

# Hemophagocytic Lymphohistiocytosis: An Updated Overview and Management Approach in the Critical Care Setting

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## ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) constitutes a rare and potentially life-threatening immunological syndrome. It manifests in both primary (genetic) and secondary (acquired) forms, exhibiting diverse clinical and laboratory features, posing challenges to accurate diagnosis, particularly within critical care settings. Early identification and intervention are of vital importance for improving patient survival. This article comprehensively explores the existing literature, encompassing the classification, pathophysiology, and clinical presentation of HLH. Special emphasis is placed on identifying prognostic factors, organ failure, and associated complications. Moreover, a detailed narrative of proposed management strategies, including immuno- and myelosuppressive options, is presented. Further research directions are suggested to enhance the understanding and treatment of this complex disorder.

**KEYWORDS** - Hemophagocytic lymphohistiocytosis, critical care, complications, inflammatory mediators

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## 1. INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe immunological disorder characterized by immune hyperactivation, possibly leading to multiple organ dysfunction and potentially life-threatening complications. Historically, HLH can be divided into two major categories based on etiology: first, primary, which is the genetic/inherited form, and secondary, which occurs as a complication of underlying conditions such as infections, malignancy, or autoimmune diseases [1]. “HLH disease” and “HLH disease mimics” are the terms presented by the North American Consortium for Histiocytosis (NACHO) recently to give more accurate and detailed definitions for HLH [2]. Due to the vague clinical symptoms of HLH, it is crucial to consider differential diagnoses to prevent unnecessary or harmful immune suppression from HLH therapy.

In general, the prevalence of HLH is estimated to be 1 in every 3000 cases in tertiary pediatric hospitals [3]. The incidence of primary HLH, in specific, ranges from 1 to 225 per 300,000 live births [4]. Limited data is available for HLH in adults, with an estimated incidence of approximately 1 in 2,000 admissions at tertiary medical centers [5].

The principal clinical and laboratory presentations encompass fever, hepatomegaly, and splenomegaly, cytopenia (including anemia, thrombocytopenia, and leukopenia), hepatic dysfunction, elevated serum levels of triglycerides and ferritin, and histopathological confirmation of hemophagocytosis (Table 1.) [1, 6, 7]. However, many patients present with atypical features and are not necessarily fulfilling the diagnostic criteria. Therefore, the diagnosis of HLH poses challenges due to the diverse triggering mechanisms, clinical presentations, and significant hematologic and immunological complications. These complexities can often lead non-hematologist healthcare providers to consider alternative causes, making the accurate diagnosis of HLH more difficult [8]. In addition, HLH can be misdiagnosed in individuals with septic shock due to overlapping causes and symptoms [9]. A retrospective analysis of patients admitted to the intensive care unit (ICU) revealed that 7 out of 9 adult patients suffering from HLH remained undiagnosed, emphasizing the need for increased awareness in the ICU settings. Patients with persistent fever, bicytopenia, and splenomegaly should raise suspicion for HLH [10].

The most frequent HLH complications necessitating admission to the ICU include multior-

gan failure, especially respiratory failure [4]. Without treatment, primary and secondary HLH carry a significant mortality rate of 44- 85% and 50-75%, respectively. Therefore, early recognition and immediate treatment are crucial to improve patient survival and minimize complications [4,11]. Therapy focuses on countering the excessive immune response, using immuno- and myelosuppressive medications such as high-dose corticosteroids and topoisomerase-II inhibitors like etoposide and/or hematopoietic stem cell transplantation (HSCT) [3].

In this review, we comprehensively summarize HLH management in critical care settings, highlighting current strategies and emerging advancements in treatment for improved patient outcomes.

**Table 1.** Revised Diagnostic Guidelines for HLH [7]

**The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled :**

- (1) A molecular diagnosis consistent with HLH
- (2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
  - Fever
  - Splenomegaly
  - Cytopenias (affecting  $\geq 2$  of 3 lineages in the peripheral blood):
    - Hemoglobin  $< 90$  g/L (in infants  $< 4$  weeks: hemoglobin  $< 100$  g/L)
    - Platelets  $< 100 \times 10^9$  /L
    - Neutrophils  $< 1.0 \times 10^9$  /L
  - Hypertriglyceridemia and/or hypofibrinogenemia:
    - Fasting triglycerides  $\geq 3.0$  mmol/L (i.e.,  $\geq 265$  mg/dl)
    - Fibrinogen  $\leq 1.5$  g/L
  - Hemophagocytosis in bone marrow or spleen or lymph nodes
  - No evidence of malignancy
  - Low or absent NK-cell activity (according to local laboratory reference)
  - Ferritin  $\geq 500$  mg/L
  - Soluble CD25 (i.e., soluble IL-2 receptor)  $\geq 2,400$  U/ml

Henter JL, Horne AC, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131.

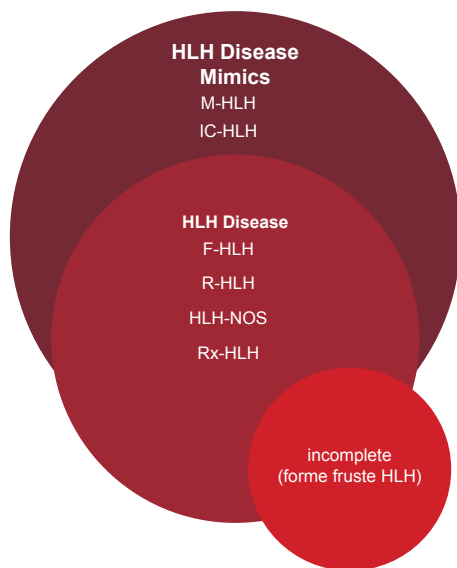
## 2. A GLANCE AT HLH

In this section, we will be briefly discussing the classification of HLH, after which we will explain the mechanism through which HLH occurs, which will tie in with the next parts, the clinical presentation of HLH and how to diagnose this entity.

**Figure 1.** HLH subgroups: Genetic HLH (primary) and acquired HLH (secondary).

HLH			
Primary			Secondary
FHL	Immunodeficiency Syndromes	Other	
FHL-1 Unknown Gene	Chediak-Higashi Syndrome	Lyst Gene	Infectious Agents
FHL-2 PFR1 Gene		RAB27A Gene	
FHL-3 UNC13D Gene	Griselli Syndrome Type 2	SH2D1A Gene	Autoinflammatory and Autoimmune disease
FHL-4 STX11 Gene	X-linked Lymphoproliferative Disease 1 and 2	BIRCA Gene	Malignancies
FHL-5 STXBP2 Gene			Acquired Immunosuppression

**Figure 2.** HLH syndrome categorization according to the North American Consortium for Histiocytosis (NACHO) [1]. Cases with a clear genetic cause are termed “familial” HLH (F-HLH), while those associated with malignant or rheumatologic disorders are labeled as M-HLH or R-HLH, respectively. Other subgroups of HLH include immune compromise-associated HLH (IC-HLH) and iatrogenic HLH (Rx-HLH). All other cases, regardless of genetic findings or infectious triggers, are classified as “HLH disease-NOS. Additionally, some patients may present with incomplete HLH picture, not meeting all criteria, also known as “forme fruste” HLH syndrome.



**2.1 CLASSIFICATION OF HLH**

HLH was historically categorized into two primary subgroups: Genetic HLH (primary) and acquired HLH (secondary), each with distinct underlying causes. Primary HLH is attributed

to specific genetic mutations in genes within the FHL (Familial Hemophagocytic Lymphohistiocytosis) subgroup. There are five main subtypes of FHL (FHL 1 through 5), and the key differences between them lie in the responsible genes and proteins. For example, FHL 2 is commonly caused by mutations in the PRF1 gene, resulting in aberrations in the perforin protein. FHL 3 arises from mutations in the UNC13D gene, which affects the Munc 13-4 protein. FHL 4 is linked to mutations in the STX11 gene, associated with the Syntaxin11 protein, and FHL 5 involves mutations in the STXBP2 (UNC18B) gene, impacting the Munc 18-2 protein [12]. While these genes are crucial in the context of FHL, it’s important to note that RhoG and CDC42 are also relevant to these cellular processes. RhoG and CDC42 are small GTPases involved in various cellular processes, including cell signaling, cytoskeletal dynamics, and cell migration [12]. Dysregulation of these genes can lead to different health conditions and, in rare cases, HLH. Accurate diagnosis and distinction between primary and secondary forms of HLH are critical for appropriate clinical management. It is less limited by age, usually manifesting in adolescents and adults; however, it can present at any age based on the underlying cause [13, 14]. (Figure 1.)

According to NACHO classification (Figure 2), “HLH disease” primarily involves immune dysregulation and requires immune suppression as a priority, and includes the following subgroups (familial HLH with a clear genetic cause, HLH linked to malignancy, rheumatologic HLH (R-HLH) or macrophage activation syndrome (MAS), iatrogenic HLH or cytokine release syn-

drome following immune-activating therapies, HLH linked to immune compromise from primary immune deficiencies or treatment-related immune suppression, and HLH not associated with specific conditions) [2]. In contrast, patients with “HLH disease mimics,” caused by conditions mimicking immune dysregulation (e.g., infections, underlying storage, and metabolic disorders), should prioritize other therapies [2]. Categorizing HLH disease into specific contexts, rather than the “primary” or “secondary” dichotomy, is essential for clear treatment decisions.

## 2.2 HLH PATHOPHYSIOLOGY

The main mechanism by which HLH occurs is the hyperactivation of Natural Killer (NK) cells and T Lymphocytes, specifically Cytotoxic T Lymphocytes (CTL), predominantly of the CD8+ subtype. The natural cytotoxicity of CD8+ CTL and NK cells is decreased; therefore, these cells are not able to perform their expected roles of eliminating tumor cells or cells infected with viruses. Instead, CD8+ CTL and NK cells perpetually secrete inflammatory cytokines, including interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-16, and IL-18, the most important of which being IFN- $\gamma$  [12]. This continuous cytokine secretion leads to the continuous activation of macrophages. Intriguingly, it is primarily due to NK cells and CD8+ T-cells failing to inactivate the macrophages. The process of inactivating macrophages necessitates the presence of perforin. However, any mutation in perforin renders this inactivation process ineffective [15]. Therefore, the intricate interactions between NK cells, CD8+ T-cells, and macrophages, coupled with the critical role of perforin in this inactivation process, underline the complexity of the immune response in conditions like HLH. Furthermore, another process at play is Toll-Like Receptor (TLR) activation, which is predominantly observed in macrophage activation syndrome. It works as a protective response against intruders to facilitate the restoration of injured tissues, and the receptor induces inflammatory responses in macrophages through the initiation of temporally defined transcriptional cascades [16, 17]. This multifaceted interplay between immune cells, cytokines, and regulatory mechanisms contributes to the development of HLH. Much more research and investigation are warranted to deepen our understanding of HLH pathophysiology, biomarkers, and bone marrow microenvironment changes and compare it with other hyper-inflammatory entities.

## 2.3 CLINICAL PRESENTATION OF HLH

The clinical presentation of HLH can be variable with different non-specific broad spectrum of inflammatory clinical and laboratory findings

that might lead to misdiagnosis. The majority of patients can have persistent unexplained fever and other symptoms like organomegaly, lymphadenopathy, pulmonary involvements, and liver dysfunction that might later progress into further organ failure [18]. More details are discussed in section 3.

## 2.4 DIAGNOSTIC CRITERIA AND WORKUP FOR HLH

Quick and timely diagnosis of HLH is of utmost importance, as the time needed to diagnose is an important determinant of the prognosis of HLH. In 2004, The Histocyte Society published diagnostic criteria for HLH consisting of 8 criteria, 5 of which must be present to diagnose HLH. However, patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfill the diagnostic criteria (Table 1) [7]. However, based on clinical observations, a considerable number of patients present with features very similar to HLH, but they do not fulfill the criteria proposed above. Therefore, having a better understanding of immune-phenotypic characteristics of monocytes and macrophages regarding their activation and overall functional properties and further studying HLH immunological microenvironment would likely provide additional information on HLH pathophysiology, which could ultimately help in early diagnosis, risk-stratification, and treatment of this complex and life-threatening disorder.

## 3. HLH MANAGEMENT IN CRITICAL CARE

### 3.1 INDICATIONS FOR ICU ADMISSION AND SUPPORTIVE CARE

HLH exhibits a wide spectrum of clinical manifestations spanning from mild ones to multiple organ failure necessitating ICU admission; given the disease's potential for rapid deterioration [19, 20]. The patient's critical care focuses mainly on the management of multiple organ failures including cardiovascular, renal, hepatobiliary, neurological, respiratory, and coagulopathy, as well as providing sufficient supportive care while initiating the immunosuppressive and HLH-targeted therapy in a timely fashion [20, 21].

Pulmonary involvement is one of the most common manifestations observed in HLH patients and is a poor prognostic factor [22]. It can be attributed to multiple factors, including the hyper-inflammatory state associated with HLH, as well as secondary conditions such as pneumonia, acute respiratory distress syndrome, sepsis-related respiratory failure, pulmonary

edema, atelectasis, and respiratory impingement caused by significant organomegaly [19, 23], frequently necessitating admission to the ICU and requiring mechanical ventilation [21].

Regarding the hemodynamic stability of HLH patients, due to an increase in cytokine release, the patients can develop septic-like shock caused by severe vasodilation, which can be present in up to 88% of ICU-admitted patients [24]. Consequently, a significant proportion of HLH patients, up to 80%, necessitate the administration of vasopressors [19].

Apart from pulmonary involvement and shock, coagulopathy represents the third prevailing manifestation, with a reported occurrence rate of approximately 60% in critically ill individuals, and it's worth mentioning that patients with hematologic conditions-related HLH exhibited a higher prevalence of coagulation disorders than those with infectious-related HLH [25]. The presence of hyper and hypofibrinogenemia, as well as disseminated intravascular coagulation (DIC) plays a pivotal role in determining the overall severity of the case and the potential for fatal hemorrhagic complications, DIC was found in up to 50% of deteriorating HLH patients. Specifically, a fibrinogen level lower than 200 mg/dl and a prolonged prothrombin time are associated with increased mortality rates [25].

Fulminant liver failure is not quite common as a presentation of HLH, present in (7-30%) as the cause of ICU admissions [19]; it is often accompanied by pyrexia, infections, and coagulopathy and carries high mortality [26]. Early diagnosis and prompt combined treatment with steroids and cyclosporin or etoposide are crucial [27].

Renal involvement is also common in HLH, the predominant form of which is acute kidney injury (AKI), observed in up to 60% of cases. Among those with AKI, approximately two-thirds require continuous renal replacement therapy due to hemodynamic instability, while one-third of the surviving patients develop chronic kidney disease within six months. The etiology of AKI in these patients can stem from various causes, including acute tubular necrosis, tumor lysis syndrome, hypoperfusion, and glomerulonephritis associated with HLH [28].

Finally, CNS involvement in HLH is frequently observed and is associated with a higher risk of poor prognosis. It accounts for approximately one-fifth of ICU admissions among HLH cases as it can manifest with severe neurological symptoms, including seizures, cranial nerve palsies, and coma [29]. Initiating HLH treatment early

is imperative to mitigate the potential long-term neurological consequences [19]. Additionally, repeated rounds of intrathecal injection therapy have shown promise in enhancing patient outcomes [30].

## 3.2. INITIAL MANAGEMENT & IMMUNOSUPPRESSIVE THERAPY FOR HLH

### 3.2.1 TREATMENT OF UNDERLYING CAUSE

In 1994, the Histiocyte Society established the first treatment protocol for HLH, known as HLH-94, which significantly increased the survival rate to 54 percent with a median follow-up of six years [31, 32].

The primary objective of therapy for HLH patients is to suppress life-threatening inflammation by targeting and eliminating immune cells. The induction therapy is based on the HLH-94 protocol. Importantly, when HLH is triggered by an acute infection or another condition such as a rheumatologic condition, it is appropriate to treat the underlying cause as this may remove the stimulus for immune activation. Some patients who are less acutely ill and stable may be able to manage the treatment of the triggering condition alone without HLH-specific therapy. This approach might allow certain patients to avoid potentially toxic treatments [33].

For patients with HLH induced by malignancies, it is essential to control the HLH first and then proceed with treating the underlying malignancy. In cases where the malignancy cannot be cured and the stimulus for HLH persists, a hematopoietic cell transplant may be considered [34, 35]. Macrophage Activation Syndrome (MAS) is a type of HLH associated with juvenile inflammatory arthritis and other rheumatologic conditions [36, 37]. Treating the underlying condition in rheumatologic patients with increased immunosuppression might yield a good response, enabling the patient to avoid specific MAS/HLH therapy [38].

Rapid diagnosis of infections is crucial, and empirical treatment with appropriate antibiotics, antifungals, antivirals, or antiparasitic agents should be initiated based on the suspected organisms [39, 40].

Patients who are clinically stable and respond quickly (within two to three days) to infection treatment may be able to avoid HLH-specific chemotherapy [3, 32]. However, severely ill patients should not have the initiation of HLH-specific therapy delayed while awaiting the resolution of systemic infections [3, 32].

### 3.2.2 CONVENTIONAL/CHEMOTHERAPY

Various antineoplastic agents target cell reproduction and interfere with the cell cycle. Some of these agents, like etoposide and methotrexate, can induce cellular apoptosis. These drugs play a key role in the HLH-94 protocol, an eight-week induction treatment that includes a high dose of dexamethasone, as recognized for its ability to efficiently cross the blood-brain barrier (compared to other forms of steroids) and etoposide. For patients with CNS involvement, intrathecal therapy is used, and hydrocortisone is added to the intrathecal methotrexate [41].

### 3.2.3 IMMUNOTHERAPY (TABLE 2)

Table 2 summarized immunotherapeutic agents for HLH/MAS treatment that are part of active clinical trials.

#### 3.2.3.1. Anti- IL-1 receptor

Interleukin (IL) -1, a cytokine primarily synthesized by macrophages, exhibits strong inflammatory and immune-enhancing properties [42]. The pathophysiology of HLH has been widely adopted as a state of “cytokine storm”. Given the limited effectiveness of etoposide in the management of HLH in adults, the interest in utilizing cytokine-directed therapy has been increasing. It is being administered in various medical centers, often in the early stages of treatment, off-label in an attempt to rescue critically deteriorating patients who do not respond to the underlying trigger treatment [15, 43]. Anakinra is an interleukin-1 receptor antagonist and one of the common agents being used to treat HLH. It is safe, well-tolerated, and has a rapid onset of action and a wide therapeutic range [44, 45]. When given in high doses, it enables minimizing the need for the usage of high doses of steroids as long as ongoing infections are being controlled with appropriate antibiotics coverage [44]. In adult HLH, anakinra is useful if the state is provoked by a rheumatological condition, otherwise, its benefit may be limited [46]. On the other hand, in critically ill pediatric HLH patients, it can be effective for both rheumatologically and non-rheumatologically triggered HLH [46].

#### 3.2.3.3. Anti-IL-6 receptor

IL-6 receptor direct antagonist, Tocilizumab (TCZ), is a monoclonal antibody [47]. It has been used for cytokine release syndrome (CRS), specifically in patients after CART cell or blinatumomab treatment [48]. Recently, it has been reported to have an increased use for checkpoint inhibitor treatment-induced HLH [48]. Tocilizumab use

in HLH-like CRS inspired the researcher’s efforts to study its use in HLH treatment [49]. A study involving 77 adult HLH cases revealed that patients treated with TCZ had poorer survival rates and experienced more infectious events compared to those receiving the conventional treatment [50]. On the other another study suggested that, after ruling out ongoing bacterial or fungal infections in critically ill patients with moderate reactive HLH not related to hematological malignancies, TCZ could be considered as an alternative treatment option [51].

#### 3.2.3.4 JAK Inhibition

HLH has shown promise in the treatment with JAK inhibitors. The cytokine signaling that is dysregulated in HLH is dependent on the JAK/STAT pathway [52]. JAK inhibitors can control the inflammatory response related to HLH by inhibiting JAK kinases. The use of JAK inhibitors, notably ruxolitinib, in the management of HLH has been examined in several trials [52]. Ruxolitinib has shown encouraging efficacy and safety in a pilot study when used as the first-line therapy for kids with secondary HLH [53]. A multicenter prospective study studied the efficacy of ruxolitinib combined with doxorubicin, etoposide, and methylprednisolone (DEP-Ru regimen) in relapsed/refractory HLH with reported complete and partial response of 15.1% and 58.5%, respectively. The overall response rate was 73.6%, with MAS-HLH and idiopathic HLH, specifically, having better outcomes with the DEP-Ru regimen than EBV- or lymphoma-associated HLH [54]. Nevertheless, it’s crucial to use JAK inhibitors with caution when treating HLH. Some JAK inhibitors have been linked to an increased incidence of viral reactivation and worsening of COVID-19-related coagulopathic complications [52].

#### 3.2.3.5 Anti- interferon Gamma

Emapalumab, a monoclonal antibody therapy, has emerged as a promising treatment for HLH. Emapalumab specifically targets and inhibits IFN- $\gamma$ . By neutralizing IFN- $\gamma$ , emapalumab helps to dampen the hyperinflammatory response and regulate immune cell activity [55]. Its efficacy has been demonstrated in clinical trials, where it has shown remarkable success in controlling HLH symptoms and improving patient outcomes, especially in individuals with primary HLH or refractory cases [55]. Emapalumab has been approved by the United States Food and Drug Administration since November 2018 for treatment of adult or pediatric primary HLH that is refractory,

relapsing, or intolerant to conventional therapy. However, treating physicians should pay very close attention to the increased risk of infections and viral reactivation [56].

#### 3.2.3.6 Anti-CD52

Alemtuzumab is a targeted therapy that specifically acts against the CD52 antigen, which is found on the surface of mature lymphocytes and antigen-presenting cells [57]. The results from a prospective trial involving over 50 pediatric patients were highly promising [58]. They demonstrate that Alemtuzumab effectively controls HLH activity while maintaining a favorable safety and tolerability profile, particularly in a vulnerable population. Remarkably, 92.3% and 91.6% of patients, respectively, survived and went on to undergo HSCT (54). Significant outcomes were observed in an observational study involving 22 patients with refractory HLH who received Alemtuzumab treatment [59]. Sixty-four percent of the patients showed a partial response to the treatment, and a noteworthy 77% of patients were able to proceed with HSCT. However, it is important to note that some patients experienced the occurrence of CMV and adenovirus viremia, with rates ranging from 23% to 32% [59].

#### 3.2.3.7 PD-1 inhibitors

Programmed death receptor 1 (PD-1) inhibitors are a type of anticancer drug known as checkpoint inhibitors [60]. In the context of NK/T-cell lymphoma-associated HLH (NK/T-LAHS), the combination of PD-1 monoclonal antibody, Nivolumab, with chemotherapy regimens has shown promising results in prolonging survival [61]. Furthermore, Nivolumab induced remission in 5 out of 7 adults with relapsed or refractory EBV-HLH, indicating its potential as an effective treatment strategy for this patient population [62].

#### 3.2.3.8 HSCT

HSCT is a crucial consideration for all patients diagnosed with familial HLH, as it represents the only curative treatment available [63, 64]. Ideally, a matched, related donor should be preferred for the transplant [63, 64]. In cases where patients with HLH do not respond to initial therapies, HSCT may still be a viable option [63]. In the absence of unambiguous genetic causes, familial history, or recurrent/refractory disease, there is no specific indication for HSCT in HLH; HSCT may be indicated in case of recurrent HLH if there is no identi-

fiable disease trigger that can eventually be managed [65]. CNS-HLH is a life-threatening condition, sometimes linked to systemic HLH [66]. HSCT is a crucial treatment for CNS-HLH, and even patients with primary HLH may benefit from immediate HSCT, regardless of active disease at the time of transplantation [66]. Patients with high-risk hematologic malignancies like acute leukemia, Burkitt lymphoma, and myelodysplastic syndromes may potentially be considered for HSCT as a consolidation therapy [67]. While in the past, HSCT was primarily utilized for patients experiencing a relapse, its usage has now expanded to include patients with challenging disease control or slow response to treatment [68]. A flare-up after a transplant can be managed with the administration of etoposide and methotrexate, and in rare instances, the option of a re-transplant may be considered [69]. It is recommended that the preparation for allogeneic HSCT be initiated promptly at the time of diagnosis [63]. Improved transplantation outcomes have been observed in patients with adequately controlled HLH activity before HSCT [70].

### 3.3. MONITORING AND FOLLOW-UP FOR HLH

Monitoring the response to initial therapy is crucial for determining the need for additional therapy, such as HSCT. The response to induction therapy is assessed by clinical evaluation and using HLH disease-specific markers. These markers are particularly useful in distinguishing disease worsening from other complications like infections or treatment toxicity [71].

Regular physical examinations are conducted to get a comprehensive view of the patient's condition, focusing on temperature, rashes, lymphadenopathy, hepatosplenomegaly, neurologic findings, and organ-specific manifestations noted during the initial presentation [72]. In addition, various laboratory tests are performed, including complete blood count with differential, coagulation studies (PT, aPTT, fibrinogen, and D-dimer), ferritin levels, renal function, electrolytes (if previously abnormal), and liver function tests (ALT, AST, total bilirubin, GGT, and LDH) [23]. Additionally, lymphocyte and cytokine markers (e.g., soluble IL-2 receptor alpha [sCD25], soluble hemoglobin-haptoglobin scavenger receptor [sCD163]) are monitored weekly to track the response to therapy [72]. CSF analysis is conducted for patients with neurologic or cerebrospinal fluid (CSF) abnormalities [3]. This evaluation is performed daily for acutely ill patients, except for CSF analysis, which is done

at each intrathecal treatment. The monitoring interval can be extended as the values normalize over time.

#### 4. PROGNOSIS OF HLH

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There are many factors affecting the prognosis and outcome of HLH, some more significant than others. Knowing these factors is of utmost importance to physicians as minimizing and addressing these factors can benefit a patient's prognosis greatly. One very important prognostic factor is CNS involvement. Patients with CNS involvement generally have worse outcomes than those without CNS involvement [73]. Another important prognostic factor is malignancy. Patients with HLH-associated malignancies have, generally, much poorer outcomes; the stimulation of monocyte phagocytic systems accounts for the generally worse outcomes experienced by patients with HLH-associated malignancies [74]. Primary or familial HLH is associated with a high mortality rate and a poor long-term outcome. On the other hand, patients who had undergone HSCT had much better survival rates [74]. Prognostic factors related directly to long-term outcomes are the age of onset, hyperferritinemia, thrombocytopenia, and high DIC score  $\geq 5$ , all of which are decidedly better in secondary HLH [75]. Therefore, secondary HLH, also known as reactive HLH, carries a better prognosis and a superior long-term survival rate. However, the long-term outcome depends on the type of secondary HLH [74, 76]. Age of onset of less than two years is an independent poor prognostic factor. Ferritin is tightly regulated by the same cytokines responsible for the cytokine storm mentioned in Section 2. Therefore, an increased ferritin level in the blood most likely implies a high level of cytokines in circulation and a poorer outcome [77]. Cytokine-induced bone marrow suppression and hemophagocytosis result in thrombocytopenia in HLH, indicating a poor outcome [78]. DIC is pathognomonic to uncontrolled pathologic immune activation in HLH and, therefore, denotes a poor outcome [79].

#### 5. CONCLUSION

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In conclusion, HLH is a rare and severe immunological disorder with diverse triggering mechanisms and clinical presentations. The diagnosis of HLH poses challenges due to its atypical features and overlapping symptoms with other conditions, leading to potential misdiagnosis. Early recognition and prompt treatment are essential for improving patient survival and reducing complications. Supportive care and timely initiation of immunosuppressive and HLH-targeted therapy are crucial in managing critically ill patients.

In summary, HLH management requires a comprehensive and individualized approach, and ongoing research is crucial to improve patient outcomes and explore new therapeutic options.

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#### DISCLAIMER

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**Table 2.** Active clinical trials on immunotherapeutic agents for HLH/MAS treatment (1)

	<b>Mechanism of Action for Immunotherapeutic agents</b>	<b>Trial Number</b>	<b>Aim of Trial</b>
<b>Zanubrutinib</b>	Bruton's tyrosine kinase inhibitor	NCT05320575	Zanubrutinib Monotherapy in Patients With HLH
<b>Emapalumab</b>	Monoclonal antibody neutralizing interferon-gamma (IFN-gamma), a key cytokine driving the inflammation and tissue damage seen in HLH.	NCT03985423	To assess the efficacy, safety and pharmacokinetics of emapalumab in adult patients with HLH
		NCT05744063	Treatment in Chinese patients with confirmed or suspected primary hemophagocytic lymphohistiocytosis (pHLH)
		NCT05001737	Treatment in children and adults with macrophage activation syndrome (sHLH/MAS) in Still's disease (including systemic juvenile idiopathic arthritis and adult onset Still's disease) or with sHLH/MAS in systemic lupus erythematosus, resending an inadequate response to high dose glucocorticoid treatment
<b>Ruxolitinib</b>	Janus kinase inhibitor	NCT04551131	Response-adapted regimen combining ruxolitinib, dexamethasone, and etoposide as a frontline therapy for patients with newly diagnosed HLH or as Salvage therapy for patients with relapsed/refractory HLH
		NCT04999878	First-line induction therapy with Ruxolitinib and Etoposide combined with DDGP regimen ( cis-Platinum, Dexamethasone, Gemcitabine and Pegaspargase) for T cell lymphoma and NK/T cell lymphoma-associated hemophagocytic syndrome
<b>PD-1 antibody</b>	Programmed death receptor 1 inhibitors	NCT05164978	DEP (liposomal doxorubicin, etoposide and methylprednisolone) together with PD-1 antibody for EBV associated HLH treatment
		NCT04084626	Treatment for Epstein-Barr Virus-associated HLH or Chronic Active EBV Infection(-CAEBV) with PD-1 antibody and Lenalidomide
		NCT05841342	Therapy efficacy predictors for chronic active epstein-barr virus infection and epstein-barr virus associated HLH
<b>Ela026</b>	Fully human , monoclonal immunoglobulin G1 (IgG1) signal regulatory protein (SIRP)-directed antibody. designed to reduce the myeloid and T cells driving the inflammation	NCT05416307	To assess the safety, efficacy pharmacokinetics and pharmacodynamics of Ela026 in participants with secondary HLH
<b>Itacitinib</b>	Selectively inhibits JAK1	NCT05063110	Treatment of non-severe sporadic HLH
<b>Tadekinig alfa (IL-18BP)</b>	A recombinant Interleukin-18 Binding Protein (r-hil-18BP) with a high affinity for IL-18, a major inflammatory cytokine.	NCT05306080	Evaluating the Safety and Feasibility of Using it as a Rescue Therapies for CAR T Cell Related Cytokine Release Syndrome (CRS) and HLH-like Syndrome

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