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THE PUERPERAL SEPSIS AND ITS FACTORS

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ABSTRACT

Neonatal sepsis remains a feared cause of morbidity and mortality in the neonatal period. Maternal, neonatal and environmental factors are associated with risk of infection, and a combination of prevention strategies, judicious neonatal evaluation and early initiation of therapy are required to prevent adverse outcomes. The following research ıs to reviews recent trends in epidemiology and provides an update on risk factors, diagnostic methods, and management of neonatal sepsis ın Al-jarrah hospıtal ın Baghdad for the peroıd between 12.9. 2018 up to 12.2.2019. the sample wıll take ın as 25 female.

KEYWORDS: Neonatal sepsis, immature immunity, early and late onset disease, Biological markers, treatment.

INTRODUCTION

Epidemiology of neonatal sepsis where the Neonatal sepsis remains a feared and serious complication, especially among very low birthweight (VLBW) preterm infants. Neonatal sepsis is divided into early- and late-onset sepsis, based on timing of infection and presumed mode of transmission. Early-onset sepsis (EOS) is defined by onset in the first week of life, with some studies limiting EOS to infections occurring in the first 72 hours due to maternal intrapartum transmission of invasive organisms. Late-onset sepsis is usually defined as infection occurring after 1 week and is attributed to pathogens acquired postnatally. Risk factors for neonatal sepsis include maternal factors, neonatal host factors, and virulence of infecting organism (Table 1).

Risk Factors for the Development of Neonatal Sepsis

SOURCE	RISK FACTOR
Early Onset Neonatal Sepsis	
	Maternal GBS Colonization
	Chrorioamnionitis
	Premature rupture of membranes
	Prolonged rupture of membranes (>18 hours)
	Maternal urinary tract infection
	Multiple pregnancies
	Preterm Delivery (<37 weeks)
Late Onset Neonatal Sepsis	
	Breakage of the natural barriers (skin and mucosa)
	Prolonged indwelling catheter use
	Invasive Procedures (eg. Endotracheal intubation)
	Necrotizing Enterocolitis
	Prolonged use of Antibiotics
	H_2-receptor blocker or proton pump inhibitor use
Neonatal*	

In the United States, widespread acceptance of intrapartum antibiotic prophylaxis (IAP) to reduce vertical transmission of Group B Streptococcal (GBS) infections in high-risk women has resulted in a significant decline in rates of EOS GBS infection.[1] Overall, it is not believed that IAP has resulted in a change in pathogens associated with EOS.

However, some studies among VLBW preterm infants have shown an increase in EOS due to *Escherichia coli*.[2] A recent study done by the Eunice Kennedy Schriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) estimated the overall incidence of EOS to be 0.98 cases per 1000 live births, with increasing rates in premature infants.[3] Studies with stratification of disease burden by gestational age and race have shown that black preterm neonates have a significantly higher incidence of neonatal sepsis as compared to the rest of the population, accounting for 5.14 cases/1000 births with a case fatality rate of 24.4%.[4]

Despite efforts to detect GBS colonization during pregnancy and provide appropriate GBS prophylaxis to colonized mothers, not all cases of early-onset GBS are prevented and GBS continues to be the most common cause of EOS in term neonates. Sepsis due to *E. coli* has increased in recent years, mainly affecting preterm newborns weighing less than 2500 grams at birth, and is considered the most common cause of EOS in this weight group. *E.coli* is frequently associated with severe infections and meningitis and it has become the leading cause of sepsis-related mortality among VLBW infants (24.5%).[4] Together GBS and *E. coli* account for about 70% of cases of EOS in the neonatal period.[5,6]

Rates of LOS are most common in preterm low birthweight infants. Studies from the NICHD NRN report that ~21% of VLBW <1500 g, developed 1 or more episode of blood culture confirmed LOS, with rates inversely related to gestational age (58% at 22 weeks GA and 20% at 28 weeks GA).[7,8]

Intrapartum antibiotic prophylaxis has not had an impact on rates of late-onset sepsis (LOS).[1,9] VLBW preterm infants are at particular risk for LOS in part because of prolonged hospitalization and prolonged use of indwelling catheters, endotracheal tubes, and other invasive procedures. Several studies have documented rates of LOS from 1.87–5.42, with decreasing rates as birth weight increases.[6,7] Coagulase-negative staphylococci (CoNS) have emerged as the most commonly isolated pathogens among VLBW infants with LOS.

Development of the Immune system and Increased Risk of Neonates to Infections.

The development of the immune system entails a number of changes that occur during the first years of life. Neonates, especially preterm infants, are relatively immunocompromised because of immaturity of the immune system as well as decreased placental passage of maternal antibodies. Here we highlight some of the components of the neonatal immune system that are immature and contribute to increased susceptibility to serious bacterial, fungal, and viral infections.

Innate Immune System

The innate immune system produces an immediate immunologic response and is capable of doing this without previous exposure to a specific pathogen. Recognition of pathogens occurs by identification of conserved biological regions known as pathogen-associated molecular patterns (PAMPs).

Recognition receptors such as Toll-like receptors, NOD-like receptors, and RIG-like receptors identify and respond to PAMPs with the production of cytokines and pro-inflammatory responses which activate the adaptive immune system.[10] Studies comparing neonatal and adult innate immune functions show that neonatal cells have a decreased ability to produce inflammatory cytokines, especially tumor necrosis factor and interleukin-[6,11]

In addition, they induce interleukin-10 production, which in itself is capable of inhibiting synthesis of pro-inflammatory cytokines.[12] Neutrophil and dendritic cell functions are also reduced; neutrophils show a decreased expression of adhesion molecules as well as a decreased response to chemotactic factors,[13,14] and dendritic cells have a decreased capacity of producing interleukin-12 and interferon (IFN) gamma.

The overall reduction in cytokine production in neonates also results in decreased activation of natural killer cells.[15] Impairment of the innate immune system leads to an increased susceptibility to bacterial and viral infection in this population.

Adaptive Immune System

The adaptive branch of the immune system is designed to eliminate specific pathogens. In newborns the adaptive immune system slowly increases its function towards an adult-like response, minimizing the otherwise overwhelming inflammatory response that would occur when infants transition from a sterile to a colonized environment.[16]

Decreased cytotoxic function (strong T-helper 2 polarization with decreased IFN-gamma production), lack of isotype switching, and overall immaturity and decreased memory (due to limited pathogen exposure at time of birth), reduce the neonate's ability to respond effectively to infections.[17–20]

For example, the reduction of cell-mediated immunity increases the risks of infections due to intracellular pathogens such as *Listeria*, *Salmonella*, Herpes Simplex virus (HSV), cytomegalovirus and enteroviruses.

Transplacental passage of maternal IgG is inversely related to gestational age and limits the functional ability of the neonate to respond to certain pathogens.[21,22] Minimal IgG is transported to the fetus in the first trimester, while fetal IgG rises in the second trimester from approximately 10% at 17–22 weeks gestation to 50% at 28–32 weeks gestation.[23,24]

Thus, preterm infants lack adequate humoral protection against a number of infant pathogens, while term infants will often be protected against the majority of vaccine-preventable neonatal infections through transplacental passage from the mother's serum. Histological studies have also demonstrated that the marginal zone of the spleen is not fully developed until 2 years of age, increasing the infant's susceptibility to encapsulated bacterial infections (*Streptococcus pneumonia*, *Haemophilus influenza*, *Neisseria meningitidis*).[25]

Finally, decreased transfer of IgA, IgG, cytokines and antibacterial peptides present in human milk may be compromised, especially in premature babies. The lack of secretory IgA decreases the ability of the neonate to respond to environmental pathogens.[26]

Complement

Complement levels increase with increasing gestational age but are only about 50% of adult levels at term. Reduced complement levels are associated with deficient opsonization and impaired bacterial killing. Although both pathways seem to be capable of being activated, there may be variations in their activation level. In addition, profound C9 deficiency has been observed in neonates reducing the ability to form bacteriolytic C5b-9 (m), which will increase the risk of acquiring severe invasive bacterial infections.[27,28]

Etiologic Agents in Neonatal Sepsis

The etiologic agents associated with neonatal sepsis in the United States have changed over time.5 In this section, we review current data on organisms associated with early- and late-onset neonatal sepsis (Table 2).

Organisms Associated with Early and Late Onset Neonatal Sepsis

Early Onset Sepsis	**Late Onset Sepsis**
Group B *streptococcus*	Coagulase negative *staphylococcus*
Escherichia coli	*Staphylococcus aureus*
Listeria Monocytogenes	*Enterococci*
Other streptococci: S. pyognes, viridans group streptococci, S. pneumonia	Multi drug resistant Gram negative rods (*E. coli*, *Klebsiella*, *pseudomonas*, *enterobacter*, *citrobacter*, *serratia*)
Enterococci	*Candida*
Non-Typable *Haemophilus influenza*	

Early Onset Sepsis

Group B-streptococcus

Despite widespread use of IAP to prevent vertical transmission of invasive GBS disease, missed opportunities for prevention exist and GBS remains the most common organism associated with EOS in the US.

According to the Centers for Disease Control and Prevention (CDC), rates of early-onset invasive GBS disease have declined by 80% since the CDC prevention guidelines were first published.[9] GBS are Gram-positive encapsulated bacteria for which 10 different serotypes have been identified; with serotype III strains responsible for the majority of disease (54%).[29]

GBS commonly colonize the GI and genital tract with rates up to 20% in the adult population.[30] Transmission occurs late in pregnancy or during labor and delivery, and the likelihood of disease as well as the severity has been associated with the density of recto-vaginal carriage.[31,32] GBS possess different virulence factors that determine its ability to cause invasive disease:

(1) capsular polysaccharide, which helps evade phagocytosis,

(2) pili, that allows adherence of GBS to the host's epithelial cells as well as transepithelial migration.

(3) C5a peptidase which inhibits human C5a, a neutrophil chemo-attractant produced during complement activation.

Among infected newborns, clinical manifestations develop very early after delivery and most infants will have signs of respiratory distress and cardiovascular instability. Infants with early-onset GBS are at increased risk for meningitis. Rapid deterioration of the clinical status is expected unless prompt antibiotic management is started. Risk of death is inversely related to gestational age, with mortality of 20–30% among infected infants less than 33 weeks gestation, compared with a mortality of 2–3% in full-term infants.[1,33]

Escherichia coli

Escherichia coli, a Gram-negative rod that commonly colonizes the maternal urogenital and GI tracts, is considered the second most common cause of neonatal sepsis in term infants and the most common cause in VLBW neonates with rates of 5.09 per 1000 live births.[3,34,35]

The antigenic structure of *E.coli* is represented by multiple antigens (O), (K) and (H) which in combination account for the genetic diversity of the bacteria. Strains with the K1 antigen have been associated with the development of neonatal sepsis and meningitis as well as with increased risk of mortality when compared with K1 negative strains36. Some studies suggest a more aggressive presentation for infants infected with *E.coli*, with a higher risk of thrombocytopenia and death in the first days of life.[3]

Several US studies have shown high rates of ampicillin resistance in E.coli strains that infect newborns. Although some studies have shown an association between intrapartum antibiotic exposure and ampicillin resistant E. coli, ampicillin resistance has increased throughout the community and a direct link between intrapartum use of ampicillin and the higher likelihood of resistance has not been established.[3,37–39]

Listeria monocytogenes

Listeria is a facultative anaerobic, Gram-positive bacterium found in soil, decaying vegetation, fecal flora and raw unprocessed food.[40] Multiple virulence factors allow *listeria* to escape the immune system, including listeriolysin that helps the organism avoid the oxidative stress of phagolysosomes, allowing intracellular replication. *Listeria* proteins Acta, phospholipase C, and lecithinase allow polymerization of actin and lysis of phagosomal membranes, enabling cell-to-cell transmission.[41,42] Pregnant women have 17% higher risk of *listeria* infection than non-pregnant women, and infection has been associated with spontaneous abortions as well as stillbirths. Early neonatal infections have a similar clinical presentation as EO GBS infections, with respiratory distress, sepsis, and meningitis.

In severe cases, patients may present with a granulomatous rash (small patches with erythematous base) known as granulomatosis infantisepticum.

Most cases of neonatal *listeria* are due to serotype 1, 2 and 4, with the latter serotype responsible for almost all cases of meningitis.[43] Suspicion for listeria sepsis should be increased in ill infants of mothers who have consumed raw milk, unpasteurized cheeses, or other unprocessed food products that have been contaminated with the organism.[44,45]

Other Bacterial Etiologic Agents Seen in Early Onset Sepsis

Other less common but important pathogens associated with EOS include other streptococci (*S. pyogenes*, viridans group streptococci, *S. pneumoniae*), *enterococci*, *staphylococci* and non-typable *Haemophilus influenzae. Streptococcus pyogenes* was once the predominant organism responsible for neonatal sepsis. Although overall incidence has decreased significantly, severe cases of EO GAS continue to be reported.

A recent literature review identified 38 cases of GAS (24 with EOS). Patients were most likely to present with pneumonia and empyema (42%) or toxic shock syndrome (17%). 70% of the isolates were M1 serotype and they were all susceptible to penicillin. Mortality was estimated to be 38% among patients with EOS.[46] Pneumococcus, groups C and G streptococci, as well as viridans streptococci clinical presentation is very similar to GBS infection and transmission, seems to be secondary to bacterial colonization of the maternal genital tract.[47–51] Enterococcal EOS is usually mild compared to LOS and it is characterized by either a mild respiratory illness or diarrhea without a focal infection. *Enterococcus faecalis* is more frequently isolated than *E. faecium* and most of the isolates remain ampicillin susceptible.[52]

Although non-typable *Haemophilus influenzae* frequently colonizes the maternal genital tract, neonatal infection is relatively rare, but with high mortality rates especially in preterm neonates.[3,53] Hershkowitz reported a cluster of 9 cases with 3 deaths;[54] similar high mortality rates were reported in a series by Takala.[55]

Late-onset Sepsis (LOS)

The increased survival of preterm low birthweight infants, particularly those who are VLBW, with need for prolonged hospitalization and use of invasive procedures and devices, especially long-term intravascular catheters, results in on-going risk of infection. LOS is largely caused by organisms acquired from the environment after birth. The following section reviews the most common organisms associated with LOS (Table 2).

Clinical Manifestations in Patients with Early and Late Onset Neonatal Sepsis

Sepsis/Meningitis	
	Temperature Instability
	Respiratory Distress
	Apnea
	Jaundice & Feeding intolerance
	Bulging fontanels
	Seizures
Other	
	Skin lesions: may occur in disseminated staphylococcal, *listeria* and *candida* infections.
	Joint and Bone: May be the preceding event

CoNS have emerged as the single most commonly isolated pathogen among VLBW infants with LOS and are associated with 22–55% of LOS infections among VLBW infants.[56,57] Staphylococcus *aureus* is associated with 4–8%[7,58] Staphylococcus commonly colonizes the human skin and mucous membranes and is capable of adhering to plastic surfaces with the subsequent formation of biofilms.

These biofilms protect the bacteria from antibiotic penetration and can produce substances that will help them evade the immune system. Although CoNS infections are usually secondary to *Staphylococcus epidermidis*, other strains such as *S. capital*, *S. haemolyticus*, and *S. hominis* have also been reported.[59] Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated in 28% of staphylococcal infections in preterm neonates with no significant differences between MRSA and methicillin-susceptible organisms in terms of morbidity, mortality, and length of hospital stay.

Overall 25% of infants infected with MRSA die, with no significant difference in death rates between infants infected with MRSA or MSSA.[58]

Gram-negative Organisms

Gram-negative organisms are associated with about one-third of cases of LOS, but 40–69% of deaths due to sepsis in this age group. Transmission occurs from the hands of health-care

workers, colonization of the GI tract, contamination of total parenteral nutrition or formulas, and bladder catheterization devices.[60,61] The most common Gram-negative organisms isolated include *E. Coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Citrobacter* and *Serratia*.[62] In some case series *Klebsiella* is recognized as the most common gram-negative agent associated with LOS, ranging from 20–31% of cases.[63,64] Infections due to *Pseudomonas* have been associated with the highest mortality.[65] *Citrobacter* is uniquely associated with brain abscesses, but dissemination can occur to other organs. Its ability to survive intracellularly has been linked to the capacity of creating chronic CNS infections and abscesses.[66,67]

Candida Infections

Infections due to *Candida* species are the third leading cause of LOS in premature infants. Risk factors of infection include low birth weight, use of broad-spectrum antibiotics, male gender and lack of enteral feedings.[68] *C. albicans and C. parapsilosis* are the species most commonly associated with disease in neonates.[69,70] Poor outcomes, including higher mortality rates and neurodevelopmental impairment, have been associated with the ability of the organisms to express virulence traits such as adherence factors and cytotoxic substances.[71] *Candida* easily grows in blood culture media, but its isolation may require larger volumes of blood than normally obtain in neonates and therefore multiple cultures may be necessary to document infection and clearance. Among those with a positive CSF culture, as many as 50% will have a negative blood culture; the discordance of blood and CSF cultures underscores the need for an LP.[68] Prompt removal of contaminated catheters is also recommended based on the ability of *Candida* species to create biofilms as well as better survival rates and neurodevelopmental outcomes in patients who had early removal and clearance of the infection.[68]

Diagnostic

Early diagnosis of neonatal sepsis is challenging because clinical characteristics are non-specific and difficult to differentiate from those of non-infectious etiologies, and because the repertoire of ancillary laboratory tests is limited and not always reliable. Blood culture remains the gold standard for diagnosis of neonatal sepsis, but the rate of positivity is low, influenced by factors such as intrapartum antimicrobial administration and limitations in blood volume per culture that can be obtained in neonates.[73,74] Here we review the standard

evaluation of neonatal sepsis, followed by a discussion of recent data on inflammatory markers and diagnostic methods in neonatal sepsis.

A neonate with signs and symptoms of sepsis (Table 3) requires prompt evaluation and initiation of antibiotic therapy. Blood, CSF (as clinical condition allows) and urine cultures (only useful after the 3rdday of life) should be obtained.[72,75,76] Chest x-ray is indicated in patients having respiratory symptoms. If disseminated herpes is suspected (herpetic skin lesions, elevated hepatic transaminases, maternal peripartum herpes infection), surface cultures from conjunctiva, mouth, skin and anus as well as Herpes DNA PCR from CSF and blood should also be ordered.[77,78] Ancillary tests such as complete blood count (CBC) and C Reactive protein (CRP) should not preclude a sepsis evaluation in a neonate since they can be normal (See below).[79] However, if positive they can be useful in supporting the diagnosis and determining length of therapy. Careful maternal and exposure history targeted towards identifying potential risk factors (Table 1) as well as a complete physical examination including skin and catheter insertion sites should be obtained.

Treatment

Prevention and Infection Control Practices

Prevention of neonatal sepsis is the goal—through implementation of what is known and development of new prevention strategies. Maternal prenatal care continues to be important for prevention of early-onset GBS sepsis with identification of maternal carriage of GBS through universal screening for all pregnant women. Early recognition of chorioamnionitis, with appropriate antimicrobial therapy for the mother, decreases maternal-fetal transmission. The recent CDC GBS prevention guidelines emphasize the need for universal maternal GBS screening at 35–37 weeks gestation and include chromogenic agar and nucleic amplification tests (NAATs) as newer diagnostic techniques that can be used to increase the yield of GBS identification. They also clarify the definition of adequate intrapartum prophylaxis as use of penicillin, ampicillin or cefazolin at least 4 hours prior to delivery (Table 4). Clindamycin and vancomycin, which can be used in penicillin-allergic patients, are not considered effective prophylaxis therapy.[9] Other potential prevention strategies include rapid GBS testing during labor and a safe and effective GBS vaccine. Diagnostic tests during labor will identify colonized women who either had a negative screen at 35–37 weeks or were not screened prior to labor. Further studies are needed to improve sensitivity and specificity of rapid tests.[98]

DISCUSSION

Delay in the synthesis of immunoglobulin and a decrease trans-placental antibody transfer in neonates, suggested that the use of IVIG could be a potential strategy for prevention of neonatal sepsis. In 1994, a randomized controlled trial in 2,416 infants failed to show a decreased incidence of nosocomial infections, morbidity/mortality, and duration of hospital stay among VLBW infants.[105]

A follow-up meta-analysis of 10 trials showed that mortality was reduced with the use of IVIG in suspected (RR, 0.58 95% CI, 0.38–0.89) and proven infection (RR, 0.55; 95% CI, 0.31–0.98), but authors caution about their conclusions based on concerns about individual study quality.[106] Recently, the International Neonatal Immunotherapy Study (INIS) randomized 3,493 infants with suspected or proven sepsis to receive either two doses of polyvalent IgG immune globulin or placebo 48 hours apart. Their primary outcome was rate of death or major disability at the age of 2 years. There was no difference in the primary outcome between the two groups (RR, 1.00; 95% confidence interval, 0.92–1.08).[107]

Due to the burden of staphylococcal infections in neonatal sepsis, different anti-staphylococcal monoclonal antibodies had been developed. These include antibodies against the capsular polysaccharide antigen, antibodies against microbial surface components that recognize adhesive matrix molecules, antibodies to clumping factor A and anti-lipoteichoic acid (LTA) antibodies.[108–110] Initial animal studies, as well as phase I and II trials in humans, showed that capsular directed antibodies and anti-clumping factor A were well tolerated and had the potential to reduce staphylococcal sepsis.[111,112] However, a meta-analysis showed that their efficacy in decreasing staphylococcal infections was limited and recommended against their use.[113] Recently, Weisman and colleagues showed safety and tolerance of pagibaximab (anti-LTA antibody) at doses of 60 and 90 mg/kg in VLBW infants, with those receiving 90 mg/kg per dose showing no staphylococcal sepsis.[110] Although these are exciting results, randomized controlled studies are needed to further confirm these findings.

CONCLUSİON

Neonatal sepsis continues to be a significant cause of morbidity and mortality in term and preterm infants. Although GBS and E. coli are the most common pathogens associated with EOS and CoNS are the most frequently isolated agents in newborns with LOS, other organisms as well as multidrug-resistant pathogens need to be considered. Development of accurate novel early diagnostic markers will allow clinicians to better assess the risk of

infection and need for antibiotic therapy. Adherence to infection control policies including attention to strict hand hygiene, antibiotic stewardship and catheter management.

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