

The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)

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ABSTRACT

Objective Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are life-threatening systemic hyperinflammatory syndromes that can develop in most inflammatory contexts. They can progress rapidly, and early identification and management are critical for preventing organ failure and mortality. This effort aimed to develop evidence-based and consensus-based points to consider to assist clinicians in optimising decision-making in the *early stages* of diagnosis, treatment and monitoring of HLH/MAS.

Methods A multinational, multidisciplinary task force of physician experts, including adult and paediatric rheumatologists, haematologist/oncologists, immunologists, infectious disease specialists, intensivists, allied healthcare professionals and patients/parents, formulated relevant research questions and conducted a systematic literature review (SLR). Delphi methodology, informed by SLR results and questionnaires of experts, was used to generate statements aimed at assisting early decision-making and optimising the initial care of patients with HLH/MAS.

Results The task force developed 6 overarching statements and 24 specific points to consider relevant to early recognition of HLH/MAS, diagnostic approaches, initial management and monitoring of HLH/MAS. Major themes included the simultaneous need for prompt syndrome recognition, systematic evaluation of underlying contributors, early intervention targeting both hyperinflammation and likely contributors, careful monitoring for progression/complications and expert multidisciplinary assistance.

Conclusion These 2022 EULAR/American College of Rheumatology points to consider provide up-to-date guidance, based on the best available published data and expert opinion. They are meant to help guide the initial evaluation, management and monitoring of patients with HLH/MAS in order to halt disease progression and prevent life-threatening immunopathology.

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are life-threatening systemic hyperinflammatory syndromes characterised by fever, elevated ferritin and other markers of systemic inflammation, inappropriately low blood cell counts, disseminated intravascular coagulopathy, hepatitis, central nervous system (CNS) inflammation and high risk for progression to multiple organ dysfunction, shock and often death.¹ The term HLH originated as a pathological description in young children, and although it predates the discovery of PRF1 deficiency or other causal genes, it is often still used to imply a 'primary' genetic defect. MAS typically arises as a complication of rheumatic diseases like systemic juvenile idiopathic arthritis (sJIA) or systemic lupus erythematosus (SLE). The current, more broad HLH definition includes MAS among the causes of 'secondary' HLH.² The task force (TF) agreed to refer to the whole spectrum of primary and secondary HLH as 'HLH/MAS'. HLH/MAS can occur in any age group, and typically develops in the setting of infectious, malignant or rheumatological diseases, or less commonly as a manifestation of underlying genetic inborn errors of immunity (IEI) that predispose to hyperinflammation. Early identification and intervention can prevent organ failure and death. Nevertheless, practice patterns in recognising and managing these conditions vary widely.³

The scope of terms such as HLH, MAS, 'cytokine storm syndrome', 'hyperinflammation', cancer immunotherapy-related 'cytokine release syndrome (CRS)', 'hyperferritinemic sepsis-induced multi-organ dysfunction' or SARS-CoV2-associated 'multisystem inflammatory syndrome of children or adults' may overlap such that multiple may reasonably apply to the same patient.⁴ Confusion regarding these terms and the proper boundaries of their application can have unintended consequences (eg, primary HLH treatment protocols are rarely indicated in the MAS subset of secondary HLH).

Recommendation

Table 1 Recognisable clinical features/patterns in HLH/MAS

| Features | Criteria* |
|--|---------------|
| 1 Systemic inflammation (elevated or rising) | |
| Fever | All |
| CRP | – |
| LDH | – |
| 2 Hyperferritinemia (elevated or rising) | All |
| 3 Cytopenias (low or dropping) | |
| Platelet count† | All |
| Leucocyte count (particularly neutrophil count) | HLH04, HScore |
| Haemoglobin | HLH04, HScore |
| 4 Disseminated intravascular coagulopathy | |
| Increased d-dimer | – |
| Low/Dropping fibrinogen‡ | All |
| Prolonged PT/INR, PTT | – |
| 5 Liver dysfunction | |
| Hepatomegaly | HScore |
| Increased ALT, AST, bilirubin | MAS16, HScore |
| Increased triglycerides | All |
| 6 Splenomegaly | HLH04, HScore |
| 7 CNS dysfunction | – |
| Encephalitis, encephalopathy, altered mental status, seizure | |
| CSF pleocytosis, elevated CSF protein, increased ICP | |
| Radiological evidence of inflammation | |

‘–’ signifies not included in any of these criteria.
 *HLH04,² MAS16¹²² or HScore,⁷ see also online supplemental table 2.
 †As acute phase reactants, low-normal values in the face of systemic inflammation may signify consumption.
 ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; CSF, cerebrospinal fluid; ICP, intracranial pressure; INR, international normalised ratio; LDH, Lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time.

The TF agreed to define and use the term *HLH/MAS* to encompass a recognisable pattern of clinical findings associated with these syndromes (as discussed in [table 1](#)). The TF defined *systemic hyperinflammation* as a state of excessive immune activation at risk of progression to HLH/MAS. Additionally, the TF identified three categories of contributors to the development of HLH/MAS: *genetic causes* of HLH/MAS, *predisposing conditions* (eg, sJIA, lymphoma, certain metabolic conditions) that increase susceptibility and *acute triggers* (eg, infections, immunotherapies).

Several important collaborative efforts have shaped the current approach to the diagnosis and management of HLH and MAS. The Histiocyte Society, and later rheumatology consortia, developed and refined classification criteria to define HLH^{2,5} or MAS.⁶ Subsequent diagnostic tools like the HScore⁷ and MS score⁸ provided more continuous measures. Several groups have developed and published consensus-based management documents that provide context-specific recommendations (see [table 2](#)).

There remains an unmet need for guidance during the *early* stages of HLH/MAS: a period between when suspicion first arises and when an underlying aetiology has been established. Early HLH/MAS can be highly variable between patients, and often involves rapid changes within the same patient. Patients may not fully meet relevant criteria, their diagnostic workup may be evolving and their condition may be rapidly deteriorating. Nevertheless, it is precisely at these early timepoints where appropriate interventions may have the best chance of

Table 2 Preceding HLH/MAS consensus publications

| | |
|--|--|
| Genetic HLH | Ehl, <i>et al</i> ⁹² |
| Malignancy-associated HLH | Lehmerberg <i>et al</i> ⁹³ (paediatric) |
| | Daver <i>et al</i> ¹⁰⁹ (adult) |
| HLH diagnosis | Jordan <i>et al</i> ⁹⁴ |
| MAS diagnosis | Ravelli <i>et al</i> ^{6,19} |
| HLH in adults | La Rosée <i>et al</i> ⁶⁷ |
| HLH in intensive care | Hines <i>et al</i> ⁷⁴ |
| Consensus publications gathered at https://www.histiocytesociety.org/HLH-Consensus . | |
| HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome. | |

preventing the worst outcomes. To address this need, an international multidisciplinary TF developed consensus-based and evidence-based guidance statements. Although collectively HLH/MAS is not rare, these guidance statements are termed points to consider (PTC) to recognise the limitations of the evidence supporting them. These PTC target a broad range of frontline, primary care and subspecialty providers and are meant to assist them in recognising HLH/MAS, identifying its contributors, intervening despite diagnostic ambiguity and monitoring for progression and organ damage.

METHODS

The American College of Rheumatology (ACR) and EULAR standardised operating procedures were followed during the project.⁹ With approval from the EULAR executive committee, and in parallel with two EULAR/ACR consensus guidance efforts in autoinflammatory diseases,^{10,11} an international, multidisciplinary TF was convened to develop PTC at the earliest stages in the recognition and management of HLH/MAS. The conveners (SWC and FdB) invited North American and European TF members with established expertise in the management of HLH/MAS to contribute. The TF consisted of 14 paediatric and adult rheumatologists, 4 haematologists/oncologists, 2 immunologists, 2 infectious disease specialists and 3 intensivists. In addition, the TF included a nurse experienced in caring for patients with HLH/MAS, two patient representatives and three methodologists.

At an initial face-to-face meeting in August 2019, the team defined the goals of the project, the target population and relevant questions using the Population, Intervention, Comparison, Outcome (PICO) format. The target audience was defined as healthcare professionals, policy makers, health insurance companies and patients and their caregivers. A systematic literature review (SLR) was performed by three team members (BS, MW, AG), with support from a librarian (DH), epidemiologist (DP) and senior methodologists (AR, EDe, DA) to identify relevant literature using PubMed, Embase and the Cochrane Library published before November 2020. Initial search terms for the SLR consisted of the full spectrum of names used to signify the syndrome of HLH/MAS. The resulting articles were filtered based on quality and relevance to PICO questions. SLR themes are discussed in brief throughout this manuscript, in the online supplemental methodology and detailed in a separate ‘SLR manuscript’.¹²

In response to the PICO questions and informed by the synthesis of SLR results and expert opinion, the TF drafted and refined overarching and specific PTC in the form of statements. Individual statements were suggested, edited and refined in two rounds of preconsensus meeting questionnaires using a secure web-based system (Jotform). These statements addressed early identification, diagnosis, monitoring and early management of

Table 3 Overarching principles

| | | LoE/GoR | LoA (0–10) Mean±SD |
|---|--|---------|-----------------------|
| A | Systemic hyperinflammation is an immunopathological continuum; the characteristic clinical and laboratory findings are individually non-specific, but when viewed collectively and longitudinally are recognisable and warrant prompt diagnostic evaluation. Therapeutic intervention may be warranted even when not satisfying specific classification/diagnostic criteria for HLH/MAS. | 5D | 9.4±1.2 |
| B | Systemic hyperinflammation can be associated with hyperferritinemia and can progress to life-threatening HLH/MAS. | 5D | 9.6±0.7 |
| C | Systemic hyperinflammation and HLH/MAS can occur in nearly any inflammatory state, but certain predisposing conditions and/or inflammatory triggers warrant a high index of suspicion.* | 2B | 9.1±1.3 |
| D | Investigating and treating modifiable contributors to systemic hyperinflammation and HLH/MAS are essential in the management of every patient. | 4C | 9.7±0.6 |
| E | HLH/MAS should be treated with an urgency based on both the degree of inflammation and extent of organ dysfunction; the goals of therapy are to prevent/limit immunopathology, preserve integrity of the ongoing diagnostic workup and minimise toxicity. | 5D | 9.7±0.7 |
| F | The evaluation and management of patients with systemic hyperinflammation suspected of having or progressing to HLH/MAS may benefit from consultation with experts in these disorders. | 5D | 9.2±1.8 |

LoE: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA using a 0–10 Likert scale.

*See text and other tables for examples/clarification.

GoR, grade of recommendation; HLH, haemophagocytic lymphohistiocytosis; LoA, level of agreement; LoE, level of evidence; MAS, macrophage activation syndrome; RCT, randomised controlled trial.

HLH/MAS as described in the SLR manuscript¹² and tables 3 and 4. The response rate for each questionnaire was 100%. The TF members were asked to indicate their agreement with each statement or item with yes or no. A free text option was provided to capture every member's comment or suggestion for modification. A request was also included for members to add items to be addressed, edited or altered. Responses to this questionnaire were reformulated as draft statements. Comments and suggestions provided in the questionnaires were used to modify the draft statements and to add additional items. The revised and amended statements were then circulated through a second round of questionnaires. After the two rounds, the draft statements were revised to incorporate all suggestions and reviewed by the TF members. These draft statements were then included for discussion at the consensus meetings.

The TF reviewed, discussed and voted on these statements in a consensus meeting held virtually over 3 days in March/April 2021. Prior to each of these consensus meetings, the results of the SLR and the draft statements were distributed to all TF members. During the meetings, statements that achieved at least 80% agreement were accepted; statements with <80% were discussed a final time in a nominal group, round robin format and were only accepted if the statement reached an 80% agreement at that point. Delphi technique was used to achieve consensus throughout the process.

Oxford levels of evidence and a grade of recommendation were assigned for each statement.^{12 13} Each TF member then assigned their level of agreement for each statement using an 11-point Likert scale from 0 to 10 (0: completely disagree, 10: completely agree).

RESULTS

Systematic literature review

Briefly, original research articles of any study design with diagnosis, treatment and monitoring of HLH/MAS that reported more than six cases were included. Of the 18 020 articles from PubMed, EMBASE and Cochrane, 258 were selected for full-text review and 167 articles were included for data extraction. Based on the expertise of TF members, SLR results¹² and discussion at consensus conferences,

the TF generated 6 overarching principles (table 3) and 24 disease-specific PTC pertaining to HLH/MAS (table 4).

Overarching principles

Recognising the complexity and urgency of management decisions in systemic hyperinflammation and HLH/MAS, the TF generated six overarching principles (table 3) that provide guidance on the early recognition of characteristic clinical features, the systematic evaluation of contributors (including genetic causes, predisposing conditions and acute triggers), the implementation of early therapies and the monitoring of HLH/MAS progression.

Points to consider

The TF generated specific statements intended to offer practical consensus-based and evidence-based guidance for clinicians making decisions at the earliest stages of HLH/MAS consideration, recognition and management (table 4).

PTC 1.1–1.5: recognition, screening and early diagnosis

Given the variety of genetic causes, predisposing conditions and acute triggers from which HLH/MAS arises, recognising the presenting features and making a diagnosis are often challenging. Existing diagnostic criteria lack both sensitivity and specificity, especially in the context of confounding conditions like lymphoma or sepsis.

Based on existing criteria, current literature and expert experience, the TF agreed on clinical and laboratory abnormalities that together establish a recognisable pattern of potentially life-threatening HLH/MAS (PTC 1.1). Individual findings are non-specific and must be evaluated collectively and longitudinally. However, recognising the pattern of clinical and laboratory abnormalities that constitute HLH/MAS is critical for prompting an aetiological workup, considering treatments and initiating a monitoring strategy before serious complications or death occur.

Ferritin is a sensitive test for HLH/MAS, and there was broad consensus that ferritin levels should be checked in all patients with new, ongoing or heightened suspicion for HLH/MAS even if prior measurements have been normal (PTC 1.1–1.3). Essentially all

Recommendation

Table 4 Consensus statements

| | | LoE/GoR | LoA (0–10) Mean±SD |
|--|--|------------------------------------|-----------------------|
| Recognition, screening and early diagnosis | | | |
| 1.1 | The following unexplained or unusually severe clinical and laboratory features, particularly if co-occurring, may represent a systemic hyperinflammatory syndrome and should prompt consideration of HLH/MAS in appropriate clinical contexts: ▶ Persistent fever. ▶ Elevated and/or rising ferritin or other markers of inflammation/damage (CRP, LDH). ▶ Inappropriately low or declining haemoglobin, platelet counts or white blood cells (neutrophils and lymphocytes). ▶ Hepatic dysfunction (increased ALT, AST, bilirubin). ▶ Coagulopathy (low fibrinogen, increased PT/INR, increased d-dimers). ▶ Splenomegaly. ▶ CNS dysfunction. | HLH: 1A MAS: 3B | 9.5±1.1 |
| 1.2 | Patients with features of a systemic hyperinflammatory syndrome that could represent or progress to HLH/MAS should have a ferritin level checked. | 1A | 10.0±0.2 |
| 1.3 | Patients with a normal ferritin but ongoing clinical suspicion for HLH/MAS should have serial ferritin testing. | 5D | 9.4±1.0 |
| 1.4 | In addition to ferritin, clinicians should obtain the following routine laboratory evaluations: CBC with differential, liver panel, fibrinogen, d-dimer, LDH and CRP. | 1A | 9.5±0.7 |
| 1.5 | Following initial laboratory evaluations, assessment of specialised biomarkers of inflammation (eg, IL-2Rα (CD25), CD163, IL-18, CXCL9, neopterin, if available) may further aid in the diagnosis of HLH/MAS. These tests should be interpreted in consultation with a specialist with expertise in HLH/MAS. | 4C | 9.2±1.2 |
| Criteria | | | |
| 2.0 | Existing classification or diagnostic criteria perform well in specific settings, but no single set of criteria is sufficient to diagnose a syndrome of HLH/MAS across all contexts. | 5D | 9.4±1.2 |
| Evaluating contributors | | | |
| 3.1 | Certain underlying infections, rheumatic diseases, malignancies, metabolic diseases and genetic inborn errors of immunity are frequently associated with HLH/MAS and clinicians should consider evaluations for these in appropriate contexts. | 2B | 9.6±0.6 |
| 3.2 | Genetic testing in patients with probable HLH/MAS can dramatically affect diagnosis and management and should be considered early. | 3B | 9.0±1.8 |
| 3.3 | Decision-making about genetic testing in patients with probable HLH/MAS is complex, should integrate age, clinical features and laboratory/functional test results, and should involve specialists with expertise in HLH/MAS. | 4C | 9.4±0.9 |
| 3.4 | In patients for whom genetic testing is indicated, next-generation sequencing (eg, targeted gene panel, whole exome or whole genome sequencing) to screen for pathogenic variants, rather than single gene Sanger sequencing, is recommended. | 5D | 9.2±1.5 |
| 3.5 | Genetic counselling to assist with consenting and interpretation of results should be offered to patients being considered for genetic testing. | 5D | 9.1±1.4 |
| Prognostic factors and CNS involvement | | | |
| 4.1 | Underlying malignancy, CNS involvement, liver failure, multiple organ dysfunction and prolonged active disease are associated with a poor prognosis in patients with probable HLH/MAS; these should prompt urgency in establishing the diagnosis of HLH/MAS, identifying triggering conditions and initiating appropriate treatment. | 2B | 9.5±1.1 |
| 4.2 | All individuals with probable HLH/MAS should undergo a complete neurological examination. Patients with any of the following should be assessed for CNS involvement: age <1 year, known genetic HLH disorder, encephalopathy, seizures, altered mental status, irritability, meningism, headache, vision changes or focal changes. | 4C | 9.2±1.5 |
| 4.3 | Assessment for CNS involvement should include brain MRI and evaluation of cerebrospinal fluid glucose, protein and cell count with differential (with pathological review of cytology) when safe to do so. | 4C | 9.5±1.0 |
| 4.4 | In patients with probable HLH/MAS, assessment for CNS involvement should not delay initiation of systemic immunomodulatory therapy. | 4C | 9.7±0.7 |
| Treatment | | | |
| 5.1 | For patients with probable HLH/MAS and persistent, severe or worsening inflammation or organ dysfunction, initiation of immunomodulatory treatment should be considered while diagnostic testing is ongoing. | 5D | 9.7±0.7 |
| 5.2 | Choice of initial immunomodulatory treatment is complex and requires balancing an assessment of urgent risk due to rapid HLH/MAS progression with potential for obscuring diagnosis of malignancy or worsening active infection. | 2B | 9.6±0.9 |
| 5.3 | Initial empiric immunomodulatory therapy in patients with rapidly progressive HLH/MAS could include high-dose glucocorticoids, anakinra and/or IVIg based on local access. | GC: 2B Anakinra: 2B IVIg: 4C | 8.9±2.1 |
| 5.4 | In addition to supportive care and immunomodulatory HLH/MAS treatment, patients should receive appropriate antimicrobial and antiviral therapies and treatment of any underlying triggers or disorders. | 4C | 9.8±0.5 |
| 5.5 | In patients for whom prolonged immunomodulatory regimens are anticipated, consideration should be given to the use of antimicrobial and/or antiviral prophylaxis in consultation with an infectious disease expert. | 2B | 9.3±1.9 |
| Monitoring | | | |
| 6.1 | In patients with probable HLH/MAS, worsening or lack of improvement in laboratory parameters of systemic inflammation (particularly ferritin), DIC, hepatitis or cytopenias may indicate disease progression and a need to re-assess diagnosis and/or treatment. | 2B | 9.6±0.8 |
| 6.2 | Patients with systemic hyperinflammation suspected of having or progressing to HLH/MAS require continuous clinical monitoring and frequent reassessment of organ dysfunction, which may necessitate ICU care. | 4C | 9.8±0.4 |
| 6.3 | Clinicians should monitor initial response to treatment by assessing clinical and laboratory markers of organ involvement at least daily and markers of systemic inflammation at least twice weekly.* | 2B | 9.3±1.0 |
| Multidisciplinary teams | | | |
| 7.0 | A multidisciplinary approach is preferred and can optimise the diagnostic workup and management of patients with systemic hyperinflammation and HLH/MAS. | 5D | 9.6±1.0 |
| LoE: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA using a 0–10 Likert scale. *See text and table 5 for examples/clarification. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CNS, central nervous system; CRP, C reactive protein; CXCL9, C-X-C motif chemokine ligand 9; DIC, disseminated intravascular coagulation; GC, glucocorticoids; GoR, grade of recommendation; HLH, haemophagocytic lymphohistiocytosis; ICU, intensive care unit; IL-2Rα, interleukin-2 receptor alpha; INR, international normalised ratio; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; LoA, level of agreement; LoE, level of evidence; MAS, macrophage activation syndrome; PT, prothrombin time; RCT, randomised controlled trial. | | | |

Table 5 Laboratory and biomarker testing in HLH/MAS

| Test | In HLH/MAS | Biology | Criteria | Monitoring frequency | Prognostic utility* | Caveats |
|-------------------------|------------|---|----------|----------------------|-----------------------------|--------------------------------|
| Complete blood count | | | | | | |
| Neutrophil count | ↓ | Affected by marrow production, proliferation, tissue sequestration, consumption | 1, 3 | F | ✓ ^{31 116} | Glucocorticoid demargination |
| Lymphocyte count | ↓ | | | F | | |
| Haemoglobin | ↓ | | 1, 3 | F | ✓ ^{3 31 70 114} | |
| Platelet count | ↓ | | 1, 2, 3 | F | ✓ ^{26 31 35 42 47} | |
| Inflammatory biomarkers | | | | | | |
| CRP | ↑ | Hepatic release in response to IL-6 | | F | ✓ ⁵³ | Blunted by IL-6 blocking drugs |
| Ferritin | ↑ | Macrophage/Hepatocyte activation | 1, 2, 3 | F | ✓ ^{35 114–117} | ↑ By iron overload |
| ESR | ↑↓ | Falls with fibrinogen consumption | | I | ✓ ¹⁰⁷ | ↑ By IVIg, dialysis |
| LDH | ↑ | Cellular death/injury | | I | ✓ ^{114 123} | ↑ With haemolysis, TMA |
| IL-2R α | ↑ | T-cell activation | 1 | I, R | ✓ ³⁰ | |
| CXCL9 | ↑ | Chemokine induced by IFN γ | | I, R | | |
| IL-18 | ↑ | Inflammasome-activated, induces IFN γ | | prn | ✓ ¹²⁴ | |
| Liver function tests | | | | | | |
| ALT, AST, bilirubin | ↑ | Hepatocyte injury | 2, 3 | F | ✓ ^{31 35 47} | |
| Triglycerides | ↑ | Cytokine inhibition of lipoprotein lipase | 1, 2, 3 | R, prn | ✓ ¹¹⁴ | Fasting |
| Albumin | ↓ | Vascular leak/third-spacing | | F | ✓ ^{70 107 114 116} | |
| Coagulopathy tests | | | | | | |
| Fibrinogen | ↓ | Fibrinogen consumption/fibrin degradation | 1, 2, 3 | F | ✓ ^{26 47 116} | |
| D-dimer | ↑ | | | F/I | ✓ ^{26 47} | |
| PT/INR/PTT | ↑ | Factor consumption | | F | ✓ | Heparin effects |
| CNS tests | | | | | | |
| Brain imaging | Abnormal | Inflammation of white or grey matter, meninges. Hypoxia | | prn | ✓ ^{3 42 76 77 81} | |
| CSF studies | ↑ | Pleocytosis and/or high protein~CNS inflammation | | prn | ✓ ^{3 42 76 77 81} | |

1=HLH-04,² 2=MAS-2016,⁶ 3=HScore.⁷

*Degree of abnormality and/or failure to improve correlated with worse outcomes.

AST, aspartate aminotransferase; CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; CXCL9, C-X-C motif chemokine ligand 9; DIC, disseminated intravascular coagulation; ESR, erythrocyte sedimentation rate; F, frequent (eg, daily); I, intermittent (eg, weekly); IFN γ , interferon gamma; IL, interleukin; LDH, lactate dehydrogenase; PRN, as needed; R, rarely (eg, monthly); TMA, thrombotic microangiopathy.

patients with HLH/MAS with systemic disease have elevated ferritin levels,^{14 15} and hyperferritinemia is part of all existing HLH/MAS criteria (table 1). Levels >500 ng/mL were 84% sensitive in paediatric patients with HLH,² and served as the cut-off in clinical trials conducted by the Histiocyte Society, but this level is associated with poor specificity in other contexts and higher ferritin cut-off values have been used.¹² The ferritin cut-off values used in paediatric HLH/MAS studies (500–2000 ng/mL) tend to be lower than in adult studies (often >10000 ng/mL),^{2 6 7} where infectious and malignant contributors predominate.¹⁶ Other conditions such as iron overload, malignancy and hepatitis commonly induce high ferritin levels even in the absence of HLH/MAS.¹⁷

Abnormalities in other widely available clinical and laboratory indicators of inflammation, coagulopathy or organ damage/dysfunction also raise the level of suspicion for HLH/MAS (PTC 1.4, table 5). However, many HLH/MAS-associated biomarkers may also indicate parallel inflammatory processes (eg, elevated LDH in thrombotic microangiopathy).¹⁸ More specialised biomarkers measuring key HLH/MAS pathways (PTC 1.5, table 5, online supplemental table 1) are increasingly available from reference laboratories. These include measures of activation of T cells (soluble interleukin (IL)-2 receptor- α /CD25, T-cell HLA-DR isotype expression), macrophages (CD163, neopterin), inflammasomes (IL-18) and the interferon-gamma pathway (IFN γ , CXCL9). Their relative specificity (compared with other inflammatory parameters in table 5) is helpful in confirming an HLH/MAS diagnosis and in monitoring. The TF recommended assessment of specialised inflammatory biomarkers, interpreted

with the aid of consultants, when available (PTC 1.5). Longitudinal assessment of both routine and specialised HLH/MAS biomarkers improves their diagnostic utility and is essential for monitoring for progression or resolution (as discussed below).¹⁹

PTC 2.0: existing criteria

Several criteria have been developed to identify patients with syndromes that may represent HLH or MAS (table 1, online supplemental table 2). The HLH-94 criteria (refined in HLH-04) were developed to classify infants and children for treatment trials targeting paediatric patients with genetic causes of HLH/MAS.^{2 5} The MAS-2016 criteria were developed to classify MAS in patients with known or strongly suspected sJIA.⁶ The HScore was developed in adults with primarily malignancy or infection-associated HLH,⁷ and the MS score to distinguish MAS from underlying sJIA.⁸ The HScore and HLH-2004 criteria have been validated in some additional contexts.^{20–23} The TF agreed that each set of criteria were useful within the context in which they were developed, but that no existing set of criteria was a sufficient diagnostic tool in all settings and populations (PTC 2). There is substantial feature overlap between criteria (table 1, online supplemental table 2).

PTC 3.1: evaluating contributors

The TF emphasised the critical importance of timely identification of underlying contributors (genetic causes, predisposing conditions and acute triggers as described in 'Introduction' section), often in a rapidly evolving and ill patient (PTC 3.1).

Recommendation

Table 6 Proportion of attributable HLH/MAS cases by primary contributor*

| | Median %, (min, max) references | |
|--------------------------------|---|--|
| | Paediatric | Adult |
| Genetic causes | | |
| Genetic HLH disorders | 12% (3–46) ^{20 27 42 44–47 49 50 66 125} | Rare ²⁷ |
| Other inborn error of immunity | 6% (2–18) ^{27 49 66 125} | Rare ²⁷ |
| Predisposing conditions | | |
| Rheumatological | 10% (2–26) ^{20 27 42–44 46–48 50 66 125} | 8% (2–26) ^{7 20 25–36 41} |
| Malignancies | 5% (2–19) ^{20 27 42 43 46 50 66 125} | 46% (26–73) ^{7 20 25–36} |
| Acute triggers† | | |
| All-cause infections | 57% (9–88) ^{20 27 42 43 46 48–50 66 125} | 27% (9–75) ^{7 20 26–36 41} |
| Viral infections | 57% (18–80) | 14% (2–33) |
| Bacterial infections | 10% (3–58) | 14% (2–45) |
| Idiopathic | | |
| Unknown aetiology | 42% (17–49) ^{27 42 44 47 125} | 18% (4–40) ^{20 27 28 31–33 35 36} |

*Summary of individual cohort studies identified in the SLR that attempted to capture all cases of HLH/MAS over a study period and aimed to identify an underlying predisposing condition or acute trigger. Results were divided by age <18 or ≥18 years. Only series with ≥30 patients, and that attributed a single contributing aetiology per patient were included. Attributable cases are described as the median percentage and range for all cohort studies included. As such, columns sum to >100%. See SLR manuscript¹² for details. Rare: <1.5%.

†The SLR did not identify studies that quantified the proportion of HLH/MAS attributable to iatrogenic triggers (eg, chimeric antigen receptor T-cell cytokine release syndrome). HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; SLR, systematic literature review.

A thorough workup should begin immediately on suspicion for HLH/MAS and should be tailored to the most likely contributors, paying particular attention to the patient's age, family history, infectious exposures/risks, recent treatments and underlying conditions. Although HLH/MAS is thought to result from the interaction of multiple host and environmental contributors, available data typically implicate a single aetiology (as reflected in table 6 and more thoroughly in SLR manuscript).¹² Additionally, >2000 case reports and series demonstrate that HLH/MAS can occur in most settings that provoke an immune or inflammatory response.¹²

Genetic causes of HLH/MAS represent a minority of all cases (particularly in adults), but they have made essential contributions to diagnostic and treatment advances. The IEI include nearly 500 genetically defined disorders,²⁴ and for most of these HLH/MAS is a rare complication. The canonical high-penetrance genetic causes of HLH are those that profoundly impair granulocyte-mediated cytotoxicity as well as the X linked lymphoproliferative syndromes (table 7). The distinction between genetic causes and variants conferring susceptibility has grown less clear with time. Nevertheless, the identification of a genetic cause/contributor has profound implications (as discussed below).

Among predisposing conditions, malignancy (especially lymphoma) is a major contributor to HLH/MAS. Investigation for underlying malignancy should be considered in all patients with HLH/MAS, particularly in adults where it occurs in nearly half of cases.^{7 20 25–37} Although MAS is most recognised and best studied in sJIA and adult-onset still disease (AOSD), SLE may be a more common cause of HLH/MAS in adults in part due to its higher prevalence.^{38–40}

Infection is the most common acute trigger of HLH/MAS. In children, infection is the most common aetiology, with a specific pathogen identified in over 50% of new HLH/MAS presentations. Broad testing for infection (eg, blood and other cultures, viral PCR, etc) should be pursued based on clinical scenario. Some infections warrant special attention for their role in HLH/MAS. Epstein-Barr virus (EBV) is a well-known trigger of HLH, particularly in individuals with genetic (table 7) or acquired immunodeficiency or certain malignancies. It is unclear why the incidence of EBV-HLH appears higher in Asia, but this is

consistent with other EBV-triggered phenotypes.^{31–34 41–49} Region-specific and season-specific infections should also be considered as causes of HLH/MAS in endemic areas, including dengue virus in tropical/subtropical climates,^{46 50 51} histoplasmosis in the mid-western and southern USA,³¹ and less frequently malaria,^{51 52} tuberculosis,^{7 25 26 32 33 36 48} scrub typhus,^{33 47 50} typhoid fever,^{42 47 50 51} tickborne diseases^{42 43 53} and leishmaniasis.^{25 42 54} Although inflammation in patients with COVID-19, multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A) rarely rises to meet HLH or MAS criteria, the pandemic normalised the need to identify and treat (SARS-CoV2) infection-associated immunopathology. Testing for genetic contributors should be considered regardless of the type of infection, particularly in young children.

The increasing use of immune effector cell cancer therapies, including chimeric antigen receptor T cells, has elevated their recognition as iatrogenic triggers of HLH/MAS. The incidence of CRS and immune effector cell-associated neurological syndrome (ICANS) is highest in leukemias and lymphomas. The distinctions between CRS/ICANS and HLH are unclear and their ideal treatment is an evolving target beyond the scope of this effort.^{55–58}

For many patients, multiple contributors interact to drive HLH/MAS. Acute infections are identified in the majority of patients with HLH/MAS with predisposing rheumatological conditions (>65%) or IEIs (>80%).^{54 59–62} In adults, the presence of multiple pathogens at the time of HLH/MAS diagnosis may increase risk of mortality.⁶³ Thus, concern for HLH/MAS should prompt consideration of multiple potential contributors regardless of known underlying conditions or aetiologies.

PTC 3.2–3.5: genetic testing

Genetic causes for HLH/MAS are likely under-recognised and their identification profoundly affects treatment, prognosis and genetic counselling (PTC 3.2, table 7). For example, screening for CNS involvement is particularly important in genetic HLH.⁴⁷ Early recognition of familial haemophagocytic lymphohistiocytosis may accelerate allogeneic haematopoietic stem cell transplantation (HSCT) and can support HSCT in affected

Table 7 Genes associated with HLH/MAS susceptibility*

| Gene | Protein | Disease acronym | Frequency of HLH/MAS† | Clinical associations‡ | Specialised testing§ | OMIM |
|---|--------------|-----------------|-----------------------|--|----------------------|--------|
| Impaired lymphocyte granule-mediated cytotoxicity | | | | | | |
| <i>PRF1</i> | Perforin | FHL2 | High | Early onset, isolated CNS | FL, NK | 603553 |
| <i>UNC13D</i> | Munc13-4 | FHL3 | High | Isolated CNS involvement | NK, Degran | 608898 |
| <i>STX11</i> | Syntaxin11 | FHL4 | High | Variable age at onset, possible risk MDS/leukaemia | NK, Degran | 603552 |
| <i>STXBP2</i> | Munc 18 to 2 | FHL5 | High | IBD, SNHL, hypogammaglobulinaemia | NK, Degran | 613101 |
| <i>RAB27A</i> | Rab27a | GS2 | High | Albinism, infection | NK, Degran | 607624 |
| <i>LYST</i> | LYST | CHS | Moderate | Albinism, infection | NK, Degran | 214500 |
| <i>AP3B1</i> | AP3 | HPS2 | Moderate/Low | Albinism, infection, bleeding | NK, Degran | 608233 |
| <i>RHOG</i> | RhoG | – | Unknown | | NK, Degran | – |
| Impaired EBV control | | | | | | |
| <i>SH2D1A</i> | SAP | XLP1 | High | Lymphoma | FL | 308240 |
| <i>ITK</i> | ITK | LPFS1 | Moderate | Lymphoma | | 613011 |
| <i>CD27</i> | CD27 | LPFS2 | Moderate | Lymphoma | | 615122 |
| <i>CD70</i> | CD70 | LPFS3 | Moderate | Lymphoma | | 618261 |
| <i>MAGT1</i> | MAGT1 | XMEN | Moderate | Lymphoma | | 300853 |
| <i>CTPS1</i> | CTPS1 | – | Moderate | Lymphoma | | 615897 |
| <i>RASGRP1</i> | RASGRP1 | – | Moderate | Lymphoma | | 618534 |
| Impaired inflammasome regulation | | | | | | |
| <i>XIAP/BIRC4</i> | XIAP | XLP2 | Moderate | IBD | FL, IL-18 | 300635 |
| <i>NLRC4</i> | NLRC4 | AIFEC, MAS | Moderate | Early onset, IBD | IL-18 | 616050 |
| <i>CDC42¶</i> | CDC42 | NOCARH | High | Early onset, rash | IL-18 | – |
| Other immune dysregulation | | | | | | |
| <i>NCKAP1L</i> | HEM1 | – | Unknown | Infection, autoimmunity | | 618982 |
| <i>RC3H1</i> | ROQUIN | – | Unknown | | | 618998 |
| <i>HAVCR2</i> | TIM3 | – | Moderate | SPTCL | | 606652 |
| Dysregulated metabolism | | | | | | |
| <i>SLC7A7</i> | SLC7A7 | LPI | Moderate | Enteral protein intolerance | | 222700 |

*List is not comprehensive, consult with appropriate specialists for appropriate breadth of testing.

†In appropriate inheritance pattern. Genes with moderate/low HLH frequency have other phenotypes.

‡Beyond those common in HLH/MAS, see [table 1](#).

§FL=flow cytometry can assess protein abundance; NK=NK function should be abnormal even in remission; Degran=CD107a mobilisation should be abnormal; IL-18=chronically and highly elevated serum IL-18.

¶Only C-terminal CDC42 mutations have been associated with HLH/MAS.

AIFEC, autoinflammation with infantile enterocolitis; CHS, Chediak-Higashi syndrome; CNS, central nervous system; FHL, familial haemophagocytic lymphohistiocytosis; GS2, Griscelli syndrome type 2; HPS2, Hermansky-Pudlak syndrome type 2; IBD, inflammatory bowel disease; LPFS, lymphoproliferative syndrome; LPI, lysinuric protein intolerance; NOCARH, neonatal-onset pancytopenia, autoinflammation, rash and episodes of HLH; SNHL, sensory neural hearing loss; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; XLP, X linked lymphoproliferative syndrome; XMEN, X linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia.

presymptomatic siblings.^{64 65} Some HLH/MAS therapeutic trials include or exclude specific genetic causes (ClinicalTrials.gov identifiers NCT04641442, NCT03113760).

When to perform genetic testing, on whom, what test(s) to send and how to interpret detected variants are complex and evolving decisions (PTC 3.3). Features suggestive of a genetic cause include young age at presentation, positive family history, consanguinity and prominent CNS disease. HLH/MAS due to cytotoxicity defects tends to present in infancy and early childhood, whereas HLH/MAS in other IEI (particularly those with EBV immunodeficiency, [table 7](#)) present in a broader age range including older children.⁶⁶ Although genetic HLH has presented in adulthood, actionable results of genetic testing in adult HLH/MAS are rare.^{25 67 68} Other relevant clinical features/contexts like albinism, inflammatory bowel disease, isolated CNS involvement and EBV-immunodeficiency suggest specific genetic causes (PTC 3.3, [table 7](#)).

Given the high prevalence of genetic causes in children and the large clinical impact of a positive finding, the TF supported early genetic testing in children and high-risk adults, preferably using multigene panels or whole exome/genome sequencing (PTC

3.4). Single-gene sequencing remains appropriate with family history of a known genetic HLH disorder, characteristic clinical features (eg, albinism), positive protein or functional testing (eg, perforin flow cytometry) or in resource-limited settings. Genetic counselling is warranted for all patients undergoing genetic testing (PTC 3.5).

PTC 4.1–4.4: prognostic factors and CNS involvement

Prognosis in HLH/MAS is dependent on multiple factors, including the nature of the underlying contributors, degree of organ dysfunction and duration of active disease (PTC 4.1). HLH/MAS can be fatal in any context, but relative to other causes malignancy-associated HLH/MAS is associated with worse survival^{33 66 69 70} and HLH/MAS in rheumatic diseases has a more favourable prognosis.^{3 40 66 71–73} EBV is associated with poor prognosis when present in patients with genetic immunodeficiency or predisposing (rheumatic or malignant) conditions,^{42 47 69} but prognosis appears better in patients with EBV as the sole contributor.^{45 46} Specific patterns of organ injury also predict poor outcomes (PTC 4.1). Liver involvement is

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common and can progress to life-threatening liver failure.⁴⁷ Patients with multiorgan dysfunction often require treatment in an intensive care unit (ICU) setting, a strong predictor of poor outcome.^{50 53 74 75}

CNS involvement is sufficiently common, insidious and dangerous to warrant specific attention. It is associated with both mortality and long-term neurological sequelae in survivors regardless of underlying contributors.^{3 42 47 76–80} It should be suspected in all patients being evaluated for HLH/MAS (PTC 4.2). CNS manifestations of HLH/MAS can be broad (tables 1 and 5), and cerebrospinal fluid (CSF) and imaging findings usually demonstrate evidence of inflammation in affected patients.⁷⁶ Incidence of CNS involvement varies by age and aetiology,^{45 47 76} and children with HLH/MAS are at higher risk than adults, especially children with genetic causes.^{47 76 81 82} Some degree of CNS involvement is present in a sizeable percentage of children with EBV-HLH,⁸³ sJIA-MAS⁷¹ and adults with secondary HLH/MAS.^{80 84 85}

CNS involvement should be considered in all patients, and all should undergo a complete neurological examination. Patients presenting under 1 year of age, those otherwise suspected of having familial disease⁴⁷ and any patient with symptoms or signs concerning for CNS dysfunction (including an unreliable exam) should undergo assessment for CNS involvement (PTC 4.2).

Assessment for CNS involvement may include CSF evaluation (glucose, protein, cell counts and often cytological review) and contrast-enhanced brain MRI as well as other testing (electroencephalogram, MR angiography, spinal imaging) as clinically indicated (PTC 4.3). Full evaluation often must await stabilisation of cardiorespiratory function, coagulopathy or intracranial pressure. Providers should not delay empiric or context-specific treatments in order to complete the CNS workup (PTC 4.4).

PTC 5.1–5.5: treatment considerations

Treatment of patients with suspected HLH/MAS requires a dynamic risk-benefit assessment. Consideration of HLH/MAS-directed immunomodulation should occur simultaneously with diagnostic evaluations (PTC 5.1–3), treatment of contributing factors (PTC 5.4) and prevention of complications (PTC 5.4–5.5).^{49 77 86} Figure 1 is intended to depict how these PTC on early diagnosis, monitoring and management may function in practice, in relation to each other and relative to the goal of context-specific treatment. Age-appropriate supportive care should follow accepted guidelines, such as the Surviving Sepsis Campaign,^{87 88} and its provision, as well as the frequency of monitoring (as discussed below) may require intensive care. ICU admission was required in over a third of children with

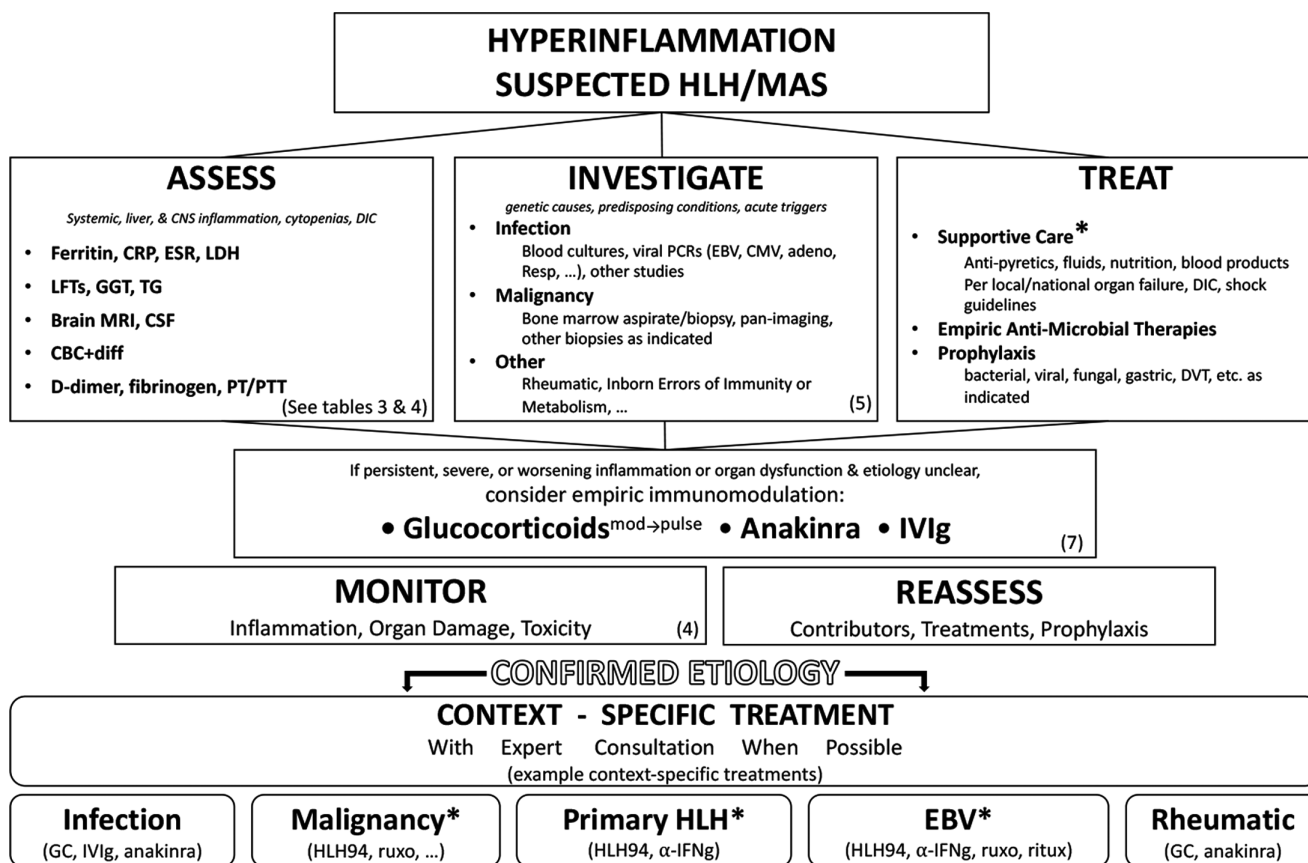


Figure 1 Summary of the approach to early or suspected HLH/MAS. When HLH/MAS is suspected, providers should (in parallel and as clinically appropriate) assess for the key features of HLH/MAS; investigate suspected contributors and treat with supportive care, with empiric and prophylactic antimicrobials, with other prophylaxis regimens, and possibly with empiric immunomodulation. Ongoing monitoring and reassessment should prompt re-evaluation of treatments being given. Patients should transition to context-specific treatment immediately on identification of a confirmed aetiology. *Addressed in separate guidance documents, see www.histiocytesociety.org/HLH-consensus. α -IFN γ , interferon-gamma neutralising antibody; CBC+diff, complete blood count with leucocyte differential; CMV, cytomegalovirus; CRP, C reactive protein; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulopathy; DVT, deep vein thrombosis; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; GGT, γ -glutamyl transferase; HLH94, HLH-94 treatment protocol 1 or current standard of care; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; LFTs, liver function tests; PT/PTT, prothrombin time/partial thromboplastin time; TG, triglycerides.

Table 8 Empiric HLH/MAS immunomodulatory treatment dosing*

| Paediatric | Adult |
|---|-------------------------|
| Glucocorticoids (GC)† | |
| a. Prednisone/Prednisolone per os or methylprednisolone intravenous 1–2 mg/kg/day | |
| b. Dexamethasone intravenous/per os 10 mg/m ² /day | |
| c. High-dose methylprednisolone intravenous 10–30 mg/kg/day (maximum 1 g/day) for 1–3 days, followed by a. or b. | |
| Intravenous immunoglobulin | |
| 1 g/kg/day×2 days | 0.4–1 g/kg/day×2–5 days |
| Anakinra‡ | |
| Intravenous (preferred) or subcutaneous 5–10 mg/kg/day | |
| Dosages derived from SLR ¹² unless otherwise noted. | |
| *This table reflects the summary of reported immunomodulatory pharmacotherapy in the literature and is not intended as a substitute for clinical judgement. | |
| †Dosing schedules and substitution with other GC and/or other (intravenous or oral) preparations can be based on preference, availability and patient need. | |
| ‡Daily dose often divided every 6–12 hours. | |
| HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; SLR, systematic literature review. | |

HLH/MAS and nearly half of adults with MAS.⁶¹ In children and adults requiring ICU admission for HLH/MAS, nearly 70% required mechanical ventilation or vasopressors/inotropes and nearly half required renal replacement therapy.^{32,50} Use of intensive care appears higher in HLH/MAS occurring in context with worse outcomes, like malignancy.^{34,71,89}

Choosing and adjusting empiric immunomodulation for suspected HLH/MAS can be challenging. Decision-making must integrate HLH/MAS severity and rate of progression, specific organ involvement, likely contributors, comorbid conditions and concurrent medications (figure 1). Ideally, targeted immunomodulation would be initiated as early as possible (PTC 5.1) and neither induce immunosuppression nor compromise the aetiological workup. In practice, determining the target and balancing these risks are essential, patient-specific challenges. Although no studies have evaluated empiric treatment of HLH/MAS prior to/regardless of aetiology, immunomodulatory treatment has dramatically improved survival in most aetiologies of HLH/MAS.^{12,49,90,91} In patients with high-risk features or progressive HLH/MAS, the TF strongly recommends considering empiric immunomodulation during the initial evaluation and management period (PTC 5.1–3). Once there is sufficient understanding of a patient's underlying contributors, management should shift to context-specific treatments and recent context-specific guidance documents may be helpful in this transition^{67,74,92–94} (figure 1, asterisks).

The TF currently endorses use of glucocorticoids (GCs), the recombinant IL-1 receptor antagonist (IL-1RA) anakinra and/or intravenous immunoglobulin (IVIg) for empiric immunomodulation in suspected HLH/MAS (PTC 5.3, figure 1, table 8). Multiple treatments may be initiated concurrently depending on clinical context and availability. Published treatment data demonstrate the strongest support for GCs across all forms of HLH/MAS.¹² The choice of GC formulation (most commonly prednisone, prednisolone, dexamethasone (DEX) or methylprednisolone (MP)) and route of administration (oral vs intravenous) should be tailored to the patient and care setting (table 8). 'Pulse' doses of intravenous MP (10–30 mg/kg/day up to 1 g, given daily) are effective in severe rheumatic and neuro-inflammatory diseases,^{95–97} and have been used successfully in HLH/MAS.⁶¹ DEX is used in HLH treatment protocols due to better CNS penetration at an initial dose of 10 mg/m²/day (~2–4 mg/kg/day

of MP). Given DEX's long half-life, shorter-acting GCs may be preferable in rapidly evolving diagnostic scenarios.

Importantly, GC administration may obscure pathological diagnosis and/or staging of leukaemia or lymphoma.⁹⁸ Therefore, definitive testing for malignancy (typically biopsy/aspirate of bone marrow, lymph node and/or other indicated tissues) should be attempted prior to GC administration when possible. GC-related immunosuppression depends on dose, duration of exposure and relevant pathogens. Although GC treatment (alongside appropriate antimicrobial treatment) prevents immunopathology in many localised infections,^{99,100} large studies have not supported its utility for immunomodulation in sepsis. Thus, the role of GC in infection-associated HLH/MAS remains patient-dependent and pathogen-dependent. Providers should monitor for other dose-dependent GC side effects like hyperglycaemia, hypertension, myopathy and psychosis.

Empiric use of anakinra and/or IVIg in early, evolving or undifferentiated HLH/MAS may provide immunomodulation without significant immunosuppression and without impairing malignancy workup. The TF supported their inclusion despite sparse data due to good pharmacological and safety profiles, strong efficacy in other systemic inflammatory diseases and significant clinical experience. Anakinra is a safe and effective treatment for many autoinflammatory and rheumatic disorders. Its rapid onset and short half-life may be desirable in rapidly evolving patients. Even used at high doses in adults with bacterial sepsis (up to 48 mg/kg/day), it showed no signal for immunosuppression and appeared to limit mortality in patients with sepsis with hepatobiliary dysfunction and coagulopathy.^{90,101} A retrospective study in secondary HLH supported the safety and possible efficacy of early anakinra use in controlling inflammation.¹⁰² IVIg has demonstrated efficacy in Kawasaki disease, and it neither obstructs cancer workup nor suppresses immune function. Notably, serological testing should be sent from samples taken prior to IVIg when feasible. Reports of its efficacy in HLH/MAS are restricted to case series. High-dose IVIg is also a substantial colloid load that can compromise cardiac function and worsen oedema. It rarely causes haemolysis or aseptic meningitis.

Clinical context is essential when considering escalation or context-specific treatment(s), and clinicians are encouraged to consult with local, regional or national experts on a case-specific basis. B-cell depletion may be useful in some patients with EBV-HLH.^{103,104} Early initiation of treatment regimens centred around the chemotherapeutic etoposide (guidelines in Ehl *et al*⁹²) have been life-saving for patients with primary HLH and severe EBV-HLH.^{49,77} Evidence for high-dose etoposide is less favourable for HLH/MAS in the context of sJIA/AOSD, although lower doses may be useful.¹⁰⁵ It is not indicated for most non-EBV infections.^{34,106–108} The utility of etoposide in malignancy-associated HLH is currently unclear.^{93,109}

For patients with increasing inflammation and/or worsening organ damage despite early immunomodulation, treatment escalation with higher doses of GC and/or alternative agents (table 9) should be considered in consultation with HLH/MAS experts. Increasing evidence supports the involvement of the IFN γ pathway in HLH/MAS. The IFN γ neutralising antibody, emapalumab, was recently approved in the USA for the treatment of refractory, recurrent, or progressive HLH.¹¹⁰ Ruxolitinib (and other JAK inhibitors) broadly targets cytokine signalling, including IFN γ , and has shown promising early results in HLH/MAS.^{111–113}

Alongside HLH/MAS-directed immunomodulation, treatment of contributing factors is critical for optimising outcomes (PTC

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Table 9 Other immunomodulatory therapies used in HLH/MAS*

| | Route | Dosing | | Adverse events† | Notes |
|--|-----------------------|--|--|---|------------------------------|
| | | Paediatrics | Adults | | |
| Etoposide (chemotherapy) | Per os Intravenous | 50–150 mg/m ² /dose 1–2 doses/week ^{45 49 61 77 105 108} | 50–150 mg/m ² /dose 1–2 doses/wk ^{31 105 108 126–129} | BM suppression , hepatotoxicity, hypotension (infusion-related), mucositis/alopecia, nausea/vomiting, secondary malignancy | Infectious screening and PPx |
| Ciclosporin† (calcineurin inhibition) | Per os Intravenous | 3–5 mg/kg/day Two times per day ^{45 49 61 77 130 131} | 2–7 mg/kg/day Twice daily ^{31 108 113 126–129} | Nephrotoxicity/HTN , hepatotoxicity, hirsutism, gingival hypertrophy, neurotoxicity | Monitor levels |
| Ruxolitinib (JAK inhibition) | Per os | 2.5–20 mg/dose ^{112 113 132} § or 25 mg/m ² /dose Two times per day | | Dyslipidaemia, cytopenias, hepatotoxicity, immunosuppression (herpes viruses) | Infectious screening and PPx |
| Emapalumab (IFN γ neutralisation) | Intravenous | Refractory HLH ¹¹⁰ : 1→10 mg/kg/dose sJIA-MAS¶: 6, then 3 mg/kg/dose every 3 days | | Immunosuppression (mycobacteria, herpes viruses, and <i>Histoplasma capsulatum</i>), HTN, infusion reactions | Infectious screening and PPx |
| Rituximab (B-cell depletion) | Intravenous | 375 mg/m ² /dose (maximum 1 g) Two times per day, separated by 2 weeks ^{103 104} | | Infusion reactions , HTN, hepatotoxicity, immunosuppression (hepatitis B), cytopenias, ↓IgG, mucocutaneous reaction, progressive multifocal leukoencephalopathy (rarely) | Specifically for EBV-HLH |

* Consultation with providers experienced in managing HLH/MAS is strongly advised prior to administration.

† List of common and important (bold) adverse events with short-term (up to 3 months) use based on (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>) and (<https://www.upToDate.com/contents/table-of-contents/drug-information/general-drug-information>).

‡ Primarily used in MAS. Can be substituted with tacrolimus (initial dose 0.1 mg/kg/day per os divided every 12 hours, targeting trough 8–20 ng/mL).

§ Weight-based dosing per indicated references. Body surface area dosing used in ongoing HLHRUXO trial NCT04551131.

¶ Dosing in ongoing sJIA-MAS trial NCT05001737.

BM, bone marrow; HLH, haemophagocytic lymphohistiocytosis; HTN, hypertension; IFN γ , interferon gamma; MAS, macrophage activation syndrome; PPx, prophylaxis; sJIA, systemic juvenile idiopathic arthritis.

5.4). This will often include empiric antimicrobial and sometimes antiviral agents, accounting for exposures/geography, comorbidities (eg, renal failure) and chronic immunosuppression. Like other aspects of HLH/MAS treatment, infectious prophylaxis should be considered early and revisited as the patient and workup evolve (PTC 5.5). Secondary infections can complicate both the inpatient and outpatient course of HLH/MAS. Antifungal and *Pneumocystis jirovecii* pneumonia prophylaxis are recommended, and are part of the HLH-94 protocol.⁵ Antifungal and antiviral prophylaxis were administered in more recent trials with newer agents like emapalumab.¹¹⁰ In addition to assistance with empiric treatment, consultation with immunocompromised infectious disease specialists may aid prophylaxis planning (PTC 5.5).

PTC 6.1–6.3: monitoring

Monitoring for disease progression, new organ involvement and damage and response to treatment begins on suspicion for HLH/MAS. Monitoring plans should be tailored to severity, organ involvement and likely contributors of HLH/MAS. Many of the biomarkers useful for diagnosing HLH/MAS also have prognostic relevance (table 5, online supplemental table 1, PTC 6.1). For example, both higher initial ferritin levels and failure of ferritin to improve during therapy associate with worse outcomes.^{71 114–118}

No comparative studies evaluate the ideal laboratory monitoring protocol. Given the propensity for rapid clinical changes, initial monitoring may include daily assessment of inflammatory biomarkers (eg, CRP, ferritin), indicators of organ damage (eg, CBC, fibrinogen, ALT) and any drug-specific monitoring. More frequent monitoring may be needed for evolving or critically ill patients and may require ICU care⁷⁴ (PTC 6.2, table 5). Lack of response to initial therapy should prompt a careful re-examination of both underlying diagnoses and therapeutic approach. When available, more specific HLH/MAS biomarkers like

sIL-2Ra, IL-18 and CXCL9 should be monitored less frequently than conventional disease activity measures like ferritin and CRP (PTC 6.5, table 4). CXCL9 may be particularly useful for monitoring response to IFN γ -blocking therapies.¹¹⁰ Specialised tests may also be helpful in distinguishing HLH/MAS relapse from acquired infection or drug reaction. Treatment response and dose-escalation criteria used in HLH/MAS trials also reflect the overlap between diagnostic and monitoring tests.¹²

PTC 7.0: multidisciplinary teams

Mounting evidence suggests that a multidisciplinary team experienced in managing HLH/MAS may improve recognition, reduce immunosuppression and improve outcomes (PTC

Box 1 Identified haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) research priorities

1. Unify nomenclature and validate criteria for diagnosis of HLH/MAS across specialties.
2. Better characterise epidemiology, contributors, management practices and outcomes in resource-limited settings.
3. Institute/Expand multicentre prospective HLH/MAS registries and biobanks.
4. Study the effect of real-time results of specialised biomarkers.
5. Study the utility of early and broad exome/genome wide testing.
6. Study the utility of multidisciplinary HLH/MAS response teams.
7. Expand and improve prospective trials in HLH/MAS:
 - a. Timing of immunomodulation undifferentiated disease;
 - b. Active comparator groups (eg, adaptive designs);
 - c. Novel early treatments.

7.0).^{119 120} Such response teams often include representatives from infectious diseases, haematology/oncology, rheumatology, immunology, pharmacy and other relevant specialties, although their optimal composition and function has not been established. Their goals include improving early identification, streamlining communication and improving consistency of care. These groups may also be able to better incorporate new findings, conduct quality improvement and engage in collaborative research.

DISCUSSION

HLH/MAS is a life-threatening immunopathological state requiring a systematic evaluation of aetiological factors and prompt intervention. It occurs in many contexts, can present to various providers and its contributors are often unclear. Thus, the TF has targeted these PTC at a broad audience to aid in recognising the clinical and laboratory features of HLH/MAS, investigating underlying contributors, initiating appropriate (empiric, targeted, and prophylactic) treatments and monitoring for response, progression and complications.

While generating the PTCs for the earliest stages of HLH/MAS, the multispecialty TF was also charged with identifying areas of substantial unmet need (box 1). Among these, TF members identified a need to standardise and harmonise the terminology used to describe and categorise patients with HLH/MAS. This nomenclature should be based on both clinical manifestations and underlying contributor(s), account for diagnostic uncertainty, apply across a range of sites and specialties and associate with validated criteria. Given the breadth of providers this change would affect, it may require a distinct, objective and international collaboration.

There is also an urgent need to expand access to, and clarify the role of routine and specialised testing for patients with suspected HLH/MAS. The TF has highlighted the importance of trending ferritin levels in recognising, diagnosing and monitoring HLH/MAS, but results are not quickly available in many locations. Specialised biomarkers (eg, sIL-2R α , IL-18, CXCL9) may be more specific for HLH/MAS, but results often do not return quickly enough to be useful in early decision-making. These tests are often unavailable outside of academic centres. Studies are needed that systematically evaluate the impact of real-time biomarker assessments on treatment decisions and patient outcomes, and that determine optimal diagnostic cut-offs.

The TF also highlighted a need to better study how rapid genetic diagnostics affects treatment stratification and outcomes for (particularly paediatric) patients presenting with HLH/MAS. Mounting data demonstrate that rapid whole-genome sequencing in high-risk populations (eg, hospitalised infants) may shorten time to diagnosis, both improving care and decreasing overall medical costs.¹²¹ Despite dramatic improvements in sequencing cost and speed, identification of actionable genetic contributors to HLH/MAS is often delayed by availability and/or restrictive payer policies. The results of these studies may encourage hospital systems and payers to support improved access and rapid results. Given the large (and rising) number of identifiable genetic variants with important management consequences, the TF encouraged broad genetic testing particularly in paediatric patients with HLH/MAS.

Therapeutically, the TF identified the need for expanded clinical research to better understand the effectiveness of existing therapies, and the need for long-term investments in basic/translational research to identify novel, targetable pathways. These studies are needed both in specific contexts as well as in HLH/MAS broadly. Specifically, studies are needed that address

the efficacy of early immunomodulation (analogous to time-to-antibiotics in sepsis) and protocolised assessment of CNS involvement. Trials of treatment efficacy are needed that use active comparators and more proximate outcomes than survival (eg, steroid exposure, length of stay, durable functional impairment and quality of life). To this end, ongoing clinical trials to test the safety and effectiveness of agents such as ruxolitinib (NCT04551131), alemtuzumab (NCT02472054), tadekinig alfa (NCT03113760), emapalumab (NCT05001737) and MAS825 (NCT04641442) in a variety of HLH/MAS settings are of vital interest.

To meet these testing and therapeutic challenges, there is also a need to improve multicentre, prospective HLH/MAS registries and biobanks. HLH/MAS overall is not particularly rare, and our SLR identified and screened over 12 000 published articles, but very few of these were prospective or controlled.¹² Studies in resource-limited countries/environments were particularly lacking. As our community builds research infrastructure and advocates for expanded access, improved turn-around times and targeted therapeutics, it must prioritise inclusion of resource-limited settings and implementation in underserved areas.

The HLH/MAS paradigm has evolved rapidly in response to genetic, biomarker, clinical and therapeutic insights. These insights reflect the diversity and intersection of contributors and suggest convergence on a shared HLH/MAS physiology and phenotype. These insights have also led to more diagnostic and therapeutic options while highlighting the wide spectrum of primary care and subspecialty providers who care for patients with early features of HLH/MAS. With these advances, the challenge of identifying and managing at-risk patients and patients with early HLH/MAS has grown. These PTC aim to translate these insights into practical guidance that will hasten recognition, streamline diagnosis and improve early management as the essential tasks needed to limit immunopathology, mitigate organ dysfunction and achieve the best outcomes for patients with HLH/MAS.

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