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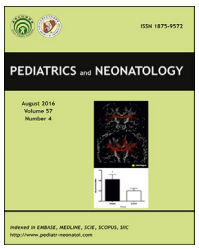

Review Article

Evaluate the diagnosis of neonatal sepsis by measuring ILs: A systematic review

Hassan Boskabadi [a], Maryam Zakerihamidi [b,*]

[a] Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Midwifery, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

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Neonatal sepsis is a dangerous and common disease among infants which is associated with high morbidity and mortality. Interleukins may be helpful for diagnosis of neonatal sepsis. Therefore, this study is conducted to investigate the role of interleukins in the diagnosis of neonatal sepsis. In this study, databases including PubMed, Cochrane Library, ISI and Google Scholar were searched up to 2016. Keywords were: Sepsis, neonatal, interleukins, prediction and diagnosis. Study inclusion criteria were: Articles about the relationship between the diagnosis of neonatal sepsis and interleukins; studies on babies; English and Persian articles and enough information from test results. Articles that had focused on adult sepsis or had used other markers except ILs or just their abstracts were available were excluded from the study. Of 100 searched studies, eventually, 16 articles were considered including 12 prospective studies, 3 cross-sectional studies and 1 retrospective study. IL6 has been studied more than other interleukins (50% of articles). ILs 6, 8 and 10 are among the initial markers of neonatal sepsis diagnosis. IL6 above 68 pg/ml had 85% sensitivity and 80% specificity, IL8 above 269.51 pg/ml had 80% sensitivity and 50% specificity, IL10 above 27 pg/ml had 60% sensitivity and 87% specificity and combined interleukins above 186.83 pg/ml had 75.63% sensitivity and 71.49% specificity in sepsis diagnosis. Interleukins can be helpful in the diagnosis of neonatal sepsis based on the results of this study. IL6 had the most sensitivity and IL10 had the most specificity for diagnosis of sepsis.
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1. Introduction

Neonatal sepsis is along with high neonatal morbidity (1–10 per 1000 live birth) and mortality (15–50%), especially in preterm babies.[1,2] Neonatal infections are a major cause of infant mortality so that in our center, it was the third leading cause of neonatal death and had allocated about 25% of causes of neonatal death to itself.[1] Neonatal sepsis is a major challenge for newborns specialists generally due to

* Corresponding author. Department of Midwifery, School of Medicine, Islamic Azad University, Tonekabon Branch, Tonekabon, Iran.
E-mail address: maryamzakerihamidi@yahoo.co.nz (M. Zakerihamidi).

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non-specific symptoms as well as the absence of an early definitive diagnostic test[2].

Since the amount of successful treatment depends on early initiation of appropriate antibiotic, empirical antimicrobial therapy usually starts very early in all infants with clinical signs of sepsis. On the other hand, this clinical practice exposes babies to adverse effects of antimicrobial agents as well. In addition, it increases the duration of hospitalization and costs and creates and expands the cases resistance to different types of bacteria.[3] Early detection of neonatal sepsis is an essential prerequisite for improving survival and treatment outcomes.[4]

It was found in a retrospective study on infants under investigation and treatment of neonatal sepsis with clinical symptoms suspected to primary infection during the first week of life that most of these infants did not require antibiotic. This means that only 10% of these infants had specified confirmed neonatal sepsis, while about 90% of babies were taking unnecessary antibiotics.[5] Conventional hematological and microbiological methods which are routinely used for diagnosis of neonatal sepsis cannot reduce deaths and serious complications of neonatal sepsis. One of the wishes of babies' specialists is to find an ideal biomarker or biomarkers to provide early, specific and valid detection of babies at risk of infection. Increasing understanding of the ability of the immune system of infants in response to infection will lead to a better identification of biomarkers for improving diagnosis, treatment and prognosis of neonatal sepsis in future.[6]

Figure 1 Search strategy and selected articles.

Isolation of microorganisms from body fluids including blood, cerebrospinal fluid and urine are methods of gold standard for diagnosis of neonatal infection. But, microbiological culture is not available before at least 36—48 h.[7] So accurate laboratory tests are required to rule out infection and reduce unnecessary antibiotic treatment.[8] So hematological parameters and interleukins may be helpful for early diagnosis of neonatal sepsis.[9] Many studies have tried to find valid initial reaction of cytokines for early diagnosis of neonatal sepsis.[10] Inflammatory process in sepsis is very complex in terms of biochemical. Based on the results of laboratory and clinical studies, it has been clear that some pro-inflammatory cytokines reach their peak very quick within one to four hours after the onset sepsis.[11] Analysis of immunological mediators may contribute to definitive and timely diagnosis of sepsis. Measuring cytokines as markers of sepsis has been taken into consideration in recent years[12] and biochemical markers such as CRP, TNF-α and ILs have been evaluated as the main indicators for early detection of neonatal sepsis.[13] Cytokines are polypeptide messengers with low molecular weight which are created by macrophages and lymphocytes in response to antigenic stimulations or products of inflammation.[12] One of identifying factors of neonatal sepsis is measuring interleukins. So that it is proposed to increase serum levels of interleukins 6, 8 and 10 as a valuable marker for early diagnosis and prediction of sepsis consequences. Levels of IL10 can predict the diagnosis of late neonatal sepsis before positive blood culture.[1] IL10 is an anti-inflammatory cytokine that is often produced by T and B lymphocytes and macrophages and its' level increases in the incidence of neonatal bacterial infections.[14] Despite recognition of various biomarkers, no single biomarker could be used exclusively for the accurate diagnosis of neonatal sepsis. However, the combination of biomarkers may improve sensitivity of detection and treatment.[6] The results of Boskabadi et al., (2013) showed that IL6 with boundary values of 10.85 pg/ml is distinctive to differentiate sepsis patients and healthy controls and values higher than 78.2 pg/ml from this factor can be used to predict neonatal mortality. IL8 in boundary values of 60.05 pg/ml is used for differentiation of specified infection from unspecified.[15] Results of a study showed that the values of IL10 and CRP in specified infection (sepsis clinical trial) were higher than the control group. The values higher than 14 pg/ml for IL10 in diagnosis of neonatal sepsis had 77.7% sensitivity, 78.8% specificity, 73.6% positive predictive value and 90% negative predictive value.[16]

As interleukins are known as one of the early inflammatory responses to infections, they are potentially

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