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doi.org/10.58931/cht.2025.4166

Hemophagocytic Lymphohistiocytosis and Other Cytokine Storm Syndromes in Adults

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and highly fatal syndrome of pathological immune activation leading to excessive inflammation, hypercytokinemia, and multi-organ failure.[1,2] HLH is broadly divided into primary HLH, driven mainly by genetic defects in cytotoxicity[3,4] and secondary HLH, a heterogeneous group of disorders with similar clinical and laboratory features to primary HLH, but characterized by hyperinflammation rather than defective cytotoxicity.[5] Primary HLH occurs nearly exclusively in children. Most adult HLH is secondary, often in the context of immunomodulatory therapy, infection, malignancy, autoimmune/autoinflammatory diseases, or immunodeficiency.

HLH falls under the umbrella concept of cytokine storm syndrome (CSS).[6] In 2020, the coronavirus disease 2019 (COVID-19) pandemic greatly amplified clinical interest and research in CSS,[6-8] and specifically the concept of a maladaptive immune response to infection.[9,10] Early on, COVID-19-CSS was compared to HLH.[11,12] However, HLH is mainly driven by the interferon-γ (IFN-γ)-chemokine ligand 9 (CXCL-9) axis, resulting in profound T cell and macrophage activation, and is characterized by very high ferritin and soluble CD25 (sCD25, synonymous with the alpha chain of the soluble interleukin (IL)-2 receptor), often with only modestly elevated C-reactive protein (CRP). In contrast, COVID-19-CSS is characterized by defective type I/type III interferon responses leading to excessive IL-6 signaling and very high CRP, which can be ameliorated by IL-6 inhibition.[13,14]

The increased interest in CSS spurred by COVID-19 has coincided with significant recent advances in our understanding of other CSS, such as thrombocytopenia, anasarca, fever/(reticulin) fibrosis, organomegaly, renal dysfunction (TAFRO) syndrome (typically associated with idiopathic multicentric Castleman disease, iMCD-TAFRO) and severe or catastrophic Still's disease. This review will provide practical guidance for clinicians in diagnosing adult HLH, differentiating it from TAFRO syndrome and Still's disease. Specifically, in section 3 and Table 2, we propose a heuristic (problem-solving strategy or shortcut) to decrease cognitive load when faced with an acutely ill patient with evolving CSS, with a focus on simple and readily available inflammatory markers (CRP, ferritin, sCD25). This heuristic can help clinicians make diagnostic and therapeutic decisions in real time.

Diagnosis of HLH

Diagnosis of HLH is challenging because initial symptoms are often nonspecific, yet prompt recognition is critical due to the rapidly progressive nature and high mortality of the disease. Clinicians should suspect HLH in patients with fever, unexplained cytopenias, hyperferritinemia, hepatosplenomegaly, liver enzyme elevation, coagulopathy, and neurologic findings, particularly in patients with predisposing conditions such as underlying lymphoproliferative disorder, autoimmune disorder, or viral infection. Diagnostic criteria and tools are summarized in **Table 1.**

The most widely used diagnostic criteria were derived from the HLH-2004 study, which was based on the observation of 369 pediatric patients, most of whom had primary HLH.[15] However, there are some limitations in applying these criteria to adults; for example, ferritin >500 µg/L is very nonspecific in adults,[16,17] and tests of cytotoxic function, such as natural killer (NK) cell activity or perforin expression by flow cytometry are rarely helpful in secondary

	HLH-2004[15]	HScore[19]	MS Score[21]
Primary Use	Pediatric HLH diagnosis	Adult HLH, predictive probability	MAS in autoimmune conditions
Key Features	Diagnosis requires presence of ≥5 of 8 criteria	Points-based score based on 9 variables	Weighted equation based on 7 variables
Ferritin	≥500 µg/L	>2,000 µg/L (weighted)	Yes
sCD25	>2400 IU/mL	Not used	Not used
LDH	Not used	Yes, Elevated (no cutoff specified)	Not used
Triglycerides	≥265 mg/dL	>132 mg/dL (weighted)	Not used
Cytopenias	Yes, ≥2 lineages	Hemoglobin <9 g/dL or platelets <100k	Yes, platelet count only
Hemophagocytosis	Yes	Yes	Not used
NK Cell Activity	Yes, decreased or absent	Not used	Not used
Fibrinogen	Yes, ≤150 mg/dL	Yes, ≤250 mg/dL	Yes
AST	Not used	Yes, >30 U/L	Not used
Hepatosplenomegaly	Yes	Yes	Not used
Fever	Yes, ≥38.5°C	Yes, ≥38.4°C	Not used
Threshold for Diagnosis	≥5 of 8 criteria	Score ≥169 (~80% HLH probability)	Score ≥-2.1 is suggestive of MAS in pediatrics and ≥-1.74 in adults
Advantages	Standardized, globally recognized	Quantitative, accommodates adults	Specific to autoimmune-associated MAS
Limitations	Not designed for adult patients; focused on cytotoxicity defects (NK function, genetic tests) rather than hyperinflammatory defects	Lack of markers of immune activation make it difficult to distinguish physiologic from pathologic immune activation	Limited applicability outside of pediatric JIA/Still's

Table 1. Diagnostic criteria and tools for HLH; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: AST: aspartate aminotransferase; **HLH:** hemophagocytic lymphohistiocytosis; **JIA:** juvenile idiopathic arthritis; **LDH:** lactate dehydrogenase; **MAS:** macrophage activation syndrome; **NK:** natural killer; **sCD25:** soluble CD25.

Typical ranges	CRP (<3.1 mg/L)	Ferritin (<300 µg/L)	sCD25* (<846 IU/mL)	Key pathology findings
HLH*	10-100 mg/L	>>3,000 µg /mL	>3,000 IU/mL	Hemophagocytosis (typically in bone marrow)
COVID-19 CSS	>100 mg/L	<3,000 µg /mL	<3,000 IU/mL	Vasculopathic changes, such as thickened, reactive endothelium in the skin[64] and intussusceptive angiogenesis in pulmonary vessels[65]
TAFRO	>>50 mg/L	<3,000 µg /mL	<3,000 IU/mL	Castleman changes in lymph node Vasculopathy is common[66] Hemophagocytes may be seen in bone marrow or tissue
Severe Still's disease	>100 mg/L	>3,000 µg /mL	<3,000 IU/mL	Skin: dyskeratotic/necrotic keratinocytes in superficial layers and vacuolar interface change [37]

Table 2. Typical inflammatory biomarker patterns and key pathology findings in four cytokine storm syndromes: a heuristic*[31,32]; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: COVID-19 CSS: coronavirus disease 2019 cytokine storm syndrome; **CRP:** C-reactive protein; **HLH:** hemophagocytic lymphohistiocytosis; **sCD25:** soluble CD25.

*Heuristic: problem solving method to decrease cognitive load.
**the authors use the "rule of 3,000" for diagnosing HLH – in most cases of adult HLH, ferritin is >3,000 µg/L and sCD25 is >3,000 IU/mL.

HLH.[18] A partial answer to this problem was the development of the HScore, which was designed to use widely available clinical and laboratory parameters to diagnose secondary HLH.[19] An HScore greater than 169 has a sensitivity of 93% and specificity of 86%, accurately classifies 90% of patients, and has similar utility to HLH-2004 in adults.[20] While the wide applicability of the HScore is one of its strengths, the deliberate omission of specialized tests of immune activation, such as sCD25 and cytokine/chemokine levels, also limits the ability of HScore to answer the practical question: "Does this patient have pathological immune activation (as opposed to a physiological response to infection, acute illness, liver disease, blood transfusion, etc.) as the explanation for their condition?"

HLH can often be triggered by an underlying autoimmune or autoinflammatory disorder (sometimes referred to as macrophage activation syndrome [MAS] in that context), and it can be challenging to distinguish between HLH and flare of pre-existing diseases such as lupus or juvenile idiopathic arthritis juvenile idiopathic arthritis (JIA)/Still's disease. Therefore, the MS score was developed based on pediatric patients to distinguish between patients with a flare of juvenile idiopathic arthritis and those with MAS/HLH. This score utilizes a weighted equation to calculate a score. A score of -2.1 or higher was shown to have 85% sensitivity and 95% specificity in distinguishing JIA from MAS.[21] A subsequent analysis in adult patients with Still's disease suggested a cutoff of ≥-1.74 for adult patients, which yielded a sensitivity of 93.5% and a specificity of 92.6% in diagnosing MAS.[22,23] We include the MS Score as an illustration of the evolving approach to diagnosing HLH; other specialized diagnostic criteria also exist for JIA, Still's disease, malignancies (most notably the

activation (e.g. IL-18, CXCL9) and cytotoxicity (NK function, perforin, and CD107a) must be sent out to the few centres that offer clinically validated tests (such as those in Toronto, Cincinnati, or the Mayo Clinic). This means the results are often not readily available for urgent therapeutic decisions. One exception is sCD25, for which the test is available in many centres. An important caveat for interpreting sCD25 is that the HLH-2004 cutoff of >2,400 IU/mL is based on the functional assay, whereas many labs utilize an enzyme-linked immunosorbent assay, which reports results in pg/mL. Unfortunately, there is no reliable conversion factor from pg/mL to IU/mL;[29] some labs suggest that 20,000 pg/mL is approximately the same as 2,400 IU/mL, but this can vary greatly depending on the laboratory and reagents used.

Considering these limitations in laboratory assessment of immune activation/hyperinflammation, we suggest a heuristic summarized in Table 2. The typical pattern for HLH includes very high ferritin and sCD25 levels (typically well over 3,000 µg/L and 3,000 IU/mL, respectively) and a modestly elevated CRP (often <100 mg/L).[30,31] In contrast, both Still's disease and TAFRO syndrome are driven largely by IL-1 (and its helper cytokine, IL-18) and IL-6 and, thus, have markedly elevated CRP levels that are often well over 100 mg/L. Further, both syndromes are characterized by low or modestly elevated sCD25, and Still's disease is well known to cause hyperferritinemia, albeit to a lesser degree than HLH.[31,32]

Still's disease is an autoinflammatory disease formerly called JIA in children and Still's disease in adults, while now both pediatric and adult cases fall under the umbrella term of Still's disease.[28,33] Like HLH, patients with Still's disease present with fever, hyperferritinemia, liver dysfunction, and organomegaly. Still's disease is typically more indolent than HLH but a subset of patients with Still's disease can present with a particularly severe illness known as catastrophic adult-onset Still's disease. These patients can be particularly challenging to distinguish from HLH.[34] CRP and sCD25 levels can help distinguish these two conditions: CRP levels >130 mg/L and sCD25 levels <3,900 IU/mL are more suggestive of Still's disease and differentiate between HLH and Still's with a sensitivity of 91% and specificity of 93%.[32] Additionally, tissue biopsy can be helpful in these patients. Importantly, hemophagocytosis in the bone marrow, liver, lymph node, and other tissues is nonspecific and can be observed in any type of CSS **(Figure 1A)**.[35,36] In Still's disease, particularly in patients with a persistent cutaneous eruption (more so than the more classic evanescent pink rash), skin biopsies may reveal dyskeratosis, apoptotic keratinocytes in the superficial epidermis and cornified layer, and vacuolar interface change. These histological findings are highly specific for Still's disease in the correct clinical context **(Figure 1B)**.[37]

TAFRO can also mimic HLH. In most cases, TAFRO is idiopathic (human herpesvirus-8 negative) multicentric Castleman's disease (iMCD-TAFRO), but TAFRO without lymphadenopathy or iMCD has been described as well.[38,39] TAFRO syndrome, first described in 2010, is a condition characterized by thrombocytopenia, anasarca (edema, pleural effusion, and ascites), fever, reticulin myelofibrosis (or renal insufficiency), and organomegaly (hepatosplenomegaly and lymphadenopathy).[40] Hemophagocytosis is often a feature of bone marrow, liver and other tissue biopsies in TAFRO **(Figure 1C)**. TAFRO is primarily driven by IL-6 and is, therefore, associated with more marked elevations in CRP than are typically seen in HLH [38], while hyperferritinemia is typically more modest in TAFRO. Anasarca is considered an obligatory feature of TAFRO. When diagnosing HLH, Still's disease, or TAFRO, tissue biopsy is crucial for TAFRO. Patients with lymphadenopathy (which is often small volume in TAFRO, <3 cm in short axis and modestly fludeoxyglucose-positron emission tomography avid) require urgent biopsy, which should be excisional whenever possible. iMCD-TAFRO is a clinicopathological diagnosis, and therefore, communication between clinician and pathologist is crucial. Often, the changes associated with MCD, such as regressed/atrophic germinal centers, expanded mantle zones with "onion skin" appearance, polyclonal plasmacytosis, prominent follicular dendritic cells, and hypervascularity, can be read as "reactive" or non-diagnostic if the pathologist is not aware that iMCD is in the clinical differential diagnosis **(Figure 1D)**.[27]

Management of HLH

Well-designed prospective clinical trials are lacking for CSS. The overall mortality for adult HLH is high, upward of 40% in most centres, and patients over 65 years and/or with critical illness have a very guarded prognosis. The HLH-94 study is the largest prospective study previously performed for HLH treatment, in which

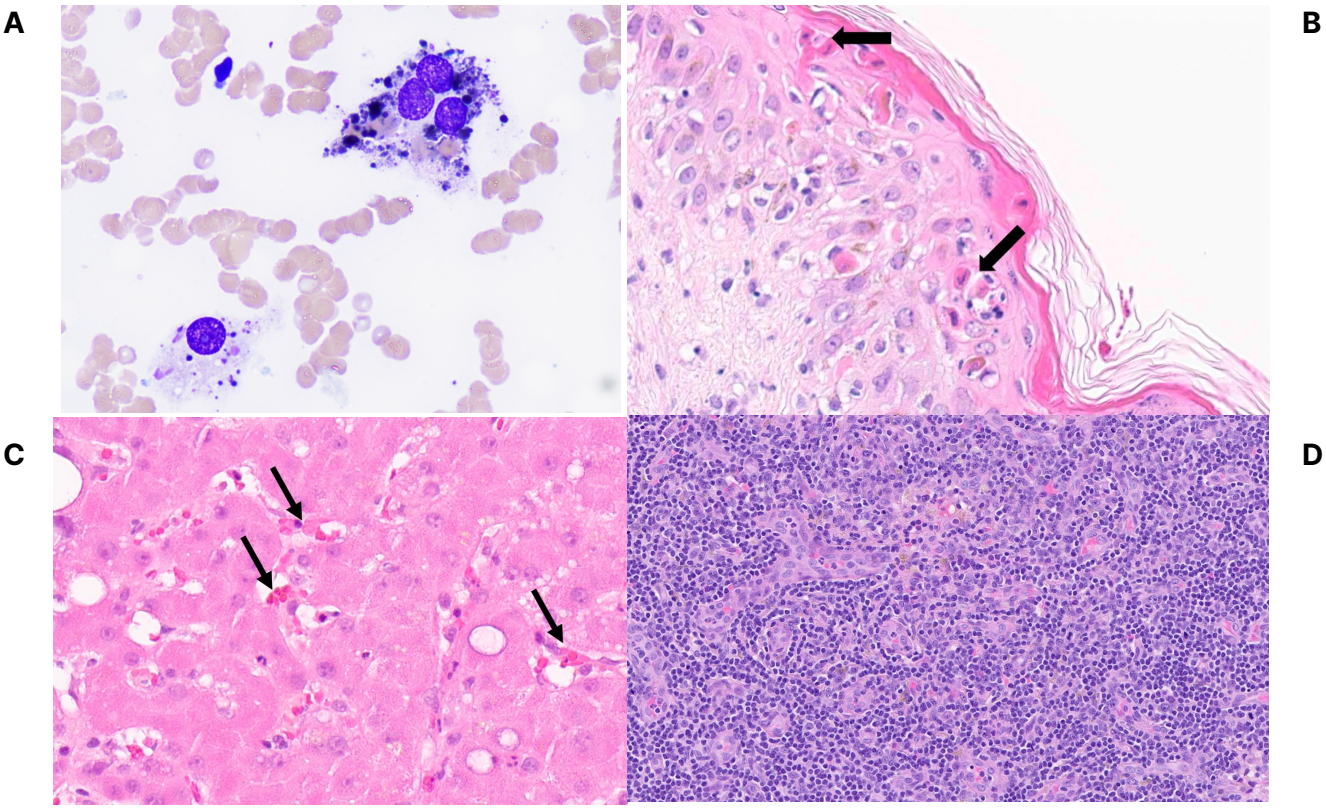

Figure 1. (A) Macrophages exhibiting haemophagocytic activity in the bone marrow of a 12-year-old girl with nodular lymphocyte-predominant Hodgkin lymphoma; *courtesy of Dr. Audi Setiadi, BC Children's Hospital*; (B) Dyskeratotic keratinocytes in the upper epidermis and cornified layer (arrows) of a 23-year-old female; characteristic of the persistent skin eruption in adult-onset Still's Disease; *courtesy of Dr. Sylvia Pasternak, Dalhousie University*; (C) Haematoxylin and eosin-stained core needle biopsy of liver showing reactive haemophagocytosis by sinusoidal Kupffer cells (arrows) in a 46-year-old man with iMCD-TAFRO; 400× magnification; *courtesy of Dr. Daniel Owen, Vancouver General Hospital*; (D) Lymph node showing hypervascular changes in a 22-year-old male with iMCD-TAFRO; *courtesy of Dr. Amrah Pirzada, Memorial University of Newfoundland*

optimized hyperinflammatory index), and critical illness.[24,25]

When approaching a patient with suspected HLH, in addition to a thorough history and physical examination, we order ferritin, sCD25, and CRP, and typically perform a bone marrow biopsy to look for specific causes such as lymphoma and infectious granulomas, as well as to examine for hemophagocytosis **(Figure 1)**. Infections, such as human immunodeficiency virus status, anaplasmosis (Atlantic Canada), Dengue fever, and tuberculosis should be assessed. We typically order Epstein-Barr virus (EBV) and cytomegalovirus viral loads (determined by PCR test). EBV is an important and distinctive cause of HLH associated with worse prognosis and, rarely, chronic active EBV.[26]

Distinguishing HLH from Other Cytokine Storm Syndromes

Identifying and accurately diagnosing patients with cytokine storm syndromes is a challenge for clinicians, particularly as these patients are often evaluated in the context of a busy inpatient consult service. While COVID-19-CSS is easily recognized because patients have an acute COVID-19 infection, HLH can be challenging to differentiate from other inflammatory syndromes, particularly severe Still's disease and iMCD-TAFRO. Diagnostic guidelines recommend measurement of cytokines such as IL-6 for iMCD,[27] and IL-18 for Still's disease,[28] but these are more helpful in theory than in practice for most clinicians. Many of the specialized tests of immune

249 pediatric patients with HLH were treated with etoposide-based therapies. This study showed significant improvement in overall survival to >50%, in a previously almost universally fatal disease.[41] While etoposide and corticosteroid-based therapy remain the standard for adults with secondary HLH,[42,43] new therapeutic tools are emerging.

Janus Kinase (JAK) inhibition with ruxolitinib has shown promise as an adjunctive therapy in HLH.[44-46] Several cytokines implicated in HLH, such as IL-2, IL-6, and IFN-γ, rely on JAK-dependent signalling pathways. Ruxolitinib has been examined as salvage therapy and is increasingly used as a first-line therapy as well for lower-risk patients, such as those with autoimmune/autoinflammatory HLH.[47-49] Our practice is to treat patients initially with dexamethasone and etoposide (often a lower dose of 75 mg/m^2) and then transition them to ruxolitinib-based therapy where possible to decrease exposure to corticosteroid and chemotherapy toxicity.

Emapalumab is a human monoclonal antibody directed against IFN-γ. It was initially studied in patients with primary HLH with relapsed/refractory disease, and response rates were greater than 60%, and overall survival was 70% at 12 months.[4] These results have also been confirmed in real-world data, in which response rates and overall survival rates were found to be comparable.[50] Studies in adults are limited, but small studies of patients with secondary HLH suggest a positive response.[51] Access to emapalumab is challenging in the Canadian context.

Other agents used to treat HLH include anakinra, an IL-1 antagonist, which may be particularly effective in patients with MAS.[52-54] IL-6 blockade with tocilizumab gained recognition in the era of the COVID-19 pandemic, where it demonstrated improved outcomes in patients with COVID-19-CSS. Small retrospective studies in HLH have also demonstrated a modest benefit in critically ill patients.[55-57] Nivolumab, an immune checkpoint inhibitor initially designed for cancer treatment, has been successfully used in patients with HLH secondary to EBV infection.[58,59]

In contrast, patients with severe Still's disease are typically treated with glucocorticoids initially. Those who are not responsive to steroids or have more severe disease can often benefit from either IL-1 or IL-6 blockade. In our experience, for severe Still's disease, rapid initiation of anakinra or tocilizumab is crucial for preventing end-organ damage and reducing toxicity from corticosteroids.[28,60,61]

The first-line treatment for iMCD-TAFRO is IL-6 inhibition with siltuximab (11 mg/kg intravenously [IV]) or tocilizumab (8 mg/kg, up to 800 mg, IV). Corticosteroids can be used as adjunctive therapy but should be tapered off quickly to minimize toxicity. Other agents that can be used for patients with relapsed or refractory disease include inhibitors of mammalian target of rapamycin, such as sirolimus, IL-1 antagonists, such as anakinra, tumour necrosis factor (TNF) inhibitors, such as adalimumab, thalidomide, and cytotoxic chemotherapy, such as lymphoma-based protocols.[39,62,63]

Conclusion

Clinicians must be able to differentiate HLH from disease mimickers, including disease entities such as Still's disease and the TAFRO variant of multicentric Castleman's disease. Simple inflammatory biomarkers (CRP, ferritin, sCD25), and histological findings from bone marrow, lymph node, and skin biopsies can be combined with clinical findings to arrive at a rapid working diagnosis. While etoposide-based therapies have classically been the mainstay of treatment, emerging therapies, including JAK inhibition and blockade of specific cytokines (IL-1, IL-6, IFN-γ, TNF), have an increasing role in treating patients.

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Financial Disclosures

M.G.: None declared.
L.C.: None declared.

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