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Review

# Neonatal sepsis

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**Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken**

## Abstract

In this paper on neonatal sepsis, after a short presentation of etiopathogenesis and physiopathology, we will briefly present the clinical picture, the diagnosis and the therapy.

Concerning diagnosis, we will focus our attention on procalcitonin (PCT), serum amyloid A (SAA), presepsin (sCD14) and metabolomics. Three practical tables complete the review.

## Keywords

Sepsis, newborn, diagnosis, therapy, presepsin, metabolomics.

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## Introduction

Sepsis is a clinical syndrome characterized by a set of hemodynamic, respiratory and metabolic alterations secondary to an infectious process that can trigger an abnormal systemic inflammatory response syndrome of the organism (SIRS). The term "newborn" indicates that the septic process occurs during the first four weeks of life, both in term infants than in preterm infants. Sepsis has an incidence of approximately 0.5-0.8/1,000 live births [1] and represents one of the most serious diseases of the neonatal period, still burdened by significant morbidity and mortality. Although there are different opinions in this regard, depending on the time of onset, there are two main forms of sepsis: early onset neonatal sepsis (EOS), which is clinically manifested within the first 72 hours after birth and in which more than 50% of cases are developed within the first 6 hours of life, and late onset neonatal sepsis (LOS), which occurs after the first 72 hours of life and usually results from nosocomial infection [2].

The rates of infection and mortality of sepsis in newborns increases with decreasing gestational age and birth weight, with a higher risk for either newborns of low birth weight (SGA) or with respiratory function depressed and in presence of maternal and perinatal risk factors.

## Etiopathogenesis

Neonatal sepsis may have bacterial, fungal or viral etiology. Among the most common bacterial pathogens we can distinguish: among the Gram-positive the Coagulase-Negative *Staphylococcus*, the *S. aureus* and the *Streptococcus* Group B; whereas among the Gram-negative, the *E. Coli*, the *Pseudomonas spp.* and the *Klebsiella spp.* With regard to the fungal forms, infections of *C. Albicans* are the most common in preterm infants, particularly if they are subjected to prolonged antibiotic therapy. We should also take into account infections due to virus and vertically transmitted in utero (congenital infections), during birth (perinatal infections) and through breast feeding (postnatal infections) [3]. The EOS are generally caused by infections due to *E. coli* and *Streptococcus* group B, which are responsible respectively for 23% and 47% of cases. The LOS are more frequently associated with infection by germs coagulase-negative staphylococci, which alone represent 39% of cases; other emerging pathogens, rare in early forms but that can cause disease after the first 7 days of life are: *Klebsiella spp.*, *Enterobacter spp.*, *P. aeruginosa* and *S. marcescens* [4, 5].

The main risk factors for neonatal sepsis include: prematurity (low gestational age and low birth weight), male gender, invasive care procedures such as vascular catheters and mechanical ventilation, the presence of comorbid conditions such as asphixia, respiratory distress and congenital immunodeficiencies. It should also be underline that the implementation of the use of intrapartum antibiotic prophylaxis has significantly reduced the incidence of EOS from *Streptococcus* group B.

## Physiopathology

The high incidence and severity of neonatal systemic infections can be attributed both to the immaturity of the defense mechanisms (particularly compromised in preterm infants) and the interaction between the pathogen and the host [6]. Sepsis is a clinical condition triggered by infectious microorganisms which, by interacting with the complement, cause the release into the circulation of a number of proinflammatory mediators such as the C3 and C5a, which can also induce vasodilation, chemotaxis and release of proinflammatory cytokines (IL1-8-6). In addition, the toxins activate the coagulation cascade that leads to an increased risk of formation of microthrombi in the microcirculation and cellular hypoxia by an altered regional perfusion [7].

The majority of short-term complications (SIRS, disseminated intravascular coagulation, septic shock and the multiple organ dysfunction syndrome) and long term (affecting the respiratory apparatus and on growth and neurologic sequelae), are closely associated to the effects of these mediators, that are not counterbalanced by an adequate synthesis of anti-inflammatory cytokines such as TNFsr, IL-1ra, IL-1rII, IL-10, TGF-b2 [8].

Newborns, especially those of low birth weight, still have an immature immune system and are therefore not able to counteract the polymicrobial flora they are exposed during and after birth. At the time of the birth, in fact, the acquired immune response is compromised both by the lack of antigenic exposure occurred within the uterus and by a dysfunction borne by T and B effectors cells [9]. For this reason, the defenses of the newborn are based almost exclusively on the innate immune response and on passive protection by maternal antibodies transmitted through the placenta [10].

Among the signs of immaturity there are some of the defenses of neonatal deficiency linked to birth weight and to some functional deficits related to some of the processes of phagocytosis and other bactericidal activities incurred by neutrophils and macrophages. These differences compared to the adult immune system may explain the increased susceptibility to infections observed in the neonatal period [11].

Moreover, the results of inflammation are represented by tissue damage and cell necrosis, which cause the release of damage-associated molecular patterns (DAMPs), also known as allarmins, that continue to carry out the inflammation acting on the PRR (pattern-recognition receptor) activated by pathogens.

## Clinical picture

In 2005, the International Pediatric Sepsis Consensus Conference defined sepsis as "the systemic inflammatory response syndrome in the presence or as a result of a suspected or proven infection" [12].

The main problem of neonatal sepsis is that they occur very often with a hidden clinical picture, accompanied by nonspecific signs and symptoms [13]: fever or hypothermia, hypovalid stream, poor sucking and feeding, lack of responsiveness, lethargy, irritability, hypotonia, respiratory distress, tachycardia or bradycardia, hypoglycemia and impaired peripheral perfusion, while body temperature may be high, low or normal (**Tab. 1**).

**Table 1.** Clinical manifestations of neonatal sepsis.

| Clinical manifestations of neonatal sepsis |
|---|
| Lethargy/irritability |
| Hypovalid stream |
| Cyanosis |
| Tachypnea |
| Intercostal retractions |
| Hypotension |
| Tachycardia/bradycardia |
| Mottled skin, petechiae, purpura |
| Revival |
| Fever |
| Diarrhea, vomiting, abdominal distention |
| Seizures |
| Hypotonia |
| Tremors |

When there is any "respiratory distress," it includes tachypnea, grunting, nasal flaring, intercostal retractions and these symptoms can often be the only clinical manifestation of sepsis with or without pneumonia. In addition, neonatal sepsis may be complicated by the appearance of metastatic foci of infection, disseminated intravascular coagulation (DIC), congestive heart failure and shock [14].

## Diagnosis

The current methods and procedures for the diagnosis of sepsis, are beset by low sensitivity and long response times, inadequate to the need to establish a quick, timely and effective therapeutic intervention. Among the hematological investigation, the total leukocyte count, the neutrophilia or neutropenia, the differential leukocyte count and the platelet count, are the ones that present wide ranges of sensitivity (17-90%) and specificity (31-100%). However, the increase of the ratio of immature neutrophils and total (I / T > 0.2) is the data with the highest sensitivity and negative predictive value, although its evaluation is operator dependent [15].

Blood count:

- Ratio of I / T> 0.2;
- Leukocytes < mmc 20,000 or < 5,000 mmc;
- Fibrinogen > 300 mg%;
- CRP > 1.5 mg%;
- Platelets < 100.000 mmc;
- Metabolic acidosis: base deficit > 7.

The main problem in the diagnostic field relates to the absence of a test that meets the criteria of an ideal marker for the early diagnosis of neonatal sepsis.

The isolation of the pathogen from biological samples such as blood, cerebrospinal fluid or urine, allows the definitive diagnosis and targeted treatment. Blood culture is the gold standard in cases of suspected neonatal sepsis and should always be performed before starting antibiotic therapy. However, the time required for culture is long (48-72 hours) and a concurrent antibiotic treatment, or the reduced volume of the sample, or the low bacterial tend to significantly reduce its sensitivity; in fact the blood culture in the newborn is positive in less than 50% of the cases, for this a blood culture negativity does not exclude the diagnosis of sepsis [16]. The execution of specific culture is controversial, since any positivity may indicate a colonization of the newborn but not the presence of systemic invasive infection. Despite their low

predictive value for sepsis (7.5%), the knowledge of pathogenic micro-organisms isolated in cultures may lead the choice to a specific antibiotic therapy. Regarding the lumbar puncture and the examination of the cerebrospinal fluid, it should be taken into account for each infant with suspected sepsis, since meningitis may complicate sepsis in approximately 15% of cases. The research in the liquor of soluble antigens of *Streptococcus* group B and *E. coli*, can be a valuable diagnostic aid [17].

An ideal marker of neonatal sepsis should be sensitive and specific, be able to discriminate among the possible etiologies of sepsis (bacterial, viral, fungal), increase early during the disease and remain high for a sufficiently long period to be dosed. It should also be useful in monitoring the disease and a guide to choosing the best antibiotic treatment.

There are some serological markers that are used for the diagnosis of neonatal sepsis (**Tab. 2**) and some of these, such as the C-Reactive Protein (CRP) and procalcitonin (PCT), are conventionally used in the neonatal intensive care. The PCR is characterized by a specificity of more than 90% and a sensitivity of 60-75%. It is produced by the liver and released into the circulation for action of IL-6 and 8, it has a short half-life of 24-48 hours and it increases after 4-6 hours after the onset of the infectious insult both when it has a bacterial or infectious nature [18]. In addition, an increase in blood levels of CRP may be formed not only in the course of acute or chronic infectious diseases but also after trauma, surgery and sometimes in patients with malignancies.

The PCT instead is produced by the C cells of the thyroid gland and extrathyroidal from neuroendocrine cells and together with IL-6 it represents one of the earliest markers of infection. Its levels increase in the circulation within 2-4 hours of exposure to the infective agent and remain so for the next 24 hours with a half-life of 24-30 hours [19]. It is also selectively produced in response to bacterial infection; but it does not increase in the course of viral or fungal infections, autoimmune diseases and cancer, though not in a significant way. However, concentrations of both the PCT that IL-6 may change even in presence of other conditions, such as fetal hypoxia, respiratory distress or in uninfected infants in the first days of life [20, 21].

Although less used in clinical practice, the protein serum amyloid A (SAA) is considered a marker of neonatal sepsis. The SAA is an apolipoprotein produced by the liver, the endothelial cells, the monocytes and the smooth muscle and is regulated by the action of certain cytokines such as IL-1, IL-6 and TNFα. Its levels can be influenced by liver function and nutritional status which reduce its usefulness then in the forms of LOS in which both can be compromised. In particular, a variant of the SAA, the des-arginine, appears to be an excellent marker of acute and chronic inflammation [22].

Among the promising markers, or those with a better sensitivity, there is the presepsin (sCD14). This marker is the fraction of the CD14, which is a glycoprotein expressed on the surface of the membrane of monocytes and macrophages with a role as a receptor for the complex lipopolysaccharide (LPS) and for proteins binding to LPS. From the point of view of clinical practice presepsin allows to discriminate between bacterial and non-bacterial infections (including the SIRS) and it has been studied and compared with PCT and IL-6 in a prospective multicenter study in adult patients [23]. From this work it is clear that this biomarker can be used, given the higher sensitivity compared to conventional markers and blood culture, for the diagnosis of bacterial and fungal sepsis.

**Table 2.** Biomarkers for managing sepsis.

| Conventional | Promising | Next generation |
|---|---|---|
| Haematological tests | CD64 | Ang-1 Ang-2 |
| CRP, SAA | CD11b | Gas-6 |
| PCT | aCD14-ST | Osteopontin |
| Cytokines (IFN-γ, IL-6, TNF-α) | LBP | sTREM-1 |
| Microbiological cultures | Molecular biology (RT-PCR) | SphK1 |
| | MBL | MALDI-TOF-MS |
| | Endotoxins | Proteomics |
| | | Metabolomics |

Even in the field of neonatal infections presepsin has proven to be a reliable marker, especially in the forms of early neonatal sepsis, in assessing the severity of the infection and in predicting the evolution towards potential complications or to death [24]. Therefore, this molecule represents a new marker of neonatal sepsis with greater sensitivity and specificity than the classical markers so far used in the clinical diagnosis (CRP and PCT).

Considering the difficulty to have an ideal marker and being the sepsis a multiorgan dysfunction that causes important changes in human metabolism, it has become more firm the hypothesis to be able to apply the metabolomic analysis in determining the metabolic changes that occur just in progress of sepsis [25]. In fact, the new holistic approach of metabolomics has the advantage of allowing, through the analysis of biological fluids, determination of metabolites of low molecular weight endogenous and exogenous factors that may be related to specific pathophysiological states.

In a recent study of Fanos et al. metabolomic techniques have been applied to evaluate changes of metabolites prior to the development of EOS and LOS. This study showed which metabolites are responsible for differences between infants with sepsis and controls: for early sepsis at the time of birth and for sepsis later than 72 hours before the clinical onset [26]. From the metabolomic analysis carried out in the group of neonates with sepsis also it can be seen an increase in urinary metabolites that are part of the fatty acid metabolism such as ketone bodies. These results highlight the possible compensatory reaction that occurs in infants with sepsis in response to a reduced level of ATP.

The data from this study suggest that in the near future we can, through the analysis of metabolomics, dose sensitive and specific metabolites of sepsis in order to implement more targeted treatments.

## Therapy

Neonatal sepsis therapy (**Tab. 3**) is undertaken by the administration of antibiotics and it has to start early on an empiric basis. The importance of an early diagnosis regards the fact that for each late hour in the administration of a specific antibiotic therapy there is a mortality increase of 7% [27]. If the symptoms appear in the first three days of life, a wide spectrum empiric therapy oriented both to negative and positive gram germs has to be administered, generally this therapy is represented by an association between an ampicillin (or other penicillin derivate) and an aminoglycosides (gentamicin, tobramicin); it is also recommended to associate a third-generation cephalosporin in case of meningitis (with a greater meningeal diffusion) or serious clinical worsening.

In LOS the starting therapy is directed towards Coagulase Negative *Staphylococci* (CoNS) and negative gram bacilli and it comprehends the administration of vancomycin and either an aminoglycoside or a third-generation cephalosporin (ceftazidime, cefotaxime).

Regarding micotic form the most used medicines in order to treat *Candida spp.* infections are fluconazol, amphotericin B deoxycholate, echinocandin and micafungin, the only label drug in the newborn in Italy.

Lastly, in viral forms, a recent study has show the efficiency, in order to prevent vertical

**Table 3.** Therapy of neonatal infections.

| Microorganism | Therapy |
|---|---|
| GBS | Ampicillin + Aminoglycoside |
| *E. coli* and others coliforms | Ampicillin + Aminoglycoside<br>or<br>Third-generations Cefalosphorins + Aminoglycoside |
| *L. monocytogenes* | Ampicillin + Aminoglycoside |
| *Streptococcus* D (*enterococcus*) | Ampicillin + Aminoglycoside |
| *Staphylococcus epidermidis-aureus* | Vancomycin or Teicoplanin |
| *Pseudomonas aeruginosa* | Ceftazidime + Aminoglycoside |
| Anaerobe | Penicillin G potassium |
| *C. fetus* | Aminoglycoside |
| *Candida spp.* | Micafungin or Amphotericin B + Fluorocytosine |
| Cytomegalovirus | Ganciclovir |

transmission of the virus, of the administration of cytomegalovirus-specific hyperimmunoglobuline to mothers that have contracted a primary infection during pregnancy [28].

For the postnatal treatment of a cytomegalovirus congenital infection, the efficiency of antiviral medicines such as ganciclovir or vanciclovir has been demonstrated in the improvement and slowdown of the progression of characteristic symptoms such as auditory disorders or chorioretinitis [29].

## Declaration of interest

The Authors declare that there is no conflict of interest.

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