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NEONATAL SEPSIS AND ITS DIAGNOSIS

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Abstract:

Introduction: *Neonatal sepsis is one of the most common causes of neonatal sepsis mortality and morbidity, despite advances in the health care. It affects mostly premature or babies with very low birth weight. The most challenging part is the variable and vague presentation of the condition, making it hard to diagnose and hence manage.*

Aim of the work: *In this study we aimed to understand the various methods to diagnose neonatal sepsis early and with higher accuracy so treatment process can be started early with more certainty.*

Methodology: *we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017. The following search terms were used: neonatal sepsis, neonatal ICU conditions, diagnosis of neonatal sepsis, newer markers to detect sepsis in neonates*

Conclusion: *Both early and late neonatal sepsis remains to be significant causes of morbidity and mortality in both term and premature infants due to non-specific signs and symptoms, making early diagnosis even harder. Several studies that tried to find better approach to sepsis diagnosis used combinations of hematological studies (like complete blood count), acute phase reactants (C reactive proteins, procalcitonin, cytokines), and cell surface markers, along with other markers to detect and assess neonatal sepsis.*

Keywords: *neonatal sepsis, complications of prematurity, diagnosis of neonatal sepsis, early detection of neonatal sepsis*

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INTRODUCTION:

Among known causes of morbidity and mortality in infants, neonatal sepsis is considered to be one of the most common. despite all medical advances in the field of neonatology and neonatal care, and despite recent declines in both long-term complications and mortality in preterm infants, neonatal sepsis continues to be a significant cause of mortality and long-term morbidities in infants, especially who were born with a very low birth weight, or who were admitted to the Neonatal Intensive Care Unit since birth **[1].**

One important characteristic of neonatal sepsis, is that all symptoms and signs associated with it are nonspecific, like hyper- or hypothermia, cyanosis and/or apnea (causing respiratory distress), difficulties in feeding the infant, irritability, decreased tone, lethargy, seizures, weak perfusion, coagulopathies, bulging fontanels, distention, increased liver span, occult (or gross) blood in stool, jaundice, along with other nonspecific signs and symptoms. Generally, the infant just "does not look right". some infants with neonatal sepsis may also suffer from hypoxia leading to respiratory acidosis **[2]**.

Despite the fact that asymptomatic infants have a low incidence of sepsis and bacteremia, this incidence is still considered important due to associated mortality in these cases. A previous report has concluded that about one percent of term infants are febrile (with a core body temperature that is higher than 37.8 °C). Of this one percent, ten percent have sepsis that was proven with culture. Although most term infants who have sepsis are febrile, most preterm infants, on the other hand, develop hypothermia. This is hypothesized to be due to difficulties with thermic control due to immature system in the first few days of life **[3]**.

METHODOLOGY:

•Data Sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1987 to March 2017. We used the following search terms during our study: neonatal sepsis, neonatal ICU conditions, diagnosis of neonatal sepsis, newer markers to detect sepsis in neonates

•Data extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

Microbiology of neonatal sepsis

A previous study was conducted to assess trends of demographic, and disease-related factors affecting neonatal sepsis, along with outcomes at Yale–New Haven Hospital **[1]**. Between 1933, and 1943, most common organisms associated with neonatal sepsis were group A streptococci and *Streptococcus pneumonia.* However, this trend started to change after late 1940s, and since then, *Escherichia coli* (*E. coli*), along with other gram-negative organisms started to become the most common causes. Starting from the early 1970s, group B streptococci started to increase in incidence and later become the most common cause of neonatal sepsis **[4]**.

Etiology of early onset sepsis (EOS)

Streptococcus agalactiae, also known as Group B streptococcus 'GBS', is an encapsulated gram-positive bacterial organism that is considered to be the most common cause of sepsis and meningitis among infants in the United States. The second most common cause of neonatal sepsis following group B streptococcus is *Escherichia coli* (*E. coli*). Neonatal sepsis due to *Escherichia coli* (*E. coli*) is usually present with severe symptoms along with meningitis. In fact, it is considered to be the most common sepsis cause leading to death in infants with very low birth weight **[5]**. Recent reports have found that more than 70% of neonatal sepsis causes are caused by group B streptococcus and *Escherichia coli* (*E. coli*), alone. Another important, but far less common cause, is *Listeria monocytogenes. Listeria monocytogenes* is associated with severe neonatal sepsis which can lead to stillbirth or spontaneous abortion if occurred earlier during pregnancy **[6]**.

Etiology of late onset sepsis (LOS)

Although preterm infants have recently had improved survival outcomes, late onset sepsis continues to be a significant cause leading to mortality or long-term morbidity, especially among infants with low birth weight. In contrast to early neonatal sepsis, organisms causing late onset sepsis are usually those that are acquired from the environment during and after birth. A study was conducted in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) centers, and included more than six thousands admitted infants. This study found that up to 70% of late onset sepsis cases were associated with an infection with a gram-positive organism (most likely coagulase-negative staphylococci) **[7]**. On the other hand, late onset sepsis cases caused by *Candida*

albicans, *Pseudomonas aeruginosa, E. coli, and Serratia marcescens,* were associated with highest mortality rates. Although the use of intrapartum antibiotic prophylaxis against group B streptococcus has increased, incidence of late onset sepsis due to group B streptococcus has not changed recently. Moreover, meningitis caused by group B streptococcus continues to be a major cause of late onset disease in infants causing morbidity and mortality. Many survivors of the disease will have long-term disabilities and neurological sequelae **[8]**.

Diagnosis of neonatal sepsis

Biomarkers of Neonatal Sepsis

Because sepsis results from inflammatory responses against infections, the best and gold standard to diagnose neonatal sepsis is to isolate and culture the bacteria from blood. However, this will take about 1-2 days to be achieved. Moreover, an attempt to isolate the bacteria from a blood sample that is about 0.5–1.0 ml is associated with relatively lower sensitivity. The reason behind this is that up to 70% of infants have low levels of bacteria in their bloodstream. Hypothetically, to achieve best sensitivity and specificity, you need to take a blood sample that is 6 ml. However, this is not reliable and cannot be done in clinical practice. Therefore, even a negative blood culture cannot totally rule out a diagnosis of sepsis in an infant. Moreover, sometimes, positive bacteria from isolated blood may be simply due to contamination or asymptomatic bacteremia **[9]**.

Other than bacterial culture, there are methods to diagnose neonatal sepsis that depend on in situ hybridization, proteomics, mass spectroscopy, polymerase chain reaction (PCR), and gene arrays. These methods have the ability to find and diagnose bacteria in bloodstream. Other indirect tests depend on evaluating the immune response against the bacteria **[10]**.

Complete blood count (CBC)

The most important factor in improving outcomes related to neonatal sepsis is earlier assessment and diagnosis followed by rapid proper management without any delay in treatment. On the other hand, it is very important to avoid the use of unnecessary antibiotics and invasive procedures. Therefore, the best approach is to use a test that high sensitivity as well as high specificity. Many studies have been conducted to assess the best diagnostic approach for neonatal sepsis. Several studies have suggested the use of complete blood count (CBC), differential count, and immature to total leukocyte ratio (I:T) in the assessment of neonatal sepsis. Despite the poor predictive value that a complete blood count can have, its use has been linked with improved detection of neonatal sepsis **[11]**.

Moreover, the presence of a low white blood cells count and low neutrophils count are both associated with higher probability of an infection, according to a study. On the other hand, the sensitivity of both measures is still considered to be relatively low **[9]**.

To rule out the presence of early neonatal sepsis within the first day of life, it is considered enough to get to normal complete blood counts with about twelve hours between each one. A negative culture at the end of the first day will further increase sensitivity and help rule out the presence of sepsis this protocol has a negative predictive value that can reach one hundred percent. However, it still does not have a high positive predictive value. Moreover, positive results are not enough to plan proper management. On the other hand, complete blood counts may be totally normal in early neonatal sepsis **[12]**.

To conclude, despite being easy to obtain, complete blood counts, differential count, and immature to total leukocyte ratio (I:T) have many limitations when used in diagnosing neonatal sepsis.

C reactive protein (CRP)

The inflammatory marker C reactive protein is considered to be one of the most markers available, cheap, and easy to be obtained. It is used almost always when approaching a case of suspected neonatal sepsis. C reactive protein is an acute phase reactant that is synthesized and secreted by the liver, and is known to increase as a response to systemic inflammation. Half-life of C reactive protein is about 1-2 days. Following the onset of an infection, C reactive protein levels take about 12 hours to increase. To increase sensitivity of C reactive protein in detecting inflammatory processes, it is serially measured every 1-2 days **[13]**. In addition to increasing sensitivity, this serial measurement of C reactive protein is useful to monitor treatment response and prognosis of infants with sepsis. It is considered to be an important guide for physicians during antibiotics therapy. C reactive protein levels have a specificity in detecting inflammation that can be up to 100%. Therefore, it is sometimes considered a ‘late’ but ‘specific’ marker for neonatal infections and sepsis. When C reactive protein levels stay normal over serial measurement, there is a very low chance that an infection is present **[14]**.

It is important to keep in mind that C reactive protein baseline levels are lower in preterm infants, and infection-induced rise in levels is also lower. Moreover, some other causes (other than infections) may lead to the elevation of C reactive proteins in this population. These include traumatic tissue injury, ischemic tissue injury, meconium aspiration syndrome, histologic chorioamnionitis, and hemolysis. Moreover, the sensitivity of C reactive protein in detecting early neonatal sepsis may be low in early phases, due to the delay in changes which might take up to 12 hours **[13]**.

In summary, C reactive protein is a highly accessible, easy to obtain test which has a relatively high specificity in detecting neonatal sepsis. However, it is still associated with significant limitations limiting its use. These mainly include elevations in its levels in some noninfectious causes, and the changes in its baseline levels according to gestational age. Further research on this marker is important to better establish its use in the diagnosis of sepsis.

Procalcitonin (PCT)

Procalcitonin (PCT) is a hepatic acute phase reactant that is release in cases of systemic inflammation. It was also found to be secreted by macrophages during inflammation. Levels of Procalcitonin (PCT) has been studies since 1990s, and was found to elevate in cases of bacterial infections starting from 4 hours following bacterial toxin exposure. Procalcitonin levels peak at eight hours and stay stable for about 1 day. Procalcitonin is known to have a half-life that is about thirty hours. An advantage of its use is that its revels are independent of gestational age. However, infants who do not have infections have a wide variety of prolcalcitonin concentrations. In early life, levels increase, peak at the end of the first day, and then return to baseline after two days **[15]**.

In cases of any neonatal early infection, late infection, or necrotizing enterocolitis, levels of procalcitonin (PCT) increase significantly. This increase is more rapid than the increase observed with C reactive protein levels, making procalcitonin a better marker for the detection of early neonatal sepsis. Moreover, procalcitonin levels are also used to predict the severity of infection, improvements following treatment, and outcomes. Another significant advantage of its use is that procalcitonin levels stay normal in other non-infectious disorders like trauma, meconium aspiration, and hypoxemia **[16]**. Procalcitonin levels have a sensitivity and a specificity for neonatal sepsis that can reach 100%, and is considered a better diagnostic test than C reactive protein levels, especially when measured serially at birth, at the first day, and at the second day **[17]**.

However, procalcitonin levels measurement still has several limitations. For example, its levels are elevated in infants who undergo resuscitation for any reason, and for infants whose mothers had chorioamnionitis. Moreover, maternal colonization of group B streptococcus, and prolonged rupture of membranes may also affect procalcitonin levels. More studies on procalcitonin levels with large samples are still required to establish better diagnostic approaches **[17]**.

Cytokines

Cytokines level in bloodstream change dramatically among exposure to any infection, even earlier than any other inflammation marker. The earliest cytokines to show an elevation in their levels upon infections are tumor necrosis factor α (TNF-α), interleukin-1β (IL-Iβ), interleukin-2 soluble receptor (SIL2R), interleukin-8 (IL-8), and interleukin-6 (IL-6). Elevation of these mentioned cytokines can precede the development of any signs of symptoms in the infant. Due to their inability to cross the placental barrier, any elevation in cytokines levels is considered alarming for the possibility of underlying neonatal sepsis **[18]**.

IL-6

Interleukin-6 (IL-6) levels in bloodstream are known to increase upon exposure to endotoxins released by bacteria. This elevation has been found to precede that of C reactive protein levels. Almost all infants who have an early neonatal sepsis show an increase in umbilical interleukin-6 levels. Interleukin-6 (IL-6) levels were shown to have sensitivity and a negative predictive value in detecting neonatal sepsis that could reach 100%. However, a major limitation in the use of interleukin-6 is its very short half-life, causing a significant decline in its levels immediately after initiation of treatment, and leading to a decrease in sensitivity to reach 58% at 48 hours. This leads to the use of interleukin-6 in diagnosing neonatal sepsis only in early cases. When interleukin-6 and C reactive protein levels are concomitantly measured, their diagnostic accuracy in detecting neonatal sepsis increase significantly **[19]**.

TNF-α

Compared to infants who do not have infections, tumor necrosis factor α (TNF-α) levels have been shown to be significantly higher in infants with infections, and this was proven in several studies.

tumor necrosis factor α (TNF-α) and interleukin-6 have several similarities when it comes to kinetics. The diagnostic accuracy of tumor necrosis factor α (TNF-α) in neonatal sepsis was found by Silveira et al. to be similar to procalcitonin. A better diagnostic approach is to measure tumor necrosis factor α (TNF-α) levels together with interleukin-6 levels. This combination has a specificity that can reach 100% in the diagnosis of neonatal sepsis, although its sensitivity is still relatively low **[20]**.

IL-8

Interleukin-8 is a cytokine that acts as a chemotactic agent and helps activating neutrophils. Moreover, it is an important indicator for the presence of sepsis and the severity of infections. Interleukin -8 is secreted from macrophages, monocytes, as well as endothelial cells. Its kinetics is similar to those of interleukin-6. Interleukin-8 can have a sensitivity and specificity that can each 91% and 100% respectively, in detecting neonatal sepsis **[21]**. A study performed on 93 neonates older than 3 days with neonatal sepsis. He found that higher levels of interleukin-8 were associated with higher mortality rates and lower survival. Measuring C reactive protein with interleukin-8 levels together could be considered a reliable diagnostic test for neonatal sepsis. This combination is associated with a sensitivity that is about 91%, although its specificity is relatively low. Larger studies on interleukin-8 and the best diagnostic approaches with it in cases of neonatal sepsis are still required **[22]**.

Cell Surface Markers

New techniques in the field of cytometry have allowed the use of cell surface antigens detection in diagnostic approaches. These tests have the advantage of being done even with volumes of whole blood that are as low as 0.05 ml. studies on CD64 and CD11β have concluded that they can be considered reliable diagnostic markers in cases of early neonatal sepsis as well as late neonatal sepsis. Studies have also found that CD64 and CD11β have a relatively high sensitivity and specificity. Expression of these molecules have been found to increase as early as minutes after bacterial exposure **[14]**.

CD11β

CD11β is a molecule that is involved in several immune responses including diapedesis, neutrophil adhesion, and phagocytosis. CD11β serum levels become detected after five minutes following exposure to bacteria. Both sensitivity and specificity of CD11β can reach 100%. Its use as a diagnostic test has been found to give more accurate results when used in early rather late neonatal sepsis cases **[23]**.

CD64

CD64 is an antibody receptor that has a high affinity, and is normally expressed with low concentrations on neutrophils. When these is a bacterial infection, CD64 expression increases dramatically on neutrophils. This has sensitivity in detecting neonatal sepsis that can reach 97%, as well as a negative predictive value up to 99%.Testing CD64 with interleukin-6 and/or C reactive protein levels will increase sensitivity to reach 100%, with a specificity that is more than 88%. Testing CD64 has allowed stopping unnecessary antibiotic treatment in suspected cases due to its high negative predictive value **[24]**.

Streimish et al. conducted a large prospective study on the use of CD64 levels to detect and diagnose neonatal sepsis **[25]**. They found that a cut-point of 2.38 for diagnosing early neonatal sepsis was associated with a sensitivity, specificity, and negative predictive value of 100%, 68% and 100% respectively. On the other hand, a cut-point value of 3.62 for diagnosing late neonatal sepsis was associated with a sensitivity, specificity, and negative predictive value of 75%, 77%, and 95%, respectively. However, these markers are still limited by their high costs limiting their use in normal clinical practice.

Genomics and Molecular Techniques

Some studies have proposed the use of molecular techniques that depend on gene detecting to diagnose early neonatal sepsis and bacterial meningitis. A study conducted by Kasper et al. concluded that the use of multiplex real-time PCR (Roche SeptiFast®) to detect neonatal sepsis in premature infants was associated with a sensitivity that is 90%, despite having relatively low specificity (80%). However, their study was still limited by several factors including high costs. These limitations prevent the use of these techniques from being the golden standard in diagnosis. The only exception for this is HSV PCR which is considered to be the best diagnostic approach in diagnosing HSV encephalitis **[26]**.

CONCLUSION:

Both early and late neonatal sepsis remains to be significant causes of morbidity and mortality in both term and premature infants. Unfortunately, symptoms and signs of neonatal sepsis are usually nonspecific, making early diagnosis even harder. Several studies have been conducted to find ideal diagnostic approaches in the diagnosis of neonatal sepsis. These

studies used combinations of hematological studies (like complete blood count), acute phase reactants (C reactive proteins, procalcitonin, cytokines), and cell surface markers, along with other markers to detect and assess neonatal sepsis. However, larger studies are still required to find tests that are associated with higher diagnostic accuracy. More recent markers have been found to have promising results in early detection of sepsis. However, these are still not well-established and need further assessment before being applied routinely in clinical practice.

REFERENCES:

1. **Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG (2005):** Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics, 116: 595-602.
2. **Gerdes JS (1991):** Clinicopathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol, 18: 361-381.
3. **Hofer N, Muller W, Resch B (2012):** Neonates presenting with temperature symptoms: role in the diagnosis of early onset sepsis. Pediatr Int, 54: 486-490.
4. **Stoll BJ *et al.* (2002):** Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med, 347: 240-247.
5. **Weston EJ *et al.* (2011):** The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J, 30: 937-941.
6. **Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL (2001):** Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics, 108: 1094-1098.
7. **Stoll BJ *et al.* (2002):** Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics, 110: 285-291.
8. **Levent F, Baker CJ, Rench MA, Edwards MS (2010):** Early outcomes of group B streptococcal meningitis in the 21st century. Pediatr Infect Dis J, 29: 1009-1012.
9. **Hornik CP *et al.* (2012):** Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J, 31: 799-802.
10. **Brozanski BS, Jones JG, Krohn MJ, Jordan JA (2006):** Use of polymerase chain reaction as a diagnostic tool for neonatal sepsis can result in a decrease in use of antibiotics and total neonatal intensive care unit length of stay. J Perinatol, 26: 688-692.
11. **Rozycki HJ, Stahl GE, Baumgart S (1987):** Impaired sensitivity of a single early leukocyte count in screening for neonatal sepsis. Pediatr Infect Dis J, 6: 440-442.
12. **Murphy K, Weiner J (2012):** Use of leukocyte counts in evaluation of early-onset neonatal sepsis. Pediatr Infect Dis J, 31: 16-19.
13. **Hofer N, Zacharias E, Muller W, Resch B (2012):** An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology, 102: 25-36.
14. **Ng PC (2004):** Diagnostic markers of infection in neonates. Arch Dis Child Fetal Neonatal Ed, 89: F229-235.
15. **Dandona P *et al.* (1994):** Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab, 79: 1605-1608.
16. **Whicher J, Bienvenu J, Monneret G (2001):** Procalcitonin as an acute phase marker. Ann Clin Biochem, 38: 483-493.
17. **Chiesa C *et al.* (2003):** C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection. Clin Chem, 49: 60-68.
18. **Miller LC, Isa S, LoPreste G, Schaller JG, Dinarello CA (1990):** Neonatal interleukin-1 beta, interleukin-6, and tumor necrosis factor: cord blood levels and cellular production. J Pediatr, 117: 961-965.
19. **Cernada M *et al.* (2012):** Cord blood interleukin-6 as a predictor of early-onset neonatal sepsis. Acta Paediatr, 101: e203-207.
20. **Silveira RC, Procianoy RS (1999):** Evaluation of interleukin-6, tumour necrosis factor-alpha and interleukin-1beta for early diagnosis of neonatal sepsis. Acta Paediatr, 88: 647-650.
21. **Mishra UK, Jacobs SE, Doyle LW, Garland SM (2006):** Newer approaches to the diagnosis of early onset neonatal sepsis. Arch Dis Child Fetal Neonatal Ed, 91: F208-212.
22. **Boskabadi H, Maamouri G, Afshari JT, Ghayour-Mobarhan M, Shakeri MT (2010):** Serum interleukin 8 level as a diagnostic marker in late neonatal sepsis. Iran J Pediatr, 20: 41-47.
23. **Nupponen I, Andersson S, Jarvenpaa AL, Kautiainen H, Repo H (2001):** Neutrophil CD11b expression and circulating interleukin-8 as diagnostic markers for early-onset neonatal sepsis. Pediatrics, 108: E12.
24. **Ng PC, Li K, Wong RP, Chui KM, Wong E, Fok TF (2002):** Neutrophil CD64 expression: a sensitive diagnostic marker for late-onset nosocomial infection in very low birthweight infants. Pediatr Res, 51: 296-303.
25. **Streimish I *et al.* (2012):** Neutrophil CD64 as a diagnostic marker in neonatal sepsis. Pediatr Infect Dis J, 31: 777-781.
26. **Kasper DC *et al.* (2013):** Molecular detection of late-onset neonatal sepsis in premature infants using small blood volumes: proof-of-concept. Neonatology, 103: 268-273.