Diagnosis and investigation of suspected haemophagocytic lymphohistiocytosis in adults: 2023 Hyperinflammation and HLH Across Speciality Collaboration (HiHASC) consensus guideline

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Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterised by persistently activated cytotoxic lymphocytes and macrophages, which, if untreated, leads to multiorgan dysfunction and death. HLH should be considered in any acutely unwell patient not responding to treatment as expected, with prompt assessment to look for what we term the three Fs—fever, falling blood counts, and raised ferritin. Worldwide, awareness of HLH and access to expert management remain inequitable. Terminology is not standardised, classification criteria are validated in specific patient groups only, and some guidelines rely on specialised and somewhat inaccessible tests. The consensus guideline described in this Health Policy was produced by a self-nominated working group from the UK network Hyperinflammation and HLH Across Speciality Collaboration (HiHASC), a multidisciplinary group of clinicians experienced in managing people with HLH. Combining literature review and experience gained from looking after patients with HLH, it provides a practical, structured approach for all health-care teams managing adult (>16 years) patients with possible HLH. The focus is on early recognition and diagnosis of HLH and parallel identification of the underlying cause. To ensure wide applicability, the use of inexpensive, readily available tests is prioritised, but the role of specialist investigations and their interpretation is also addressed.

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterised by persistently activated cytotoxic T cells and natural killer (NK) cells, which drives activation of macrophages and histiocytes, resulting in excessive proinflammatory cytokine production. Multisystem manifestations of this process are non-specific and include fever, cytopenias, coagulopathy, rashes, and organ dysfunction.[1] Mortality is high, with recent data suggesting an overall 1-year survival of 56%.[2] This mortality rate can, in part, be attributed to a lack of awareness of the disease and delays in diagnosis, resulting in missed opportunities to initiate treatment.[3–5]

This Health Policy provides a broad overview of HLH and a systematic approach to the diagnosis and relevant investigations that can be implemented in everyday clinical practice. This information is intended for all clinicians involved in the management of acutely unwell adults.

HLH can be a primary or secondary process. Primary HLH results from mutations in genes affecting lymphocyte cytotoxicity, often via the function of T cells and NK cells or immune regulation,[6] and occurs principally in children, although it is increasingly recognised in adults. Conversely, secondary HLH is more frequent in adults.[7] Causes of secondary HLH include infections, malignancy, autoimmune and autoinflammatory disorders, some therapeutic interventions, and pregnancy.[7]

At presentation, the HLH driver or trigger is often unclear, mandating a uniform approach to initial assessment and investigation. Historically, hyperinflammation associated with rheumatological disorders has been termed macrophage activation syndrome. Using different terms risks missing shared thinking and learning, whereas a multispecialty, collaborative approach to HLH has been shown to improve outcomes.[8–10] For the purposes of this Health Policy, primary and secondary HLH and macrophage activation syndrome are referred to as HLH.

1-year survival in HLH varies significantly depending on the particular driver. Recent UK data show 1-year survival of 74% in a rheumatological cohort, compared with 21% in patients with a haematological malignancy.[2] Similar data have been reported using other methods from cohorts in Germany and France.[3,11] There is evidence that HLH incidence is increasing; this increase might relate to improved recognition or the increasing use of new therapies, such as chimeric antigen receptor (CAR) T-cell therapy, which can be complicated by HLH.[2] Recognition of the association between COVID-19, hyperinflammation, and cytokine storm has also contributed to raised awareness.[12]

This guideline facilitates prompt recognition of HLH using the three Fs mnemonic: fever, falling blood counts, and raised ferritin. Subsequent investigations to confirm the diagnosis of HLH and identify the probable driver or trigger are explained, as well as the role of specialist tests and their interpretation. We highlight the importance of a

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multidisciplinary approach to HLH and advise when to contact specialist teams. Finally, some areas of unmet clinical need are given particular focus, including central nervous system (CNS) and cardiac manifestations of HLH, primary HLH in adults, HLH driven by intravascular lymphoma, and HLH complicating CAR T-cell therapy.

Improving awareness of HLH and providing a practical, real-world approach to its diagnosis and investigation are key to improving outcomes, driving service development, and reducing inequity of access to treatment.

Consensus guideline preparation

On June 22, 2018, 12 clinicians from across the UK took part in the inaugural meeting of the Hyperinflammation and HLH Across Speciality Collaboration (HiHASC). The agreed purpose of the group was to reduce death from HLH by working collaboratively to break down barriers between different specialities, share clinical experience, and raise awareness of the syndrome. Since then, the group has grown and now has over 200 members who meet bimonthly, with specialists from rheumatology, haematology, infection, neurology, acute medicine, and critical care. The HiHASC website is hosted by the charity HistioUK.

For more on **HiHASC** see https://www.hihasc.org

To produce this guideline, a self-nominated working group of 21 HiHASC members met regularly between June, 2019, and May, 2022, both face to face and online, convened by the HiHASC cochairs JJM and RST. There was wide speciality representation, including paediatric and adolescent specialists and trainee physicians, with the group comprising five adult haematologists, an adolescent and adult haematologist, an infectious disease specialist, a virologist, a neurologist, seven adult rheumatologists, an adolescent and adult rheumatologist, two paediatric rheumatologists, and two intensive care specialists. The aims of the working group were to agree recommendations to facilitate the early identification of HLH in specialist and non-specialist settings and establish the appropriate investigations to identify the HLH driver. The initial scope was defined following review of relevant literature and through discussion of shared experience and barriers to care. The group did not follow a formal guideline or Delphi approach.

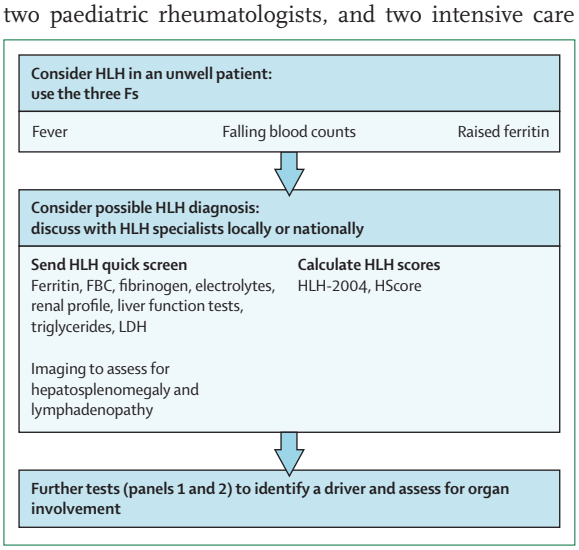

Figure 1: **Approach to a patient with possible HLH**
Externally cooled patients (eg, on renal replacement or extracorporeal membrane oxygenation circuits) could have falsely normal temperature readings. HLH=haemophagocytic lymphohistiocytosis. FBC=full blood count. LDH=lactate dehydrogenase. HScore=HLH-probability calculator.

Once the scope and aim of the guideline were agreed, contributors researched and provided sections for a first draft. The group debated the literature and clinical experience, and the draft was revised through multiple iterations. The guideline was presented at two HiHASC meetings to enable discussion of the proposed format and approach among the wider HiHASC membership. Based on feedback from this exercise, a further, updated review of English-language literature on PubMed was conducted between May 13 and May 18, 2022. Any areas in which the draft guideline differed from practice (identified across the literature) were discussed by the working group until a consensus was reached. A final consensus guideline approach was endorsed by the working group on behalf of the wider HiHASC membership.

Summary of overall approach to diagnosis of HLH

HLH can present acutely, with a syndrome resembling sepsis, or as a prodrome of mild features that evolve more gradually;[13] either scenario means HLH can be missed. The core tenets of this guidance are to consider HLH in unwell patients and maintain vigilance for evolving HLH. Serial assessments for HLH could, therefore, be indicated.[14] The threshold for assessment for possible HLH should be low, with the following three-step framework enabling prompt investigation (figure 1).

The first step is to recognise potential HLH in a patient using the three Fs; namely, fever, falling blood counts, raised ferritin (temperature might be falsely reassuring in externally cooled patients, such as those on renal replacement therapy or extracorporeal membrane oxygenation circuits and those on antipyrectic agents). The second step is to establish the likelihood of HLH diagnosis using simple biomarkers and scoring systems to facilitate early treatment (quick screen); for adult patients, the HScore is usually the most relevant scoring system.[15] The third step is to, in parallel, investigate the driver or trigger of HLH and assess organ involvement and disease severity (further test approach).

There is no single diagnostic test or classification criteria with sufficient specificity and sensitivity to accurately diagnose HLH, but over 90% of patients met the initial three Fs screen in the HLH-2004 study.[16] In the following section, we review the evidence for the use of biomarkers of inflammation, the role of bone marrow biopsy, and the diagnostic and probability criteria for

HLH (HScore and HLH-2004 criteria) to justify the approach of quick screen followed by further tests in HLH.

HLH recognition and diagnosis

Initial evaluation and quick screen tests

All patients should have a detailed history (or collateral history) to include screening for malignancy, autoimmune or autoinflammatory disorders, risk of infection (including foreign travel and sexual history), parental consanguinity as a clue to potential genetic disorders, familial disorders (including death at a young age), and vaccination history. Physical examination should include a full systemic examination, particularly for the presence of rashes, bruising, oedema, lymphadenopathy, hepatosplenomegaly, synovitis, signs of infection, and neurological abnormalities.

If HLH is suspected, an initial quick screen of tests should be sent without delay (figure 1). This quick screen should include blood tests and imaging to complete an HScore, although bone marrow or tissue evidence of haemophagocytosis is not mandatory in early screening (see later information on haemophagocytosis). Baseline blood testing should include full blood count, renal profile, ferritin, liver function tests (to include aspartate transaminase and lactate dehydrogenase), triglycerides, and fibrinogen.[13] A typical set of HLH bloods shows raised ferritin, cytopenia (often with relative thrombocytopenia first), transaminitis, low fibrinogen, and high triglycerides. Additional findings in patients with HLH commonly include hyponatraemia, hypoalbuminemia, high C-reactive protein, and raised D-dimer. Clinicians should be mindful that erythrocyte sedimentation rate and fibrinogen might initially be elevated in inflammatory states but subsequently fall; moreover, some patients will have falling blood counts that are still within the normal range early in the process. Results of the quick screen should be available within 6–12 h, enabling the clinician to make a rapid assessment of the probability of HLH.

If the diagnosis of HLH is deemed probable following the quick screen, patients should undergo a complete HLH investigation (panel 1, 2). We advise that patients should be discussed with local or regional specialists at this point, although this discussion should not delay investigation and treatment. Ideally, patients should be discussed in a multidisciplinary setting involving representation from at least rheumatology, infectious diseases, and haematology, enabling further guidance on investigations and management.[8,9] We strongly encourage early engagement with critical care teams. An example of a timeline is shown in figure 2.

Ferritin

Ferritin is the most widely used marker to screen for and monitor HLH; it is reasonably inexpensive and widely available. Hyperferritinaemia should always prompt consideration of HLH in the differential diagnosis. In paediatric patients, ferritin is highly sensitive and specific for HLH, with one study showing that ferritin concentrations of more than 10 000 µg/L have a 90% sensitivity and 98% specificity for HLH.[17] The threshold by which ferritin is deemed to be clinically significantly elevated in adults ranges from 2000 µg/L to 10 000 µg/L.[15,18] In adults, elevated ferritin can also be seen in hepatocellular injury, malignancy, infection, iron

***Panel 1:* Tests to consider for patients with suspected HLH of unknown driver**

Haematology
- Coagulation screen, blood film, erythrocyte sedimentation rate, D-dimer, reticulocytes, bone marrow biopsy

Biochemistry
- Renal profile, liver function tests, lactate dehydrogenase, C-reactive protein, iron profile, vitamin B12 or folate, troponin, NT-proBNP, urine protein–creatinine ratio

Rheumatology
- Complement C3 and C4, antinuclear antibodies, antineutrophilic cytoplasmic antibodies, extractable nuclear antigen, anti-double-stranded DNA antibodies

Microbiology
- Three bacterial blood cultures (ideally before antibiotics)

Virology

Blood
- Serum save (ideally before blood products)
- Serology for Epstein-Barr virus; cytomegalovirus; HIV; hepatitis viruses A, B, C, and E; parvovirus B19; and human T-lymphotropic virus 1 (ideally before blood products)
- Epstein-Barr virus and cytomegalovirus PCR

Respiratory viral throat swab PCR
- Influenza A and B, enterovirus, and SARS-CoV-2

Swab of ulcers
- Ulcers swabbbed for herpes simplex virus PCR

Immunology
- Soluble CD25, cytokine testing, lymphocyte subsets, and natural killer cell activity

Imaging
- Chest x-ray, PET-CT (or CT of neck, chest abdomen, and pelvis with contrast), ultrasound if delay for cross-sectional imaging, electrocardiogram, and echocardiogram

Additional tests for patients with neurological symptoms or signs

All patients
- Brain MRI with gadolinium (do MRI before lumbar puncture to avoid false-positive meningeal enhancement)
- Lumbar puncture
  For all: cell count, opening pressure, glucose, protein and matched oligoclonal bands with or without cytospin (≥10 mL), bacterial culture, and viral PCR
  Patient-specific: immunoglobulins, syphilis serology, fungal and tuberculosis cultures

Consider
- Neurophysiology
- Targeted CNS biopsy

Panel 2: Tests to further investigate the HLH driver or trigger

Evaluation for infection

All patients with an unclear driver should have an infectious disease investigation. Depending on infectious diseases consult or travel history, consider:

Parasites

- Malaria film or rapid diagnostic test; *Toxoplasma* and *Leishmania serology*

Other

- Syphilis, *Coxiella*, *Brucella*, endemic mycoses, and *Rickettsia*
- Consider QuantiFERON test (unreliable for diagnosing active tuberculosis)
- If Epstein-Barr virus viraemia, consider investigating which lymphocyte compartments are harbouring Epstein-Barr virus

Tissue biopsy infection tests

- Tuberculosis and leishmaniasis

Tests to ensure no adverse effects of immune suppression (depending on travel history)

- Consider Strongyloides and Trypanosoma cruzi serology

Additional tests in immunocompromised people

- Recommended: PCR for adenovirus, hepatitis C virus, herpes simplex virus, human herpes virus 6 (if history of HIV, allogenic bone marrow transplant, chimeric antigen receptor therapy, and solid organ transplant), and parvovirus
- Consider human herpes virus 8 PCR, hepatitis E virus PCR, cryptococcal antigen, beta-D-glucan (possible false positive after intravenous immunoglobulin), and stool microscopy for ova, cysts, and parasites

Evaluating for malignancy

Early biopsy is recommended. Steroids might mask lymphoma.

Bone marrow biopsy

- Aspirate smear
- Flow cytometry
- Cytogenetics if lymphoma or other malignancy

Other biopsy sites

- As determined by imaging:
- Lymph node (core or excision)
- Deep skin (for intravascular or cutaneous lymphoma)
- Liver or spleen
- Any [^{18}F]fluorodeoxyglucose avid site

Evaluating for primary HLH

If considering primary HLH:

- CD107a granule release assay (if abnormal, send for genetic analysis)
- Protein expression (perforin, SH2D1A, or XIAP; if abnormal, send for genetic analysis)
- Flow cytometry-based assays

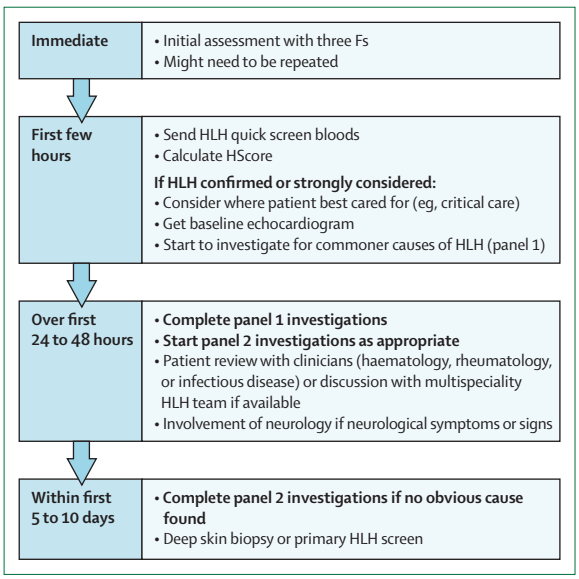

Figure 2: **An approximate timeline of the investigations for a patient with possible HLH**

HLH= haemophagocytic lymphohistiocytosis. HScore=HLH-probability calculator.

overload, renal failure, and adult-onset Still's disease.[19] One study of hospital inpatients who had ferritin concentrations exceeding 1000 µg/L identified HLH in less than 1% of cases.[20] The median maximum ferritin in patients with HLH was significantly higher, at 14 242 µg/L, than the median maximum ferritin of 2467 µg/L identified across the whole cohort. Two additional studies showed a median ferritin at presentation of HLH of 5000–6000 µg/L.[15,19] Therefore, although clinicians need to be mindful that elevated ferritin is not specific for HLH, ferritin should be promptly tested in all cases of suspected HLH, with elevated ferritin raising suspicion of this condition. Peak ferritin in HLH is often higher than ferritin at presentation, and rapid increases can be seen. Serial ferritin measurements are, therefore, recommended to monitor trends or confirm diagnosis if diagnostic thresholds are not met at initial presentation.

Soluble CD25

Soluble CD25, also known as soluble interleukin (IL)-2 receptor, is one of the disease markers specified in HLH-2004 and was elevated in 97% of paediatric patients.[16] Clinically significantly raised soluble CD25 makes HLH increasingly probable, but can also be seen in other conditions associated with T-cell activation, such as rheumatological diseases and haematological malignancies.[21,22] The specificity and sensitivity of soluble CD25 appear to be poor in the critical care setting.[23] A particular role for soluble CD25 in identifying HLH associated with malignancy has recently been suggested, with a combination of raised soluble CD25 (>3900 U/mL) and ferritin (>1000 µg/L) showing 84% sensitivity and 81% specificity and predicting high mortality risk.[24] Routine testing for soluble CD25 is not readily available in many parts of the world,[25,26] and even when it is possible to access the test, turnaround time can lead to diagnostic delay. The literature supporting the role of soluble CD25 in identifying patients with malignancy-associated HLH should add weight to the argument for improved access to testing. In the meantime, waiting for soluble CD25 results should not delay treatment.

Cytokine profiling, lymphocyte panels, and NK cell activity

Persistent activation of macrophages, NK cells, and cytotoxic T lymphocytes in patients with HLH leads to

excessive cytokine production, and this cytokinaemia is thought to contribute to HLH-related multiorgan failure and mortality. In paediatric populations, elevated interferon (IFN)γ and IL-10 are associated with HLH,[27] with increased concentrations of these cytokines predicting disease severity.[28] In adults with HLH, the data are more limited than in paediatric populations, but raised plasma concentrations of IFNγ and tumour necrosis factor (TNF), and increased serum concentrations of IL-1 receptor antagonist, intercellular adhesion molecule-1, IL-6, IL-12, and IL-18 have been identified.[29,30] When compared with cytokine concentrations in patients with other febrile illnesses, certain patterns might be suggestive of one type of driver rather than another,[31,32] but none of these tests are validated in routine clinical practice.

Routine lymphocyte subset panels can be useful for assessment of lymphocyte immunity, particularly in patients with low CD4 counts.[33] Low or absent NK cell activity is an HLH-2004 criterion[16] and can be associated with poor outcome.[34]

Cytokine profiling, lymphocyte subset panels, and NK cell activity are not widely accessible in many countries or outside of specialist centres, so at present we do not advocate depending on these results for management decisions.

The role of bone marrow biopsy

The presence of haemophagocytosis on bone marrow biopsy is neither sufficient nor required to make a diagnosis of HLH. In the HLH-2004 study, haemophagocytosis was found on bone marrow smears in 82% of paediatric patients.[16] In a retrospective study of 314 adults who had a bone marrow biopsy taken for suspected HLH or for whom haemophagocytosis was reported on bone marrow examination, 70% of patients with a final diagnosis of HLH had haemophagocytosis on bone marrow biopsy, as did 39% of patients for whom the diagnosis of HLH was rejected.[11] In people with HLH, haemophagocytosis has been identified in tissue other than the bone marrow, such as the liver.[35]

Haemophagocytosis on bone marrow aspirate alone is sufficient to declare the presence of haemophagocytosis for diagnostic purposes.[36] The trephine biopsy might be of use while investigating the driver of HLH—analysis should be directed at detecting malignant infiltrates, and appropriate microbiological sampling should also be considered (see the later section on investigating the HLH driver or trigger).

HLH criteria and scoring systems

Two commonly used scoring systems have been developed to aid prediction of whether a patient has HLH. Serial calculations of these scores might be required where there is a high index of suspicion for HLH but the threshold for diagnosing HLH is not met on initial score. The HScore is the most appropriate scoring system in adult patients.

The HLH-2004 diagnostic criteria

The HLH-1994 (HLH-94) diagnostic criteria were proposed by the Histiocyte Society for a prospective trial.[37] The criteria were revised for HLH-2004, with individuals meeting at least five of eight diagnostic criteria considered to have HLH[16] (panel 3). Although these criteria are widely used, there are limitations to their use in routine adult practice. First, they were designed for and validated in a paediatric population. There is an emphasis on genetic diagnoses, and the ferritin threshold of 500 µg/L lacks specificity for HLH in adult populations. Second, the criteria include specialist tests, such as soluble CD25 and NK cell function, which might risk diagnostic delay. Finally, other widely recognised features of HLH in adults, such as elevated transaminases, are not included, even though HLH with normal liver function is unusual.[18]

The HLH-probability calculator (HScore)

The HScore is a free online calculator to assess the probability of HLH (panel 4).[15] The score is constituted of nine variables, including three clinical (underlying immunosuppression, fever, and organomegaly), five from routine blood tests (ferritin, triglycerides, aspartate transaminase, fibrinogen, and cytopenia), and one histopathological (tissue haemophagocytosis), which are weighted in the score calculation. A total score out of 337 is produced, with probability of HLH ranging from less than 1% for scores less than 90 to more than 99% for scores more than 250. A cut-off HScore of 169 has been shown to identify HLH with 93% sensitivity and 86% specificity.[15] In an analysis of 2623 critically ill adults with ferritin concentrations of more than 500 µg/L, a HScore of 168 was associated with 100% sensitivity and 94% specificity for HLH and showed improved reliability when compared with the HLH-2004 criteria.[38] However, results must be interpreted in clinical context—for instance, post-chemotherapy cytopenia or liver dysfunction secondary to a hypotensive liver injury could be wrongly attributed to HLH, making the HScore potentially unreliable.

The advantages of the HScore are its validation in adult populations, including those in critical care, use of widely available laboratory markers, and dynamic prediction of HLH probability. The only test in the HScore that requires invasive examination is the category of tissue haemophagocytosis, which is relatively lightly weighted in the score calculation, compared with other tests, confirming evidence from the literature that demonstration of haemophagocytosis is neither required nor specific for diagnosis of HLH.[39]

Assessment of disease severity and particular organ involvement

Severity assessment

Initial review should include an assessment of severity and consideration of higher levels of care and monitoring. Evaluation of patients on general hospital wards has

For more on the **HScore calculator** see https://saintantoine.aphp.fr/score/

Panel 3: **HLH-2004 diagnostic criteria for HLH, adapted from Henter and colleagues[16]**

HLH is diagnosed if criterion 1 or 2 has been fulfilled.

Criterion 1
Molecular diagnosis consistent with HLH.

Criterion 2
Diagnostic criteria for HLH fulfilled (five of eight):

- Fever
- Splenomegaly
- Cytopenia (affecting more than two of three lineages: haemoglobin <90 g/L, platelets <100 × 10^9/L, neutrophils <1·0 × 10^9/L)
- Hypertrigylceridemia or hypofibrinogenemia (or both; fasting triglycerides ≥3·0 mmol/L, fibrinogen ≤1·5 g/L)
- Haemophagocytosis in bone marrow, spleen, or lymph node
- Low or no natural killer cell activity
- High ferritin (≥500 µg/L)
- High soluble CD25 (≥2400 U/mL)

Panel 4: **Criteria for scoring and number of points for HLH probability calculator (HScore), adapted from Fardet and colleagues[15]**

- Known underlying immunosuppression: 0 (no) or 18 (yes)
- Temperature: 0 (<38·4°C), 33 (38·4–39·4°C), or 49 (>39·4°C)
- Organomegaly: 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
- Number of cytopenias: 0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
- Ferritin: 0 (<2000 ng/mL), 35 (2000–6,000 ng/mL), or 50 (>6000 ng/mL)
- Triglyceride: 0 (<1·5 mmol/L), 44 (1·5–4 mmol/L), or 64 (>4 mmol/L)
- Fibrinogen: 0 (>2·5 g/L) or 30 (≤2·5 g/L)
- Serum aspartate aminotransferase: 0 (<30 IU/L) or 19 (≥30 IU/L)
- Haemophagocytosis features on bone marrow aspirate: 0 (no) or 35 (yes)

shown the need for early identification for admission to intensive care.[40–42] Poor prognostic factors include older age, malignancy-driven disease, markedly high ferritin, more severe cytopenia, low albumin, and CNS involvement.[2,3,11,13,24–26] Our group recognises particular challenges with CNS and cardiovascular manifestations of HLH, for which the literature is scarce.

Suspected CNS involvement in HLH

Involvement of the CNS in both primary HLH and secondary HLH is well described and recognised as a poor prognostic factor.[13] Most studies have been performed in children with primary HLH, of whom up to a third had neurological involvement, which was associated with worse prognosis.[43] Similar findings have been described in adults with HLH.[44] Prompt recognition and appropriate management of neurological manifestations in HLH are important to optimise outcomes and direct HLH treatment.[43]

The range of neurological manifestations of HLH is broad.[45] Any neurological symptom in the context of HLH requires a full neurological examination. Early involvement of a neurologist is recommended to localise the deficit, direct investigations, and advise on management and expected prognosis of the neurological dysfunction. HLH can present with isolated neuroinflammatory disease, but more commonly, CNS involvement is part of a systemic presentation.[46,47] Autopsy has revealed histological evidence of HLH in the brain.[48] CNS dysfunction might also be due to brain or meningeal infiltration by the HLH trigger; MRI of the brain with gadolinium can be helpful to differentiate between these two scenarios and, if indicated, to target brain biopsy.

All patients with neurological dysfunction should have a lumbar puncture, [49] which, ideally, should take place after MRI to avoid false-positive leptomeningeal enhancement. Routine cerebrospinal fluid analyses should be done, including opening pressure, cell count, protein, glucose, bacterial culture, viral PCR, and oligoclonal band testing. Specific virus panels, such as PCR analysis for herpes simplex virus 1, herpes simplex virus 2, varicella zoster virus, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, and enterovirus, are also recommended. Specialist cerebrospinal fluid analysis for cytology, cytospin, immunoglobulins, syphilis, tuberculosis, and neurodegenerative markers should be performed if indicated. Cerebrospinal fluid neopterin has been reported in primary HLH as a helpful marker of CNS inflammation, but it is non-specific and elevated in many CNS infections and autoinflammatory conditions.[50,51]

In the context of an otherwise normal neurological examination, encephalopathy is suggested by a fluctuating or reduced level of consciousness, intermittent confusion, agitation or irritability, or episodic seizures. In this context, the brain MRI might be normal, with cerebrospinal fluid being acellular and showing normal or borderline elevated protein, reflecting altered blood–brain barrier permeability. Encephalopathy in a patient with HLH represents global neuronal dysfunction and might be secondary to sepsis, metabolic derangement, or drug toxicity, or an effect of cytokine storm.[52] Focus should be on the management of HLH, with the expectation of neurological recovery in line with systemic improvement. Seizure activity is seen in encephalopathy of any cause. Electroencephalogram can differentiate between encephalopathy (generalised slowing) and epileptiform activity and can guide specific antiseizure management.[53]

Patients with HLH and cardiovascular dysfunction

Although there is a paucity of research into cardiovascular dysfunction in HLH, case reports increasingly recognise cardiovascular dysfunction as an important cause of mortality in HLH.[54–56] Associations can be made with disease processes that show crossover with HLH, including sepsis, cytokine release syndrome, myocarditis, and pericarditis.[57,58]

Through multidisciplinary working, we have observed that cardiovascular dysfunction in patients with HLH often presents with tachycardia despite fluid resuscitation; hypotension is a less common or later presentation. Without an appropriate index of suspicion and investigation, the clinical presentation of impending cardiovascular collapse can be very late.

Baseline cardiovascular investigations should include troponin (with a rise suggestive of cardiac strain), NT-proBNP (with concentrations >1000 pg/mL suggestive of cardiac inability to manage fluid load), electrocardiogram, and transthoracic echocardiogram.[59] Small pericardial effusions are commonly seen in patients presenting to critical care. Global longitudinal strain is a more sensitive tool for assessing cardiac dysfunction and is associated with increased morbidity and mortality.[60] All patients with HLH and possible cardiovascular dysfunction should have daily troponin testing with serial NT-proBNP and transthoracic echocardiogram monitoring at 72-h intervals during the acute phase of illness. Significant cardiovascular dysfunction should prompt consideration of continuous cardiac monitoring and transfer to a specialist centre.

Investigation of the HLH driver or trigger

Identification of the driver of HLH is critical; idiopathic HLH is associated with a particularly poor outcome.[61] Panel 1 includes tests aimed at confirming the diagnosis of HLH and investigating for common triggers. The aim should be to complete these tests in the first 24–48 h. Panel 2 describes further tests that should be considered over the first few days, with some tests only appropriate for certain patient groups.

Evaluation for infection

Worldwide, viral infection is the most frequently identified cause of HLH.[26] Infection is seen as either the primary driver of HLH or the trigger in a patient already at risk, for instance, a patient with known lymphoma or systemic lupus erythematosus (panel 5). If there is concern regarding an infectious trigger, a specialist infectious disease review is advised. Examination of the patient should target areas not well visualised in cross-sectional imaging (the recommended imaging is outlined later), including skin rashes, cardiac murmurs, oral and genital ulcers, and urinalysis.

Initial infection screening (panel 1) should include three sets of blood cultures, as well as blood collection for serology (Epstein-Barr virus; cytomegalovirus; hepatitis viruses A, B, C, and E; HIV; human T-lymphotropic viruses 1 and 2; and parvovirus) and PCR (cytomegalovirus and Epstein-Barr virus). Viral throat swabs for PCR of respiratory viruses, including SARS-CoV-2, are also advised. Clinicians should be mindful of misinterpreting results following treatment with intravenous immunoglobulin because of passive transfer of antibodies from the donor;[62] pre-treatment serum save is recommended.

Bone marrow aspirate can be sent for microscopy and PCR if *Leishmania* is suspected, as well as for acid-fast bacilli microscopy, mycobacterial culture, and *Mycobacterium tuberculosis* PCR. Aspirate smears of splenic biopsies can be sent for microscopy, *Leishmania* PCR, and mycobacteriology. If other tissue is obtained, for example liver biopsy, it can also be sent for tuberculosis culture and PCR. Metagenomic next-generation sequencing, if available, might be a helpful tool to identify infectious triggers.[63]

Epstein-Barr virus

Epstein-Barr virus is implicated in HLH in several ways. For example, primary Epstein-Barr virus infection or reactivation of latent Epstein-Barr virus can trigger HLH.[64] In these cases, a high viral load is usually detectable. It is important to assess Epstein-Barr virus status by PCR and serology in new HLH diagnoses. If Epstein-Barr virus is detected, serology is advised to distinguish primary infection from reactivation. Serial PCR samples should then be taken to monitor the trend of the viraemia. If

***Panel 5:* Infectious precipitants of HLH**

Viral

Epstein-Barr virus, herpes viruses (cytomegalovirus, herpes simplex virus, human herpes virus 6, and varicella zoster), parvovirus B19, adenovirus, enterovirus, influenza A and B, SARS-CoV-2, human T-lymphotropic virus 1, hepatitis viruses, HIV, dengue virus, and Ebola virus

Bacterial

Mycobacteria spp, *Legionella* spp, *Mycoplasma* spp, *Rickettsia* spp, *Staphylococcus* spp, *Escherichia Coli, Treponema* spp, *Coxiellaceae* spp, and *Brucella* spp

Parasitic

Plasmodium spp (send malaria films if recent travel to a malaria endemic area), *Leishmania* spp (might cause HLH, but can mimic HLH by causing cytopenias and organomegaly; consider if recent travel to Mediterranean littoral country), *Toxoplasma* spp, *Trypanosoma* spp, and *Strongyloides* spp

Fungal

Histoplasma (fungal infections rarely cause HLH, but consider in immunodeficient patients; eg, acquired immune deficiency syndromes, lymphoma, and bone marrow transplant recipients), *Pneumocystis jiroveci, Candida* spp, and *Aspergillus* spp

Epstein-Barr virus viraemia is felt to be the principal driver of HLH, consideration of genetic testing for primary HLH is advised.[65] Epstein-Barr virus reactivation can occur as a bystander effect of HLH triggered by an alternative driver. In these cases, the detectable viral load is usually low. Therefore, once Epstein-Barr virus has been detected in a patient with HLH, other major causes of HLH should be excluded to ensure that Epstein-Barr virus reactivation is not a contributory factor. Finally, Epstein-Barr virus-driven lymphomas might trigger HLH.[66] Epstein-Barr virus-driven lymphoma should be excluded via a combination of serum lactate dehydrogenase, cross-sectional imaging, and biopsy.

Evaluation for malignancy

In adults, clinical suspicion for malignancy (especially lymphoma) must remain high, given its relative frequency and association with poor outcome.[2] All patients with suspected HLH should have a haematological review. Cross-sectional imaging should be requested to identify any underlying malignancy and possible areas to biopsy and to exclude a focus of infection. PET-CT is the imaging modality of choice; however, if this method is not feasible or will result in undue delay, contrast-enhanced CT of the neck, thorax, abdomen, and pelvis is adequate.

Where possible, steroid use should be deferred until imaging has been performed and tissue samples obtained, to reduce the risk of masking a lymphoma. Steroid-sparing cytokine-directed therapy, such as anakinra, can be considered first-line therapy in this context, but steroids are often started before tissue sampling as time-critical management is needed; histology results should be interpreted with caution in this context, and multiple, repeated tissue biopsies might be required to optimise diagnostic yield. Some patients initially labelled as having idiopathic HLH might in fact have malignancy-associated HLH, only identified after multiple rounds of investigation.[67] Soluble CD25, if available, can be a helpful non-invasive screening tool.

Although T-cell lymphoma is the most common haematological malignancy recognised to drive HLH, we also advise considering intravascular B-cell lymphoma, an under-recognised driver. Intravascular B-cell lymphoma is a rare type of extranodal diffuse large B-cell lymphoma characterised by a proliferation of neoplastic cells within the vascular lumen.[68] Intravascular B-cell lymphoma is challenging to diagnose as presentation is often non-specific and lymphadenopathy is absent. Increased recognition of the disorder and earlier diagnosis have resulted in survival rates of 46–60%.[69,70] If intravascular B-cell lymphoma is suspected, bone marrow aspiration and trephine should be performed as the first-line investigation. If these tests are non-diagnostic, random incisional deep skin biopsies (6 mm or 8 mm) should be taken from three separate fat-containing areas of normal-appearing skin from the thigh, abdomen, and upper arm.[71] Standard punch biopsy is inadequate for intravascular B-cell lymphoma diagnosis as intravascular B-cell lymphoma typically resides in the hypodermic adipose tissue.

Evaluation for autoimmune and autoinflammatory disease

The most common rheumatological diseases associated with HLH are adult-onset Still's disease, systemic juvenile idiopathic arthritis, and systemic lupus erythematosus.[7] Systemic juvenile idiopathic arthritis and adult-onset Still's disease are recognised to be part of the same disease spectrum and particularly predispose people to HLH; IL-18 is a specialist test useful in confirming the diagnosis and monitoring of HLH in this patient group.[72] Systemic juvenile idiopathic arthritis causes overt HLH in 10% of patients and subclinical HLH in a further 30–40%.[73,74] Other rheumatological conditions associated with HLH include sarcoidosis, Kawasaki disease, rheumatoid arthritis, systemic sclerosis, vasculitis, Sjögren's syndrome, and myositis.[7,75,76] Concomitant immunomodulating therapies can also predispose to infection or trigger HLH in people with known autoimmune or inflammatory disease; therefore, increased vigilance to HLH is required in these patient groups.[7]

Patients with suspected rheumatic disease should be reviewed by a rheumatologist. Autoantibody testing should include antinuclear antibodies, antineutrophil cytoplasmic antibodies, and antibodies to extractable nuclear antigen as well as, when appropriate, complement levels, anti-double-stranded DNA antibodies, antiphospholipid antibodies, myositis panel, and immunoglobulins.

HLH is also associated with other systemic inflammatory diseases, such as inflammatory bowel disease,[77] which should be considered during a full systems review and investigated promptly if suspected.

Evaluation for suspected primary HLH

Although HLH has historically been considered a condition of childhood onset, genetic defects are increasingly being identified in adults with HLH.[8] For example, in one study, 14% of adults diagnosed with HLH were found to have pathogenic mutations in genes including *PRF1, MUNC13-4*, and *STXBP2*.[78] These mutations tended to cause partial defects of function rather than complete loss. This partial loss of function might explain the later age of onset; two adults with genetic defects in this study had HLH onset when they were older than 70 years.

Testing for primary HLH should be considered in patients with a history of recurrent infection, those with dysmorphic features or dyspigmentation, people with consanguineous parents, and people with a family history of a known mutation predisposing to HLH or unexplained death at a young age. Testing for primary HLH should also be considered in patients with HLH secondary to Epstein-Barr virus or cytomegalovirus in the absence of lymphoma or where no other driver is identified. Discussion with a

paediatrician should be considered, as paediatricians are likely to be more familiar with genetic disease clinical phenotypes. Testing for primary HLH is required to help stratify the likelihood of HLH recurrence and assess risk of HLH in family members, and, ultimately, identify the need for bone marrow transplantation. Immunological investigations for patients with suspected primary HLH are summarised in the table. Sometimes, tests need to be repeated after the patient has recovered as low cell counts can be a feature of being acutely unwell.

Multiple specialist assays for primary HLH are available but can be subdivided into four main categories. The first category is analysis of immunoglobulin levels and T-cell subsets, which can identify other associated immunodeficiency. The second category of specialist assays is flow cytometry-based assays that detect the absence, presence, or reduction of surface protein expression. These assays are useful to quickly confirm a suspected diagnosis of primary HLH. Proteins including perforin, SH2D1A, XIAP, CD27, and CD70 have all been associated with primary HLH and are amenable to testing.[79] If perforin is low, further *PRF1* mutation analysis is indicated.[79] Mutation testing in *SH2D1A* and *XIAP* is only indicated in male patients. If SH2D1A is low, *SH2D1A* genetic analysis to investigate a diagnosis of X-linked lymphoproliferative syndrome type 1 is indicated.[80] If XIAP is low, investigation for a mutation in *XIAP* and underlying X-linked lymphoproliferative syndrome type 2 is indicated.[80] Alterations in the expression of CD27 and CD70 are rare but associated with Epstein-Barr virus-driven HLH.[81]

Another category of specialist assays for primary HLH is flow cytometry assays to detect the functional ability of T cells or NK cells to degranulate following stimulation. Granule release assays detecting molecules such as CD107a (also known as LAMP-1) might be helpful in the diagnosis of unexplained adult-onset HLH.[82]

Finally, genetic sequencing for known susceptibility genes or whole-exome sequencing can be conducted. In addition to established genes known to cause primary HLH, to date, 92 polymorphisms have been identified in genes not classically associated with HLH but thought to predispose to HLH.[83] Genetic testing can sometimes be appropriate even if the functional tests are normal, for instance, if HLH is considered to be part of an immunodeficiency syndrome.

Specific patient groups

Immunocompromised patients

Immunocompromised people are at increased risk of severe HLH, and additional pathogens might drive HLH in this group[2] (panel 2). Groups of patients considered immunocompromised include those on long-term immunosuppressive agents, recipients of allograft bone marrow transplant or solid organ transplant, and those with primary immunodeficiency disorders, HIV, or malignancies, particularly if receiving chemotherapy. Additional screening for infection in immunocompromised patients should include PCR for human herpesvirus 6, hepatitis C, and adenovirus. When appropriate, samples could be sent for PCR testing for human herpesvirus 8, herpes simplex virus, parvovirus, and hepatitis E. Samples could also be tested for cryptococcal antigen, and beta-D-Glucan, and stools could be tested for ova, cysts, and parasites.

CAR T-cell therapy recipients

An increasing number of people with haematological malignancies are being treated with CAR T-cell therapy. Acute toxicities following this therapy include cytokine release syndromes, neurological dysfunction, B-cell aplasia, and severe cytopenias. Activation of CAR T cells when encountering target antigen results in the production of proinflammatory cytokines such as TNF and IFNγ, which drive secretion of additional proinflammatory factors, including IL-1 and IL-6. The clinical manifestations of this process mimic HLH, including symptoms such as pyrexia, raised ferritin, raised lactate dehydrogenase, clotting derangement, and organ dysfunction.[84] Neurological sequelae of CAR T-cell

	Assay target	Notes
T-cell subsets	T-memory panel includes B cells ($CD19^+$), NK cells ($CD56^+$), $CD4^+$, $CD8^+$, naive ($CD45^+$, $CD27^+$), and effector ($CD45^+$, $CD27^-$) cells and memory ($CD45^-CD27^-$) T-cell subsets	Useful in the investigation of primary immunodeficiency
Flow cytometry-based assays of protein expression	Perforin*, SH2D1A† (men only), XIAP‡ (men only), CD27–CD70§	Useful to quickly confirm a suspected diagnosis of primary HLH
Functional flow cytometry-based degranulation or granule release assay	CD107a	A useful test; if low, suggests mutation of any of primary HLH types 3–5, GS-2, CH, HP-2; abnormal degranulation can be used to fulfil HLH-2004 diagnostic criteria (NK function)
Genetic testing by NGS	All known HLH genes (92 currently)	Primary immunodeficiency NGS panel (TIGeR) includes primary immunodeficiency genes

NK=natural killer. HLH=haemophagocytic lymphohistiocytosis. GS=Griscelli syndrome. CH=Chediak-Higashi syndrome. HP=Hermansky-Pudlak synfrome. NGS=next-generation sequencing. TIGeR=translational implementation of genomics for rare diseases. *If low, do *PRF1* mutation analysis. †If low, do *SH2D1A* mutation analysis (X-linked lymphoproliferative syndrome type 1). ‡If low, do *BIRC4* mutation analysis (X-linked lymphoproliferative syndrome type 2). §Rare, only for patients with Epstein-Barr virus-driven HLH.

Table: **Specialist immunological tests for HLH**

Search strategy and selection criteria

We searched PubMed using the search terms "(HLH OR Haemophagocytic Lymphohistiocytosis OR Macrophage Activation Syndrome OR Cytokine Release Syndrome) AND (diagnos* OR investigat*)" between May 13 and May 18, 2022, to include all publications from Jan 1, 2000, until the day of the search. Case reports were excluded, and abstracts were screened for the remaining publications, with those primarily addressing laboratory or genetic tests not currently available in clinical practice being excluded. Included texts were examined in full; references of key publications were screened to identify further relevant literature.

therapy, such as seizures, can also mimic CNS HLH. Therefore, CAR T-cell therapy-driven cytokine release syndrome might be difficult to distinguish from HLH.

Approximately 3·5% of patients are estimated to develop HLH after CAR T-cell therapy,[85] and this patient group appears to be associated with increased CAR T-cell expansion and persistence;[86] moreover, HLH development is associated with poor outcomes in this group.[87] HScores are considered unreliable in this setting. Proposed criteria for diagnosing CAR T-cell therapy-related HLH are a peak ferritin measurement of more than 10 000 µg/L during the cytokine release syndrome phase of illness, in addition to two of the following: organ toxicities greater than grade 3 involving the liver, kidney, or lung, or haemophagocytosis in the bone marrow or other organs.[84] When investigating the precipitant of HLH in CAR T-cell therapy recipients, particular attention should be paid to excluding infectious triggers, with a focus on virology.

Conclusions

This HiHASC consensus guideline provides a comprehensive approach to the diagnosis and investigation of suspected HLH for physicians who treat adult patients in hospital settings. The approach includes early clinical recognition using the three Fs (fever, falling blood counts, and raised ferritin), alongside parallel diagnostic and investigative tests. We strongly advocate cross-speciality input to the assessment of all patients with HLH to improve outcomes.

HiHASC collaborative group

On behalf of HiHASC, with particular recognition of the input from Amit Patel and Kimberley Gilmour.

Contributors

JJM, RST, and SM conceived of the idea and wrote the initial HiHASC Health Policy. MFC reformatted and rewrote the Health Policy to prepare for publication. AJ reviewed and edited this Health Policy. All authors contributed to the discussions, writing, and review of the Health Policy and the revisions to prepare for publication.

Declaration of interests

AC reports payment or honoraria from CSL, Griffols, Akcea, Biogene, Neurodiem, and Bristol Myers Squibb. AC also reports honoraria from Lupin (£1000) and CSL (£1000) for advisory board participation and support from CSL for attending the Peripheral Nerve Society annual congress, Miami 2022. MBr reports membership of the Medicines and Healthcare products Regulatory Agency Commission of Human Medicines Expert Advisory Group and National Health Service England's Covid medicines Expert Working Group. MBi reports consulting fees from Lilly, Incyte, Roche, and Beigene; and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Tevapharma and Celltrion. JJM reports funding from the UCLH Charity Grant funding given to the HLH Service to establish biobank and fund consultant time (£160 000 paid to UCLH). All other authors declare no competing interests.

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