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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Handling editor Mary K Crow

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This article is published simultaneously in Arthritis & Rheumatology.

Received 6 March 2023
Accepted 27 April 2023
Published Online First 24 July 2023

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ABSTRACT

Objective Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are life-threatening systemic hyperinflammatory syndromes that can develop in many 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, haematologists/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).
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 HLH2 (4) or MAS.7 Subsequent diagnostic tools like the HScore7 and MS 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 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 (PCT) 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 pediatric 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 all the words used to identify 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. Although collectively HLH/MAS is not rare, these guidance statements are termed points to consider (PCT) 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.

### Recommendation

#### Table 1 Recognisable clinical features/patterns in HLH/MAS

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

‘†’ signifies not included in any of these criteria.
*HLH04,4 MAS16,67 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.

#### Table 2 Preceding HLH/MAS consensus publications

| Genetic HLH | Ehl, et al60 |
| Malignancy-associated HLH | Lehmburg et al74 (paediatric) |
| HLH diagnosis | Jordan et al82 |
| MAS diagnosis | Ravelli et al59 |
| HLH in adults | La Rosée et al87 |
| HLH in intensive care | Hines et al91 |


HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.
HLH/MAS as described in the SLR manuscript 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. 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 18020 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 results and discussion at consensus conferences, the TF generated 6 overarching principles (table 3) and 24 diseasespecific 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

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**Table 3 Overarching principles**

<table>
<thead>
<tr>
<th>LoE/GoR</th>
<th>LoA (0–10)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>SD</td>
<td>9.4±1.2</td>
</tr>
<tr>
<td>B Systemic hyperinflammation can be associated with hyperferritinemia and can progress to life-threatening HLH/MAS.</td>
<td>SD</td>
<td>9.6±0.7</td>
</tr>
<tr>
<td>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.</td>
<td>2B</td>
<td>9.1±1.3</td>
</tr>
<tr>
<td>D Investigating and treating modifiable contributors to systemic hyperinflammation and HLH/MAS are essential in the management of every patient.</td>
<td>4C</td>
<td>9.7±0.6</td>
</tr>
<tr>
<td>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.</td>
<td>SD</td>
<td>9.7±0.7</td>
</tr>
<tr>
<td>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.</td>
<td>SD</td>
<td>9.2±1.8</td>
</tr>
</tbody>
</table>

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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. |
5.1 For patients with probable HLH/MAS and persistent, severe or worsening inflammation or organ dysfunction, initiation of immunomodulatory treatment should be considered.

5.2 Choice of initial immunomodulatory treatment is complex and requires balancing an assessment of urgent risk due to rapid HLH/MAS progression and potential for obscuring diagnosis of malignancy or worsening active infection.

5.3 Initial empirical immunomodulatory therapy in patients with rapidly progressive HLH/MAS could include high-dose glucocorticoids, anakinra and/or IVIg based on local access.

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.

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.

5.6 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.

5.7 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.

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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.

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.*

7.0 A multidisciplinary approach is preferred and can optimise the diagnostic workup and management of patients with systemic hyperinflammation and HLH/MAS.
patients with HLH/MAS with systemic disease have elevated ferritin levels\(^1\), 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)\(^12\), 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 3). However, many HLH/MAS-associated biomarkers may also indicate parallel inflammatory processes (eg, elevated LDH in thrombotic microangiopathy).\(^15\) More specialised biomarkers measuring key HLH/MAS pathways (PTC 1.5, table 3, 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\(\gamma\)/ 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 was validated in some additional contexts.\(^20\) 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).

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**Table 5 Laboratory and biomarker testing in HLH/MAS**

<table>
<thead>
<tr>
<th>Test</th>
<th>In HLH/MAS Biology</th>
<th>Criteria</th>
<th>Monitoring frequency</th>
<th>Prognostic utility*</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count</td>
<td>↓</td>
<td>Affected by marrow production, proliferation, tissue sequestration, consumption</td>
<td>2, 3</td>
<td>F</td>
<td>31 311 116</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>↓</td>
<td></td>
<td></td>
<td>F</td>
<td>116</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>↓</td>
<td></td>
<td></td>
<td>F</td>
<td>114</td>
</tr>
<tr>
<td>Platelet count</td>
<td>↓</td>
<td></td>
<td></td>
<td>F</td>
<td>35 42 47</td>
</tr>
</tbody>
</table>

**Inflammatory biomarkers**

- CRP: ↑ | | | | | |
- Ferritin: ↑ | | | | | |
- ESR: ↑↓ | | | | | |
- LDH: ↑ | | | | | |
- IL-2Rα: ↑ | | | | | |
- CXCL9: ↑ | | | | | |
- IL-18: ↑ | | | | | |

**Liver function tests**

- ALT, AST, bilirubin: ↑ | | | | | |
- Triglycerides: ↑ | | | | | |
- Albumin: ↓ | | | | | |
- Vascular leak/third-spacing: F | | | | | |

**Coagulopathy tests**

- Fibrinogen: ↓ | | | | | |
- D-dimer: ↑ | | | | | |
- PT/INR/PTT: ↑ | | | | | |

**CNS tests**

- Brain imaging: Abnormal | | | | | |
- Pneumocystis jirovecii pneumonia (PCP): pm | | | | | |
- Cerebrospinal fluid (CSF): pm | | | | | |

1=HLH-04, 2=MAS-2016, 3=HScore.\(^7\)

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

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 3). However, many HLH/MAS-associated biomarkers may also indicate parallel inflammatory processes (eg, elevated LDH in thrombotic microangiopathy).\(^15\) More specialised biomarkers measuring key HLH/MAS pathways (PTC 1.5, table 3, 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\(\gamma\)/ 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).\(^19\)
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). Additionally, >2000 case reports and series demonstrate that HLH/MAS can occur in most settings that provoke an immune or inflammatory response.

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, and for most of these HLH/MAS is a rare complication. The canonical high-penetrance genetic causes of HLH are those that profoundly impair granule-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. Although MAS is most recognised and best studied in sJIA and adult-onset still disease (AOSD), SLE may be considered as iatrogenic triggers (eg, chimeric antigen receptor T-cell cytokine release syndrome). HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; SLR, systematic literature review.

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

<table>
<thead>
<tr>
<th>Primary contributor</th>
<th>Paediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic HLH disorders</td>
<td>12% (3–46)</td>
<td>Rare</td>
</tr>
<tr>
<td>Other inborn error of immunity</td>
<td>6% (2–18)</td>
<td>Rare</td>
</tr>
<tr>
<td>Predisposing conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>10% (2–26)</td>
<td>8% (2–26)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>5% (2–19)</td>
<td>46% (26–73)</td>
</tr>
<tr>
<td>Acute triggers†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause infections</td>
<td>57% (9–48)</td>
<td>27% (9–75)</td>
</tr>
<tr>
<td>Viral infections</td>
<td>57% (18–80)</td>
<td>14% (2–33)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>10% (3–58)</td>
<td>14% (4–45)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown aetiology</td>
<td>42% (17–49)</td>
<td>18% (4–60)</td>
</tr>
</tbody>
</table>

*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 manuscript 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.

Consistent with other EBV-triggered phenotypes, 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, histoplasmosis in the mid-western and southern USA, and less frequently malaria, tuberculosis, scrub typhus, typhoid fever, tickborne diseases, and leishmaniasis. Although infection 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 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.

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%). In adults, the presence of multiple pathogens at the time of HLH/MAS diagnosis may increase risk of mortality. 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. Early recognition of familial haemophagocytic lymphohistiocytosis may accelerate allogeneic haematopoietic stem cell transplantation (HSCT) and can support HSCT in affected cases.
presymptomatic siblings. 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 3.5). 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. Although genetic HLH has presented with EBV immunodeficiency, table 7 in present a broader age range including older children. 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, perform 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 and HLH/MAS in rheumatic diseases has a more favourable prognosis. EBV is associated with poor prognosis when present in patients with genetic immunodeficiency or predisposing (rheumatic or malignant) conditions, but prognosis appears better in patients with EBV as the sole contributor. Speciﬁc patterns of organ injury also predict poor outcomes (PTC 4.1). Liver involvement is

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Genes associated with HLH/MAS susceptibility*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>Protein</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>PRF1</td>
<td>Perforin</td>
</tr>
<tr>
<td>UNC13D</td>
<td>Munc13-4</td>
</tr>
<tr>
<td>STX11</td>
<td>Syntaxin1</td>
</tr>
<tr>
<td>STXB2</td>
<td>Munc 18 to 2</td>
</tr>
<tr>
<td>RAB27A</td>
<td>Rab27a</td>
</tr>
<tr>
<td>LYST</td>
<td>LYST</td>
</tr>
<tr>
<td>APOB1</td>
<td>APOB1</td>
</tr>
<tr>
<td>RHOG</td>
<td>RHOG</td>
</tr>
<tr>
<td>Impaired EBV control</td>
<td></td>
</tr>
<tr>
<td>SN201A</td>
<td>SAP</td>
</tr>
<tr>
<td>ITK</td>
<td>ITK</td>
</tr>
<tr>
<td>CD27</td>
<td>CD27</td>
</tr>
<tr>
<td>CD70</td>
<td>CD70</td>
</tr>
<tr>
<td>MAGT1</td>
<td>MAGT1</td>
</tr>
<tr>
<td>CTPS1</td>
<td>CTPS1</td>
</tr>
<tr>
<td>RASGRP1</td>
<td>RASGRP1</td>
</tr>
<tr>
<td>Impaired inflammasome regulation</td>
<td></td>
</tr>
<tr>
<td>XIAP/BIRC4</td>
<td>XIAP</td>
</tr>
<tr>
<td>NLRC4</td>
<td>NLRC4</td>
</tr>
<tr>
<td>CDC42</td>
<td>CDC42</td>
</tr>
<tr>
<td>Other immune dysregulation</td>
<td></td>
</tr>
<tr>
<td>NCKAP1L</td>
<td>HEM1</td>
</tr>
<tr>
<td>RC3H1</td>
<td>ROQUIN</td>
</tr>
<tr>
<td>HAVCR2</td>
<td>TIM3</td>
</tr>
<tr>
<td>Dysregulated metabolism</td>
<td></td>
</tr>
<tr>
<td>SLCTA7</td>
<td>SLCTA7</td>
</tr>
</tbody>
</table>

*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.
§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; HP2, Hermansky-Pudliak syndrome type 2; IBD, inflammatory bowel disease; LPPS, lymphoproliferative syndrome; LPI, lymosin protein intolerance; NOCARH, neonatal-onset pancytopenia, autoinflammation, rash and episodes of HLH; SNHL, sensory neural hearing loss; SPTCL, subcutaneous paninculitis-like T-cell lymphoma; XLP, X linked lymphoproliferative syndrome; XMEN, X linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia.
Recommendation

common and can progress to life-threatening liver failure.\textsuperscript{47} Patients with multiorgan dysfunction often require treatment in an intensive care unit (ICU) setting, a strong predictor of poor outcome.\textsuperscript{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.\textsuperscript{4 \textasciitilde}2\textsuperscript{4} 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.\textsuperscript{46 47 76} Incidence of CNS involvement varies by age and etiology,\textsuperscript{46 47 76} and children with HLH/MAS are at higher risk than adults, especially children with genetic causes.\textsuperscript{47 76 81 82} Some degree of CNS involvement is present in a sizeable percentage of children with EBV-HLH,\textsuperscript{83} sJIA-MAS\textsuperscript{71} and adults with secondary HLH/MAS.\textsuperscript{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 disease\textsuperscript{47} 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).\textsuperscript{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,\textsuperscript{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\textsubscript{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; IVlg, intravenous immunoglobulin; LDH, lactate dehydrogenase; LFTs, liver function tests; PT/PTT, prothrombin time/partial thromboplastin time; TG, triglycerides.
HLH/MAS and nearly half of adults with MAS. 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. Use of intensive care appears higher in HLH/MAS occurring in context with worse outcomes, like malignancy.

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.

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 (figure 1, table 8).

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. The choice of GC formulation (most commonly prednisone/prednisolone intravenous) 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, 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. A retrospective study in secondary HLH supported the safety and possible efficacy of early anakinra use in controlling inflammation. 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. Early initiation of treatment regimens centred around the chemotherapeutic etoposide (guidelines in EhI et al) have been life-saving for patients with primary HLH and severe EBV-HLH. Evidence for high-dose etoposide is less favourable for HLH/MAS in the context of sJIA/AOSD, though lower doses may be useful. It is not indicated for most non-EBV infections. The utility of etoposide in malignancy-associated HLH is currently unclear.

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 IFNγ pathway in HLH/MAS. The IFNγ neutralising antibody, emapalumab, was recently approved in the USA for the treatment of refractory, recurrent, or progressive HLH. Ruxolitinib (and other JAK inhibitors) broadly targets cytokine signalling, including IFNγ, and has shown promising early results in HLH/MAS.

Alongside HLH/MAS-directed immunomodulation, treatment of contributing factors is critical for optimising outcomes (PTC 5.3–5.12).
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. Antifungal and antiviral prophylaxis were administered in more recent trials with newer agents like emapalumab. Antifungal and antiviral prophylaxis were administered in more recent trials with newer agents like emapalumab.

### Table 9  
Other immunomodulatory therapies used in HLH/MAS*

<table>
<thead>
<tr>
<th>Therapeutic Modality</th>
<th>Route</th>
<th>Dosing</th>
<th>Adverse events†</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide (chemotherapy)</td>
<td>Per os Intravenous</td>
<td>50–150 mg/m²/dose 1–2 doses/wk</td>
<td>BM suppression, hepatotoxicity, hypotension (infusion-related), mucositis/alopoeia, nausea/vomiting, secondary malignancy</td>
<td>Infectious screening and PPx</td>
</tr>
<tr>
<td>Ciclosporin (calcineurin inhibition)</td>
<td>Per os Intravenous</td>
<td>3–5 mg/kg/day Two times per day</td>
<td>Nephrotoxicity/HTN, hepatotoxicity, hirsutism, gingival hypertrophy, neurotoxicity</td>
<td>Monitor levels</td>
</tr>
<tr>
<td>Ruxolitinib (JAK inhibition)</td>
<td>Per os</td>
<td>2.5–20 mg/dose 100, 127, 127 §</td>
<td>Dyslipidaemia, cytopenias, hepatotoxicity, immunosuppression (herpes viruses)</td>
<td>Infectious screening and PPx</td>
</tr>
<tr>
<td>Emapalumab (IFNγ neutralisation)</td>
<td>Intravenous</td>
<td>Refractory HLH110, 1–10 mg/kg/dose sJIA-MAS¶, 6, then 3 mg/kg/dose every 3 days</td>
<td>Immunosuppression (mycobacteria, herpes viruses, and <em>Histoplasma capsulatum</em>), HTN, infusion reactions</td>
<td>Infectious screening and PPx</td>
</tr>
<tr>
<td>Rituximab (B-cell depletion)</td>
<td>Intravenous</td>
<td>375 mg/m²/dose (maximum 1 g) Two times per day, separated by 2 weeks</td>
<td>Infusion reactions, HTN, hepatotoxicity, immunosuppression (hepatitis B), cytopenias, ↓IgG, mucocutaneous reaction, progressive multifocal leukoencephalopathy (rarely)</td>
<td>Specifically for EBV-HL</td>
</tr>
</tbody>
</table>

*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).
‡Dosing in ongoing sJIA-MAS trial NCT05001737.
§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; IFNγ, interferon gamma; MAS, macrophage activation syndrome; PPx, prophylaxis; sJIA, systemic juvenile idiopathic arthritis.

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.

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 care. 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 IFNγ-blocking therapies. 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.

### 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
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 multisubspecialty 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-2Ra, 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. 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 MAS823 (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. 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.
Recommendation

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Acknowledgements The task force is grateful to the librarian Darren Hamilton (London Health Sciences Center, London, Ontario, Canada) for his contribution to the systematic literature search, Brian Feldman and Joan Moore for their support in conducting the Delphi process and EULAR and the ACR for financial and logistical support. This project is part of a series of “points to consider” consensus efforts (overseen by EdE and RG-M) to standardise the diagnosis and care of patients within major groups of known autoinflammatory diseases including (1) the IL-1 mediated diseases CAPS, TRAPS, MKD and DIRA; (2) the autoinflammatory interferonopathies chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), STING-associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutières syndrome and (3) the early diagnosis and management of inflammatory conditions with the potential progression to HLH/MA5. This research was supported in part by the intramural research programme of the National Institute for Allergy and Infectious Diseases. We are grateful for the invaluable financial and organisational support from the Autoinflammatory Alliance and the Systemic JIA Foundation, who substantially contributed to an international meeting and workshop organisation in August 2019 that developed the outline of the points to consider project. The funds for that meeting came largely from patient fundraisers, online fundraising and the work of countless volunteers who made this project possible.


Contributors To the conception or design of the work: BS, AR, DA, RS, ED, RG-M, FBD, RAM, SWC. Acquisition, analysis or interpretation of data for the work: all authors. Drafting the work or revising it critically for important intellectual content: all authors. Final approval of the version to be published: all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Funding This work was funded by European Alliance of Associations for Rheumatology/American College of Rheumatology (CLII120). KK was supported by K12HD047349. SWC was supported by R01HD098428.

Competing interests CA participated in a DSMB for Sobi and OPNA. HB received consulting fees from FirstThought, Guidpoint and Kyria Therapeutics. EMB received research support from ABBCBio and consulting fees from Sobi and Genzyme. SWC received research support from Novartis and ABBCBio, has performed consulting for Simcha and Apollo therapeutics and received travel support from Sobi. RQG has received research support from Sobi, consulting fees from Sironax, speakers’ bureau payments from Sobi and Lilly, participated on the DSMB for Sobi, Pfizer and AbbVie. RG-M has received research support from IFM, Lilly, Sobi and Regeneron, and participates on a DSMB for AstraZeneca. AG has received research support from Sobi, Novartis and Newcombe, royalties from UpToDate, consulting fees from Ethos, payments from Novartis for educational materials. LAH has received research support from BMS and Sobi, consulting fees from Sobi, Pfizer and Adaptive Biotechnologies. MH has received research support from Incyte. AH has received honoraria from Sobi and Novartis. RAM has received honoraria for PracticePoint Communications, and participates on the DSMB for Horizon. KEN has received research support from Incyte and owns stock in Incyte. AR has received honoraria from AbbVie, Alexion, Novartis, Pfizer, Reckitt, Bendixen and Sobi. GS has received consulting fees from Sobi and Novartis. SV has received research support from Sobi, consulting fees from Sobi and Novartis.

Patient consent for publication Not applicable.

Ethics approval This study was reviewed and approved by all task force members and the EULAR and ACR Executive Committees prior to submission.

Provenance and peer review Not commissioned; externally peer reviewed.

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AQP4-methylprednisolone improves visual outcomes after optic neuritis in patients with critical prognostic factor for hemophagocytic lymphohistiocytosis.


Recommendation


