Review article

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CERTAIN IMMUNE MECHANISMS INVOLVED IN NEONATAL SEPSIS DEVELOPMENT

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Development of neonatal sepsis, especially in preterm neonates, is one of the main factors for high morbidity and mortality in the neonatal period. Preterm neonates, with incompletely matured immune system, have enhanced susceptibility to sepsis development, compared to term infants. Innate immune system activation represents the main protective mechanism, in preterm neonates, against sepsis development. Different components of the innate immune system provide basic protection, as well as they may serve as early biomarkers for neonatal sepsis development. In this review, we analyzed basic mechanisms of innate immune response to pathogen presence and different markers included in the initiation of the inflammatory process. Better understanding the mechanisms involved in sepsis development may provide earlier prediction of sepsis development and results in more potent therapeutic efficiency.

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Key words: *neonatal sepsis, preterm neonates, immune system, innate immunity*

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Introduction

Neonatal sepsis represents a leading cause of morbidity and mortality in preterm infants. With a high rate of morbidity and mortality, preterm neonates are especially vulnerable due to their immune system immaturity and lack of maternal protection (1). The coexistence of other respiratory or cardiovascular disorders may also have an impact on preterm sepsis development (2). On the other hand, based on the time it occurs, preterm sepsis may be formed as early onset sepsis (EOS), which develops in the first 72 h of life and late onset sepsis (LOS), which occurs after the first 72 h of life. The development of EOS is associated with infections, transmitted vertically, from mother to infant, while LOS is usually caused by pathogens collected by delivery or the community environment (3).

Appropriate and efficient treatment of neonatal sepsis may diminish morbidity and mortality rates in neonates. Therefore, recognition of early markers, signs and symptoms of neonatal sepsis represents key factors to overcome harmful effects, especially in preterm neonates. However, since nonspecific symptoms and signs are often presented during neonatal sepsis development, the diagnosis of neonatal sepsis is very difficult, and a consensus definition still lacks (3, 4). Identification of a specific pathogen, by positive blood culture, provides a gold standard for sepsis diagnosis. Nevertheless, antibiotic administration and low bacteriemia may provide false or delayed results (5). Moreover, in recent years, novel techniques (pathogen genome hybridization and polymerase chain reaction) have been used to determine the pathogen presence. The results showed that these procedures provide no information about antibiotic resistance, nor the distinction between viable or nonviable pathogens (6), indicating that positive blood culture still provides better results (3, 7).

Taking into account that inflammation has a key role in sepsis development, different studies have been conducted to evaluate the potential role of some pro- and anti-inflammatory mediators (8, 9). However, the precise mechanism of neonatal response to infection is not clearly identified, resulting in no reliable and rapid marker for neonatal sepsis development (7). Therefore, the current study intended to provide the basic mechanisms of the immune system, as well as its components, involved in neonatal sepsis development and to provide a better understanding of this pathological process with possible implications in therapeutic strategies.

Epidemiology

Usually, preterm birth is termed as birth before 37 weeks of gestation and remains the

main cause of neonatal death (10). It is estimated that preterm birth incidence in the USA is around 13%, in other developed countries is between 4.5–8%, while in the European Union is in the range of 5–10% (11, 12). Also, it is observed that, besides preterm mortality, consequences of preterm birth may persist in the neonatal period as well as in adulthood (12). On the other hand, EOS incidence is around 20 per 1,000 infants (infants born before 29 weeks of gestation), and LOS incidence is in the range of 12–28% (infants born before 26 weeks of gestation), with increasing incidence as gestational age decreases (13, 14). Furthermore, neonatal sepsis (EOS and LOS) induce a neonatal mortality rate between 5–20% in developed countries, while the rate of mortality rises to 70% in middle or low-income countries (2). Accordingly, a rapid and respectable marker for neonatal sepsis prediction is a major challenge in neonatal sepsis treatment.

Certain Immune Mechanisms in Neonatal Sepsis Development

In recent years, most of the research has focused on determining specific inflammatory components which may serve as potential biomarkers for early diagnosis of neonatal sepsis. Initial research proposed a potential role of some acute-phase reactant proteins, including C-reactive protein (CRP) and procalcitonin (PCT). Even though CRP can induce opsonization and to activate the complement system, this protein has a 24–48 h half-life and needs 10–12 h to reach elevated plasma levels (15), indicating that CRP is not able to serve as an early predictor of neonatal sepsis development but, rather, as monitoring factor of sepsis therapy efficiency (3). Additionally, levels of PCT showed physiologically altered values during the neonatal period (16), suggesting that this biomarker may not provide enough diagnostic ability to rule out neonatal sepsis (4).

Innate Immunity

Following the birth, the immune system in neonates is not fully developed, especially in preterm neonates (17). An incompletely developed innate and adaptive immune system, together with a lack of communication between these both immune system parts, often leads to sepsis development in preterm neonates (4). Transplacental antibodies transmission from mother to fetus represents the main defense mechanism from different pathogens. Taking into account that this process is enhanced after 32 weeks of gestation, preterm neonates usually lack this way of protection (18). Consequently, immune system protection is mainly based on the innate immunity, which is not very potent due to its immaturity. In line with this, previous findings demonstrate that various soluble proteins and peptides in blood plasma, with antimicrobial properties and opsonization ability, have been significantly reduced in preterm neonates (19). These antimicrobial proteins and peptides (APPs) are mainly cationic molecules released by neutrophils, eosinophils, monocytes and epithelial cells of the gastrointestinal or respiratory system, including defensins, caprotectin, protegrins, lactoferrins and lysosomes (20). All APPs have the ability to bind to various pathogens and provide elimination of pathogens through different mechanisms. This was supported by previous findings indicating that application of lactoferrin reduces the incidence of LOS in preterm neonates (21).

As part of innate immunity, complement system activity (classical, alternative and lectin pathway of activation) is also reduced in preterm neonates (4). Namely, in preterm neonates, there is decreased production of C1 and C4 components (involved in classic pathway activation), factor B (included in alternative pathway activation) and mannose-binding lectin (necessary for lectin pathway activation) compared to the term infants (22). The inability of complement activation leads to a reduction of phagocytosis activity and eradication of different pathogens, enabling preterm neonates to be especially susceptible to infection.

The presence of different pathogens initiates the formation of an inflammatory process, together with the production of innate proteins and activation of leukocytes. Polymorphonuclear leukocytes, during sepsis in preterm neonates, rapidly decrease in number, have delayed apoptosis and show potential to aggregate with decreased diapedesis function (23). Since their number in the medulla is depleted, immature and dysfunctional forms of leukocytes are released, and the process of phagocytosis is globally reduced (4). On the other hand, initiation of the inflammatory process results in innate immunity protein production, including CRP, PCT, collectins, lactoferrin and others. In addition, sepsis development induces the elevation of serum proteins with opsonization function (mainly IgM). Nevertheless, the total number of these proteins, as well as opsonization activity of blood plasma, is reduced in preterm neonates, compared to the term infants (24).

Pathogens and their products are sensed by transmembrane pattern recognition receptors (PRRs), including toll-like receptors (TLRs), which bind to the surface of the microorganisms. Up to now, there are 11 different TLRs in humans, and they play a key role in controlling the inflammation process (25). TLRs can recognize lipopolysaccharide endotoxins (LPS) on Gram-negative bacteria and byproducts of Gram-positive bacteria, mycoplasmas and yeast (26). The activation of TLRs leads to increased neutrophil activity, elevated cytokine and chemokine production and enhanced chemotaxis and immunoglobulin secretion. However, these mechanisms are significantly decreased in preterm neonates compared to the term infants (12).

Furthermore, it has been shown that sepsis development in preterm neonates results in markedly reduced expression of genes related to TLRs, suggesting the depleted innate immune response in preterm neonates (27). Similar findings revealed overexpression of genes related to innate immune response and inflammatory processes in preterm neonates, but fold changes have decreased further than those observed in term infants (28).

Other Immune Mechanisms

The TLRs activation leads to an immune response characterized by the production of pro-cytokines and chemokines (IL-1, IL-6, TNF-α, IL-12, IL-18, IL-8, MCP-1) via mitogen-activated protein kinases (MAPK) and the transcription nuclear factor κB (NF-κB) (29). The majority of cytokines are produced by activated lymphocytes and macrophages. Producing pro-inflammatory cytokines provides activation of endothelial cells and expression of cellular adhesion molecules, which results in increased leukocyte requirement and diapedesis. However, developed sepsis in preterm neonates markedly reduces production of most pro-inflammatory cytokines, mainly by decreased production of Myeloid Differentiation Factor (MyD88) (30). In line with previous findings, an earlier report showed reduced signaling through TLRs in preterm neonates, indicating reduced protection against different pathogens (31).

The characteristics of secreted cytokines and pathogens have a huge effect on the process of differentiation of T helper precursor cells (Th) toward Th1 or Th2 cells. IFN-γ, IL-2 and TNF-β are the main cytokines produced by Th1 cells, and they provide cellular and phagocytic activity. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-13 and promote antibody production and humoral immunity. On the other hand, to control the intensity of inflammatory response, anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGF-β) are secreted by lymphocytes, Th2 cells and macrophages (4). Balanced control of cytokine secretion is crucial to control inflammatory activity and to prevent multiple organ dysfunction. Therefore, monitoring the total amount of these cytokines may provide a better understanding of sepsis development and treatment efficiency, since appropriate treatment would turn these cytokines to baseline levels. However, overexpression of the curtained component, named before, may lead to inconsistent inflammatory response in different populations, especially in preterm neonates, where all the components of the immune system show relative immaturity (3).

Conclusion

With high morbidity and mortality rates, neonatal sepsis in preterm neonates represents one of the leading major public health concerns around the world. Immaturity of the immune system in preterm neonates may contribute to increased susceptibility to infection. Innate immune system activation usually provides basic protective mechanisms against inflammatory response, initiated at the beginning of neonatal sepsis development. Production of different biomarkers during initiation of the immune response, secretion of various cytokines and chemokines, may serve as potential predictive factors for neonatal sepsis development. Additionally, better understanding the basic immune mechanisms, especially during innate immune system activation, may clarify sepsis development and simultaneously enable potent treatment efficiency. Further research and additional cohort studies are required to develop effective preventive methods for reducing the neonatal morbidity and mortality.

References

1. Raynor LL, Saucerman JJ, Akinola MO, Lake DE, Moorman JR, Fairchild KD. Cytokine screening identifies NICU patients with Gram-negative bacteremia. Pediatr Res 2012; 71(3): 261-6. [CrossRef] [PubMed]
2. Korang SK, Safi S, Nava C, Gordon A, Gupta M, Greisen G, et al. Antibiotic regimens for early-onset neonatal sepsis. Cochrane Database Syst Rev 2021; 5(5): CD013837. [CrossRef] [PubMed]
3. Vucic J, Vucic M, Stankovic T, Stamenkovic H, Stankovic S, Zlatanovic D. Potential role of IFN-γ and IL-5 in sepsis prediction of preterm neonates. Open Med 2021; 16(1): 139-45. [CrossRef] [PubMed]
4. Parra-Llorca A, Pinilla-Gonzlez A, Torrejón-Rodríguez L, Lara-Cantón I, Kuligowski J, Collado MC, et al. Effects of Sepsis on Immune Response, Microbiome and Oxidative Metabolism in Preterm Infants. Children (Basel) 2023; 10(3): 602. [CrossRef] [PubMed]
5. Biondi EA, Mischler M, Jerardi KE, Statile AM, French J, Evans R, et al. Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. JAMA Pediatr 2014; 168(9): 844-9. [CrossRef] [PubMed]
6. van den Brand M, van den Dungen FAM, Bos MP, van Weissenbruch MM, van Furth AM, de Lange A, et al. Evaluation of a real-time PCR assay for detection and quantification of bacterial DNA directly in blood of preterm neonates with suspected late-onset sepsis. Crit Care 2018; 22(1): 105. [CrossRef] [PubMed]
7. Pammi M, Flores A, Leeflang M, Versalovic J. Molecular assays in the diagnosis of neonatal sepsis: a systematic review and meta-analysis. Pediatrics 2011; 128(4): e973-85. [CrossRef] [PubMed]
8. 8. Caron JE, La Pine TR, Augustine NH, Martins TB, Kumánovics A, Hill HR. Severely depressed interleukin-17 production by human neonatal mononuclear cells. Pediatr Res 2014; 76(6):522–7. [CrossRef] [PubMed]
9. Ng PC, Lam HS. Biomarkers for late-onset neonatal sepsis: cytokines and beyond. Clin Perinatol 2010; 37(3): 599–610. [CrossRef] [PubMed]
10. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet 2005; 365(9462): 891-900. [CrossRef] [PubMed]
11. Jenkins-Manning S, Flenady V, Dodd J, Cincotta R, Crowther C. Care of women at risk of preterm birth: a survey of reported practice in Australia and New Zealand. Aust N Z J Obstet Gynaecol 2006; 46(6): 546-8. [CrossRef] [PubMed]
12. Daskalakis G, Psarris A, Koutras A, Fasoulakis Z, Prokopakis I, Varthaliti A, et al. Maternal Infection and Preterm Birth: From Molecular Basis to Clinical Implications. Children (Basel) 2023; 10(5): 907. [CrossRef] [PubMed]
13. Flannery DD, Puopolo KM. Neonatal Early-Onset Sepsis. Neoreviews 2022; 23(11): 756-70. [CrossRef] [PubMed]
14. Coggins SA, Glaser K. Updates in Late-Onset Sepsis: Risk Assessment, Therapy, and Outcomes. Neoreviews 2022; 23(11): 738-55. [CrossRef] [PubMed]
15. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology 2012; 102(1):25-36. [CrossRef] [PubMed]
16. Chiesa C, Pellegrini G, Panero A, Osborn JF, Signore F, Assumma M, et al. C-reactive protein, interleukin-6, and procalcitonin in the immediate postnatal period: influence of illness severity, risk status, antenatal and perinatal complications, and infection. Clin Chem 2003; 49(1): 60-8. [CrossRef] [PubMed]
17. Wynn JL, Neu J, Moldawer LL, Levy O. Potential of immunomodulatory agents for prevention and treatment of neonatal sepsis. J Perinatol 2009; 29(2): 79-88. [CrossRef] [PubMed]
18. van den Berg JP, Westerbeek EA, van der Klis FR, Berbers GA, van Elburg RM. Transplacental transport of IgG antibodies to preterm infants: a review of the literature. Early Hum Dev 2011; 87(2): 67-72. [CrossRef] [PubMed]
19. Strunk T, Currie A, Richmond P, Simmer K, Burgner D. Innate immunity in human newborn infants: prematurity means more than immaturity. J Matern Fetal Neonatal Med 2011; 24(1): 25-31. [CrossRef] [PubMed]
20. Kai-Larsen Y, Gudmundsson GH, Agerberth B. A review of the innate immune defence of the human foetus and newborn, with the emphasis on antimicrobial peptides. Acta Paediatr 2014; 103(10): 1000-8. [CrossRef] [PubMed]
21. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. JAMA 2009; 302(13): 1421-8. [CrossRef] [PubMed]
22. 22. McGreal EP, Hearne K, Spiller OB. Off to a slow start: under-development of the complement system in term newborns is more substantial following premature birth. Immunobiology 2012; 217(2): 176-86. [CrossRef] [PubMed]
23. Koenig JM, Stegner JJ, Schmeck AC, Saxonhouse MA, Kenigsberg LE. Neonatal neutrophils with prolonged survival exhibit enhanced inflammatory and cytotoxic responsiveness. Pediatr Res 2005; 57(3): 424-9. [CrossRef] [PubMed]
24. Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nat Rev Immunol 2007; 7(5): 379-90. [CrossRef] [PubMed]
25. Gruber EJ, Leifer CA. Molecular regulation of TLR signaling in health and disease: mechano-regulation of macrophages and TLR signaling. Innate Immun. 2020; 26(1): 15-25. [CrossRef] [PubMed]

26.Luo H, He J, Qin L, Chen Y, Chen L, Li R, et al. Mycoplasma pneumoniae lipids license TLR-4 for activation of NLRP3 inflammasome and autophagy to evoke a proinflammatory response. Clin Exp Immunol 2021; 203(1): 66-79. [CrossRef] [PubMed]
27.Webber RJ, Sweet RM, Webber DS. Circulating Microvesicle-Associated Inducible Nitric Oxide Synthase Is a Novel Therapeutic Target to Treat Sepsis: Current Status and Future Considerations. Int J Mol Sci 2021; 22(24): 13371. [CrossRef] [PubMed]
28.Vance JK, Rawson TW, Povroznik JM, Brundage KM, Robinson CM. Myeloid-Derived Suppressor Cells Gain Suppressive Function during Neonatal Bacterial Sepsis. Int J Mol Sci 2021; 22(13): 7047. [CrossRef] [PubMed]
29.Ng PC, Li K, Wong RP, Chui K, Wong E, Li G, et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. Arch Dis Child Fetal Neonatal Ed 2003; 88(3): F209-13. [CrossRef] [PubMed]
30.Yao YM, Osuchowski MF, Wang JH, Pan ZK. Editorial: Immune Dysfunction: An Update of New Immune Cell Subsets and Cytokines in Sepsis. Front Immunol 2021; 12: 822068. [CrossRef] [PubMed]
31.Sadeghi K, Berger A, Langgartner M, Prusa AR, Hayde M, Herkner K, et al. Immaturity of infection control in preterm and term newborns is associated with impaired toll-like receptor signaling. J Infect Dis 2007; 195(2): 296-302. [CrossRef] [PubMed]

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IMUNOLOŠKI MEHANIZMI UKLJUČENI U RAZVOJ NEONATALNE SEPSE

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Razvoj neonatalne sepse, posebno kod preterminske novorođenčadi, predstavlja jedan od glavnih faktora značajnog morbiditeta i mortaliteta u neonatalnom periodu. Prevremeno rođena novorođenčad kod kojih imunološki sistem nije u potpunosti razvijen, pokazuju pojačanu osetljivost za razvoj sepse u odnosu na novorođenčad rođenu u terminu. Aktivacija urođenog imuniteta kod prevremeno rođene novorođenčadi predstavlja jedan od glavnih mehanizama koji se suprostavljaju razvoju sepse. Različite komponente urođenog imuniteta omogućavaju osnovnu zaštitu i mogu poslužiti kao rani biomarkeri za razvoj sepse. U ovom radu analizirani su bazični mehanizmi urođenog imuniteta na prisustvo patogena, kao i različiti biomarkeri koji su uključeni u pokretanje inflamatornog procesa. Bolje razumevanje mehanizama uključenih u nastanak sepse može biti od koristi za ranu predikciju sepse, što doprinosi efikasnijem terapijskom pristupu.

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***Ključne reči**: neonatalna sepsa, preterminska novorođenčad, imunološki sistem, urođeni imunitet*