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Review Article in

Management of Neonatal sepsis: Epidemiology, Diagnosis and Prevention

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ABSTRACT

Neonatal sepsis is an important cause of neurocognitive sequelae and neonatal mortality. Neonatal sepsis is a clinical syndrome with hemodynamic changes and other systemic clinical manifestations resulting from the presence of pathogenic microorganisms (bacteria, viruses, or fungi) in normally sterile fluid, such as blood or cerebrospinal fluid (CSF) in the first month of life. Neonatal sepsis is classified according to the time of onset as early or late.

Objectives: To define the neonatal sepsis, the epidemiology, clinical features and to discuss the latest updates in the management and antibiotic therapy and how you prevent the condition.

Methods: Electronic searches will be conducted in MEDLINE, Embase, The Cochrane Library, CINAHL, ZETOC). We will include randomized controlled trials of different perspective in the management of the neonatal sepsis.

Keywords: Early-onset, late onset, Neonatal sepsis, Diagnosis, Treatment.

INTRODUCTION

Neonatal sepsis is a clinical syndrome with hemodynamic changes and other systemic clinical manifestations resulting from the presence of pathogenic microorganisms (bacteria, viruses, or fungi) in normally sterile fluid, such as blood or cerebrospinal fluid (CSF) in the first month of life. [(1)] Neonatal sepsis is an important cause of neurocognitive sequelae and neonatal mortality. [(2,3)]

An accepted definition of sepsis in neonates is lacking. According to the report on the expert meeting on neonatal and paediatric sepsis of EMA (2010), neonatal sepsis can be defined by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or as a result of suspected or proven infection (positive culture, microscopy or polymerase chain reaction) .[(4)]

(Table 1): Clinical signs & Laboratory signs:

Clinical signs	Laboratory signs
• Modified body temperature: core temperature greater than 38,5 °C or less than 36 °C AND/OR temperature instability	• White blood cells (WBC) count: 20,000 x109 cells/L
• Cardiovascular instability: bradycardia (mean HR less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers or congenital heart disease OR otherwise unexplained persistent	• Immature to total neutrophil ratio (I/T) greater than 0.2

depression over a 0.5 h time period) OR tachycardia (mean HR greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs and painful stimuli OR otherwise unexplained persistent elevation over a 0,5 h to 4 h time period) AND/OR rhythm instability reduced urinary output (less than 1 mL/kg/h), hypotension (mean arterial pressure less than the 5th percentile for age), mottled skin, impaired peripheral perfusion	
• Skin and subcutaneous lesions: petechial rash, sclerema	• Platelet count 15 mg/L OR procalcitonin ≥ 2 ng/ml (The cut-off for procalcitonin in neonatal sepsis has not been clearly defined, as the currently available published data are still controversial).
• Respiratory instability: apnoea episodes OR tachypnea episodes (mean respiratory rate (RR) over 2 SD above normal for age) OR increased oxygen requirements OR requirement for ventilation support	• Glucose intolerance confirmed at least 2 times: hyperglycaemia (blood glucose >180 mg/dL or 10 mMol/L) OR hypoglycaemia (glycaemia < 45 mg/dL or 2.5 mMol/L) when receiving age specific normal range glucose amounts
• Gastrointestinal: feeding intolerance, poor sucking, abdominal distention	• Metabolic acidosis: Base excess (BE) <-10 mEq/L OR Serum lactate > 2 mMol/L
• Non-specific: irritability, lethargy and hypotonia	

Table 1 show the Clinical signs and laboratory signs (presence of at least two clinical symptoms and at least two laboratory signs) associated with neonatal sepsis according to the report on the expert meeting on neonatal and paediatric sepsis of EMA (2010). Neonatal sepsis is classified according to the time of onsets early or late. In general, early neonatal sepsis is considered when the clinical condition appears within the first 72 h of life. The exception to this definition is neonatal sepsis caused by *Streptococcus agalactiae*, which, although having a perinatal etiology, can occur within the first 7 days of life. Late neonatal sepsis is that which starts after 72 h of life.[(1)] For the purposes of this article, early neonatal sepsis will be considered as starting within the first 72 h of life and late neonatal sepsis after 72 h of life. The etiological agents of early and late neonatal sepsis are quite distinct. Early neonatal sepsis is acquired in the peripartum period, before or during childbirth; therefore, the microorganisms are usually from the maternal genitourinary tract. According to data from the American Neonatology Network, Gram-positive microorganisms are the etiological agents in 62% of early neonatal sepsis cases, and in 43% of the total. The identified microorganism is *Streptococcus agalactiae*. Gram-negative microorganisms comprise 37 % of the etiological agents of early neonatal sepsis, of which 29% are *Escherichia coli*.[(5)] Late neonatal sepsis occurs most often in infants who remain hospitalized for long periods,

such as preterm or full-term infants who require prolonged hospitalization and invasive procedures, with the most common microorganisms being those acquired in the hospital setting. According to the American Neonatology Network, in 79% of the situations, the identified microorganisms are Gram-positive, with coagulase-negative Staphylococcus occurring in 57% of the total and *Staphylococcus aureus* in 12%. Gram-negative microorganisms constitute 19% of the total, with *Escherichia coli* being the most frequently identified among them, accounting for 7% of the total. Fungi are found in 6% of cases of late neonatal sepsis.[6] Data published by the Brazilian Neonatal Research Network show results that are similar to the American findings regarding the etiological agents of late neonatal sepsis.[7] Eventually, late sepsis can manifest in newborns in the out-of-hospital setting; the most common microorganisms are those of community origin, such as *Staphylococcus aureus* and *Escherichia coli.* Neonatal sepsis can also have a viral etiology; however, the present review focuses on discussing bacterial neonatal sepsis.

EPIDEMIOLOGY

The incidence of neonatal sepsis varies from nursery to nursery and is generally estimated to range from 1-10 per 1000 live births. According to *Alden* et al. the frequency of sepsis among very small preterm babies is much higher Although diagnostic and therapeutic possibilities have been improved during the last years fatality rates of 20 to 50 per cent are still reported from large centers. [8]

Although many developing countries have achieved substantial decreases in deaths in the post-neonatal period and in children aged 1–4 years, neonatal death rates have decreased more slowly, with an estimated 3 million neonatal deaths worldwide every year. [9]

RISK FACTORS

Neonates are theoretically immunocompromised as several components of the immune system are not fully developed at birth.[10, 11] This is especially true for preterm newborns, as they are additionally immunocompromised due to an even more immature immune system.[12,13,14,15,16] Prematurity and low birth weight are therefore major risk factors and accordingly, a multi-center observational study showed that neonatal sepsis were most common in premature (82%) and low birth weight neonates (81%). [17] For early onset neonatal sepsis, the risk factors are multiple gestation, maternal intra-partum

fever, maternal urinary tract infection or chorioamnionitis, prolonged labour, preterm rupture of the membrane (PROM), prolonged PROM > 18 h, and meconium aspiration syndrome. [18,19,20]

Late onset sepsis also has several risk factors such as mechanical ventilation, intravascular catheterization, failure of early enteral feeding with breast milk, a prolonged duration of parenteral nutrition, surgery, underlying respiratory and cardiovascular diseases, and hospitalization. [1,21,22 ,23,24]

DIAGNOSIS: EARLY NEONATAL SEPSIS

Early diagnosis remains challenging due to non-specificity of both clinical symptoms and laboratory findings. [25]

The clinical signs are from different systems and can be grouped as follows: a) apnea, difficulty breathing, cyanosis; b) tachycardia or bradycardia, poor perfusion or shock; c) irritability, lethargy, hypotonia, seizures; d) abdominal distension, vomiting, food intolerance, gastric residue, hepatomegaly; e) unexplained jaundice; f) body temperature instability; g) petechiae or purpura. To take into account the clinical signs, ideally the newborn should show manifestations in three distinct systems, or two clinical signs indistinct systems associated with a maternal risk factors. [26]

Laboratory Tests: If early neonatal sepsis is suspected, blood culture and CSF samples should be collected. Urinalysis is not indicated, since urinary infection in early neonatal sepsis is unusual. Complete blood count (CBC) and serum C-reactive protein have a better negative predictive value than a positive predictive value. The most common CBC findings are immature to total neutrophil ratio (I/T ratio) >0.2, leukopenia (below 5000), or leukocytosis (>25,000). Serial low C-reactive protein levels (serum levels below 10 mg/L) help to rule out the diagnosis of neonatal sepsis in a newborn with negative blood culture. [1]

PREVENTION OF EARLY NEONATAL SEPSIS CAUSED BY STREPTOCOCCUS AGALACTIAE:

Briefly, the CDC recommends the following for the prevention of sepsis caused by *Streptococcus agalactiae* [21]: • Universal screening (for all pregnant women) of

streptococcal colonization between 35 and 37 weeks of gestation. • During labor or at the time of membrane rupture, chemo-prophylaxis should be administered to all pregnant women colonized by streptococcus. • Women with identified streptococcus in urine cultures (atany concentration) during pregnancy should receive intrapartum chemoprophylaxis. • Women who had a previous child with streptococcal infection should receive chemoprophylaxis. • If the screening result is not known, the patient should receive chemoprophylaxis in the following cases: (1) labor at gestational age less than 37 weeks; (2) time of membrane rupture > 18 h; (3) presence of fever during labor (≥ 38 ◦C).• For intrapartum prophylaxis, the following antimicrobial regimen is recommended: crystalline penicillin: 5000,000intravenous units as a loading dose and 2,500,000 intravenous units every four hours until delivery. As a second-line therapy, intravenous ampicillin with a loading dose of 2 g can be used, and 1 g intravenous every four hours until delivery.

DIAGNOSIS: LATE NEONATAL SEPSIS

Clinical manifestations, as well as early neonatal sepsis, vary considerably and are nonspecific. The clinical signs originate from different systems and can be grouped as follows: a) apnea, difficulty breathing, cyanosis; b) tachycardia or bradycardia, poor perfusion or shock; c) irritability, lethargy, hypotonia, seizures; d) abdominal distension, vomiting, food intolerance, gastric residue, hepatomegaly; e) unexplained jaundice; f) body temperature instability; g) petechiae or purpura.[(26)] In the case of a preterm newborn hospitalized for a long period in the neonatal ICU with suspected clinical signs of sepsis, the collection of blood culture, CSF, and sterile urine (suprapubic puncture or catheter sample) is recommended for cultures.[(1)] Blood samples containing 1 mL of blood should be collected from two separate sites. The most frequently identified microorganism in late neonatal sepsis is coagulase-negative Staphylococcus, and the distinction between finding a contaminating agent or not is attained through the positivity of blood cultures collected at two different sites. The positivity of both blood cultures is indicative that coagulase-negative Staphylococci is the etiological agent of sepsis. Complementary laboratory tests, such as complete blood count and C-reactive protein, have a better negative predictive value than a positive predictive value, similarly as in early neonatal sepsis. However, on certain occasions, the result of the serum C-reactive protein level in combination with the clinical picture

helps to direct treatment decision-making. The cutoff point for C-reactive protein is 10 mg/L.

PREVENTION OF LATE NEONATAL SEPSIS

Some measures are indicated in the prevention of late neonatal sepsis:

1. Hand washing or use of alcohol gel: Hand washing and/or use of alcohol gel is the most effective measure to prevent infections. Microorganisms are carried by the hands when handling a patient. The five moments of hand hygiene recommended by the World Health Organization should be emphasized:

- Before contact with the patient.
- Before the procedure is performed.
- After risk of exposure to biological fluids.
- After contact with the patient
- After contact with areas near the patient.

2. Appropriate and well-defined care bundles, with central intravascular catheters and endotracheal tubes that are closely followed to reduce contamination. [(27)]

3. Trophic enteral feeding: early onset of trophic feeding stimulates the gastrointestinal tract, stimulating intestinal maturity, preventing villous atrophy, and also decreasing bacterial translocation and invasion through the intestinal mucosa. [(28)]

4. Use of breast milk: breast milk contains significant concentrations of IgA and oligosaccharides that give it anti-infectious properties. The exclusive use of breast milk results in more diverse intestinal microbiota, which leads to a lower probability of infections. [(29,30)]

5. Probiotics: although there are meta-analyses showing that probiotics may be useful in preventing late neonatal sepsis, there are still many questions regarding their routine use. The studies were performed with different types of probiotics, different dosages, and highly variable treatment times, which makes the generalization of results very difficult. [(31,32)]

6. Lactoferrin: there are conflicting studies regarding the role of lactoferrin as a protective factor against late neonatal sepsis. An Italian collaborative randomized trial included 472 very low birth weight infants: the lactoferrin group with 153 patients, the

lactoferrin and probiotic group with 151 patients, and the placebo group (glucose5 %) with 168 patients, treated from birth to 30 days of life. Late sepsis was significantly lower in the groups that received lactoferrin.[33] However, a recently published collaborative randomized clinical trial was carried out in the United Kingdom with 2203 newborns, of gestational age <32 weeks: 1099 in the lactoferrin group up to 34 weeks of corrected gestational age and 1104 in the control group receiving sucrose up to 34 weeks of corrected age. There was no significant difference in the incidence of late sepsis. [34] At this time, the indication of lactoferrin as a preventive measure for late neonatal sepsis is still under evaluation

ANTIBIOTIC THERABY

Antibiotics are among the most prescribed drugs in the paediatric population. With increasing concerns regarding microbial resistance leading to potential multidrug resistant infections, antibiotic stewardship programs have been developed. The main goal of these programs is optimization of the use of antibiotics. Moreover, unnecessary use should be reduced since antibiotics do interfere with the development of the gut microbiome in early stages of life, influencing the risk of developing several diseases such as asthma, diabetes and obesity later in life.[35,36]

When bacterial infection is probable or proven, parenteral antibiotics are usually prescribed for at least 7 days. Occasionally, when intravenous (IV) access problems occur, or when hospital referral is not possible, as in low-and-middle-income countries (LMICs), newborns are treated with oral antibiotics. In high-income countries (HICs), the full course is generally completed IV. [25]

The most commonly recommended and used first-line treatment for both early and late onset neonatal sepsis is a beta-lactam antibiotic (most commonly ampicillin, flucloxacillin and penicillin) combined with an aminoglycoside (most commonly gentamicin). However, there has been an increased use of alternative protocols using a cephalosporin (most commonly cefotaxime) or a glycopeptide (most commonly vancomycin) as a first line option to treat especially late onset sepsis, due to increased resistance among the most common pathogen such as coagulase-negative staphylococci. Ampicillin combined with a third-generation cephalosporin agent (most commonly cefotaxime) is also used as an alternative for early onset sepsis. Other

regimens such as cephalosporins (as monotherapy) are also used. Guidelines may differ due to local antibiotic resistance of the most common pathogens or whether the empirical regimen is supposed to cover the common but low virulence coagulase-negative staphylococci (for late onset sepsis) .Vancomycin is often considered if staphylococcal infection is suspected. [37]

CONCLUSION

The urgent and fast management of Neonatal sepsis is one of the major topics in the neonatology. The optimal treatment of infants with suspected early-onset sepsis is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once the pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). The use of the oral antibiotics was unprefered and controversial . Until the late 2 decades, a lot of studies showed the importance of the oral route medically and economically in the community health. When neonatal sepsis is suspected, always collect samples for bacteriological analysis before starting the empirical treatment. The decision to start empirical antibiotic therapy and the choice of the most appropriate treatment regimen are crucial. Avoiding routine vancomycin use in the empirical antibiotic regimen in late neonatal sepsis is important to prevent bacterial resistance and invasive fungal infections. The main protective mechanisms against neonatal sepsis are hand washing and the use of breast milk.

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