



# Neutrophil CD11b as a promising marker for early detection of neonatal sepsis

Ju Sun Heo, MD

Department of Pediatrics, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

## Key message

- Neonatal sepsis is a global problem and significant cause of neonatal mortality and adverse short- and long-term outcomes.
- Due to severe limitations diagnosing neonatal sepsis, there is a critical need to identify reliable specific biomarkers for early detection.
- nCD11b might be an accurate and rapid biomarker for the early detection of neonatal sepsis.

Sepsis refers to a systemic infection involving the bloodstream that is of bacterial, viral, or fungal origin. Sepsis, a major threat to global health, was declared a key healthcare priority by the World Health Organization.<sup>1)</sup> Sepsis peaks in extreme age groups, including the neonatal population. A relatively immature cellular and humoral immune system, poor skin and mucosal barrier function, organ immaturity, and exposure to medical procedures such as central venous catheters and tracheal intubation are all risk factors for neonatal sepsis. In a systematic review by Fleischmann-Struzek et al.,<sup>2)</sup> the population-level estimate for neonatal sepsis was 2,202 per 100,000 live births for an estimated 3.0 million cases worldwide, with a mortality rate of 11%–19%. Neonatal sepsis has also been linked to adverse short- and long-term outcomes. Surviving term and preterm neonates are at high risk of later neurodevelopmental impairment and cerebral palsy, which could cause great socioeconomic burden.<sup>3)</sup>

Challenges to defining sepsis include a heterogeneity of definitions, a lack of standardized terminology, and the need for the diagnosis to be related to outcomes. Accordingly, updated international consensus definitions for sepsis and septic shock within the adult population were developed by the Sepsis-3 group as “life-threatening organ dysfunction caused by a dysregulated host response to infection” and “subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality,” respectively.<sup>4)</sup> Such attempts were previously made for pediatric sepsis.<sup>5)</sup> However, this definition is unsuitable for the neonatal population, especially premature neonates. Thus, there is currently no consensus definition of neonatal sepsis, and definitions vary greatly among hos-

pitals and studies.<sup>3)</sup>

One major obstacle to diagnosing neonatal sepsis is its lack of specific clinical symptoms and signs, such as apnea, bradycardia, respiratory distress, feeding intolerance, and lethargy. The other problem is that blood culture, the gold standard for the diagnosis of neonatal sepsis, is less sensitive and more time-consuming than other methods. These factors lead to the overuse of empirical antibiotics, resulting in antibiotic resistance and serious complications of an altered microbiome, including mortality and necrotizing enterocolitis. For this reason, the identification of reliable and specific biomarkers for the early detection of neonatal sepsis is urgently needed.

Many studies have investigated biomarkers of neonatal sepsis. Acute-phase proteins, complement system components, chemokines, cytokines, adhesion molecules, and cell surface markers have been studied for their diagnostic value for the early detection of neonatal sepsis.<sup>6,7)</sup> Table 1 summarizes the advantages and disadvantages of representative biomarkers. However, none completely fulfill the characteristics of the ideal biomarker for neonatal sepsis. Thus, a combination of 2 or more biomarkers has been studied to increase the diagnostic accuracy.

Neutrophil CD11b (nCD11b), of the  $\beta$ -integrin adhesion protein family, is important for neutrophil migration to the site of infection.<sup>8)</sup> It is expressed in very low levels on the surfaces of unstimulated neutrophils, but the levels increase within 5 minutes of exposure to bacterial products and peak within 30 minutes.<sup>9)</sup> Several studies have assessed the diagnostic performance of nCD11b for neonatal sepsis.<sup>9–13)</sup> Weirich et al.<sup>9)</sup> assessed the diagnostic value of nCD11b for predicting early-onset or suspected infection in at-risk neonates. Its negative and positive predictive values, sensitivity, and specificity were 100%, 99%, 96%, and 100%, respectively. The level was increased at the initial evaluation but could not distinguish between the viral and bacterial infections. Ng et al.<sup>13)</sup> investigated the ability of nCD11b to identify late-onset clinical sepsis among very low birth weight infants and found that it peaked at the time of evaluation for suspected clinical sepsis (0 hour). At that time, the sensitivity and specificity were 70% and 72%, respectively. However, the

Corresponding author: Ju Sun Heo, MD, Department of Pediatrics, Korea University Anam Hospital, Korea University College of Medicine, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea

E-mail: heojs08@korea.ac.kr, <https://orcid.org/0000-0001-8928-289X>

Received: 11 April, 2020, Revised: 20 June, 2020, Accepted: 28 July, 2020

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2021 by The Korean Pediatric Society

**Table 1. Biomarkers of neonatal sepsis**

Biomarker	Characteristics	Advantage	Disadvantage
CRP	Acute-phase reactant	Minimal transplacental passage of maternal CRP Best single marker at 24–48 hr	CRP elevation in noninfectious conditions Low sensitivity during early stages of infection
IL-6	Proinflammatory cytokine	Not influenced by GA High sensitivity in both EOS and LOS High sensitivity during early stages of infection	Decrease rapidly after initial response
IL-8	Proinflammatory cytokine	Not influenced by GA or postnatal age	Decrease rapidly after initial response
TNF- $\alpha$	Very early proinflammatory cytokine	Rapid rise within 2–4 hr of infection onset Not influenced by GA or postnatal age	
CD 64/Fc gamma receptor I	High-affinity Fc receptor for immunoglobulin G1 and G3	The level increase up to 10 times within 4–6 hr	
PCT	Acute-phase reactant	High diagnostic accuracy: LOS>EOS	PCT levels increase physiologically during the first few days of birth $\rightarrow$ Limited usefulness for EOS Different reference level according to age and GA
Serum amyloid A	Early acute-phase reactant	Increase quickly at onset of neonatal sepsis	Change of level with age
LBP	Soluble pattern-recognition molecule	Rapid rise within 6–8 hr after onset of an acute infection Increased level persist for more than 24 hr Stable level with less physiological fluctuations in the first 2 days of postnatal life Less affected by other obstetrical events	
suPAR	Multifunctional glycoprotein released during inflammation	Present in various body fluids, such as plasma, pleural, bronchoalveolar lavage, urine, and cerebrospinal fluid	Cannot discriminate bacterial from viral infections Monitoring the response to treatment: less reliable

CRP, C-reactive protein; EOS, early-onset sepsis; GA, gestational age; IL, interleukin; LBP, lipopolysaccharide-binding protein; LOS, late-onset sepsis; PCT, procalcitonin; suPAR, soluble form of the urokinase-type plasminogen activator receptor; TNF, tumor necrosis factor.

sensitivity decreased rapidly after 24 hours and 48 hours (to 25% and 24%, respectively). Du et al.<sup>11)</sup> reported the diagnostic value of the combination of nCD11b and neutrophil CD64. Compared to nCD11b alone, the specificity and positive predictive value were increased, but sensitivity was unchanged. According to a meta-analysis of 305 preterm neonates and 538 preterm/term neonates, nCD11b had high accuracy for diagnosing neonatal sepsis with an overall pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and overall accuracy of 0.82, 0.93, 11.51, 0.19, and 0.90, respectively.<sup>14)</sup> The sensitivity and specificity of nCD11b were higher in preterm/term neonates than in preterm neonates. However, none of studies to date have only focused on full-term neonates.

In a case-control study of 75 full-term neonates classified into sepsis, suspected sepsis, and control groups, Elmeneza et al.<sup>15)</sup> reported that nCD11b is a sensitive marker for early-onset sepsis and suspected sepsis, even in full-term neonates. The mean nCD11b level was highest in the sepsis group, followed by the suspected sepsis and control groups. The best nCD11b cutoff value of the sepsis group was 0.695 ng/mL. They demonstrated that the diagnostic accuracy was enhanced with the combined use of nCD11b with erythrocyte sedimentation rate versus nCD11b

with C-reactive protein. This is meaningful data that can extend the diagnostic utility of nCD11b to full-term neonates. However, the application of the cutoff value in clinical situations is limited due to small sample sizes. Additional data on the differences in nCD11b level by pathogen type would increase its clinical significance.

The present evidence indicates that nCD11b might be an accurate and rapid biomarker for the early detection of neonatal sepsis in full- and preterm neonates. The clinical application of nCD11b could help limit the overuse of antibiotics in low-risk infants. However, nCD11b alone is not an ideal biomarker for neonatal sepsis; thus, further large studies of a combination of biomarkers are needed to increase its diagnostic value, while the lack of detection facilities and its low cost-effectiveness should be addressed to enable its clinical application.

#### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

See the article “Role of neutrophil CD11b expression in diagnosis of early-onset neonatal sepsis in full-term infant” [https://](https://doi.org/10.3345/cep.2020.00626)

## References

1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority - A WHO resolution. *N Engl J Med* 2017;377:414-7.
2. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. *Lancet Respir Med* 2018;6:223-30.
3. McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. *Pediatr Res* 2020;88:14-26.
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
5. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2-8.
6. Deleon C, Shattuck K, Jain SK. Biomarkers of neonatal sepsis. *Neo Reviews* 2015;16:e297-308.
7. Sharma D, Farahbakhsh N, Shastri S, Sharma P. Biomarkers for diagnosis of neonatal sepsis: a literature review. *J Matern Fetal Neonatal Med* 2018; 31:1646-59.
8. O'Hare FM, Watson W, O'Neill A, Grant T, Onwuneme C, Donoghue V, et al. Neutrophil and monocyte toll-like receptor 4, CD11b and reactive oxygen intermediates, and neuroimaging outcomes in preterm infants. *Pediatr Res* 2015;78:82-90.
9. Weirich E, Rabin RL, Maldonado Y, Benitz W, Modler S, Herzenberg LA, et al. Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. *J Pediatr* 1998;132:445-51.
10. Aydin M, Barut S, Akbulut HH, Ucar S, Orman A. Application of flow cytometry in the early diagnosis of neonatal sepsis. *Ann Clin Lab Sci* 2017;47:184-90.
11. Du J, Li L, Dou Y, Li P, Chen R, Liu H. Diagnostic utility of neutrophil CD64 as a marker for early-onset sepsis in preterm neonates. *PLoS One* 2014;9:e102647.
12. Genel F, Atlihan F, Gulez N, Kazanci E, Vergin C, Terek DT, et al. Evaluation of adhesion molecules CD64, CD11b and CD62L in neutrophils and monocytes of peripheral blood for early diagnosis of neonatal infection. *World J Pediatr* 2012;8:72-5.
13. Ng PC, Li K, Wong RP, Chui KM, Wong E, Fok TF. Neutrophil CD64 expression: a sensitive diagnostic marker for late-onset nosocomial infection in very low birthweight infants. *Pediatr Res* 2002;51:296-303.
14. Qiu X, Li J, Yang X, Tang J, Shi J, Tong Y, et al. Is neutrophil CD11b a special marker for the early diagnosis of sepsis in neonates? A systematic review and meta-analysis. *BMJ Open* 2019;9:e025222.
15. Elmeneza S, Mohamed W, Elbagoury I, Bahagat K. Role of neutrophil CD11b expression in diagnosis of early-onset neonatal sepsis in full-term infant. *Clin Exp Pediatr* 2020 Apr 14 [Epub]. <https://doi.org/10.3345/cep.2019.01319>.

**How to cite this article:** Heo JS. Neutrophil CD11b as a promising marker for early detection of neonatal sepsis. *Clin Exp Pediatr* 2021;64:28-30. <https://doi.org/10.3345/cep.2020.00626>.