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SUPPLEMENT ARTICLE

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# Macrophage activation syndrome in pediatrics

Alessandra Alongi[1] | Roberta Naddei[2] | Laura De Miglio[3] | Valentina Natoli[1] | Angelo Ravelli[1,4,5]

[1]Università degli Studi di Genova, Genoa, Italy

[2]Università degli Studi di Napoli Federico II, Napoli, Italy

[3]Università degli Studi del Piemonte Orientale, Novara, Italy

[4]IRCCS Istituto Giannina Gaslini, Genoa, Italy

[5]Sechenov First Moscow State Medical University, Moscow, Russian Federation

**Correspondence**
Prof. Angelo Ravelli, Clinica Pediatrica e Reumatologia, IRCCS Istituto G. Gaslini, via G. Gaslini 5, 16147 Genoa, Italy.
Email: angeloravelli@gaslini.org

## Abstract

Macrophage activation syndrome (MAS) is a serious, potentially life-threatening, hyperinflammatory condition, which belongs to the spectrum of hemophagocytic lymphohistiocytosis (HLH) and can complicate several immunologic and rheumatic disorders. MAS is characterized by a dysfunctional immune response that is similar to that seen in other forms of HLH. Because MAS may pursue a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are fundamental. Recently, a set of classification criteria for MAS complicating sJIA has been developed through a multinational collaborative effort. High-dose parenteral corticosteroids remain the mainstay of treatment of MAS.

**KEYWORDS**

activation, inflammation, macrophage

Macrophage activation syndrome (MAS) is a serious, potentially life-threatening hyperinflammatory condition, which belongs to the spectrum of hemophagocytic lymphohistiocytosis (HLH) and can complicate several immunologic and rheumatic disorders. The term HLH describes a group of histiocytic disorders driven by the uncontrolled activation of T cells and macrophages exhibiting haemophagocytic activity. The current classification of histiocytic disorders includes MAS among the forms of HLH occurring in the context of pre-existing disorders, such as infectious, rheumatic, and oncological diseases (so-called secondary or acquired HLH), as opposed to the primary or familiar forms, in which known genetic defects can be identified. Among pediatric rheumatic disease, MAS is observed most commonly in patients with systemic juvenile idiopathic arthritis (sJIA). The estimated prevalence of MAS in sJIA is around 10%, but increasing evidence suggests that subclinical forms of the syndrome may occur in another 20%-30% of patients with this disease. MAS can also be encountered in juvenile systemic lupus erythematosus, Kawasaki disease, and juvenile dermatomyositis.[1]

Current pathogenic views suggest that primary and secondary HLH represent a unique spectrum of illnesses, in which different mechanisms at various levels converge in the self-perpetuating activation of T cells and macrophages, which, in turn, leads to massive and sustained hyperproduction of pro-inflammatory cytokines, namely interferon-gamma (IFNγ). In primary HLH, this scenario is due to the alteration of immunoregulatory pathways caused by genetic defects involving the perforin-mediated cytotoxicity pathway. In MAS, multiple mechanisms are thought to contribute to macrophage and T-cell hyperactivation, including infectious triggers, hypomorphic genetic mutations, and the specific cytokine milieu that characterizes some rheumatologic disorders. Specifically, the unbalanced production of biologically active IL-18 seems to play a major role in predisposing patients with sJIA to MAS. The common end-stage of these different pathways is the overwhelming release of pro-inflammatory mediators such as IFNγ, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (sometimes described as "cytokine storm") resulting in the typical clinical and laboratory abnormalities of MAS.[2]

Clinically, MAS is characterized by the acute onset of unremitting high fever, drop in all three blood cell lines, hyperferritinemia, hepatosplenomegaly, liver dysfunction, and clotting abnormalities with hemorrhagic manifestations. If untreated, MAS may progress to multi-organ failure and have a fatal outcome. Encephalopathy is

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reported in around one-third of cases and is occasionally related to coexistent thrombotic microangiopathy. The finding of hemophagocytosis in the bone marrow aspirate, although suggestive for the diagnosis, is not pathognomonic and may be absent, particularly in the earlier stages of the syndrome.[3,4]

Many clinical disorders, including sepsis, viral diseases (most frequently EBV), infections from intracellular pathogens, particularly visceral leishmaniasis, may mimic some features of MAS. Also, some clinical and laboratory features of MAS are similar to those of the underlying rheumatologic illness. For these reasons, timely recognition of MAS can be difficult. However, early diagnosis and prompt appropriate treatment are fundamental and can be life-saving for the patient.

To provide criteria that facilitate recognition of MAS, a great effort has been made in the last years to develop diagnostic tools for the syndrome, with a great focus on sJIA.[5] Diagnostic criteria primarily developed for the genetic forms of HLH, such as the HLH-2004 diagnostic guidelines,[6] have demonstrated low sensitivity for MAS in sJIA.[7] In 2005, preliminary diagnostic guidelines for MAS in sJIA were published.[8] In the past few years, an international collaborative effort was carried out to develop specific classification criteria for MAS complicating sJIA, which was based on both expert consensus and collection of data from over 1,000 patients with MAS or conditions potentially confusable with MAS. According to these criteria, which were named "2016 classification criteria for MAS complicating sJIA," the diagnosis of MAS in a febrile patient with known or suspect sJIA requires a serum ferritin level > 684 ng/mL and at least two of the following four criteria: platelet count ≤ 181 × $10^9$/L, aspartate aminotransferase > 48 units/L, triglyceride concentration > 156 mg/dL, and fibrinogen ≤ 360 mg/dL.[9] In the routine clinical setting, it has been suggested that the dynamics of laboratory biomarkers over time may be more useful to capture the occurrence of the syndrome than the increase or decrease above or below an absolute threshold. An expert panel within the same above-mentioned international collaborative project identified platelet count, ferritin, and AST as the parameters whose change over time is more relevant for the early diagnosis of sJIA-associated MAS.[10]

As no controlled studies on the treatment of MAS are available, the management of this condition is merely based on anecdotal experience.[1-3] The mainstay of the therapy of MAS is traditionally based on the parenteral administration of high doses of corticosteroids. In the mid-1990s, the use of cyclosporine was advocated, based on its proven benefit in the management of familial HLH. The administration of high-dose intravenous immunoglobulin, cyclophosphamide, plasma exchange, and etoposide has provided conflicting results. With the recent advent and use of a variety of biologic agents, novel therapeutic approaches are being evaluated as first-line therapy for MAS. The most promising results have been obtained with the administration of the IL-1 inhibitor, anakinra, which has entered into the current therapeutic protocols for MAS, particularly in cases that are refractory to corticosteroids or cyclosporine. The role of other therapeutic options, particularly the anti-IFNγ antibody and IL-18 inhibitors, is being explored.

**Key Message**

Our article outlines the main clinical and laboratory manifestation of macrophage activation syndrome in pediatric rheumatic diseases and highlight the main clues that help to make a timely diagnosis.

In conclusion, MAS is a potentially life-threatening complication of rheumatic disorders, particularly sJIA. Although the pathophysiology of MAS is unclear, it is characterized by a dysfunctional immune response that is similar to that seen in other forms of HLH. Because MAS may pursue a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are fundamental. Recently, a set of classification criteria for MAS complicating sJIA has been developed through a multinational collaborative effort. High-dose parenteral corticosteroids remain the mainstay of treatment of MAS. However, the distinctive efficacy of cyclosporine has led to propose the use of this medication as first-line treatment. The administration of cytokine inhibitors, particularly IL-1 blockers, is effective in severe and refractory instances of the syndrome.

## ORCID

*Angelo Ravelli* https://orcid.org/0000-0001-9658-0385

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