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NEONATAL SEPSIS

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ABSTRACT

Neonatal sepsis is associated with severe morbidity and mortality in the neonatal period. Clinical manifestations range from subclinical infection to severe local or systemic infection. Neonatal sepsis is divided into three groups as early-onset neonatal sepsis, late-onset neonatal sepsis and very late-onset neonatal sepsis according to the time of the onset. It was observed that the incidence of early-onset neonatal sepsis decreased with intrapartum antibiotic treatment. However, the incidence of late-onset neonatal sepsis has increased with the increase in the survival rate of preterm and very low weight babies. The source of the causative pathogen may be acquisition from the intrauterine origin but may also acquisition from maternal flora, hospital or community. Prematurity, low birth weight, chorioamnionitis, premature prolonged rupture of membranes, resuscitation, low APGAR score, inability to breastfeed, prolonged hospital stay and invasive procedures are among the risk factors. This article reviews current information on the definition, classification, epidemiology, risk factors, pathogenesis, clinical symptoms, diagnostic methods and treatment of neonatal sepsis.

Neonatal sepsis defines the systemic condition that arises from the bacterial, viral or fungal origin, associated with hemodynamic changes and clinical findings and causing severe morbidity and mortality. Its incidence varies depending on the definition of the case and the population studied and is between 1 and 5 in 1000 live births. The clinical manifestations range from subclinical infection to severe focal or systemic disease. While the infectious agent may arise from intrauterine or maternal flora, it may also be of the hospital or community origin. It is classified as early-onset, late-onset and very late-onset neonatal sepsis according to the time of onset of the findings. While early-onset neonatal sepsis describes

cases where clinical manifestations occur in the first three days of life (<72 hours), some researchers consider this limit as the first seven days of life. In connection with this, late-onset neonatal sepsis describes cases diagnosed on 4^{th}-30^{th} days of life or cases diagnosed after the first seven days.[1,2] Very late-onset neonatal sepsis, on the other hand, describes sepsis cases diagnosed in infants who are hospitalized in the neonatal intensive care unit from the first 30 days of life until discharge. Epidemiological studies related to neonatal sepsis since the early 1980s have shown a decrease in early-onset neonatal sepsis cases, especially with *Group B Streptococcus (GBS)*, with the improvement of obstetric care and the use of intrapartum antibiotic prophylaxis; while they show an increase in late-onset neonatal sepsis associated with increased survival rates and long hospitalization times of premature babies.[3,4]

Terminology

Suspected sepsis: Regardless of whether there is a clinical symptom or not, the presence of sepsis risk factors in the baby or findings suggesting sepsis in follow-up.[5]

Clinical sepsis: Clinical and laboratory findings are present, but the failure to show the causative microorganism.[5]

Proven sepsis: Clinical and laboratory findings are present, and demonstration of the pathogenic microorganism in cultures taken from the sterile field.[5]

Pathophysiology and Causative Microorganisms

Causative microorganisms of early-onset neonatal sepsis are generally vertically transmitted from the mother. Microorganisms in the mother's birth canal, cervix, vagina, and rectum are known to cause chorioamnionitis by crossing intact or ruptured membranes before or during labor.[6] Nevertheless, severe clinical findings and bacteremia findings starting from birth, especially in babies without rupture in membranes and born by cesarean section, suggest placental transmission.[7] Chorioamnionitis, which is one of the most important risk factors in early-onset neonatal sepsis, is defined as an acute inflammation of fetal membranes and amniotic fluid. It often develops due to the microinvasion of amniotic fluid as a result of prolonged rupture of membranes. Fever, leukocytosis, foul-smelling or intense discharge, abdominal tenderness in the mother and fetal tachycardia are among the clinical findings of chorioamnionitis. However, chorioamnionitis may also present with a pathological laboratory finding without clinical findings.

Diagnostic Methods

Clinical Findings in Neonatal Sepsis

Signs and symptoms are generally non-specific in neonatal sepsis. Therefore, the differential diagnosis is important. While more than one organ or system findings may occur in early-onset neonatal sepsis, signs of infection in late and very late- onset neonatal sepsis may be multisystemic or focal (such as meningitis, pneumonia, omphalitis, osteomyelitis, septic arthritis).[6] Neonatal sepsis can present with groaning, contraction of the accessory muscles of respiration, nasal wing breathing, apnea, cyanosis, tachypnea in the respiratory system; bradycardia/tachycardia, peripheral circulatory disturbance, hypotension, prolonged capillary refill time in the cardiovascular system; nutritional intolerance, difficulty sucking, vomiting, diarrhea, abdominal distention, hepato-splenomegaly, jaundice in the digestive system; sclerema, cutis marmaratus, pustule, abscess, petechiae, purpura in the skin; and lethargy, hypotonicity, sleepiness, weak or high-pitched crying, bulging fontanelle, irritability, convulsion, hypoactivity, bodytemperature regulation problems and difficulty sucking in the central nervous system.

Laboratory Methods

Blood Culture

The gold standard for the diagnosis of neonatal sepsis is the growth of pathogenic microorganisms in body fluids (blood, urine, cerebrospinal fluid, pleural fluid, peritoneal fluid, joint fluid) that are expected to be sterile. Therefore, the amount of the sample and the method of obtaining the sample are important. Minimum amount of blood required for blood culture should be 0.5-1 ml. It is recommended to take two different samples, preferably from two different regions. No growth in culture may be related to insufficient sample, mother's antibiotic use, antibiotic dose applied before sampling, low amount of bacteria in the blood or short term bacteremia.[5]

After the area that the blood culture will be taken is cleaned and prepared with an antibacterial solution, samples are taken from the arterial or venous route. Data on sterilization of intravenous catheter sites indicate that cleaning for 30 seconds or two consecutive cleansings is superior to a single, short (5-10 seconds) disinfection. Simultaneous blood culture using catheter and periphery from patients with a central venous catheter is important in distinguishing catheter-related bloodstream infections.

Cerebrospinal Fluid (CSF) Culture

The use of CSF culture in newborns with suspected sepsis is controversial. Culture-proven bacterial meningitis occurs in about 0.25 per 1000 live births. Meningitis accompanies 20-25% of newborns with sepsis and 13% of early-onset neonatal sepsis. Although there is no consensus on performing lumbar puncture in infants diagnosed with early neonatal sepsis, it should definitely be performed in infants with blood culture positivity and clinically considered meningitisHowever, antibiotherapy should not be delayed to perform a lumbar puncture. On the other hand, although it is rare in asymptomatic term babies, meningitis is still seen as a complication of neonatal sepsis, and there are sources suggesting lumbar puncturein the assessment of all sick newborns.

Urine Culture

In infants diagnosed with early-onset neonatal sepsis, urine culture does not need to be evaluated as part of early-onset neonatal sepsis since the amount of urine is limited and the rate of positivity in the urine culture is low, especially in the first 72 hours of life. Urinary tract infection assessment should be performed with the bladder catheter or suprapubic bladder aspiration since there is a high risk of contamination in samples taken with urine bags.Urine culture in infants diagnosed with late-onset neonatal sepsis should be part of the evaluation of sepsis.

Tracheal Aspirate Culture

Tracheal aspirate culture may help diagnosis in babies who are diagnosed with sepsis and need mechanical ventilation due to respiratory failure; however, the risk of colonization and contamination should be considered when evaluating the result.It can be taken as a sample in patients with ventilator-associated pneumonia or in cases whose amount and characteristics of secretion varies, but it should be known that its diagnostic value is low. It is not recommended to take tracheal aspirate cultures in prolonged intubation due to rapid colonization following intubation.

Superficial Swab Cultures

Cultures obtained from superficial regions, such as the axilla, umbilical cord, outerear canal, nasopharynx and orogastric tubes, show poor correlation with pathogens isolated from sterile areas. Routine collection of superficial swab cultures is not recommended in neonatal sepsis, as it has a low predictive value and can lead to erroneous assumptions in determining the factor.

Complete Blood Count Components and Peripheral Smear

Many studies have been conducted on the diagnosis of neonatal sepsis, such as complete blood count, white blood cell count (WBC), absolute neutrophil count and the ratio of immature neutrophil count to total neutrophil count (I/T). The WBC upper limit is set at 30.000-40.000/mm^3 in many sepsis screening protocols. However, it is noteworthy that leukocytosis was not detected in one-third of cases diagnosed with sepsis.[6 7 8] Although the normal value of WBC has a very wide range, it can be affected by the time and place of collection of the sample, the gestational week of the baby, and factors other than sepsis.[6, 7 8 9] Among the factors other than sepsis that change the value of WBC are conditions, such as preeclampsia, intraventricular hemorrhage, perinatal asphyxia, meconium aspiration, pneumothorax, convulsions and prolonged crying.

The sensitivity of the complete blood count samples taken immediately after birth was found to be low in the evaluation of sepsis. Due to its weak positive and negative predictive value, the benefit of the use of complete blood count as a biomarker in neonatal sepsis has not been proven. However, studies show that serial normal complete blood count measurements can be reliable in excluding sepsis.

Another parameter used in sepsis assessment among complete blood count is neutrophil count. The presence of neutropenia is more valuable than neutrophilia, especially in the first postnatal 48 hours in the diagnosis of sepsisIt should be noted that as the gestational age decreases, the lower limit of absolute neutrophil count decreases. In addition, hypertension, maternal fever, asphyxia, meconium aspiration syndrome, mode of delivery, periventricular hemorrhage, reticulocytosis, hemolytic disease and pneumothorax are known to affect the neutrophil count.[7]

In the evaluation of peripheral smear, vacuolization, Döhle bodies and toxic granulation are guiding in the diagnosis of bacterial sepsis The I/T ratio drops from 0.16 at birth to 0.12 at 60 hours. I/T ratio of ≥0.2 is considered significant in the diagnosis of sepsis. However, I/T ratio may cause erroneous interpretation in cases,such as perinatal asphyxia, maternal hypertension and long-term oxytocin induction. It should also be kept in mind that the technique of peripheral smear, theknowledge and experience of the investigator can affect the results.

Thrombocytopenia is a non-specific late finding of neonatal sepsis. It was found that the platelet count below 100000/mm^3 for the first 10 days of the postnatal period and below

150000/mm^3 in later periods are associated with sepsis In 50% ofthe cases with the bacterial infection, platelet count was found to be below 100.000/mm^3 Accompanying bacterial infections more frequently, thrombocytopenia is also seen in viral infections.

C-Reactive Protein (CRP)

CRP, which is a pentameric structure, containing 187 amino acids and synthesized from hepatocytes, and an acute-phase protein, is one of the most easily available and most frequently used laboratory tests in the diagnosis of neonatal sepsisIts synthesis is stimulated by cytokines, primarily interleukin-6 (IL-6), IL-1 and tumor necrosis factor-α (TNF-α). Its half-life is between 24-48 hours. The normal lower limit is considered as 1 mg/dL in the neonatal periodIt takes 10-12 hours for it to reach the measurable level in the serum, so its reliability is low in the early diagnosis of neonatal sepsis. Serial CRP measurements have been shown to increase sensitivity in the diagnosis of sepsis 24 to 48 hours after the onset of symptoms Serial CRP measurements are also used to evaluate the antibiotic response. Although CRP serum level rises mainly with infections, it may also rise due to non-infectious causes, such as premature rupture of the membranes, maternal fever, fetal distress, difficult birth, and perinatal asphyxia. This causes low specificity of CRP for early neonatal sepsis.

Treatment

Antimicrobial treatment of neonatal infections is divided into two as the treatment of suspected (empirical) or known (definitive) pathogens. Whether there is early orlate-onset of symptoms, and the infection is nosocomial or community-acquired, affects antimicrobial selection. Although it is important to take appropriate culture samples before starting antibiotherapy, this should not delay starting treatment.

Empirical Treatment

Empirical treatment of early-onset bacterial infections should include ampicillin and an aminoglycoside antibiotic (usually gentamicin). Renal function tests should be evaluated at the beginning of treatment with gentamicin, and serum gentamicin level should be checked in infants whose antibiotherapy will be completed. If renal function tests are normal in babies whose treatment is completed after 48 hours, gentamicin level examination is not necessary. The use of third and fourth generation cephalosporins should only be added to the treatment in case of suspected gram-negative meningitis. The use of third-generation cephalosporins and vancomycin has been associated with an increase in vancomycin-resistant enterococci and extended-spectrum β-lactamase (ESBL)-producing gram-negative bacteria (GNB).[10]

Empirical use of third-generation cephalosporins is not recommended, as it causes an increased risk of invasive candidiasis in long-term administration as well as resistance development.[11] Ampicillin and third- generation cephalosporin regimen have been shown to be no more effective than the combination of ampicillin and gentamicin.[12] Ampicillin + gentamicin is synergistic in the treatment of infections that arise from GBS and *L. monocytogenes*, but cephalosporins are not effective against *L. monocytogenes*.

Empirical treatment of late-onset neonatal sepsis usually includes vancomycin and an aminoglycoside antibiotic group, effective for *coagulase-negative Staphylococci, S. aureus* and gram-negative organisms. However, as in early-onsetsepsis, if gram-negative meningitis is suspected, the addition of third-generation cephalosporins should be considered.[11] Carbapenem group antibiotic use can be an option considering local resistance levels or if the patient has previously used a third-generation cephalosporin antibiotic.[13] The use of piperacillin + tazobactamand ampicillin + sulbactam is gradually increasing in the treatment of infections that occur during neonatal intensive care unit hospitalization; however, penetrationof tazobactam into the central nervous system is unreliable and it should not be used to treat meningitis. However, β-lactamase inhibitor sulbactam is known to reach high concentrations in CSF when combined with ampicillin.[14] Rapid and aggressive treatment should be initiated when fungal infections, such as candidiasis, aspergillosis and zygomycosis, are suspected. Empirical antifungal therapy with amphotericin B deoxycholate can be considered in high-risk babies with risk factors for invasive candidiasis.

Treatment should be continued for 7-10 days in the diagnosis of clinical sepsis. The clinical condition of the baby, laboratory examinations and response to the treatment are monitored. The improvement of clinical findings in the first 24-48 hours from the start of treatment, the normalization of CRP level, I/T ratio and white blood cell count in 48-72 hours indicates an appropriate response is received.[5] It is often difficult to determine an appropriate antibiotic treatment period for suspected sepsis when cultures are negative. Standard practice in babies who are fine and have no clinical or hematological evidence for infection is to stop antibiotherapy if there is no culture growth after 48 hours.[11]

Pathogen-Oriented Treatment

Once the pathogens have been identified, treatment should be reorganized according to the type and sensitivity. When looking at the treatment regimens, in babies with bacteremia and sepsis that arise from GBS, gentamicin is often used in combination with ampicillin or

penicillin, but there are insufficient data to suggestthat the aminoglycoside addition improves the result. However, it is common practice to use a combination of these two drugs in the first few days of treatment, and then continue treatment with just ampicillin or penicillin. Although ampicillin alone is sufficient in the treatment of L. monocytogenesis, aminoglycosides show synergistic effects. Enterococci should be treated with an antibiotic containing penicillin, and aminoglycoside can be added to the treatment if the synergistic effect is documented. Aminoglycoside therapy may be discontinued when cultures result as sterile. Ampicillin-resistant enterococcal infections can be treated with vancomycin without the addition of aminoglycosides. In *S. aureus* infections, vancomycin is used for treatment until the susceptibility profile is concluded, while it is continued in patients with MRSA. If MSSA is detected, cefazolin can be used as an alternative treatment in conditions other than CNS infections and endocarditis. *Coagulase-negative staphylococcal* infections require treatment with vancomycin. Ampicillin (if sensitive) or an aminoglycoside is sufficient for the treatment of gram-negative enteric bacterial infections. However, if meningitis is suspected, third-generation or fourth-generation cephalosporin (for example, cefotaxime, ceftazidime, or cefepime if Pseudomonas spp is the causative agent) orcarbapenem should be used. Carbepenem is the best option in the treatment of Enterobacteriaceae strains that produce extended-spectrum beta-lactamase (ESBL),while cefepime may also be considered. Infections that arise from *Enterobacteriacaea* strains that produce carbapenemase are treated with colistin in addition to carbapenem, or high-dose tigecycline, or a regimen containing aminoglycoside. It is appropriate to use clindamycin, ampicillin + sulbactam or metronidazole in the treatment of anaerobic infections; if CNS involvement is present, metronidazole is preferred. When fungal infections are evaluated, Amphotericin B deoxycholate is the first choice for the treatment of invasive candidiasis.[15] Fluconazole can be used as an alternative therapy in thetreatment of patients with sensitive fungal infections and patients without prophylaxis given.[16] Liposomal amphotericin or echinocandin (caspofungin or micafungin) can be used in the treatment of hepatic or splenic candidiasis. Antibiotics and their frequently used doses in the neonatal period are summarizedin.[17,18]

Antibiotic doses

AMIKACINIM, IV**Gestational age <30 weeks:**PNA ≤14 days: 15 mg/kg/dose every 48 hoursPNA ≥15 days: 15 mg/kg/dose every 24 hours **Gestational age between 30-34 weeks:** PNA ≤60 days: 15 mg/kg/dose every 24 hours **Gestational age ≥35 weeks:**PNA ≤7 days: 15 mg/kg/dose every 24 hoursPNA ≥8 days: 17,5 mg/kg/dose every 24 hoursAMPICILLINIM,

IV**Gestational age ≤34 weeks:**PNA ≤7 days: 50 mg/kg/dose every12 hoursPNA 8-28 days: 75 mg/kg/dose every 12 hours**Gestational age >34 weeks:** PNA ≤28 days: 50 mg/kg/dose every 8 hours**Meningitis:**PNA ≤7 days (IV): 200- 300 mg/kg/days every 8 hoursPNA >7 days (IV): 300 mg/kg/days every 6 hoursCEFOTAXIMEIM, IV**Gestational age <32 weeks:**PNA <14 days: 50 mg/kg/dose every 12 hoursPNA 14-28 days: 50 mg/kg/dose every 8 hours **Gestational age ≥32 weeks:**PNA ≤7 days: 50 mg/kg/dose every 12 hoursPNA 8-28 days: 50 mg/kg/dose every 8 hoursMEROPENEMIV**Birth weight ≤ 2 kg**PNA ≤14 days: 20 mg/kg/dose every 12 hoursPNA 15-28 days: 20 mg/kg/doz every 8 hoursPNA 29-60 days: 30mg/kg/dose every 8 hours**Birth weight > 2 kg**PNA ≤14 days: 20 mg/kg/dose every 8 hoursPNA 15-60 days: 30 mg/kg/dose every 8 hoursPIPERACILLIN – TAZOBACTAMIV **Birth weight ≤ 2 kg**PNA ≤7 days: 100 mg/kg/dose every 8 hoursPNA 8- 28 days: PMA ≤ 30 GH 100 mg/kg/dose every 8 hoursPMA >30 GH 80 mg/kg/ dose every 6 hoursPNA 29-60 days: 80mg / kg/dose every 6 hours**Birth weight > 2 kg**PNA ≤ 60 days: 80 mg / kg/dose every 6 hours VANCOMYCINIVLoading dose: 20mg/kg/dose **Gestational age <28 weeks:** Serum Creatinine<0.5 mg/dL 15 mg/kg/dose every 12 hoursSerum Creatinine 0.5-0.7 mg/dL 20 mg/kg/dose every 24 hoursSerum Creatinine 0.8- 1 mg/dL 15 mg/kg/dose every 24 hoursSerum Creatinine 1.1- 1.4 mg/dL 10 mg/kg/dose every 24 hoursSerum Creatinine>1.4 mg/dL 15 mg/kg/dose every 48 hours **Gestational age >28 weeks:** Serum Creatinine<0.7 mg/dL 15 mg/kg/dose every 12 hoursSerum Creatinine 0.7-0.9 mg/dL 20 mg/kg/dose every 24 hoursSerum Creatinine 1-1.2 mg/dL 15 mg/kg/dose every 24 hours Serum Creatinine 1.3-1.6 mg/dL 10 mg/kg/dose every 24 hours Serum Creatinine>1.6 mg/dL 15 mg/kg/dose every 48 hoursTEICOPLANINIVLoading dose: 16 mg/kg/doseMaintenance dose: 8 mg/kg/dose every 24 hours.

The duration of treatment is determined by the site of infection and the clinical response of the patient. Bacteremia without infection focus is usually treated for 7- 10 days. Although there are few randomized controlled studies on antibiotherapy periods in premature babies with very low birth weight, duration of antibiotherapy can be extended until day 10-14 in infants younger than 32nd gestational weeks.[11] Gram-negative bacteremia treatment is also extended until 10th-14th days. The duration of treatment in uncomplicated GBS meningitis is usually until day 10-14, while the duration is extended in focal complications.[11] In gram-negative bacterial meningitis, treatment is continued for 21 days or for another two weeks after the first negative CSF culture.[20]

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