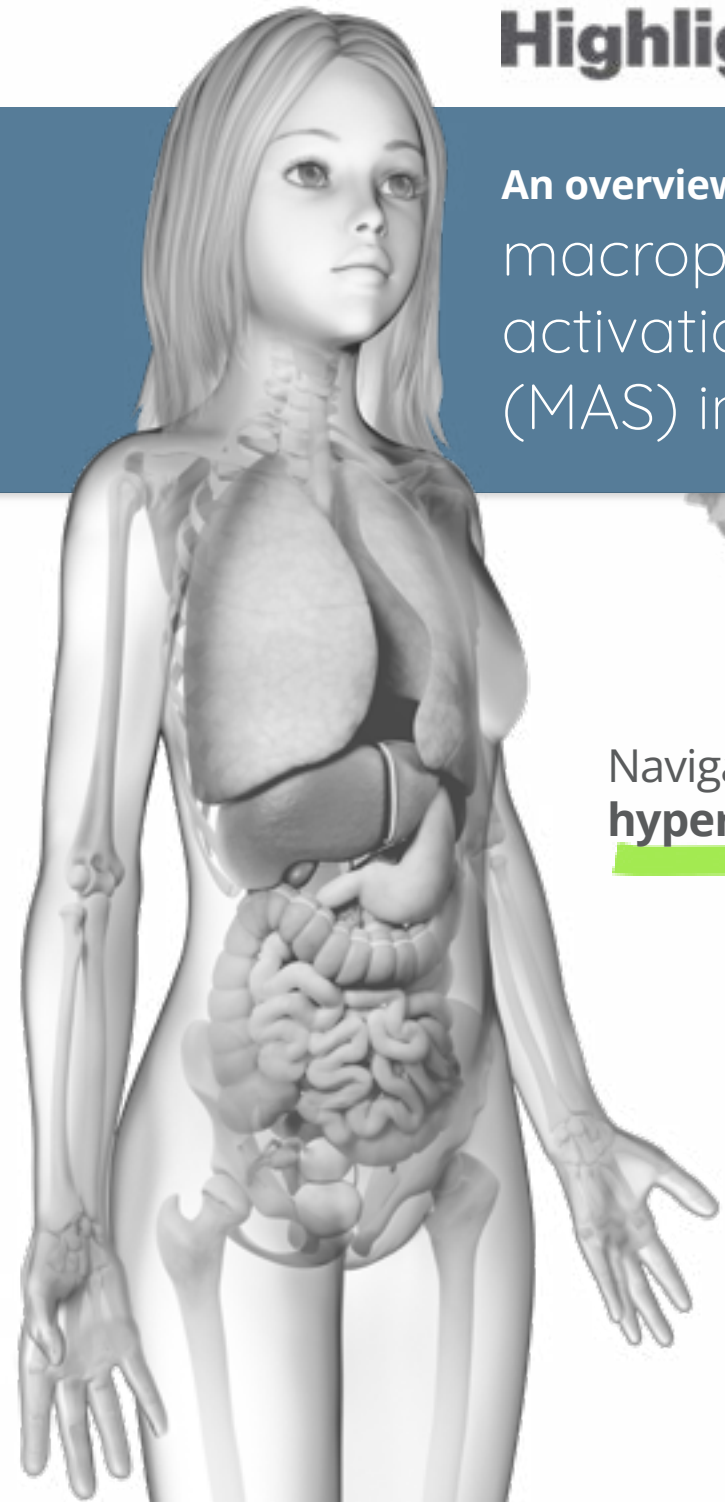


Highlight MAS

An overview of

macrophage activation syndrome (MAS) in Still's disease

Navigating a
hyperinflammatory threat

sobi

What is **HLH**?

Hemophagocytic lymphohistiocytosis (HLH) is a dangerous, life-threatening hyperinflammatory syndrome associated with excessive proinflammatory cytokine production and a variety of underlying triggers.[1,2]

These triggers can include[3]:

Genetic predisposition

Infections

Chronic Inflammation

Malignancy

Rheumatological conditions

What is MAS?

MAS is a rare and potentially fatal syndrome that can occur in patients with underlying rheumatic disease, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD).[4]

MAS is characterized by[4,5]:

- Dangerous systemic hyperinflammation
- Continual activation and expansion of T lymphocytes and macrophages driven by the proinflammatory cytokine, interferon gamma (IFNγ)

Prevalence and presentation of MAS

Prevalence of MAS in Still's disease (sJIA and AOSD)

MAS is thought to be underdiagnosed, but it has been found to occur most commonly in patients with sJIA and AOSD. Patients may also develop MAS as the first sign of an underlying rheumatic disease, so it's important to maintain suspicion of MAS in patients who may not yet be diagnosed.[3,6,7]

MAS in Still's disease is estimated to occur in up to[4,8]:

15%
of adults with AOSD

10%
of patients with sJIA

The clinical presentation of MAS can overlap with[4,9-13]:

- Malignancy
- Liver failure
- Infection
- Immune disorders
- Anemia
- Kawasaki disease
- Flares of rheumatic disease, including AOSD, sJIA, and lupus

Pathophysiology of MAS

In MAS associated with underlying rheumatic disease, a dysregulated inflammatory immune response is triggered that cannot be shut off by the normal mechanisms of the immune system.[11] This inflammatory state is associated with an **abnormal activation of T cells and macrophages**, resulting in **excessive cytokine production and hyperinflammation**.[12]

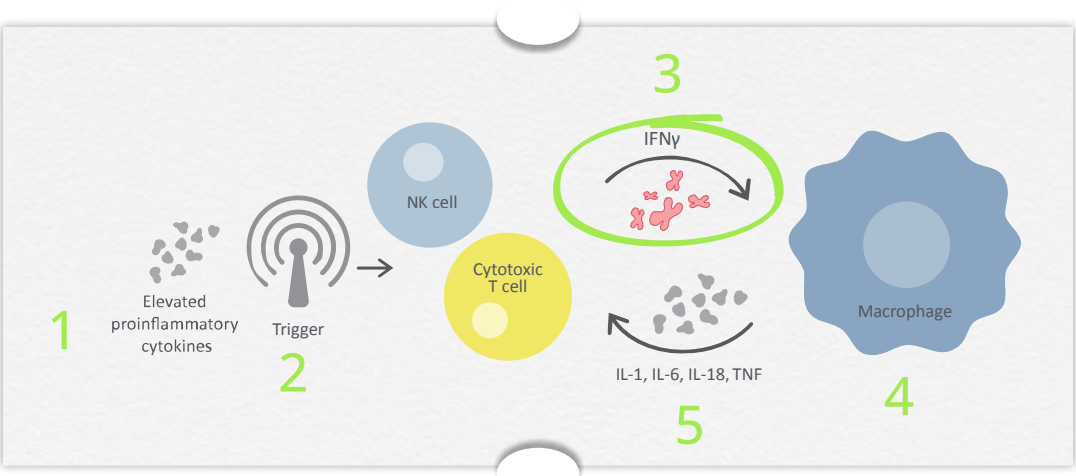
IFNγ is a cytokine that has been identified as **a key driver of hyperinflammation** and plays a critical role in the hyperinflammatory mechanism of MAS.[5,14]

Elevated IFNγ levels have been found in patients with MAS in sJIA.[15]

Pathophysiology of MAS (cont'd)

High IFNγ levels drive a dangerous feedback loop of hyperinflammation

IFNγ is a key cytokine that activates macrophages. In patients with HLH, these macrophages produce an excess of proinflammatory cytokines through a dysregulated feedback loop.[5,14]



1 **In sJIA and AOSD, IL-18 and other proinflammatory cytokines are elevated** as a characteristic of underlying rheumatic disease. **IL-18 promotes IFNγ production** in NK cells and T cells.[10,16,17]

2 **Genetic predisposition, chronic inflammation, or infectious triggers** may overlap to trigger a dysregulated inflammatory state.[1]

3 **High IFNγ levels over activate macrophages** and increase monocyte sensitivity to IFNγ stimulation.[18]

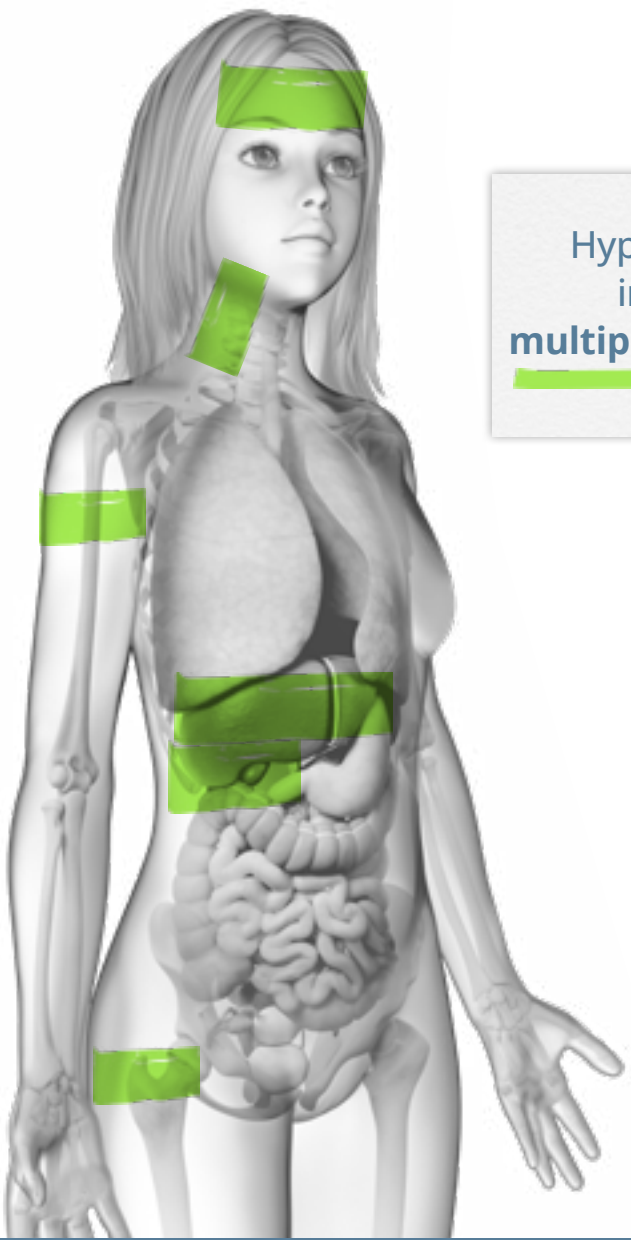
4 **Activated macrophages release proinflammatory cytokines**, including IL-1β, IL-6, IL-18, and TNF, which are responsible for the cytokine storm in MAS.[5]

5 **A continuous feedback loop of cytokine production** and macrophage activation results in hyperinflammation and potentially irreversible multiorgan damage.[19]

IL=interleukin; NK=natural killer; TNF=tumor necrosis factor.

Signs and symptoms of MAS

MAS symptoms can **closely resemble those of sepsis or a rheumatic disease flare**, making diagnosis a challenge. However, without prompt recognition and management, MAS can cause irreversible organ damage or death.[12]



Hyperinflammation in MAS affects **multiple organ systems.**[12]

Signs and symptoms of MAS (cont'd)

Do you recognize these signs and symptoms in your patient?

Physical manifestations

- **Persistent fever**[10]
- **Seizures and CNS involvement**[6,10]
- **Hepatosplenomegaly**[12,20]
- **Kidney dysfunction**[12]
- **Pulmonary dysfunction**[10]
- **Rash**[3,10]
- **Signs of general malaise**[21]

Laboratory assessments[6,11,12,15]

- Cytopenias
- Coagulopathies
- Hyperferritinemia
- Hypofibrinogenemia
- Hypertriglyceridemia
- Elevated CXCL9
- Elevated sCD25
- Elevated IL-18
- Elevated LDH
- Liver function impairment
- Hemophagocytosis

CNS=central nervous system; CXCL9=chemokine (C-X-C motif) ligand 9; LDH=lactate dehydrogenase; sCD25=soluble cluster of differentiation 25.

Inflammatory **biomarkers** in MAS

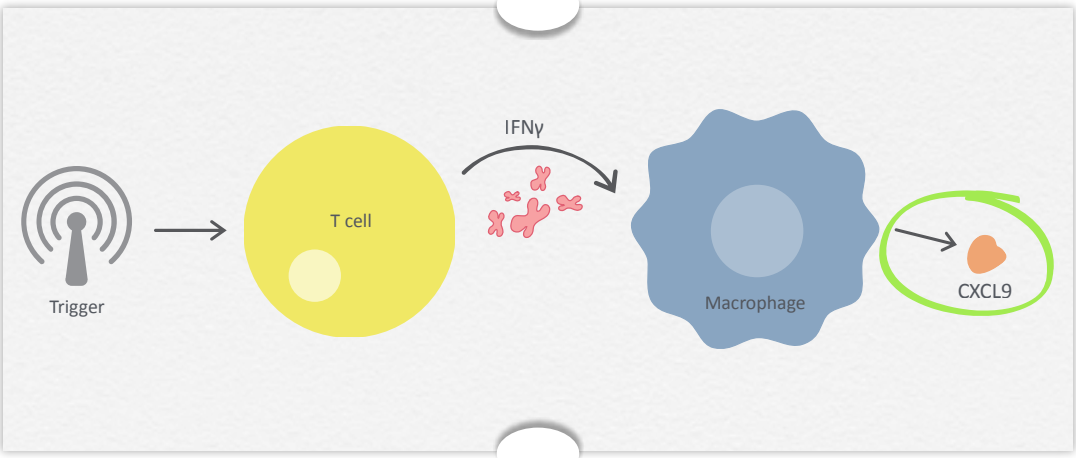
A variety of inflammatory biomarkers associated with MAS can be measured to evaluate key disease pathways and their specificity may be helpful for identifying MAS.[2]

Biomarker	Context
CXCL9	CXCL9 as a biomarker for IFNγ activity, a key driver of hyperinflammation in MAS, can be useful for identifying and monitoring MAS.[15]
CRP, ESR, LDH	CRP, ESR, and LDH are commonly available tests which may help assess the extent of hyperinflammation in patients with suspected MAS.[6] Persistently high CRP levels and increasing D-dimers, in combination with a fall in ESR and platelet count, may suggest early stages of MAS development in febrile patients with underlying rheumatic disease.[17] LDH is a general marker of cellular death or injury that is commonly elevated in patients with MAS.[2]
sCD25/ sIL-2rα	sCD25, also known as sIL-2rα, is an inflammatory marker of T-cell activation that can be helpful for MAS diagnosis and as an indicator of treatment response.[2,17]
IL-18	IL-18 testing can help measure inflammasome activation, which can lead to the development of MAS in certain contexts.[19] Elevated IL-18 can be observed in patients with Still's disease, but significant elevations above a patient's baseline may suggest development of MAS.[5,19]
Neopterin, CD163	Neopterin and CD163 testing can indicate the activation and inflammatory status of macrophages, which are essential for MAS pathology.[5,12,17]

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.

CXCL9 and IFNγ

CXCL9 is a chemokine (a type of cytokine) released almost exclusively by IFNγ-activated macrophages. The primary function of CXCL9 is to attract T cells into inflamed tissues. It is stable and easily measurable in serum at nanogram concentrations.[14,22]



CXCL9 levels have been shown to correlate with other abnormal laboratory markers observed in MAS such as neutrophil and platelet counts, LDH, and ALT.[14]

CXCL9 testing may help identify high IFNγ levels resulting from T-cell overactivation—a hallmark of MAS.[15]

ALT=alanine aminotransferase.

Diagnosing MAS

Currently, there is no single set of criteria that has been validated for diagnosing MAS across all patient populations. However, if you suspect MAS in your patients with underlying rheumatic disease, there are a **range of laboratory assessments and inflammatory biomarkers that may help you narrow down a diagnosis**.[2]

ACR/EULAR classification criteria

The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) have codeveloped classification criteria for identifying MAS in patients with sJIA.[4]

A febrile patient with known or unsuspected sJIA is classified as having MAS if they have[4]:

Ferritin levels >684 ng/mL **and** any 2 of the following lab abnormalities:

Platelet count
≤181 × 10^9/L

Aspartate aminotransferase
>48 U/L

Triglycerides
>156 mg/dL

Fibrinogen
≤360 mg/dL

Other diagnostic criteria options to consider

The **MS Score** is an equation that uses the 2016 ACR/EULAR classification as a starting point to assess the probability that a patient with sJIA has MAS.[23]

The **HScore** is a diagnostic tool developed to estimate a patient's risk of having a hemophagocytic syndrome, such as MAS. It features 9 clinical, biologic, and cytologic parameters that are individually weighted.[24]

Managing MAS

Initial treatment for MAS typically involves steroid therapy, which can pose various risks associated with prolonged use. Adult and pediatric patients receiving steroids may experience dose-dependent side effects such as hyperglycemia, hypertension, myopathy, psychosis, growth suppression, and continued uncontrolled destructive hyperinflammation. Additional treatment approaches may include immunosuppressive therapies, which do not specifically target key drivers of hyperinflammation in MAS.[2]

Up to 33% of pediatric patients and up to 80%* of adult patients may have an unsatisfactory response to glucocorticoid pulse therapy.[7,22,25,26]

*According to data collected from individual centers.

There are 3 main goals for managing patients with MAS[2,10,12]:

Stabilize the patient

Controlling hyperinflammation

Identify potential triggers

Work to identify any conditions that may have triggered the MAS episode.

Minimize toxicities

Minimize steroid exposure from broadly acting agents.

Prompt recognition and **timely management** of MAS are essential for your patients.[1]

Recognizing the most common hyperinflammatory signs and symptoms of MAS is often the first step in pursuing a diagnosis. Understanding how these manifestations present in patients and how they differ from other similar conditions, such as sepsis or rheumatic disease flares, can help shorten the time to diagnosis and suitable treatment.[2]

For more information and resources about diagnosing and managing MAS, visit **www.HighlightHLH.com/MAS**

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