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ORIGINAL ARTICLE

# Endocan and Soluble Triggering Receptor Expressed on Myeloid Cells-1 as Novel Markers for Neonatal Sepsis

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sTREM-1

*Background:* Neonatal sepsis is an important cause of neonatal morbidity and mortality in the neonatal intensive care unit. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) has been evaluated in sepsis and septic shock, and it was found to be valuable in distinguishing septic cases from nonseptic cases. Endocan is constitutively expressed by endothelial cells, and high levels of endocan may be of relevance for the promotion of systemic inflammation. The aim of this study was to investigate whether the levels of sTREM-1 and endocan were increased in late-onset neonatal sepsis.
*Methods:* Patients were classified into septic and nonseptic groups. Blood was collected from a peripheral vein of all septic newborns and healthy newborns at the time of initial laboratory evaluation before any treatment, and within 48—72 hours after initiation of treatment. Serum sTREM-1 and endocan measurements were performed when the study was finished.
*Results:* The study population comprised of 50 neonates: 20 nonseptic neonates and 30 septic neonates. The groups were similar with regards to baseline characteristics. The initial measurements of interleukin-6 (IL-6), sTREM-1, endocan, and immature/total neutrophil ratio (I/T ratio) were significantly higher in septic neonates in comparison with nonseptic neonates.

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Receiver operating characteristic (ROC) curve analyses revealed that IL-6, sTREM-1, endocan, and I/T ratio resulted in significant areas under the curve (AUC) with respect to early identification of septic neonates. Soluble TREM-1 and IL-6 performed best to distinguish septic neonates from nonseptic neonates. Univariate logistic regression analysis showed that increased IL-6 and sTREM-1 were strong predictors of neonatal late-onset sepsis.
*Conclusion:* Serum sTREM-1, IL-6, endocan levels, and I/T ratio increased in septic neonates. However, the diagnostic accuracy of circulating sTREM-1 seemed to be better than endocan and I/T ratio, but lower than IL-6.


## 1. Introduction

In spite of advances in neonatal care, neonatal sepsis represents a serious problem in newborns. Late-onset sepsis (LOS) in neonates is defined as infection becoming clinically evident $>$ 72 hours after birth, and it usually appears due to nosocomially acquired organisms.[1] One study revealed an incidence of 0.44% for LOS with a mortality rate of 9%.[2] Of the neonates evaluated for neonatal sepsis, only 3—8% had culture-proven sepsis. This disparity arose from the cautious approach to the management of neonatal sepsis.[3] Because early signs of sepsis in newborns are nonspecific, diagnostic studies are often ordered and treatment initiated in neonates before the presence of sepsis has been proven.[4] Since mortality from untreated sepsis could be as high as 50%, most clinicians believed that the hazard of untreated sepsis did not allow them to wait for confirmation with positive culture results. Therefore, most clinicians initiate treatment in advance.[5]

Inflammation and endothelial activation are critical determinants of the host response and represent an explanation for the complex pathophysiology in sepsis. Accordingly, biomarkers pertaining to inflammation and endothelial activation might be useful in the diagnosis and follow-up of sepsis. Human triggering receptor expressed on myeloid cells-1 (TREM-1) is a 30-kDa glycoprotein belonging to the immunoglobulin superfamily. It plays a considerable role in the innate immune response against invading microorganisms and is selectively expressed in neutrophils and monocytes/macrophages.[6] Expression of TREM-1 is highly upregulated in septic states. Increased levels of TREM trigger the release of proinflammatory cytokines, increase surface expression of cell receptors, and activate neutrophil degranulation. Additionally, expression of TREM-1 is extremely upregulated in septic states and thus is significantly increased in human blood (also known as soluble form sTREM-1).[7] In this context, sTREM-1 has been evaluated in the blood of adults with sepsis, septic shock, and community-acquired pneumonia and it was found to be valuable in distinguishing infected from noninfected patients.[8,9]

Endocan, initially known as endothelial cell-specific molecule-1, is a soluble 50-kDa dermatan sulfate proteoglycan that is constitutively expressed by endothelial cells in lungs and kidneys and can be detected in human blood.[10] Inflammatory cytokines, such as interleukin (IL)-1$\beta$ and tumor necrosis factor (TNF)-$\alpha$, stimulate the upregulation of endocan mRNA and the secretion of endocan from endothelial cells.[11] The secreted form circulates in the human bloodstream and can be detected easily. It is suggested that serum endocan levels were four-fold higher in sepsis patients at intensive care unit admission compared with healthy adult individuals. In the same study serum endocan levels were found to be higher in patients with septic shock than in patients with severe sepsis or sepsis, representing endothelial damage and correlating with the severity of disease and outcome. High levels of endocan have also been detected in patients with cancer.[12] Other studies have described that endocan is not specific for systemic inflammatory diseases. However, high levels of endocan may be of relevance for the promotion of systemic inflammation.[13]

The aim of this study was to investigate whether levels of sTREM-1 and endocan were increased in infected neonates at the first neonatal intensive-care unit (NICU) admission, and to assess their possible value in early diagnosis and follow-up of LOS. We analyzed traditional biomarkers, interleukin-6 (IL-6) and immature/total neutrophil ratio (I/T ratio), as well as sTREM-1 and endocan levels to evaluate septic neonates in NICUs.

## 2. Methods

### 2.1. Study design

This prospective study was conducted in two different level III NICUs (Kanuni Sultan Süleyman Teaching and Research Hospital, Ankara, Turkey and Gülhane Military School of Medicine, Istanbul, Turkey). The study protocol was approved by the local Ethical Committee of Gulhane Military School of Medicine and Teaching Hospital and written informed consent was obtained from the first-degree relatives before admission to the study. The study population included late preterm (gestational age of $>$ 34 weeks) and term neonates who were evaluated for LOS during the period of January 2012 to December 2012. Inclusion criteria were postnatal age $\geq$ 72 hours, the presence of nonspecific signs of sepsis (temperature instability, apneic spells, need for supplemented oxygen, need for ventilation,