

Review Article

Etiology and risk factors of early and late onset neonatal sepsis

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ABSTRACT

Neonatal sepsis is a systemic disease caused by bacterial organisms, viral infections, or fungus that causes hemodynamic abnormalities and other clinical symptoms resulting in severe complications and may progress into mortality. Parturition can be used to diagnose organisms caused by the premature onset of sepsis in some cases, but only after an average of three days of life. Clinical manifestations of infection may also diagnose the organisms caused by the early onset of sepsis. Late sepsis can refer to any incident of sepsis from delivery to discharge in high-risk newborns, and the majority of them have been hospitalized for a lengthy period. Late-onset Guillain-Barré syndrome infections generally refer to the infections that occur between one week and up to three months post-labor. The precise load fraction for newborn sepsis varies by context, with differing load estimations between nations with varying lead levels. With the diversity of treatments utilized, explaining the degree of obstetric palsy is crucial and complicated. When comparing birthing sepsis rates, it is critical to understand if a tiny figure represents a total birth rate or another rate, such as a hospital admission number. As stated, it is critical to evaluate if population estimates based on the numbers of neonatal sepsis episodes have been recorded. This article aims to review the literature regarding neonatal sepsis from different aspects including, the etiology, risk factors, and different types and onset of neonatal sepsis.

Keywords: Neonatal sepsis, Bacteremia, Infants, Newborn

INTRODUCTION

Neonatal sepsis is a systemic disease caused by bacterial organisms, viral infections, or fungus that causes hemodynamic abnormalities and other clinical symptoms

resulting in severe complications and may progress into mortality. Despite the years of clinical expertise and advancements in caring for newborns with confirmed or suspected sepsis, difficulties such as the lack of a clear definition of neonatal sepsis remain an unmet need.¹ Generally, sepsis has been defined as the separation of

pathogens from sterile human body fluids such as the bloodstream or cerebrospinal fluid. However, because sepsis can be induced by potent inflammatory cytokines or as known as cytokines storm, the term systemic inflammatory response syndrome (SIRS) has also been used to demonstrate the involvement of neonatal sepsis.

According to the onset and length of the sepsis episode, neonatal sepsis is categorized as either early or late-onset. The early onset generally manifests clinically during the first three days (72 hours) of life.¹ Some clinicians refer to the early infection caused mainly through group B *Streptococcus* as occurring fewer than seven days postpartum. The early-onset infection is generally exposed early in the pregnancy or during labor and indicates a direct transfer from the mother to the newborn. Late-onset infections occur after the delivery or beyond seven days after labor. Mainly they are caused by organisms found in contact with the environment of the hospital or community.

Parturition can be used to diagnose organisms caused by the premature onset of sepsis in some cases, but only after an average of three days of life. Clinical manifestations of infection may also diagnose the organisms caused by the early onset of sepsis. Late sepsis can refer to any incident of sepsis from delivery to discharge in high-risk newborns, and the majority of them have been hospitalized for a lengthy period. Late-onset Guillain-Barré syndrome infections generally refer to the infections that occur between one week as well as up to three months post-labor.²

The precise load fraction for newborn sepsis varies by context, with differing load estimations between nations with varying lead levels. With the diversity of treatments utilized, explaining the degree of obstetric palsy is crucial and complicated. When comparing birthing sepsis rates, it is critical to understand if a tiny figure represents a total birth rate or another rate, such as a hospital admission number. As previously stated, it is critical to evaluate if population estimates based on the numbers of neonatal sepsis episodes have been recorded.³ In the United States, the incidence of neonatal congenital sepsis ranges from one to four illnesses per 1000 live births, depending on location and temporal variations. Although this correlation has not been found in preterm newborns, full-term male newborns had a greater risk of sepsis than full-term female infants. It was reported that the occurrences of newborn clinical sepsis were decreased after the widespread implementation of intrapartum antibiotic prophylaxis, which was related to a decrease in early Guillain-Barré syndrome sepsis. The hospitalization rates in full-time babies are declining slowly but steadily and are significantly lower among preterm newborns at the period of observation.⁴ This article aims to review the literature regarding neonatal sepsis from different aspects including, the etiology, risk factors, and different types and onset of neonatal sepsis.

LITERATURE REVIEW

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27th November 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing etiology and risk factors of early and late onset neonatal sepsis were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

DISCUSSION

Pathophysiology and mechanism of neonatal sepsis

In utero newborns, neonatal sepsis is caused by a passing or, more often, ascending germ that enters the uterus from the lumen of the vagina following membrane breach. Furthermore, the newborn infant may get sick due to exposure to bacteria, viruses, or fungi that may be present throughout the birth canal's transit. Aerobic and anaerobic bacteria have been found in the human birth canal, leading to increased amniotic fluid infection or natural neonate infection during labor or childbirth.^{5,6}

Chorioamnionitis is caused by a minor infiltration of amniotic fluid, which is generally caused by a prolonged rupture of the chorioamnionitis membrane. Chorioamnionitis, I associated with clinical manifestations such as fever, leukocytosis, urine with bad odor, abdominal discomfort, and fetal symptoms. Chorioamnionitis may also be accompanied by aberrant laboratory or pathological findings that support the illness. The grade of histopathological chorioamnionitis varies with the pregnancy stage and is strongly connected to the timing of gastric rupture.^{7,8} The presence of *Ureaplasma* spp. in the respiratory tract of preterm babies is linked to bronchopulmonary dysplasia. Maternal and congenital investigators are doing active research on the perception of maternal chorioamnionitis as well as the maternal outcomes.⁹

Antibodies, comprising phagocytes, naturally destroying cells, antigen-presenting cells, and the filling system, are given immunity throughout the first three months of life. Preterm births are more common when neutrophil activity is low, and immunoglobulin levels are low. Babies with undeveloped immune systems become more vulnerable to harmful natural chemicals as they grow older. For example, contact with people in the hospital setting such as physicians and nurses, contaminated dietary sources, and surrounding contaminated environment. The most prevalent source of postpartum infection in hospitalized children in hand contamination, highlighting the need for hand hygiene.¹⁰ Late hemorrhage is more manifested in newborns with modest venous access than babies without

the central venous access, which is typically adult, and these infections can be correlated with the gram positive organisms such as coagulase negative *Staphylococci* as well as the *Streptococci*. The meningitis is usually associated in late onset cases caused by the substantial spread through the choroid plexus to the central nervous system.¹⁰

Infection with microorganisms, bacteria, or fungus can cause neonatal sepsis. *Streptococcus agalactiae* and *Escherichia coli* are the most frequent pathogens linked with neonatal sepsis. From 2006 to 2009, about 400,000 neonates in the United States were exposed to neonatal sepsis in late-onset or delayed onset. Infection with germs, bacteria, or fungus can cause neonatal sepsis. *Streptococcus agalactiae* and *Escherichia coli* are the most frequent pathogens linked with neonatal sepsis. From 2006 to 2009, there were around 400,000 births in the United States, with 389 babies becoming infected early. Most Guillain-Barré syndrome infected newborns (73%) were full-time, but 81% of *E-coli*-infected infants were preterm; infection rates have increased with reduced birth weight. The total death rate was 16%.¹¹

Candida spp. is frequently linked with erythematous dermatitis in the early stages of newborn birth infections.¹² *E-coli*, other gram-negative aerobes, *L monocytogenes*, and *Staphylococcus aureus* infection may be linked with late neonatal sepsis. In recent years, the occurrence of infant listeriosis has decreased substantially.¹³ However, in the critical care unit, coagulase-negative *Staphylococci* are the most prevalent pathogens isolated from newborns with sepsis.^{14,15} Herpes simplex virus (HSV) and enterovirus are the most prevalent viral causes of sepsis, and both are frequently linked with late submissions. HSV infection in neonates is correlated with severe disease onset and mortality. For up to nine days, symptoms of the disease can cause a sepsis-like clinical presentation and can be confined to the skin, eyes, and mouth, including the central nervous system, or spread to the liver, lungs, and adrenal glands. HSV-1 or HSV-2 infection can cause neonatal HSV, and HSV-1 has grown considerably in tandem with an increase in HSV-1-related sexually transmitted diseases.²⁴⁻²⁶ Infectious neonates with an enterovirus may develop meningoencephalitis, myocarditis, and hepatitis after malnutrition, tiredness, fever, irritability, hypoperfusion, and jaundice. Infants under ten days old infected with echoviruses, parechoviruses, and coxsackievirus B due to maternal dementia are unable to respond to a significant immune response and do not benefit from maternal immunological transmission.¹⁶⁻¹⁸ An increasing number of common infections are generally identified after a long-term hospital stay in newborns regarding fungal infections. *Candida* spp is the third most prevalent cause of newborn birth abnormalities in infants weighing less than 1500 g, with *Candida parapsilosis* emerging as a significant pathogen in the neonates with the central venous diagnosis.¹⁹

Risk factors

The most important element in assisting an infection that might progress to sepsis is premature development or low birth weight. Preterm and low-weight babies are three to ten times more likely to be infected than a typical newborn at birth. Immune dysfunction and a lack of maternal antibodies can increase the risk of infection in preterm babies. Furthermore, premature babies may require prolonged intravenous infusion, endotracheal intubation, or other invasive procedures that establish a portal for entry or disrupt prevention and admission protocols, placing them at risk of hospital-acquired infection. Furthermore, low levels of 25-hydroxyvitamin D in newborns have been linked to primary sepsis.²⁰

Maternal history informs us about exposure to infectious diseases, bacterial colonization, immunological, and reproductive variables such as premature pregnancy, chorioamnionitis, and urinary tract infections. When there is maternal chorioamnionitis, the incidence of birthing sepsis increases substantially. Premature labor, underlying diseases, invasive processes, inoculum size, infectious disease, genetic susceptibility, natural antibodies, retainer response, and the acquisition of IgG antibodies in a chronic manner are all factors that contribute to the development of neonatal bacterial colonization and sepsis.

Breathing or breathing microorganisms into amniotic fluid can result in the delivery of pneumonia or systemic infections, with symptoms most frequently noticed before delivery such as anxiety and tachycardia, during delivery as apnea, respiratory depression, and shock, or after a few hours, and up to two days as respiratory depression, hemodynamic instability, or shock. Furthermore, Guillain-Barré syndrome maternal bacteriuria, a high burden of Guillain-Barré syndrome colonization, is a significant risk factor for detecting neonatal Guillain-Barré syndrome infection.²⁰

Diagnosis

Temperature instability, hypotension, poor absorption of pallor and pigmented skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory depression, sighing, cyanosis, irritability, fatigue, fainting, malnutrition, abdominal cramps, jaundice, petechiae, purpura, and bleeding are all symptoms of bacterial sepsis. Early symptoms may be modest, such as apnea or tachypnea with relapse, nasal congestion, sighs, or tachycardia. Respiratory failure, high blood pressure, heart failure, shock, kidney failure, liver failure, brain edema or thrombosis, adrenal hemorrhage or malfunction, bone marrow (neutropenia, thrombocytopenia, anemia), and the spread of intravascular coagulation are recent consequences of sepsis.²¹ The clinical appearance of non-communicable immune failure might be similar to that of congenital sepsis. In addition, infectious and non-infectious causes might coexist in the same host. Clinical findings, for example, have revealed that pulmonary

respiratory illness linked with a surfactant deficit may be related to bacterial pneumonia.²¹

Traditionally, a verified laboratory is obtained by isolating the causal agent in the sterile body fluids such as blood components, cerebrospinal fluid, urine analysis, and peritoneal fluid analysis. Examples of aseptically acquired volume are crucial for increasing the diagnosis. A minimum of 0.5-1 ml of fluid should be collected for blood cultures, ideally from two separate venipunctures at two different locations. True viruses may be found in both cultures. In the presence of a medium-sized catheter, blood vessels can be identified concurrently, one from the surrounding environment and one from the catheter, to determine the best moment of separation.²² Compared to catheter-related blood infections, this aids in identifying bacterial infections in the cavity and influences clinical care. Because specific pathogens may only be detected in cerebrospinal fluid rather than blood during sepsis testing, lumbar punctures should be performed on symptomatic newborns.²³ Automated blood culture methods monitor samples and alert when a positive signature is detected, assisting in pathogen identification. Laser-desorption ionization time-of-flight mass spectrometry can aid in the early identification of organisms in blood cultures, allowing antibiotic therapy focused on detecting blood-borne infections.²⁴ Using multiplex PCR in the blood sample, researchers were able to identify common bacterial and fungal infections and genes that fight viruses within hours of body development.²⁵ Similar approaches have been applied in cerebrospinal fluid samples to increase bacterial detection time.²⁶ Because urinary tract infections do not occur in the first three days of life, the urge for suprapubic bladder or urinary catheterization is not investigated as part of the early onset sepsis examinations. Urinary tract infections, on the other hand, are prevalent in newborns. Therefore the cause of urinary tract infection should be investigated with late clinical manifestations of sepsis.²⁷

Treatment and management

Antibiotics or other antimicrobials should be provided once the bacteria and their problems have been recognized, as well as the place or regions of infection. Penicillin or ampicillin are more effective against Guillain-Barré syndrome, but gentamicin provides interaction until blood pressure and cerebrospinal fluid are no longer at risk of generating adverse effects, at which time it may be discontinued. For *L. monocytogenes*, ampicillin alone is sufficient; however, in rare situations, an aminoglycoside is also given at the start of treatment.²⁸ Because most, if not all, of these coagulase-negative *Staphylococci* isolates are resistant to Beta-lactam medicines, including penicillinase-resistant penicillinase, vancomycin is the treatment of choice in established infections. In situations of coagulase-negative *Staphylococcal* bacteremia without a cause, rifampin may be helpful. Linezolid and daptomycin are two additional treatments that should be used if the first-line medications

do not work or if the patient develops resistance to them.²⁸ Amphotericin deoxycholate remains a non-invasive treatment for candidiasis in instances of meningitis; hepatic or splenic candidiasis can be treated with liposomal amphotericin or echinocandin. Fluconazole has the potential to be an effective allergy treatment. The underlying pathology of the child influences successful treatment results, the duration of good culture, the severity of the disease, and the capacity to remove the source of the infection is linked with venous central tube access.²⁸

Antimicrobial drugs for suspected or known viral infections are used to treat neonatal diseases. The early or late presentation and exposure (public versus hospital status at the beginning of the infection) are the essential aspects are the comprehensive and detailed history and physical and cultural exams of various clinics. While obtaining cultures before the commencement of antimicrobial therapy may be beneficial in optimizing physical recovery, the delivery of antimicrobial treatment should not be unnecessarily delayed by the collection of species in newborns with ocular infections. In general, aggressive therapy should target the antibacterial patterns of the most prevalent bacterial isolates identified in the infant care room or community settings.²⁹

Early treatment for suspected Gram-negative meningitis should include ampicillin and aminoglycosides (usually gentamicin), which are third- or fourth-generation cephalosporin medications. Carbapenems, such as meropenem, are required to treat infections caused by gram-negative bacilli-gram-negative formation. Treatment with piperacillin-tazobactam and ampicillin-sulbactam is increasingly common in critically ill newborn infants; however, the penetration of tazobactam into the central nervous system is incompatible and should not be used for the treatment of meningitis. When combined with ampicillin, however, the beta-lactamase inhibitor sulbactam appears to gain a higher concentration in cerebral fluid.²⁹

Fungal infections, such as candidiasis, aspergillosis, and zygomycoses, should be treated immediately if suspected and detected. Antifungal treatment with amphotericin deoxycholate can be considered in high-risk children with a high risk of chronic candidiasis. A high dose and dose of antimicrobial can help reduce toxicity if the antibiotic is given for more than three days, as well as in the treatment of certain diseases such as meningitis, which requires the involvement of cerebrospinal fluid.³⁰

CONCLUSIONS

The widespread use of antibiotic prophylaxis raises concerns about the formation of resistance between interactions, and ongoing active monitoring will be required to keep these concerns under control. The relevance of coagulase-negative *Staphylococci* as colonic chemicals and in contrast to viruses in neonates remains

an essential topic of research, particularly given the growing worry about vancomycin resistance. Non-traditional diagnostics done by conventional and sepsis schools to anticipate and identify septic babies are current research topics. As the newborn microbiome forms, it is critical to minimize antibiotic exposure to reduce necrotizing enterocolitis and associated sequelae such as asthma, obesity, inflammatory bowel disease, and neurological problems.

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