Macrophage Activation Syndrome in Children: Diagnosis and Management

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Macrophage activation syndrome is a severe yet under-recognized complication encountered in pediatric rheumatology. It manifests as secondary hemophagocytic lymphohistiocytosis leading to a hyper-inflammatory state resulting from an underlying cytokine storm. If unchecked, it may lead to multiorgan failure and mortality. Early diagnosis and timely initiation of specific therapy is pivotal for a successful outcome. This review outlines the key clinical and laboratory features and management of macrophage activation syndrome.

Keywords: *Hyper-inflammation, Secondary hemophagocytic lymphohistiocytosis,* Juvenile idiopathic arthritis.

Macrophage activation syndrome (MAS) is a form of secondary hemophagocytic lymphohistiocytosis (sHLH) and one of the most commonly encountered pediatric rheumatic emergencies [1]. While these terms are often used interchangeably, MAS is typically used for sHLH with an underlying rheumatic disorder. MAS is most often reported with systemic juvenile idiopathic arthritis (sJIA) [2]. Additionally, it is seen with Kawasaki disease (KD), juvenile systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM) [3,4]. A single centre analysis of 31 children with MAS identified the under-lying disease as sJIA in 84%, SLE in 13% and KD in 3% with the overall mortality being 32% [5]. MAS can compli-cate any chronic inflammatory condition at onset or during the course of the disease [6-8]. sHLH can also be triggered by a variety of other inflammatory conditions viz., underlying infection, malignancy or primary immuno-deficiencies [9].

MAS leads to fulminant manifestations in nearly 10% of children with sJIA, though up to 30% of children with sJIA may have subclinical MAS [2,7,10]. A retrospective study from India reported MAS affecting 1.3% of 950 children diagnosed with KD and coronary artery abnormalities were more frequent, affecting 41.7% of the subset with MAS [3]. Although, MAS is increasingly recognized since its early reports in the 1980s, it seems that a significant proportion of children are either not diagnosed or diagnosed late. This review highlights the pathogenic mechanisms, salient clinical features and the management strategies for MAS.

PATHOGENESIS

The cytolytic dysfunction of natural killer (NK) cells and cytotoxic T-lymphocytes (CTL) is the key inciting event in MAS/primary HLH [9]. While recessive null mutations in *PRF1, UNC13D, STXBP2, STX11, RAB27A,* and *LYST*, which adversely affect granule processing in the CTL and NK cells' function, are known to be associated with primary HLH, there is increasing evidence to suggest that the susceptibility to cytokine storms in sHLH could be along a continuum of genetic deficiency, with monoallelic, biallelic and polygenic defects [11-13]. Of the various implicated genetic defects in fHLH, *LYST, MUNC13-4,* and *STXBP2*, nearly one-third were detected in subjects with sJIA, MAS on whole-exome sequencing. The described heterozygous mutations may constitute the first hit in the genetically-susceptible individual resulting in a subtle underlying impairment in the cytolytic pathways, that turns into an exaggerated immune response subsequent to a second trigger by either an unknown/self-antigen (as in juvenile SLE) or an infectious agent (viral, bacterial, or fungal). This would potentially culminate in an unrestrained activation of immune cells, and subsequent frank hyper-inflammatory state. Antigen-induced T cell hyper-stimulation in MAS/sHLH is not matched with degranulation due to the underlying cytolytic dysfunction. Such persistent activation of CTL and macrophages results in a cytokine storm; most notably involving the massive release of TNF and interleukins: IL-6, IL-1b, and IL-18 [9]. The resultant cytokine storm usually exhibits good

correlation with serum ferritin levels. Ferritin is the storage form of iron, and is an acute phase reactant. Cytokine-mediated macrophage activation in MAS results in hepatic injury and release of ferritin [14]. One of the most consistent laboratory markers of MAS/sHLH is hyper-ferritinemia. Amongst other effects, ferritin has been shown to inhibit lymphocyte division and granulocyte proliferation.

Activation of macrophages leads to hemo-phagocytosis, a cardinal feature of MAS that can be demonstrated histopathologically in the bone marrow, liver, and spleen. However, bone marrow examination shows HLH with positive CD163 macrophages in only up to 60% of cases, and this finding may not be evident during the initial stages [15]. CD163 and CD25 are markers of activated macrophages which mediate endocytosis of haptoglobin-hemoglobin complexes, and the elevated levels of these surface markers, i.e., soluble interleukin-2 receptor alpha chain (sCD25) and soluble CD163 (sCD163) may be sensitive indicators of detecting MAS. **Fig. 1** demonstrates the pathogenic mechanism for MAS.

The prototype animal model of sJIA MAS is the IL-6 transgenic mouse, wherein LPS induces a hyper-inflammatory state akin to MAS, thus recapitulating the occurrence of infection-triggered sJIA MAS. While IL-6-induced stimulation of macrophages accentuates further cytokine production (excess IL-1, IL-6 or IL-18), in vitro experiments have suggested its association with a transient NK cell dysfunction resulting in decreased degranulation i.e., low perforin and granzyme expression on stimulated NK cells in the inflamed microenvironment

[16]. The other crucial arm of inflammation is macrophage hyperfunction, with various defects translating into a systemic hyperin-flammatory state. The macrophage phenotype also changes from M1 (pro-inflammatory) to M2 (anti-inflammatory) in response to external stimuli amid the changing inflammatory milieu [9]. The underlying hyper-cytokinemia and inflammatory cascade form the basis for anti-cytokine therapies in sJIA.

Apart from sJIA, MAS can complicate other rheumatic disorders like juvenile SLE, KD and JDM. In juvenile SLE, defective clearance of self-antigens (due to defects in the dendritic cells and the complement cascade) may contribute to MAS. There is some evidence that the different cytokines may have a major role in the pathogenesis of MAS depending on the underlying rheumatic disorder: soluble TNF receptor (sTNFR)-I levels for SLE, serum IL-18 levels for JDM, and serum sTNFR-II levels for KD and sJIA [17]. A study from Japan, which measured cytokine levels in 36 patients with MAS complicating sJIA, showed a positive correlation of serum sTNFR-II/I ratio with disease activity. This correlation still appeared to exist in the patients treated with the anti-IL-6 drug tocilizumab [18]. The authors suggest that the serum sTNFR-II/I ratio may be a helpful biomarker to assist diagnosis of MAS in sJIA patients receiving tocilizumab.

CLINICAL AND LABORATORY FEATURES

Timely recognition of MAS is of utmost importance for suitable management and successful outcome. A high degree of suspicion is warranted, and it should be considered in any febrile child with underlying rheumatic disease. The
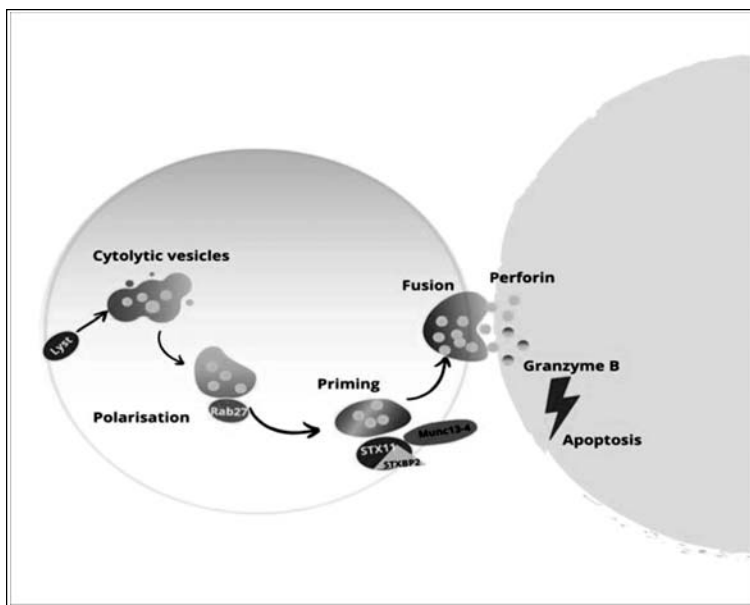

Fig. 1 Immune pathways implicated in macrophage activation syndrome.

persistent high-grade fever, especially in those who are not on any long term immunosuppression, is one of the most important features of MAS. The typical fever in sJIA changes from an intermittent pattern to a non-remitting fever in MAS, and this change in the pattern of fever may be an early clue to differentiate MAS from the underlying disease flare. However, sometimes children with ongoing immunosuppression (steroids) may not mount the typical high persistent fever but have other clinical and laboratory features suggestive of MAS. Absence of fever has also been observed in children on biologicals [15], and it seems that fever may not be an absolute finding in all cases of MAS.

The underlying cytokine storm in MAS results in multiorgan involvement and can have varied clinical features. Many patients will have hepatosplenomegaly and lymphadenopathy. Hemorrhagic manifestations secondary to thrombocytopenia, coagulopathy and liver dysfunction include petechial spots, mucosal bleeding, severe gastrointestinal bleeding, and disseminated intravascular coagulation. Central nervous system (CNS) involvement in the form of drowsiness, headache, seizures and altered behavior; from mild confusional state to frank coma, has been reported in 30-35% patients; and often heralds a worse prognosis. Unless promptly recognized, MAS can lead to multiorgan involvement, including cardiac, pulmonary, and renal failure. The reported mortality of MAS varies from 10-35%; however, early recognition and prompt treatment can improve survival rates. Differentiating the underlying disease flare and MAS

is often challenging **Table I** summarizes the major differences.

MAS in SLE: MAS is most commonly described with sJIA; however, it is increasingly being recognized with other rheumatic disorders, particularly SLE. Based on international cohort data, patients with oral/nasal ulcers, arthritis, serositis, renal, CNS or hematologic involvement at diagnosis of SLE are more likely to develop MAS [19]. Borgia, et al. [8] have reported that 9% of children with SLE had MAS, and the majority (68%) had features of MAS at the disease onset. The diagnosis of MAS in SLE is often more challenging because of the overlapping features like fever, organomegaly and cytopenias in both disease flare and MAS. However, lymphadenopathy and cytopenias are more frequently observed in MAS as compared to active SLE. While comparing the clinico-laboratory differences between MAS and active SLE without MAS, all clinical features of MAS except fever have better specificity than sensitivity. In contrast, fever is the most sensitive with low specificity. Hyperferritinemia, hypertriglyceridemia, elevated lactate dehydrogenase and hypofibrinogenemia are known to have the best sensitivity and specificity in differentiating MAS from active lupus [15]. Akin to sJIA, MAS in SLE can be life-threatening, with mortality ranging from 5-11% [8,15] and therefore needs a high index of suspicion for timely diagnosis of MAS in this population.

CLASSIFICATION CRITERIA AND DIAGNOSIS

The diagnosis of MAS is often challenging, especially

Table I Differentiating Features Between Macrophage Activation Syndrome and Disease Flare

Clinical and laboratory parameter	Macrophage activation syndrome	Disease flare	
		SLE	sJIA
Fever	+++	++	++
Hepato-splenomegaly	+	±	±
Hemorrhages	++	-	-
CNS dysfunction	++	±	-
Hemoglobin	Low	Normal to low	Normal
Platelet count	Low	Normal to low	Highly elevated
Erythrocyte sedimentation rate	Normal to low	Normal to elevated	Normal to elevated
C-reactive protein	Elevated	Normal to elevated	Normal to elevated
Aspartate aminotransferase	Elevated	Elevated	Normal
Alanine aminotransferase	Elevated	Normal	Normal
Lactate dehydrogenase	Elevated	Normal	Normal
Ferritin[a]	Elevated	Normal	Normal
Fibrinogen	Low	Normal	Normal
Triglycerides	Elevated	Normal	Normal

[a]*Hyperferritinemia has the best sensitivity and specificity, followed by increased lactate dehydrogenase level, hypertriglyceridemia, and hypofibrinogenemia for diagnosis of MAS. SLE: systemic lupus erythematosus, SJIA: systemic onset juvenile idiopathic arthritis.*

Box I Pediatric Rheumatology International Trials Organisation Macrophage Activation Syndrome Classification Criteria (2016) [2]

A febrile child with known or suspected sJIA is classified as having MAS if the serum ferritin >684 ng/mL and ≥2 of the following:

• Platelets ≤181×10^9/L

• Aspartate aminotransferase (AST) >48 U/L

• Triglycerides >156 mg/dL

• Fibrinogen ≤360 mg/dL

during the early phase of the disease. The HLH-2004 criteria, originally designed for enrolment in clinical treatment trial, are often used for classification of MAS but lack sensitivity, especially for early detection of MAS. In addition, some of the features described in the HLH-2004 criteria overlap with features observed in active rheumatic diseases in the absence of MAS. Some of these challenges have been addressed in the proposed 2016 MAS in sJIA classification criteria by the Pediatric Rheumatology International Trials Organisation (PRINTO) (**Box I**), which have a sensitivity of 73% and specificity of 99% [2]. Although originally described for children with sJIA, these criteria have also been found to be useful for other rheumatic conditions like SLE and KD. Recently, these criteria have also been used to classify MAS associated with pediatric multisystem inflammatory syndrome temporally related with COVID-19 (PIMS-TS) [20].

The various laboratory parameters including falling total white cell count, low platelet counts, low fibrinogen and low ESR, suggest the diagnosis of MAS. It is difficult to clinch the diagnosis of MAS using a single clinical or laboratory parameter. Kostik, et al. [21] proposed a combination of more than three of the following laboratory parameters to predict an early diagnosis of MAS in sJIA reliably: declining platelet (≤211×10^9/L) and white blood cell counts (≤9.9×10^9/L); decreased albumin (≤2.9 g/dL) and fibrinogen (≤1.8 g/L); elevated ferritin (>400 µg/L), aspartate aminotransferase (>59.7 U/L) and lactate dehydrogenase (>882 U/L); and proteinuria.

More recently in 2019, the novel MAS/sJIA (MS) score was developed in an attempt to improve discrimination between active sJIA and MAS [21]. An international cohort of several hundred patients with sJIA, with and without MAS, were analyzed to identify clinical and laboratory parameters which distinguished the conditions. The MS score includes seven variables: central nervous system dysfunction, hemorrhagic manifestations, active arthritis, platelet count, fibrinogen, lactate dehydrogenase and ferritin. The total score ranges between –8.4 to 41.8 with a value ≥–2.1 showing the best performance. Although the

authors reported a good performance in a validation cohort, a separate study compared the MS score with the H-score for identification of MAS in 71 patients with sJIA and found that the H-score performed slightly better [23].

An additional measure to help recognition of MAS in the context of sJIA, which is simpler than the MS score or H-score, is the ferritin to ESR ratio. A study using data from a large international cohort found that a ferritin/ESR ratio >21.5 has a sensitivity and specificity of 82% and 78%, respectively for diagnosing sJIA-MAS versus active sJIA without MAS [24]. In light of the challenges faced while applying the available criteria in clinical practice, it is crucial to meticulously observe for evolving clinical features and trends of laboratory variables in order not to miss a diagnosis of MAS.

Hyperferritinemia forms part of the HLH-2004 and the 2016 MAS in sJIA criteria with thresholds of 500 ng/mL and 684 ng/mL, respectively. In clinical practice, in patients diagnosed with MAS, ferritin is usually >1000 ng/mL and frequently >10,000 ng/mL. In a systematic review by Sarangi, et al. [15], the median ferritin in children with MAS, sepsis and familial HLH was 37 680 ng/mL, 8775 ng/mL and 3234 ng/mL, respectively. One study, which analyzed all children admitted to Texas Children's Hospital over two years with ferritin > 500 ng/mL, found that a ferritin >10 000 ng/mL was 90% sensitive and 96% specific for HLH [26]. A retrospective analysis over three years of children with ferritin >10 000 ng/mL at 11 UK centres identified 153 patients, but HLH/MAS was not entertained as a diagnostic possibility in 23.2% of these children [27]. This
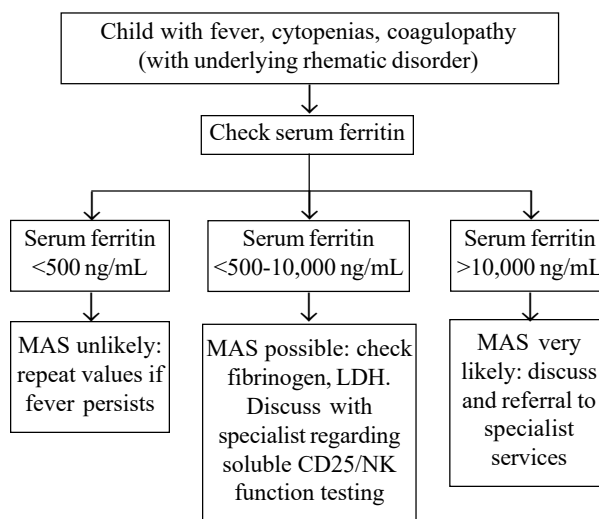
Child with fever, cytopenias, coagulopathy (with underlying rhematic disorder)

↓

Check serum ferritin

Serum ferritin <500 ng/mL	Serum ferritin <500-10,000 ng/mL	Serum ferritin >10,000 ng/mL
MAS unlikely: repeat values if fever persists	MAS possible: check fibrinogen, LDH. Discuss with specialist regarding soluble CD25/NK function testing	MAS very likely: discuss and referral to specialist services

Fig. 2 Guide to early diagnosis and referral for macrophage activation syndrome (*adapted from: Sen ES, Steward CG, Ramanan AV. Diagnosing haemophagocytic syndrome. Arch Dis Child. 2017;102:279-84 [28]*).

highlights the importance of improving education and awareness of HLH/MAS amongst all clinicians caring for children. We recommend that a child with fever, cytopenias and/or coagulopathy with ferritin >10 000 ng/mL be referred to specialist services for evaluation and management of probable MAS/sHLH (**Fig. 2**) [28].

TREATMENT

Timely diagnosis and intervention are pivotal for dampening the underlying cytokine storm and curtailing the morbidity and mortality associated with MAS. The treatment is aimed at mitigating the underlying cytokine storm using immunosuppression and controlling the inciting trigger. In clinical practice, ascertaining the underlying infectious trigger is often not possible. Empirical antibiotics and/or antifungals are instituted in parallel with the immunosuppressive therapy to cover the probable infectious trigger. The treatment of MAS secondary to sJIA is based on the evidence generated from case series, and the same protocol is usually extrapolated for management of MAS secondary to other rheumatic disorders [29-31].
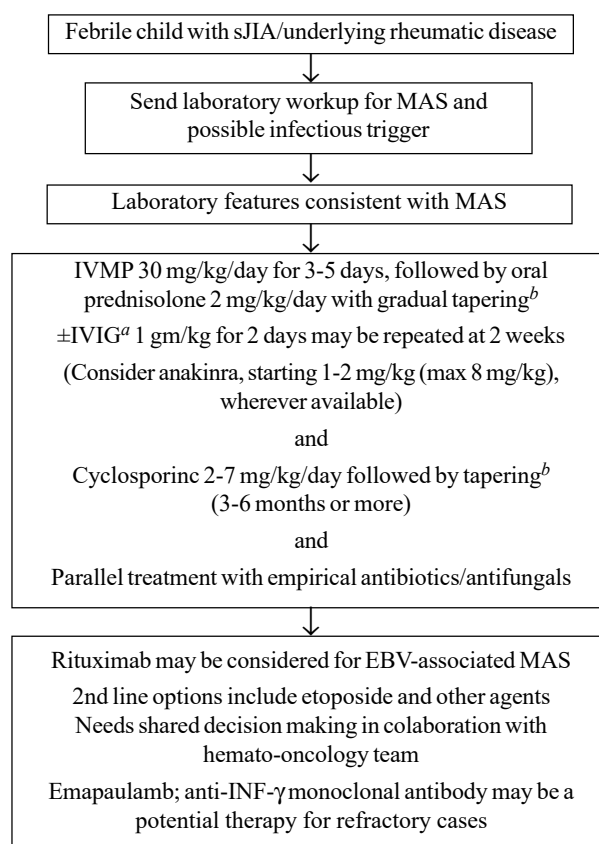
Intravenous methylprednisolone (IVMP) pulse therapy, 30 mg/kg/day (maximum 1g) for 3 to 5 days, followed by oral prednisolone is the most widely used first-line therapy [31,32]. The oral steroids are initiated at a dose of 2 mg/kg/day and gradually tapered while monitoring the clinical and laboratory parameters. They are usually continued for a few weeks until normalisation of hematological abnormalities. Subsequent doses of steroids are titrated as per the need of the underlying disease. There are a few reports of replacing IVMP with dexamethasone palmitate (dose varying from 7.5 to 10 mg/day) in refractory cases or CNS involvement in MAS [33].

The calcineurin inhibitor cyclosporine A has shown efficacy in other histiocytic disorders, and this has led to its use in MAS. Addition of cyclosporine with steroids in the management of MAS results in rapid control of the underlying cytokine storm, in addition to limiting the excessive use of corticosteroids. However, in the acute setting of patients with multiorgan dysfunction, cyclosporine should be used with caution due to its neurotoxic and nephrotoxic side effects. The optimal duration of cyclosporine in MAS is unclear, and it has been used for a variable duration from 3 months to 2 years [34]. It should be continued until the normalization of all laboratory parameters, followed by tapering to prevent relapses. We usually consider oral cyclosporine in a dose of 2-7 mg/kg/day for a period of 3-6 months.

Intravenous immunoglobulin (IVIG) has also been used in the treatment of MAS, and it may be considered as adjunctive therapy to IVMP [35,36]. Given the relative safety and favorable adverse effect profile, it seems prudent to use IVIG as an adjunct to IVMP, especially in Indian settings where underlying infection always remains a possibility. We usually consider using IVIG as initial therapy when the clinical suspicion of concomitant infection is high.

Cytokine-specific therapy using biological agents like anti-IL-1 (anakinra) is increasingly used in the treatment of MAS in sJIA; with improved benefit with an early institution [37]. The use of anakinra is usually considered at an early stage if there is no response to IVMP [30]. Although a common starting dose of anakinra is 2 mg/kg/day, it may be escalated up to 8 mg/kg/day in refractory cases. In cases of shock and poor peripheral absorption, intravenous anakinra can be recommended [38]. Other anti-cytokine therapeutic options for use in MAS include IL-1α and IL-18 blockers [39]. However, non-availability of these agents precludes their use in India. The utility of other biological agents like anti-IL-6 receptor monoclonal antibody tocilizumab and anti-TNF agents (etanercept) in treating MAS secondary to various

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Febrile child with sJIA/underlying rheumatic disease

↓

Send laboratory workup for MAS and possible infectious trigger

↓

Laboratory features consistent with MAS

↓

IVMP 30 mg/kg/day for 3-5 days, followed by oral prednisolone 2 mg/kg/day with gradual tapering[b]

±IVIG[a] 1 gm/kg for 2 days may be repeated at 2 weeks

(Consider anakinra, starting 1-2 mg/kg (max 8 mg/kg), wherever available)

and

Cyclosporinc 2-7 mg/kg/day followed by tapering[b] (3-6 months or more)

and

Parallel treatment with empirical antibiotics/antifungals

↓

Rituximab may be considered for EBV-associated MAS

2nd line options include etoposide and other agents Needs shared decision making in colaboration with hemato-oncology team

Emapaulamb; anti-INF-γ monoclonal antibody may be a potential therapy for refractory cases

[a]*Initiating IVIG where underlying infection cannot be ruled out seems a reasonable practical approach. In such scenarios IVMP can be given after 48 hr of IVIG and antibiotic coverage;* [b]*gradual tapering based on clinical and hematological parameters.*

Fig. 3 Management strategy for macrophage activation syndrome (MAS).

rheumatic disorders remains unclear. The children with sJIA on tocilizumab may remain afebrile with lower cell counts and ferritin levels while they develop MAS, compared to those developing MAS without tocilizumab therapy [40]. As discussed previously, the serum sTNFR-II/I ratio may be a helpful biomarker to identify the onset of MAS in these patients on tocilizumab treatment [18]. Rituximab, a monoclonal antibody to CD20, may be considered in EBV-triggered MAS [41]. A dose of 375 mg/m^2 weekly for four weeks has shown successful results in this setting.

MAS refractory to initial IVMP and cyclosporine is often challenging to manage. In refractory cases, additional use of etoposide may be considered [42]. However, this may be complicated with fatal myelosuppression and opportunistic infections. There are anecdotal reports of successful outcomes with the use of cyclophosphamide in refractory MAS [42,43]. Recently, emapalumab, a fully human IgG1 anti–INF-γ monoclonal antibody has shown its efficacy in children with primary HLH [44]. There is preliminary data suggesting effectiveness of emapalumab in MAS associated with sJIA, although this, and its potential role in MAS secondary to other underlying rheumatic disorders, needs to be further studied [45]. Treatment of refractory MAS is often challenging and should be tailored judiciously in consultation with the hemato-oncology team. **Fig. 3** summarizes the treatment approach for MAS. Hematopoietic stem cell transplantation (HSCT) is a curative option for primary/familial HLH. ten Cate, et al. [46] shared their experience of allogenic stem cell transplant carried out in a child with refractory sJIA who succumbed to MAS following this modality [46]. With the availability of more specific cytokine-targeted therapy with favorable outcome, HSCT is not advocated for treatment of refractory MAS.

CONCLUSION

Macrophage activation syndrome is one of the commonest pediatric rheumatic emergencies. It is most frequently reported with sJIA; although, it can be a complication of any underlying rheumatic disorder. Impaired cytolytic function and the resultant cytokine storm lead to laboratory and clinical manifestations, including, in some cases, fulminant multiorgan dysfunction. Timely diagnosis and judicious use of immunosuppressive agents is pivotal for a successful outcome.

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