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Review Article

Newer Insights in Etiology and Pathogenesis of Neonatal Sepsis

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Abstract

Neonatal sepsis is a pathophysiological response to the presence of microorganisms or their toxins in the blood during the first 28 days of life. Despite advances in neonatal intensive therapy and care, sepsis is still an important cause of morbidity and mortality in neonates, especially preterm and low birth weight neonates. Early neonatal sepsis manifests itself in the first 72 hours of life. The main risk factor for early neonatal sepsis is chorioamnionitis, and the most important causative are *Streptococcus* group B and *Escherichia coli*. Late neonatal sepsis manifests itself after 72 hours of life, and most often occurs in preterm neonates. Among the causative agents of late neonatal sepsis, coagulase-negative *Staphylococcus* dominates. The neonates are highly dependent of the innate immune system to defend against infection. In the pathophysiological response of the organism to infection, microcirculation, neutrophils and monocytes are first activated, and then the complement and the coagulation system. Also, mitochondrial dysfunction contributes to tissue damage in neonatal sepsis. The delayed response of adaptive immunity in the neonatal period is compensated by transplacental transfer of IgG antibodies originated from the mother, but also the IgA antibodies that the neonates receive from mother's milk. Compared to adults, the immune response have quantitative and qualitative differences, which contributes to their increased susceptibility to infection.

Keywords: *Neonate; Sepsis; Neonatal immunity; Microorganisms.*

Introduction

Despite advances in neonatology and neonatal intensive therapy and care, sepsis is still an important cause of morbidity and mortality in neonates, especially preterm and low birth weight (LBW) neonates. Neonate's immune system is developing, and they have little immunological memory, which increases their vulnerability to microorganisms and infection (1,2). Data on the incidence of sepsis in the neonatal period, during the first four weeks of life, are scarce and missing from many countries in the world. The Global Burden Disease (GBD) Study published in 2018 estimated 1.3 million annual cases of neonatal sepsis, approximately 937 cases per 100000 live births, and 203000 deaths associated with neonatal sepsis (3-5).

Definition of neonatal sepsis

Bacteriemia refers to bacteria in the bloodstream that are alive and capable of reproducing. However, when the immune response is inadequate, either due to immaturity, congenital immune disorders, or becomes overwhelmed, microorganisms, their parts and toxins spread, and septicemia occurs. Undiagnosed and untreated bacteremia leads to the development of systemic inflammatory response syndrome (SIRS), sepsis, septic shock and multiple organ dysfunction syndrome (MODS) (6,7).

Neonatal sepsis is a pathophysiological response to the presence of microorganisms or their toxins in the blood during the first 28 days of life. Neonatal sepsis is classified by age of onset and timing of the sepsis episode as early-onset sepsis (EOS) and late-onset sepsis (LOS). Early-onset sepsis is defined as infection of a sterile site before 72 hours after birth, and LOS refers infection after 72 hours of life (8,9,10).

Risk factors and etiology of early-onset neonatal sepsis

Early-onset sepsis is usually due to vertical transmission of microorganisms from mother to neonate and may be acquired before or during delivery. Risk factors for the EOS include maternal and fetal/neonatal factors. The main material risk factor for EOS is chorioamnionitis, an intraamniotic infection, often as a result of prolonged rupture of the chorioamniotic membrane (PROM) which allows microbial invasion of the amniotic fluid (1,10,11). Research has shown that approximately 40% of neonates, especially born preterm, with EOS are born to mothers with chorioamnionitis (12-14). Other maternal factors associated with an increased risk for EOS in the neonates include maternal colonization by *Streptococcus β-haemolyticus* group B (GBS), inadequate maternal intrapartum antibiotic prophylaxis for GBS infection, intrapartum maternal fever, maternal urinary tract infection, PROM which lasts longer than 18 hours and obstetric interventions. The important neonatal risk factors for EOS are prematurity and LBW (< 2500 g). Also, meconial amniotic fluid, perinatal asphyxia (Apgar score < 6), need for endotracheal intubation (ETT) and insertion of an umbilical vascular catheter is associated with increased risk for EOS (1, 8,10,11,15-18).

Studies indicate that the most important causative microorganisms for EOS in the term and late preterm neonates are GBS and gram-negative enteric bacilli, predominantly *Escherichia coli*. In very preterm neonates, born before 32nd weeks of gestation, *Escherichia coli* is a more common cause of EOS compared with GBS. Other bacteria, causative agents of EOS in the neonates, whose cumulative frequency is about 30%, are shown in Table 1 (10, 17-19).

Table 1. Etiology of early-onset neonatal sepsis.

Term and late preterm neonates (more than 34 weeks of gestation)	Preterm neonates less than 34 weeks of gestation
GBS *Escherichia coli*	*Escherichia coli* GBS
Listeria monocytogenes *Staphylococcus aureus* Coagulase-negative *staphylococci* *Enterococcus sp.* untyped *Haemophylus influenzae* gram-negative bacteria (including *Klebsiella*, *Enterobacter*)	

Risk factors and etiology of late-onset neonatal sepsis

Late-onset sepsis in the neonates is usually due to horizontal transmission of microorganisms from the community or the hospital. The leading risk factor for LOS in the neonates is prematurity. The incidence of LOS is inversely proportional to gestational age and birth weight. Late-onset sepsis is a complication of treatment of preterm neonates in neonatal intensive care units (NICU). Other factors associated with prematurity and an increased risk of LOS are immaturity of the innate and adaptive immune response, insufficient breastfeeding, long-term total parenteral nutrition, need for ETT and mechanical ventilation, as well as presence of a central venous catheter (CVC) (1,10,15,16,20). Extensive and prolonged use of antibiotics allows proliferation of resistant bacteria in neonatal microbial flora and increased risk for sepsis (19,21,22).

Late-onset neonatal sepsis is most often caused by gram-positive bacteria. Coagulase-negative *staphylococci* are the most commonly isolated bacteria in neonates with LOS. *Staphylococcus aureus* is the most common cause of LOS in the neonates with CVC. In approximately of 20% neonates, gram-negative bacteria are causes of LOS. Late-onset neonatal sepsis caused by fungi typically affects very LBW neonates. The most common fungi that cause LOS are *Candida albicans* and *Candida parapsilosis*.

In developing countries, gram-negative bacteria are the most common causes of LOS in the neonates (1,8,10,17-20). The Etiology of LOS is shown in Table 2.

Table 2. Etiology of late-onset neonatal sepsis.

Bacteria	Fungi
Gram-positive bacteria – Coagulase-negative *staphylococci* – *Staphylococcus aureus* – GBS – *Enterococcus sp.* Gram-negative bacteria – *Escherichia coli* – *Klebsiella* – *Enterobacter* – *Citrobacter* – *Pseudomonas* – *Serratia* – *Acinetobacter*	*Candida albicans* *Candida parapsilosis*

The role of skin and epithelial barriers in neonatal sepsis

The skin and mucous membranes of the gastrointestinal tract (GIT), respiratory tract, and genitourinary tract are covered by a continuous epithelium consisting of tightly connected cells that provide a physical barrier to the penetration of microorganisms. Epithelial cells also produced antimicrobial proteins and peptides (APP), including defensins and cathelicidins, which kill microorganisms by damage their outer membranes. Thus, mucous membranes represent chemical barriers against infection (23,24).

Vernix caseosa is a protective layer on the skin surface of late preterm and term neonates, which improves its function as a physical barrier to the penetration of microorganisms. Vernix caseosa is produced by the fetal sebaceous glands during the last trimester of pregnancy and is absent in extremely preterm neonates. Also, vernix contains APP and antioxidants which can kill or inactivate microorganisms that cause neonatal sepsis, such as GBS, *Escherichia coli* and *Candida* (23,25,26).

In preterm neonates, there is immaturity of the skin and incompletely developed stratum corneum of the skin. Also, skin and mucous membranes are injured by various invasive diagnostic and therapeutic procedures (ETT, venipuncture, placement of a CVC, bladder catheterization). These are factors that reduce the efficiency of the skin and mucous membranes as a physical and chemical barrier against microorganisms and increases the risk of sepsis (8,23,24).

The respiratory tract is the site of daily intake of a huge number of microorganisms that are normally found in the environment. However, the presence of an endotracheal tube and/or the use of positive pressure ventilation (PPV) can lead to injury of epithelial cells and decrease in mucociliary clearance, which further increases the risk of infection. Surfactant proteins A and D (SP-A, SP-D), lung collectins, are essential components of innate immune system. These proteins play an important role in host defense and regulate inflammation during bacterial, viral and fungal infection. A surfactant deficiency as a consequence of prematurity or of injury associated with mechanical ventilation increases the risk of developing neonatal infection (23,27-30).

The mucosa of the GIT, soon after birth, is colonized by bacteria that form the intestinal microbiota. In the presence of the microbiota type 3 intestinal innate lymphoid cells produces interleukin (IL)-17, drives neutrophilia and can protect the neonates of the infection. Damage to the mucosa of the GIT, as a result of prolonged use of antibiotics, hypoxia and other stress conditions, lead to the translocation of bacteria and the development of necrotizing enterocolitis (NEC) and LOS in the neonates. In preterm neonates, additional factors, such as lower acidity of gastric contents, intestinal hypomotility and less amount of protective mucus, increase the risk of developing sepsis (23,31-34).

Invasion of the subepithelial space and activation of innate immunity

After damage to the skin and mucous membranes, microorganisms penetrate through the layer of epithelial cells, pass through the basal membrane and enter the subepithelial space, where they come into contact with cells of the innate immune response. Microorganisms recognition by local immune sentinel cells. As a result of contact between microorganisms, their parts and toxins, and components of innate immunity, an inflammatory response develops. The cells and molecules of innate immunity recognize structures which are common to different classes of microorganisms but are absent on human cells. The molecules of microorganisms that stimulate innate immunity are called pathogen-associated molecular patterns (PAMPs) and these are usually structures necessary for their survival and infectivity, including cell wall and membrane components (lipopolysaccharide (LPS) of gram-negative bacteria, peptidoglycan of gram-positive bacteria), nucleic acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), flagellum and carbohydrates. These PAMPs are recognized by pattern recognition receptors, and they are found on the surface of phagocytes, dendritic cells, and many other cell types. Also, molecules that are released from damaged or necrotic host cells, recognized by the innate immune system, are called damage-associated molecular patterns (DAMPs). Cellular receptors for microorganisms and damaged cells belong to several protein families, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors, retinoic acid-inducible protein 1 like receptors (RLRs), peptidoglycan recognition proteins and β_2-integrins. The most important among them are TLRs and there are 10 types in human population. Each type of TLRs is specific for a certain component of the microorganism. For example, TLR-2 recognizes peptidoglycan, TLR-4 is specific for LPS. Also, the protein flagellin, which is part of bacterial flagella, signals through TLR-5 and TLR-9 recognizes unmethylated CpG double-stranded DNA. Nucleic acids, such as single-stranded or double-stranded RNA, which are part of the viral cell, recognized by TLR-3, TLR-7 and TLR-8 (23,24,35,36). In the GIT after birth, there is a reduced reactivity of TLRs to LPS, which probably represents a form of adaptation of the neonates to avoid a strong response to gram-negative bacteria colonizing the GIT (37). Activation of TLRs by PAMPs and DAMPs generates signals and triggers the production and activation of various transcription factors. The most important transcription factor is nuclear factor kB (NF-κB), which stimulate expression of inflammatory cytokines and chemokines, as well as endothelial adhesion molecules that play important roles in the regulation of the inflammatory process (23,24,38,39). Because TLRs play the most important role in recognition and response to microorganisms, polymorphisms or mutations in genes for individual TLRs are associated with increased risk for the development of sepsis in the neonates. Function of other types of receptors for microorganisms, such as NLRs or RLRs, has not been extensively studied in neonates with sepsis (9,23,40).

Changes in blood vessels in inflammation

Endothelial cells form a single layer of cells that lines all blood vessels and provides a barrier and regulation of the exchange of substances between the circulating blood and the surrounding tissues. Endothelial cells are interconnected by adherent junctions and tight junctions. The endothelial cell layer is covered by an extracellular structure called glycocalyx, which is rich in carbohydrates. The studies have shown the significant role of vascular endothelial activation in the early stage of inflammation caused by infection (41,42). During tissue damage caused by the action of microorganisms and infection, there is a reaction of microcirculation blood vessels. First, there is a short-term vasoconstriction of arterioles, followed by vasodilation with increased arterial blood flow. Due to its extracellular apical position, microorganisms in the blood first react with the glycocalyx and lead to its disruption. Damage to the glycocalyx increases the permeability of endothelial cells associated with capillary leakage, the release of proteins and fluids into the interstitial space, hypovolemia and edema formation. As a result of protein and fluid transudation into the interstitium, blood viscosity increases, blood flow slows down, increasing exposure of leukocytes to endothelial adhesion molecules and their adhesion to the surface of the endothelium. The disruption of glycocalyx and activation of vascular endothelium creates a prothrombotic environment and can make a contribution to diffuse microvascular thrombosis (10,41,43,44).

Vasoactive mediators, such as platelet activating factor, thromboxane, leukotrienes, nitric oxide (NO), histamine, bradykinin, and prostaglandins, produced by activated leukocytes, platelets, and endothelial cells, change vascular tone and contribute to vascular permeability. The balance of NO, a vasodilator, and endothelin-1, a vasoconstrictor, can be disrupted due to damage to the vascular endothelium, which consequently leads to ischemia and tissue damage (9,23).

The role of phagocytes in pathogenesis of neonatal sepsis

Two types of phagocytes participate in inflammation, neutrophils and monocytes. The main role of these cells is phagocytosis, recognition, ingestion and killing of microorganisms. Neutrophils or polymorphonuclear leukocytes are the first cells in early stage of inflammation, especially in response to bacteria and fungi. Neutrophils arrive at the focus of infection 6-24 hours after the initial damage, but they live for only several hours in tissues. Chemokines, bacterial products or cytokines (especially IL-8), stimulate migration of neutrophils in the focus of infection. Reactive oxygen and nitrogen species produced by neutrophils during phagocytosis, as well as the lysosomal enzyme called myeloperoxidase, which is found in their azurophilic granules, have a strong bactericidal effect (8,9,24). Neutrophils in neonates have quantitative and qualitative deficiencies, which reduces their ability to fight infection and increases the risk of developing sepsis. In neonates, especially those born prematurely, there is a limited reserve of neutrophil progenitors in the bone marrow, the proliferative pool of neutrophils is reduced, which results in decreased development and production of neutrophils. Neutropenia increases the risk for the development of bacterial infection, and it's especially often seen in neonatal sepsis caused by gram-negative bacteria. Neonatal neutrophils also have functional limitations, such as reduced mobility due to inadequate adhesion to the vascular endothelium, migration and chemotaxis towards the focus of infection and reduced phagocytosis capacity. In addition, neutrophils in the neonatal period have fewer cytotoxic granules in the cytoplasm, which reduces their ability to kill microorganisms (45,46,47).

After 24-48 hours of the initial tissue damage in the infection, neutrophils are replaced by monocytes. Monocytes are less numerous in the peripheral blood compared to neutrophils and move more slowly, so they arrive later at the focus of infection. During inflammation, monocytes migrate to extravascular tissues and differentiate into cells called macrophages, which provide long-term protection against infection. In addition to performing phagocytosis, monocytes have other important roles in host defense, such as the production of cytokines that regulate and initiate inflammation, remove dead tissues and initiate the process of tissue repair (24). In neonates, monocytes/macrophages have a completely preserved ability to phagocytose, ingest and kill microorganisms due to the strong production of reactive oxygen species (ROS). However, in the neonatal period, monocytes/macrophages have a reduced ability to produce proinflammatory cytokines (48,49).

Mediators of inflammation

In response to microorganisms, macrophages, dendritic cells, mast cells, endothelial cells, fibroblasts, platelets and other cell types produce cytokines, various molecules and substances, that participate in the inflammation process. Proinflammatory cytokines lead to the activation of the vascular endothelium, increase the expression of endothelial adhesion molecules and facilitate the production of chemokines, which leads to the migration of leukocytes to the focus of infection. Also, these cytokines participate in the activation of the complement system, as well as the activation of the coagulation and fibrinolysis system. In addition, they stimulate the production of vasoactive substances. The main proinflammatory cytokines are tumor necrosis factor alpha (TNF-α), IL-1β, IL-6 and IL-8 which are mainly produced by macrophages. Compared to adults, neonates with sepsis produce lower levels of proinflammatory cytokines, such as IL-1β, TNF-α, interferon-γ (IFN- γ), and IL-12 (9,23,50).

In inflammation, cells also produce anti-inflammatory mediators, which antagonize and modulate the effects of proinflammatory cytokines. The leading anti-inflammatory role is played by IL-10 and transforming growth factor beta (TGF-β). Also, endogenous cortisol has an anti-inflammatory role, it reduces the intensity of the systemic inflammatory response in severe sepsis and septic shock. Cortisol production by adrenal cortex cells increases in the early stage of neonatal septic shock. However, in neonates born before 32nd weeks gestation, there is a condition called transient or relative adrenal insufficiency (RAI) as a result of the developmental immaturity of adrenal cortex. In conditions with increased demands for cortisol, such as sepsis and septic shock, RAI causes insufficient production of cortisol, which contributes to hemodynamic instability and hypotension in preterm neonates (50,51,52). If the homeostasis of inflammatory mediators is disturbed due to excessive production of proinflammatory cytokines, a "cytokine storm" occurs, which results in the development of SIRS and MODS (9,53).

Measurement of the concentration of proinflammatory and anti-inflammatory cytokines in the blood of neonates with sepsis has been shown to be useful for early diagnosis of sepsis and prediction of disease severity (50). Proinflammatory cytokines, including IL-1, IL-6 and TNF-α, stimulate hepatocytes to increase the synthesis and production of positive acute-phase reactants, such as C-reactive protein (CRP), procalcitonin (PCT), serum amyloid A (SAA), lactoferrin, haptoglobine and fibrinogen.

IL-6 is the main cytokine that stimulate CRP production. Measuring the concentration of acute-phase reactant proteins is important in clinical practice for diagnosing sepsis and monitoring the effectiveness of therapy (23).

Role of complement system in host defense and pathogenesis of neonatal sepsis

The complement system consists of several proteins, mostly from the group of proteolytic enzymes, whose activation breaks down other complement proteins. In addition, the complement system participates in the regulation of the inflammation process, by activating the coagulation system, increasing the production of proinflammatory cytokines, activating leukocytes and increasing their migration to the focus of infection (24,54). There are three pathways of activation of the complement system cascade, the alternative, classical and lectin pathways. The main component of complement system is plasma protein called C3, which is broken down by enzymes into proteolytic fragments, C3a i C3b. Fragment C3a facilitates phagocytosis and fragment C3b initiates the next steps of activation complement system, resulting in the formation of a multiprotein complex called the membrane attack complex (MAC), that insert into cell membrane of microorganisms, leads to its disruption, increased permeability and osmotic lysis (24).

The complement system in neonates is under development and has reduced functional capacity. The neonates, especially very preterm neonates, have reduced basal levels of proteins of the complement system, which increases their susceptibility to infections. Dysregulation of the complement system results in excessive activation of the vascular endothelium and production of proinflammatory cytokines, leading to SIRS, sepsis, and septic shock (2,9,54).

Activation of the coagulation cascade in neonatal sepsis

The coagulation system is composed of several plasma proteins that are activated by the action of various substances that are released from damaged tissue or by inflammation. Coagulation consists of three pathways, the extrinsic, intrinsic, and common pathways. The result of the activation of the coagulation system is the creation of thrombin, which breaks down fibrinogen and creates a fibrin clot. It creates a procoagulant state in the microcirculation surrounding the focus of infection, which it aims to prevent further dissemination of infection, keeps microorganisms at the site of inflammation, which are phagocytosed by neutrophils and macrophages. In addition, the activation of this system aims to prevent bleeding. Certain features of neonatal hemostasis, such as decreased levels of vitamin K-dependent coagulation factors, decreased thrombin generation, and decreased levels of coagulation inhibitors, increase the risk of bleeding in the neonatal period. Also, reduced platelets function, especially in preterm neonates, increases the risk of bleeding. Neonatal sepsis is often associated with thrombocytopenia, probably due to damage to the vascular endothelium and activation of the reticulo-endothelial system, as well as increased platelet consumption and decreased level of thrombopoietin (23,55,56).

A massive, uncontrolled and prolonged inflammatory response resulting from damage to the vascular endothelium and systemic activation of the coagulation system leads to the emergence of disseminated intravascular coagulation (DIC). This acquired condition of consumptive coagulopathy leads to bleeding, but also to microvascular thrombosis, due to the deposition of fibrin in small blood vessels. This results in inadequate tissue perfusion and the occurrence of MODS. The development of DIC is correlated with an elevated serum concentration of IL-6. Laboratory findings in DIC include prolongation of the prothrombin time (PT), prolongation of the activated partial thromboplastin time (aPTT), low fibrinogen, elevated D-dimers, and hemolytic anemia (23,57,58).

Mitochondrial dysfunction in neonatal sepsis

Oxidative phosphorylation or phosphorylation related to electron transport is the main metabolic pathway for the production of cellular energy in the form of adenosine triphosphate (ATP). Enzyme complexes that participate in the process of electron transport are located on the inner mitochondrial membrane. Although oxidative phosphorylation is extremely important for cellular metabolism, during the process itself, ROS are created and free radicals spread, which lead to cell damage. During sepsis, there is a dysfunction of electron transport in mitochondrial enzyme complexes, which reduces the production of ATP for normal cell functioning. Also, mitochondrial dysfunction leads to disturbance of vascular endothelium homeostasis, microcirculation damage and development of hyperinflammation, accompanied by increased production of ROS. Damage to mitochondria during sepsis leads to increased oxidative stress, reduced glutathione concentrations, mitochondrial membrane disruption, and leakage of mitochondrial DNA (mDNA) into the circulation, which can be recognized by the host's innate immune cells as DAMPs, contributing to the persistence of systemic inflammation. Overall, mitochondrial dysfunction is a important mechanism contributing to organ failure in neonatal sepsis and poor clinical outcome (9,10,59).

Adaptive immune response and passive immunoglobulins in neonatal infections

Neonates are highly dependent on components of the innate immune system to defend against infection during the first days of life. Adaptive components of the immune system have a delayed response in the neonatal period. In EOS, the protective role of adaptive immunity is completely absent, since it takes 5-7 days for the multiplication of specific clones of T- and B-lymphocytes and the creation of immunological memory. Compared to adults, neonatal lymphocytes, as the main cells of adaptive immunity, have significant quantitative and qualitative differences. The proliferative capacity and ability to activate T-lymphocytes in response to the microorganism are limited, and B-lymphocytes have a predominantly "naive" phenotype. Memory B-lymphocytes are rare. The most abundant class of antibodies produced by neonatal B-lymphocytes is IgM (23,60,61,62).

The delayed response of adaptive immunity in the neonatal period is compensated for by passive immunity. Starting from the 20th weeks of gestation, transplacental transfer of maternal antibodies to the fetus occurs. These antibodies are predominantly of the IgG class, and they provide protection against infection in the first six months of life. All IgG antibodies in neonates are of maternal origin. As a result of a shorter gestation period, preterm neonates have a lower serum concentration and diversity of IgG antibodies compared to term neonates, disappearing from the circulation earlier, which contributes to their increased susceptibility to developing sepsis. Neonatal immunity and neonate defense against infection is also contributed by the amount of antibodies that the neonate receives from mother's milk through breastfeeding (23,62,63).

Conclusion

Neonatal sepsis is a devastating condition and significant cause of morbidity and mortality, especially in preterm neonates. Since the clinical signs of neonatal sepsis are nonspecific, knowledge of risk factors originating from the mother and/or the neonate can help identify the group of neonates who are at the highest risk for developing sepsis and its complications. Complex molecular and cellular systems are involved in the pathophysiology of neonatal sepsis. Numerous cytokines and acute-phase reactants produced during sepsis may be useful as biochemical markers for early diagnosis, monitoring of the effects of therapy and as predictors of outcome. Future research into the pathogenesis of neonatal sepsis should identify new markers for rapid and precise biochemical diagnosis.

Conflict of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

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