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Neonatal Sepsis: A Problem of Semantics and Classification

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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 is difficultly reached. This is partly due to questions of semantics and classification, responsible for an abusive use of neonatal sepsis as a diagnosis beyond this period. More so, the limitation of neonatal sepsis to bacterial etiology due to its frequency and severity has led to an increasing misunderstanding of sepsis. On the other hand, problems of classification and differentiation with regards to the age at onset of sepsis may be misleading as well. These confusions are further amplified by the diversity of the literature available on the subject, the plurality of language concepts and translation bias. Scientists worldwide may therefore be faced with linguistic challenges as far as infections in neonates and slightly beyond 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, exposing the problems of semantics involved and propose some linguistic adjustments to consider.

Keywords: Neonatal sepsis; Ant biotherapy; Bacteria

Background

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]. The incidence of neonatal sepsis in high-income countries is estimated between 1 and 12 per 1000 live births [2]. Whereas the incidence in low and middle-income countries is higher, with about 62.5 % neonatal emergencies being attributed to sepsis in some settings [3]. 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 [4]. Frequently reported risk factors include low birth weight (<2500grams) and preterm, febrile illness in the mother within 2 weeks prior to delivery, Foul smelling and/or meconium stained amniotic fluid, prolonged rupture of membranes (>24 hours), repetitive vaginal examinations during labor, prolonged and difficult delivery with instrumentation, as well as difficult resuscitation [5]. 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, prelacteal feeding, ventilation, and aspiration of feeds [6]. 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 common cause of mortality [7]. Other bacteria involved are Streptococcus pneumoniae, Staphylococcus aureus, and Enterococcus species. Gram-negative enteric bacilli such as Enterobacter species, Haemophilus and Listeria monocytogenes [8]. 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 [9]. Because of its severity and incidence, there have gradually been a focalization on bacterial sepsis, and less for

others, with non-bacterial pathogens 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 [10]. Some viruses such as rubella virus, cytomegalovirus may equally be involved in congenital infections, with an onset which is earlier before the neonatal period, while seasonal viruses including influenza virus, respiratory syncytial virus (RSV), adenoviruses, rhinoviruses, and rotaviruses may sometimes be implicated in neonatal sepsis as well [11]. On the other hand, very few fungal pathogens apart from Candida species are responsible for sepsis in neonates [12]. 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 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 [13]. 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 as a result of the penetration of a pathogen into the bloodstream, creating a septic state [14]. 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 [15]. 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 [16]. 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 [17]. Unexpectedly, Fever could be rare and hypothermia considerably common. 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 [18]. 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. Cardiac signs such as cyanosis, desaturation, bradycardia, poor perfusion, reduced capillary refill, and hypotension may occur as well [19]. Convulsion, neurologic deficits and irritability are frequent symptoms, whereas attenuated reflexes, hypotonia, 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 [20]. 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 historically relied 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 [21]. 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 [22]. Best obstetrical practices, effective newborn care and neonatal immunization is also a necessity, while caesarean delivery may sometimes be indicated in case of active genital tract infection such as Herpes Simplex Virus [23]. 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 [24]. 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. 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. Supportive care is important as well and can't be dissociated from the overall management of neonatal sepsis [25].

The Problems of Semantics and Classifications

A problem of semantics may be described as an issue with linguistic processing. That is one which relates spoken utterances and understanding. More so, 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 [26]. 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 or belongs to the neonate. The second term is sepsis, a noun which denotes a state of diffused infection, accompanied by a systemic inflammatory response. There are several classifications of neonatal sepsis, but they are almost all based on the age at onset of the sepsis. Some other grouping may involve the prematurity character of the neonate. As a matter of fact, 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. In premature neonates, EOS is defined as occurring within the first 72 hours of life as well. Furthermore, some subdivision of EOS into very early onset neonatal sepsis (within 24 hours) and early onset sepsis (within 24 hours to 6 days) have been suggested by some authors [27]. 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. Another 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 [28]. Late-onset neonatal sepsis (LOS) has also been variably 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. A progressive adoption of 72 hours as the lower limit age and 90 days as the upper limit age has been noted, with the term very late onset neonatal sepsis consecrated to sepsis in infants above 30 days of life. This definition of LOS may likely contain some exaggeration concerning the upper limit age between 90 and 120 days, which largely exceeds the neonatal period. In effect, the neonatal period in pediatrics corresponds to the first 28 days of life after delivery. Therefore, a strict consideration of neonatal sepsis as diagnosis from a sematic stand point would imply a restriction to this population, in occurrence, "infants within the neonatal period of development having sepsis". The incorrect attribution of this diagnosis to infants beyond this period and up to 90-120 days of life might seemingly have microbiological and therapeutic rationale, but poses a problem of classification as well. 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 doesn't change greatly. Based on this hypothesis, some authors suggested the impact on antibiotherapy is not necessarily significant and so may be identical throughout the first three to four months of life. Nevertheless, the predominance of community and nosocomial pathogens in late onset neonatal sepsis and early infancy (by principle), has led to practical presumptive adjustments such as the use of cloxacillin in replacement of ampicillin. This illustrates possible microbiological variability; with therapeutic implications throughout infancy to consider, starting with the delimitation of neonatal sepsis diagnosis, to prevent resistances and therapeutic failure. From the definition of sepsis, two conditions seem indispensable for its occurrence: diffuse infection and systemic inflammatory response syndrome (SIRS) [29]. 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. The term 'septicemia' was formerly used to denote the spread of pathogens through the blood stream in sepsis, indicating its 'diffuse' nature. Therefore, an infection in a neonate may be localized or circumscribed 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. Neonatal sepsis is not purely a syndrome, but is mainly characterized by the systemic inflammatory response syndrome, although not pathognomonic of sepsis [30]. In effect the SIRS may be induced by other causes such as trauma or injury and neoplasia. "Neonatal sepsis" is thus a diagnosis from a semiological stand point and a pathology from a clinical point of view. Although neonatal sepsis of bacterial etiology is the most severe, it is necessary to remind that sepsis may equally be of viral, fungal, protozoan or mycoplasmal origin [31]. 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 sepses, they could also rightly be considered as "neonatal: pneumonia, encephalitis, meningitis, or pyelonephritis" respectively, 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 [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. "Neonatal sepsis" being defined as an 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. Infections without SIRS in neonates would correspond to "neonatal infections", with less severity. Neonatal sepsis could be attributed a "proper name" when its focal origin is known. Therefore, "neonatal sepsis" as a definite diagnosis might be considered more appropriate for sepsis in neonates when there is no identifiable focus, from a semiological basis. Neonatal sepsis is not a syndrome per se, but is characterized by the systemic inflammatory response syndrome which is neither pathognomonic. The etiologies of neonatal sepsis are diverse and might be of bacterial, viral, fungal, protozoan or mycoplasmal origin.

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Conflict of Interest

The authors declare that they have no competing interest.

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