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EVALUATE THE DIAGNOSIS OF NEONATAL SEPSIS BY MEASURING INTERLEUKINS: A SYSTEMATIC REVIEW

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Abstract

Neonatal sepsis is a clinical condition that manifests within the first month of a newborn's life and is accompanied by systemic bacteremia. Early onset sepsis (EOS) and late onset sepsis (LOS) are the two categories that make up neonatal sepsis (LOS). The first hour of birth is when signs of early-onset sepsis appear in babies, and 90 percent of symptoms appear during the first 24 hours of life. We determined the levels of CRP, IL-6, IL-8, TNF-, and sCD163 in the serum of infected, non-infected, and control neonates prior to the administration of antibiotics, at 24 hours after the administration of antibiotics, and at 48 hours after the administration of antibiotics during the course of this study, which took place over the course of two years. Our findings add credibility to the use of early IL-6 testing as a technique for the quick detection of neonatal sepsis. This is particularly true in babies who were delivered to women who had risk factors. In a previous study, the level of IL-6 was not demonstrated to be predictive of neonatal sepsis in neonates who did not have any risk factors. This was the case even though the study was conducted in neonates who did have risk factors.

Keyword: *Infection; Interleukin; Neonatus; Sepsis; Umbilical cord*

INTRODUCTION

Neonatal sepsis is a clinical syndrome accompanied by systemic bacteremia that occurs within the first month of life. Neonatal sepsis is divided into early onset sepsis (EOS) and late onset sepsis (LOS). Early onset sepsis occurs in the first hour of life, 90% of symptoms in infants occur within the first 24 hours.[1,2] Study shows that 2.7/5.9 million deaths in children <5 years occur in the neonatal period with three-quarters of cases in the first week of life and >70% of neonatal deaths occurring in Africa and Southeast Asia, which are a quarter of the causes of death and the main cause of hospitalization baby stay.[3]

The incidence of neonatal sepsis in Asia in 2005-2013 was 4%. Neonatal sepsis accounted for 54% of child deaths in South Asia in 2013.[3] Bacteria E. coli, Klebsiella sp. and S. aureus are the most common pathogens causing EOS in developing countries with S. aureus, pneumonia and pyogenes being the most common pathogens causing LOS.[4,5] The clinical manifestations of sepsis are non-specific depending on the phase and the underlying infection. Each phase of sepsis causes hemodynamic changes. The hyperdynamic phase of sepsis is when cardiac output increases to fulfill the metabolic needs of the body's tissues.[6]

Clinical signs include body temperature regulation changes including hyperthermia or hypothermia, chills, tachycardia, and tachypnea / hyperventilation. The clinical manifestations of the early phase of sepsis are difficult to distinguish from ordinary infectious diseases, especially in neonates and children with severely compromised immunity.[7] Death from severe infections in developing countries is a substantial problem despite the advent of antibiotic therapy. Effective interventions adjunct to standard therapy for severe infections can improve clinical outcomes and reduce mortality.[8]

Action must be taken to look for biomarkers used to predict sepsis. Research shows that patients with sepsis experience increased production of proinflammatory cytokines, such as interleukins IL-1β, IL-6, and tumor necrosis factor (TNF)-α. MHC class I degradation by NK cells and NK cell lytic activity.[9,10] Interleukin-1 (IL-1), IL-6, IL-8 and tumor necrosis factor (TNF) which are the most important regulators of CRP synthesis which increase in 4-6 hours with a peak of 36-50 hours.[11,12] This article is a systematic review conducted to determine the relationship between sepsis in neonates and interleukins.

METHODS

Protocol

The methodology of this investigation was carried out in accordance with the guidelines set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020.

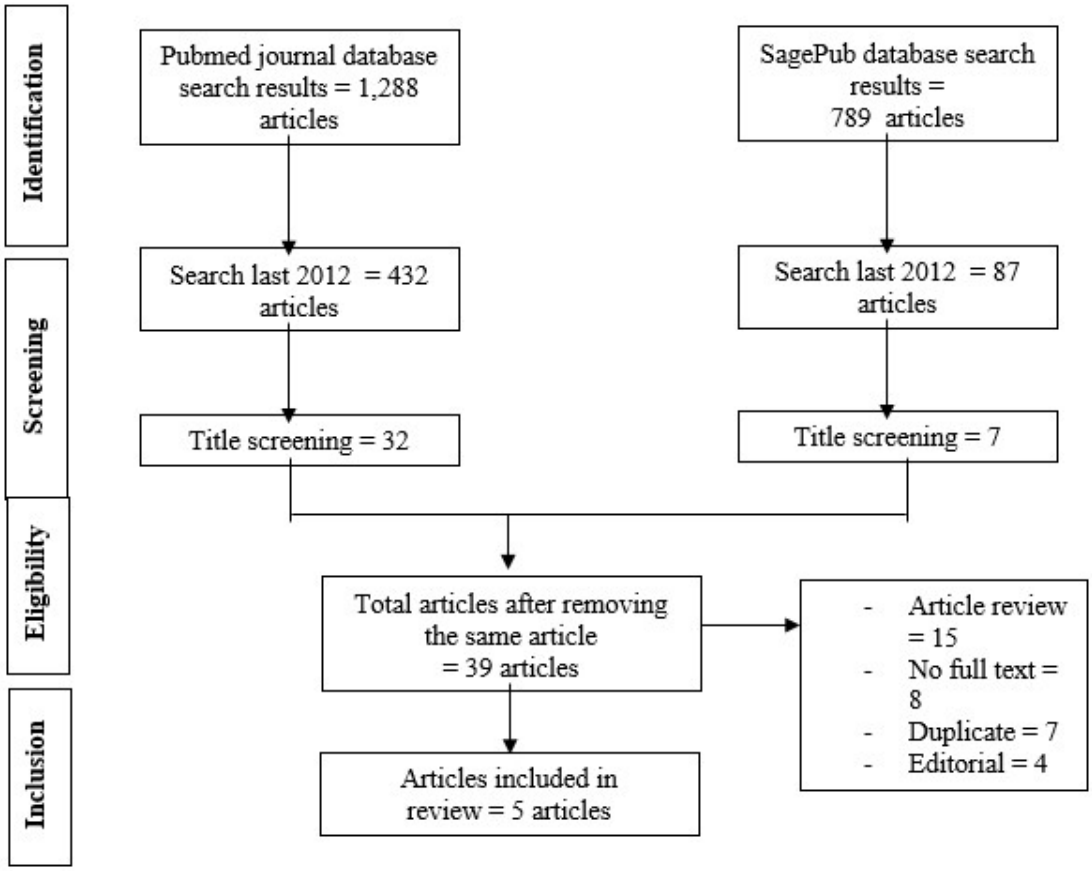

Figure 1. Article search flowchart

Criteria for Eligibility

This review of the relevant literature intends to demonstrate the association between neonatal sepsis and interleukins by evaluating or analyzing the findings of prior research conducted on the topic. This is a significant issue that is brought up in the recent study. Participation in research projects requires that they fulfill all of the following criteria: 1) Articles must be written in English and highlight or focus on correlations between newborn sepsis and interleukin in order to be considered for publication. Articles must also be submitted in the appropriate format. 2) This assessment took into account articles that were published after 2012 but prior to the time period that was the focus of this systematic analysis. Editorials, submissions that do not include a DOI, already published review articles, and entries that are extremely similar to those that have been previously published in a journal, for instance, will not be accepted for publication.

Search Strategy

The search for studies to be included in the systematic review was carried out from January, 26th 2023 using the PubMed and SagePub databases by inputting the words: "neonatal sepsis" and "interleukins". Where *("neonatal sepsis"[MeSH Terms] OR ("neonatal"[All Fields] AND "sepsis"[All Fields]) OR "neonatal sepsis"[All Fields]) AND ("interleukine"[All Fields] OR "interleukines"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields])* is used as search keywords.

Data retrieval

After completing a literature analysis that included an examination of the titles and abstracts of previously conducted research, the author changed the inclusion and exclusion criteria. The newly established criteria are explained in the supplemental materials for this study. This revealed the different facets of the issue that require additional examination, as well as its scope. The author arrived at this result after performing research on numerous other studies with a similar structure. During the process of conducting a systematic review, only papers that met all inclusion criteria were considered.

This ensured that only relevant information was discovered throughout the search. Our team did not evaluate research ideas that did not meet all of our evaluation parameters. Thus, it was ensured that a comprehensive examination would be conducted. This endeavor revealed essential information about the studies, including their titles, authors, publication dates, locations, sorts of study activities, and parameters. These are the different widely available product categories. These are abilities that can be acquired via practice. Depending on the information source, this information may be presented in a variety of formats.

Quality Assessment and Data Synthesis

Before picking which publications to explore, each author independently researched a piece of research indicated in the titles and abstracts of the papers. Then, the complete texts of publications that match the inclusion criteria for the systematic review will be evaluated to determine which papers will be included in the review. This defines the articles that will be evaluated. To facilitate article selection for the review. Which studies meet the criteria for inclusion in the review?

RESULT

Ganesan, et al (2018) study in India showed CRP level more than 13.49 mg/l demonstrated a sensitivity of 80% and a specificity of 65.70% respectively. The sensitivity of the IL-6 >51.29 pg/ml test was 100%, but the specificity was only 62.86%, whereas the sensitivity of the hs-CRP test was 90%, but the specificity was only 32.86%. The combination of IL-6 and CRP demonstrated a sensitivity and specificity that were respectively 100% and 75.71%.[13]

Prashant, et al (2014)[14] showed CRP >19,689 ng/ml had a sensitivity of 68%, specificity of 92%, for IL-6 at >95.32 pg/ml had a sensitivity of 54%, specificity of 96%, for IL-8 at >70.86 pg/ml had a sensitivity of 78%, specificity of 70%, for sCD163 at >896.78 ng/ml had a sensitivity of 100%, specificity of 88% for the diagnosis of infection before antibiotics. TNF-α levels of >12.6 ng/ml showed 100% sensitivity and 72% specificity for the diagnosis of inflammation.

Cobo, et al (2013) showed incidence of EONS was 7% of all cases. Eighteen percent of women suffered from funisitis. Umbilical cord IL-6 was substantially greater in women who were complicated with EONS compared to women who were not complicated with EONS [median (range) 389.5 pg/mL (13.9-734.8) vs. 5.2 (0.1-801-4), p0.001]. The level of IL-6 found in the umbilical cord was the sole factor that could reliably predict early-onset newborn sepsis (odds ratio 13.6, p = 0.004).[15]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Interleukin	Result
Ganesan, 2018[16]	India	Cross sectional study	Eighty neonates	IL-6	CRP levels >13.49 mg/l had sensitivity and specificity of 80% and 65.70%, respectively. IL-6 >51.29 pg/ml had 100% sensitivity and 62.86% specificity, while hs-CRP had 90% sensitivity and 32.86% specificity. The combination of IL-6 and CRP demonstrated 100% sensitivity and 75.71% specificity.
Prashant, 2013[14]	India	Cross sectional study	100 neonates	IL-6	The cut of levels for CRP at >19,689 ng/ml had a sensitivity of 68%, specificity of 92%, for IL-6 at >95.32 pg/ml had a sensitivity of 54%, specificity of 96%, for IL-8 at >70.86 pg/ml had a sensitivity of 78%, specificity of 70%, for sCD163 at >896.78 ng/ml had a sensitivity of 100%, specificity of 88% for the diagnosis of infection before antibiotics. TNF-α levels of >12.6 ng/ml showed 100% sensitivity and 72% specificity for the diagnosis of inflammation.
Cobo, 2013[15]	Spain	Prospective cohort study	176 women with PPROM	IL-6	The rate of EONS was 7%. Funisitis was present in 18% of women. Umbilical cord IL-6 was significantly higher in women complicated with EONS than without [median (range) 389.5 pg/mL (13.9-734.8) vs 5.2 (0.1-801-4), p<0.001]. Umbilical cord IL-6 was the only independent predictor of early-onset neonatal sepsis (odds ratio 13.6, p = 0.004).
Fadilah, 2022[17]	Indonesia	Prospective cohort study	40 neonates	IL-6	40 neonates were born to mothers with sepsis risk factors; 13 (32.5%) developed clinical sepsis. Significantly more infants with elevated IL-6 developed neonatal sepsis (55.5%) than those with normal IL-6 (13.6%). After multivariate analysis incorporating other significant variables, the risk factors predictive of clinical early-onset neonatal sepsis were IL-6 [RR 5.54 (95%CI 1.68-18.25); P=0.016], prematurity [RR 4.92 (95%CI 1.66-14.59); P=0.014], and initial Apgar score [RR 3.38 (95%CI 1.34-3.38); P=0.046].
Kung, 2022[18]	Austria	Retrospective cohort study	1,695 neonates	IL-6	The AUC for interleukin-6 was 0.84–0.91 in all neonates, 0.88–0.89 in very-preterm and 0.89–0.91 in very-low-birthweight infants. Using interleukin-6 cut-off values of 80 pg/ml on day of life 1, 40 pg/ml on day of life 2–7 and 30 pg/ml after day of life 7, a sensitivity of 75% and a specificity of 81% for culture-confirmed sepsis were achieved. In very-preterm infants, the corresponding values were 74% for sensitivity and 83% for specificity and in very-low-birthweight infants 74% and 86%, respectively.

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DISCUSSION

Because of the non-specific nature of the symptoms and the late emergence of the condition, neonatal sepsis is still a significant cause of mortality among infants. This is due to the fact that the symptoms are frequently misunderstood, which is a direct result of the late emergence of the condition. During the course of this study, which spanned the course of two years, we determined the levels of CRP, IL-6, IL-8, TNF-α, and sCD163 in the serum of infected, non-infected, and control neonates prior to the administration of antibiotics, at 24 hours after the administration of antibiotics, and at 48 hours after the administration of antibiotics.[19,20]

Due to the delayed onset of symptoms and the non-specific clinical presentation of neonatal sepsis, neonatal sepsis continues to be a major cause of death in newborns. The blood culture is the gold standard for the diagnosis, but it is time consuming and it is often negative. This could be because of insufficient sample collection, the use of antibiotics intra-partum, intermittent or low density bacteraemia, or any combination of these factors. In this study, IL-6, the most frequent acute phase reactant CRP, and high-sensitivity CRP (hs-CRP) were tested in order to determine which of the above indicators, either on their own or in combination, would be the most accurate and reliable predictor of newborn sepsis.[14,16]

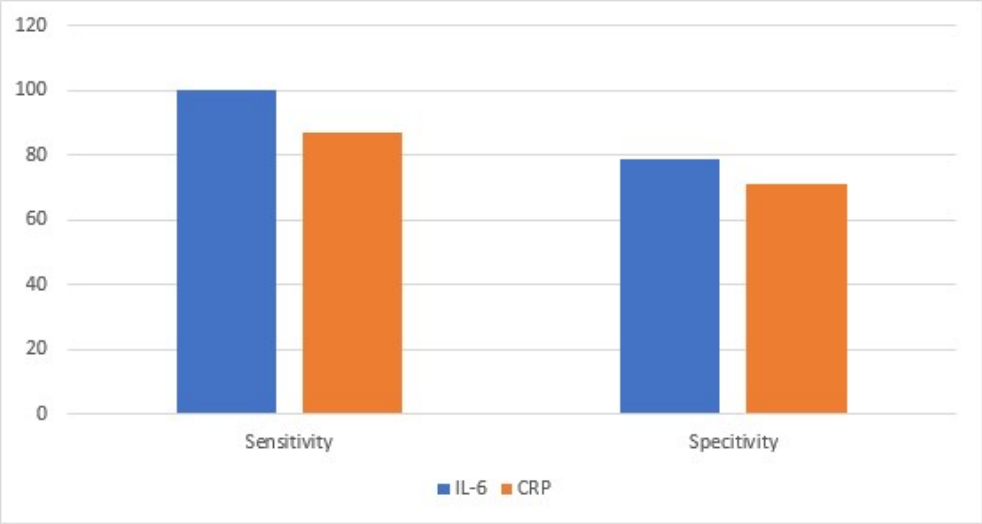

Figure 2. Sensitivity and specivity IL-6 and CRP for diagosis neonatal sepsis

When compared with the levels found in normal healthy controls, the clinically suspected cases of newborn sepsis group has a serum level of interleukin-6 (IL-6) that is considerably greater. This finding is consistent with the findings of other investigations.[16,21] According to the findings of a study carried out by Smulian and colleagues, the level of IL-6 had a highly substantial value even in the umbilical cord blood of septic newborns. Within the cohort of neonates with a clinical suspicion of having sepsis, we found a sensitivity of one hundred percent for IL-6.[22]

Interleukins are a group of cytokines that were first seen to be expressed by white blood cells. The function of the immune system depends in large part on interleukins, and rarely deficiencies of a number of them have been described, complete with autoimmune disease or immune deficiency. The majority of interleukins are synthesized by helper CD4+ T lymphocytes, as well as via monocytes, macrophages, and endothelial cells. Interleukins promote the development and differentiation of T, B, and hematopoietic cells.[23]

IL-6 signaling activates the Ras-Raf, P3K/AKT and JAK/STAT pathways. Activation of pro-tumorigenic and anti-apoptotic activities occurs through the regulation of different pathways. Interleukin-6 is a cytokine with various biological activities. Interleukin 6 is a mediator for substituting the immunoglobulin class and for regulating the acute phase response. Interleukin-6 is an indicator of inflammation in the body. IL-6 is an endogenous biochemical that is active during B-cell maturation and inflammatory processes. Interleukin-6 can act as a pyrogen and can cause fever during infectious, non-infectious and autoimmune diseases.[24]

The link between IL-6 and the IL-6 receptor (IL6RA, CD126) is what starts the IL-6 signaling process. This connection induces the dimerization of gp130 and gp130 proteins (IL6RB, CD130), which ultimately results in a complex of hexameric structures that are capable of signaling. It is possible to find IL-6R in a form that is capable of dissolving in bodily fluids. This form of IL-6R has the potential to bind to IL-6, which in turn triggers the trans IL-6 signaling cascade, which ultimately results in the production of gp130.[24]

Macrophages and monocytes are the cells that create interleukin-6 in response to other inflammatory cytokines such as tumor necrosis factor (TNF)-beta and interleukin-11. During the time when the immune system is at rest, IL-6 receptors may be detected on normally active B cells, cells in the liver germ cells, and myeloid cells, as well as on normal T lymphocytes. IL-6 is responsible for the generation of inflammatory responses by starting transcription factors that are present in multiple different inflammatory pathways.[24]

The acute expression of IL-6 plays a significant role in the process by which various cell populations are activated. When it acts on hepatocytes, IL-6 decreases levels of cytochrome P450, transferrin, fibronectin, and albumin while simultaneously initiating the production of several acute phase proteins. These proteins include serum amyloid A (SAA), fibrinogen, hatoglobin, C-reactive protein, hepcidin, and antichotrypsin. The C-reactive protein, often known as CRP, is a reliable indicator of inflammation, and its expression is linked to the cytokine IL-6.[24]

Chronic inflammatory anemia and hypoferremia can be brought on if levels of hepcidin that have been activated by IL-6 can block the ferroportin 1 iron transporter in the intestinal epithelium, hepatocytes, and macrophages. Increased differentiation of helper T cells that produce IL-17, which plays a key role in the initiation of autoimmune tissue damage, can be attributed to the combination of TGF-β and IL-6.[24]

In a study that was carried out by Buck et al,[25] it was also demonstrated that the sensitivity was comparable in culture-positive neonates and clinical sepsis neonates. According to the findings of a study carried out by Messer et al,[26] sensitivity

is present from birth right up until the first 12 hours of life. The other studies conducted by Kocabas et al. and Prashant et al.[14] showed different sensitivity results when compared to our study. This may be due to differences in the type of sample collected, that is venous blood or umbilical vein blood, the age of neonate at the onset of infection, mainly due to the difference in the inclusion criteria, and the absence of standardized cut-off value for IL-6 in these studies could be the factors contributing to the variation in sensitivity.

There was a statistically significant association between prematurity and early-onset newborn sepsis. It is possible that preterm infants receive less transplacental immunoglobulin than their term counterparts do because the passive transfer of transplacental immunoglobulin only occurs in the third trimester of pregnancy, while preterm infants are born in the second trimester. This could explain why preterm infants are more likely to experience neonatal sepsis than term infants. In our research, we did not find any significant association between PROM and early-onset newborn sepsis. Antibiotic treatment given to the mother for PROM or preterm PROM has the potential to lower the number of newborns who develop early-onset sepsis.[1,27]

When compared to the cord blood of the control neonates, the amount of IL-6 that was found in the venous blood indicated a substantial rise. Similar to CRP, IL-6 exhibited a substantial rise in the infected newborns as well as the non-infected neonates when compared to the control neonates at all time intervals.[28] This indicates that IL-6 levels are elevated not only during infection but also during inflammation. When compared to the survivors, the non-survivors had a large rise in IL-6 at all three time periods. This was the case across the board. The pattern that was seen in the serial measurements of CRP was also seen in the serial measurements of IL-6.[28,29]

After 24 hours of treatment with antibiotics, the neonates who were not infected experienced a decrease in their IL-6 levels, whereas the infected group experienced a rise in their levels. It is fascinating to see that even in the infected neonates, the levels of IL-6 diminish after 24 hours of antibiotic treatment in the survivors, but continue to grow in the non-survivors. This is the case with the neonates who did not survive the infection. According to our findings, IL-6 has a high level of specificity when determining if an infection is present and is 100% sensitive when predicting death at 48 hours following antibiotic treatment.[28,29]

Gram-positive organisms, fungi and viruses initiate an inflammatory response by releasing exotoxins/superantigens and antigen components of cells. The primary proinflammatory cytokines produced are TNF α, IL-1, 6, 8, 12 and IFN. The increase in IL-6 and 8 reached peak levels 2 hours after the introduction of endotoxin. These cytokines affect organ function directly or indirectly through secondary mediators (nitric oxide, thromboxane, leukotrienes, platelet activating factor (PAF)), prostaglandins, and complement. These proinflammatory mediators activate multiple cell types, initiate the sepsis cascade and result in endothelial damage.[30]

CONCLUSION

Our findings lend credence to the use of early IL-6 testing as a method for the speedy diagnosis of neonatal sepsis, particularly in newborns who were delivered to women who had risk factors. In a prior investigation, the presence of IL-6 was not shown to be predictive of newborn sepsis in neonates who did not have any risk factors.

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