apart from *Candida* species are responsible for sepsis in neonates [15].

Most pathogens responsible for neonatal sepsis are colonizers of the maternal urogenital tract from which they may ascend through the vagina and the cervix to infect the chorion, the amnios (chorioamnionitis) and the placenta, contaminating the amniotic fluid. This is favored by prematurely and prolonged ruptured membranes occurring before the start of labor. Due to this phenomenon, the infant may be infected in utero or on its passage through the birth canal during delivery. Moreover, hematogenic contamination from an infected mother through the placenta is also possible, just as environmental and community borne neonatal infections [16,17].

The pathophysiology of sepsis in neonates may be explained as an immunological response mainly from the innate and less from the adaptive immune system, occurring because of the penetration of a pathogen into the bloodstream, creating a septic state [18]. This induces a systemic inflammatory response, which is more or less responsible for the signs, symptoms and biological manifestations observed (SIRS). Maternal transfer of IgG via the placenta is proportional to gestational age and makes preterm infants more vulnerable. IgA, IgG, cytokines and antibacterial peptides are low as well in term neonates and only rises with continuous breastfeeding, meanwhile the full functionality of the spleen is acquired with time as the neonate develops [3,18]. Due to the immaturity of the immune system in neonates, the progression of bacteremia is rapid and clinical manifestations may be subtle, in which case sepsis may evolve towards severe sepsis and eventually septic shock [18].

The clinical manifestations of neonatal sepsis are diverse and mainly depend on gestational age and the severity of the infection. They may occur as early as within the first 24 h of life [4]. Unexpectedly, hypothermia is considerably common, although fever may be more frequent. Some general symptoms include lethargy, poor activity, poor feeding and hypothermia, while anuria and acidosis seems nonspecific. Common respiratory symptoms are apnea, tachypnea, grunting, nasal flaring, and intercostal retractions [19]. Digestive symptoms such as abdominal cramps (wriggling or squirming), vomiting, diarrhea, hematemesis and melena need to be investigated, while abdominal distension, hepatomegaly and splenomegaly are important signs. Cardiovascular signs such as cyanosis, desaturation, bradycardia, poor perfusion, reduced capillary refill, and hypotension

may occur as well [19]. Convulsion, functional impotence and irritability are frequent symptoms, whereas attenuated reflexes, hypotonia, neurologic deficits and bulging fontanelle are common neurological signs to look for. Rash, petechiae, purpura, and jaundice are the main reported cutaneous signs. It is important to recall that subtle changes in respiratory status, temperature instability, or feeding problems can be the first signs of a life-threatening infection in a neonate [4,19]. Therefore, considering the non-specificity of the semiology of neonatal sepsis, all symptomatic neonates should be suspected of neonatal sepsis until it is proven otherwise.

Although novel diagnostic tools from biomarkers to molecular diagnosis such as acute phase reactants (C-reactive protein, ferritin, lactoferrin, neopterin, procalcitonin, serum amyloid A), cytokines (tumor necrosis factor-alpha, Interleukins), Leucocyte surface markers, endotoxin and Polymerase chain reaction offer substantial promises for detecting neonatal sepsis, the paraclinical diagnosis for neonatal sepsis has been historically relying on full blood count, urinalysis, cerebrospinal fluid analysis and blood culture which is the gold standard. However, a combination of anamnestic information, physical examination and laboratory findings appears to be indispensable and more reliable [20].

Primary prevention of neonatal sepsis is by optimal prenatal follow-up including vaccinations. Intrapartum chemoprophylaxis with penicillin for mothers with prenatal GBS-positive cultures or unknown GBS status is a recommended preventive therapy as well [21,22]. Best obstetrical practices and effective neonatal immunization are also a necessity, while caesarean delivery may sometimes be indicated in case of active genital tract infection such as Herpes Simplex Virus [21]. Good hygiene and dietetic practices is encouraged. Mothers' education to recognize danger signs, which may enable prompt diagnosis and management, is necessary and has a key role in the prevention of microbial dissemination in neonates.

The early diagnosis of neonatal sepsis, just as the choice of antibiotics for an infant with suspected sepsis depends upon the predominant pathogen and antibiotic sensitivity pattern of a given region. However, a broad-spectrum antibiotherapy is often recommended, especially in developing countries, and the treatment is usually started before a definitive causative agent is identified [21-23]. The antibiotherapy consists of a penicillin, usually ampicillin, which targets GBS plus an aminoglycoside such as gentamicin for synergistic effect. A third generation cephalosporin such as cefotaxim (with the advantage of not inducing jaundice) covering the gram-negative bacteria is often combined, especially when meningitis is suspected [21-23]. In case of community acquired neonatal sepsis, cloxacillin targeting staphylococcus aureus may be used in replacement of ampicillin. Because of the continuous emergence of bacterial resistance, combinations like ceftazidim/amikacin, imipenem/amikacin, and ciprofloxacin are respectively used as 2nd, 3rd and 4th line drugs in some settings [21-23]. Supportive care is important as well and cannot be dissociated from the overall management of neonatal sepsis.

Semantics and Classification Controversies

A problem of semantics may be described as an issue with linguistic processing. That is one, which relates spoken utterances and understanding. Furthermore, semantics is concerned about the combination of words and the meaning derive from them. Whereas, classification may be defined as grouping into categories of common characters to render studies easier (to the sense of Aristotle). As far as the diagnosis “neonatal sepsis” is concerned, it may be considered as sepsis of the neonate or sepsis occurring during the neonatal period [21]. In effect, breaking down the name gives two different terms. The first term is “neonatal” which is an adjective relating to or referring to that which is proper and belongs to the neonate (a developing infant within the first 28 days of life). The second term is sepsis, a noun that denotes a state of diffused infection, accompanied by a systemic inflammatory response [4,18]. Therefore, a strict Cartesian comprehension of the combined terms suggests a state of diffused infection, accompanied by a systemic inflammatory response occurring within the first 28 days of life. However, in current practice this consideration is not always true, as infants up to 3-4 months might rightly or not be attributed the diagnosis of “very late onset neonatal sepsis” which sounds confusing and controversial [23-29].

There are several classifications of neonatal sepsis, but they are almost all based on the age at onset of the sepsis [24-27]. Some other grouping may involve the prematurity character of the neonate. Actually, early-onset neonatal sepsis (EOS) has been variably defined as occurring within 72 hours in infants hospitalized in NICU for one reason or another, against 7 days in term infants previously in good health [24-29]. In premature neonates, EOS is defined as occurring within the first 72 hours of life as well. Some further subdivisions of EOS into very early onset neonatal sepsis (within 24 hours) and early onset sepsis (within 24 hours to 6 days) have been suggested [30]. However, the most commonly accepted definitions of EOS in all newborns tend to consider the onset of sepsis within 72 hours of neonatal life, which may best represent the balance between etiology and pathophysiology including microbial invasion and patency, which is rapid in newborns. A statement, which is constant about EOS whatever the definition considered, is the mode of contamination, which occurs in a vertical mode, from mother to infant (materno-fetal), taking place before or during delivery [23-29].

Late-onset neonatal sepsis (LOS) has also been controversially defined as sepsis occurring after 72 hours in NICU infants and after 7 days of life in term infants, up to the age of 90 to 120 days [23-29]. A progressive adoption of 72 hours as the lower limit age and 90 days as the upper limit age for LOS has been noted, with the term “very late onset neonatal sepsis” consecrated to sepsis in infants above 30 days of life [23]. However, these definitions of LOS may likely contain some exaggeration concerning the upper limit age between 90 and 120 days, which largely exceeds the neonatal period of 28 days. Although the controverted attribution of this diagnosis to infants beyond this period and up to 90-120 days of life is believed to have microbiological and therapeutic rationale, it however poses a problem of classification and semantics as

well [23-29]. The most advanced justification for this extensive consideration is thought to stem from clinical relevance, with respect to similarities of bacterial ecology predominance within the first three months of life which is commonly believed not to change greatly. Based on this hypothesis, some authors suggested the impact on antibiotherapy is not significant and so may be identical throughout the first three to four months of life [23-29]. However, the predominance of community and nosocomial pathogens in late onset neonatal sepsis, and even more in very late onset neonatal sepsis, together with the impact of immunological reinforcement in growing infant (by principle) is to consider as well [3,16-18]. This suggests microbiological variability; with therapeutic implications throughout infancy, and hence a necessity for the delimitation of ‘neonatal sepsis diagnosis’, to prevent microbial resistances and therapeutic failure [31].

Another controversy is the fact that neonatal sepsis is often confused with neonatal infection and both terms falsely used interchangeably. From the definition of sepsis, two conditions seem indispensable for its occurrence: diffuse infection and systemic inflammatory response syndrome (SIRS) [32]. It might be important to recall that an infection may be superficial or localized without necessarily inducing the SIRS, which is somehow specific to deep, diffuse, systemic and severe infections. In fact, the term ‘septicemia’ was formerly used to denote the spread of pathogens through the blood stream in sepsis, indicating its ‘diffuse’ nature [18]. Therefore, an infection in a neonate may be localized, circumscribed or milder without SIRS, in which case it would appropriately be called a “neonatal infection”, while “neonatal sepsis” would be a deeper term for illustrating the severity of an infection. Emphasis should be laid on the fact that neonatal sepsis is not a syndrome per se, but is mainly characterized by the systemic inflammatory response syndrome, which is neither pathognomonic of sepsis. In effect, the SIRS may be induced by other causes apart from infection, such as trauma, injury or neoplasia [23,32]. “Neonatal sepsis” is thus a diagnosis from a semiological standpoint, a pathology from a clinical point of view, and is distinguishable from “neonatal infection”. Although neonatal sepsis of bacterial etiology could be the most severe, it is necessary to remind that sepsis may equally be of viral, fungal, protozoan or mycoplasmal origin [12,15].

Most of the time, sepsis may be triggered from an obvious or evident starting point or infected part of the body, which is therefore known, and is called the “focus”. In such cases the diagnosis of neonatal sepsis might be attached with the focal origin which could be pulmonary, cerebral, meningeal, or urinary just to name a few. Despite the fact that they all are neonatal sepsis, they could rightly be considered as “neonatal: pneumonia, encephalitis, meningitis, or pyelonephritis” respectively without it being controversial, as calling things by their real names gives them existence. Sometimes, sepsis in neonates might occur without an obvious focal origin, and the proof for the infection is only determined by complementary exams [20,32]. The diagnosis “neonatal sepsis” may best fit such situations, where a “proper name” to the sepsis cannot be attributed due to the absence of a focus.

Conclusion

Considering semantic and classification constraints, together with microbiological and therapeutic implications, the following suggestions can be made in order to end a number of controversies related to neonatal sepsis. The term “Neonatal sepsis” might better be defined as a state of diffused infection inducing a systemic inflammatory response, occurring within the first 28 days of life. It could be of early onset within 72 hours or late onset within 72 hours to 28 days of life. Beyond this period, infections with SIRS in infants might simply be known as “sepsis” though managed with “neonatal sepsis therapeutic approach” up to the age of 90 days at onset of the sepsis. Neonatal sepsis should not be considered a syndrome on its own, but should be characterized by the systemic inflammatory response syndrome, although not pathognomonic of sepsis. Infections in neonates without the SIRS would correspond to “neonatal infections”, which are less severe compared to sepsis. Neonatal sepsis could be attributed a “proper name” when its focal origin is known. Therefore, “neonatal sepsis” as a definite diagnosis per se might be considered more appropriate for sepsis in neonates without an identifiable focus, from a semiological basis. The etiologies of neonatal sepsis should be discussed in their diversity and by order of severity, as possibly being of bacterial, viral, protozoan, mycoplasmal or fungal origin.

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