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REVIEW

Macrophage Activation Syndrome

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Macrophage activation syndrome (MAS) is a state of immune hyperactivation that can result in life-threatening multisystem end-organ dysfunction. Often termed a "cytokine storm," MAS occurs among the rheumatic diseases most typically in Still's disease but also in systemic lupus erythematosus and Kawasaki disease. MAS can also accompany infection, malignancy, and inborn errors of immunity. This review provides a practical, evidence-based guide to the understanding, recognition, and management of MAS in children and adults, with a primary focus on MAS complicating Still's disease.

Case presentation

A previously healthy 17-year-old male patient presented with three weeks of daily fever to 39°C, spiking in the afternoons and accompanied by transient rash and arthralgias. Physical examination showed a nontoxic but uncomfortable young man, with a temperature 38.5°C; the spleen tip was palpable, and a macular and linear erythematous rash was noted on the trunk, but the examination was otherwise normal. Laboratory test results revealed a white blood cell count of 15,000/μL (75% neutrophils), hematocrit 37%, platelets 453,000/μL, erythrocyte sedimentation rate (ESR) 83 mm/h, C-reactive protein (CRP) 8 mg/dL, ferritin 850 ng/mL, and normal aspartate transaminase (AST) and alanine transaminase (ALT). Interleukin (IL)-18 was 36,000 pg/mL (normal <800 pg/mL), and CXCL9 was 230 pg/mL (normal <121 pg/mL). Infectious and oncologic evaluation results were negative, including viral serologies. He was started on naproxen awaiting prior authorization for the recombinant IL-1 receptor antagonist anakinra, which was declined by his insurer. While taking naproxen, his fevers improved partially, appearing every few days for two weeks before worsening abruptly. On re-evaluation, he was pale and ill, with temperature 40°C, pulse 130, and blood pressure 107/65 mm Hg. His hematocrit level had decreased to 31%, and his platelets were now 230,000/μL, with ESR 45 mm/h, CRP 16 mg/dL, ferritin 43,000 ng/mL, AST 450 U/L, ALT 430 U/L, IL-18 180,000 pg/mL, and CXCL9 3,200 pg/mL. Polymerase chain reaction testing for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) was negative. He was treated with pulse glucocorticoids and anakinra 3 mg/kg per day intravenously (IV) twice daily, improving gradually over two weeks before being discharged with a prescription for anakinra 100 mg subcutaneously (SC) twice daily and a slow glucocorticoid taper. He was transitioned to the anti–IL-1β antibody canakinumab 300 mg SC monthly and remains in clinical remission off glucocorticoids and with normal CRP, ferritin, and CXCL9, although IL-18 remains elevated at 8,300 pg/mL.

What is macrophage activation syndrome?

The term "macrophage activation syndrome" (MAS) was coined in 1993 to describe an intensely inflammatory syndrome observed in children with rheumatic diseases and characterized by the presence of bone marrow macrophages engulfing other hematopoietic cells.[1] The term is now considered to encompass forms of hemophagocytic lymphohistiocytosis (HLH) that arise in the context of systemic rheumatic diseases rather than from a primary monogenic cause in children or adults.[2] More generally, the term describes a clinical syndrome characterized by a set of hallmark features, irrespective of underlying cause. These features, as they emerge in routine clinical tests, are summarized in the 2016 American College of Rheumatology (ACR)/EULAR classification criteria for MAS in the setting of Still's disease (a term we employ here to include both systemic juvenile idiopathic arthritis and adult-onset Still's disease, as per recent consensus recommendations) (Table 1), as well as in an ACR/EULAR consensus report on MAS.[3–5] Developed and tested in pediatrics, the ACR/EULAR criteria have also been employed for adults with Still's disease.[6] Patients with MAS exhibit severe systemic inflammation, usually with fever, together with the following.

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Table 1. 2016 ACR/EULAR classification criteria for MAS in the setting of Still's disease*

Criteria
Both of:
Known/suspected Still's disease with fever
Ferritin >684 ng/mL
Plus any two of:
Platelet count ≤81 × 10^9/L
AST > 48 U/L
Triglycerides > 156 mg/mL
Fibrinogen ≤360 mg/dL

* Modified from Ravelli et al.[3] The criteria were developed for Still's disease beginning before age 16 years (systemic juvenile idiopathic arthritis) but have been applied in patients older at onset. These criteria were developed for classification, not diagnosis, and may not be met by some patients with evolving or established MAS who would benefit from treatment. ACR, American College of Rheumatology; AST, aspartate transaminase; MAS, macrophage activation syndrome.

Elevated ferritin. Ferritin is an iron-binding protein released by activated macrophages, but also by other sources, including hepatocytes. An acute-phase reactant, ferritin is often elevated in inflammation; however, disproportionate ferritin elevation is a key marker of MAS, potentially reflecting release from erythrocyte-consuming hemophagocytes and other activated macrophages.[7, 8] There is no threshold at which ferritin becomes diagnostic for MAS, but very high values should trigger consideration of the diagnosis.[9] For example, in one large series, patients with Still's-associated MAS exhibited median ferritin levels >5,000 ng/mL, 10-fold higher than patients with active Still's disease without MAS.[10]

Low platelet count and other markers of disseminated intravascular coagulation. Ordinarily, systemic inflammation induces thrombocytosis, reflecting the induction of thrombopoietin by IL-6, among other factors. A platelet count lower than expected for the extent and duration of inflammation suggests either lack of marrow response (eg, from leukemic infiltration) or peripheral consumption, as in disseminated intravascular coagulation (DIC). MAS usually features at least subclinical DIC, so relative thrombocytopenia is an important clinical clue. Related features include elevated D-dimer and low fibrinogen, the latter translating into a paradoxical decline in ESR, because depletion of this positively charged hepatic acute-phase reactant prevents negatively charged red blood cells from forming the stack-like clusters (rouleaux) that drive ESR elevation.

Transaminase elevation. Hepatitis is a common manifestation of MAS. Although less specific than hyperferritinemia or markers of DIC, transaminase elevation retains diagnostic value, with transaminase values commonly several fold above the upper limit of normal.[3,11]

Further hallmarks of MAS are discussed below. However, the clinician should be on the alert for MAS in any patient with intense systemic inflammation, relative thrombocytopenia, and transaminitis, measuring ferritin as the first additional marker of MAS. Serial laboratory studies can provide additional evidence, in particular rising ferritin and transaminases and falling platelets.[11,12] Critically, failure to satisfy classification criteria should not delay initiation of treatment for patients in whom trends in clinical and laboratory parameters suggest progression toward MAS.[13]

Disease context is central to the suspicion for MAS. In pediatric rheumatology, MAS is encountered most often in patients with Still's disease, which is accompanied by subclinical MAS in up to one-third of patients.[14,15] Active Still's disease is considered the trigger of MAS in more than half of patients, with infections (most commonly EBV) implicated in approximately one-third.[11] MAS is also observed in patients with Kawasaki disease, systemic lupus erythematosus (SLE), severe infectious illness (bacterial or viral, including HIV and influenza), immunodeficiency or other immunoregulatory disorders, and malignancy, especially leukemia and lymphoma.[5,16] In adults, infection and malignancy are dominant causes of MAS, such that MAS should be suspected when severe inflammation arises in such patients, and should be considered carefully in patients presenting with MAS in the absence of another known predisposing condition.[5,17] In children, malignancy accounts for an estimated ∼5% to 8% of HLH.[5,16] Figure 1 depicts an approximate distribution of causes of MAS in children and adults.

Pathogenesis of MAS

There is an unusually direct connection between the pathogenesis of MAS and the strategies used to diagnose and treat it. Particularly critical have been insights gained from primary HLH, a set of rare inborn errors of immunity that present as MAS in infancy or early childhood, often from defects in cell-cell killing mediated by perforin, a protein expressed by $CD8^+$ T cells, NK cells, and other lineages. Perforin helps terminate immune responses through a critical negative feedback mechanism depicted in Figure 2. Antigen-presenting cells (APCs) such as macrophages and dendritic cells present antigen to T cells, and these in turn promote further APC activation, including enhanced expression of antigen-presenting major histocompatibility complex (MHC) molecules, through cytokines such as interferon (IFN)γ. A vicious cycle is avoided because activated T cells kill APCs, limiting further antigen presentation and cytokine production. Perforin also allows NK cells to kill activated T cells and virus-infected cells. In primary HLH, genetic deficiency of perforin or of the molecules required to deliver it to the cell surface leads to a vicious cycle in which progressively larger numbers of APCs and T cells become activated, contributing to a toxic cytokine storm.

Abundant evidence supports this vicious cycle model of MAS. Mice lacking perforin develop lethal systemic inflammation

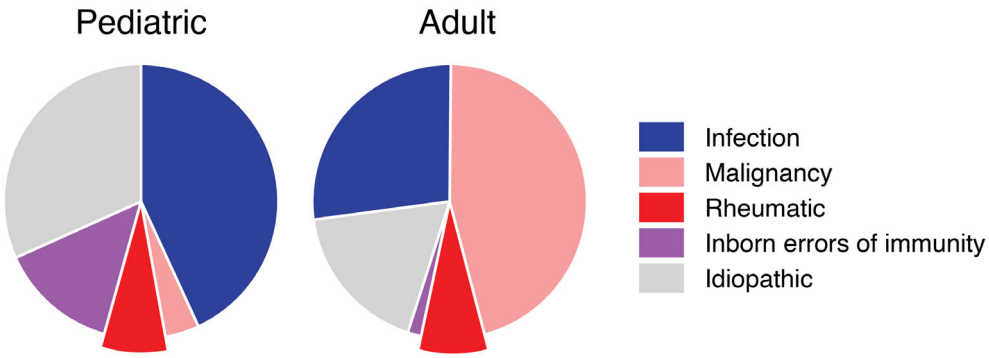

Figure 1. Causes of macrophage activation syndrome in children and adults. Data from a systemic literature search by Shakoory et al of a published series of ≥30 patients in which a single etiology was provided for each patient. Pediatric: <18 years at diagnosis, adult: ≥18 years at diagnosis. Adapted from Shakoory et al.[5]

when infected by virus, rescued by interference with IFNγ or $CD8^+$ T cells, the main source of IFNγ.[18] Interestingly, viral titers are similar in animals with and without perforin early in disease, when IFNγ levels are rising most sharply, indicating that uncontrolled viremia itself is not the main culprit; instead, perforin deficiency results in excessive antigen presentation by APCs and in persistent cytokine production from cytotoxic lymphocytes in prolonged contact with cells they are unable to kill.[19–21] Perforin also contributes to activation-induced cell death of $CD8^+$ T cells and to NK cell–mediated cytotoxic control of activated lymphocytes.[22,23] Finally, exuberant expression of the high-affinity IL-2 receptor alpha chain CD25 by activated $CD8^+$ T cells deprives regulatory

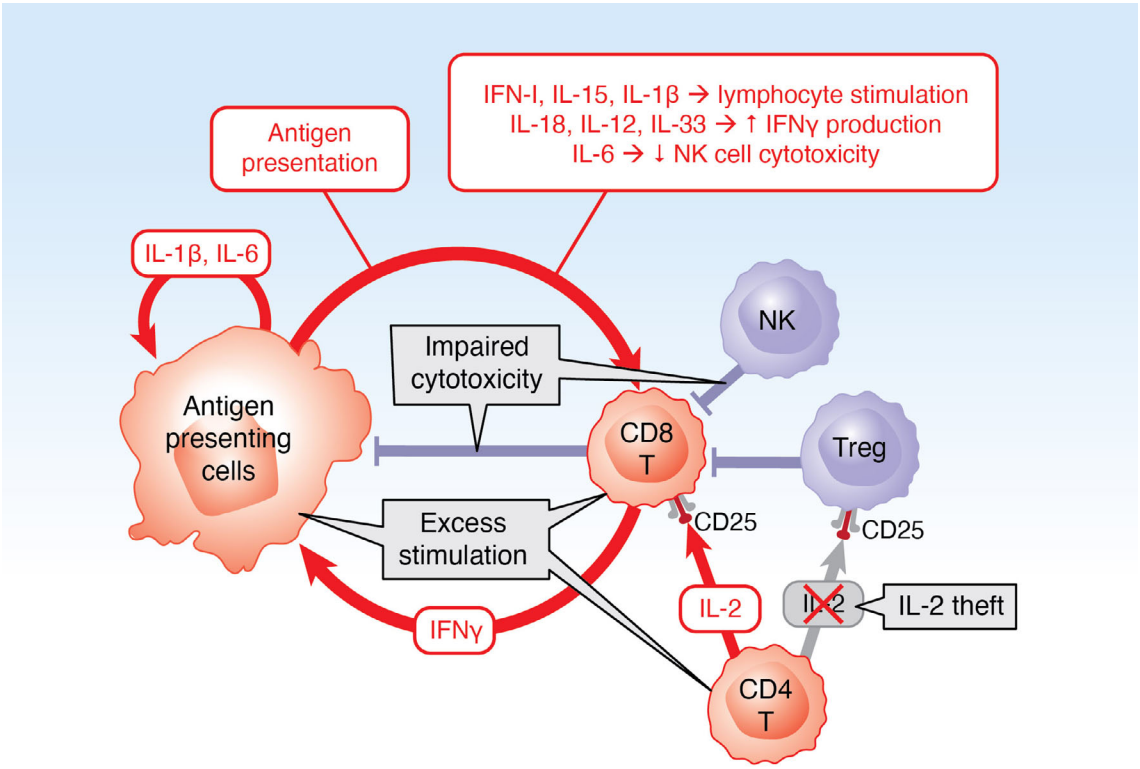

Figure 2. The vicious cycle of macrophage activation syndrome (MAS). Antigen-presenting cells (macrophages and dendritic cells) and lymphocytes (primarily $CD8^+$ T cells) form a cytokine-generating vicious cycle driven by multiple activation pathways (red arrows). Under normal conditions, this positive feedback loop is stopped by inhibitory pathways (blue), including killing of activated antigen-presenting cells and lymphocytes, Treg cells, and elimination of triggers such as viruses (not shown). In MAS, factors leading to uncontrolled activation of this vicious cycle (gray boxes) include genetic and acquired defects in cell-cell killing, excess stimulation (Still's disease activity, infection, malignancy), and "IL-2 theft" by highly activated $CD8^+$ T cells expressing the high-affinity IL-2 receptor α chain CD25. IFN, interferon; IL, interleukin. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43052/abstract.

T cells of the IL-2 they need to survive ("IL-2 theft"), reducing their numbers and contributing to Teff cell dysregulation.[24,25]

MAS can also be induced in mice by repeated administration of the Toll-like receptor ligand CpG, especially together with blockade of the immunoregulatory protein IL-10.[26] In this system, $CD8^+$ T cells are not required, demonstrating that hyperstimulation of innate immune cells can be sufficient to generate a cytokine storm.

Human data also support this explanatory model. Excess IFNγ activity, as assessed by measurement of the IFNγ-induced chemokine CXCL9, marks MAS in patients with Still's disease.[27–29] IL-18, likely from a hematopoietic source, promotes IFNγ release by T cells, in conjunction with IL-12 and IL-15; correspondingly, patients with Still's disease with high IL-18 levels are predisposed to MAS.[30,31] Exuberant T cell activation is evident in high levels of soluble CD25 (sCD25).[15] MAS is characterized not only by IFNγ (a type II IFN) but also by high levels of type I IFNs (IFN-I), a large family of cytokines including IFNα and IFNβ. IFN-I acts together with IL-15 (also elevated in MAS) to expand a population of highly activated circulating lymphocytes, termed cycling lymphocytes because they express the dividing cell marker Ki67; these lymphocytes, predominantly $CD8^+$ T cells but also $CD4^+$ T cells and NK cells, are recognizable by the surface markers CD38 and HLA-DR (MHC II) and are likely an important source of IFNγ in MAS.[32–34] The cytokine IL-33 is also elevated in both human and murine MAS, promoting T cell activation and IFNγ production.[35–37]

Therapeutic interventions support the vicious cycle model. Most informatively, blockade of IFNγ with emapalumab ameliorates both primary HLH and severe MAS associated with Still's disease, confirming a pivotal role for this mediator in human disease.[38,39] Less specific but also informative is the efficacy of interventions directed at myeloid cell activation (the IL-1 inhibitor anakinra), T cell activation (tacrolimus, cyclosporine, etoposide, JAK inhibitors), and IFN signaling, both type I and type II (JAK inhibitors) (discussed further below). Interestingly, humans lacking the IFNγ receptor and mice genetically deficient in IFNγ can still develop MAS, indicating that this cytokine, although often pivotal, is only one of multiple pathways to cytokine storm.[40]

Mechanisms downstream of these key mediators remain to be fully elucidated. One participant in this process is mechanistic target of rapamycin complex 1 (mTORC1). This protein complex assembles in response to multiple different types of signals, including nutritional status, hormones, and cytokines. Patients with Still's disease exhibit mTORC1 activation, amplified markedly during MAS, including in bone marrow hemophagocytes.[41] Drivers of mTORC1 activation include the proinflammatory cytokines IL-1β, IL-6, IFNγ, and IL-18, suggesting likely contributors to mTORC1 engagement during MAS. Interestingly, mTORC1 overactivation is sufficient to convert both murine and human monocytes into hemophagocytes. In murine models, mTORC1 blockade with rapamycin attenuates MAS, whereas mice in whom mTORC1 is constitutively activated due to deletion of its endogenous inhibitor TSC2 develop MAS spontaneously, showing that mTORC1 is both necessary and sufficient for MAS in mice.[41] Rapamycin has been employed successfully in a patient with refractory Still's disease but has yet to be reported in MAS.[42]

Diagnosis of MAS

The pathophysiologic model outlined highlights additional opportunities for diagnosis and monitoring of MAS, and to differentiate MAS from its clinical mimics. Of special value are the following.

1. **CXCL9**. A chemokine released in response to IFNγ, CXCL9 serves as a reliable measure of IFNγ activity. Typically normal even in active Still's disease, CXCL9 rises during MAS to levels ranging from a few fold to a log or more above normal.[27,28] Active MAS in the presence of a normal CXCL9 is quite unusual. The monocyte product adenosine deaminase 2 (ADA2) is a sensitive marker of IFNγ activity, with a greater dynamic range than CXCL9 and thus potentially of even better discriminative value, but is rarely available for clinical use.[28] Circulating IFNγ is elevated in MAS, but the magnitude of the change is smaller than with CXCL9, and highly sensitive tests identify measurable levels of this cytokine even in active Still's disease without MAS, limiting specificity.[27,37]
2. **IL-18**. Unlike CXCL9 and ADA2, IL-18 is often elevated in clinically inactive Still's disease, rising further with disease activity even in the absence of MAS; however, during MAS, elevation is often extreme, providing considerable sensitivity and specificity.[9,28,43] IL-18 elevation is especially characteristic of MAS in Still's disease and in a monogenic autoinflammatory disease associated with hyperactivity of the NLRC4 inflammasome; elevation is less marked, although generally still detectable, in primary HLH and in MAS associated with infection or malignancy.[43–45] Other conditions associated with high IL-18 are autoinflammatory diseases due to mutations in *CDC42*, *PSTPIP1*, *WDR1*, and *XIAP*.[30] In Still's disease, IL-18 often remains elevated even after disease control, although marked elevation is likely a marker of risk to relapse into MAS and so justifies caution in medication tapering.
3. **sCD25**. Activated T cells express and then shed CD25, the alpha chain of the IL-2 receptor that confers high sensitivity to this prosurvival and pro-proliferative cytokine. Levels of sCD25 (also called soluble IL-2 receptor) rise markedly as a reflection of T cell hyperactivation in MAS.[15] Infectious, autoimmune, and neoplastic conditions also raise the level of sCD25, limiting the specificity of this marker.[46,47]

4. **Cycling lymphocytes**. Marked elevation of $CD38^+HLA\text{-}DR^+$ cycling lymphocytes is readily identified by flow cytometry and represents a hallmark of MAS.[32–34]

Typically, the laboratory abnormalities of MAS emerge together, such that elevation in one value in the absence of others should trigger consideration of other entities. For example, isolated elevation of sCD25 can be seen in leukemia and lymphoma, whereas hyperferritinemia out of proportion to sCD25 can be observed in primary T cell immunodeficiency complicated by infection.[2,48]

In young children, primary HLH is a key consideration in patients presenting with MAS.[5] Features favoring this diagnosis, most importantly early age at onset (≤1.6 years) and low neutrophil count ($\leq 1.4 \times 10^9$/L), are summarized in the MAS/HLH score.[49] Prompt recognition of primary HLH is important because these children can deteriorate rapidly and require close management in preparation for bone marrow transplantation.[2] Certain causes of primary HLH are amenable to direct testing; for example, expression of perforin, SAP, and XIAP proteins.[2] Interestingly, genetic testing of children with Still's disease and MAS identified heterozygous variants in HLH-associated genes in 30% or more of patients (compared with 10% of children with Still's disease without MAS and healthy controls), further underscoring the similarity between these diseases and suggesting a threshold model of genetic susceptibility to MAS under inflammatory stress.[50] Genetic testing for HLH-associated gene variants is essential early in the evaluation of patients who may have primary HLH and should be considered in patients with atypical or refractory MAS.

CRP elevation is essentially ubiquitous in MAS but offers no specificity compared to clinical mimics of MAS such as Still's disease flare.[10,28] Nevertheless, CRP does meaningfully reflect systemic inflammation in patients with MAS and therefore is a useful marker to monitor improvement. Because IL-6 blockade directly antagonizes CRP release, measurement of CRP in patients receiving tocilizumab is less informative.[51]

Other tests can be useful on a case-by-case basis. Dysfunctional cell-cell killing by NK cells is evident in both primary and secondary HLH, either through an underlying genetic defect or induced transiently by IL-6.[52,53] This defect can be quantitated by examining in vitro NK cell killing of target cells and by testing expression of CD107a, a protein brought to the cell surface by perforin-containing vesicles. However, lymphopenia and the impact of glucocorticoid therapy render such tests of limited utility in many clinical contexts. Triglyceride levels rise in MAS, potentially reflecting suppression of macrophage-derived lipoprotein lipase.[54] IL-33 elevation is relatively specific for MAS among other causes of fever in children but is rarely available clinically.[37]

Although hemophagocytosis is characteristic of MAS, bone marrow biopsy is not a regular part of the diagnostic evaluation, except as necessary to rule out leukemia or other diagnoses. The reason is that both sensitivity and specificity are limited; almost 40% of bone marrow biopsy samples from patients with MAS lacked detectable hemophagocytosis, whereas patients with Still's disease can have hemophagocytes in the absence of overt MAS.[11,14] Imaging can demonstrate enlarged liver, spleen, and lymph nodes but is directed primarily at assessing end-organ involvement.

Additional testing in patients with MAS is related to alternate underlying diagnoses or disease triggers. A common trigger of MAS is viral infection, including EBV, CMV, adenovirus, HHV6/8, HIV, and SARS-CoV-2; testing for these viruses can be useful and may have therapeutic implications.[2,30] In patients with SLE and MAS, MAS is commonly part of the initial presentation, such that SLE and MAS are often diagnosed concurrently; typical SLE autoantibodies are present.[55] A peripheral blood smear can identify evidence of leukemia, including leukemic cells and teardrop red blood cells; lactate dehydrogenase and uric acid levels are nonspecific but suggestive markers of enhanced leukocyte turnover in leukemia and lymphoma. Hepatosplenic T cell lymphoma and intravascular lymphoma may require tissue biopsy for diagnosis.

Vigilance is required for patients with Still's disease receiving treatment with biologic agents, because the hallmarks of MAS may be less evident. IL-6 blockade with tocilizumab markedly attenuates CRP elevation and reduces the prevalence of fever and the level of ferritin; IL-1β blockade with canakinumab somewhat lowers ferritin but does not appear to abrogate fever.[51]

Therapeutic options in MAS

Treatment seeks to address the axes of the MAS vicious cycle (Figure 3) and is reviewed in the ACR/EULAR consensus report on MAS.[5] Key agents in routine use are as follows (please see Table 2 for details of use).

Glucocorticoids. These agents rapidly suppress inflammation, through suppression of lymphocyte proliferation, NF-κB signaling, and other mechanisms, and are the foundation of MAS treatment, indicated at diagnosis in essentially every patient, with the exception of very mild disease or stable patients awaiting lymph node or bone marrow biopsy to exclude malignancy. Typically, treatment is initiated via daily IV "pulse" therapy of methylprednisolone 30 mg/kg (maximum 1,000 mg), often for three days, followed by dosing of 1 to 2 mg/kg per day IV divided.[13] The duration of glucocorticoid therapy is variable but typically extends with taper to 4 to 8 weeks. The HLH-94 and HLH-2004 regimens for primary HLH employ dexamethasone instead of methylprednisolone.[56]

Anakinra. Use of this short-acting recombinant IL-1 receptor antagonist for MAS has not been studied in a randomized controlled trial but is supported by extensive observational

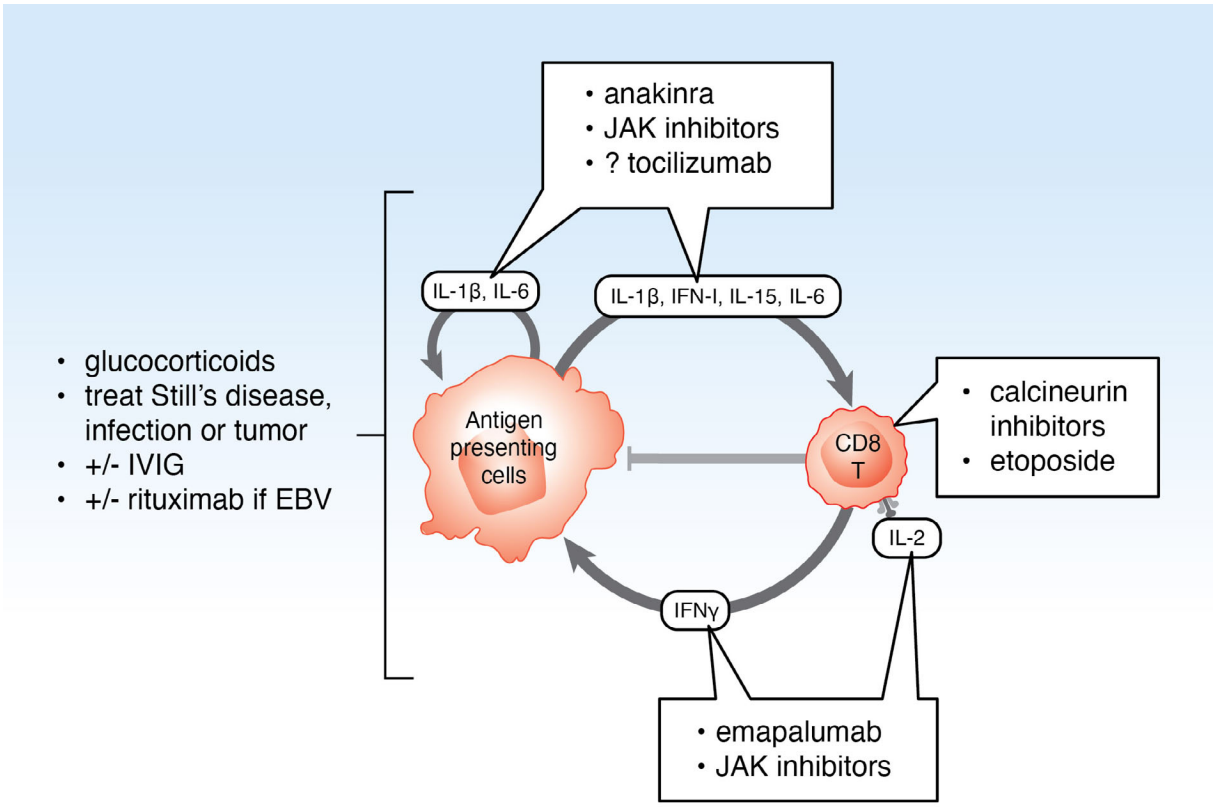

Figure 3. Blocking the vicious cycle in macrophage activation syndrome (MAS). Glucocorticoids are broadly immunosuppressive and form the foundation of treatment. Anakinra, JAK inhibitors, and tocilizumab block cytokines derived from antigen-presenting cells that stimulate T cells, including IL-1β, type I IFNs, and IL-6; JAK inhibitors also block IL-2, IL-12, and IL-15. Calcineurin inhibitors (tacrolimus and cyclosporine) reduce T cell activation and thereby production of IFNγ and IL-2, and etoposide depletes cycling lymphocytes, especially activated $CD8^+$ T cells. Emapalumab blocks IFNγ, as do JAK inhibitors. Treatment of Still's disease activity, infection, or malignancy reduces overall immunostimulation. Rituximab reduces antigen load in EBV-associated MAS. IVIG may control infectious triggers while blocking other immunostimulants or dampening inflammation via inhibitory Fc receptors, although is generally considered a weak agent against MAS. Not shown are investigational targets including IL-18, IL-33, and mechanistic target of rapamycin complex 1. EBV, Epstein-Barr virus; IFN, interferon; IL, interleukin; IVIG, intravenous immunoglobulin. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43052/abstract.

experience.[13,57] It is useful especially in MAS associated with Still's disease, given the pivotal contribution of IL-1 to systemic inflammation in this condition. Therapy of MAS typically requires elevated dosing, 5 to 10 mg/kg per day or higher, divided two to four times a day SC or (more typically) IV.[58] Although first-line anakinra monotherapy is appropriate for many cases of new-onset Still's disease, it is generally insufficient for Still's accompanied by MAS, in which combination therapy with glucocorticoids should be employed.[59] Canakinumab (monoclonal anti–IL-1β) is less useful for MAS treatment because of its long half-life, limited dose-escalation options, poorer central nervous system (CNS) penetration, and cost, although accelerated dosing has been effective in some patients with Still's disease with MAS.[60]

JAK inhibitors. The Janus kinases mediate signals from multiple pathways relevant to MAS, including IFNγ (JAK1, JAK2), IFN-I (JAK1), IL-2 (JAK1, JAK3), IL-12 (JAK2), and IL-15 (JAK1, JAK3). Correspondingly, JAK inhibitors have proved useful in MAS.[13] In mice, JAK1 inhibition was sufficient to control HLH driven by repeat injection of CpG, but viral-induced disease required both JAK1 and JAK2 blockade.[61] A study of ruxolitinib (JAK1/2 selective) as first biologic in 54 children with HLH found an overall response rate approaching 70%, with 42% achieving remission; patients with EBV-associated HLH (in the absence of EBV-induced lymphoproliferative disease) exhibited the best overall response, at approximately 80%.[62]

Calcineurin inhibitors. Tacrolimus and cyclosporine target activated T cells to inhibit proliferation and production of cytokines including IL-2 and IFNγ. These calcineurin inhibitors are often paired with glucocorticoids and anakinra. Studies in HLH found no clear benefit to adding cyclosporine to etoposide,

Table 2. Therapeutic options in MAS*

Medication	Dose	Level of evidence	Notes
Glucocorticoids	Methylprednisolone 30 mg/kg IV (max 1,000 mg) daily × 1–3 d; dexamethasone 10 mg/m^2/d or 0.3 mg/kg/d (usual max 10 mg/d) IV or by mouth; maintenance dosing: methylprednisolone, prednisolone, or prednisone 1–2 mg/kg/d IV or by mouth, typically divided every 12 h (usual max 60 mg/d)	2B	"Pulse" steroids often used at diagnosis to secure rapid control, followed by lower-dose steroids to maintain control. Dexamethasone may be advantageous for CNS disease. Taper gradually over 1–2 mo. Consider PJP and gastrointestinal prophylaxis if therapy is prolonged.
Anakinra	5–10 mg/kg/d divided every 6–12 h IV or SC; usual max 100 mg/dose	3	IL-1 antagonist. Half-life 4–6 h favors divided dosing. Canakinumab (anti–IL-1β) is an alternative but typically not preferred for MAS because of longer half-life and less flexibility in dosing.
Tacrolimus	0.1 mg/kg/d by mouth divided every 12 h	3	Calcineurin inhibitor. Tough level goal before third dose <20 ng/mL. Monitor blood pressure, electrolytes.
Cyclosporine (Sandimmune for IV; Neoral or Gengraf by mouth)	3–7 mg/kg/d by mouth divided every 12 h or 3–5 mg/kg/d IV divided ever 12 h	3	Calcineurin inhibitor. Preparations are not interchangeable. Trough level goal before third dose 50–100 ng/mL. Monitor electrolytes, magnesium, blood pressure; consider daily drug levels in setting of evolving organ dysfunction. Consider discontinuation if concern for PRES.
Ruxolitinib	5–50 mg/d or 50 mg/m^2/d (max 25 mg/dose) divided every 12 h. Typical starting regimen: ≤10kg: 2.5 mg by mouth every 12 h; 10–20 kg: 5 mg by mouth twice daily; >20 kg: 10 mg by mouth twice daily	2B	JAK inhibitor. If ruxolitinib is not available, can substitute another JAK inhibitor. Reduce dose for liver or renal impairment or if coadministered with itraconazole, voriconazole, or posaconazole.
IVIG	1 g/kg/d IV × 2 d	3	Immunomodulatory mechanism undefined; use as part of combination therapy with other agents. Monitor for fluid overload and hemolysis.
Emapalumab	6 mg/kg day 1, then 3 mg/kg every 3–4 d	2B	IFNγ antagonist. Dose and frequency may be increased up to 10 mg/kg per 3 d for inadequate response. Monitor CXCL9 to confirm functional IFNγ blockade. Tested in combination with cyclosporine and anakinra, but not other biologics. Consider antiviral (valacyclovir), antifungal (fluconazole), and PJP (eg, TMP/SMX) prophylaxis; test for tuberculosis before therapy is initiated (need not delay start unless high risk); baseline plus periodic monitoring for EBV, CMV, and adenovirus by qPCR.
Etoposide	50–150 mg/m^2 per dose 1–2 times per wk (wk 1–2) then weekly (wk 3–8)	2B	Deletes cycling lymphocytes. Should be administered with hematology/oncology supervision. Secondary malignancy risk.
Rituximab	375 mg/m^2 per dose (frequency targeted to EBV titer)	3	Delete B cells as source for EBV; for use as adjuvant therapy in EBV-triggered MAS. Follow CD19 count and EBV PCR.

* Dosing and recommendations adapted from references Halyabar et al[13] and Shakoory et al,[5] and from the Boston Children's Hospital Evidence-Based Guideline for HLH and MAS, version 31.[85] Level of evidence assigned by author as per van der Heijde et al[86]: 1A, meta-analysis of randomized controlled trials; 1B, at least one randomized controlled trial; 2A, at least one controlled study without randomization; 2B, at least one type of quasiexperimental study; 3, descriptive studies, such as comparative studies, correlation studies or case–control studies; 4, expert committee reports or opinions and/or clinical experience of respected authorities. CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; IFN, interferon; IL, interleukin; IV, intravenous; IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jirovecii* pneumonia; MAS, macrophage activation syndrome; PCR, polymerase chain reaction; PJP; PRES, posterior reversible encephalopathy syndrome; qPCR, quantitative PCR; TMP/SMX, trimethoprim/sulfamethoxazole.

whereas some patients experienced hypertension and related complications, such that this combination is generally avoided.[56,63]

Emapalumab. This monoclonal antibody neutralizes IFNγ. Emapalumab was effective for primary HLH refractory to conventional therapy in most patients including etoposide and dexamethasone, with a response rate of approximately 65%, leading to US Food and Drug Administration approval for this indication.[38] In Still's disease–associated MAS refractory to high-dose glucocorticoids with or without anakinra and cyclosporine, emapalumab controlled disease in 13 of 14 patients enrolled in a single-arm clinical trial.[39] Comparable efficacy was reported in real-world observational data.[64] Interestingly, in patients taking anakinra in whom this therapy was withdrawn upon initiation of emapalumab, Still's disease tended to flare; we therefore generally continue both agents together. Given the key role of IFNγ in immune defense, patients treated with emapalumab receive concomitant antiviral, antifungal, and anti–*Pneumocystis jirovecii* pneumonia prophylaxis. Emapalumab is cleared much more rapidly when levels of IFNγ are high (half-life 3 days vs 24 days with low levels), such that more frequent dosing may be required in some patients, especially early in MAS.[29,39] Cost remains an important limiting factor for the use of this agent; at Boston Children's Hospital, the current hospital charge for a 28-day course of emapalumab for a 20-kg child is approximately $1.5 million.

Etoposide. Etoposide is a cytotoxic agent that binds DNA topoisomerase II to induce double-strand breaks, triggering apoptosis during mitosis. In murine HLH, etoposide selectively depletes activated T cells, likely explaining its utility.[65] Etoposide has long been standard of care in primary HLH, contributing to the marked improvement in survival in this previously almost uniformly fatal condition.[56] In MAS associated with rheumatic diseases, etoposide is typically reserved for rescue therapy, principally because of concern over secondary malignancies, although this rate is fortunately low (~0.5% at five years).[56]

Other agents can be useful for MAS under some circumstances. MAS associated with EBV infection may benefit from rituximab to deplete EBV-infected B cells and thereby reduce circulating viremia.[66] The efficacy of intravenous immunoglobulin (IVIG) is supported by small uncontrolled series, although its mechanism of action in MAS is unclear, and experience suggests that it is unlikely to be particularly potent.[67–69] IL-18 blockade is not commercially available but can be considered on a compassionate-use basis (ClinicalTrials.gov identifier: NCT04641442, testing the bispecific IL-1β/IL-18 monoclonal antibody MAS825 in patients with autoinflammation due to mutations in *NLRC4* or *XIAP*).[70,71]

The role of IL-6 blockade in MAS treatment is not defined. Although effective in Still's disease without MAS, tocilizumab does not clearly reduce the incidence of MAS (as is the case also for canakinumab).[72,73] Levels of IL-6 in the blood do not distinguish active Still's disease from Still's–associated MAS, and indeed high IL-6 levels often correlate with a course of Still's disease with more arthritis and less MAS.[31,74] Yet there are clear reasons to expect a role for IL-6 in MAS, including improvement in NK cell cytotoxic function with IL-6 blockade and a murine model of IFNγ-dependent MAS that arises through IL-6 excess.[53,75] Tocilizumab is effective in inflammation associated with CAR-T cell therapy or SARS-CoV-2 infection, although neither of these states closely resembles Still's disease–associated MAS.[76] Correspondingly, tocilizumab has been used for MAS.[69,77] We do not typically employ tocilizumab for this indication, given limited evidentiary support, interference with interpretation of CRP and ferritin, and concerns over compromised antibacterial defense; yet no direct evidence underlie this reluctance.[13,51]

Just as control of Still's disease activity contributes to treatment of MAS, so treatment of underlying infection and/or malignancy is critical in patients with MAS associated with these conditions, presumably to reduce antigenic load. Successful treatment of MAS without effective therapy of the underlying disease is uncommon, likely accounting for the high mortality of MAS associated with cancer.[16,17]

Choosing treatment and monitoring response

Treatment of MAS is not standardized. Intensity of therapy is generally proportionate to illness severity. The vicious cycle depicted in Figure 2 confers upon MAS the propensity to intensify rapidly. It is important for the clinician not to be reassured if the patient appears relatively well, or to mistake "normal" platelet count or falling ESR as evidence of improvement. Primary HLH is typically managed by hematology/oncology specialists using etoposide, but this agent is generally not indicated for MAS related to Still's disease unless other options have failed.

An algorithm for treatment of MAS in suspected Still's disease is provided in Figure 4, with drug dosing and monitoring detailed in Table 2. These guidelines incorporate input from MAS experts at Boston Children's Hospital and beyond[5,13] but reflect the author's current approach rather than consensus recommendations and are not intended to define standard of care. We begin with pulse-dose methylprednisolone together with IV anakinra. Anakinra may be used alone in some patients with mild MAS under close monitoring, especially if glucocorticoid use would complicate ongoing evaluation for hematologic malignancy. We add ruxolitinib as a third agent if the response is not brisk. If control remains incomplete but the patient is stable, we add tacrolimus, monitoring blood pressure and drug levels carefully; cyclosporine is an alternative, although we tend to choose tacrolimus based on side effect profile. IVIG may be added at any time as adjuvant therapy, with its principal advantage being lack of immunosuppression, although experience suggests IVIG contributes only marginally to response. Rituximab may contribute to

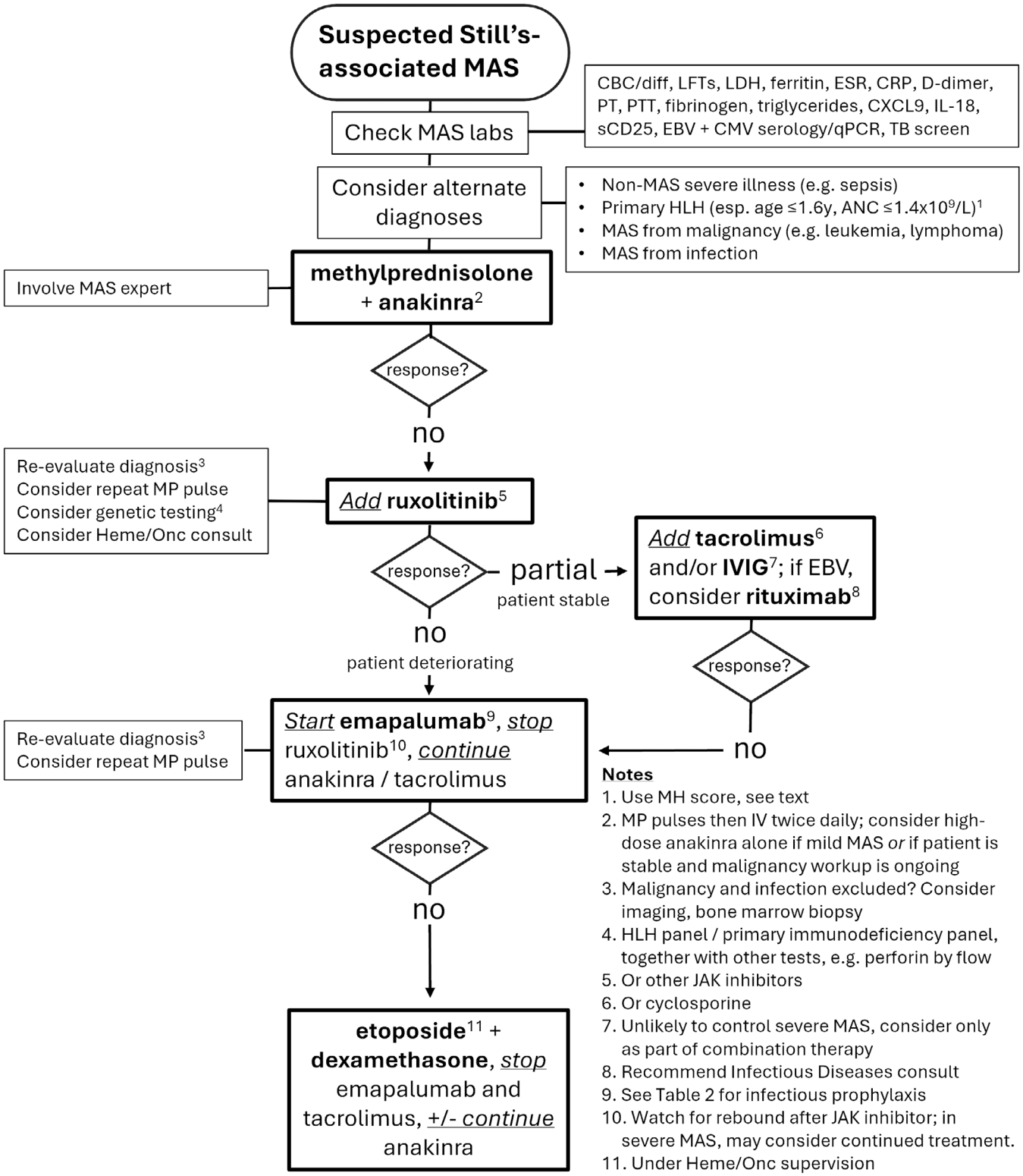

Figure 4. Treatment algorithm for suspected Still's-associated MAS. Supporting data for this order of treatment are very limited; the algorithm thus reflects expert opinion not standard of care. The duration of each step will vary with the patient's clinical condition. Biomarkers should be followed closely throughout. See Table 2 for dosing and toxicity monitoring, and see text for rationale, recommended laboratory monitoring schedule, and evidence base. ANC, absolute neutrophil count; CBC, complete blood cell count; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; Heme/Onc, hematology/oncology; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; IV, intravenous; IVIG, IV immunoglobulin; LDH, lactate dehydrogenase; LFT, liver function test; MAS, macrophage activation syndrome; MP, methylprednisolone; PT, prothrombin time; PTT, partial thromboplastin time; qPCR, quantitative polymerase chain reaction; sCD25, soluble CD25; TB, tuberculosis.

treatment of EBV-triggered MAS by reducing antigen load. If disease continues to worsen, we proceed to emapalumab, adding this therapy to ongoing high-dose IV steroids, anakinra, and/or calcineurin inhibitor. Combination therapy with emapalumab and JAK inhibition has not been reported in humans, and its safety is unknown, although this strategy is effective in mice and could be considered for very severe disease.[78] If emapalumab is not available or ineffective, we proceed with etoposide, typically switching from methylprednisolone to dexamethasone in conformity with the HLH-2004 regimen and for possible benefit with respect to CNS penetration.[56] For continued refractory disease, allogenic bone marrow transplantation may be considered, especially for patients in whom genetic testing shows an associated HLH variant.[64] Glucocorticoids are continued throughout, and repeat pulses may be helpful if deterioration continues. Importantly, the order of treatments proposed is based on experience rather than data. Choices are often driven by drug availability and cost; for example, emapalumab is better supported by efficacy data than some other options and could arguably be considered earlier in the algorithm but for its prohibitive cost profile. If anakinra were not available, we would employ pulse glucocorticoids and ruxolitinib as initial treatment. Infectious diseases consultation can help guide antimicrobial prophylaxis, especially in patients taking emapalumab or taking combination immunosuppressants, with attention to drug–drug interactions (eg, ruxolitinib with azole antifungals).

Therapeutic response monitoring is critical. As MAS improves, fever and hypotension abate, ferritin and D-dimer levels fall, platelets and fibrinogen rise, and transaminases normalize. These variables should be tracked daily at the start of treatment, adjusting therapy as needed to ensure continued improvement; specialized testing (CXCL9, IL-18, sCD25) is commonly obtained twice weekly. Although initial evidence of response is typically evident within days of initiating effective therapy, for severe MAS, improvement may lag by several weeks. Ferritin, transaminases, and platelet count respond most rapidly, whereas CXCL9 and sCD25 normalize more slowly.[39,62] IL-18 improves even more slowly and commonly remains elevated in patients with Still's disease without MAS.[28]

MAS of the CNS

A particularly difficult diagnostic challenge is MAS affecting the CNS. In a series of 193 patients with primary HLH, 37% of patients had seizures, meningitis, or mental status changes; 52% had abnormal cerebrospinal fluid (CSF) findings; and 15% of survivors had neurologic sequelae including development delay and epilepsy.[79] CNS involvement can occur even in the absence of systemic HLH, posing a major diagnostic challenge.[56] Such cases typically are diagnosed by a combination of clinical features, imaging abnormalities, testing for genetic causes of HLH, and/or biopsy, where findings include meningeal infiltration, perivascular lymphocytic infiltrates, and often (but not invariably) hemophagocytes.

In Still's disease–associated MAS, one-third of patients exhibit CNS manifestations, with seizures in 9%.[11] The CSF may reveal evidence of macrophage activation; often measured in this context is neopterin, a metabolite released by macrophages exposed to IFNγ and elevated also in the peripheral blood of patients with MAS, although with less discriminative value than other markers.[74] CNS MAS is treated similarly to peripheral MAS; dexamethasone may be favored over other glucocorticoids because of superior CNS penetration, although at the high doses of methylprednisolone employed in MAS, any difference is likely small.[80] In contrast to primary HLH, in Still's disease–associated MAS, intrathecal chemotherapy is rarely (if ever) required, and isolated CNS MAS has not been reported. CNS MAS must be distinguished from thrombotic or hemorrhagic stroke from DIC, venous sinus thrombosis, infection, malignancy, and posterior reversible encephalopathy syndrome (PRES), a failure of intracerebral vasoregulation leading to intracerebral edema and tissue compromise that—despite the name—is neither invariably posterior nor always fully reversible. Risk factors for PRES include hypertension and renal dysfunction; calcineurin inhibitors have been implicated as possible triggers, although the relationship remains uncertain; concern over PRES as well as efficacy underlie our preference for ruxolitinib over calcineurin inhibitors for patients who do not respond briskly to glucocorticoids and anakinra.[63]

Still's disease–associated lung disease

Recurrent MAS and high levels of the MAS-associated cytokine IL-18 are risk factors for the development of a chronic inflammatory and fibrotic lung disease termed Still's disease–associated lung disease.[81] Disease onset before age two is a further risk factor, although adults may also be affected. Concern over a causal role for biologics has led some physicians and patients to withdraw therapy, but this strategy can precipitate MAS and is not generally recommended.[4] Awareness of Still's disease–associated lung disease is important because pre-existing undiagnosed disease could complicate MAS management through reduced pulmonary reserve and pulmonary hypertension. Patients with Still's disease who have had MAS should be monitored for associated lung disease, especially for patients in whom Still's disease began early in childhood.[82,83]

Prognosis

MAS is a dangerous condition, with appreciable mortality. In the largest series of MAS associated with pediatric Still's disease, one-third of patients required intensive care unit admission, and 28 of 347 (8%) died.[11] MAS associated with malignancy typically has a much poorer prognosis, with all-cause mortality often exceeding 50%.[16,17,57] Early recognition and treatment of MAS

benefits from a coordinated approach among hospitalists and consulting services, leading to improved outcomes and reduced mortality.[84] Patients who have had one episode of MAS are at risk for further episodes, such that vigilant monitoring is essential, especially during medication changes and infectious illness. Note that we continue anakinra therapy through stressors such as infection or surgery, both because anakinra typically does not increase infection risk and because abrupt discontinuation can precipitate MAS, especially during stress; discontinuation of JAK inhibitors can similarly risk MAS rebound, requiring case-by-case decision-making in the face of infection or surgery.

In conclusion, MAS is a clinical syndrome associated with Still's disease but also SLE, Kawasaki disease, infection, malignancy, and inborn errors of immunity. Considerable advances have been made in understanding its pathogenesis, facilitating prompt recognition and improved management, although treating children and adults with MAS remains a major clinical challenge.

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AUTHOR CONTRIBUTIONS

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