Macrophage Activation Syndrome

Not Just for Rheumatologists Anymore

Sonia Iosim, MD, Lauren A. Henderson, MD, MMSc*

KEYWORDS

- Macrophage activation syndrome • Cytokine storm syndromes
- Hemophagocytic lymphohistiocytosis • Systemic juvenile idiopathic arthritis
- Adult-onset Still's disease

KEY POINTS

- Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis share an underlying pathophysiology.
- Early recognition and prompt treatment of MAS are essential to prevent multi-organ damage and death.
- Anti-cytokine therapies for MAS are highly effective and have a favorable safety profile.

MACROPHAGE ACTIVATION SYNDROME—WHAT IS IN A NAME?

Macrophage Activation Syndrome in Historical Context

A subset of children and adults with Still's disease are at risk of developing a syndrome characterized by unrelenting fever, hepatic dysfunction, cytopenias, coagulopathy, and neurologic involvement.[1–3] Initially, there was speculation that this constellation of symptoms could be due to Reye's syndrome; however, in 1984, Hadchoel and colleagues cast doubt on the causative role of aspirin.[4] In this case series of patients with juvenile arthritis, liver pathology was notable for enlarged resident macrophages and the bone marrow contained "large macrophages with phagocytozed material." The authors hypothesized that activated macrophages might play a central role in this curious syndrome. It was not until 1993 that the term macrophage activation syndrome (MAS) appeared in the literature to describe this entity.[5]

The Problem of Nomenclature for Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

The most widely used nomenclature for hemophagocytic lymphohistiocytosis (HLH) divides the condition into primary/familial and secondary forms of the disease. Familial

Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
* Corresponding author. 1 Blackfan Circle, Karp Family Research Building, 10th Floor, Boston, MA 02115.
E-mail address: lauren.henderson@childrens.harvard.edu

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Abbreviations	
ACR	American College of Rheumatology
AIFEC	autoinflammation with infantile enterocolitis
AOSD	adult-onset Still's disease
CNS	central nervous system
CSF	cerebral spinal fluid
EULAR	European Alliance of Associations for Rheumatology
fHLH	familial hemophagocytic lymphohistiocytosis
HLH	hemophagocytic lymphohistiocytosis
IL-18BP	IL-18 binding protein
JAK	janus kinases
IVIG	intravenous immune globulin
MAS	macrophage activation syndrome
MDT	multidisciplinary team
NOCARH	neonatal onset of pancytopenia, autoinflammation, rash, and episodes of HLH
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus

HLH (fHLH) classically presents in patients with inherited, null defects of genes in the cytolytic pathway. In such patients, disease onset is usually in the first year of life and is fatal without stem cell transplantation. Secondary HLH was originally thought to develop in patients without genetic risk factors. It is usually triggered by an inciting inflammatory state such as an infection, malignancy, or rheumatologic disease, although a subset of patients do not have an identified cause. Secondary HLH in the setting of autoimmune disease is designated as MAS. This binary classification system for HLH is not absolute, and there are overlapping characteristics between fHLH and secondary HLH (sHLH). Individuals with primary/fHLH almost always become symptomatic in the setting of a trigger, most commonly infection. In addition, individuals with secondary HLH can have underlying genetic contributions from hypomorphic mutations in fHLH genes as well as other genes not traditionally associated with fHLH.[6,7] Importantly, the primary/familial and secondary forms of the disease are highly related and share an underlying pathophysiology.[8,9]

Confusion over HLH/MAS nomenclature has resulted in an inexact use of terms that often differs by medical subspecialties. The North American Consortium of Histiocytic Disorders recently advanced the concept of HLH as a syndrome that includes many different conditions that present with symptoms that fit the HLH pattern (**Fig. 1**A).[10] MAS is also used widely to describe hyperinflammation that occurs not only in rheumatologic diseases but also associated with infections, primary immune deficiencies, metabolic disorders, and other conditions. To complicate matters further, cytokine storm syndrome (CSS) has become another popular umbrella term that encompasses many different disorders characterized by elevated cytokines, systemic inflammation, and organ dysfunction beyond what is expected in the clinical circumstance (see **Fig. 1**B).[11] Practitioners should beware that HLH, MAS, and CSS are often used interchangeably depending on the context and the medical discipline.

MACROPHAGE ACTIVATION SYNDROME IN RHEUMATOLOGIC DISEASES

Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

In pediatric rheumatology, MAS is most frequently recognized in patients with systemic juvenile idiopathic arthritis (sJIA). sJIA is distinguished from other forms of chronic inflammatory arthritis in children by profound systemic inflammation and overactivation of the innate immune system and associated cytokines (IL-1β, IL-6,

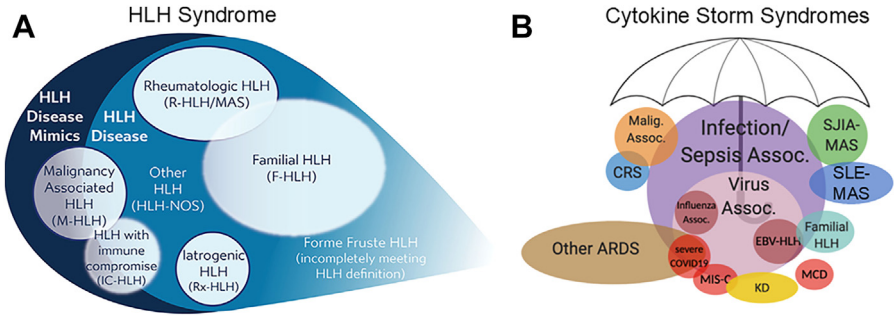

Fig. 1. Evolving nomenclature in HLH and MAS. Several new naming systems have been proposed to define HLH and MAS. (*A*) The North American Consortium for Histiocytosis (NACHO) advanced the concept of HLH as a syndrome that encompasses all patients who present with the HLH clinical pattern, including those with HLH disease mimics as well as those with true HLH disease that requires immunosuppression. (*B*) Cytokine storm syndromes is an umbrella term that is used to include a broader range of conditions characterized by elevated cytokines, systemic inflammation, and organ dysfunction beyond the expected normal response. ARDS, acute respiratory distress syndrome; CRS, cytokine release syndrome; EBV, Epstein–Barr virus; HLH, hemophagocytic lymphohistiocytosis; KD, Kawasaki disease; MAS, macrophage activation syndrome; MCD, multicentric Castleman disease; MIS-C, multisystem inflammatory syndrome in children; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus. ([*A*] *Adapted from* Jordan MB, et al. Challenges in the diagnosis ofhemophagocytic lymphohistiocytosis: Recommendations from the North AmericanConsortium for Histiocytosis (NACHO). Pediatr Blood Cancer 2019;66(11):e27929. https://doi.org/10.1002/pbc.27929. PMID: 31339233; PMCID: PMC7340087; with permission; and [*B*] Figure created by Scott Canna and modified from Henderson LA, et al. Onthe Alert for Cytokine Storm: Immunopathology in COVID-19. Arthritis Rheumatol2020;72(7):1059–63. https://doi.org/10.1002/art.41285. PMID: 32293098; PMCID: PMC7262347; with permission; and *Data from* Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383(23): 2255–73.)

IL-18).[12–15] Around 10% of patients with sJIA will develop full-blown MAS with even more manifesting subclinical features of this syndrome.[16,17] Older case series document mortality around 20% for sJIA-associated MAS, although outcomes have since improved significantly.[17,18]

Macrophage Activation Syndrome in Diseases Characterized by Inflammasome Activation

MAS is also known to develop in several other diseases in pediatric rheumatology that share the innate immune activation and the cytokine fingerprint of sJIA. A central characteristic of these disorders is excessive signaling by one or more inflammasomes, resulting in production of caspase-1 that cleaves pro-IL-1β and pro-IL-18 into their active forms.[19] This includes cryopyrin-associated periodic syndromes, mevalonate kinase deficiency, and familial Mediterranean fever, neonatal onset of pancytopenia, autoinflammation, rash, and episodes of HLH (NOCARH) syndrome, and autoinflammation with infantile enterocolitis (AIFEC).[20–26]

Macrophage Activation Syndrome in Adults with Rheumatologic Diseases

Adult-onset Still's disease (AOSD) is essentially the equivalent of sJIA in the adult population and the term Still's disease is often used to encompass both sJIA and AOSD. Like children with sJIA, patients with AOSD are at high risk of developing MAS.[27,28] Even in more recent reports, the fatality rate from AOSD-associated MAS is around

5%.[29] MAS is underrecognized in both pediatric and adult patients with systemic lupus erythematosus (SLE).[30,31] In a single-center retrospective study of childhood-onset SLE, 9% of patients had MAS at some point in their disease course.[30] While Still's disease, inflammasome-related disorders, and SLE are most frequently associated with MAS, it has been linked with many more rheumatologic diseases.

THE SHARED PATHOPHYSIOLOGY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Much of what is known about the biologic basis of MAS is derived from fHLH (**Fig. 2**). All identified gene defects associated with fHLH result in impaired cytolytic activity, which is the ability of $CD8^+$ T and natural killer (NK) cells to mobilize cytolytic granules to the immunologic synapse and induce apoptosis in an infected, target cell.[32–35] Impaired cytotoxicity leads to ongoing stimulation between T/NK cells and antigen-presenting cells and production of pro-inflammatory cytokines, particularly interferon

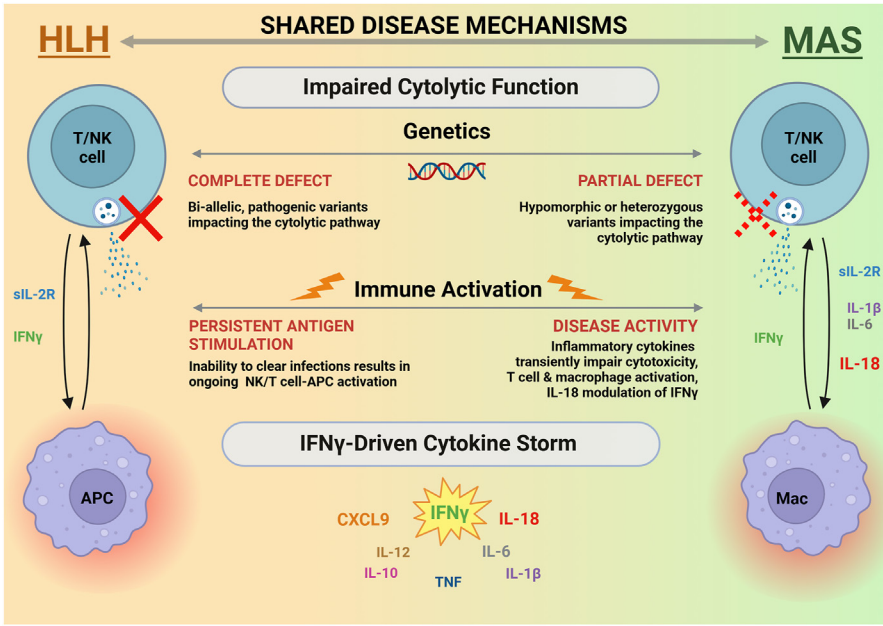

Fig. 2. HLH and MAS as a spectrum of related diseases with a shared pathophysiology. HLH and MAS share the common disease mechanisms of impaired cytolytic function and IFNγ-driven cytokine storm. In this figure, specific examples of fHLH and sJIA-associated MAS are used. fHLH is characterized by genetic variants that abolish or significantly reduce cytolytic function. This results in an inability to clear infections and ongoing cross-talk between T/NK cells and antigen-presenting cells, culminating in IFNγ-driven cytokine storm. In sJIA-associated MAS, reduced cytolytic function may result from hypomorphic gene variants in this pathway. In addition, disease activity results in production of inflammatory cytokines (IL-1β, IL-6, and IL-18) and T cell/macrophage activation that can further impair cytolytic activity (IL-6) and result in IFNγ-mediated cytokine storm (IL-18). In both conditions, soluble IL-2 receptor (sIL-2R), secreted by active T cells, and CXCL9, an IFNγ-induced chemokine, are reliable markers of the hyperinflammation. Other cytokines also play a role in cytokine storm, including IL-1β, IL-6, IL-10, IL-12, and TNF. APC, antigen-presenting cell; HLH, hemophagocytic lymphohistiocytosis; mac, macrophage; MAS, macrophage activation syndrome. (*Created in* BioRender. Henderson, L. (2025) https://BioRender.com/z79f077.)

gamma (INFγ).[9,36–38] The dual hits of impaired cytolytic activity coupled with interferon gamma (IFNγ)-driven cytokine storm are also responsible for MAS (see Fig 2). For the purposes of this section of the review, sJIA will be used as a model; however, the same factors that drive MAS in sJIA are likely contributory to other rheumatologic diseases.

Impaired Cytolytic Activity in Macrophage Activation Syndrome

It is now appreciated that genetic factors contribute a spectrum of risk across most forms of HLH and MAS.[39,40] Gene variants that abolish cytolytic activity typically lead to early-onset disease that is characteristic of fHLH. Individuals who carry hypomorphic or even heterozygous mutations in fHLH-related genes may present at older ages with variable disease severity when a sufficient environmental trigger is encountered.[39–41] Whole exome sequencing of a small cohort of patients with sJIA showed that close to 36% of children who developed MAS harbored heterozygous, rare, and protein-damaging variants in known fHLH genes.[6] By contrast, a much smaller proportion of sJIA patients without MAS carried similar gene changes.[6] Further, the authors identified additional genes with rare and protein-altering variants that were present in at least 2 children with sJIA-associated MAS. Many of these genes were linked with cellular functions that are important for cytotoxicity such as microtubule organization or vesicle transport.[6] These findings have been replicated in larger studies.[42] Thus, a substantial proportion of patients with sJIA who develop MAS have a genetic predisposition to impaired cytolytic activity.

Overwhelmingly, MAS develops in sJIA patients with active disease.[18] There is some evidence to indicate that the cytokine milieu of active sJIA, particularly IL-6, impairs cytolytic activity and increases the risks of MAS. When NK cells from healthy controls are exposed to IL-6, granzyme and perforin expression decreases and NK cell-mediated lysis of target cells is depressed.[43] Many patients with sJIA in MAS have NK cell dysfunction that is reversible and normalizes once the MAS resolves and sJIA disease control is attained.[43–45] This evidence suggests that uncontrolled sJIA results in impaired cytolytic activity that may contribute to the development of MAS. The important clinical implication is that adequate disease control in patients with sJIA is essential to lower their risk of developing MAS.

Interferon Gamma-driven Cytokine Storm in Macrophage Activation Syndrome

Several lines of evidence have converged to define IFNγ as a key cytokine that differentiates MAS from active disease in sJIA. Mouse models of MAS are characterized by elevated levels of IFNγ.[46,47] One transgenic mouse that carriers a construct resulting in overexpression of human IL-6 (similar to sJIA) developed MAS after treatment with toll-like receptor stimulation to mimic infection.[47] These mice had high levels of IFNγ and were rescued by neutralization of IFNγ.[47] In a study of patients with sJIA that examined over 100 circulating immune proteins, chemokine ligand 9 (CXCL9), an IFNγ-inducible chemokine, was the best analyte to differentiate MAS from active disease.[48] Other reports have replicated these findings.[49] IFNγ-related proteins correlated with laboratory parameters of MAS such as ferritin, alanine aminotransferase (ALT), neutrophil count (inverse correlation) and platelet count (inverse correlation).[49] In the small numbers of patients with sJIA studied to date, targeted blockade of IFNγ was effective in treating MAS but did not prevent flares of sJIA, indicating that the cytokine drivers of sJIA disease versus sJIA-MAS differ.[50]

IL-18 in Macrophage Activation Syndrome

Stratospheric levels of IL-18 are unique to rheumatologic MAS and not typically found in other forms of HLH.[51–54] These very high levels of IL-18 are observed in several

rheumatologic diseases characterized by inflammasome activation and risk of developing MAS, including sJIA, AOSD, NOCARH and AIFEC.[15,24,53,54] Shimizu and colleagues[15] showed that patients with sJIA could be divided into those with IL-6 versus IL-18 dominant disease. Those in the IL-18 dominant subset had exceedingly high levels of IL-18 (mean level of 101,809 pg/mL) and MAS subsequently developed exclusively in this group.[15] Other studies have confirmed the association between IL-18 and risk of MAS in sJIA.[13,52]

Unlike IFNγ-related proteins that are specifically elevated in sJIA patients with concurrent MAS, IL-18 is increased in sJIA patients with and without MAS. This likely reflects the inflammasome activation that is intrinsic to this disease. IL-18 is almost entirely measured as total IL-18, which encompasses circulating IL-18 bound and sequestered by IL-18 binding protein (IL-18BP).[55] Most patients with inflammasome-mediated autoinflammation have exuberant IL-18 production that is initially controlled by IL-18BP; however, eventually this endogenous compensatory mechanism is depleted and free IL-18 is unleashed.[56,57] It is free IL-18 that is hypothesized to be directly associated with MAS, although difficulty in measuring free IL-18 has limited the testing of this theory.[51] The connection between IL-18 and MAS is thought to be mediated through IFNγ. Indeed, IL-18 was once known as IFNγ-inducing factor and has the ability to powerfully modulate and amplify the effects of IFNγ.[57,58] Thus, patients with rheumatologic diseases characterized by inflammasome activity and IL-18 production are poised to develop IFNγ-driven cytokine storm and MAS when compensatory mechanisms to control IL-18 are depleted. The role of IL-18 in sJIA-associated MAS again highlights the importance of fully controlling disease activity to minimize the threat of MAS.

THE IMPORTANCE OF EARLY RECOGNITION OF MACROPHAGE ACTIVATION SYNDROME

Rapid Diagnosis of Macrophage Activation Syndrome Is Essential

The clinical experience of rheumatologists is that early recognition and treatment of MAS is paramount. Identifying MAS before significant organ dysfunction occurs is vastly easier to manage and results in favorable outcomes for patients. In part, early treatment is possible due to the proliferation of anti-cytokine therapies that are effective for MAS and have an excellent safety profile compared to chemotherapy-based protocols. Therefore, there is little downside in initiating these anti-cytokine therapies as soon as possible. The importance of the timely identification of MAS was recently underscored by a combined effort from the European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) to develop consensus-based guidelines to facilitate the early diagnosis of MAS.[59]

Limitations of the Hemophagocytic Lymphohistiocytosis 2004 Diagnostic Criteria for Macrophage Activation Syndrome

Multiple diagnostic tools are available to aid in the recognition of MAS; however, all are associated with shortcomings and should be used with caution, particularly the HLH 2004 Diagnostic Criteria. This diagnostic system requires an affirmative molecular diagnosis for HLH or the presence of 5 of 8 clinical criteria: fever, splenomegaly, cytopenias, elevated triglycerides and/or hypofibrinogenemia, hemophagocytosis, depressed NK cells function, hyperferritinemia, and elevated soluble IL-2 receptor.[60] These criteria were developed to identify a homogenous population of children with HLH for clinical trials testing chemotherapy-based protocols and do not prioritize rapid diagnosis, which is essential in the clinical setting.[60,61] Instead, the requirement for genetic, functional, and specialized testing almost always ensures a delay in

diagnosis while results are awaited. Recent recommendations from the Histiocyte Society's Working Group for HLH in Adults emphasized that pending test results should not delay treatment of HLH in adults where clear-cut genetic causes of the disease are less common.[62]

The HLH 2004 Diagnostic Criteria also lacks specificity in the adult population where chronic medical conditions alter the specificity of several cut-off values, particularly ferritin. While a ferritin value of 500 ng/mL or more may be sufficient to consider fHLH in children, much higher ferritin levels are observed in adults with conditions such as renal disease, hepatic injury, hemolytic anemia, and hematologic malignancies.[63] The HLH 2004 Diagnostic Criteria also performs poorly in patients with rheumatologic MAS compared to other diagnostic tools.[64] When MAS develops in the context of a highly inflammatory condition, baseline blood cell counts and ferritin values are higher than in individuals with other forms of HLH and the cutoff values in the 2004 Criteria lack specificity in this patient population. In total, most rheumatologists avoid using the HLH 2004 Diagnostic Criteria for MAS and they should never be used to restrict access to well-tolerated anti-cytokine therapies.

Importance of Recognizing Clinical Trends Indicative of Macrophage Activation Syndrome

Patients with rheumatologic MAS and other forms of HLH almost always present with a core pattern of symptoms and laboratory abnormalities that a vigilant clinician should be able to recognize easily (Table 1). As outlined in the 2022 EULAR/ACR points to consider in the Early Diagnosis and Management of Suspected HLH/MAS, the constellation of persistent fever, rising ferritin/inflammatory markers, inappropriately declining blood cell counts, hepatic dysfunction, coagulopathy, splenomegaly, and central nervous system (CNS) dysfunction should raise concern for HLH/MAS.[59] All of these parameters can easily be evaluated clinically or are accessible through laboratory testing that results within hours (**Table 1**). The 2023 Hyperinflammation and HLH Across Specialty Collaboration developed the "3 F's" mnemonic to help clinicians remember some of these features: fever, falling blood counts, and raised ferritin in an unwell patient.[65] Educating house staff, critical care physicians, and emergency medicine clinicians to recognize these patterns is essential so that prompt referral to HLH/MAS specialists can be made at disease onset. If the initial clinical picture remains unclear, closely monitoring the patient for progressive organ dysfunction and trending laboratory studies is immensely helpful.[66–68] A consistent pattern or worsening laboratory features, particularly an exponential increase in ferritin that is not explained by another cause, are highly concerning for HLH/MAS.

In rheumatology, there is the added difficulty of recognizing MAS in the setting of an inflammatory disease. Yet, there are key features that allow for the differentiation of disease activity from MAS.[8] In Still's disease, the fevers are typically quotidian or double quotidian, while MAS is characterized by unrelenting fevers.[18] The encephalopathy, hepatic dysfunction, and coagulopathy that are pervasive in MAS are rare patients with sJIA and AOSD with active disease alone.[18] Many patients with inflammatory disorders display a leukocytosis and thrombocytosis such that even normal cell counts can be concerning for evolving MAS.

Biomarkers of Macrophage Activation Syndrome

Biomarkers that reflect the underlying pathophysiology of MAS and provide more specificity for the disease process than conventional acute-phase reactants are now widely used to diagnose and manage MAS (see **Table 1**).

Table 1
Clinical and laboratory assessment to recognize hemophagocytic lymphohistiocytosis/ macrophage activation syndrome early in the disease course

Feature	Assessment Tools	Turn-Around Time
Initial Rapid Evaluation[a]		
Persistent fever	HPI, examination, vital signs	Immediate
HSM	Examination	Immediate
CNS involvement	HPI, examination	Immediate
Systemic inflammation	CRP, LDH, ferritin	Several hours
Cytopenias	CBC w/diff	Several hours
Hepatic dysfunction	LFTs w/bilirubin, GGT, TG	Several hours
Coagulopathy	PT/PTT/INR, Ddimer, Fibrinogen, ESR	Several hours
Second Tier Assessment[b]		
End-organ involvement	HPI and examination. May include brain/ spine MRI, LP, bone marrow biopsy, chest imaging, echocardiogram, abdominal US	1–2 d
Infectious trigger	HPI and examination. May include blood cultures, viral testing (EBV, CMV, HHV6, adenovirus, flu, HIV, SARS-CoV-2, and others), and/or eval for other pathogens. TB testing before immunosuppression.	1–5 d
Rheumatologic trigger	HPI, FH, examination. May include IL-18, C3, C4, IgG, u/a, muscle enzymes, autoantibodies (ANA, dsDNA, RF, ENA panel)	1–5 d
Oncologic trigger	HPI and examination. May include CXR, abdominal US, flow cytometry, bone marrow biopsy, PET-CT	1–5 d
Cytokine storm[c]	sIL2R, CXCL9, IL-18	5–7 d
Impaired cytolytic activity[c]	T/B/NK cell subsets, NK cell function, CD107a, perforin/granzyme/SAP/XIAP expression	5–7 d
Genetic predisposition[c]	FH and genetic testing for fHLH, monogenic autoinflammatory disorders, inborn errors of immunity	1–4 wk

Abbreviations: ANA, antinuclear antibody; CBC w/diff, complete blood cell count with differential; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CXR, chest x-ray; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FH, family history; GGT, gamma-glutamyl transferase; HHV6, human herpes virus 6; HIV, human immunodeficiency virus; HPI, history of present illness; HSM, hepatosplenomegaly; LDH, lactate dehydrogenase; LFTs, liver function tests; LP, lumbar puncture; MRI, magnetic resonance imaging; NK, natural killer; PET-CT, positron emission tomography; RF, rheumatoid factor; SAP, SLAM-associated protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sIL2R, soluble IL-2 receptor; TB, tuberculosis; TG, triglycerides; u/a, urine analysis; US, ultrasound; XIAP, X-linked inhibitor of apoptosis protein.

[a] The initial evaluation can be performed within several hours and repeated overtime to determine whether there is a trend of consistent worsening in the clinical status and laboratory abnormalities that is concerning for HLH/MAS.

[b] Depending on the clinical presentation, portions of the second-tier assessment can be sent to identify the underlying cause of the HLH/MAS and monitor the degree of the cytokine storm. This table includes possible testing and is not meant as an exhaustive list. Testing in this category should not delay the initiation of HLH/MAS-directed therapy in a critically ill patient.

[c] At most institutions, these tests need to be sent to an outside laboratory and take up to a week or more to result.

IL-18

Total IL-18 is chronically elevated in many patients with Still's disease and other autoinflammatory conditions due to disease activity and increased levels do not necessarily indicate active MAS.[51] Instead, IL-18 burden is thought to reflect the likelihood of developing MAS in the future.[13,53] This laboratory value can be tracked serially to ensure that treatment leads to adequate disease control, declining IL-18 levels, and reduced MAS risk. Further, highly elevated IL-18 in a patient who presents with new-onset HLH/MAS strongly suggests a diagnosis of Still's disease or other inflammasome-related disorder. In one study, a total IL-18 level greater than 24,000 pg/mL distinguished MAS from fHLH with 83% sensitivity and 94% specificity.[51] While total IL-18 testing is available clinically, it is typically a send-out test that renders it less useful in the acute setting. Measured IL-18 levels vary depending on the assay technique and values from different laboratory are often not comparable. Finally, free IL-18, the biologically active form of this cytokine, is likely more clinically relevant in active MAS but is difficult to measure and not accessible in the clinical setting.

CXCL9

Since INFγ-driven cytokine storm is a key feature of HLH and MAS, there is great interest in accurately measuring this cytokine. CXCL9 is an IFNγ-induced chemokine that is reliably measured in the circulation and correlates with IFNγ levels.[49,69] In patients with Still's disease, CXCL9 levels spike with the onset of MAS and decline when the hyperinflammation resolves, making it a dynamic biomarker of active MAS.[49] Compared to patients with fHLH where CXCL9 values around 1 to 2000 pg/mL are common, those with rheumatologic MAS typically display much higher values (10–100,000 pg/mL or higher), potentially reflecting an increased load of IFNγ in these patients.[48,49,70] Like IL-18, CXCL9 is a send-out test at many institutions and is often not available to guide real-time decision-making.

Novel macrophage activation syndrome biomarkers

Biomarkers associated with macrophages/monocytes have been identified on a research basis to distinguish MAS from active rheumatologic disease, including adenosine deaminase 2 and neopterin.[71,72] While neither one of these tests is widely used in the clinical setting, neopterin is one of the few markers that is available clinically for measurement in the cerebral spinal fluid (CSF). As CNS involvement in patients with HLH and MAS can occur when systemic disease is quiescent, CSF neopterin levels often provide important information about neuroinflammation.[73] Recently, increased proportions of $CD38^{+}HLADR^{+}$ T cells, also called cycling T cells, were found in patients with HLH and MAS.[74,75] This T-cell population is easily measured by flow cytometry and represents a promising future biomarker for MAS/HLH.

ANTI-CYTOKINE THERAPIES FOR MACROPHAGE ACTIVATION SYNDROME

Traditionally, many of the same medications used to treat HLH were employed with some success in patients with MAS, including glucocorticoids, cyclosporine, and even etoposide.[4,18,76,77] High-dose intravenous immune globulin (IVIG; 1–2 gm/kg) is sometimes used to treat MAS, potentially due to its ability to induce anti-inflammatory cytokines, inhibit IFNγ signaling, and suppress monocytes/macrophages and T cells.[78–80] The efficacy of IVIG is likely limited and it is often used in patients with mild disease who may have relative contraindications (infections, ongoing diagnostic workup) to more aggressive immunosuppressive therapy or glucocorticoids.[68,76,81] Overtime, the therapeutic landscape has shifted from these traditional therapies toward medications that target cytokines central to the pathogenesis of MAS.

IL-1 Blockade

Anakinra is a recombinant IL-1 receptor antagonist that is frequently used to treat Still's disease and other autoinflammatory conditions.[82–85] While the literature supporting the use of anakinra for MAS is relatively sparse, the clinical experience is that it is very effective for rheumatologic MAS when used at high doses, often 10 mg/kg/day or higher. It is widely accepted as the best first-line treatment of MAS in patients with Still's disease, especially when it is combined with glucocorticoids.[68,86–90] In one retrospective, single-center study of 44 patients with secondary HLH or MAS treated with anakinra, factors associated with favorable outcomes included a diagnosis of sJIA (100% survival) and early start to anakinra treatment.[86] Other anti-IL-1 therapies, such as canakinumab (IL-1β monoclonal antibody) or rilonacept (IL-1β trap), are not typically employed for MAS due to lack of efficacy and/or the difficulty of providing the high-dose regiments of these medications that are needed to treat MAS.[8]

In addition to rheumatologic MAS, anakinra is increasingly used to treat infection-associated HLH. Originally, anakinra was studied in a large, multicenter, randomized controlled trial of patients with sepsis where massive doses of anakinra (1–2 mg/kg/hr) were given.[91] There was no difference between the treatment and placebo groups in the primary end point of all-cause mortality at 28 days, although secondary analyses showed improved survival in patients with organ dysfunction who were randomized to receive anakinra.[91] No increase in mortality or serious adverse events was observed in the anakinra versus placebo arms.[91] A subsequently reanalysis of data from this clinical trial restricted to a small number of patients with features of MAS, defined as hepatobiliary dysfunction and disseminated intravascular coagulation, showed a statistically significant reduction in mortality in patients who received anakinra (35%) compared to placebo (65%).[92] During the coronavirus disease 2019 pandemic, the SAVE-MORE randomized controlled trial showed that at day 28, patients at risk for respiratory failure who were treated with anakinra had improved clinical status and mortality compared to the placebo group.[93] These results do not provide direct evidence for the efficacy of anakinra in infection-associated HLH; however, they do underscore the safety of using anakinra in the context of severe infection. Therefore, there is little downside in starting anakinra early in patients with rheumatologic MAS or in those with other forms of HLH where there is concern for an infectious trigger. Anakinra is increasingly recommended in treatment algorithms for children and adults with new-onset HLH or MAS in order to prioritize early treatment, even while the diagnostic evaluation may be ongoing.[68,94–97] In these protocols, anakinra is typically combined with glucocorticoids and sometimes IVIG and/or cyclosporine. Anecdotally, anakinra appears to be less effective for fHLH and HLH associated with malignancy.[86]

INFγ Neutralization

Emapalumab is a monoclonal antibody that binds and neutralizes IFNγ and is Food and Drug Administration approved for primary/fHLH.[70] Given the central role of IFNγ in perpetuating cytokine storm in MAS, it is not surprising that emapalumab also shows promise in this patient population. In a small (n = 14), multicenter, open-label, single-arm trial for Still's disease, a 28 day course of emapalumab resulted in MAS remission at 8 weeks in 13 out of 14 patients.[50] These patients had failed first-line therapy for MAS with high-dose glucocorticoids and over half had also received cyclosporine and/or anakinra, highlighting the severity of disease in this group. Secondary outcomes included improvement in laboratory parameters of MAS and reduction of the glucocorticoid dose from 15.7 mg/kg/day at baseline to 0.56 mg/kg/day at

week 8. While emapalumab for the primary HLH trial was started at 1 mg/kg/day, this study protocol used a loading dose of 6 mg/kg/day followed by 3 mg/kg every 3 days for 2 weeks and then 3 mg/kg twice a week for the remaining 2 weeks.[70] The study drug was well tolerated, with no deaths and 9 serious adverse of which only 1 was attributed to emapalumab. Notably, 5 out of 14 patients experienced CMV-related events. Six patients who were not maintained on anakinra had flares of Still's disease during emapalumab therapy, indicating that emapalumab is effective for MAS but not the underlying rheumatologic disease. In the clinical setting, emapalumab is often used for patients with MAS who fail first-line treatments with glucocorticoids and anakinra. It appears that patients can undergo a short course of emapalumab to treat MAS and then return to more standard rheumatologic therapies for their underlying disease.

Cytokine Inhibition with Janus Kinases Inhibitors

IFNγ signals through janus kinases (JAK) 1/2 and several other cytokines related to MAS (IL-2, IL-6, IL-12, and others) also utilize the JAK-signal transduction and activation of transcription (STAT) pathway.[98] The literature and ongoing clinical trials have primarily focused on the JAK 1/2 inhibitor ruxolitinib for HLH and MAS with several case series and pilot studies demonstrating efficacy for this drug as first-line or salvage therapy.[90,99–101] In one open-label, prospective, single-center study of 52 children with various forms of HLH, including 11 patients with systemic autoinflammatory disorders, ruxolitinib was given for 28 days as first-line therapy with glucocorticoids.[102] Patients with an unfavorable response underwent "individualized intensification therapy," most commonly etoposide. The primary outcome was overall response rate at 28 days, which was achieved in 69% of study participants. Importantly, patients with autoinflammatory conditions had the highest overall survival rate (100%), while those with chronic-active Epstein–Barr virus infection had the lowest overall survival rate (32%). The median time to first response for patients receiving ruxolitinib was rapid at 2 days. While all patients with a complete response to ruxolitinib maintained it throughout the follow-up period, patients with a partial response required additional therapy. Thus, patients without rapid and complete improvement on ruxolitinib monotherapy will need additional therapies. Fortunately, close to half of the participants who required intensification therapy had a subsequent complete response, indicating there is little downside to starting ruxolitinib and escalating to etoposide in nonresponders. The side effect profile for those who only received ruxolitinib was favorable with only 7 adverse events (cytopenias, n = 6; pancreatitis, n = 1) reaching grade 3 or above in severity. While this study is promising, it is based on single-center results that need to be replicated more widely. Clinically, ruxolitinib is increasingly used for rheumatologic MAS in patients who fail conventional therapies such as glucocorticoids and anakinra. Perceived advantages of this medication compared to emapalumab include the oral formulation along with some evidence to suggest that JAK inhibitors may be effective for both MAS and underlying rheumatologic disease activity.[103] Optimal dosing regimens of ruxolitinib for this population remain to be defined.

MULTIDISCIPLINARY TEAMS TO TREAT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

As HLH/MAS is increasingly considered a spectrum of highly related diseases, there is momentum to develop multidisciplinary teams (MDTs) to manage affected patients.[68,104–106] MDTs bring together subspecialties that previously treated MAS (rheumatology, immunology) and HLH (hematology, oncology) in isolation to allow

clinicians to share their expertise effectively. Other disciplines (critical care, neurology, hepatology, infectious disease, stem cell transplant, genetics, and others) are frequently incorporated into MDTs because of the multi-organ dysfunction that is common in these patients. The pace of disease course in HLH/MAS is typically one of rapid deterioration unless effective immunomodulatory therapy is instituted promptly. Therefore, many MDTs develop algorithms tailored to their institutional environment to aid in the timely diagnosis and treatment of patients (**Table 2**).[68] Given the ever-expanding armamentarium of treatments available for HLH/MAS, these algorithms allow clinicians to reach consensus in advance about which medications should be used as first-line and salvage therapies with the goal of reducing time-to-treatment and practice deviations. While high-quality studies supporting the

Table 2
Example of a treatment algorithm developed by a multidisciplinary team for macrophage activation syndrome

Illness Severity	Concern for Serious Infection	Medication to Consider
First-line Medications for MAS[a,b]		
Moderate	Yes	Anakinra IVIG
	No	Anakinra Methylprednisolone or dexamethasone Cyclosporine or tacrolimus IVIG
Critical[c]	N/A	Anakinra Methylprednisolone pulses[d] Cyclosporine or tacrolimus IVIG
Salvage Therapy for Refractory[e] MAS[f]		
N/A	Contraindicated in infections with pathogens favored by IFNγ neutralization[g]	Emapalumab[h]
N/A	N/A	Ruxolitinib[i]

Abbreviations: IVIG, intravenous immunoglobulin; MAS, macrophage activation syndrome; N/A, not applicable.

[a] This treatment algorithm was developed by clinicians at Boston Children's Hospital. Any treatment and/or medication recommendations within the pathway are provided for educational reference only; it is not intended as medical advice for individual patient care. Decisions about evaluation, diagnosis, and/or treatment are the responsibility of the patient's treating clinician and should always be tailored to the individual patient's clinical care needs.

[b] First-line medications in the treatment algorithm can be used alone or in combination based on the discretion of the treating provider(s).

[c] Critical illness defined as admission to the intensive care unit or intermediate care unit, hemodynamic instability, need for ventilatory support, neurologic deterioration (altered mental status, seizures, encephalopathy), and/or serious end-organ damage.

[d] Methylprednisolone 30 mg/kg (maximum 1000 mg) intravenous for 3 d followed by lower dose glucocorticoid treatment.

[e] Patient failed 2 or more of the first-line therapies.

[f] Recommended salvage therapy includes treatment with emapalumab or ruxolitinib based on the discretion of the treating provider(s). The safety of using emapalumab and ruxolitinib together has not been studied.

[g] Particularly mycobacteria, herpes zoster, and histoplasma capsulatum infections.

[h] Clinical trials studying emapalumab in patients with MAS permitted concurrent treatment with glucocorticoids, cyclosporine, and/or anakinra.

[i] Ruxolitinib should be dose reduced if used with azoles.

MDT approach are lacking, there is some evidence to indicate that a collaborative management strategy through MDTs improves clinician satisfaction and outcomes for patients.[104,107]

SUMMARY

MAS is a serious and potentially fatal complication that develops in patients with rheumatologic diseases, especially conditions driven by the inflammasome-related cytokines IL-1β and IL-18. As in other forms of HLH, this hyperinflammatory syndrome is driven by a combination of impaired cytolytic activity and IFNγ-driven cytokine storm. The cornerstone of effective treatment of MAS includes early recognition and prompt initiation or immunomodulatory therapies that target the inflammatory cytokines central to disease pathogenesis.

CLINICS CARE POINTS

- Disease control in rheumatology patients is essential to lower their risk of developing MAS.
- MAS/HLH share a core pattern of clinical symptoms and laboratory abnormalities that can be assessed quickly with a physical examination and basic laboratory testing.
- Early recognition and treatment of MAS is a key strategy to improve patient outcomes.
- An increasing number of anti-cytokine therapies with a favorable safety profile are effective for MAS and can be used early in the disease course.
- MDTs bring together clinicians from multiple subspecialists to manage patients with HLH/MAS collaboratively in order to diagnose and implement appropriate therapies in a timely manner.

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