Review article

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NEONATAL SEPSIS

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Neonatal sepsis (NS) refers to a group of physical and laboratory findings occuring as a response to invasive infection in neonates. In early-onset sepsis (EOS) symptoms occur within the first 7 days, while in late-onset sepsis (LOS) between the 7th and 30th day of life. NS is a major cause of newborn morbidity and mortality. Improvements in intensive care have decreased the impact of EOS in term infants, with a reported incidence of approximately 1 – 2 cases per 1000 live births. Preterm infants are more prone to both EOS and LOS. Despite intrapartum prophylaxis against *Streptococcus agalactiae* (group B streptococcus, GBS), GBS remains the leading cause of EOS in term infants. In preterm infants the most common etiologic agents are gram negative rods (*Escherichia coli*, *Klebsiella* species, other *Enterobacteriaceae*) and *Pseudomonas*. Staphylococci and Enterococci more commonly cause LOS. Signs and symptoms of NS are nonspecific. A significant number of patients have meningitis. A definitive diagnosis is based on positive blood culture. Laboratory tests such as White Blood cell Count, C Reactive Protein or Procalcitonin can be helpful in establishing the diagnosis. Treatment should be directed towards maintaining adequate organ perfusion. The choice of antibiotics is influenced by the timing of NS occurrence. EOS should be treated with ampicillin plus gentamicin, or ampicillin plus cefotaxime. In neonates with community-acquired LOS empiric therapy includes cefotaxime or ceftriaxone plus ampicillin. For hospital-acquired LOS, the choice of antimicrobials should be based on the prevailing nosocomial flora. The overall fatality rate in NS ranges from 5 to 10% and survivors remain at high risk (20%) for neurologic sequelae and lifelong impairments.

Key words: Neonate ▪ Sepsis ▪ Meningitis

Introduction

Neonatal sepsis (NS) is an important cause of morbidity and mortality among newborn infants. Although the incidence is low, the potential for serious adverse outcomes, including death, is of such great consequence it makes neonatal sepsis one of the most urgent conditions in pediatrics which demands quick and cautious evaluation and rapid start of treatment.

Classification and risk factors

Neonatal sepsis is an invasive infection in an infant within 30 days of life, manifested by systemic signs of infection and/or isolation of a microorganism from the blood stream. The classification of early-onset sepsis (EOS) and late-onset sepsis (LOS) is made according to the infant`s age at the onset of symptoms. This division is important because of the assumed etiology, pathogenesis and treatment. EOS can manifest as generalized sepsis, pneumonia and/or meningitis, and clinical signs appear in the first days of life, in most cases within the first 24 hours of life. LOS occurs from 8 to 30 days of life in otherwise healthy term neonates in the community, as well as in premature infants in Neonatal Intensive Care Units (NICUs). Regardless the timing of occurrence, all NS episodes can be classified into confirmed or clinically suspected sepsis. Confirmed sepsis are those manifesting at least two clinical and/or laboratory signs with positive blood culture; suspected sepsis are those manifesting at least two clinical and/or laboratory signs suggestive for infection without bacteriological confirmation. In cases of suspected blood contamination, a diagnosis of confirmed sepsis requires two blood cultures, drawn on separate occasions, which are positive for the same bacteria (1). Improvements in neonatal intensive care have decreased the impact of EOS in term infants, and its reported overall incidence is approximately 1 – 2 cases per 1000 live births. Preterm infants, particularly very low birthweight infants (VLBW), are much more prone to EOS, as well as to LOS, than neonates with heavier birthweight, with a reported incidence ranging from 15 to 30 cases per 1000 live VLBW births (2, 3, 4).

Risk factors for NS are prematurity (gestational age <37 weeks, sepsis is more than seven-times more common in preterm neonates compared to term neonates), respiratory distress syndrome (RDS), invasive procedures during hospitalization, premature rupture of membranes (>18 hours before delivery) chorioamnionitis, maternal fever during labor or maternal urinary tract infection during pregnancy, vaginal and/or rectal GBS maternal colonization, male gender and congenital malformations (3, 4, 5, 6, 7).

In EOS, the onset of symptoms is within the first seven days of life (7, 8). In LOS the onset of symptoms is from the eighth day of the life until the first month or later (9, 10). Early-onset infection usually originates from vertically transmitted microorganisms causing amnionitis or during vaginal delivery from bacteria colonizing or infecting the mother`s lower genital tract.

LOS more frequently originates from direct contact with care providers and environmental sources, but it can be also acquired by maternal vertical transmission resulting in neonatal colonization that evolves into later infection (9, 11).

The disruption of the intact skin or mucosa, as well as invasive procedures in intensive care units (ICU) and the use of forceps or electrodes, placed for intrauterine monitoring during delivery, increase the risk for LOS. The most important risk factor, which contributes to the risk and severity of sepsis, is prematurity, among others such as fetal hypoxia, acidosis, hypothermia, inherited metabolic disorders (galactosemia), prolonged NICU-stay, previous antibiotic

treatment, chorioamnionitis and maternal colonization with GBS (12, 13). *Streptococcus agalactiae* (group B streptococcus, GBS) remains the leading cause of EOS in term infants. In preterm infants, gram negative enteric bacteria, *Escherichia coli*, *Klebsiella* species other *Enterobacteriaceae* and *Pseudomonas* species are the most common etiologic agents of neonatal sepsis. Staphylococci and Enterococci more commonly cause LOS. The incidence of early-onset GBS sepsis has declined by 80% with the use of intrapartum antibiotic prophylaxis. Vaginal and rectal cultures of women at term may show GBS colonization rates of up to 30%. At least 35% of their infants also become colonized. The density of infant colonization determines the risk of early-onset invasive disease, which is 40 times higher with heavy colonization (which is according to Whitney et al. defined as isolation of bacteria from urine or sheep blood agar plates). Only 1/100 of colonized infants develop invasive disease due to GBS, and >50% of them develop clinical signs of disease within the first 6 h of life. Other cases of early-onset sepsis are caused by gram negative bacteria, including *Escherichia coli*, *Klebsiella* species, and gram positive organisms (Listeria monocytogenes, Enterococcus faecalis, Streptococcus bovis, Staphylococcus aureus and others). Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis and Neisseria gonorrhoeae are rare, although possible causes (7, 8, 11).

Staphylococci (Staphylococcus aureus, coagulase negative staphylococcus-CoNS) inserted from children`s skin or environment into the bloodstream are usually associated with intravascular devices. Contaminated respiratory equipment could be a source of infection in hospital-acquired outbreaks of Pseudomonas aeruginosa pneumonia or sepsis. Although universal screening and intrapartum antibiotic prophylaxis for GBS have significantly decreased the rate of early-onset disease due to this organism, the rate of late-onset GBS sepsis has remained unchanged, which is consistent with the hypothesis that late-onset disease is usually acquired from the environment (14).

Candida spp and other fungal species are an increasingly important cause of late-onset sepsis, especially among very low birthweight infants in a NICU setting, occurring in 12 to 13% of such neonates. Risk factors for neonatal systemic fungal disease include prolonged (>10 days) use of central intravascular devices, hyperalimentation, antecedent antibiotic use, necrotizing enterocolitis or other abdominal pathology as well as previous surgery (15).

Differential diagnosis

Because the clinical findings are nonspecific, it is often difficult to differentiate neonatal bacterial sepsis from other infectious diseases of newborn age, including disseminated viral infections (herpes simplex virus, enterovirus, cytomegalovirus, influenza viruses, respiratory syncytial virus), spirochetal infections (syphilis) and parasitic infections (toxoplasmosis). Other pathologies that may present with similar non specific symptoms include neonatal hypoxia, hypoglycemia, hypothyroidism, inborn errors of metabolism, cyanotic congenital heart disease and neonatal respiratory distress (5, 6, 12, 16).

Clinical presentation

Since the signs and symptoms of sepsis are subtle and nonspecific, in the presence of of risk factors for sepsis any deviation from a newborn infant`s usual pattern of activity or feeding should be carefully considered, because it may be an early symptom of a systemic bacterial infection. The most common early symptoms include diminished spontaneous activity, less vigorous suckling, apnea, bradycardia (<100 beats per minu-

te), tachycardia (>180 beats per minute) and temperature instability - hypothermia (RT <36 °C) or hyperthermia (RT >38 °C). Fever is present in only 10 to 15% of cases but when sustained (e.g. >1 h), it easily indicates infection. Other symptoms and signs include respiratory distress, neurologic findings, jaundice, vomiting, diarrhea and abdominal distention (17, 18, 19).

Laboratory evaluation

A definitive diagnosis of NS is established by a positive blood culture. The normal White Blood Cell Count (WBC) in neonates varies, but values <5,000/μl or >20,000/μl are considered abnormal. The absolute band count is not sensitive enough to predict sepsis, but a ratio of immature and total polymorphonuclear leukocytes of <0.2 has a high negative predictive value.

The platelet count may fall hours to days before the onset of clinical sepsis, but more often remains elevated until a day or so after the neonate becomes ill. Thrombocytopenia is sometimes accompanied by other findings of disseminated intravascular coagulation (DIC), e.g. increased D-dimers, decreased fibrinogen and prolonged prothrombin time.

Elevated C-reactive protein (CRP) is not essential for diagnosis, but sequential assessment of CRP is useful in guiding the duration of antibiotic therapy. Limited data have lately reported that elevated procalcitonin (PCT) concentration (greater than 0.5 ng/ml) is better than CRP in early detection of a bacterial infection (20, 21, 22, 23). Auriti et al. demonstrated that in VLBW neonates, a serum PCT value >2.4 ng/ml prompts early empirical antibiotic therapy, while in normal-birth-weight infants, a PCT value ≤2.4 ng/ml carries a low risk of missing a NS (24).

PCT is the prohormone of calcitonin and occurs in very low concentrations in the serum of healthy people. Preferentially it is induced in bacterial sepsis, especially in severe sepsis and septic shock. PCT can therefore be used to discriminate systemic inflammation due to bacterial pathogens from other causes, and can also be used to monitor the progress and prognosis of patients with sepsis. PCT levels are higher in non-survivors and decline with a good response to antibiotic therapy. In neonates, PCT increases physiologically in the first 72 hours of life. As a consequence PCT may be a more reliable marker for EOS within the first 12 hours of life than CRP (24, 25), setting the cut off value over 2.4 ng/ml. This choice limits the sensitivity but increases the specificity of this test in neonates in the first days of life.

A lumbar puncture (LP) should be considered in all neonates as soon as they are able to tolerate the procedure, because clinical signs suggesting meningitis may be lacking in young infants. Acute bacterial meningitis (ABM) occurs in as many as 15% of neonates with bacteremia and is more common in the first month than at any other time of life. Among infants with invasive GBS disease, 5 to 10% with early-onset and approximately 25% of those with late-onset infections have meningitis. The clinical presentation of neonatal meningitis is indistinguishable from that of uncomplicated neonatal sepsis. Cerebrospinal fluid (CSF) examination typically reveals pleocytosis with neutrophilic predominance, elevated protein and low glucose level.

A urine culture obtained by catheter or bladder tap should be included in sepsis evaluation for infants >6 days of age, because in younger infants a positive urine culture is a reflection of high-grade bacteriemia rather than an isolated urinary tract infection. Other cultures should be taken from possible sources of infection (umbilicus, skin defects) before commencement of treatment. A chest X-ray should be obtained in all infants with suspected NS, particularly in those with respiratory distress (26, 27, 28).

Treatment

General supportive measures, including respiratory and hemodynamic management should be combined with antibiotic treatment in the management of neonatal sepsis. Since sepsis may manifest with nonspecific clinical signs and its effects may be devastating, early initiation of empiric antibiotic therapy is recommended, based on the infant`s age, likely pathogens, the susceptibility of organisms to antibiotics in a particular nursery and the presence of an apparent source of infection. Drugs are later adjusted according to the sensitivities and site of infection. If bacterial cultures show no growth by 48 – 72 h and the neonate appears well, antibiotic therapy could be stopped (Fig. 1) (5, 6, 12, 29).

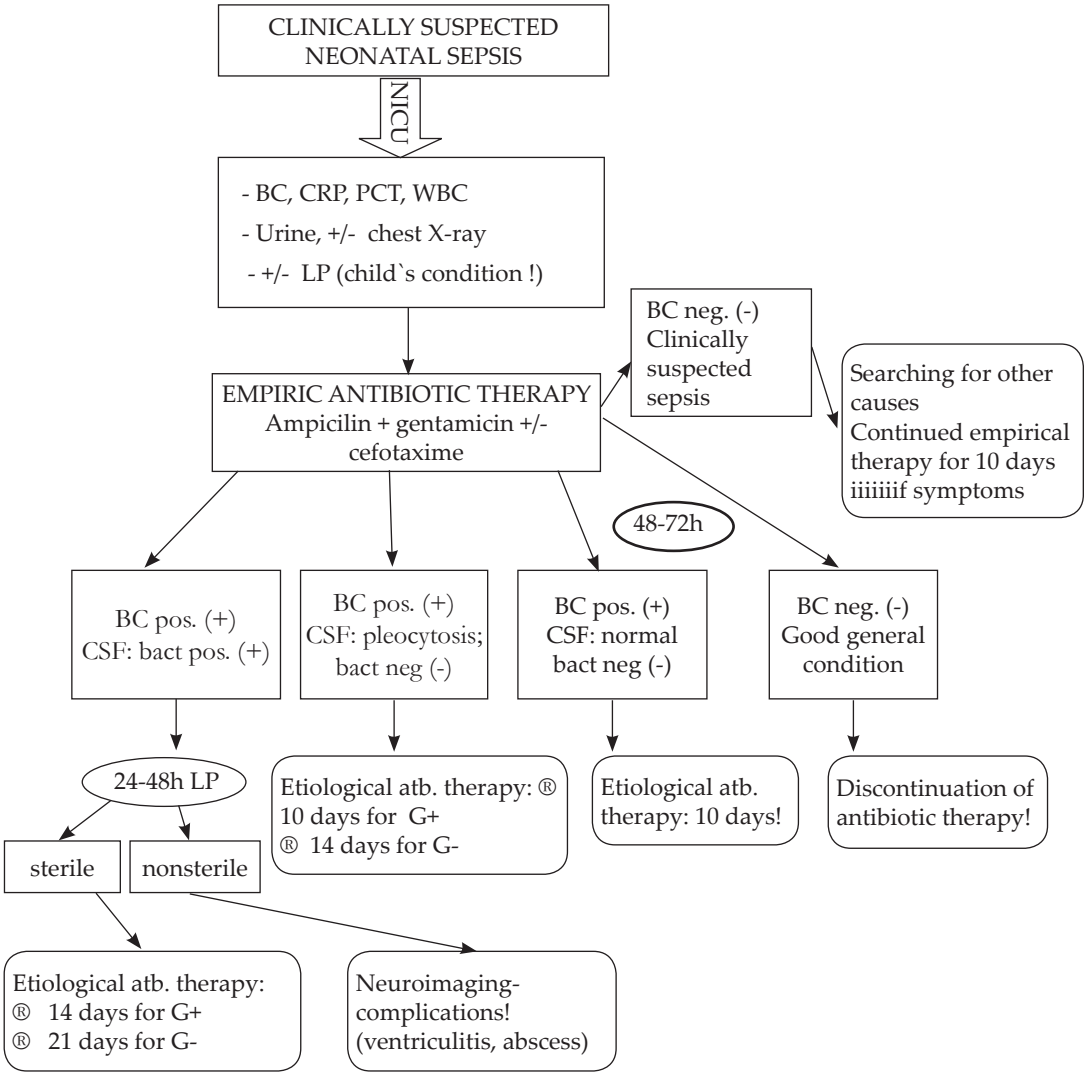

Fig. 1 *Algorithm of procedures in neonates with clinically suspected sepsis.*

The empirical antibiotic regimen for suspected early-onset sepsis consists of ampicillin or penicillin G and an aminoglycoside, usually gentamicin. Cefotaxime may be added or substituted for the aminoglycoside if meningitis is suspected. If a foul-smelling amniotic fluid is present at birth, therapy for anaerobes (e.g. clindamycin, metronidazole) should be added.

Previously well infants admitted with presumed late-onset community-acquired sepsis should also receive therapy with ampicillin plus gentamycin or ampicillin plus cefotaxime. If gram-negative meningitis is suspected, ampicillin, cefotaxime +/- aminoglycoside may be used. In late-onset hospital-acquired sepsis, the initial therapy should include vancomycin (active against methicillin-resistant Staphylococcus aureus) plus an aminoglycoside. If *Pseudomonas aeruginosa* is prevalent in the nursery, ceftazidime may be used instead of an aminoglycoside. Because *Candida* may take 2 to 3 days to grow from blood culture, initiation of amphotericin B therapy and removal of the infected catheter prior to positive blood or CSF cultures in all newborns with suspected candidaemia may be life saving. If the infection is thought to arise from organisms found in the gastrointestinal tract (e.g. anaerobic bacteria), clindamycin or another suitable agent (e.g. metronidazole) should be added.

Specific antimicrobial therapy is given as soon as a pathogen is isolated and its pattern of antimicrobial susceptibility is seen (26, 29, 30, 31, 32, 33).

When GBS is identified as the sole causative organism, the antimicrobial therapy may be changed to penicillin G alone. *Escherichia coli* sepsis could be treated with ampicillin monotherapy, and for patients with ampicillin-resistant *Escherichia coli*, the choice of definitive therapy includes gentamicin or cefotaxime for a 10 to 14-day course. Meropenem is only recommended for the treatment of systemic infections caused by extended-spectrum beta-lactamase producing organisms. For other gram-negative extrameningeal infections, ampicillin or cefotaxime are used, and Listeria monocytogenes sepsis is treated with an ampicillin and gentamicin combination because of the ineffectiveness of cephalosporin (34, 35). Once sterility of the CSF is achieved, the combination is continued for 7 to 14 days. Cefotaxime alone is used to complete a minimum of 21 days or 14 days of therapy after CSF sterility is documented.

Lumbar punctures should be repeated routinely at 24 to 48 hours after the initiation of antimicrobial therapy to document CSF sterilization, which is a criterion for discontinuing combination therapy for some pathogens (e.g. GBS, Listeria). The persistence of viable organisms for more than 48 hours after initiation of antimicrobial therapy is an indication for diagnostic neuroimaging, because it may indicate purulent focus (ventriculitis, abscess). New guidelines suggest obtaining a neuroimaging study 48 to 72 hours before the anticipated end of therapy (31, 32, 36, 39).

In neonates with culture proven sepsis, the duration of therapy is generally 10 days. A 14-day course is sufficient for neonates with uncomplicated GBS and other gram-positive meningitides. A 21-day course is the minimum for neonates with meningitis resulting from *Escherichia coli* and other gram-negative pathogens.

In most cases, symptomatic infants with proven sepsis improve clinically within 24 to 48 hours after the initiation of antimicrobial treatment. A repeated, sterile blood culture after 24 to 48 hours of therapy is obtained to determine the response. Also, serum CRP begins to decrease after 48 to 72 hours in responsive infants.

In the unusual circumstance that the cultures are negative, and an infant`s clinical condition nevertheless gives concern regar-

ding a systemic infection, antibiotic therapy can be extended until a definite diagnosis is established to explain the clinical findings or to complete a 10-day course of antibiotics. For neonates with CSF pleocytosis and bacteremia, but a negative CSF culture, a 10-day treatment for gram-positive bacteremia and a 14-day treatment for gram-negative bacteremia are recommended (4, 5, 6, 2, 29, 30, 34).

Immunotherapy used as an adjuvant for the prevention and treatment of neonatal sepsis holds promise. However, for most of these therapies tested to date, clinical trials have failed to demonstrate a significant effect on neonatal outcomes. Some systematic reviews on the use of IVIG to treat neonatal systemic infections suggest potential benefit, and targeted antibody therapy warrants further study. Probiotic therapy and nutritional additives warrant product standardization and future rigorous study for regulatory approval as a drug. Other therapeutic options, such as colony stimulating factors and lactoferrin, may benefit patients meeting specific criteria, but require further testing in young infants with clear benefit prior to widespread use (40, 41, 42).

Prevention, outcome and evaluation

To prevent neonatal sepsis comprehensively, a multi-interventional program needs to be developed that includes effective maternal vaccination, a reduction in preterm deliveries and limited exposure of term infants to potential pathogens. The primary intervention to prevent neonatal sepsis is the use of intrapartum antibiotic prophylaxis in mothers with documented GBS colonization, a previous birth of an infant with GBS disease or GBS bacteriuria during current pregnancy.

The overall fatality rate in children with NS is between 5 and 10% (with meningitis around 10%). However, mortality is lower in term infants with GBS sepsis, ranging from 2 to 3% for early-onset and 1 to 2% for late-onset disease. Clinical features associated with mortality include birth weight less than 2500 g, absolute neutrophil count less than 1500/ml, hypotension, apnea and pleural effusion. The mortality rate is higher in neonates with early-onset *Escherichia coli* sepsis (around 4%).

Although advances in infant intensive care have helped in reducing NS mortality, survivors remain at high risk (around 20%) for neurologic sequele and lifelong impairments. Long-term neurologic sequelae occur in as many as 30% of survivors of GBS meningitis and this number rises to 55% in children with gram-negative meningitis. Neurologic impairments include developmental delay, seizure disorders, cerebral palsy, hearing and sight loss, dystonia, hydrocephalus and other. Long-term follow-up for survivors of neonatal sepsis and meningitis includes monitoring of hearing, visual acuity and developmental status (38, 39, 43, 44).

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