Recommendations for the management of hemophagocytic lymphohistiocytosis in adults

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Abstract:
Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T-cells. The primary (genetic) form, caused by mutations affecting lymphocyte cytotoxicity and immune regulation, is most common in children, while the secondary (acquired) form is most frequent in adults. Secondary HLH is commonly triggered by infections or malignancies but may also be induced by autoinflammatory/autoimmune disorders, in which case it is called macrophage activation syndrome (MAS or MAS-HLH). Most information on the diagnosis and treatment of HLH comes from the pediatric literature. Although helpful in some adult cases, this raises several challenges. For example, the HLH-2004 diagnostic criteria developed for children are commonly applied, but not validated for adults. Another challenge in HLH diagnosis is that patients may present with a phenotype indistinguishable from sepsis, or multiple organ dysfunction syndrome (MODS). Treatment algorithms targeting hyperinflammation are frequently based on pediatric protocols, such as HLH-94 and HLH-2004, which may result in overtreatment and unnecessary toxicity in adults. Therefore, dose reductions, individualized tailoring of treatment duration, and an age dependent modified diagnostic approach are to be considered. Here we present expert opinions derived from an interdisciplinary working group on adult HLH, sponsored by the Histiocyte Society, to facilitate knowledge transfer between physicians caring for pediatric and adult patients with HLH, with the aim to improve the outcome for adult patients affected by HLH.

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T-cells. The primary (genetic) form, caused by mutations affecting lymphocyte cytotoxicity and immune regulation, is most common in children, while the secondary (acquired) form is most frequent in adults. Secondary HLH is commonly triggered by infections or malignancies but may also be induced by autoinflammatory/autoimmune disorders, in which case it is called macrophage activation syndrome (MAS or MAS-HLH). Most information on the diagnosis and treatment of HLH comes from the pediatric literature. Although helpful in some adult cases, this raises several challenges. For example, the HLH-2004 diagnostic criteria developed for children are commonly applied, but not validated for adults. Another challenge in HLH diagnosis is that patients may present with a phenotype indistinguishable from sepsis, or multiple organ dysfunction syndrome (MODS). Treatment algorithms targeting hyperinflammation are frequently based on pediatric protocols, such as HLH-94 and HLH-2004, which may result in overtreatment and unnecessary toxicity in adults. Therefore, dose reductions, individualized tailoring of treatment duration, and an age dependent modified diagnostic approach are to be considered. Here we present expert opinions derived from an interdisciplinary working group on adult HLH, sponsored by the Histiocyte Society, to facilitate knowledge transfer between physicians caring for pediatric and adult patients with HLH, with the aim to improve the outcome for adult patients affected by HLH.
Introduction

Hemophagocytic lymphohistiocytosis (HLH) has become more widely recognized in adults with all ages affected. Patients often suffer from recurrent fever, cytopenia, liver dysfunction, and a sepsis-like syndrome that may rapidly progress to terminal multiple organ failure. Subspecialists in hematology/oncology, infectious diseases, rheumatology/clinical immunology, gastroenterology/hepatology, neurology, emergency medicine, intensive care, and general medicine are challenged by this rare, multifaceted syndrome. Physicians should be aware of HLH since early recognition may prevent irreversible organ damage and subsequent death. Although familial (primary) HLH (FHL), a major HLH subtype in children, can also occur in adolescents and young adults, secondary (acquired) HLH (sHLH) is by far most common in these age groups. The treatment protocols HLH-94 and HLH-2004 have been established as scientific cornerstones for diagnosis, classification, and treatment of HLH in patients less than 18 years.

Our current views on HLH are driven by lessons learned in pediatrics, and pediatricians still often consult on adults with HLH. However, HLH triggers, organ reserve, fitness, and clinical presentation of HLH differ between the pediatric and adult age groups. Transferring pediatric precepts regarding pathogenesis, diagnostics, and treatment of HLH to adult patients may confer risks. Therefore, the HLH Steering Committee of the Histiocyte Society developed these recommendations for diagnosis and treatment of HLH in adults, as a complement to previously published recommendations on etoposide-based therapy in HLH.
Methods

Procedure

The recommendations are based on expert opinion supported by best available evidence from studies supporting the individual statements. They were initially proposed and discussed by e-mail, and then selected and structured in a telephone conference. After further refinement by e-mail, each statement was discussed, revised, and voted on in a personal meeting, followed by final refinement by e-mail.

The consensus strength for the statements was classified as follows:

- Strong consensus: more than 95% of participants agree
- Consensus: 75%-95% of participants agree
- Majority Agreement: 50-75% of participants agree
- No consensus: 50% or less of participants agree

Constitution of Recommendation Committee

The authors represent the current members of the Working Group “HLH in Adults” of the Histiocyte Society (www.histiocytesociety.org). The current head of the Working Group (PLR) served as coordinator. The following medical subspecialties were represented: Adult Hematology/Oncology and Internal Medicine (7) (PLR, RM, NB, SB, MG, YW, ZW), Pediatric Hematology/Oncology (6) (TvBG, MJ, AK, KEN, GJ, JIH), Rheumatology/Clinical Immunology (3) (adult: JvL, AR; pediatric: AH), Intensive Care (2) (adult: GL; pediatric: MH), and Genetics/Clinical Immunology (1) (JGH).

Pathogenesis and epidemiology of HLH

Statement 1: Primary and secondary HLH, including MAS-HLH, are hyperferritinemic hyperinflammatory syndromes with a common terminal pathway, but with different pathogenetic roots.
HLH is an aberrant hyperinflammatory, hyperferritinemic immune response syndrome, driven by T cells and associated with a potentially fatal cytokine storm. The term macrophage activation syndrome (MAS-HLH) refers to a subset of patients with HLH arising on a background of systemic autoinflammation/autoimmunity and should be restricted to patients with Still’s disease, lupus, vasculitis, and other related autoimmune systemic diseases, since its treatment may differ from that recommended for other forms of sHLH (see Statement #14).

The current view of sHLH pathogenesis is an inability of the immune system to adequately restrict stimulatory effects of various triggers. Inherited variations in HLH-associated genes, well characterized in pediatric HLH may play a role in adult-onset HLH, but acquired immune dysfunction in response to infections, malignancies, and autoinflammatory/autoimmune disorders seems to be the leading cause in adults (Table 1).

**Statement 2:** HLH-triggers including occult malignancies require a meticulous search for the underlying disease that should be continued despite ongoing HLH-treatment.

Infections are the most prevalent triggers of HLH. In adults, in particular with increasing age, malignancies are another major cause, primarily lymphomas (Table 1). A variety of malignancies are associated with HLH in adults, including T-cell or natural-killer (NK) lymphomas (35%), B-cell lymphomas (32%), leukemias (6%), Hodgkin lymphoma (6%), other hematologic neoplasms (14%), solid tumors (3%), and other non-specified neoplasms (3%).
The epidemiology of HLH varies substantially due to population heterogeneity and variable underlying triggers\textsuperscript{17-22}. A large literature review on adult HLH reported a mean age of HLH onset of 49 years (males 63\%)\textsuperscript{10}. The reported incidence of malignancy-associated HLH varies from 1\% in patients with hematological malignancies (0.36/100,000 individuals/year)\textsuperscript{17}, to a cumulative incidence rate of 2.8\% in patients with malignant lymphoma\textsuperscript{23}, and 9\% of patients with acute myeloid leukemia (AML) after intensive induction therapy\textsuperscript{22}.

Diagnosis of HLH in adults

Statement 3: The diagnosis of HLH in adults is recommended to be based on the HLH-2004 diagnostic criteria in conjunction with clinical judgement and the patient’s history.

\textit{Strong Consensus}

The HLH-2004 diagnostic criteria

In 1991, the Histiocyte Society proposed a standardized set of five diagnostic criteria for HLH used for the prospective HLH-94 clinical trial\textsuperscript{24}. These criteria were revised for HLH-2004, where individuals needed to meet at least 5 of 8 diagnostic criteria (Table 2)\textsuperscript{4,5}. On occasion, HLH may be strongly considered, and HLH-directed therapy initiated, even though five criteria are not fulfilled (see statements #4, 6, 7, 10, 13)\textsuperscript{6}

Hyperferritinemia should always prompt including HLH in the differential diagnosis\textsuperscript{25}. Ferritin values characteristic for HLH in adults are often above 7,000-10,000 µg/L and may, rarely, surpass 100,000 µg/L\textsuperscript{26}. Ferritin levels over 10,000 µg/L are over 90\% sensitive and specific for HLH in children, though other criteria need to be met to make diagnosis. While a ferritin in this range should also raise a strong suspicion of
HLH in adults, hyperferritinemia is less specific, and other features of the clinical context are critical for diagnosis in adults\textsuperscript{27,28}. Soluble IL-2 receptor (sIL-2r, also sCD25), one of the diagnostic criteria in HLH-2004, has recently been reported as a good to excellent low-cost diagnostic test for adult HLH, with an area under the curve (AUC) of 0.90 (95% confidence interval, 0.83-0.97) compared with AUC 0.78 (0.67-0.88) for ferritin\textsuperscript{29,30}. The HLH-2004 criteria, developed for children, are not validated formally for adults and remain based on expert opinion. Various case series have used modified HLH-2004 criteria\textsuperscript{19,21,31-41}.

Other diagnostic tools

Other features supporting an HLH diagnosis that are not part of the HLH-2004 criteria include hyperbilirubinemia, hepatomegaly, transaminitis (present in the vast majority of patients with HLH), and elevated lactate dehydrogenase (LDH) and D-dimer levels, the latter usually elevated even when international normalized ratio (INR) and partial thromboplastin time (PTT), and fibrinogen, are normal. These findings may help to discriminate HLH from septic shock and conditions such as autoimmune hemolytic anemia, and they are also useful in assessing response to therapy.

The HLH-probability calculator (HScore), with graded clinical and laboratory parameters, is a web-based online calculator (http://saintantoine.aphp.fr/score/) developed retrospectively in adult patients that may be a helpful diagnostic tool (Table 3)\textsuperscript{42}. The pattern of inflammatory cytokines (elevated levels of interferon-gamma and interleukin (IL)-10, with only modestly elevated IL-6 levels) has high diagnostic accuracy for sHLH and may be a useful approach to differentiate HLH from infection and to monitor patients, but the utility of this pattern of changes needs to be verified in children and adults outside of China\textsuperscript{43-45}. For diagnosis using
Clinical phenotypes

Many adult patients with HLH present with the triad of fever, bicytopenia with potential bleeding diathesis, and splenomegaly. Wasting and fatigue may occur. Edema, purpura, dyspnea, diarrhea, diffuse bleeding, icterus, and an overall sepsis-like appearance are extremes of severe HLH with onset of organ failure. Mild initial signs, including recurrent fevers, lymphadenopathy, organomegaly, rash, and arthralgias, may progress with an unexpected rapidity and severity. These signs and symptoms despite adequate antimicrobial therapy and/or without detectable infectious focus along with a dramatic clinical progression serve as red flags for possible HLH. No single clinical or laboratory parameter has sensitivity and specificity to allow an unambiguous HLH diagnosis. Close clinical observation with repeated physical examinations and laboratory assessments are mandatory for diagnosis.

Statement 4: Diagnostic tests for genetic HLH include functional assessment of lymphocyte cytotoxicity and guided genetic testing. They are useful for detecting potential genetic predisposition to HLH in select patients, but pending results must not delay the clinical decision to treat HLH.

Consensus

Functional and genetic testing are not generally recommended in adult patients with HLH since abnormalities rarely are detected. Genetic defects leading to FHL, with impairment of lymphocyte cytotoxicity, and genetic alterations in related disorders are presented in Table 4. Although most patients with underlying genetic defects show the features summarized in Table 4, cellular expression of perforin, SLAM-associated protein (SAP), X-linked inhibitor of apoptosis protein (XIAP) proteins, or
CD107a (a glycoprotein necessary for degranulation [exocytosis] of perforin-containing granule from cytotoxic lymphocytes) may be normal or nearly normal in rare cases. To determine whether a patient has an inherited form of HLH, genetic analyses (i.e., next generation sequencing, gene panels, whole exome sequencing) along with functional testing (i.e., NK-cell cytotoxicity and CD107a upregulation) will be needed. This is particularly true for patients with a family history of consanguinity and/or HLH, partial albinism, recurrent disease, and young male adults with Epstein-Barr virus (EBV) infection or lymphoproliferation. Testing should also be considered for HLH patients with unknown trigger. Importantly, pending results must not delay the clinical decision to treat HLH.

Although primary HLH is rare in adults, mutations in HLH-associated genes can be detected in adult patients with HLH (Table 5). In the US, a rate of 7% (12/175) is reported. However, the predominant locus, the A91V mutation in PRF1, is considered a hypomorphic mutation that is present in up to 10% of healthy Caucasians. Although these hypomorphic alleles may constitute a risk factor for HLH, the vast majority of individuals carrying these mutations have no clinical symptoms.

**Statement 5:** Lymphoma as a hidden trigger of HLH may be difficult to detect. Use of positron emission-tomography (PET) guided imaging, repetitive tissue sampling, and consultation of a lymphoma reference pathologist, are recommended.

*Strong Consensus*

About 40-70% of HLH cases in adults are malignancy-associated, either triggered by the malignancy itself at presentation or seen after initiation of chemotherapy, the latter may occur even in patients in remission, thought to be due to
Immunosuppression and/or infection\textsuperscript{15}. Patients therefore need a thorough cancer workup with special consideration of Hodgkin and non-Hodgkin lymphoma (NHL). Atypical presentation and certain lymphoma subtypes (i.e. Hodgkin; diffuse large B-cell lymphoma, intranasal subtype; NK/T-cell lymphoma; angioimmunoblastic T-cell-lymphoma; anaplastic large cell lymphoma; panniculitis-like T-NHL; intravascular B-cell lymphoma (IVBCL); and peripheral T-cell-lymphoma) are more strongly associated with HLH\textsuperscript{54,55}. Computed tomography (CT)-scan enhanced by PET (PET-CT), followed by biopsy of suspicious lesions, is advised to reveal occult disease\textsuperscript{56}. An elevated sCD25/ferritin ratio has been reported in lymphoma-associated HLH\textsuperscript{57}. Tumor-infiltrating reactive lymphocytes can mask an underlying lymphoma. Thus, close interaction between clinicians, pathologists and immunologists is required to determine the correct diagnosis. In individuals with HLH of unknown cause and splenomegaly, splenectomy may be considered to detect lymphomas hiding in the spleen or perisplenic tissue. This is justified in clinical circumstances that strongly support lymphoma (history of B-symptoms, weight loss, elevated sCD25/ferritin ratio)\textsuperscript{58}.

**Treatment of adult patients with HLH**

**Statement 6:** HLH-94 treatment components, including etoposide, are highly effective in treating hyperinflammation in adults with HLH.

*Strong Consensus*

The heterogeneity of adult HLH prohibits a “one size fits all-protocol”. The HLH-94 protocol drastically improved the nearly uniformly fatal outcome in pediatric HLH to a long-term survival above 50\%\textsuperscript{3}. The HLH-94 protocol consists of corticosteroids, typically dexamethasone, cyclosporine A (CSA), intrathecal therapy, and etoposide,
to delete activated T-cells and suppress inflammatory cytokine production (Figure 1)\(^5^9\). Etoposide, a chemotherapeutic agent, has high specificity against T-cell proliferation and cytokine secretion in mice\(^6^0\). However, adult and especially elderly patients may have chronic comorbidities making them more vulnerable to end organ damage caused by cytokine storm in HLH and HLH-94 chemotherapy. Reduced etoposide frequency from twice weekly to once a week, with or without reduction of dose from 150 mg/m\(^2\) to 50-100 mg/m\(^2\), should be considered. In the HLH-2004 study, CSA was administrated upfront instead of after 8 weeks as in HLH-94 and pre-SCT mortality was reduced from 27% to 19% (\(P = 0.064\) adjusted for age and sex). Since this improvement not was significant and since CSA is associated with side effects as well as contraindications, particularly early in the disease course, HLH-94 remains the recommended standard of care\(^5\). In HLH-94, intrathecal therapy is only suggested in case of progressive neurological symptoms after 2 weeks of therapy, or if an abnormal CSF has not improved by then (Figure 1).

The risk for children of developing treatment-related AML in the HLH-2004 and HLH-94 studies was 0.3% (1/368) - 0.4% (1/249) at a median follow-up of 5.2 and 6.2 years, respectively\(^3,5,6\) and 1/81 (1.2%) in patients with EBV-HLH treated with a median cumulative etoposide dose of 1500 mg/m\(^2\) BSA, with a median follow-up of 44 months\(^6^1\). The need to stay below a cumulative dose of 2-3 g/m\(^2\) should be kept in mind, particularly in HLH patients without malignancy\(^6^1\).

**Allogeneic stem cell transplantation**

Adults with primary HLH may need allogeneic hematopoietic stem cell transplant (alloSCT), which has dramatically improved outcome in children\(^6^2\). Transplant-related mortality in children using reduced intensity conditioning (RIC) has been reported to
compare favorably to myeloablative conditioning (MAC)\textsuperscript{63}. A retrospective European Society of Blood and Marrow Transplantation (EBMT) study does not show superiority of RIC over MAC in adults\textsuperscript{64}. Decisions regarding transplantation should be made on clinical grounds and in consultation with experts in HLH and alloSCT. Inactive HLH before transplantation is strongly associated with better survival\textsuperscript{65}. Patients with primary HLH and non-malignant sHLH may be candidates for RIC as well as MAC. The pre-transplant conditioning regimen in malignancy-associated HLH may be guided by disease-specific protocols as provided by local standards, which includes MAC to optimally control the underlying disease. In patients in whom HLH-causing mutations are detected, HLA-typing of close relatives should also integrate screening for the same gene mutations, to avoid a stem cell source with the same pathogenic bi-allelic mutation(s).

**Statement 7**: The variable severity of HLH, including MAS-HLH, demands graded intensity and length of treatment. Treatment should be tailored to control hyperinflammation and to treat identified disease triggers.

*Strong Consensus*

An HLH-diagnosis may be suspected, but not confirmed, by the presence of 5 of 8 HLH-2004 criteria. Resolution of HLH without HLH-specific treatment has been observed, particularly in infection-associated HLH\textsuperscript{66}. In moderately active HLH, the decision to start HLH-directed treatment depends on clinical judgement and assessment of organ function. Pulsed corticosteroids and elements of HLH-94 (dexamethasone 10 mg/m\textsuperscript{2} with/without a modified dose of etoposide) may be employed. A clear indication for immediate administration of etoposide is severe HLH presenting with imminent organ failure\textsuperscript{33,67}. Individualized, modified HLH-94-like treatment has been suggested in sHLH\textsuperscript{68}. Because etoposide is mainly cleared by
the kidneys, dose reduction is recommended if renal function is impaired based on
age-specific norms (for dose recommendations see Ehl et al. 2018), while no dose
reduction of etoposide is recommended for isolated hyperbilirubinemia and/or
elevated transaminases.

Addition of intravenous immunoglobulins (IVIG) (up to 1.6 g/kg in split doses over 2-3
days) may be considered, since IVIG has anti-inflammatory potential by inhibiting
complement activation, blocking antibody Fc-fragments and macrophage Fc-
receptors, and by neutralizing cytokines. However, the use of IVIG has been
questioned, at least in adult-onset Still’s disease. Anakinra may reduce mortality in
sepsis patients with MAS features.

Many patients with sHLH require less than 8 weeks of etoposide. Although patients
may be continued through the full course (8 weeks) of etoposide in the absence of
major toxicities, we recommend a weekly reevaluation of the need of continued
etoposide therapy. Patients with residual disease after 8 weeks may benefit from
maintenance therapy and possibly alloSCT. For those requiring alloSCT due to
underlying genetic mutations, HLH-94 maintenance therapy is often recommended
after the initial 8 weeks of therapy. CSA may be replaced by tacrolimus, but both
need careful drug level monitoring and toxicity assessment.

**Statement 8:** Secondary infections are a major cause of fatality and may erroneously
be diagnosed as HLH relapse.

*Strong Consensus*

Certain HLH triggers carry the inherent risk of acquired cellular immunodeficiency,
such as Hodgkin lymphoma, T-cell lymphomas or human immunodeficiency virus
Additionally, HLH-directed treatment depletes leukocytes (T-/B-cells and granulocytes). For patients requiring such treatment, administration of broad antimicrobial prophylaxis against *Pneumocystis jirovecii* and fungi is recommended. Hospitalization in units with high efficiency particulate air (HEPA)-filtered air should be considered. We also suggest antiviral prophylaxis due to severe T-cell depletion.

**Malignancy-associated HLH**

**Statement 9:** Malignancy-associated HLH (Mal-HLH) comes in two forms:

“Malignancy-Triggered HLH” as a presenting feature of the malignancy at diagnosis or at relapse and “HLH During Chemotherapy”, in most cases induced by infections. Differentiating these HLH-subtypes is important, as the therapeutic approach differs markedly.

**Strong Consensus**

Malignancy-associated HLH has the worst prognosis of all HLH subgroups. The risk of developing Mal-HLH increases with age. Lymphoma-associated HLH is the major cause of Mal-HLH, with region-specific subtype distribution (e.g., increased rate of NK/T-cell and EBV-triggered lymphoma in Asia).

**Malignancy-triggered HLH**

Treatment of malignancy-triggered HLH needs to balance HLH-specific and tumor-specific treatment. Corticosteroids are often used as first-line treatment to combat inflammation. In highly active HLH, or if severe organ damage is imminent, dose-adjusted etoposide (50–100 mg/m²) may be used prior to tumor-specific treatment. Etoposide can be added to CHOP- or CHOP-like protocols (CHOEP or DA-EPOCH). Patients with aggressive lymphomas should be considered for evaluation of involvement of the central nervous system (CNS), with lumbar puncture and cerebral
magnetic resonance imaging\textsuperscript{74}. Prophylactic or therapeutic age-adapted high-dose intravenous methotrexate may be considered individually to prevent CNS-relapse (this treatment is not well tolerated by older patients). Patients in remission eligible for treatment intensification may be candidates for autologous stem cell transplantation (autoSCT), using high dose etoposide-containing chemotherapy as primary consolidation; this recommendation is based on the assumption that the dismal prognosis of lymphoma-associated HLH can be overcome by high-dose chemotherapy which has been demonstrated in T-cell NHL\textsuperscript{75}. A decision towards consolidation by alloSCT requires careful individual assessment (see Statement #12)\textsuperscript{76}.

The coincidence of HLH and lymphoma, particularly EBV-driven lymphoma in younger patients, should trigger expert consultation and germline genetic testing, since evidence of HLH-associated mutations may support primary allogeneic, and not autologous, SCT\textsuperscript{77}. Early HLA-typing and donor search in Mal-HLH is advised in selected malignancies with potential indication for primary consolidation by alloSCT (e.g. Burkitt lymphoma, acute leukemias, myelodysplastic syndromes)\textsuperscript{73}.

**HLH During Chemotherapy**

“HLH During Chemotherapy” develops during or after treatment for a malignant disorder and is probably under-recognized. In neutropenic patients after induction chemotherapy for AML, as many as 9\% may develop HLH with infections (fungal, bacterial, central-line associated) as the most frequent trigger\textsuperscript{22}. Diagnosis is obscured by pre-existing neutropenia, liver functional abnormalities that may be attributed to toxic drug effects, and ferritin elevation that may be secondary to transfusion-related iron-overload.
HLH has to be considered when cytopenia is unduly prolonged after chemotherapy, fever persists in spite of antibiotic treatment, and other HLH parameters are present. These patients benefit from anti-inflammatory treatment with corticosteroids (1–2 mg prednisolone/kg or dexamethasone 5-10 mg/m²) and, possibly, 1.6 g/kg IVIG over 2–3 days. Etoposide should be used sparingly, as bone marrow recovery is central for immune reconstitution. Ongoing monitoring is required to detect recurrent malignant disease as a potential alternate HLH trigger. Where available, ferritin, sCD25, and bone marrow assessment (activated macrophages and/or hemophagocytosis) can help in distinguishing those who are neutropenic as the result of chemotherapy versus those who have underlying HLH.

**Infection-associated HLH**

**Statement 10:** Viral infections, in particular EBV, HIV, cytomegalovirus (CMV) or Influenza, are common triggers of HLH.

*Strong Consensus*

**EBV-HLH**

In one review of 2197 adults with HLH, viral infections were the most frequent trigger, dominated by EBV. The prognosis of EBV-HLH has greatly improved when promptly treated by HLH-94, but the variable severity of EBV-HLH demands graded intensity and length of treatment. Rapid clinical deterioration, in particular in treatment-naïve EBV-infected patients, mandates etoposide treatment without delay. A more conservative approach with a short course of corticosteroids (with/without IVIG) is justified in patients with less severe disease or improving clinical manifestations. Monitoring of ferritin, sCD25, cell counts, and EBV-DNA in
affected patients, aids in assessing treatment response. EBV-DNA levels of more than $10^3$ copies/mL have been reported relevant for the development of EBV-HLH.

As EBV replicates in B-cells, addition of rituximab (e.g. 375 mg/m$^2$ once weekly, 2–4 times) to HLH-directed therapy may be effective to clear the reservoir of virus in EBV-triggered HLH. Monitoring of ferritin, sCD25, cell counts, and EBV-DNA may guide on the number of rituximab doses. However, in many cases EBV-HLH is associated with infection of T-cells and/or NK-cells, irrespective of the patients’ ethnic background or the clinical course, so rituximab cannot replace the anti-T-cell therapy with corticosteroids with/without etoposide as suggested above. In patients with continuously rising or sustained high levels of EBV-DNA, SCT should be considered, such as in chronic active EBV.

HIV-HLH

The prognosis of HLH in patients with HIV has improved in the era of highly active antiretroviral treatment (HAART). Lymphomas and opportunistic infections are the most important triggers to look for. A short transient treatment of overt inflammation by corticosteroids (with/without IVIG) is recommended. In a large series of HIV-HLH patients, etoposide was administered in about half. The wide spectrum of potential viral triggers mandates virus-specific treatment on a case-by-case basis.

Statement 11: HLH induced by intracellular infections such as tuberculosis, leishmaniasis or rickettsia disease usually does not need HLH-94-like treatment, but responds to specific antimicrobial treatment.

Strong Consensus
Patients infected by pathogens that target the monocyte-macrophage system may develop HLH, but immunosuppression as HLH-94 should be avoided since they usually respond well to specific antimicrobial treatment. Leishmania is an endemic pathogen around the world and treatment with (liposomal) amphotericin B cures leishmaniasis. Rickettsia disease is treated by tetracyclines or chloramphenicol, while tuberculosis requires quadruple antibiotic treatment and adaptation according to resistance testing.

Salvage treatment for relapsed and refractory HLH

Statement 12: Salvage treatment for adults with refractory/relapsing HLH usually requires intensification using combined chemotherapy and consolidation with alloSCT.

Strong Consensus

Mortality in adult HLH ranges between 20% to 88%, primarily due to refractory HLH, secondary infections, and progression of the underlying triggering disease. In a prospective study, liposomal doxorubicin, etoposide and high-dose methylprednisolone resulted in 27% complete and 49% partial remission within 4 weeks.

In infection-associated HLH, in particular EBV-HLH, reactivations are common if treatment intensity is only moderate or tapered too fast; such reactivations commonly respond to treatment intensification. For patients with EBV-HLH and persistent high EBV-genome copy numbers or chronic active EBV, and refractory/relapsing lymphoma, alloSCT is recommended. In primary HLH, reactivations and/or persistence of hyperinflammation are frequent until curative alloSCT is performed.
Data on the efficacy of salvage agents for HLH are limited. The anti-CD52 antibody alemtuzumab (median dose 1 mg/kg split over a median of four days) has been reported to be beneficial in refractory pediatric patients; in young adults a reduced dose or a prolonged maintenance (as in chronic lymphocytic leukemia) has been used\textsuperscript{89,90}. Other salvage options include CHOP-like protocols plus etoposide, and targeted inhibition of Janus kinase (JAK)-signaling with ruxolitinib\textsuperscript{91,92}. Plasmapheresis or use of cytokine adsorption columns may aid in rescuing critically ill patients from a deleterious cytokine storm\textsuperscript{93,94}. In November 2018, the US Food and Drug Administration (FDA) approved emapalumab (anti-interferon-gamma monoclonal antibody) as a second line therapeutic agent for primary HLH in children and adults, after completion of an initial study in which 27 patients with relapsed/refractory disease were included. Emapalumab has the potential to be more readily tolerated than etoposide, though there has not yet been significant experience in the treatment of adults\textsuperscript{95}.

As a general rule, in patients with refractory HLH, treatment decisions need to be individualized according to the most likely triggering cause. In patients with malignancy-associated HLH, treatment of the malignancy guides the salvage approach (intensification of chemotherapy). Contact with a HLH reference center is recommended.

**HLH and MAS-HLH in the Intensive Care Unit**

**Statement 13:** In critically ill patients with persistent fever, cytopenias, and organomegaly, particularly in confirmed or presumed cases of sepsis, sepsis-like
syndromes, and/or evolving multi-organ failure, suspicion for HLH should be raised and further HLH testing initiated.

**Strong Consensus**

Intensivists may be the first to diagnose HLH in patients with multiple organ dysfunction syndrome (MODS)\(^{96,97}\). Familiarity with HLH is important due to the nonspecific symptoms and laboratory findings, and since the hyperinflammatory state of HLH can also be observed in sepsis, MODS, and other cytokine storm syndromes. The condition “hyperinflammatory sepsis” (also described as “MAS-like”) refers to patients that typically have less severe hyperinflammation and may not fulfill the HLH diagnosis\(^{72,98-100}\). Importantly, HLH, MODS, and sepsis can co-exist, with sepsis serving as the possible HLH trigger\(^{2,98,101}\). HLH should be considered in deteriorating critically ill patients with a disproportionate inflammatory response (e.g. persistent fever, unresponsiveness to vasopressors, need for extracorporeal life support (ECLS)), inexplicable cytopenias, and organ failure not responding to appropriate therapy, anti-microbial treatment and aggressive supportive care\(^{96,102}\). Screening for HLH should follow the HLH-2004 criteria, including bone marrow investigation (see Statement #3). Fever, one of the criteria, needs special consideration as it can be masked by frequent use of antipyretics, continuous renal replacement therapy, and ECLS.

Therapy should be individualized and include HLH or MAS-HLH-directed treatment (see Statements #6,7,10,12,14) with consideration of standard supportive care and adjunctive critical care therapies\(^{96,102-105}\). Reevaluation of clinical condition should be frequent (at least every 12 hours) to determine if initial or additional HLH-directed therapy should be added.
Clinical management of MAS-HLH

Statement 14: Treatment of MAS-HLH is different from that recommended for HLH due to partial pathogenetic diversity.

Strong Consensus

HLH in patients with underlying rheumatic conditions is historically called macrophage activation syndrome (MAS/MAS-HLH). MAS-HLH, a form of sHLH increasingly recognized in adults, has been reported in association with almost all systemic rheumatic conditions. An overwhelming immune activation leads to a systemic cytokine storm but the initiating factors might be different in MAS-HLH as compared to other forms of HLH, although MAS-HLH commonly, as other forms of sHLH, is triggered by infections.

Currently, there are no accepted classification criteria for adult MAS-HLH. Several criteria have been developed for children, but these still need validation in adult patients (see Statement #3). Notably, symptoms of MAS-HLH may be different in patients treated with biologic agents.

Early recognition and diagnosis of MAS-HLH is essential for efficacious management. A personalized and graded treatment approach is advised. Conventionally, corticosteroids are the first-line treatment. High-dose pulse methylprednisolone (1 g/day, for three-five consecutive days) is one frequent initial approach. CSA (2–7 mg/kg/day) can be added in patients with insufficient immediate response, as well as IL-1-blocking therapy with anakinra; a dose of 2-6-10 mg/kg/day subcutaneously in divided doses is suggested. The experience with anti-IL-6-blockade with tocilizumab is also increasing. Finally, in patients with severe active disease or CNS-involvement despite steroids, CSA, and/or anakinra, etoposide in a
reduced dose (50-100 mg/m$^2$ once weekly) may be very effective$^{106}$; such treatment should preferably be discussed with an expert but still not delayed.

**HLH-like cytokine storm induced by novel immunotherapies**

**Statement 15:** Novel immunotherapies may induce a cytokine storm resembling HLH that requires specific treatment.

*Strong Consensus*

With the advent of novel T-cell engaging immunotherapies, reports of treatment associated cytokine release syndrome (CRS) have repeatedly emerged$^{117,118}$. These T-cell immunotherapies include engineered T-cells, such as chimeric antigen receptor modified T-cells (CART) targeting CD19, and blinatumomab, a bispecific T-cell engager (BiTE) antibody, which connects CD3-positive T-cells to CD19-positive target B-cells$^{119,120}$. Both these agents are approved for treatment of B-acute lymphoblastic leukemia (B-ALL). CART-cells are also approved in relapsed/refractory B-NHL. CART-cells and blinatumomab induce a cytokine response that strongly resembles other forms of HLH.

The anti-IL-6 antibody tocilizumab has been used with notable rapid resolution of CRS in patients after CART or blinatumomab treatment. More recently, there are increasing reports of treatment-induced HLH also in patients treated with CTLA4- and PD1/PDL1-directed checkpoint antibodies (ipilimumab, pembrolizumab, nivolumab, avelumab, atezolizumab), used in a wide variety of cancer subtypes. Treatment interruption or corticosteroids alone have been used with meaningful responses$^{121,122}$. A CART-associated toxicity working group suggests that suspected HLH should be managed with anti-IL-6 therapy and corticosteroids for organ toxicities of grade 3 or
higher, and if the patient has no improvement clinically or serologically within 48 hours, additional therapy with etoposide 75–100 mg/m$^2$ should be considered\textsuperscript{23}.

**Summary & Perspectives**

During recent years, interest in adult HLH has increased markedly and as a result HLH in adults is more frequently diagnosed. The dramatic therapeutic success in pediatric HLH has also positively affected the survival of adults with HLH. However, there are profound differences between adult and pediatric HLH: genetic HLH is rare in adults; pediatric diagnostic criteria are suboptimal; frequent (often occult) underlying malignancies or other conditions require a different diagnostic work-up; and pediatric treatment regimens may have to be adapted on a case-by-case basis.

In adults, HLH-associated mortality remains high, especially in patients with underlying malignancies. Although the drugs used in pediatric HLH are effective in adult HLH, there is a need for novel agents. Interesting trials testing alternative therapeutic approaches have been initiated, including those incorporating ruxolitinib (JAK1/2 inhibitor) (ClinicalTrials.gov Identifiers: NCT02400463; NCT03795909; NCT03533790), anakinra (IL-1 blockade) (NCT02780583), alemtuzumab (NCT02472054), and emapalumab (anti-interferon-gamma monoclonal antibody) (NCT01818492). It is anticipated that the increased awareness of HLH together with a more rapid diagnostic work-up and new therapeutic approaches will improve the prognosis of HLH in adults, as has been the case in children.
Acknowledgments

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Authorship Contributions

PLR initiated the report, which was planned and coordinated by PLR and JIH. ACH, MH, TvBG, RM, NB, SB, JGH, MG, MJ, AK, JvL, GL, KEN, AVR, YW, ZW, and GJ all contributed with text proposals and revisions, and all authors voted on all statements. PLR and JIH drafted the manuscript, which was reviewed and approved by all authors.

Conflict of Interest Disclosures

No competing financial interests: PLR, MH, TvBG, RM, NB, SB, MG, JAMvL, GL, YW, ZW, GJ, JGH, JIH.

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KEN: Research support from Incyte Pharmaceuticals and Alpine Biosciences.

AVR: Speaker fees/Honoraria: SOBI, Novartis, Lilly and Roche.
References


Figure legends

Figure 1: Overview of the HLH-94 treatment protocol. Note that dose and frequency adjustments of this protocol are advised for adult patients (see Statement #7).

Figure 2: Treatment algorithm for adult patients with HLH including MAS-HLH. The HLH-94 pediatric treatment protocol is the consensus mainstay treatment for newborns, toddlers and children up to 18 years, where genetic causes of HLH are enriched. Individual adaptation regarding length and dosing of the HLH-94 treatment plan in adults is warranted. Allogeneic hematopoietic stem cell transplant (alloSCT) can cure primary HLH and may be applied in patients with high risk hematologic malignancy as consolidation treatment or in relapsed HLH after successful salvage treatment. Treatment in adults cannot be standardized, and needs tailoring according to the underlying condition and HLH-initiating trigger (infection, malignancy, autoimmune/autoinflammatory, drug-induced, other causes). In relapsed/refractory (r/r) HLH, treatment intensification with chemotherapy, use of the anti-CD52 antibody alemtuzumab, cytokine adsorption using filter columns or plasma exchange, off-label treatment with the JAK2-inhibitor ruxolitinib, or the anti-Interferon-gamma antibody emapalumab have shown reasonable efficacy.

CS: corticosteroids; CSA: Cyclosporine A; IVIG: polyvalent immunoglobulins; CART: chimeric antigen receptor T-cells; *: off-label in EBV-HLH
**Table 1**: Causes of primary and secondary HLH.

1. Primary HLH (Mendelian inherited conditions leading to HLH) (Table 4)
   a. Defects in the cytolytic function of cytotoxic T-cells and/or NK-cells \(^{13,46,51}\)
   b. Defects in inflammasome regulation \(^{124,125}\)

2. Secondary HLH (apparently non-Mendelian HLH) \(^{10}\)
   a. Infections (mainly viruses as EBV, HIV and CMV but also bacteria, parasites and fungi) \(^{14}\)
   b. Malignancies (mainly malignant lymphoma) \(^{15}\)
   c. Macrophage activation syndrome in autoinflammatory or autoimmune disorders \(^{113}\)
   d. Other causes (organ or stem cell transplantation, metabolic, traumatic, iatrogenic [immunosuppression, vaccination, surgery, hemodialysis] causes and, rarely, pregnancy) \(^{10,14}\)
Table 2: HLH-2004 Diagnostic Criteria

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 (5 out of the 8 criteria below).

* Fever
* Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
  - hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L),
  - platelets <100 x 10^9/L,
  - neutrophils <1.0 x 10^9/L.
* Hypertriglyceridemia and/or hypofibrinogenemia:
  - fasting triglycerides ≥3.0 mmol/L (i.e. ≥265 mg/dL),
  - fibrinogen ≤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 ≥500 microgram/L
  - Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml

Comments:
(1) If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.
(2) The following findings may provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein, (b) histological picture in the liver resembling chronic persistent hepatitis (biopsy).
(3) Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, VLDL ↑, HDL ↓.
Table 3: Parameters and points in the HScore

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of points (criteria for scoring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known underlying immunosuppression*</td>
<td>0 (no) or 18 (yes)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>0 (&lt;38.4), 33 (38.4–39.4), or 49 (&gt;39.4)</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)</td>
</tr>
<tr>
<td>No. of cytopenias†</td>
<td>0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)</td>
</tr>
<tr>
<td>Ferritin (microg/L)</td>
<td>0 (&lt;2,000), 35 (2,000–6,000), or 50 (&gt;6,000)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0 (&lt;1.5), 44 (1.5–4), or 64 (&gt;4)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>0 (&gt;2.5) or 30 (≤2.5)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>0 (&lt;30) or 19 (≥30)</td>
</tr>
<tr>
<td>Hemophagocytosis on bone marrow aspirate</td>
<td>0 (no) or 35 (yes)</td>
</tr>
</tbody>
</table>

* Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine A, azathioprine).

† Defined as a hemoglobin level of 9.2 g/L and/or a leukocyte count of ≤5x10⁹/L and/or a platelet count of ≤110x10⁹/L
**Table 4:** Genetic alterations in primary HLH and related disorders of immunoregulation.

<table>
<thead>
<tr>
<th>Defective immune function</th>
<th>Gene* (locus)</th>
<th>Syndrome</th>
<th>Clinical features</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic granule content</td>
<td><strong>PRF1</strong> (10q21-22)</td>
<td><strong>FHL2</strong></td>
<td>Decreased/absent perforin expression (FC)</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic exocytosis pathway</td>
<td><strong>UNC13D</strong> (17q2)</td>
<td><strong>FHL3</strong></td>
<td>Low CD107a expression (degranulation assay, FC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STX11</strong> (6q24)</td>
<td><strong>FHL4</strong></td>
<td>Low CD107a expression (degranulation assay, FC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STXBP2</strong> (19q13)</td>
<td><strong>FHL5</strong></td>
<td>Low CD107a expression (degranulation assay, FC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>RAB27A</strong> (15q21)</td>
<td>Griscelli type 2</td>
<td>Abnormal granule pattern in CBC and hair shafts, low CD107a expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>LYST</strong> (1q42-43)</td>
<td>Chediak-Higashi</td>
<td>Abnormal granule pattern in CBC and hair shafts, low CD107a expression</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic T-cell signaling</td>
<td><strong>SH2D1A</strong> (Xq24-25)</td>
<td><strong>XLP1</strong></td>
<td>EBV-lymphoproliferation</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>BIRC4</strong> (Xq25)</td>
<td><strong>XLP2</strong></td>
<td>Refractory colitis, EBV-lymphoproliferation</td>
<td></td>
</tr>
<tr>
<td>Inflammasome regulation, excess apoptosis, NOD signal</td>
<td><strong>NLRC4</strong> (2p22.3)</td>
<td></td>
<td>Recurrent autoinflammation, enterocolitis</td>
<td></td>
</tr>
</tbody>
</table>

* Genes associated with other rare immune deficiencies that may cause the HLH syndrome include **ITK** (5q33), **CD27** (12p13.13), **RAG1** & **2** (11p12), **IL2RG** (Xq13.1), **IL7RA** (5p13.2), **CD3E** (11q23.3), **BTK** (Xq22.1), **FAS** (10q23.31), **WAS** (Xp11.23), **ATM** (11q22.3), **NEMO** (Xq28), **STAT1** (2q32.2), **DKC1** (Xq28), **MEFV** (16p13.3), **TNFRSF1A** (12p13.31); as well as **CYBB** (Xp21.1-p11.4), **CYBA** (16q24.2) and **NCF1** (7q11.23) which encode the phagocyte NADPH oxidase complex affected in chronic granulomatous disease. **©, 46, 126**.

Abbreviations: CBC, complete blood count; EBV, Epstein-Barr virus; FC, Flow cytometry; FHL, familial hemophagocytic lymphohistiocytosis; NOD, nucleotide-binding oligomerization domain-like receptor; XIAP, X-linked IAP (Inhibitor of Apoptosis); XLP, X-linked lymphoproliferative syndrome.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Mut. freq.</th>
<th>PRF1</th>
<th>STXB2</th>
<th>SH2D1A</th>
<th>UNC13D</th>
<th>STX11</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. 2011</td>
<td>14%</td>
<td>7/11^*</td>
<td>1/1</td>
<td>n.s.</td>
<td>2/5</td>
<td>n.s.</td>
<td>≥18</td>
</tr>
<tr>
<td>Sieni et al. 2012</td>
<td>n/a</td>
<td>6/0</td>
<td>1/0</td>
<td>2(m)/0</td>
<td>2/0</td>
<td>n.s.</td>
<td>23 (18-43)</td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>7%</td>
<td>6/3</td>
<td>n.s.</td>
<td>1(m)/1(f)</td>
<td>0/1</td>
<td>0/7</td>
<td>20 (13-56)</td>
</tr>
<tr>
<td>Cetica et al. 2016</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥18</td>
</tr>
<tr>
<td>Chen et al. 2018</td>
<td>32%</td>
<td>1/2</td>
<td>0/1</td>
<td>0</td>
<td>1/2</td>
<td>0</td>
<td>≥18</td>
</tr>
</tbody>
</table>

# bi/hemi/mo: biallelic / hemizygous / monoallelic mutations.

& Some are double heterozygous patients, with mutations in two different genes.

† The study included all age groups.

* Only bi-allelic variations reported. Specific mutant site not reported for patients ≥18 years.

m: male, f: female.
INITIAL THERAPY  →  CONTINUATION THERAPY / HSCT  →

(dexamethasone daily)  (dexamethasone in pulses)

Dexa (mg/m2)

10mg
5mg
2.5mg
1.25mg

VP-16

CSA

I.T. therapy (↑ ↑ ↑ ↑)

Weeks

1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21  22  23  24 →

Dexa = Dexamethasone daily (10 mg/m² for 2 weeks, 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week, and taper and discontinue during one week). Then pulses every second week with 10 mg/m² for 3 days.

VP-16 = Etoposide 150 mg/m² iv.

CSA = Cyclosporin A aiming at blood levels of around 200 μg/L (monoclonal, trough value). Start at week 9, or possibly earlier, but not earlier than week 3 (see new recommendations, ref 6)

I.T. therapy = Methotrexate doses: <1 yr 6 mg, 1-2 yrs 8 mg, 2-3 yrs 10 mg, >3 yrs 12 mg, per dose. Start only if progressive neurological symptoms or if an abnormal CSF not has improved.
Recommendations for the management of hemophagocytic lymphohistiocytosis in adults


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