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REVIEW ARTICLE

SEPSIS IN NEWBORNS: MODERN ASPECTS OF A SERIOUS DISEASE

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ABSTRACT

The review examines the epidemiology of neonatal sepsis, risk factors for the development of this disease, pathogenesis, etiology and sensitivity of pathogens to antibiotics, and presents modern methods of diagnosis and treatment. Methods of prevention and promising areas of research for neonatal sepsis are discussed.

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INTRODUCTION

Sepsis is one of the leading causes of morbidity and mortality among newborns, especially premature infants. Worldwide, three million newborns (22/1000 live births) are diagnosed with sepsis each year, and 11–19% of them die (1–6). A recent study estimates the worldwide incidence of neonatal sepsis at 28.24 cases per 1000 live births. The incidence of early-onset sepsis (EOS) increases with decreasing gestational age and is up to 6 cases per 1000 infants born at <34 weeks' gestation or 20 cases per 1000 infants born at <29 weeks' gestation. Moreover, preterm infants have high rates of mortality associated with EOS (up to 40% among extremely low gestational age infants). Based on birth weight, the incidence of EOS in very low birth weight infants (less than 1500 g at birth - VLBW) ranges from 9 to 11 cases per 1000 births. These rates increase in late-onset sepsis, where it is around 12–28% among preterm infants 22–26 weeks' gestation, with mortality approaching 35% among the most vulnerable infants at the lowest gestational age (7). According to the literature, the incidence of early neonatal sepsis in Europe ranges from 0.28 to 2.1 episodes per 1000 live births. In the United States, the incidence is 7.4/1000 in preterm infants, 0.76/1000 in late preterm infants (36–37 weeks gestational age), and 0.31/1000 in term infants. Late-onset sepsis (LOS) occurs after the first 72 hours of life, with the highest incidence reported between the tenth and twenty-second day. The incidence of LOS is inversely related to gestational age and birth weight (1, 3, 5). Data from the United Kingdom report an incidence of late-onset sepsis of 8 episodes per 1000 among all newborns (live births), in 16–30% of very low birth weight newborns and in 50% of extremely low birth weight newborns (8). According to another study, the incidence of late-onset sepsis in very low birth weight preterm infants (birth weight ≤1500 g) ranges from 20% to 35% (9). In a study from Nepal, the overall neonatal mortality rate for culture-positive sepsis was 15.94%, which was consistent with studies in Egypt and India (10). Newborns who have had sepsis are at higher risk of developing chronic pathologies of the respiratory tract, kidneys, gastrointestinal tract and nervous system, and therefore much attention is currently being paid to the prevention and successful treatment of this disease, as well as reducing the incidence of complications (1 , 2, 7, 12, 14, 15).

Definition: There is currently no consensus on a consensus definition of neonatal sepsis. Sepsis is often defined as "life-threatening organ dysfunction caused by an impaired body response to infection" (7, 15). Neonatal sepsis is also considered as a clinical syndrome in a newborn, characterized

by systemic signs of infection and the release of microbes from the blood (13). There are several definitions of neonatal sepsis, which usually include clinical, microbiological and biochemical information (4). Neonatal sepsis is considered as a generalized infectious disease with an acyclic course, caused by opportunistic bacterial microflora, which is based on dysfunction of the body's immune system with the development of a focus (foci) of purulent inflammation or bacteremia, a systemic inflammatory reaction and multiple organ failure in infants in the first month of life (12, 16). The term "neonatal sepsis" refers to systemic infections of newborns (12, 16). Currently, researchers note that due to the heterogeneity of the definitions used, it is difficult to compare the results of observations both in early and late-onset sepsis, and in sepsis in full-term and preterm infants, as well as current studies with results obtained previously (4, 15, 17). Likewise, comparing full-term and preterm infants using the same definition or treatment plan is also challenging. Therefore, consensus is needed on specific definitions of term and preterm neonatal sepsis (4). According to some authors, it is also necessary to standardize clinical studies of sepsis with the definition of main results that can be compared between studies for correct interpretation (1, 2, 4, 7, 11, 17). Currently, neonatal sepsis is divided into early-onset sepsis and late-onset sepsis (9, 13, 18, 19).

Early-Onset Sepsis (EOS). Clinical manifestations of EOS are usually observed within the first 72 hours after delivery. (An exception to this definition is neonatal sepsis caused by Streptococcus agalactiae, which, although of perinatal etiology, may occur within the first 7 days of life.) The disease develops, as a rule, as a result of vertical transmission of infection from mother to baby, as well as during infection during childbirth. Pathogens are usually represented by microflora, which is detected in the mother (1, 8, 20, 21). *Late-Onset Sepsis (LOS)* is diagnosed after 72 hours of birth. Most often, it occurs in premature newborns, who for various reasons (low body weight, respiratory distress syndrome - RDS, neurological disorders, etc.) are forced to stay in the intensive care unit of the hospital for a longer time (7, 8, 9, 19, 22).

Etiology: The etiological structure of neonatal sepsis is very diverse. It is mainly represented by opportunistic bacteria and fungi of the genus *Candida*. Among the bacterial microflora, gram-positive cocci (*Streptococcus group* B, *Staphylococcus epidermidis*, S*aphylococcus aureus*, lis, Enterococcus faecium) and gram-negative bacteria (family Enterobacteriaceae) *Enterococcus faecalis*, *Acinetobacter spp*., *Pseudomonas spp*., including *Pseudomonas aeruginosa*, *Stenotrophomonas maltofilia*, *Haemophilus spp*. and others). From *Enterobacteriaceae* are most often sown during sepsis *E. col* and *Klebsiella pneumoniae* (with a frequency of up to 70%), much less *Serratia marcescens*, *Enterobacter spp*., *Citrobacrer spp*., *Proteus spp*. and others (less than 5%) (5, 8, 11, 12, 13, 21, 22). *Candida spp*. are most often represented by the species *Candida albicans* (up to 28.3%) and *Candida krusei* (up to 8%), much less often are *Candida thropicalis* and *Candida pseudothropicalis* (less than 1%) (16, 21, 23, 24). According to a number of researchers, important causative agents of early neonatal sepsis are *Streptococcus agalactiae* (*GBS - Str. agalactiae),* and *Escherichia coli (E. coli)*, which account for up to 70% of the spectrum of pathogens in both full-term and premature infants. The majority (76.6%) of invasive *GBS* cases occurred in full-term infants, and the pathogens belonged to five serotypes (Ia, Ib, II, III and V). Other pathogens (*Streptococcus viridans, Streptococcus pneumoniae, Staphylococcus aureus – S. aureus, Enterococcus spp., Enterobacteriaceae*, and *Listeria monocytogenes*) are less common. Fungal infections, especially *Candida spp*., occur more frequently in preterm infants, and very low birth weight infants may present with symptoms of early-onset sepsis within the first 24 hours of life (1, 8). Pathogens responsible for the development of late sepsis are usually microorganisms from the hospital environment, especially in the intensive care unit. The most common pathogens are coagulase-negative *Staphylococcus* (causing 53–78% of sepsis episodes), *Staphylococcus aureus*, and gram-negative bacteria, predominantly *Escherichia coli, Klebsiella spp., Enterobacter spp., Pseudomonas spp., Citrobacter spp.*, and *Serratia marcescens*. It should be noted that the incidence of fungal infection *Candida spp*. Very low birth weight newborns are of great concern due to their severe course and difficulties in treatment (3, 8, 10, 20). According to Indian data, the main bacteria causing neonatal sepsis (both EOS and LOS) are *Klebsiella spp*.. (23%), *E. coli* (14%) and *Acinetobacter spp*. (8%) (13). Data from the Delhi Neonatal Infection Study (DeNIS) showed that the incidence of overall sepsis and culture-positive sepsis (culture confirmed) was 14.3% and 6.2%, respectively. Early sepsis accounted for 83% of the total number of sepsis cases. Important bacteria isolated were *Acinetobacter spp*. (22%), *Klebsiella spp*., (17%) and *E. coli* (14%). Bacteria isolated from EOS were similar to LOS bacteria. Among the isolated microorganisms, higher rates of multidrug resistance were observed (13). It must be said that in economically developed countries the frequency of positive blood cultures is quite high (up to 60% of the number of children with clinically diagnosed sepsis) (3, 13). In a recently completed international study that included 19 hospitals in 11 countries in Asia (Bangladesh, China, India, Thailand and Vietnam), Africa (Kenya, South Africa, Uganda), Europe (Italy, Greece) and South America (Brazil), *Klebsiella pneumoniae*, coagulase-negative *Staphylococcus*, *Acinetobacter spp*. and *S. aureus* were the most important pathogens isolated from blood cultures of neonates with sepsis (NeoOBS - unpublished data, cited in Adhisivam Bethou and Ballambattu Vishnu, 2022). Compared to many high-income countries, Gram-negative organisms have been identified as the main causative agents of neonatal sepsis in poor regions. Thus, *Salmonella spp*. in sub-Saharan Africa, *Salmonella typhi* and *Salmonella* paratyphi fever in South and Southeast Asia, and *Burkholderia pseudomallei* in Southeast Asia have been frequent causative agents of sepsis in infants. Gram-positive *Streptococcus suis* has been a common cause of sepsis in Southeast Asia (21). Gram-negative microflora (*Enterobacteriaceae* and *Pseudomonas aeru*ginosa) are associated with the highest mortality rate in sepsis. In a study from Nepal, the overall neonatal mortality rate for culture-positive sepsis was 15.94%, which was consistent with studies conducted in Egypt and India (10). Overall, there are clear geographic differences in the predominant etiology of neonatal sepsis between countries. This reinforces the importance of site-specific antibiotic policies. Almost all authors note that with sepsis in most cases there is a monoinfection. Identification of more than two bacterial pathogens is quite rare and usually occurs in premature infants (up to 5%). It is also noted that the pathogen isolated from the blood most often coincides in species composition with the microflora of the respiratory tract, intestines and discharge from the umbilical wound (3, 10, 13, 20, 21).

Table Clinical course of neonatal sepsis

Organ systems	Clinical manifestations of disorders
Respiratory system	Respiratory failure: tachypnea or bradypnea; perioral or general cyanosis, apnea, retraction of the compliant areas of the chest, expiratory noises, the need for additional oxygen support (hardware ventilation, non-invasive ventilation - CPAP, oxygen tent, mask). Auscultation: weakened breathing, possible crepitus. Respiratory or mixed acidosis.
The cardiovascular system	Tachycardia or bradycardia, rhythm disturbances, arterial hypotension, expansion of the borders of the heart, general edema syndrome. The need for hemodynamic support. Changes in central venous pressure, decreased ejection fraction and cardiac output, ECG changes of a metabolic nature.
Nervous system	Syndrome of inhibition of unconditioned reflexes (lethargy, apathy, muscle hypotension, coma). Syndrome of increased neuro-reflex excitability (motor activity, unemotional cry). Neonatal seizures, coma. Ultrasound: hypoxic-ischemic damage to the central nervous system, intraventricular hemorrhage, disturbances in the bioelectrical activity of the cerebral cortex. Neurosonography– cerebral edema, hypertensive-hydrocephalic syndrome. Cerebrospinal fluid (CSF) - there may be a slight increase in protein levels with normal or increased cytosis.
Kidneys and urinary tract	Edema. Oliguria (less than 1 ml/hour against the background of adequate infusion therapy), anuria. Changes in clinical urine analysis (protein, bacteria, fungi, increased levels of leukocytes and red blood cells). Increased levels of creatinine, urea, potassium in the blood serum.
Digestive system	Refusal to suck or weak sucking, inability to enteral nutrition, regurgitation, vomiting, diarrhea. Changes in the coprogram: mucus and «greens» in the stool, undigested lumps. Pathological weight loss. Hepatomegaly. Jaundice, increased levels of AST and ALT, impaired bilirubin conjugation, cholestasis. X-ray signs of intestinal paresis. Ulcerative necrotizing enterocolitis. Intestinal dysbiosis.
Hemostasis disorders	Skin hemorrhages, bleeding, thrombosis. Hypo- or hypercoagulation in the hemostasiogram. Increased activated partial thromboplastin time. Prolongation of thrombin time, increased content of fibrin degradation products, depression of fibrinolysis. Decreased protein C levels. Skin hemorrhages, bleeding, thrombosis.
Skin condition	Pale, gray, icteric tint, rash, swelling, sclerema, marbling, cyanosis, necrosis

Risk factors for the development of neonatal sepsis: Significant risk factors for the development of sepsis in the neonatal period are premature birth and low birth weight. RDS, low Apgar scores, need for resuscitation, multiple pregnancies increase the risk of early sepsis, while invasive procedures such as frequent blood sampling, endotracheal intubation, mechanical ventilation, catheter/tube insertion, insufficient breastfeeding or breastfeeding absence, prolonged parenteral nutrition, low gastric acid levels and surgical interventions increase the risk of developing late sepsis and the risk of death. Maternal risk factors include febrile labor, massive bacterial colonization of the genital tract with opportunistic pathogens, preterm onset of labor, premature rupture of membranes (>18 hours), chorioamnionitis, and urinary tract infection. Attention is also paid to maternal infection with viruses (1, 2, 8, 13, 14,19, 25). In pregnant women infected with *Str. agalactiae*, which did not receive antibiotic prophylaxis, the likelihood of developing early neonatal sepsis in newborns is 25 times higher than in infants of uncolonized mothers. In women with premature rupture of the amniotic membrane, newborns are four times more likely to become infected with bacterial microflora (1, 9).

The most important risk factors for late neonatal sepsis are: 1) prematurity: compared with term infants, premature infants have lower production of proinflammatory cytokines and activation of natural killer cells, reduced cell-mediated immunity and placental transfer of immunoglobulins, and lower serum complement levels. 2) Violation of natural barriers: damage and ruptures of the skin and mucous membranes can become an entry point for bacterial invasion. 3) Central catheters installed for a long time are an entry point for bacteria. 4) Invasive procedures, such as tracheal intubation: the risk of sepsis increases with the number of neonatal intubations; Accidental extubations requiring frequent reintubation are important causes of infection. 5) The use of H_2 blockers reduces the protective mechanism and increases the risk of bacterial invasion, because stomach acidity acts as a barrier to bacterial growth and invasion. 6) Long-term use of empirical antibiotic therapy for early neonatal sepsis for more than five days increases the incidence of late neonatal sepsis, especially with insufficient use of breast milk and excessive prescription of third generation cephalosporins (23, 22, 26).

A high mortality rate was revealed in sepsis, which mainly developed in the first 72 hours of life. Predictors of mortality in patients with neonatal sepsis included prematurity, low birth weight, platelet count <150,000 cells/mm^3, creatinine >1.1 g/dL, development of septic shock, and use of invasive mechanical ventilation (26).

Pathogenesis: A newborn during physiological childbirth, passing through the birth canal, can be colonized by opportunistic microflora of the lower parts of the mother's genital tract. The baby can be colonized by infected amniotic fluid. In these cases, early-onset sepsis may develop as a result of vertical transmission of the pathogen. Late-onset sepsis usually occurs due to horizontal transmission of bacteria: from medical personnel or the hospital environment. Sometimes pathogens transmitted vertically can lead to early neonatal colonization, but the infectious process does not develop immediately, and the infection manifests itself after 3-4 days. A number of factors, such as hypoxia, acidosis, hypothermia and some hereditary metabolic disorders reduce the protective mechanisms of the newborn and can contribute to a more severe course of sepsis (8). Since newborns have weak anti-infective protection, they may develop an infection in the uteros. Reduced neutrophil function and low immunoglobulin concentrations are the reason that premature newborns are more susceptible to the negative effects of bacteria (11, 12, 19). In the pathogenesis of sepsis, in addition to the virulence of the pathogen, uncontrolled inflammation on the part of the macroorganism is important. Cytokine storm (hypercytokinemia) is characterized by increased activation of T cells, macrophages and natural killer cells with excessive release of various inflammatory cytokines and chemical mediators (interleukins, chemokines, tumor necrosis factor-alpha, interferon, growth factors). These inflammatory mediators lead to the activation of immune cells and the latter's release of a new portion of mediators, and also trigger of a cascade of plasma protein enzymatic processes, including fibrinolysis, coagulation and complement activation. This hyperreactivity of the macroorganism causes tissue destruction at the site of inflammation. In addition, the inflammatory reaction spreads to neighboring tissues and, as it develops, becomes systemic (7, 11, 12). There is a redistribution of blood flowing through the vascular beds of the skin and

gastrointestinal tract to vital organs such as the brain and heart in sepsis. Changes in microcirculation are characterized by increased capillary permeability, hypovolemia, edema formation, increased adhesion of leukocytes to endothelial surfaces, increased reactive oxygen species (ROS) and decreased erythrocyte plasticity. Damage to mitochondria and disturbances in energy supply are important in the development of sepsis (7). Altered tone and reactivity of arteriolar smooth muscle cells due to impaired nitric oxide synthesis and capillary blockage with platelets and fibrin clots as part of disseminated intravascular coagulation also contribute to the pathogenesis of sepsis. Inflammatory molecules, including nitric oxide, carbon monoxide, and ROS, can have damaging effects on multiple components of the mitochondrial electron transport chain complexes (7, 14, 15).

Pathogen-associated molecular patterns (PAMPs), which are found in the bacterial cell wall (peptidoglycans, lipoproteins and lipopolysaccharides), bind to toll-like receptors (TLRs) of host cells, further catalyzing several inflammatory pathways. It is important to note that antibiotics do not act against PAMPs, and inflammatory processes continue even after the death of the pathogen and sanitization of the source of infection. Intracellular signals called damage associated molecular patterns (DAMPs), including S100 proteins, heat shock proteins, high mobility group box-1 protein, uric acid and transformed matrix proteins (TMPs)), are also vital for modifying the response to a specific infectious agent. PAMPs and DAMPs, which are released either as a result of inflammation or exposure to infection, are identified by corresponding recognition receptors located on the surface of cells. They thereby stimulate (primarily or additionally) the inflammatory cascade. As a result of activation of these biochemical reactions, septic shock may develop, which is accompanied by multiple organ failure syndrome (7, 17).

Clinical diagnosis of neonatal sepsis: Diagnosing sepsis in newborns is challenging because the symptoms of the disease are nonspecific and can occur in both non-infectious conditions and localized infection. Therefore, in many cases, treatment of sepsis is initiated upon clinical suspicion while awaiting the results of ongoing investigations and laboratory tests. For clinicians, initial diagnosis, resuscitation, and treatment within the first few hours of symptom onset are important (13, 21, 27). The general clinical picture in a newborn with sepsis is described as follows: the child looks bad, pasty, lethargic, breathing heavily, refuses food or sucks weakly, nutrition is not fully absorbed (13, 21). In early neonatal sepsis, pathological weight gain, edema, compaction of subcutaneous fat (sclerema), hemorrhagic syndrome and thrombosis, early appearance and rapid progression of jaundice, respiratory disorders (retraction of the compliant areas of the chest, heavy noisy breathing, respiratory rate > 60 per minute, apnea for more than 15 seconds) are noted in the absence of pronounced radiographic changes, progressive hypothermia (t<36.2°C) or fever (t>38.0°C) subject to the appropriate temperature conditions, hepatosplenomegaly, regurgitation and vomiting, oliguria, hypotension. Manifestation of septic shock is possible (8). With late neonatal sepsis, there is a gradual onset of the disease with the formation of a typical septic status: gray skin color, “marbling” of the skin, pathological weight loss or a flat body weight curve, prolonged jaundice, dyspeptic disorders, neurological and respiratory disorders, hemorrhagic syndrome, disorders blood circulation. The general clinical picture of neonatal sepsis is presented in the table (summarized scientific literature: 8, 11, 12, 15, 19, 20, 22). As can be seen from the table, it is important in the diagnosis of sepsis to detect signs of multiple organ failure, which is characterized by severe dysfunction of at least two organs, taking into account age-related characteristics. When diagnosing neonatal sepsis, it is also important to pay attention to the following symptoms that characterize the systemic inflammatory response: tachycardia more than 160 beats per minute or bradycardia (<110 beats per minute); anorexia, depression and/or seizures; oliguria (diuresis less than 1 ml/kg/min on the first day of life and less than 2 ml/kg/min on subsequent days with adequate fluid therapy), increased serum C-reactive protein > 6 mg/l and serum procalcitonin levels >2 ng/ml; lactic acidosis, hyperglycemia, leukocytosis (taking into account age indicators: 1-2 days >30 $00x10^9$, 3-7 days >20 $000x10^9$, >7 days of life > $15000x10^9$/liter) or leukopenia (leukocytes <5000 x 10^9 /liter), and also the above-mentioned hypothermia or fever, anorexia, central nervous system depression and/or convulsions.

If sepsis is suspected, dynamic monitoring of the child's condition is necessary. Sepsis in the neonatal period must be assumed in two situations:

- In the first three days of life, the presence of severe infectious toxicosis and at least three of the listed signs of a systemic inflammatory response.
- In newborns older than 3 days in the presence of a primary infectious-inflammatory focus (related to the environment) and at least three of the listed signs of a systemic inflammatory response.

A presumptive diagnosis is an indication for prescribing empirical antibacterial therapy, as well as carrying out the entire necessary amount of therapeutic measures. It is advisable to either confirm or reject the suspected diagnosis of sepsis within 5–7 days. The disappearance of signs of a systemic inflammatory response in parallel with the sanitation of the source of infection or the absence of a connection between the clinical manifestations of a systemic inflammatory response and the infection argues against the diagnosis of sepsis. The diagnosis of sepsis can be established immediately in the presence of a primary septic focus and metastatic purulent-inflammatory foci with a single pathogen in combination with laboratory indicators. However, it must be borne in mind that in case of sepsis in a newborn, it is not always possible to identify the source of infection (35, 39).

It is important to point out that many authors associate the development of long-term neurological complications with neonatal sepsis. Severe neonatal infection is associated with brain damage, neurodevelopmental delay, and cerebral palsy. Early infection doubles the risk of complications such as bronchopulmonary dysplasia, periventricular leukomalacia, intraventricular hemorrhage and retinopathy of prematurity. Chorioamnionitis and an increased risk of cerebral palsy are characteristic not only of preterm but also of full-term newborns. The most common complication is white matter lesions, which are characterized by focal cystic periventricular leukomalacia and/or diffuse necrosis, while any form of neonatal infection, including pneumonia with or without sepsis, meningitis with or without sepsis, and necrotizing enterocolitis with or without sepsis is associated with an increased risk of neurodevelopmental delays (8, 13, 21).

Neonatal Sequential Organ Failure Assessment (nSOFA) scores: The "Neonatal Sequential Organ Failure Assessment - nSOFA" scale has been proposed to predict mortality among premature infants with very low birth weight and patients with late-onset sepsis in newborns. Neonates with an nSOFA score greater than 4 had higher mortality compared with those with an nSOFA score less than 4. The nSOFA scores are useful for identifying organ dysfunction associated with mortality risk and are not influenced by pathogen, sex, hospital, or extreme prematurity. It is suggested that this indicator may serve as a basis for developing a consensus definition of sepsis in preterm infants (22, 28). Experience in using the nSOFA Scale in Russia has shown that the method is an adequate tool for measuring the severity of organ dysfunction and predicting mortality in premature newborns, regardless of the etiology of the disease (29).

EOS calculator: Kaiser Permanente Northern California (California, USA) has developed sepsis risk calculators for the treatment of late preterm and full-term neonates with risk factors for developing sepsis with early onset EOS (31). The risk score for developing EOS before newborn screening is calculated based on the local incidence of EOS, gestational age, time of rupture of membranes (membranes), maximum maternal body temperature during labor, maternal group *B streptococcus* colonization, and duration of antibiotic use during treatment. Based on population risk, a multivariate risk prediction model is used to estimate the likelihood of EOS in a given newborn and provides treatment recommendations. If the risk of EOS is ≥ 1/1000 live births, blood culture is recommended, and if the risk is ≥ 3/1000 live births, antibiotic therapy is recommended. Use of the EOS calculator in the United States in infants with gestational age at birth ≥34 weeks resulted in fewer antibiotic courses, laboratory tests, and hospitalizations without an increase in mortality or readmission. However, further research into the safety of this diagnostic system should be carried out to take into account differences in health care practices in different countries (8, 30). For preterm infants <34 weeks' gestational age and neonates with late-onset sepsis, EOS risk calculators are not valid (3, 30).

Biomarkers: Early diagnosis of sepsis and timely initiation of therapy can be achieved using biomarkers in a healthcare setting. The main biomarkers of neonatal sepsis include procalcitonin, interleukin-6, presepsin, C-reactive protein (CRP) and neutrophil gelatinase-associated lipocalin (NGAL). The use of these biomarkers, by eliminating the waiting phase for blood culture results, helps, in combination with clinical indicators, to initiate patient treatment in a timely manner, monitor therapeutic response, prevent the development of complications and reduce hospital stay. Many authors believe that biomarkers will be indispensable in the future in the diagnosis of neonatal sepsis (3, 5, 8, 13, 19, 21, 32). Optimal diagnosis requires identification of clinical signs in combination with laboratory results. According to international consensus, for the diagnosis of neonatal infection, the presence of a positive blood culture or at least laboratory and clinical criteria is a prerequisite (8).

Procalcitonin (PCT): This biologically active peptide is a precursor of calcitonin and is secreted in response to bacterial toxins circulating in the macroorganism. PCT values usually increase in newborns after delivery, reach a maximum at 24 hours and subsequently decrease to <0.5 μg/L by 72 hours. According to some authors, a PCT threshold value of 0.5 μg/L is valuable for the diagnosis of sepsis with late onset (8, 13). If there is no provoking stimulus, PCT is cleared from the bloodstream within 24-36 hours and is therefore used to assess the effectiveness of antibiotic treatment. PCT has higher sensitivity, specificity, and positive predictive value compared to CRP.

Given that PCT may be elevated in non-infectious conditions such as asphyxia and intraventricular hemorrhage, and the marked discrepancy between normal values between term and preterm neonates during the first 72 hours, it may not be useful as a sole marker of sepsis. Prophylactic antibiotics in cases of suspected bacterial infection may be discontinued once PCT levels have normalized and symptoms have resolved. However, PCT is not a sufficiently informative marker of early-onset sepsis (8, 13, 19, 33). In our clinic, the use of a PCT test in newborn premature infants with severe pneumonia showed that infants with a PCT level ≥10 ng/ml in the blood serum had a significantly longer severe condition, as well as a more frequent complicated course of the disease with the development of pneumothorax in 10.4% of infants, outcome in sepsis in 12.5% of infants, death in 10.4% of infants compared with infants with a PCT test value ≥2.0 but <10.0 ng/ml ($p<0.05$). This indicates the possible use of a PCT test to predict the development of severe complications (sepsis) in pneumonia in newborns (16).

C-Reactive Protein (CRP): CRP is an acute-phase inflammatory protein and one of the most readily available laboratory tests for diagnosing neonatal sepsis. Its synthesis is enhanced by cytokines, primarily interleukin-6 (IL-6), IL-1, and tumor necrosis factor-alpha (TNF-α). As with PCT, CRP levels may be elevated in noninfectious conditions such as meconium aspiration, asphyxia, and intraventricular hemorrhage. Depending on the method used to measure CRP, its normal threshold may vary. Those neonates born physiologically, especially those requiring instrumental treatment, may have CRP values >10 mg/L. There is often a discrepancy between CRP levels between preterm and term neonates with the same condition. Due to lack of sensitivity and specificity, a single CRP value cannot be used to diagnose neonatal sepsis. However, if two consecutive CRP values are normal, there is usually no bacterial sepsis (negative predictive value 99%). In this regard, for the diagnosis of early neonatal sepsis, two-time sequential determination of CRP in blood serum is recommended (8, 10, 19). According to a recent Cochrane review (2019), the CRP level at the initial assessment of an infant with suspected late-onset sepsis is not accurate for diagnosis (33). Studies have shown that PCT is a more informative biomarker than CRP for the early diagnosis of sepsis. As for determining the level of cytokines and molecular diagnostic methods, although they have greater sensitivity in late sepsis, they are currently not widely available in practical healthcare, because expensive and require the use of special equipment.

Other methods of diagnosis of neonatal sepsis: Currently, traditional laboratory diagnostic methods continue to be used as markers of systemic inflammation, namely, a clinical blood test measuring the number of leukocytes, erythrocytes, platelets, hematocrit, determination of the leukocyte formula and the ratio of immature and mature granulocytes. Lumbar puncture (if possible, given the child's condition) is indicated in patients with suspected meningitis (up to 30% of patients

with bacteremia develop meningitis). For sepsis, indicators: cytosis > 20/3; protein > 1 g/l; sugar < 70-80% of blood concentration. However, the test is often not very informative for diagnosing early sepsis. A coagulogram is also examined (signs of disseminated intravascular coagulation syndrome are possible); determine indicators of the acid-base state (in sepsis the characters are acidosis, base deficiency, hypoxemia, hypercapnia, lactatemia); X-rays of the chest and abdominal organs are performed; Ultrasound of organs, EchoCG + ECG (11, 12).

A sepsis diagnostic system based on the molecular method of multiplex polymerase chain reaction PCR quantitative amplification in real time (qPCR) is considered promising for the rapid and accurate detection of this disease. However, using this method it is not possible to distinguish between active infection and recently destroyed infections. Bacterial PCR assays do not distinguish between viable and nonviable microorganisms, free and cell-associated DNA, and do not provide sufficient information about antibiotic resistance. In addition, there is a high probability of detecting contaminating microorganisms from the external environment, which requires clinical correlation with the results of the method (4, 7, 8, 13, 19). Biomarkers such as interleukins (IL-6, IL-4 and IL-10), tumor necrosis factor-alpha (TNF-alpha), serum amyloid A (SAA) and CD64 cell surface antigen are expensive and are not routinely used for diagnosis . Some promising biomarkers of necrotizing enterocolitis are fecal calprotectin; an intestinal protein that binds fatty acids, claudins and trefoil factor 3 (34). Currently, there are automated systems for microbiological diagnosis of sepsis. Thus, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is effective for the early detection of microbes in the blood. This Nobel Prize-winning method is considered the most promising for the rapid identification of isolates and their antimicrobial susceptibility (10).

Blood culture: The gold standard for diagnosing neonatal sepsis is blood culture (1, 3, 8, 13, 23, 21). When bacterial cell counts are low, 60% of blood cultures may be false negative with a sample volume of 0.5 mL. In this regard, when studying blood culture, it is necessary to introduce at least 1 ml of blood into the culture vial. Multiplex PCR is used to quickly identify the most common bacteria and fungi that cause sepsis, as well as their antibiotic resistance genes (3, 30, 36, 41). To increase the inoculability of bacterial pathogens in blood culture, it is recommended to follow the following rule. Often, a patient with sepsis will experience an increase in body temperature at approximately the same time of day. This is due to the fact that the pathogen enters the bloodstream from the source of infection at approximately the same time of day. Then, within about two hours, blood phagocytes (neutrophils) are activated, destroy the pathogen and release its breakdown products, which leads to a pyrogenic reaction. Therefore, if it is possible to establish the time of the cyclic rise in temperature, then it is advisable to take blood for culture approximately two hours before an attack of fever, when the pathogen has not yet been destroyed by phagocytes and is viable.

Treatment of neonatal sepsis: Treatment of neonatal sepsis, like the treatment of other infectious and inflammatory diseases, should be carried out in two stages with the sequential use of empirical and targeted antibacterial therapy, which is the basis for the complex treatment of this disease (9, 10, 21, 27, 29, 32, 35). In the available scientific literature, you can find more than 200 options for the use of antibiotics in newborns with sepsis. This is not surprising, since treatment is carried out taking into account the huge species diversity of pathogens, the even greater diversity of pathogen resistance to antibiotics, which constantly changes over time and requires constant epidemiological monitoring. The basic rule for prescribing empirical treatment remains the need to use antibiotics that cover the possible range of pathogens sensitive to them in the hospital or region. The question of the advisability of monotherapy or combination therapy remains an open and intensively discussed problem. Proponents of the latter point to a better outcome in sepsis. In addition, there is the possibility of pathogen association, and there are proven mechanisms of additive or synergistic effects of drugs. In addition, the success of combination therapy also appears to be associated with an increased likelihood of pathogen sensitivity to at least one of the antibiotics. Proponents of monotherapy warn about the danger of the spread of multidrug-resistant strains with intensive use of antibiotics. However, with monotherapy, the effect is often insufficient, which requires a change in medication. In this regard, doctors face a serious challenge when choosing an antibiotic and maintaining the optimal balance between the expected effect of treatment and minimal negative effects (6, 8, 10, 13, 21).

The monotherapy is now recommended in most cases for early sepsis in infants. The exceptions are a) neutropenia and sepsis with gram-negative bacteria and multidrug resistance and b) *Streptococcus pneumoniae* bacteremia. If combination therapy is used empirically, its recommended duration is no more than 3–5 days (1, 6, 8, 10, 21, 32). For sepsis caused by *Acinetobacter baumannii*, combination therapy with colistin/sulbactam is indicated as more effective than colistin monotherapy. Colistin/sulbactam improved the clinical and microbiological effect of treatment and reduced mortality (21).

Of particular concern are multidrug-resistant Gram-negative bacteria, which are associated with high morbidity and mortality in infants. The emergence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* represents another challenge in the treatment of neonatal sepsis, and despite their relative rarity, carbapenem-resistant *Enterobacteriaceae* are a growing global threat (8, 10). The current recommendation is to follow the principles of an antibiotic stewardship program, which includes strengthening infection prevention and control, prescribing appropriate antibiotics only when needed and in appropriate doses, keeping antibiotics to the shortest possible duration, and reviewing therapy once culture results are available. Audit of antibiotics used and close monitoring of microbial resistance patterns in intensive care units are also important components of antibiotic stewardship. Early administration of antibiotics active against the pathogen is the cornerstone in the treatment of neonatal sepsis. Recent evidence suggests that empirical selection of antibiotics for treatment is based on the suspected pathogen. According to foreign authors, the combination of ampicillin and gentamicin is the most suitable treatment method against common pathogens in most countries - *GBS* and *E. coli*. If meningitis is suspected, it is recommended to replace the aminoglycoside with an extended-spectrum cephalosporin (cefotaxime). Ceftriaxone is not recommended for use in newborns because it increases serum bilirubin levels. The proposed first-line drug for the treatment of late sepsis is flucloxacillin (or ampicillin) in combination with gentamicin. Second-line treatment is the use of vancomycin or teicoplanin, as well as a broad-spectrum antibiotic against gram-negative

bacteria (piperacillin/tazobactam). When a specific pathogen is isolated, treatment must be targeted (8, 13). A study by Bhishma Pokhrel., *et al*., (2018) recommended a combination of piperazine-tazabactam and ofloxacin as first-line empiric therapy (successful in 50% of isolates) and vancomycin and meropenem as second-line. For late-onset sepsis in infants due to Gram+ bacteria, two dosing regimens are currently being explored in the literature: The optimized regimen consists of a loading dose of vancomycin (25 mg/kg) followed by 15 mg/kg for 5 ± 1 days every 12 or 8 hours , depending on gestational age. The standard regimen is a 10 ± 2-day course of vancomycin at a dose of 15 mg/kg every 24 hours, every 12 hours, or every 8 hours, depending on gestational age (36). For late sepsis in newborns with a birth weight of less than 1500 g, caused by coagulase-negative *Staphylococcus* or *S. aureus*, courses of monotherapy with oxacillin and vancomycin were obtained with comparable good clinical efficacy. The use of oxacillin made it possible to reduce the frequency of formation of *Enerorococcus spp*. autostrains resistant to vancomycin (24). To improve the effectiveness of early diagnosis and treatment of sepsis, a new edition of the guideline was proposed in 2021, including a set of activities called «The Surviving Sepsis Campaign (SSC) guidelines or The Hour-1 Bundle». Analysis of the application of the Recommendations showed that doctors pay attention to the prescription of broad-spectrum antibiotics, the need for blood cultures before administering antibiotics, and measurement of blood lactate levels. The duration of antibacterial therapy should be determined depending on the site of infection, microbiological etiology, patient response to treatment and monitoring of sanitation of the site of infection (32). Antibacterial therapy for sepsis must be combined with syndromic and pathogenetic therapy. Optimal temperature conditions and oxygen supplementation, parenteral nutrition with the fastest possible transition to enteral nutrition (preferably breastfeeding) must be provided. For many years, intravenous immunoglobulins have been effectively used in neonatal sepsis as replacement therapy, since newborns have a deficiency of endogenous immunoglobulins (20). It is important that the use of complex therapy, including antibiotics and supportive treatment with detoxification measures, suppresses the synthesis of molecular patterns associated with damage, weakens their effect on the tissues of the macroorganism, and promotes the elimination of toxins. To increase the effectiveness of antibacterial therapy for sepsis in newborns and reduce the consequences of possible complications, O.J. Butranova *et al*., (2023) suggest taking into account the pharmacokinetics of a particular patient when prescribing antibiotics. The correct dosing regimen is essential for safe and effective antibiotic therapy, but its choice in the newborn is complicated by the high variability in the maturation of organ systems that affect drug absorption, distribution, metabolism, and excretion. At the same time, population pharmacokinetics is necessary for the development of standard drug regimens. However, it should be taken into account that the neonatal population is very heterogeneous, and this heterogeneity is mainly determined by gestational and postnatal age, so the determination of individual pharmacokinetics, if technically possible, will improve treatment (37).

To prevent the development of late sepsis and ulcerative necrotizing enterocolitis, and to correct disorders of the intestinal microbiocenosis in newborns with sepsis, a number of authors are considering the possibility of prescribing probiotics (6, 7, 38). This is due to a significant disruption in the formation of normal microflora of the digestive tract in newborns receiving massive antibacterial therapy, especially with broad-spectrum drugs. There is also a rapid development of resistance to antibiotics in intestinal microflora against the background of antibacterial therapy (6). In recent years, there have been reports of a possible negative effect of probiotics on the course of sepsis in some newborns, with possible penetration of probiotic bacteria into the blood. Titki Kulkarni *et al*., (2022) reviewed 16 studies that reported 32 preterm infants with probiotic sepsis. Most infants were less than 32 weeks gestational age at birth. Bifidobacterium spp. were cultured in their blood. (in 19 children), Lactobacillus spp. (in 10), Saccharomyces (in 3). In 29 out of 32 cases these were probiotic strains introduced with the drug. 29 children were treated with antibacterial drugs, and 3 received antifungal treatment. The development of probiotic sepsis is associated with severe immaturity of the gastrointestinal tract and low local immunity, which leads to increased permeability of the intestinal barrier to microbes. Although such a complication is extremely rare, one must keep in mind its possible development, especially in very premature infants. The authors draw attention to the need to optimize probiotic therapy in such children (38).

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Prevention of neonatal sepsis: The development of early sepsis in recent years has been significantly reduced by conducting a program of screening mothers for infection and appropriate timely antibiotic prophylaxis. According to many authors, compliance with epidemiological measures (hand hygiene, use of disposable sterile bags for the care of patients with sepsis, monitoring of hospital microflora), early initiation of trophic feeding and the use of exclusively (if possible) breast milk; if possible, reducing the duration of catheter use and probes are proven means of preventing neonatal sepsis (8, 11-14, 21). Prophylactic use in newborns of probiotics containing bifidobacteria and/or lactobacilli, complexes of bifidobacteria with lysozyme or immunoglobulins (lactoglobulins) significantly reduces the incidence of severe neonatal infection, including sepsis (16, 35, 39, 40).

Promising directions for research in neonatal sepsis: The high morbidity and mortality of newborns from sepsis dictates further research aimed at significantly reducing these indicators. To achieve this goal, many authors (2, 4, 7, 9, 11, 12, 13, 15, 17, 21, 27, 33, 34, 38, 40) consider the following areas promising:

- It is important to assess maternal risk factors for infection and undergo a thorough clinical examination during pregnancy. The development of measures for basic care of the mother and newborn includes umbilical cord hygiene, clean childbirth, maintaining the physiological body temperature of the newborn, and breastfeeding. According to the forecast, these measures should reduce neonatal mortality from serious infections by 20-50% (13).
- Development of modern fast and highly informative methods for early laboratory diagnosis of sepsis in newborns, including methods of molecular genetic research. Future studies should be aimed at identifying new genomic and proteomic markers for rapid and accurate detection of neonatal sepsis. The emergence of new technologies that make it possible to type and characterize microorganisms without the need to use traditional cultivation methods will significantly speed up the diagnosis and prescription of rational antibiotic therapy.
- Development of clinical and laboratory indicators for predicting the development of sepsis and its complications.
- Microbiological control of the change in the prevailing hospital microflora in hospitals.
- The active use of antibiotics for prevention and treatment and the subsequent development of resistance in microbes is a serious concern. In this regard, macroepidemiological analysis of the spread of multidrug-resistant pathogens at the city, regional, national and global levels is relevant.
- Conducting timely, adequate antibacterial and supportive therapy in infants with sepsis and other severe infections. Conducting research on the possible reduction of the duration of antibiotic use for the prevention and treatment of hospital infections. Determining clear indications for monotherapy and combination antibiotics in infants with sepsis.
- Development of clear indications and regimens (choice of antibiotic, dose, duration of antibiotic use) for prophylactic antibiotic therapy in clinically healthy infants, especially in infants with negative blood cultures, but with risk factors for the development of sepsis. Recommendations for local sanitation with oral antiseptic chlorhexidine and selective decontamination of the digestive tract for the prevention of hospital-acquired infections in infants require further study.
- Long-term clinical observation of infants who suffered sepsis at neonatal age. Monitor and evaluate long-term outcomes of the respiratory, nervous system, kidneys and digestive tract.

CONCLUSION

Neonatal sepsis remains a widespread and serious disease. Active study of its main aspects (risk factors, etiology, pathogenesis, prevention and treatment) can improve the situation. However, further unification of efforts is necessary to develop new approaches to rapid and accurate laboratory diagnosis, monitoring of antibacterial resistance of pathogens, selection of adequate treatment and monitoring of its effectiveness.

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