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Neutrophil CD11b in Early-onset Neonatal Sepsis

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Abstract:

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. 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. Neonatal sepsis has also been linked to adverse short- and longterm outcomes. Surviving term and preterm neonates are at high risk of later neurodevelopmental impairment and cerebral palsy, which could cause great socioeconomic burden. Neutrophil CD11b (nCD11b), of the β-integrin adhesion protein family, is important for neutrophil migration to the site of infection. 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. Several studies have assessed the diagnostic performance of nCD11b for neonatal sepsis.

Keywords: Neutrophil, CD11b, Early-onset Neonatal Sepsis.

Introduction:

Neonatal sepsis differs from sepsis in adults, and is defined as a systemic inflammatory response syndrome due to suspected or proven infectious etiology in neonates **(1).**

An important early event in sepsis is the generation and release of cytokines by immune cells in response to invasion by bacteria and their toxins. These cytokines induce activation of leucocytes. During neutrophil activation, surface adhesion molecules including L-selectin, CD43, CD44 and CD50 are expressed and cleaved from neutrophil cell surface, down-regulating their expression on activated neutrophils. In contrast, the leucocyte integrin Mac-1 (CD11b/CD18) and CD64 behave as activation antigens on neutrophils, increasing their expression on the surface of the cell after its activation and hence, are considered as specific neutrophil-surface activation markers **(2).**

Cluster differentiation 11b (CD11b) (also known as α2 integrin or Mac-1), forms a heterodimer with CD18 (ß2 integrin). It is an adhesion molecule, expressed mainly on monocytes, macrophages, dendritic cells, neutrophils, natural killer cells, and lymphocytes. It plays a critical role in immune regulation and inflammation **(3).**

Functions of neutrophil CD11b (nCD11b):

1. **Cell adhesion and extravasation**:

   Neutrophil CD11b mediates neutrophil adhesion to endothelial cells and facilitates their migration across the endothelium to the site of infection. This is crucial in the early stages of neonatal sepsis when neutrophil recruitment to infected tissues is impaired **(4).**

2. **Phagocytosis**

   CD11b binds to complement-opsonized pathogens (via iC3b) and enhances their uptake and destruction. Effective phagocytosis is vital for pathogen clearance during neonatal sepsis **(5).**

3. **Cytokine signaling:**

   CD11b participates in signaling cascades that regulate neutrophil activation, cytokine release, and reactive oxygen species (ROS) production **(6).**

4. **Immune regulation**

   CD11b modulates neutrophil activity, balancing pro-inflammatory responses with anti-inflammatory effects to prevent excessive tissue damage **(4).**

CD11b and Neonatal Immune Response

CD11b expression on neutrophils and monocytes is essential for pathogen recognition and clearance. However, in neonates, the regulation of CD11b expression differs significantly from adults, leading to altered immune response during sepsis **(7).**

A study by **Ng et al. (8)** demonstrated that CD11b expression on neutrophils is significantly elevated in neonates with sepsis compared to healthy controls. This finding highlights its potential as a diagnostic marker. Furthermore, the study revealed a correlation between elevated CD11b expression and severity of the disease, suggesting its prognostic value.

In neonatal sepsis, the overactivation of CD11b can contribute to irregular immune responses, including excessive leukocyte recruitment and endothelial injury. This can exacerbate inflammation and lead to tissue damage, systemic inflammatory response syndrome (SIRS), and multiorgan dysfunction syndrome (MODS). Conversely, insufficient CD11b expression may impair the host's ability to clear pathogens, prolonging infection and increasing susceptibility to sepsis **(9).**

Neutrophil CD11b is expressed in very low levels on the surfaces of unstimulated neutrophils, but the levels increase within 5 minutes of exposure to bacterial products mainly to lipopolysaccharides present in the wall gram-negative bacteria, and peak within 30 minutes **(10).**

Weirich et al. 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 **(11).**

Ng et al. 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 sensitivity decreased rapidly after 24 hours and 48 hours (to 25% and 24%, respectively) **(8).**

This meaningful data 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 **(12).**

Considering the high mortality associated with neonatal sepsis, a diagnostic marker with a very high sensitivity and negative predictive value approaching 100% is very necessary to reduce antimicrobial unnecessary treatment and hospitalization. Because of the advances in flowcytometric technology, this study paid attention to CD11b, a neutrophil surface antigen, and its sensitivity and specificity in diagnosis of neonatal sepsis. CD11b (Mac-1, CR3) is an α subunit of the β2 integrin adhesion molecule. It is normally expressed at a very low concentration on the surface of non-activated neutrophils. CD11b increases on the neutrophil surface within 5 minutes of exposure to bacteria or endotoxin **(12).**

The best cutoff point of CD11b was >0.695 ng/ml; it had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 100% in the sepsis group. In the suspected sepsis group, CD11b showed 88% sensitivity and 80% specificity with a PPV of 81.5% and an NPV of 87% at a cutoff point >2.0009. Similar values were detected by one study, while other studies reported different values. The different findings might be explained in several ways, such as differences in GA or CD11b measurement methods. The total leukocyte count, absolute neutrophil count, and CRP and ESR levels were less useful as markers for early diagnosis of sepsis **(13).**

CRP can be used as a late indicator of neonatal sepsis because it increases slightly in the initial disease phase. Unlike CRP, CD11b does not require newly formed protein synthesis. The combination of CD11b with CRP improved the sensitivity and NPV to 100%, but the specificity and PPV remained nearly the same in the suspected sepsis group. The combined use of CD11b and ESR improved the sensitivity and NPV to 100% and enhanced the specificity and PPV to 96% and 96.2%, respectively **(14).**

The absence of a correlation between CD11b and other hematological parameters indicated that CD11b is a sensitive marker whose level increased early in the disease process while the other parameters remained unchanged .The clinical practice of treating infants with suspected infection using broad-spectrum antimicrobials increases the risk of invasive fungal infection and promotes the development of resistant bacterial strains. The use of a preventive strategy and application of safe standards can decrease the infection rate within the NICUs. Although the incidence of sepsis is lower in term infants than in preterm infants, the potential for serious adverse outcomes, including death, is of great consequence; thus, caregivers should have a low threshold for evaluation and treatment for possible sepsis in any infant regardless of condition **(15).**

In a case-control study of 75 full-term neonates classified into sepsis, suspected sepsis, and control groups, they 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 **(15).**

clinical significance of CD11b

1. **Autoimmune Diseases**
   Dysregulation of CD11b is associated with autoimmune conditions like lupus and rheumatoid arthritis. Its role in mediating inflammatory responses makes it a therapeutic target for these diseases **(16).**
2. **Cancer**
   CD11b on myeloid-derived suppressor cells (MDSCs) play a significant role in tumor progression. Thus, modulating CD11b may exhibit a beneficial role in suppressing cancer cells **(17).**
3. **Infectious Diseases**
   CD11b is crucial in defending against bacterial and fungal infections, and its deficiency can lead to increased susceptibility to infections **(4).**
4. **Therapeutic Target**

CD11b presents an attractive target for therapeutic intervention in neonatal sepsis; because of its role in regulation of immunity. Strategies aimed at modulating CD11b activity could help balance the immune response, reducing excessive inflammation and ensuring microbiome killing. Monoclonal antibodies targeting CD11b or its ligands

have shown promise in preclinical models of sepsis by mitigating leukocyte-mediated tissue damage and improving survival rates **(6, 18).**

References:

1. Nyenga, A.M., Mukuku, O., & Wembonyama, S.O. (2021). Neonatal sepsis: A review of the literature. *Theory and Clinical Practice in Pediatrics*, 3(1), 94-101.
2. Celik, I.H., Hanna, M., Canpolat, F.E. et al. (2022). Diagnosis of neonatal sepsis: the past, present and future . *Pediatric Research*, 91, 337-350.
3. Bouti, P., Klein, B.J.A.M., Verkuijlen, P.J.H., et al. (2024). SKAP2 acts downstream of CD11b/CD18 and regulates neutrophil effector function. *Frontiers in Immunology*. 15,1344761.
4. Duan, M., Zhang, X., Lou, Y., et al, (2024). Deletion of Tmem268 in mice suppresses anti infectious immune responses by downregulating CD11b signaling. *EMPO Reports*. 25(6), 2550–2570.
5. Vandendriessche, S., Mattos, M.S., Bialek, E.L., et al. (2024). Complement activation drives the phagocytosis of necrotic cell debris and resolution of liver injury. *Frontiers in Immunology*. 15,1512470.
6. Gao, Y., Zhou, A., Chen, K., et al. (2024). A living neutrophil Biorobot synergistically blocks multifaceted inflammatory pathways in macrophages to effectively neutralize cytokine storm. *Chemical Science.* 15(6), 2243-2256.
7. Fouad, N. A., Fouad, M. A., Assar, E. H., et al. (2020). Combination of procalcitonin, CRP and CD11b biomarkers in early detection of neonatal sepsis. *Egypt J Immunol*, 27(1), 77-86.
8. Ng, P.C., Li, K., Wong, R.P.O., et al. (2002). Neutrophil CD64 expression: a sensitive diagnostic marker for late-onset nosocomial infection in very low birthweight infants. *Pediatric Research,* 51(3), 296–303.
9. Swoboda, S., Gruettner, J., Lang, S., et al. (2014). Expression of CD11b (MAC-1) and CD162 (PSGL-1) on monocytes is decreased under conditions of deep hypothermic circulatory Therapeutic Medicine, arrest. *Experimental and Therapeutic Medicine.* 8(2), 488–492.
10. Hincu, M.A., Zonda, G.I., Stanciu, G.D., et al. (2020). Relevance of Biomarkers Currently in Use or Research for Practical Diagnosis Approach of Neonatal Early-Onset Sepsis. *Children*, 7(12), 309.
11. Weirich, E., Rabin, R. L., Maldonado, Y., et al. (1998). Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. *The Journal of Pediatrics*. 132(3), 445-451.
12. Heo, J.S. (2021). Neutrophil CD11b as a promising marker for early detection of neonatal sepsis. *Clin Exp Pediatr*, 64 (1), 28-30.
13. Mishra, U.K., Jacobs, S.E., Doyle, L.W., et al. (2006). Newer approaches to the diagnosis of early onset neonatal sepsis. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 91(3), F208-F212.
14. Elsayed, M.S., Hassan, A.A., Hashim, A.M., et al. (2021). The role of Hematological Scoring System (HSS) in early diagnosis of Neonatal Sepsis. *Annals of Neonatology Journal*, 3(1), 85–106.
15. Elmeneza, S., Mohamed, W., Elbagoury, I., et al. (2021). Role of neutrophil CD11b expression in diagnosis of early-onset neonatal sepsis in full-term infant. *Clinical and Experimental Pediatrics*, 64(1), 44–45.
16. Villanueva V, Li X, Jimenez V, et al. (2022). CD11b agonists offer a novel approach for treating lupus nephritis. *Translational Research*, (245),41-54.
17. Yang, C., Li, L., Ye, Z., et al. (2024). Mechanisms underlying neutrophils adhesion to triple-negative breast cancer cells via CD11b-ICAM1 in promoting breast cancer progression. *Cell Communication and Signaling.* 22(1), 340.
18. Zhang, Y.L., Bai, J., Yu, W.J., et al. (2024). CD11b mediates hypertensive cardiac remodeling by regulating macrophage infiltration and polarization. *Journal of Advanced Research.* 55, 17–31.