Hemophagocytic Lymphohistiocytosis: New Grading Classification and Targeted Therapies

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Abstract: Hemophagocytic lymphohistiocytosis (HLH), both primary/familial HLH and secondary HLH, is associated with multiorgan dysfunction caused by excessive immune activation and cytokine release. The high morbidity and mortality rates are in part due to diagnostic challenges leading to a delay in treatment initiation. The diagnosis, which uses the Histiocyte Society clinical criteria from 2004 and the HScore, remains challenging, with limited improvement in outcomes. No grading system is available for HLH. Although etoposide with dexamethasone remains the most frequently used first-line regimen, various new therapies are now being employed in the management of HLH. The interferon gamma inhibitor emapalumab, the Janus kinase signal transducer and activator of transcription pathway inhibitor ruxolitinib, and the interleukin 6 (IL-6) inhibitor tocilizumab have been trialed in HLH management, with additional treatment options being inhibition of IL-18 and tumor necrosis factor alpha. Here, we summarize current management options for HLH; we also propose a new grading system for HLH based on Common Terminology Criteria for Adverse Events version 5.0 as well as on known prognostic factors (eg, abnormal bilirubin and transaminase levels, elevated creatinine level, respiratory failure, neutropenia, hypertriglyceridemia, hypoalbuminemia, and coagulopathy), which could standardize the diagnosis and guide prompt and appropriate management.

Keywords
Grading classification, hemophagocytic lymphohistiocytosis (HLH), risk factors, targeted therapy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, frequently fatal syndrome of pathological immune activation characterized by hyperactivation of lymphocytes and histiocytes, excessive cytokine release, and progressive multiorgan dysfunction. Familial (primary) HLH, including familial hemophagocytic syndromes 2 through 5 (FHL2-5), X-linked lymphoproliferative syndrome types 1 and 2 (XLP1+2), and several albinism syndromes with immunodeficiency, such as Griscelli syndrome type 2 (GS2), Chediak-Higashi syndrome, and Hermansky-Pudlak syndrome type 2 (HPS2), arises owing to inherited defects in genes involved in cytotoxic granule-mediated apoptosis.[1] Familial HLH, typically presenting in infancy, occurs in approximately 1 per 50,000 to 100,000 live births, although the rate may be higher in populations in which consanguinity is common.[2,3] However, the rate may be underestimated, as HLH can be the initial presentation of inborn errors of immunity beyond familial HLH, with up to 25% of cases currently classified as secondary HLH (sHLH) potentially linked to an underlying genetic immune disorder.[4,5] The French National Registry of Primary Immunodeficiencies (CEREDIH) reports an overall prevalence ranging from 3.8 to 15.4 per 100,000 in children and from 1.3 to 5.4 per 100,000 in adults.[6]

The acquired form, sHLH, results from various triggers, such as autoimmune or autoinflammatory diseases, infections, and malignancies. Although HLH was initially thought to be a pediatric disease, recognition in adults has grown, with nearly 40% of cases now diagnosed beyond childhood. Historically, the overall estimated incidence of sHLH was 1 to 2 cases per million per year.[7] However, the incidence of HLH diagnoses has increased significantly in the last 2 decades, with an annual increase of 11%.[8] The majority of HLH cases (approximately 70%) were in individuals aged 15 years and older, indicating a higher prevalence in adults than in children. Specifically, the incidence of HLH in children younger than 5 years showed no increase during the study period, contrasting with significant increases in older age groups. The rising incidence of HLH in adults may be attributed to increased awareness and improved diagnostic techniques, alongside a growing prevalence of associated comorbidities. A wide range of conditions may trigger sHLH, particularly in adults, including Epstein-Barr virus infection,[9] hematologic malignancies,[10] systemic lupus erythematosus,[11] and more recently immunotherapies such as immune checkpoint inhibitors[12] and chimeric antigen receptor (CAR) T-cell therapy.[13]

Diagnosis

The true incidence of sHLH is not well established, mainly owing to challenges in its diagnosis, which is based mostly on clinical criteria established in the 2004 guidelines of the Histiocyte Society.[14] Key diagnostic criteria include prolonged fever, splenomegaly, cytopenias (anemia, thrombocytopenia, and leukopenia), hypertriglyceridemia, hyperferritinemia, elevated levels of soluble CD25 (sCD25), and diminished natural killer (NK) cell activity. Notably, the HScore has been developed to assist in the diagnosis, offering a scoring system that combines clinical features and laboratory findings to provide an estimated probability of HLH.[15,16] One limitation of the HScore is potential overlap with other conditions that present with similar laboratory and clinical features. For example, in patients undergoing CAR T-cell therapy, the HScore may not reliably distinguish HLH from cytokine release syndrome or other immune-related complications.[17] The overlap of clinical symptoms can obscure the diagnosis, emphasizing the necessity for a high index of suspicion, especially in cases with unexplained fever and cytopenias.

The diagnosis of HLH relies on the HLH-2004 criteria and the HScore, both of which have been validated in various clinical settings.[15,18] A recent multicenter validation found that the original HLH-2004 criteria with a decreased cutoff of 4 had the best performance across 13 validation cohorts, achieving a mean sensitivity of 86.5% and a mean specificity of 86.1% for HLH diagnosis.[18] The original HLH-2004 criteria were followed by the revised HLH-2004 criteria and the HScore, which had mean sensitivities of 83.8% and 82.4%, respectively. The commonly used HScore cutoff for diagnosing HLH is 169, although population-specific adjustments have been proposed.[19,20] The HScore is a cost-effective and readily applicable tool, especially in resource-limited settings, because it does not require specialized tests to evaluate NK cell activity or sCD25 levels. Furthermore, reliance on bone marrow biopsy for hemophagocytosis and specialized tests (eg, sCD25) can delay the diagnosis in clinical practice.

Identifying prognostic risk factors for mortality in HLH remains challenging owing to the heterogeneous nature of the disease, which requires distinguishing between primary and secondary HLH and evaluating for diverse underlying triggers, such as infections, malignancies, and autoimmune conditions. Studies vary in their methodologies, with some reporting odds ratios (ORs) and others hazard ratios (HRs), limiting direct comparisons. Additionally, different studies employ varying cutoff thresholds for the same biomarkers, complicating pooled analysis. With increasing awareness of HLH diagnosis, rising incidence, and emerging therapeutic options, it is essential to recognize moderate- and high-risk mortality factors, as summarized in Tables 1A and 1B.

Elevated bilirubin levels are a significant prognostic factor in patients with HLH, particularly in pediatric

Table 1A. Factors Associated With Increased Risk for Mortality Following HLH in Pediatric Patients*

1-3 times greater risk	>3 times greater risk
Etoposide use[46]	Albumin <20 g/L[22,36,46-48]
Hypofibrinogenemia (≤1.5 g/L)[39,48]	Neutrophils <0.5×10^9/L[22,23,30]
	Bilirubin >1.8 mg/dL[21-24]
	aPTT >65 s[21,23,36]
	CNS involvement[24,30,41,48]
	DIC[31]
	Hyperferritinemia (>2000 μg/L)[24]
	Platelets <40×10^9/L[22,24,41,48]
	ARDS[31]
	Hemoglobin <60 g/L[47]
	Renal insufficiency (CrCl <90 mL/min/1.73 m^2)[30,31]
	INR >1.68[23]
	Lactate dehydrogenase >4310 U/L[22,23,36]

ARDS, acute respiratory distress syndrome; aPTT, activated partial thromboplastin time; CNS, central nervous system; CrCl, creatinine clearance; DIC, disseminated intravascular coagulopathy; HLH, hemophagocytic lymphohistiocytosis; INR, international normalized ratio.

*Cutoff values for continuous variables varied across the included studies, reflecting differences in patient populations, timing of measurement, assays, and analytic methods. To facilitate comparison and improve generalizability, when multiple thresholds were reported for the same risk factor, we summarized the lowest (minimal) threshold associated with increased mortality risk. Accordingly, the cutoffs presented should be interpreted as conservative "rule-in" values rather than universally applicable, definitive thresholds.

populations. In a cohort of 91 pediatric patients, hyperbilirubinemia was independently associated with early fatal outcomes.[21] Similarly, Bin and colleagues reported a relative risk of 2.86 (95% CI, 0.83-9.88) when the bilirubin level was more than 2 times the upper limit of normal (ULN), indicating a trend toward poor prognosis despite borderline significance.[22] In another pediatric population, Kogawa and colleagues found significantly higher bilirubin levels among nonsurvivors of HLH associated with Epstein-Barr virus infection (*P*=.016).[23] In a multicenter retrospective analysis including 232 children, elevated bilirubin (>50 μmol/L) was associated with treatment failure or death (adjusted HR, 3.2; 95% CI, 1.3-8.1; *P*=.011).[24] Similar data have been reported in adults with HLH, in whom hyperbilirubinemia (≥2 mg/dL) was correlated with increased mortality (HR, 6.2; 95% CI, 2.1-18.2; *P*=.0009).[25]

Like bilirubin, both aspartate transaminase (AST) and alanine transaminase (ALT) have been independently associated with prognosis in HLH. A study of 204 adult patients with HLH found that levels of AST below 119 U/L were associated with a better prognosis, with an HR of 0.405 (95% CI, 0.169-0.967).[26] Elevated levels of ALT (≥40 U/L) were associated with a worse prognosis, with an HR of 1.716 (95% CI, 1.092-2.696; *P*=.019).[27] In a different study, AST levels of at least 111 U/L (HR, 1.005; 95% CI, 1.001-1.008; *P*=.004) and ALT levels of at least 41 U/L (HR, 1.016; 95% CI, 1.001-1.031; *P*=.034) were identified as independent risk factors for mortality in adults with sHLH.[28]

The association between elevated creatinine and poor prognosis in HLH may be attributed to cytokine-mediated injury, hypoperfusion, hemophagocytic infiltration, and complement activation. Renal impairment in HLH can result from systemic inflammation, cytokine storms, and multiorgan failure, all of which are hallmarks of the disease.[29] A study of 24 childhood cases of HLH in Thailand identified renal insufficiency as one of the adverse risk factors for early death (HR, 28.2; 95% CI, 2.1-373.8).[30] Another study, involving 170 pediatric patients with HLH, incorporated creatinine into a nomogram model for predicting 28-day mortality, highlighting its prognostic utility in this population.[31] A retrospective study of 85 adults with sHLH found that elevated creatinine levels were an independent risk factor for mortality, with an HR of 1.016 (95% CI, 1.001-1.031).[28] Another study, of 204 adult patients, identified elevated creatinine (≥118 μmol/L) as one of the independent prognostic factors for 90-day overall survival (OS; HR, 4.127; 95% CI, 1.708-9.972; *P*=.002).[26]

Table 1B. Factors Associated With Increased Risk for Mortality Following HLH in Adults*

1-3 times greater risk	>3 times greater risk
Age ≥65 y[26–28,33]	Bilirubin >2 mg/dL[25]
Albumin <25 g/L[35,45,49]	Bleeding events[33]
ALT ≥41 U/L	
AST ≥111 U/L[26,28,49]	
CRP >15.5 mg/L[50]	
EBV infection[49]	
Hyperferritinemia (>1000 μg/L)[26,37,49]	
Hypofibrinogenemia (≤150 mg/dL)[33,37,38]	
Creatinine ≥118 μmol/L[26,27,50]	
Hepatomegaly[49]	
Lactate dehydrogenase >687 U/L[26]	
Malignancy-associated HLH[49,51,52]	
Platelets <40×10^9/L[34,40,42,52]	
Neutrophils ≤1.21×10^9/L[33]	
aPTT ≥47.3 s[26,33,35]	
PT ≥17.1 s[26,35,52]	
Troponin I ≥2.15 ng/mL[28]	
Interleukin 6 >70 pg/mL[53]	
ARDS[32]	

ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; PT, prothrombin time; y, years.

*Cutoff values for continuous variables varied across the included studies, reflecting differences in patient populations, timing of measurement, assays, and analytic methods. To facilitate comparison and improve generalizability, when multiple thresholds were reported for the same risk factor, we summarized the lowest (minimal) threshold associated with increased mortality risk. Accordingly, the cutoffs presented should be interpreted as conservative "rule-in" values rather than universally applicable, definitive thresholds.

Respiratory failure is a common complication in HLH, often manifesting as acute respiratory distress syndrome (ARDS). Studies have shown that patients with HLH in whom ARDS develops have a significantly poorer prognosis. For instance, in a retrospective study of 50 critically ill patients with HLH, the presence of respiratory failure was significantly associated with decreased survival, with a median OS of 0.259 months vs 2.5 months in those without respiratory failure (P=.001).[32] Similarly, a pediatric retrospective analysis involving 170 patients identified ARDS as a strong predictor of mortality, with an OR of 9.02 (95% CI, 2.59-72.74; P=.001), underscoring the critical effect of respiratory compromise on outcomes in both adults and children with HLH.[31]

HLH is often complicated by coagulopathy, which manifests as thrombocytopenia, hypofibrinogenemia, and prolonged clotting times, including the activated partial thromboplastin time (aPTT). These coagulation abnormalities are associated with an elevated risk of bleeding and poor outcomes. Studies have consistently shown that coagulation dysfunction is a critical prognostic factor in HLH, influencing both short- and long-term survival rates.[33,34] Prolonged aPTT has been identified as an independent risk factor for poor prognosis in patients with HLH. In a retrospective study of 141 patients with sHLH, multivariate analysis revealed that an aPTT of at least 47.3 seconds was associated with an increased risk of mortality (HR, 1.684; 95% CI, 1.058-2.681; P=.028).[33] In a retrospective analysis of 151 patients with HLH performed to evaluate clinical characteristics and

biochemical parameters for predicting 30-day mortality, both the aPTT (43.50 vs 35.50 seconds; *P*<.001) and prothrombin time (PT)/international normalized ratio (INR) (1.21 vs 1.09; *P*<.001) were significantly prolonged in the nonsurvivors.[35] In a pediatric retrospective analysis of 227 children with a diagnosis of HLH whose median age was 25 months, an aPTT of at least 65 seconds was found to be an independent risk factor for poor OS (OR, 3.094; 95% CI, 1.195-8.008; *P*=.02).[36]

Like a prolonged aPTT, low fibrinogen levels have been consistently associated with worse survival outcomes. A study of 179 adults with sHLH found that fibrinogen levels of no more than 1.34 g/L were independently associated with inferior OS (HR, 2.27; 95% CI, 1.46-3.84; *P*=.02).[37] In a different analysis, of 293 adult patients with sHLH, each decrease of 1 U in the fibrinogen level was associated with a 32% decrease in survival when the serum fibrinogen levels were no more than 1.76 g/L (HR, 0.68; 95% CI, 0.55-0.83; *P*<.001).[38] In pediatric HLH, hypofibrinogenemia is also a critical prognostic factor. A study of 91 pediatric patients found that low fibrinogen levels, particularly when combined with hypertriglyceridemia, were associated with an elevated risk of multiple organ dysfunction syndrome (86.2%; OR, 16.24; *P*=.0002) and 30-day mortality (57.1%; OR, 5.78; *P*=.0187).[39]

Thrombocytopenia is a well-established prognostic factor in HLH. Studies have consistently shown that lower baseline platelet counts are associated with increased mortality rates in both adult and pediatric patients. For instance, a retrospective study of 292 adults with sHLH found that a decreased platelet count was associated with an elevated risk of mortality, with an adjusted HR of 1.84 (95% CI, 1.05-3.24; *P*=.024).[40] Similarly, in pediatric HLH, platelet counts below $44\times10^6/mm^3$ were identified as a significant predictor of early mortality (OR, 8; 95% CI, 1.3-49; *P*=.024).[41] Another pediatric study, which included 116 patients with HLH, found that platelet count normalization within 2 weeks of therapy was a strong predictor of resolution after initial treatment, with an OR of 18.4 (95% CI, 2.7-122.9; *P*= .003).[22] The prognostic value of the platelet count is further supported by its inclusion in various predictive models. For example, a novel prognostic model for adult HLH includes the platelet count as one of the independent risk factors.[34,42]

Several studies have highlighted the prognostic significance of the absolute neutrophil count in HLH. A retrospective study of 141 patients with sHLH found that an absolute neutrophil count of 1.21×10^9/L or less was an independent prognostic factor for poor outcomes (OR, 1.671; 95% CI, 1.059-2.635; *P*=.027).[33] In 116 pediatric patients with HLH, an absolute neutrophil count of less than 0.5×10^9/L was a risk factor for early mortality, with a risk ratio of 5.01 (95% CI, 1.55-16.20; *P*=.007).[22]

Hypertriglyceridemia is frequently observed in patients with HLH and is one of the diagnostic criteria. It arises from cytokine-mediated inhibition of lipoprotein lipase, hepatic dysfunction, and immunosuppressive treatments.[43] In adult populations with HLH, elevated triglycerides (TGs) are associated with poor prognosis. A study of 247 adult patients with sHLH found that OS was worse in those with a TG level greater than 3.08 mmol/L than in those with a TG level of 3.08 mmol/L or less (40 vs 160 days; *P*=.007).[44] In an analysis of 117 pediatric patients, those with elevated TG values (>3.0 mmol/L) within 72 hours of hospitalization in combination with low fibrinogen (<150 mg/dL) showed increasing trends of multiple organ dysfunction syndrome (OR, 4.88; 95% CI, 1.05-22.57; *P*=.0425).[39]

Hypoalbuminemia in HLH is often caused by cytokine-induced liver dysfunction, which impairs albumin synthesis. In adult HLH, hypoalbuminemia is consistently identified as an independent predictor of poor prognosis. Studies have shown that low albumin levels correlate with higher mortality rates and shorter OS. In a meta-analysis that included 291 patients with HLH, the difference in the albumin level between the experimental group (fatal cases) and the control group (survival cases) was significant in most studies, with a pooled mean difference of −3.80 g/dL and a 95% CI of −5.11 to −2.49, highlighting the albumin level as a potential prognostic indicator.[35] Similarly, a systematic review of 23 studies of sHLH highlighted a low albumin level (<2.8 g/dL) as one of the most frequently reported adverse prognostic factors.[45] In a pediatric single-center experience, low albumin levels were associated with increased mortality risk, with an OR of 2.3 (95% CI, 1.48-3.43, *P*=.001).[46] In another pediatric analysis, low albumin (<25 g/L) in non–malignancy-related HLH was associated with worse outcomes (HR, 7.71; CI, 3.10-19.19, *P*<.001).[47]

Given these data, we propose a new HLH grading system to enhance prognostic precision by adapting the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) framework on the basis of maximum severity of organ dysfunction (Table 2). This approach assigns standardized grades (0-5) to critical parameters often affected in HLH: hepatic (bilirubin, transaminases), renal (creatinine), respiratory, hematologic (platelet and neutrophil counts), coagulation (fibrinogen, aPTT), and metabolic (TG, albumin). The daily grade is defined as the highest grade of any of the subcategories. For instance, bilirubin elevations greater than 3 times the ULN or transaminase levels at least 5 times the ULN could correspond to grade 3 hepatic injury. Similarly, decreased oxygen saturation at rest (eg, a reading of <88% by pulse oximetry) would indicate a

Table 2. Proposed Grading Classification of HLH

	Grade 1	Grade 2	Grade 3	Grade 4	References
Hepatic					
Bilirubin level	>1.5×ULN if baseline was normal; >1.5×baseline if baseline was abnormal	>1.5-3.0×ULN if baseline was normal; >1.5-3.0×baseline if baseline was abnormal	>3.0-10.0×ULN if baseline was normal; >3.0-10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal	21-25
Transaminase levels	>3.0×ULN if baseline was normal; >3.0×baseline if baseline was abnormal	>3.0-5.0×ULN if baseline was normal; >3.0-5.0×baseline if baseline was abnormal	>5.0-20.0×ULN if baseline was normal; >5.0-20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal	26-28,49
Renal					
Creatinine level	>1.5×ULN if baseline was normal; >1.5×baseline if baseline was abnormal	>1.5-3.0×ULN if baseline was normal; >1.5-3.0×baseline if baseline was abnormal	>3.0-6.0×ULN if baseline was normal; >3.0-6.0×baseline if baseline was abnormal	>6.0×ULN if baseline was normal; >6.0×baseline if baseline was abnormal	26,27,30,31,50
Blood					
Activated partial thromboplastin time	>1.5×ULN	>1.5-2.5×ULN	>2.5×ULN; bleeding		21,23,26,33,35,52
Fibrinogen level	<1.0-0.75×LLN; if abnormal, <25% decrease from baseline	<0.75-0.5×LLN; if abnormal, 25%-50% decrease from baseline	<0.5-0.25×LLN; if abnormal, 50%-75% decrease from baseline	<0.25×LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	33,37-39,48
Platelet count	<LLN-75,000/mm^3; <LLN-75.0×10^9/L	<75,000-50,000/mm^3; <75.0-50.0×10^9/L	<50,000-25,000/mm^3; <50.0-25.0×10^9/L	<25,000/mm^3; <25.0×10^9/L	22,24,33,34,40-42,48,52
Absolute neutrophil count	<LLN-1500/mm^3; <LLN-1.5×10^9/L	<1500-1000/mm^3; <1.5-1.0×10^9/L	<1000-500/mm^3; <1.0-0.5×10^9/L	<500/mm^3; <0.5×10^9/L	22,23,30,33
Triglyceride level	150-300 mg/dL; 1.71-3.42 mmol/L	>300-500 mg/dL; >3.42-5.7 mmol/L	>500-1000 mg/dL; >5.7-11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L, life-threatening consequences	39,43,44
Albumin level	<LLN-3 g/dL; <LLN-30 g/L	<3-2 g/dL; <30-20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	22,35,36,45-49

ULN, upper limit of normal; LLN, lower limit of normal.

grade of 3, directly influencing therapeutic urgency. This model mirrors strategies used in previous frameworks for grading clinical tumor lysis syndrome, as well as modified diagnostic criteria and grading for sinusoidal obstruction syndrome, such as Cairo-Bishop criteria, but it is tailored to the inflammatory and immunopathologic context of HLH.[54,55] Using this standardized, complication-based system to indicate severity could streamline triage, guide immunosuppressive intensity, and harmonize clinical trial endpoints.

Management

The prompt identification and initiation of treatment are essential for the management of HLH. The availability of fast turnaround times for inflammatory cytokine panels is critical for the timely diagnosis and monitoring of response to treatment. The development of semiautomated microfluidic enzyme-linked immunosorbent assay (ELISA) systems and multiplex assays has significantly improved the turnaround time for cytokine panel analysis. These technologies allow the simultaneous measurement of multiple biomarkers, such as soluble interleukin 2 receptor alpha (sIL-2Rα) and C-X-C motif chemokine ligand 9 (CXCL9), in serum samples. By insourcing these assays, laboratories can reduce turnaround times by approximately 2 days and achieve cost savings.[56,57]

In addition to the treatment used, the prognosis in HLH depends on the patient's age, the underlying cause, whether organ dysfunction is present, laboratory markers, and the cytokine profile. Older adults have higher mortality rates, whereas children younger than 6 years have better outcomes with timely treatment.[27,58] Survival is worse in cases of malignancy-associated HLH, especially HLH due to T-/NK-cell lymphomas, than in infection- or autoimmune-related cases.[59]

Etoposide, in combination with dexamethasone, has revolutionized the treatment of HLH, particularly in pediatric patients. The HLH-94 protocol, which includes etoposide and dexamethasone, has significantly improved 5-year survival rates from less than 5% in the 1980s to approximately 60% in contemporary studies.[60] In adults, the role of etoposide and dexamethasone is more controversial and treatment is highly variable, with different approaches documented. Mortality rates in adult HLH range from 42% to 75% and the 30-day mortality is 20% to 27%, indicating poorer outcomes.[61] In a recent meta-analysis, etoposide-based therapy demonstrated significantly improved overall response in adult patients with HLH (1.95; 95% CI, 1.51-2.53).[62] During the past 30 years, despite numerous advances in our understanding of HLH pathophysiology, no significant changes were made to the first-line treatment option.

Interferon Gamma Inhibition

Interferon gamma (IFN-γ) is a well-established proinflammatory cytokine that mediates the final damage of the stem cell compartment in HLH. It is known to inhibit the production of several hematopoietic cell types.[63,64] Furthermore, IFN-γ leads to cytopenias by preventing the engagement of thrombopoietin to its receptor (c-MPL), which is a primary positive regulator of hematopoietic stem and progenitor cell survival.[65] Emapalumab (Gamifant, Sobi), a fully human anti–IFN-γ monoclonal antibody, has emerged as a promising therapeutic option for patients with HLH, particularly primary HLH (Figure). In the initial clinical trial, patients treated with emapalumab showed an overall response rate of 64.7%, with 26% achieving a complete response and 30% achieving a partial response.[14] At the last observation, 20 of 27 patients (74%) in the previously treated group were alive, with an estimated probability of survival of 73.4% (95% CI, 52.2 to 86.4) at 12 months.[66] During emapalumab treatment, CXCL9 levels rapidly and markedly decreased (median, 30% of the baseline level on day 5). The median time to response was 8 days in the patients who received emapalumab. Emapalumab has also been used off label in patients with sHLH, including those with underlying rheumatologic, malignancy, or infectious triggers. In a real-world study of 51 patients with sHLH, emapalumab demonstrated 12-month survival probabilities of 85.7% for patients with underlying rheumatologic disease, 23.5% for those with underlying malignancy, and 55% for patients in the "others" category.[67]

JAK/STAT Inhibition

The Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway has a vital role in inflammation, so that it is an important target for medical therapy in many inflammatory and immune-mediated disorders. Inhibitors of the JAK/STAT pathway are being increasingly used in the treatment of rheumatoid arthritis,[68] skin disorders,[69] inflammatory bowel disease,[70] malignancies, and other autoimmune conditions.[71] HLH, both primary and secondary, is associated with the overproduction of cytokines like IFN-γ, tumor necrosis factor, and various interleukins (IL-1, -6, -10, and -18).[1] Many of these cytokines result in activation of the JAK/STAT signaling pathway,[72] with a potential for JAK/STAT pathway inhibitors in the management of HLH. Wei and colleagues demonstrated tolerance of ruxolitinib (Jakafi, Incyte) as salvage therapy for refractory/recurrent HLH.[73] Meyer and colleagues showed that the addition of ruxolitinib to dexamethasone, already an important agent in the management of HLH, may ultimately improve treatment outcomes.[74] More recently, Keenan and colleagues have studied agents like the JAK1 inhibitor itacitinib and the JAK2 inhibitor fedratinib (Inrebic, Bristol-Myers Squibb) along with the JAK1/2 inhibitor ruxolitinib in mouse models.[75]

Interleukin 6 Inhibition

The IL-6 signaling pathway involves binding to its receptor, IL-6R, and activating the gp130 transmembrane protein, which triggers intracellular signaling cascades such as the JAK/STAT pathway.[76] This pathway promotes the production of acute-phase proteins and sustains the inflammatory response. In HLH, the dysregulated production of IL-6 creates a positive feedback

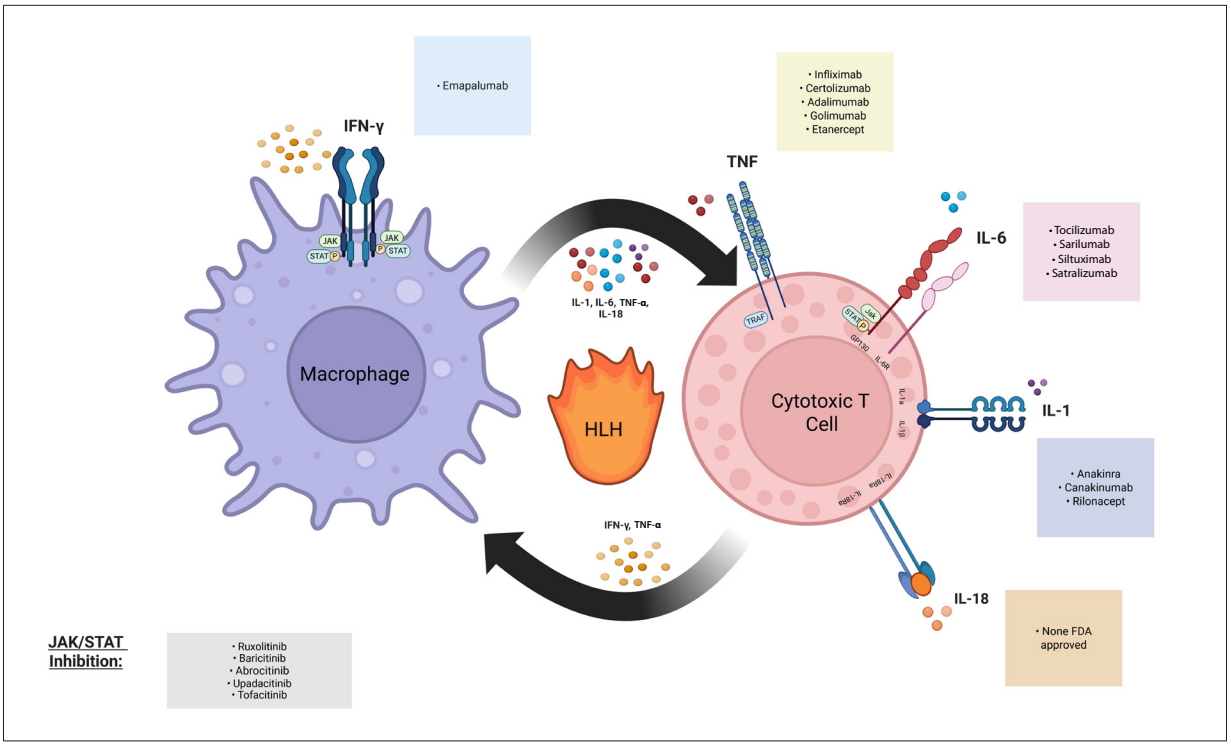

Figure. Schematic representation of HLH-driven cytokine storm and targeted treatments. Figure created in BioRender. Schaefer, E. (2025) https://BioRender.com/lb7xhli.

FDA, US Food and Drug Administration; HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL, interleukin; JAK/STAT, Janus kinase signal transducer and activator of transcription.

loop, amplifying the cytokine storm and worsening the clinical manifestations of the disease.[77] Tocilizumab is a humanized anti–IL-6R antibody that binds to soluble and membranous IL-6R and competitively blocks the binding of IL-6 to IL-6R or soluble IL-6R.[77] A recent study has demonstrated the potential benefit of IL-6 blocking in critically ill patients with hemophagocytic syndrome.[78] Remission was observed in 8 of 9 patients after tocilizumab (88.9%).

Interleukin 18 Inhibition

IL-18 is a central proinflammatory cytokine that is elevated in both primary and secondary HLH, although its role and magnitude differ by etiology. IL-18 has induced IFN-γ and amplified immune dysregulation, and it has emerged as a compelling therapeutic target. In genetic forms of HLH, IL-18 levels can exceed 100,000 pg/mL, more than 100-fold higher than normal, owing to constitutive or dysregulated inflammasome activation.[79] Patients with sHLH—often triggered by infections, malignancies, or autoimmune diseases—also demonstrate elevated IL-18 levels; these are typically in the range of 5000 to 20,000 pg/mL although occasionally higher, particularly in macrophage activation syndrome (MAS).[80] Tadekinig alfa, a recombinant human IL-18–binding protein, is a naturally occurring inhibitor that binds free IL-18. In a recent open-label phase 2 study, 23 patients were treated for adult-onset Still disease.[81] Irrespective of the tadekinig alfa dose, a response rate of 50% was observed.

Tumor Necrosis Factor Alpha Inhibition

Tumor necrosis factor alpha (TNF-α) is a central mediator of inflammation, playing a pivotal role in the cytokine storm observed in HLH/MAS. It promotes the activation of immune cells, including macrophages and T lymphocytes, leading to the release of other proinflammatory cytokines such as IL-1, IL-6, and IFN-γ.[82] The role of TNF-α inhibition in HLH is unclear. Some case reports indicate that patients with MAS have shown rapid improvement when treated with TNF-α blockade[82,83]; however, some patients experienced worsening of their MAS symptoms after the initiation of TNF-α therapy.[84]

Interleukin 1 Beta Inhibition

Cytokine IL-1, which plays an important role in the normal immune response, is markedly elevated in HLH because of the abnormal activation of inflammatory cells. The IL-1 inhibitor anakinra (Kineret, Sobi) has been

approved for the management of various immune-mediated and rheumatologic disorders, with increasing use in the management of both children and adults with HLH. When Bami and colleagues used anakinra with or without dexamethasone in 6 children with sHLH, HLH remission occurred in all patients without the use of etoposide.[85] In adults with sHLH, Lee and colleagues demonstrated a higher OS rate at 1 year in those treated with anakinra and corticosteroids than in those who received the etoposide-containing treatment regimen.[86] Although the difference was not statistically significant (HR, 0.29; *P*=.25*)*, anakinra was noted to be well tolerated overall. Additional studies are needed, but anakinra remains an alternative for consideration, especially when etoposide cannot be used.

Conclusion

The true incidence and prevalence of HLH remain challenging to quantify accurately because many cases go unrecognized or are misclassified, particularly within the spectrum of sHLH and overlapping inflammatory syndromes. Although some studies estimate an incidence of 1 to 2 per million annually, this figure likely underrepresents the burden of disease, especially with the emerging recognition of HLH in adults and nonclassic presentations. Compounding the diagnostic uncertainty are the limitations of current criteria, such as HLH-2004 and the HScore, whose estimated sensitivity and specificity of approximately 85% lead to false negatives and delayed diagnoses. More importantly, these criteria are binary and do not incorporate a system for grading organ dysfunction or HLH severity, features that limit their clinical utility in tailoring aggressive or targeted therapies.

To address this problem, we propose a novel HLH grading framework, adapted from the CTCAE v5.0, that integrates the biomarkers and types of organ dysfunction most often implicated in HLH: bilirubin, transaminase, creatinine, fibrinogen, platelet, neutrophils, triglyceride, and albumin levels and the aPTT. This grading approach would allow clinicians to assess the maximum organ involvement attributable to HLH and tailor immunotherapy or adjunctive treatments on the basis of severity, akin to the models used in veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) and tumor lysis syndrome.[54,55] Ultimately, a CTCAE-based HLH grading system could facilitate more precise clinical trial stratification and enhance outcome prediction in future HLH research. The introduction of such a system holds promise for guiding advanced therapies, particularly immunotherapies. Agents such as ruxolitinib, the IFN-γ inhibitor emapalumab, and the IL-1 inhibitor anakinra are being increasingly employed, especially in refractory or relapsed HLH. However, clear criteria for escalation remain elusive. A grading framework would support clinical trials, personalized treatment escalation, and the early deployment of targeted biologics in severe HLH, potentially improving survival and reducing treatment-related morbidity.

Disclosures

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