EJR European Journal of Rheumatology

DOI:10.5152/eurjrheum.2025.24007

Case Report

# Early Onset Neonatal Sepsis Induced Macrophage Activation Syndrome

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## Abstract

Neonatal sepsis manifests as a dysregulated release of acute phase reactants due to suspected or proven infectious etiology leading to a systemic inflammatory state. This immune dysregulation can trigger a cytokine storm leading to macrophage activation syndrome (MAS). Macrophage activation syndrome has been postulated to manifest as sepsis with multi-organ dysfunction. Prompt suspicion of MAS is important as immunomodulatory therapy can reduce mortality and morbidity. We present 2 preterm neonates with early onset neonatal sepsis, where appropriate antibiotic therapy and supportive measures were ineffective. Macrophage activation syndrome was suspected in these 2 cases due to worsening thrombocytopenia and transaminitis. Additional investigations of ferritin, triglyceride, fibrinogen, and NT-Pro BNP fulfilled the recent classification criteria for MAS. The addition of Intravenous immunoglobulin (IVIG) and methylprednisolone led to improvement in clinical and laboratory outcomes in 1 neonate; however, other succumbed to massive pulmonary and intracranial bleeding. Early immunomodulatory therapy in neonatal sepsis-induced MAS can reduce mortality and morbidity.

**Keywords:** Macrophage activation syndrome, neonatal early-onset sepsis, cytokine storm

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**Cite this article as:** Kumar C, Gummadi A, Deshmukh N, Pothala R, Poornima Bathina S, Dodda D. Early onset neonatal sepsis induced macrophage activation syndrome. *Eur J Rheumatol*.2025, 12(2), 0007, doi: 10.5152/eurjrheum.2025.24007.

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Received: April 3, 2024
Revision Requested: June 10, 2024
Last Revision Received: September 13, 2024
Accepted: October 3, 2024
Publication Date: July 23, 2025



## Introduction

Sepsis is a leading cause of neonatal mortality. It manifests as a dysregulated release of acute phase reactants due to suspected or proven infectious etiology leading to a systemic inflammatory state. Clinical presentation ranges from systemic inflammatory response syndrome to severe sepsis, septic shock, and multiorgan dysfunction syndrome (MODS).[1] Appropriate antibiotic therapy, supportive measures, and certain adjunctive therapies are the mainstay of treatment. Mortality is high in those with MODS, despite appropriate source reduction and supportive care. Many authors have postulated this to be due to macrophage activation syndrome (MAS), triggered by infection leading to a cytokine storm.[1-3] This sparks the discussion of the role of immunomodulatory therapy if MAS is suspected. However, the literature is sparse on neonatal and pediatric sepsis-induced MAS. We hereby report 2 cases of early-onset neonatal sepsis-induced MAS, its management, and review of the literature. Informed consent was obtained from the patients' parents and ethical approval was obtained from the Ankura Hospital Ethics Committee (Approval number: ANKURA/EC/BMHR/2025/5-01 Date: 30/01/2025)

## Case Presentation

The first case was a preterm male neonate with intrauterine growth restriction (IUGR) (33 weeks; birth weight—1400 g) who developed respiratory distress syndrome, fever, shock, dyselectrolytemia, leucopenia, thrombocytopenia, and feed intolerance. Blood culture at admission was growing multidrug-resistant *Klebsiella pneumoniae*. The neonate received sensitive antibiotics and other supportive care. However, despite this, he continued to have worsening thrombocytopenia, coagulopathy, and bleeding manifestations. Multiplex polymerase chain reaction (PCR) for other viral and bacterial etiologies was negative. Immune dysregulation and hyperinflammation were considered to be acting behind this MODS. The neonate had elevated inflammatory markers: C-reactive protein (CRP)—93 mg/L, procalcitonin—27 ng/mL, N-terminal pro-brain natriuretic peptide (NT-Pro-BNP)—48 000 pg/mL, aspartate aminotransferase (AST)—82 U/mL, interleukin-6 (IL-6)—899 pg/mL, triglyceride—257 mg/dL, ferritin—630 ng/mL, and fibrinogen—187 mg/dL. He met the MAS 2016 criteria and was initiated on IVIG 2 g/kg followed by methylprednisolone 30 mg/kg/day for 5 days, and then tapering prednisolone for the next 2 weeks.[4] Due to an inadequate response, he received 2 weeks of therapy of Anakinra (IL-1 receptor antagonist). Cardiac evaluation revealed normal

cardiac function and coronary diameter. He received 14 days of sensitive antibiotics therapy. He was discharged home after normalization of platelet counts and coagulopathy and was thriving well at the 6-week follow-up.

The second case was a preterm male neonate with IUGR (31 weeks; birth weight—1200 g). He developed respiratory distress syndrome and received noninvasive respiratory support and intratracheal surfactant administration. Soon after the birth, he developed fever, generalized edema, hypotension, respiratory failure, and hyperglycemia, and was initiated on mechanical ventilation and vasopressor therapy. He was initiated on first-line antibiotics. Blood culture at admission showed growth of multidrug-resistant *Escherichia coli*. Sensitive antibiotics commenced along with the continuation of supportive measures. However, he continued to remain febrile and subsequently developed anemia, leucopenia, thrombocytopenia, coagulopathy, bleeding manifestation, and dyselectrolytemia. Multiplex PCR did not reveal other viral or bacterial infections. Due to non-response to sensitive antibiotics, a work-up for MAS was considered. He had elevated Procalcitonin—54 ng/mL, NT-Pro BNP—42 800 pg/mL, IL-6—525 pg/mL, AST—100 U/mL, Triglyceride—205 mg/dL, D-dimer—10 000 ng/mL, Ferritin—992 ng/mL, and Fibrinogen—170 mg/dL. He met the criteria for MAS and received IVIG 2 g/kg followed by Methylprednisolone 30 mg/kg/day along with blood products transfusion.[4] However, despite this, he developed massive pulmonary hemorrhage and severe grade intraventricular hemorrhage and succumbed to the illness.

## Discussion

The dysregulation of the host immune system in sepsis has been described in literature ranging from MAS-like hyperinflammation to blunted immune responses, like immune paralysis, which determines the outcome.[5,6] The underlying etiopathogenesis of MAS involves the release of cytokines like tumor necrosis factor alpha and several interleukins (IL) such as IL-6, IL-1β, and IL-18 by the activated macrophages/monocytes. The triggering factor here is severe sepsis which induces a cascade of inflammatory states. This also leads to the production of several biomarkers like ferritin and triglycerides, typically elevated in MAS. Consumptive coagulopathy leads to the depletion of fibrinogen levels. Identification of this abnormal immunological response in pediatric and neonatal sepsis is challenging for clinicians. This differs from pediatric rheumatological illnesses complicating into MAS, which have been well described. Many authors have postulated MODS in sepsis as a possible manifestation of sepsis induced MAS.[1-3] Nandy et al reported that significantly higher numbers of children met MAS criteria when they manifested sepsis with MODS as compared to the initial stage of septic shock, although this needs to be validated in larger studies.[2] Analysis of individual components of MAS criteria showed ferritin having the highest sensitivity and serum fibrinogen having the maximum likelihood ratio.[2] The prognostic value of these individual markers has also been studied. Ferritin levels greater than 500 ng/mL and fibrinogen levels less than 150 mg/dL have been associated with adverse outcome in sepsis.[7] However, composite criteria of MAS are more reliable for declaring sepsis-induced MAS and this is less stringent than earlier criteria.[4] Demonstration of hemophagocytosis by invasive tests is not relevant as the diagnostic criteria are satisfied by the presence of ≥2 criteria with elevated ferritin in a febrile patient with an underlying predisposing factor (neonatal sepsis here). The physician should start considering the diagnosis of MAS if there is no appropriate response to adequate source reduction in 48-72 hours in cases of neonatal sepsis. Immunomodulatory therapy is the mainstay of treatment countering the hyperinflammatory state of MAS. There has been a transition to safer immunomodulator agents, including IVIG and methylprednisolone, in the 2016 MAS classification criteria rather than using chemotherapeutics when Hemophagocytic lymphohistiocytosis (HLH) 2004 criteria were followed.[4] Recent studies have shown good survival outcomes in sepsis with MODS treated with IVIG ± methylprednisolone.[8-11] These immunomodulatory therapies were beneficial in the recent pandemic as well, when used for multisystem inflammatory syndrome in neonates and children.[12] The important message to be withdrawn from these cases is that MAS should be suspected upfront in neonatal sepsis when the clinical condition is not responding to a sufficient duration of appropriate antibiotic therapy and supportive measures, especially with worsening thrombocytopenia and transaminitis. Macrophage activation syndrome can be diagnosed by some additional investigations, and if meeting MAS criteria, early immunomodulatory therapy can reduce mortality and morbidity. First-line immunomodulation should include IVIG and steroids, and biological drugs such as anakinra need to be considered upfront in refractory cases.

### Main Points

- Macrophage activation syndrome should be suspected in neonatal sepsis if there is an inadequate response to appropriate antibiotic therapy and supportive measures, especially with worsening thrombocytopenia and transaminitis.
- Additional investigations including ferritin, fibrinogen, triglyceride, and AST, and application of the 2016 MAS classification criteria help in early diagnosis.
- Prompt treatment with immunomodulators, including IVIG and methylprednisolone, improve the outcome.

**Data Availability Statement:** The data that support the findings of this case are available on request from the corresponding author.

**Ethics Committee Approval:** Ethical approval was obtained from the Ankura Hospital Ethics Committee. Approval number: ANKURA/EC/BMHR/2025/5-01 Date: 30/01/2025.

**Informed Consent:** Written informed consent was obtained from the patients' parents who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept- CK and AG; Design- CK, ND, AG; Supervision- CK, AG; Resources- RP, SPB, DD; Materials- RP, SPB, DD; Data collection and/or Processing- RP, SPB, DD; Analysis and/or Interpretation- CK; Literature Search- RP, SPB, DD; Writing- CK, AG; Critical Review- CK, ND, AG.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

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