Neonatal Sepsis

Ilkay Ozmeral Odabasi, Ali Bulbul
Department of Neonatology, Sariyer Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

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 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 be 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.

Keywords: Early-onset; late onset; neonatal; sepsis; diagnosis; treatment.

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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 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 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.\[6\]

**Proven sepsis:** Clinical and laboratory findings are present, and demonstration of the pathogenic microorganism in cultures taken from the sterile field.\[3\]

Epidemiology Research shows that an average of 2.6 million newborns die every year and three-quarters of these deaths occur in the first week of life.\[6, 7\] In a study conducted between 2000-2013, data of one hundred and ninety-four countries were evaluated in which the causes of death were investigated in the neonatal period, and the mortality rate due to sepsis was found to be 15%. In this study, it was determined that 2.8 million babies died in the neonatal period and 430,000 of these babies died due to sepsis and severe infections.\[8\] Neonatal sepsis ranks third among the causes of neonatal death following prematurity and inapartum-related complications.\[9\] In the late neonatal period (7-27 days), the most common cause of death was sepsis, with a rate of 37.2%.\[8\] Neonatal death and sepsis frequency differ between populations. In their reports that Lawn et al. presented epidemiological data, 99% of newborn deaths occurred in low- and middle-income countries and 1% in high-income countries.\[7\]

The incidence of early-onset neonatal sepsis ranges from 1 to 5 per 1000 live births. This incidence has been shown to decrease with intrapartum antibiotic therapy.\[10, 11\] However, the incidence of late-onset neonatal sepsis increased with the increase in the survival rate of preterm and very low birth weight infants.\[12\] The incidence of late-onset neonatal sepsis is reported to vary between 0.61% and 14.2% in hospitalized newborn babies.\[12\] When classified by birth weight, the rate of early-onset neonatal sepsis in 1000 live births was reported to be 0.57 in babies over 2500 grams, and 10.96 in babies with a birth weight of between 401-1500 grams.\[12\] The incidence of late-onset neonatal sepsis was reported as 51.2% in infants between 501-750 grams of birth weight, 15-25% in infants below 1500 grams and 1.6% in infants above 2500 grams.\[2\]

### Maternal Risk Factors

Chorioamnionitis, premature rupture of membranes (>18 hours), intrapartum maternal fever (>38 ºC), delivery earlier than 37 weeks of gestation, maternal *group B streptococcal (GBS)* colonization and other conditions that increase the risk of GBS infection in the newborn (the mother’s positive vaginal-rectal GBS screening cultures in the late stages of pregnancy, having a history of GBS-infected baby in a previous pregnancy, detection of GBS positive bacteriuria during pregnancy, positive intrapartum nucleic acid amplification tests for GBS) increases the risk of early neonatal sepsis.\[13, 16\] In the presence of early membrane rupture and chorioamnionitis, the incidence of early-onset sepsis is 1-3%, i.e., the risk of early neonatal sepsis is increased 10-fold.\[17\] While early-onset sepsis rate caused by *Group B streptococci* was 2 in 1000 live births and mortality was 50% in the 1960s, today, antibiotic prophylaxis and early treatment reduced morbidity and mortality rates.\[18\] However, GBS screening and intrapartum antibiotic prophylaxis do not eliminate but decrease the risk of GBS infection. The effectiveness of prophylaxis was determined between 86-89%.\[19\] In a study where approximately 400,000 babies were evaluated in the United States and the rate of early-onset sepsis was found to be 0.98 per 1000 live births, mothers of 57% of babies diagnosed with early neonatal sepsis were reported to have GBS prophylaxis.\[12\] CDC (Centers for Disease Control and Prevention) recommends GBS screening during 35-37, gestational weeks and intrapartum prophylaxis in cases with the indication in preventing early neonatal sepsis.\[19\]

The incidence of GBS carriers in a study that evaluated 500 women in Turkey in 2016 was discovered as 13.6%.\[20\] In another study where a total of 150 pregnant women were screened, the prevalence of GBS carriers in pregnant women and frequency of colonization in newborns were evaluated, approximately 32% of the pregnant women and 17.3% of the newborns were found to be colonized with GBS.\[21\] In another study conducted in our country, 500 pregnant women and newborn babies of these pregnant women were evaluated, and maternal and infant coloniza-
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. 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. 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. Pathogens that cause sepsis vary according to geographical differences and countries. The most common pathogens in early-onset neonatal sepsis are GBS and Escherichia coli (E. coli) when coagulase-negative staphylococci (CONS) are excluded. Although some centers consider CONS growth as pathogens for disease, some centers consider this growth as contamination. In studies, cases with the CONS positivity in a single culture were excluded from the study, while cases considered clinically significant in different studies were accepted as pathogens and included in the study. Stoll et al. defined the cases with CONS growth in blood culture in three groups. Patients with CONS growth in two consecutive blood cultures taken within two days, or with CONS growth in single blood culture and C-reactive protein (CRP) elevation within two days after blood cultures were defined as a definitive infection. Patients with CONS growth at blood culture while receiving treatment with vancomycin, oxacillin or a semisynthetic antistaphylococcal agent for at least five days were defined as suspected infection; cases with blood culture positivity without accompanying CRP elevation or use of antibiotics were defined as contamination. In data from the UK, GBS was detected in 58% of early-onset sepsis cases and E. coli in 18%. These rates were found to be in the United States as 43% and 29%, respectively. Listeria monocytogenes (L. monocytogenes), Group A, C and G streptococci, Streptococcus pneumoniae (S. pneumoniae), Streptococcus viridans (S. viridans), Haemophilus influenzae (H. influenzae), Staphylococcus aureus (S. aureus), Klebsiella and CONS are less common. However, they are among the causative organisms for early-onset neonatal sepsis factors. In emerging countries, however, gram-negative bacteria (Klebsiella, Enterobacter, Acinetobacter, E. coli) are in the foreground. Ureaplasma parvum and Ureaplasma urealyticum are the most common factors isolated from the placenta and amniotic fluid in patients with histologically detected chorioamnionitis; however, colonization of Ureaplasma strains in the respiratory system has been associated with bronchopulmonary dysplasia in preterm infants. In our country, when the different studies are examined, the most common factors are found as K. pneumoniae, S. aureus and CONS. Late-onset neonatal sepsis often shows horizontal transmission from individuals responsible for the care of the baby, from environmental or nosocomial sources. In the case of vertical transmission, early colonization of the baby occurs as an infection in the late period. Metabolic factors, including hypoxia, acidosis, hypothermia, and hereditary metabolic disorders (e.g., galactosemia), are likely to contribute to the risk and severity of neonatal sepsis. These factors are thought to disrupt the host’s immune response. When late-onset neonatal sepsis is analyzed, CONS takes the first place as causative organisms in 53.7% -77.9% of cases in developed countries and 35.5% -47.4% of cases in developing countries. In the United States, S. aureus, Candida spp., E. coli, Klebsiella spp., Enterobacter spp. are listed as the most frequent factors, following CONS. The most frequently detected organisms in Australia are CONS, S. aureus, Klebsiella spp., Pseudomonas spp., Candida spp., E. coli and Enterobacter spp., respectively. In the study by Aksoy et al. from Turkey, K. pneumoniae and S. aureus were found to be the most common factors in late-onset neonatal sepsis. In the study of Türkmen et al., S. epidermidis was the most common agent and Candida was the second. In a study by Özkan et al. in preterm infants, CONS was found to be the most common factor in late-onset neonatal sepsis. In the study of Özdemir et al., S. aureus was the most common cause of late sepsis, followed by K. pneumoniae and S. epidermidis, respectively. CONS was the most frequent factor in the study of Bülbül et al., in which they evaluated the nosocomial infections in the neonatal intensive care unit, whereas MSSA and K. pneumonia were found in the second place.

S. aureus infections are reported to be more frequent, especially in patients with catheters. In a study conducted in the UK, where 117 sepsis episodes with S. aureus growth were evaluated, the central catheter was determined in 50% of the cases. Especially in babies with long-term hospitalization due to prematurity, increased frequency of systemic infections caused by Candida spp. is seen. Although there
is a difference between the institutions, *Candida* spp. is reported to be the third most frequent agent of late-onset neonatal sepsis in babies weighing <1500 gr.\[13\] Herpes Simplex Virus (HSV), which is often presented with late-onset neonatal sepsis is one of the most common factors when viral factors of neonatal sepsis are considered. Its frequency in the United States has been reported to be 1 in 3200 births.\[19\] Despite the progress in diagnosis and treatment, it remains important concerning morbidity and mortality. It has been reported that 85% of babies diagnosed with disseminated HSV disease before antiviral treatment and 50% of those with central nervous system involvement died before one year of age. Another viral factor in late-onset neonatal sepsis is enteroviruses. Enterovirus infections can present with nonspecific lethargy, poor nutrition, fever, restlessness, hypoperfusion, jaundice, meningoencephalitis, myocarditis and hepatitis.\[46\] The frequency of enterovirus in the newborn period is not known exactly.

**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).\[23\] 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 marmoratus, pusule, abscess, petechiae, purpura in the skin; and lethargy, hypotonicity, sleepiness, weak or high-pitched crying, bulging fontanelle, irritability, convolution, hypoactivity, body temperature regulation problems and difficulty sucking in the central nervous system.\[13, 23, 27\]

**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.\[41\] 90% of growth takes place within the first 48 hours.\[42\] While the growth of the microorganism in blood culture is diagnostic in the neonatal period, the failure to produce it does not exclude the diagnosis.\[23, 27\] 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.\[43\] Simultaneous blood culture using catheter and periphery from patients with a central venous catheter is important in distinguishing catheter-related bloodstream infections.\[13\] Results obtained with manual laboratory methods showed that 96% of cultures taken before antibiotic administration was positive at the end of 48th hour and 98% at 72nd hour.\[14\] However, laboratory automation has significantly reduced the time required to detect positive cultures.\[45\] In automated laboratory methods, 94% of cultures taken before antibiotic treatment were positive within 24 hours (except for coagulase-negative Staphylococcus, Corynebacteria or yeast), and 97% were positive within 36 hours.\[46\]

**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.\[47, 48\] Meningitis accompanies 20-25% of newborns with sepsis and 13% of early-onset neonatal sepsis.\[49–51\] 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 meningitis.\[23, 27, 47\] Blood cultures cannot detect causative microorganisms in 15% to 50% of babies with bacterial meningitis.\[52, 53\] Taking CSF culture before or just after the administration of antibiotics may increase the likelihood of bacteriological diagnosis.\[47, 54, 55\] However, antibiotic therapy 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 puncture in the assessment of all sick newborns.\[56\]
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 sepsis. It 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.

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. It is not recommended to take tracheal aspirate cultures in prolonged intubation due to rapid colonization following intubation.

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 sepsis. Its 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 period. It 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 mea-
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.[23, 27, 64]

High Sensitivity-CRP (hs-CRP)

High Sensitivity CRP (hs-CRP) is more sensitive than conventional CRP in the diagnosis of neonatal sepsis. While the normal lower value of conventional CRP is accepted as 1 mg/dL, this value is 1 mg/L for hs-CRP.[82] In studies conducted, infected newborns with high hs-CRP values were reported to have a significant increase in hs-CRP compared to non-infected newborns.[83] In another study, it was reported that there is no risk of infection when the hs-CRP value is detected as <0.5 mg/L, there is low infection risk when the value is between 0.5–1 mg/L, moderate infection risk when between 1–3 mg/L, and there is a high risk of infection at values >3 mg/L.[84] As a result, more studies are needed to evaluate the role of hs-CRP in use as a neonatal sepsis marker.

Procalcitonin

Procalcitonin (PCT), which is the prohormone of calcitonin and used as the acute-phase reactant protein, consists of 116 amino acids. PCT is encoded by the Calc-1 gene and synthesized by macrophage and hepatocytes.[85] The PCT level rises rapidly 2-4 hours after exposure to bacterial endotoxin, reaches a peak in 6-8 hours and remains high for 24 hours.[86] The half-life of PCT is 24-30 hours. Due to its rapid rise from the onset of bacterial sepsis, it is considered a better marker for early diagnosis of neonatal sepsis compared to CRP. In healthy newborns, plasma PCT concentrations increase gradually after birth, reaching peak levels in about 24 hours (in the range of 0.1-20 ng/mL), and then falls to normal values below 0.5 ng/mL in 48-72 hours.[87] Procalcitonin over 2-2.5 ng/ml after postnatal 72 hours should suggest infection.[88]

Prematurity, intracranial hemorrhage, asphyxia, neonatal hypoxemia, resuscitation, chorioamnionitis where neonatal infection does not develop, maternal GBS colonization, prolonged membrane rupture, prenatal antibiotic use, surfactant administration, postpartum antibiotic use and very low birth weight may cause false positives. Thus, increases in the PCT level should be interpreted correctly.[89-91] It was concluded that PCT is a useful biomarker for early diagnosis of newborn sepsis in critically ill patients in meta-analyses.[92]

Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF)

Matrix Assisted Laser Desorption Ionization-Time of Flight, MALDI-TOF) started to take place among the new diagnostic tests based on the identification of microorganisms. MALDI-TOF is a mass spectrometer tool that allows rapid and accurate identification of the species within a wide range of gram-negative and gram positive bacteria, as soon as the organism is present in the culture.[93-95] It, therefore, allows organisms to be diagnosed earlier than blood culture and targeted antibiotic therapy to start earlier.[96] Its routine use is not yet common in the neonatal period.

Molecular Methods

Nucleic acid analysis methods are important in recognizing the morphological, metabolic or cytopathic features of microorganisms with no culture possibility or which grow slowly. Molecular technologies are being studied to enable rapid identification of gram-negative and gram positive bacteria in the diagnosis of sepsis. Amplification of nucleic acids can be done by methods, such as replication of the target nucleic acid (polymerase chain reaction), replication of the nucleic acid probe (ligase chain reaction) or signal duplication (branched-probe DNA determination).[97] Polymerase chain reaction targets conserved regions of the 16s ribosomal RNA gene, which is common to all bacteria and not found in organisms other than bacteria.[98] In the study conducted by Dutta et al.[96] PCR analysis was performed before and after the initiation of antibiotic therapy in clinically suspected sepsis cases; and the sensitivity, specificity, positive and negative predictive values of PCR were found as 96.2%, 96.3%, 87.7% and 98.8%, respectively. It was shown that the patients who had PCR positivity in the sample taken before antibiotic therapy, continued their positivity at the 12th hour after antibiotic therapy, but that there was no PCR positivity at the 24th and 48th hours. This test, which may be useful in early diagnosis, is not recommended for use in patients whose antibiotic treatment is continued for more than 12 hours.[98]

While it is advantageous that a small amount of sample is sufficient and the test can be run in body fluids, such as surgical tissues and effusions, the disadvantages are the weakness of clinical correlation due to the inability to distinguish between active infection and past infection and high probability of detecting contamination.[96] As a result, comprehensive studies evaluating a larger number of cases for routine clinical use in newborns with suspected sepsis are required.
Serum Amyloid A (SAA)

Serum Amyloid A (SAA) is an apolipoprotein synthesized by the liver, of whom the synthesis is controlled by IL-1, IL-6 and TNF-α. It is secreted in response to injury or infection. It is known to play a role in inflammation and stimulate the release of IL-8 from neutrophils. In a study comparing SAA, CRP, IL-6 and WBC in preterm infants with sepsis, it was reported that mortality and SAA levels in newborn babies were inversely proportional. In another study, SAA levels in septic babies were shown to be significantly higher at 0, 24 and 48 hours, compared to SAA levels in non-septic babies. However, compared to CRP, SAA has been reported to show a sharper and faster rise and also to return to normal faster. As a result, SAA can be used as a useful marker in early detection of neonatal sepsis if rapid and reliable kits are used.

Lipopolysaccharide Binding Protein (LBP):

The lipopolysaccharide-binding protein interacts with endotoxins produced by Gram-negative bacteria species and transfers them to CD14 immune cells. LBP is produced by hepatocytes, epithelium, muscle cells, and its level rises approximately 6-8 hours after the onset of acute infection. Another advantage of LBP, which has high sensitivity and negative predictive value in the diagnosis of early-onset neonatal sepsis, is that it is less affected by physiological changes and obstetric events that occur within the first two postnatal days.

Cytokines and Chemokines

Cytokine levels change rapidly during the neonatal sepsis course. Cytokines, such as IL-6, IL-1β, IL2R, IL-8 and TNF-α primarily increase in response to bacterial infections. This increase occurs before clinical symptoms or positive standardized diagnostic tests. Also, the levels of cytokines in the newborn baby in the first few hours of life indicate the risk of infection. Interleukin- 6 (IL-6)

Interleukin-6 stimulates the production of acute-phase reactants, such as CRP from the liver by releasing from B and T lymphocytes, monocytes, endothelial cells and fibroblasts in the acute-phase of infections. The advantage of using IL-6 as a marker of sepsis is that there is a rapid increase in concentration just before the CRP level rises and immediately after the onset of bacteremia. However, its half-life is being very short and its level is being normalized within 24 hours after the start of antimicrobials appear to be disadvantages. Thus, IL-6 has a narrow window of opportunity. IL-6 levels obtained from umbilical cord were found to be high in early neonatal sepsis cases. Studies have shown that IL-6 has better sensitivity and negative predictive value compared to CRP when used as an early phase biomarker. Also, its combination with other sepsis markers, such as TNF-α and CRP, has been shown to have higher sensitivity and negative predictive value in the diagnosis of early-onset neonatal sepsis.

IL-8

IL-8 is a pro-inflammatory cytokine produced by monocyte, macrophage, fibroblast and endothelial cells. It is known to be responsible for the activation and chemotaxis of neutrophils. IL-8 guides both in the diagnosis and recognition of the severity of neonatal sepsis. Its sensitivity was detected as 80-91% and specificity as 76-100% in determining neonatal sepsis. The combination of IL-8 with CRP as a biomarker has been shown to have higher sensitivity and specificity in newborns considered suspicious sepsis and help reducing antibiotic use. IL-8 level increases rapidly within 2-4 hours from the start of an infection and then decreases within four hours. This makes IL-8 similar to IL-6, to be used as only an early marker of infection. As a result, there are studies indicating that IL-8 may play a role in the diagnosis of neonatal sepsis, but more studies are needed to provide strong evidence to support its use.

Tumor Necrosis Factor Alpha (TNF- α)

It is a proinflammatory cytokine produced by activated phagocytes during systemic infection and inflammation. It has pharmacokinetic properties similar to IL-6. The increase in TNF-α level is independent of the pregnancy week of the newborn and postnatal age. In studies comparing septic newborns and healthy newborns, TNF-α levels have been shown to be significantly higher in septic cases. When combined with IL-6, it shows 60% sensitivity and 100% specificity in the diagnosis of sepsis. In a meta-analysis study, TNF-α was found to show a moderate accuracy both in the diagnosis of early-onset neonatal sepsis (sensitivity 66%, specificity 76%) and in the diagnosis of late-onset neonatal sepsis (sensitivity 68%, specificity 89%).

Other Chemokines

Chemokines that can be used with other inflammatory markers in the diagnosis of neonatal sepsis include monokines, RANKES, MCP-1 and IP-10. While the use of chemokine as a biomarker provides an advantage since it rises very early compared to CRP after the onset of infection; causes, such as decreased levels within approximately 24 hours after the start of treatment, need of special tools for
the study of the test and difficulty to reach the test limit its use. However, more studies are needed for their widespread and safe use.

**Cell Surface Markers**

Cell surface markers can be determined by flow cytometry. Studies are conducted on the use of cell surface antigens as biomarkers, such as CD11b (100% specificity, 100% sensitivity), CD64 (83% specificity and 82% sensitivity), sCD163. CD64 is a high-affinity Fc receptor for immunoglobulin G, of which its expression is increased in response to infection. Its level increases ten-fold in activated neutrophils 4-6 hours after the onset of bacterial infection. Its level decreases to normal within a few days after the infection is suppressed. The combination of CD64 with PCT, CRP and WBC has been shown to increase sensitivity in the early diagnosis of sepsis.

CD11b (Mac-1, CR3) is the α subunit of the b2-integrin adhesion molecule and is expressed at low concentration in inactivated neutrophils. Its level rises five minutes after the onset of bacterial infection and it is thought to be a good biomarker for early detection of neonatal sepsis. In the study of Weirich et al., CD11b was detected in all babies with proven sepsis, but not in newborns without sepsis. In the diagnosis of neonatal infection, negative predictive value, positive predictive value, sensitivity and specificity of CD11b were detected as 100%, 99%, 96% and 100%, respectively. Nupponen et al. showed that CD11b has 100% sensitivity and specificity in the detection of neonatal sepsis in their studies comparing newborns with suspected infections and healthy newborns. Adib et al. showed that the sensitivity and negative predictive value of the combination of CD11b with CRP reached 100% in the diagnosis of neonatal sepsis. Current studies have shown that CD11b has good diagnostic accuracy as a biomarker for neonatal sepsis. However, the insufficiency and high cost of the centers where the examination can be carried out are among the factors limiting their routine use.

Soluble CD163 (sCD 163) reduces the oxidative damage that arises from hemolysis by clearing circulating free hemoglobin with the help of haptoglobin. It binds to gram-negative and gram-positive bacteria, stimulating the synthesis of proinflammatory cytokines, such as TNF-α, IL-1b, IL-6 and IL-10. In a study comparing CRP, IL-6, IL-8, TNF-α and sCD163, it is concluded that sCD163 is the strongest predictive marker for the differentiation of infected and uninfected newborns before antibiotic therapy is started.

**Other Biomarkers**

Other biomarkers that draw attention in the diagnosis and treatment of sepsis are suPAR, angiopoietins, pentraxin 3 (PTX3), STREM-1 and inter alpha inhibitory proteins (IaIp). However, further studies are needed to support their routine use.

**Diagnostic Algorithms**

Early diagnosis of sepsis is difficult due to the absence of specific symptoms and the suboptimal diagnostic value of the laboratory findings. This causes high levels of empirical antimicrobial use. In the literature, sepsis scores were tried to be created with different combinations of inflammatory response parameters, laboratory tests and physical examination findings. Töllner developed the first known newborn sepsis scoring system in 1982 to identify sepsis using clinical and basic laboratory evaluations (Table 1). The Pediatric Committee (PDCO) of the European Medicines

| Table 1. Töllner sepsis scoring system |
|---------------------------------------|
| Score  | 0          | 1          | 2          | 3          |
| Change in skin color                  | Absent     | Moderate   | Evident    |
| Peripheral circulatory disorder       | Absent     | Impaired   | Evident    |
| Hypotonia                            | Absent     | Moderate   | Evident    |
| Bradycardia                          | Absent     | Present    |            |
| Apnea                                 | Absent     | Present    |            |
| Respiratory distress                  | Absent     | Present    |            |
| Hepatomegaly                          | Absent     | >4cm       |            |
| GIS finding                           | Absent     | Present    |            |
| Leukocyte count                       | Normal     | Leukocytosis|           |
| Left shifting                         | Absent     | Moderate   | Leukopenia |
| Thrombocytopenia                      | Absent     | Present    | Evident    |
| Metabolic acidosis                    | Normal     | >7.2       | <7.2       |

If the total score is below 5, it is normal, between 5-10 it is suspected, and above 10 points, it is considered as definite sepsis.
Agency (EMA) proposed EMA sepsis criteria for standardization of the definition of neonatal sepsis in 2010 (Table 2).[137] However, the adequacy and reliability of the use of a single scoring system in the diagnosis of sepsis have not been proven yet.

Today, online early-onset neonatal sepsis calculators are also used to predict the possibility of early-onset neonatal sepsis and to guide decisions regarding initiation of antibiotic therapy (https://neonatalsepsiscalculator.kaiserpermanente.org).

**Treatment**

Antimicrobial treatment of neonatal infections is divided into two as the treatment of suspected (empirical) or known (definitive) pathogens. Whether there is early or late-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 antibiotic therapy, this should not delay starting treatment.

**Table 2. EMA sepsis scoring system**

| Clinical Findings | Laboratory Findings |
|-------------------|---------------------|
| **Body temperature:** | Leukocyte count: |
| >38.5 ºC or <36 ºC and/or temperature irregularities | <4.000/mm³ or >20.000/mm³ |
| **Cardiovascular instability:** | Immature/total neutrophil ratio: |
| Bradycardia or tachycardia and/or rhythm irregularity | ≥0.2 |
| Urine amount <1 ml/kg/hour | |
| Hypotension | |
| Impaired peripheral perfusion | |
| **Skin and subcutaneous lesions:** | Platelet Count: |
| Petechiae | <100.000/mm³ |
| Sclerema | |
| **Respiratory instability:** | CRP >15mg/L (1.5 mg/dL) or procalcitonin ≥2 ng/mL |
| Apnea or Tachypnea or Increased oxygen demand or Increased need for ventilation support | |
| **Gastrointestinal:** | In blood sugar monitoring (at least twice): |
| Nutritional intolerance | Hyperglycemia (>180 mg/dL or 10 mMol/L) or Hypoglycemia (<45 mg/dL or 2.5 mMol/L) |
| Insufficient breastfeeding | |
| Abdominal distention | |
| **Non-specific:** | Metabolic acidosis: |
| Irritability | Base deficit >10 mEq/L or Serum lactate >2 mMol/L |
| Lethargy | |
| Hypotonia | |

Positivity in at least two of the clinical categories and at least two of the laboratory categories is considered as clinical sepsis. It can be used up to postnatal 44 weeks.

**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 antibiotic therapy will be completed. If renal function tests are normal in babies whose treatment is completed after 48 hours, gentamicin level examination is not necessary.[23] The use of third and fourth generation cephalosporins should only be added to the treatment in case of suspected gram-negative meningitis.[13] 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).[138] 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.[139] Ampicillin and third-generation cephalosporin regimen have been shown to be no more ef-
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-onset sepsis, if gram-negative meningitis is suspected, the addition of third-generation cephalosporins should be considered.[139] Carbapenem group antibiotic use can be an option considering local resistance levels or if the patient has previously used a third-generation cephalosporin antibiotic.[141] The use of piperacillin + tazobactam and ampicillin + sulbactam is gradually increasing in the treatment of infections that occur during neonatal intensive care unit hospitalization; however, penetration of 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.[142] 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.[13]

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.[15] 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.[139]

**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 suggest that 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.[24] Although ampicillin alone is sufficient in the treatment of *L. monocytogenes*, 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) or carbapenem should be used. Carbenepen 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 *Enterobacteriaceae* 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.[143] Flucytosine can be used as an alternative therapy in the treatment of patients with sensitive fungal infections and patients without prophylaxis given.[144] 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 summarized in Table 3.[145, 146]

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.[147] 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.[139] In gram-negative bacterial meningitis, treatment is continued for 21 days or for another two weeks after the first negative CSF culture.[148]
| Antibiotic          | Administration Route | Dosing                                                                 |
|--------------------|----------------------|----------------------------------------------------------------------|
| AMIKACIN           | IM, IV               | **Gestational age <30 weeks:**                                        |
|                    |                      | PNA ≤14 days: 15 mg/kg/dose every 48 hours                            |
|                    |                      | PNA ≥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 hours                            |
|                    |                      | PNA ≥8 days: 17.5 mg/kg/dose every 24 hours                           |
| AMPICILLIN         | IM, IV               | **Gestational age ≤34 weeks:**                                        |
|                    |                      | PNA ≤7 days: 50 mg/kg/dose every 12 hours                            |
|                    |                      | PNA 8-28 days: 75 mg/kg/dose every 12 hours                            |
|                    |                      | **Gestational age >34 weeks:**                                        |
|                    |                      | PNA ≤28 days: 75 mg/kg/dose every 8 hours                            |
| CEFOTAXIME         | IM, IV               | **Meningitis:**                                                       |
|                    |                      | PNA ≤7 days (IV): 200-300 mg/kg/days every 8 hours                   |
|                    |                      | PNA >7 days (IV): 300 mg/kg/days every 6 hours                        |
|                    |                      | **Gestational age <32 weeks:**                                        |
|                    |                      | PNA ≤14 days: 50 mg/kg/dose every 12 hours                            |
|                    |                      | PNA 14-28 days: 50 mg/kg/dose every 8 hours                           |
|                    |                      | **Gestational age ≥32 weeks:**                                        |
|                    |                      | PNA ≤7 days: 50 mg/kg/dose every 12 hours                            |
|                    |                      | PNA 8-28 days: 50 mg/kg/dose every 8 hours                            |
| MEROPENEM          | IV                   | **Birth weight ≤ 2 kg**                                              |
|                    |                      | PNA ≤14 days: 20 mg/kg/dose every 12 hours                            |
|                    |                      | PNA 15-28 days: 20 mg/kg/dose every 8 hours                           |
|                    |                      | PNA 29-60 days: 30 mg/kg/dose every 8 hours                           |
|                    |                      | **Birth weight > 2 kg**                                              |
|                    |                      | PNA ≤14 days: 20 mg/kg/dose every 8 hours                            |
|                    |                      | PNA 15-60 days: 30 mg/kg/dose every 8 hours                           |
| PIPERACILLIN - TAZOBACTAM | IV         | **Birth weight ≤ 2 kg**                                              |
|                    |                      | PNA ≤7 days: 100 mg/kg/dose every 8 hours                             |
|                    |                      | PNA 8-28 days: PNA ≤ 30 GH 100 mg/kg/dose every 8 hours              |
|                    |                      | PNA >30 GH 80 mg/kg/dose every 6 hours                               |
|                    |                      | PNA 29-60 days: 80 mg/kg/dose every 6 hours                          |
|                    |                      | **Birth weight > 2 kg**                                              |
|                    |                      | PNA ≤60 days: 80 mg/kg/dose every 6 hours                            |
| VANCOMYCIN         | IV                   | Loading dose: 20 mg/kg/dose                                           |
|                    |                      | **Gestational age <28 weeks:**                                        |
|                    |                      | Serum Creatinine <0.5 mg/dL 15 mg/kg/dose every 12 hours             |
|                    |                      | Serum Creatinine 0.5-0.7 mg/dL 20 mg/kg/dose every 24 hours          |
|                    |                      | Serum Creatinine 0.8-1 mg/dL 15 mg/kg/dose every 24 hours           |
|                    |                      | Serum Creatinine 1.1-1.4 mg/dL 10 mg/kg/dose every 24 hours          |
|                    |                      | Serum 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 hours             |
|                    |                      | Serum Creatinine 0.7-0.9 mg/dL 20 mg/kg/dose every 24 hours          |
|                    |                      | Serum 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 hours            |
|                    |                      | Loading dose: 16 mg/kg/dose                                           |
| TEICOPLANIN        | IV                   | Maintenance dose: 8 mg/kg/dose every 24 hours                        |
Supportive Treatments

Treatments that increase the number or function of neutrophils, including granulocyte transfusions, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, and intravenous immune globulin (IVIG) treatments, are also considered in the treatment of neonatal sepsis. However, many studies have failed to show that GM-CSF or G-CSF has a significant effect on the reduction in mortality. Considering the use of IVIG, in the Cochrane review of the International Neonatal Immunotherapy Study (INIS Collaborative Group), which included over 7000 babies, IVIG infusions used in neonatal sepsis have been shown to have no effect on morbidity or long-term mortality. The use of pentoxifylline, which works by reducing TNF-α concentrations associated with sepsis and improving microcirculation, has been evaluated in two studies with randomized control and it was shown to cause an improvement in survival rates in babies with proven sepsis. However, further studies are needed on this subject.

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References

1. American Academy of Pediatrics. Group B streptococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. p.762.
2. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed 2015;100:F257–63.
3. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 2005;116:595–602.
4. Shim GH, Kim SD, Kim HS, Lee HJ, Lee JA, et al. Trends in epidemiology of neonatal sepsis in a tertiary center in Korea: a 26-year longitudinal analysis, 1980-2005. J Korean Med Sci 2011;26:284–9.
5. Satar M, Arsoy AE, Çelik İH. Türk Neonatoloji Derneği Yenidoğan Enfeksiyonları Tanı ve Tedavi Rehberi 2018. Available at: http://www.neonatologyn.org.tr/wp-content/uploads/2017/12/yenidoğan_enfeksiyonları_tan%C4%B1_ve_tedavi_rehberi_2018.pdf. Accessed Apr 9, 2020.
6. Wang H, Liddell CA, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:957–79.
7. Law J, Coons S, Suman J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why?. Lancet 2005;365:891–900.
8. Oza S, Lawn J, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000-2013. Bull World Health Organ 2015;93:19–28.
9. Liu L, Johnson HL, Cousens S, Scott S, Lawn J, et al; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–61.
10. Centers for Disease Control and Prevention (CDC). Perinatal group B streptococcal disease after universal screening recommendations—United States, 2003-2005. MMWR Morb Mortal Wkly Rep 2007;56:701–5.
11. Centers for Disease Control and Prevention (CDC). Trends in perinatal group B streptococcal disease - United States, 2000-2006. MMWR Morb Mortal Wkly Rep 2009;58:109–12.
12. Stoll BJ, Hansen NL, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs K, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Strep tococcal and E. coli disease continues. Pediatrics 2011;127:817–26.
13. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017;390:1770–80.
14. Osrin D, Vergnano S, Costello A. Serious bacterial infections in newborn infants in developing countries. Curr Opin Infect Dis 2004;17:217–24.
15. Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics 2012;129:1006–15.
16. Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics 2011;128:e1155–63.
17. Guzik DS, Winn K. The association of chorioamnionitis with preterm delivery. Obstet Gynecol 1985;65:11–6.
18. Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. Am J Obstet Gynecol 2008;198:440–50.
19. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease-revised guidelines from CDC, 2010. MMWR Recomm Rep 2010;59:1–36.
20. Alp F, Fındık D, Dagi HT, Arslan U, Pekin AT, Yılmaz SA. Screening and genotyping of group B streptococcus in pregnant and non-
pregnant women in Turkey. J Infect Dev Ctries 2016;10:222–6.
21. Kadanali A, Altoparlaik U, Kadanali S. Maternal carriage and neonatal colonisation of group B streptococcus in eastern Turkey: prevalence, risk factors and antimicrobial resistance. Int J Clin Pract 2005;59:437–40.
22. Eren A, Kütükcüercan M, Oğuzoğlu N, Unal N, Karateke A. The carriage of group B streptococci in Turkish pregnant women and its transmission rate in newborns and serotype distribution. Turk J Pediatr 2005;47:28–33.
23. Edwards MS, Baker CJ. Sepsis in the newborn. In: Gershon AA, Hotze PJ, Katz SL, editors. Krugman's Infectious Diseases of Children. 11th ed. Philadelphia: Mosby; 2004. p. 545–61.
24. Ferrieri P, Wallen LD. Newborn Sepsis and Meningitis. In: Gleason CA, Juul SE, editors. Avery’s Diseases of the Newborn. 10th ed. Philadelphia, PA: Elsvier; 2018: p. 553–65.
25. Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011;96:F9–14.
26. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110:285–91.
27. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am 2004;51:939–ix.
28. Bhat YR, Lewis LE, K EV. Bacterial isolates of early-onset neonatal sepsis and their antibiotic susceptibility pattern between 1998 and 2004: an audit from a center in India. Ital J Pediatr 2011;37:32.
29. Türkmen MK, Teilli M, Ersen S, Güzünler M, Eyigör M. Evaluation of the Cases of Neonatal Sepsis and of Antibiotic Sensitivities in a Neonatal Intensive Care Unit. ADU Tıp Fak Derg 2010;11:15–20.
30. Aksoy H, Orbay E, Akin Y, Vitrinel A. A Retrospective Study of Cases with Neonatal Sepsis. Türk Aile Hek Derg 2002;6:18–23.
31. Ožkan H, Cetinkaya M, Koksal N, Celebi S, Hacımustafaoglu M. Culture-proven neonatal sepsis in preterm infants in a neonatal intensive care unit over a 7 year period: coagulase-negative Staphylococcus as the predominant pathogen. Pediatr Int 2014;56:60–6.
32. Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Wilson C, Nizet V, Maldonado Y, Remington J, Klein J, editors. Remington and Klein’s Infectious Diseases of the Fetus and Newborn Infant. 8th ed. Philadelphia: Elsevier Saunders; 2016. p. 217–71.
33. Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr 2013;162:1120–4.
34. Hammoud MS, Al-Tair A, Thalib L, Al-Sweih N, Pathan S, Isaac D. Incidence, aetiology and resistance of late-onset neonatal sepsis: a five-year prospective study. J Paediatr Child Health 2012;48:604–9.
35. Leal YA, Álvarez-Nemegyei J, Velázquez JR, Rosado-Quib U, Diego-Rodríguez N, Paz-Baeza E, et al. Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. BMC Pregnancy Childbirth 2012;12:48.
36. Özdemir AA, Elgormiş Y. Retrospective evaluation of the cases with neonatal sepsis and antibiotic resistance of the causing microorganisms. Med Bull Sisli Etfal Hosp 2016;50:319–24.
37. Bülbül A, Taşdemir M, Pullu M, Okan F, Bülbül L, Nuhoglu A. Nosocomial infection in the neonatal intensive care unit. Med Bull Sisli Etfal Hosp 2009;43:27–32.
38. Vergnano S, Menson E, Smith Z, Kennea N, Embleton N, Clarke P, et al. Characteristics of Invasive Staphylococcus aureus in United Kingdom Neonatal Units. Pediatr Infect Dis J 2011;30:850–4.
39. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289:203–9.
40. Modlin JF. Treatment of Neonatal Enterovirus Infections. J Pediatr Infect Dis Soc 2016;5:63–4.
41. World Health Organization. WHO guidelines on drawing blood: best practices in phlebotomy. 2010. Available at: https://apps.who.int/iris/bitstream/handle/10665/44294/9789241599221_eng.pdf;jsessionid=85132E3A2460EFCB6853B8F16209D4BC?sequence=1. Accessed Apr 18, 2017.
42. Satar M, Özlü F. Neonatal sepsis: a continuing disease burden. Turk J Pediatr 2012;54:449–57.
43. Malathi I, Millar MR, Leeming JP, Hedges A, Marlow N. Skin disinfection in preterm infants. Arch Dis Child 1993;69:312–6.
44. Pichichero ME, Todd JK. Detection of neonatal bacteremia. J Pediatr 1979;94:958–60.
45. Pauli J Jr, Shekhawat P, Kehl S, Sasidharan P. Early detection of bacteremia in the neonatal intensive care unit using the new BACTEC system. J Perinatol 1999;19:127–31.
46. García-Prats JA, Cooper TR, Schneider VF, Stager CE, Hansen TN. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics 2000;105:523–7.
47. Wiswell TE, Baumgart S, Gannon CM, Spitzer AR. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed?. Pediatrics 1995;95:803–6.
48. Holt DE, Halket S, de Louvois J, Harvey D. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed 2003;88:F85–9.
49. Hamada S, Vearncombe M, McGeer A, Shah PS. Neonatal group B streptococcal disease: incidence, presentation, and mortality. J Matern Fetal Neonatal Med 2008;21:53–7.
50. Grimwood K, Darlow BA, Gosling IA, Green R, Lennon DR, Martin DR, et al. Early-onset neonatal group B streptococcal infections in New Zealand 1998-1999. J Paediatr Child Health 2002;38:272–7.
68. Schmutz N, Henry E, Jopling J, Christensen RD. Expected ranges

67. Christensen RD, Rothstein G, Hill HR, Hall RT. Fatal early onset

66. Murphy K, Henry E, Jopling J, Christensen RD. Expected ranges

65. Phillip AG, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980;65:1036–41.

64. Arnon S, Litmanovitz I. Diagnostic tests in neonatal sepsis. Curr Opin Infect Dis 2008;21:223–7.

63. Chiesa C, Panero A, Osborn JF, Simonetti AF, Pacifico L. Diagnosis of neonatal sepsis: a clinical and laboratory challenge. Clin Chem 2004;50:279–87.

62. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr 1979;95:89–98.

61. Rozycki HJ, Stahl GE, Baumgart S. Impaired sensitivity of a single early leukocyte count in screening for neonatal sepsis. Pediatr Infect Dis J 1987;6:440–2.

60. Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980;65:1036–41.

59. Evans ME, Schaffner D, Cassady G. Endotracheal intubation and its relationship to bacterial colonization and systemic infection of newborn infants. Pediatrics 1976;58:816–23.

58. Harris H, Wirtschafter D, Cassady G. Endotracheal intubation and its relationship to bacterial colonization and systemic infection of newborn infants. Pediatrics 1976;58:816–23.

57. Ruangkit C, Satpute A, Vogt BA, Hoyen C, Viswanathan S. Incidence and risk factors of urinary tract infection in very low birth weight infants. J Neonatal Perinatal Med 2016;9:83–90.

56. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol 2010;37:421–38.

55. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed 2003;88:F173–8.

54. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture and its relationship to bacterial colonization and systemic infection of newborn infants. Pediatrics 1976;58:816–23.

53. Shattuck KE, Chonmaitree T. The changing spectrum of neonatal meningitis over a fifteen-year period. Clin Pediatr (Phila) 1992;31:130–6.

52. Visser VE, Hall RT. Lumbar puncture in the evaluation of suspected neonatal sepsis. J Pediatr 1980;96:1063–7.

51. Neto MT. Group B streptococcal disease in Portuguese infants younger than 90 days. Arch Dis Child Fetal Neonatal Ed 2008;93:F90–3.

50. Visser VE, Hall RT. Lumbar puncture in the evaluation of suspected neonatal sepsis. J Pediatr 1980;96:1063–7.

49. Shattuck KE, Chonmaitree T. The changing spectrum of neonatal meningitis over a fifteen-year period. Clin Pediatr (Phila) 1992;31:130–6.

48. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001;108:1169–74.

47. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed 2003;88:F173–8.

46. Benitez WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol 2010;37:421–38.

45. Ruangkit C, Satpute A, Vogt BA, Hoyen C, Viswanathan S. Incidence and risk factors of urinary tract infection in very low birth weight infants. J Neonatal Perinatal Med 2016;9:83–90.

44. Klein JO, Marcy SM. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, editors. Remington's Infectious Diseases of the Fetus and Newborn. Philadelphia: WB Saunders, 1983. p. 679–735.

43. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early-onset neonatal sepsis. Pediatr Infect Dis J 2012;31:16–9.

42. Christensen RD, Rothstein G, Hill HR, Hall RT. Fatal early onset group B streptococcal sepsis with normal leukocyte counts. Pediatr Infect Dis 1985;4:242–5.

41. Schmutz N, Henry E, Jopling J, Christensen RD. Expected ranges for blood neutrophil concentrations of neonates: the Manroe and Mouzinho charts revisited. J Perinatol 2008;28:275–81.

40. Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK Jr, Smith PB, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev 2012;88 Suppl 2:S69–74.

39. Ng PC, Lam HS. Diagnostic markers for neonatal sepsis. Curr Opin Pediatr 2006;18:125–31.

38. Da Silva O, Ohlsson A, Kenyon C. Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review. Pediatr Infect Dis J 1995;14:362–6.

37. Spector SA, Ticknor W, Grossman M. Study of the usefulness of clinical and hematologic findings in the diagnosis of neonatal bacterial infections. Clin Pediatr (Phila) 1981;20:385–92.

36. Manzoni P. Hematologic Aspects of Early and Late-Onset Sepsis in Preterm Infants. Clin Perinatol 2015;42:587–95.

35. Berger C, Uehlinger J, Ghefti D, Blau N, Fanconi S. Comparison of C-reactive protein and white blood cell count with differential in neonates at risk for septicemia. Eur J Pediatr 1995;154:138–44.

34. Papoff P. Use of hematologic data to evaluate infections in neonates. In: Christensen R, editor. Hematologic Problems of the Neonate. Philadelphia: WB Saunders; 2000. p. 389–404.

33. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis—a systematic review. Infect Dis (Lond) 2015;47:117–24.

32. Ismail AQ, Gandi A. Using CRP in neonatal practice. J Matern Fetal Neonatal Med 2015;28:3–6.

31. Russell GA, Smyth A, Cooke RW. Receiver operating characteristic curves for comparison of serial neutrophil band forms and C reactive protein in neonates at risk of infection. Arch Dis Child 1992;67:808–12.

30. Celik IH, Demirel FG, Uras N, Oguz SS, Erdeve O, Biyikli Z, Dilmen U. What are the cut-off levels for IL-6 and CRP in neonatal sepsis? J Clin Lab Anal 2010;24:407–12.

29. Pourcyrous M, Bada HS, Korones SB, Baselski V, Wong SP. Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatrics 1993;92:431–5.

28. Franz AR, Steinbach G, Kron M, Pohlndt F. Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infections. Pediatrics 1999;104:447–53.

27. Wasunna A, Whitelaw A, Gallimore R, Hawkins PN, Pepys MB. C-reactive protein and bacterial infection in preterm infants. Eur J Pediatr 1990;149:424–7.

26. Edgar JD, Gabriel V, Gallimore JR, McMillan SA, Grant J. A prospective study of the sensitivity, specificity and diagnostic performance of soluble intercellular adhesion molecule 1, highly sensitive C-reactive protein, soluble E-selectin and serum amyloid A in the diagnosis of neonatal infection. BMC Pediatrics 2010;10:22.

25. Ganesan P, Shanmugam P, Sattar SB, Shankar SL. Evaluation of IL-6, CRP and hs-CRP as Early Markers of Neonatal Sepsis. J Clin
85. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. Ann Clin Biochem 2001;38:483–93.
86. Dandonia P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et al. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994;79:1605–8.
87. Stocker M, Fontana M, El Helou S, Wegscheider K, Berger TM. Use of procalcitonin-guided decision-making to shorten antibiotic therapy in suspected neonatal early-onset sepsis: prospective randomized intervention trial. Neonatology 2010;97:165–74.
88. Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Calò Carducci F, et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infect Dis 2017;17:302.
89. Chiesa C, Pellegrini G, Panero A, Osborn JF, Signore F, Assumma M, et al. C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection. Clin Chem 2003;49:60–8.
90. Assumma M, Signore F, Pacifico L, Rossi N, Osborn JF, Chiesa C. Serum procalcitonin concentrations in term delivering mothers and their healthy offspring: a longitudinal study. Clin Chem 2000;46:1583–7.
91. Lee J, Bang YH, Lee EH, Choi BM, Hong YS. The influencing factors on procalcitonin values in newborns with noninfectious conditions during the first week of life. Korean J Pediatr 2017;60:10–6.
92. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13:426–35.
93. Croxatto A, Prod`hom G, Greub G. Applications of MALDI-TOF mass spectrometry in clinical diagnostic microbiology. FEMS Microbiol Rev 2012;36:380–407.
94. Barnini S, Ghelardi E, Bruculieri V, Morici P, Lupetti A. Rapid and reliable identification of Gram-negative bacteria and Gram-positive cocci by deposition of bacteria harvested from blood cultures onto the MALDI-TOF plate. BMC Microbiol 2015;15:124.
95. Lagacé-Wiens PR, Adam HJ, Karlowsky JA, Nichol KA, Pang PF, Guenther J, et al. Identification of blood culture isolates directly from positive blood cultures by use of matrix-assisted laser desorption ionization-time of flight mass spectrometry and a commercial extraction system: analysis of performance, cost, and turnaround time. J Clin Microbiol 2012;50:3324–8.
96. Malcolmson C, Ng K, Hughes S, Kisson N, Schina J, Tilley PA, et al. Impact of Matrix-Assisted Laser Desorption and Ionization Time-of-Flight and Antimicrobial Stewardship Intervention on Treatment of Bloodstream Infections in Hospitalized Children. J Pediatr Infect Dis Soc 2017;6:178–86.
97. Ovali F. Bakteriyel enfeksiyonlar. In: Dağoğlu T, Ovali F, editros. Neonatoloji. İstanbul: Nobel Tıp Kitabevleri; 2017. p. 759.
98. Dutta S, Narang A, Chakraborty A, Ray P. Diagnosis of neonatal sepsis using universal primer polymerase chain reaction before and after starting antibiotic drug therapy. Arch Pediatr Adolesc Med 2009;163:6–11.
99. Yuan H, Huang J, Lv B, Yan W, Hu G, Wang J, et al. Diagnosis value of the serum amyloid A test in neonatal sepsis: a meta-analysis. Biomed Res Int 2013;2013:520294.
100. Arnon S, Litmanovitz I, Regev R, Lis M, Shainkin-Kestenbaum R, Dolfin T. The prognostic virtue of inflammatory markers during late-onset sepsis in preterm infants. J Perinat Med 2004;32:176–80.
101. Arnon S, Litmanovitz I, Regev RH, Bauer S, Shainkin-Kestenbaum R, Dolfin T. Serum amyloid A: an early and accurate marker of neonatal early-onset sepsis. J Perinatol 2007;27:297–302.
102. Behrendt D, Dembinski J, Heep A, Bartmann P. Lipopolysaccharide binding protein in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004;89:F551–4.
103. Delsosto D, Opal SM. Future perspectives on regulating pro- and anti-inflammatory responses in sepsis. Contrib Microbiol 2011;17:137–56.
104. Turner D, Hammerman C, Rudensky Y, Goia C, Schimmel MS. Procalcitonin in preterm infants during the first few days of life: introducing an age related nomogram. Arch Dis Child Fetal Neonatal Ed 2006;91:F283–6.
105. D’Alquen D, Kramer BW, Seidenspinner S, Marx A, Berg D, Gronbeck P, et al. Activation of umbilical cord endothelial cells and fetal inflammatory response in preterm infants with chorioamnionitis and funisitis. Pediatr Res 2005;57:263–9.
106. Miller LC, Isa S, LoPreste G, Schaller JG, Dinarello CA. Neonatal interleukin-1 beta, interleukin-6, and tumor necrosis factor: cord blood levels and cellular production. J Pediatr 1990;117:961–5.
107. Mehr S, Doyle LW. Cytokines as markers of bacterial sepsis in newborn infants: a review. Pediatr Infect Dis J 2000;19:879–87.
108. Kishimoto T. The biology of interleukin-6. Blood 1989;74:1–10.
109. Hodge G, Hodge S, Han P, Haslam R. Multiple leucocyte activation markers to detect neonatal infection. Clin Exp Immunol 2004;135:125–9.
110. Küster H, Weiss M, Willeitner AE, Detlefsen S, Jeremiah I, Zbojan J, et al. Interleukin-1 receptor antagonist and interleukin-6 for early diagnosis of neonatal sepsis 2 days before clinical manifestation. Lancet 1998;352:1271–7.
111. Smulian JC, Vintzileos AM, Lai YL, Santiago J, Shen-Schwarz S, Campbell WA. Maternal chorioamnionitis and umbilical vein interleukin-6 levels for identifying early neonatal sepsis. J Matern Fetal Med 1999;8:88–94.
112. Smulian JC, Bhandari V, Campbell WA, Rodis JF, Vintzileos AM. Value of umbilical artery and vein levels of interleukin-6 and soluble intracellular adhesion molecule-1 as predictors of neonatal hematologic indices and suspected early sepsis. J Matern Fetal Med 1997;6:254–9.
113. Silveira RC, Prociunoy RS. Evaluation of interleukin-6, tumour necrosis factor-alpha and interleukin-1beta for early diagnosis of neonatal sepsis. Acta Paediatr 1999;88:647–50.

114. Reinsberg J, Dembinski J, Dorn C, Behrendt D, Bartmann P, van Der Ven H. Determination of total interleukin-8 in whole blood after cell lysis. Clin Chem 2000;46:1387–94.

115. Franz AR, Sieber S, Pohlandt F, Kron M, Steinbach G. Whole blood interleukin 8 and plasma interleukin 8 levels in newborn infants with suspected bacterial infection. Acta Paediatr 2004;93:648–53.

116. Mishra UK, Jacobs SE, Doyle LW, Garland SM. Newer approaches to the diagnosis of early onset neonatal sepsis. Arch Dis Child Fetal Neonatal Ed 2006;91:F208–12.

117. Resch B, Gussenleitner W, Müller WD. Procalcitonin and interleukin-6 in the diagnosis of early-onset sepsis of the neonate. Acta Paediatr 2003;92:243–5.

118. Bemer R, Niemeyer CM, Leititis JU, Funke A, Schwab C, Rau U, et al. Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. Pediatr Res 1998;44:469–77.

119. Ng PC, Cheng SH, Chui KM, Fok TF, Wong MY, Wong W, et al. Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birth-weight infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F221–7.

120. de Bont ES, Martens A, van Raan J, Samson G, Fetter WP, Okken PJ, van Raan AJ. Procalcitonin and interleukin-6 in the diagnosis of late-onset sepsis in newborns with sepsis. Acta Paediatr 1994;83:696–9.

121. Lv B, Huang J, Yuan H, Yan W, Hu G, Wang J. Tumor necrosis factor-α as a diagnostic marker for neonatal sepsis: a meta-analysis. ScientificWorldJournal 2014;2014:471463.

122. Ng PC, Li K, Chui KM, Leung TF, Wong MY, Wong W, et al. Diagnostic value of plasma levels of tumor necrosis factor alpha (TNF alpha) and interleukin-6 (IL-6) in newborns with sepsis. Acta Paediatr 1994;83:696–9.

123. Silveira RC, Procianoy RS. Evaluation of interleukin-6, tumour necrosis factor-alpha and interleukin-1beta for early diagnosis of neonatal sepsis. Acta Paediatr 1999;88:647–50.

124. Weirich E, Rabin RL, Maldonado Y, Benitz W, Modler S, Herzenberg LA, et al. Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. J Pediatr 1998;132:445–51.

125. Nupponen I, Andersson S, Järvenpää AL, Kautiainen H, Repo H. Neutrophil CD11b expression and circulating interleukin-8 as diagnostic markers for early-onset neonatal sepsis. Pediatrics 2001;108:E12.

126. Mantovani A, Garlanda C, Doni A, Bottazzi B. Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008;28:1–13.

127. Adib M, Ostadi V, Navaei F, Saheb Fosoul F, Oreizi F, Shokouhi R, et al. Evaluation of CD11b expression on peripheral blood neutrophils for early detection of neonatal sepsis. Iran J Allergy Asthma Immunol 2007;6:93–6.

128. Graversen JH, Madsen M, Moestrup SK. CD163: a signal receptor scavenging haptoglobin-hemoglobin complexes from plasma. Int J Biochem Cell Biol 2002;34:309–14.

129. Fabrik BQ, Dijkstra CD, van den Berg TK. The macrophage scavenger receptor CD163. Immunobiology 2005;210:153–60.

130. Prashant A, Vishwanath P, Kulkarni P, Sathyarayana P, Gowdara V, Nataraj SM, et al. Comparative assessment of cytokines and other inflammatory markers for the early diagnosis of neonatal sepsis—a case control study. PLoS One 2013;8:e68426.

131. Sprong T, Peri G, Neeleman C, Mantovani A, Signorini S, van der Meer JW, et al. Pentraxin 3 and C-reactive protein in severe meningococcal disease. Shock 2009;31:28–32.

132. Mankhambo LA, Banda DL; IPD Study Group, Jeffers G, White SA, Balmer P, et al. The role of angiogenic factors in predicting clinical outcome in severe bacterial infection in Malawian children. Crit Care 2010;14:R91.

133. Siahanioudi T, Margeli A, Tsirogianni C, Charoni S, Giannaki M, Vavourakis E, et al. Clinical value of plasma soluble urokinase-type plasminogen activator receptor levels in term neonates with infection or sepsis: a prospective study. Mediators Inflamm 2014;2014:375702.

134. Saldir M, Tunc T, Cekmez F, Cetinkaya M, Kalayci T, Fidanci K, et al. Endocan and Soluble Triggering Receptor Expressed on Myeloid Cells-1 as Novel Markers for Neonatal Sepsis. Pediatr Neonatol 2015;56:415–21.

135. Chaaban H, Singh K, Huang J, Siryaporn E, Lim YP, Padbury JF. The role of inter-alpha inhibitor proteins in the diagnosis of neonatal sepsis. J Pediatr 2009;154:620–2.

136. Töllner U. Early diagnosis of septicemia in the newborn. Clinical studies and sepsis score. Eur J Pediatr 2002;161:331–7.

137. European Medicines Agency (EMA). Report on the Expert Meeting on Neonatal and Paediatric Sepsis. London: 2010. Available at: https://www.ema.europa.eu/en/documents/report/report-expert-meeting-neonatal-paediatric-sepsis_en.pdf. Accessed Apr 13, 2020.

138. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacteria. Lancet 2000;355:973–8.

139. Leonard EG, Dobbs K. Postnatal Bacterial Infections. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin’s Neonatal-Perinatal Medicine. 10th ed. Elsevier; 2015. p. 734–50.

140. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics 2006;117:67–74.

141. Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol 2013;30:131–41.
142. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Paediatr Drugs 2013;15:93–117.

143. American Academy of Pediatrics. Candidiasis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. p. 263.

144. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–50.

145. Bradley JS, Nelson JD, Barnett ED, Cantey JB, Kimberlin DW, Palumbo PE, et al. Nelson's Pediatric Antimicrobial Therapy. 25th ed. American Academy of Pediatrics; 2019. Available at: https://bibop.ocg.msf.org/docs/10/L010PEDX12E-P_Nelsons-Pediatric-Antimicrobial-Therapy_2019.pdf. Accessed Apr 13, 2020.

146. American Academy of Pediatrics. Tables of antibacterial drug dosages. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. p. 914.

147. Sivanandan S, Soraisham AS, Swarnam K. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Int J Pediatr 2011;2011:712150.

148. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.

149. Castagnola E, Dufour C. Role of G-CSF GM-CSF in the management of infections in preterm newborns: an update. Early Hum Dev 2014;90 Suppl 2:S15–7.

150. Carr R, Brocklehurst P, Doré CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMES trial): a single-blind, multicentre, randomised controlled trial. Lancet 2009;373:226–33.

151. Marlow N, Morris T, Brocklehurst P, Carr R, Cowan F, Patel N, et al. A randomised trial of granulocyte-macrophage colony-stimulating factor for neonatal sepsis: childhood outcomes at 5 years. Arch Dis Child Fetal Neonatal Ed 2015;100:F320–6.

152. Mathias B, Szpila BE, Moore FA, Efron PA, Moldawer LL. A Review of GM-CSF Therapy in Sepsis. Medicine (Baltimore) 2015;94:e2044.

153. INIS Collaborative Group, Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med 2011;365:1201–11.

154. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database Syst Rev 2015:CD001239.

155. Haque KN, Pammi M. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev 2011:CD004205.