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REVIEW ARTICLE

The challenges of neonatal sepsis management☆

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KEYWORDS
Neonatal sepsis;
Sepsis calculator;
Vancomycin;
Coagulase-negative *Staphylococcus*;
Group B *Streptococcus*

Abstract

Objectives: To present current evidence on the etiology, risk factors, diagnosis, and management of early and late neonatal sepsis.

Source of data: Non-systematic review of the Medline (PubMed), Scopus, Web of Science, Cochrane, and Google Scholar databases regarding the following terms: neonatal sepsis, early neonatal sepsis, late neonatal sepsis, empirical antibiotic therapy, sepsis calculator, vancomycin, newborn, preterm newborn.

Data synthesis: Neonatal sepsis is a frequent cause of neonatal morbidity and mortality. Its diagnosis is difficult. Continuous observation of the patient is critical to diagnostic suspicion. When neonatal sepsis is suspected, bacteriological tests should be collected. Vancomycin should not be routinely using in the empirical antibiotic regimen in late neonatal sepsis, and the main protective mechanisms against neonatal sepsis are handwashing and the use of breast milk.

Conclusions: Newborns constitute a group that is more vulnerable to sepsis. Knowledge of risk factors and etiological agents allows a better approach to the newborn with sepsis.

PALAVRAS-CHAVE
Sepse neonatal;
Sepsis calculator;
Vancomicina;
Estafilococo coagulase negativo;
Estreptococo grupo B

Os desafios no manejo da sepse neonatal

Resumo

Objetivos: Apresentar evidências atuais na etiologia, fatores de risco, diagnóstico e manejo da sepse neonatal precoce e tardia.

Fontes de dados: Revisão não sistemática feita nas bases de dados Medline (PubMed), Scopus, Web of Science, Cochrane, Google Scholar sobre os temas sepse neonatal, sepse neonatal precoce, sepse neonatal tardia, antibioticoterapia empírica, sepsis calculator, vancomicina, recém-nascido, recém-nascido pré-termo.

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Síntese de dados: A sepse neonatal é uma causa frequente de morbimortalidade neonatal. O seu diagnóstico é difícil. A observação contínua do paciente é fundamental para uma suspeição diagnóstica. Ao se suspeitar de sepse neonatal devem-se coletar exames bacteriológicos. Não usar, rotineiramente, vancomicina no esquema empírico de antibiótico na sepse neonatal tardia. Os principais mecanismos protetores da sepse neonatal são a lavagem de mãos e o uso do leite materno.

Conclusões: Os recém-nascidos constituem um grupo mais vulnerável à sepse. O conhecimento dos fatores de risco e dos agentes etiológicos permite uma melhor abordagem do recém-nascido séptico.

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]

Neonatal sepsis is classified according to the time of onset as 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 microorganismscomprise 37 % of the etiological agents of early neonatal sepsis, of which 29 % are *Escherichia coli*.[4]

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.[5] 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.[6]

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.

Early neonatalsepsis

The incidence of early sepsis in the United States is around 0.77 cases per 1000 live births, and when considering only newborns above 34 weeks of gestational age, it is around 0.5 cases per 1000 live births.[7,8] Since intrapartum antibiotic therapy was implemented for pregnant women colonized with *Streptococcus agalactiae*, the incidence of early neonatal sepsis has fallen sharply in the United States, and in services that screen and prevent perinatal streptococci infection.

The risk factors for early sepsis that have been pointed out are:

1 *Streptococcus agalactiae* colonization: A pregnant woman colonized with *Streptococcus agalactiae* who has not undergone intrapartum prophylaxis has a 25-foldhigher probability of having a newbornwith early neonatal sepsis than a non-colonized mother.[9]
2 Amniotic membrane rupture for more than 18 h: newborns from mothers with amniotic membrane rupture for more than 18 h are four times more likely to have an infection than those born to mothers without rupture.[10]
3 Chorioamnionitis: the presence of chorioamnionitis increases the possibility of early neonatal infection.[11]

Diagnosis

The clinical manifestations vary considerably and are nonspecific, which makes the diagnosis of early neonatal sepsis difficult and predisposes to excessive antibiotic use.

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 in distinct systems associated with a maternal risk factor.[12]

The Kaiser Permanente Northern California group, which encompasses 14 hospitals with obstetric and neonatal care, was concerned about the over-requesting of tests to rule out neonatal sepsis and the overuse of antibiotics for suspected early neonatal sepsis, and thus created a calculator for newborns with a gestational age of 34 weeks or over, which takes into account gestational age, time of ruptured amniotic membrane, maternal body temperature, presence or absence of *Streptococcus agalactiae* colonization, and use or non-use of antibiotics in the period immediately prior to delivery to determine the likelihood of a newborn having early neonatal sepsis. Considering the importance of some clinical signs, especially those of respiratory origin, the calculator has been improved by including the newborn's clinical signs in the first 24 h of life.[13,14] This calculator is available free of charge Early-Onset Sepsis (EOS calculator for both iPhone and Android).

Studies using retrospective or prospective data were carried out to assess the usefulness and accuracy of the calculator. Applying the calculator has been shown to decrease antibiotic use in late preterm or full-term preterm infants by approximately 40 %, without increasing the risk of false negative results.[8,15–17]

Another strategy that has been used in an attempt to reduce the use of antibiotics and over-requesting of laboratory tests is to take into account the careful and frequent observation of clinical signs in newborns at risk of early neonatal sepsis. A European study that closely observed clinical signs showed a decrease in antibiotic use and decreased hospital length of stay.[18] In a recent publication, the American Academy of Pediatrics suggests that close clinical observation within the first 48 h may be more effective than the EOS calculator in determining late preterm and full-term newborns with early neonatal sepsis.[19]

For newborns with a gestational age of 34 weeks or less, the most important risk factor is the presence of chorioamnionitis, defined by maternal hyperthermia equal to or greater than 39 °C, or between 38 °C and 39 °C accompanied by at least one of the following clinical signs: maternal leukocytosis, purulent vaginal discharge, or fetal tachycardia.

The risk of early sepsis is high when preterm birth occurs after spontaneous labor, when there is prolonged rupture of the amniotic membrane, or in the presence of chorioamnionitis. The most adequate approach in these situations is to collect blood culture, cerebrospinal fluid, and complementary exams, and to start empirical antibiotic therapy. The risk of early sepsis is low when the delivery is by caesarean section, without ruptured amniotic membrane and without labor; for instance, in patients with pre-eclampsia who need to have their pregnancy interrupted for obstetric reasons.[20]

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]

Antibiotic therapy

The empirical antibiotic treatment protocol in our Unit is ampicillin and gentamicin. This antibiotic regimen covers the microorganisms that most commonly cause early neonatal sepsis. The ampicillin spectrum is adequate for *Streptococcus agalactiae* and for *Listeria*, which occurs very rarely in Brazil. Gentamicin has an adequate spectrum for Gram-negative microorganisms and especially for *Escherichia coli*. After obtaining blood culture results with the antibiogram test, the antibiotic regimen should be established with the specific drug indicated by the results.

In case of meningitis, with *Streptococcus agalactiae* being the etiological agent, it is recommended to adjust ampicillin to the appropriate dose indicated for the treatment of meningitis. If the microorganism is unknown or in the case of a Gram-negative microorganism, changing the antibiotic to cefepime is indicated.

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, chemoprophylaxis should be administered to all pregnant women colonized by streptococcus.
- Women with identified streptococcus in urine cultures (at any 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 ($\geq$ 38 °C).
- For intrapartum prophylaxis, the following antimicrobial regimen is recommended: crystalline penicillin: 5000,000 intravenous 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.

Late neonatal sepsis

Late neonatal sepsis is that which occurs after 72 h of life; it is more frequent in very low birth weight infants with long-term hospitalization in a neonatal intensive care unit (ICU) or in late preterm or full-term infants requiring prolonged hospitalization. The incidence of at least one first positive blood culture after 72 h of life in very low birth weight preterm infants (birth weight $\leq$1500 g) varies from 20 % to 35 %, depending on the assessed service.[5,6,22]

The microorganisms most often associated with late neonatal sepsis are Gram-positive (79 %), especially coagulase-negative *Staphylococcus*. Infections caused by Gram-negative microorganisms also occur, and the incidence of fungal sepsis has become important in numerous centers.

The occurrence of viral infections, especially respiratory syncytial virus and rhinovirus, has been frequently reported in newborns with a clinical picture similar to that of bacterial neonatal sepsis admitted to neonatal ICUs.[23]

The most important risk factors for late neonatal sepsis are:

1 Prematurity: compared to full-term infants, preterm infants have lower pro-inflammatory cytokine production, lower natural killer (NK) cell activation, decreased cell-mediated immunity, decreased placental transfer of immunoglobulins, and lower levels of serum complement.[24]
2 Breach of natural barriers: lesions and lacerations of skin and mucosa can be a portal of entry for bacterial invasion.
3 Long term indwelling central catheters are portals of entry for bacteria.
4 Invasive procedures, *e.g.*, tracheal intubation: the risk of sepsis increases with the number of times the newborn has been intubated; accidental extubations requiring frequent reintubation are important causes of infection.
5 Use of H2 blockers: gastric acidity acts as a barrier to bacterial proliferation and invasion; the use of H2 blockers decreases the defense mechanism and increases the risk of bacterial invasion.[25]
6 Prolonged use of empirical antibiotic therapy: the use of empirical antibiotic therapy for early neonatal sepsis for more than five days increases the incidence of late neonatal sepsis, especially in units with scarce use of breast milk and over-prescription of third-generation cephalosporins.[26,27]

It is important to note that late sepsis also occurs in full-term newborns, post-discharge. A study carried out in the United States, analyzing 4255 blood cultures collected from 160,818 full-term newborns who returned to the emergency department, aged between 1 week and 3 months, showed a positivity of 0.57 per 1000 newborns, and the most commonly found microorganism was *Escherichia coli*. The initial source of infection in these patients was a urinary tract infection.[28] Screening for urinary tract infection in late neonatal sepsis should always be performed.

Diagnosis

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.[12]

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 *Staphylococcus* 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.

The clinical picture of the newborn is crucial for the suspicion of neonatal sepsis and, after the result of blood culture, it is the main information to guide the need for treatment. A newborn in good general condition will only be indicated for antibiotic therapy if the blood culture is positive, regardless of the CBC or C-reactive protein results. On the other hand, a newborn with clinical signs showing disease will not have indication for antibiotic therapy only if the blood culture is negative and if they have at least two sequential low C-reactive protein levels 24 h apart. In this situation, the clinician should consider that the signs of the disease are of a non-infectious bacterial etiology.

Antibiotic therapy

Empirical antibiotic therapy should take into account the most likely etiological agents and their responses to antibiotic therapy. Although the most common microorganism in late neonatal sepsis is methicillin-resistant coagulase-negative *Staphylococcus*, this does not mean that the initial empirical regimen should include vancomycin. Several studies have shown that not using vancomycin in the initial empirical antibiotic regimen does not increase mortality, duration of bacteremia, and complications attributed to late neonatal sepsis.[29–32]

The indiscriminate and excessive use of vancomycin is an important factor in the emergence of multiresistant flora and the increased occurrence of invasive fungal infection.

Krediet et al. studied 66 newborns with sepsis caused by coagulase-negative *Staphylococcus* who received three distinct treatment regimens: 25 received cephalothin, 15 received vancomycin, and 26 started the treatment with cephalothin and then switched to vancomycin. Although 22 of the 25 cephalothin-treated patients had methicillin-resistant coagulase-negative *Staphylococcus*, the cephalothin treatment was maintained and the patients recovered without any complications or recurrence.[33]

Currently, there are antibiotic use management regimens for neonatal ICUs that predict the initial use of oxacillin in the initial empirical regimen for late neonatal sepsis and eventual change to vancomycin, only when there is no improvement in the patient's clinical condition after 48 h of oxacillin use.[29,32] Sepsis caused by coagulase-negative *Staphylococcus* usually has a milder course and a subacute evolution, which allows patients to be observed for 48 h on oxacillin use and the eventual change only if there is no adequate response to oxacillin use.

The empirical antibiotic therapy protocol for late neonatal sepsis in our Unit includes oxacillin and amikacin. Amikacin is used to cover Gram-negative microorganisms that can occur in hospital-acquired sepsis. After microorganism identification, the antibiotic therapy should be directed by the antibiogram test, except in cases of oxacillin-resistant coagulase-negative *Staphylococcus*, in which it is maintained depending on the *in vivo* response to oxacillin.

In case of meningitis, adjustment of antibiotic therapy according to the identified microorganism and antibiogram test are recommended. If the etiological agent is unknown, change of the antibiotic regimen to cefepime is indicated.

Prevention of late neonatal sepsis

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

1 Handwashing or use of alcohol gel: Handwashing 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: 1. before contact with the patient; 2. before the procedure is performed; 3. after risk of exposure to biological fluids; 4. after contact with the patient; 5. 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.[34]
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.[35]
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.[36,37]
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.[38,39]
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 (glucose 5 %) with 168 patients, treated from birth to 30 days of life.Late sepsis was significantly lower in the groups that received lactoferrin.[40] 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.[41] At this time, the indication of lactoferrin as a preventive measure for late neonatal sepsis is still under evaluation.

Conclusions

Management of neonatal sepsis is always a challenge. Neonatal sepsis is a frequent cause of neonatal morbidity and mortality, especially in developing countries. Its diagnosis is difficult, since clinical signs are nonspecific and complementary exams have low accuracy. Continuous observation of the patient, knowing how to take into account clinical signs, and observing risk factors are essential for diagnostic suspicion. 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 handwashing and the use of breast milk.

Conflicts of interest

The authors declare no conflicts of interest.

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