Consensus-Based Guidelines for the Recognition, Diagnosis, and Management of Hemophagocytic Lymphohistiocytosis in Critically Ill Children and Adults

Melissa R. Hines, MD[1]
Tatiana von Bahr Greenwood, MD[2]
Gernot Beutel, MD[3]
Karin Beutel, MD[4]
J. Allyson Hays, MD[5]
AnnaCarin Horne, MD, PhD[2]
Gritta Janka, MD, PhD[6]
Michael B. Jordan, MD[7]
Jan A. M. van Laar, MD[8]
Gunnar Lachmann, MD[9]
Kai Lehmberg, MD[10]
Rafal Machowicz, MD, PhD[11]
Päivi Miettunen, MD[12]
Paul La Rosée, MD[13]
Bita Shakoory, MD[14]
Matt S. Zinter, MD[15]
Jan-Inge Henter, MD, PhD[2]

OBJECTIVE: Hemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome that often requires critical care support and remains difficult to diagnose. These guidelines are meant to aid in the early recognition, diagnosis, supportive care, and treatment of patients with hemophagocytic lymphohistiocytosis in ICUs.

DATA SOURCES: The literature searches were performed with PubMed (MEDLINE).

STUDY SELECTION: Keywords and medical subject headings terms for literature search included "macrophage activation syndrome," hemophagocytic lymphohistiocytosis," and "hemophagocytic syndrome."

DATA EXTRACTION: The Histiocyte Society developed these consensus recommendations on the basis of published reports and expert opinions with level of evidence provided for each recommendation. They were endorsed by the Society of Critical Care Medicine.

DATA SYNTHESIS: Testing for hemophagocytic lymphohistiocytosis should be initiated promptly in all patients admitted to ICUs with an unexplained or disproportionate inflammatory response, especially those with rapid clinical deterioration. Meeting five or more of eight hemophagocytic lymphohistiocytosis 2004 diagnostic criteria serves as a valuable diagnostic tool for hemophagocytic lymphohistiocytosis. Early aggressive critical care interventions are often required to manage the multisystem organ failure associated with hemophagocytic lymphohistiocytosis. Thorough investigation of the underlying triggers of hemophagocytic lymphohistiocytosis, including infections, malignancies, and autoimmune/autoinflammatory diseases, is essential. Early steroid treatment is indicated for patients with familial hemophagocytic lymphohistiocytosis and is often valuable in patients with acquired hemophagocytic lymphohistiocytosis (i.e., secondary hemophagocytic lymphohistiocytosis) without previous therapy, including macrophage activation syndrome (hemophagocytic lymphohistiocytosis secondary to autoimmune/autoinflammatory disease) without persistent or relapsing disease. Steroid treatment should not be delayed, particularly if organ dysfunction is present. In patients with macrophage activation syndrome, whose disease does not sufficiently respond, interleukin-1 inhibition and/or cyclosporine A is recommended. In familial hemophagocytic lymphohistiocytosis and severe, persistent, or relapsing secondary macrophage activation syndrome, the addition of prompt individualized, age-adjusted etoposide treatment is recommended.

CONCLUSIONS: Further studies are needed to determine optimal treatment for patients with hemophagocytic lymphohistiocytosis in ICUs, including the use of novel and adjunct therapies.

KEY WORDS: extracorporeal life support; hemophagocytic lymphohistiocytosis; hyperferritinemia; macrophage activation syndrome; multiple organ failure

DOI: 10.1097/CCM.0000000000005361

Hemophagocytic lymphohistiocytosis (HLH) is a syndromic disorder (**Tables 1** and **2**; and **Supplementary Table 1**, http://links.lww.com/CCM/G882) characterized by severe hyperinflammation in the setting of immune dysfunction with concomitant immune system activation (i.e., persistent antigen presentation and adaptive or innate immune system activation) (1, 2). In primary (genetic) HLH, immune dysfunction is irreversible and most often due to autosomal recessive

TABLE 1.
Hemophagocytic Lymphohistiocytosis 2004 Criteria (3–6)

A) Molecular Diagnosis	**Pathogenic Biallelic Mutation in Genes Associated With HLH: *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *LYST*, *RAB27A*, *XIAP*, *SH2D1A*, and *NLCR4***		
B) Clinical and Laboratory Criteria	**For Clinical Diagnoses, Greater Than or Equal to Five of The Eight Criteria Below Must Be Met**		
Feature	**Cutoff**	**Assumed Mechanism**	**Comments**
HLH-2004 diagnostic criteria			
Fever		Elevated cytokines	May be altered by antipyretics & steroids
Splenomegaly		Infiltration by lymphocytes and histiocytes	
Cytopenia	≥ 2 cell lines	Suppression by cytokines and hemophagocytosis	Check for toxic marrow failure in patients after chemotherapy
Hemoglobin	< 90 g/L (neonates < 100 g/L)		
Platelets	$< 100 \times 10^9$/L		
Neutrophils	$< 1 \times 10^9$/L		
Hypertriglyceridemia or hypofibrinogenemia	≥ 265 mg/dL (≥ 3 mmol/L) ≤ 150 mg/dL (≤ 1.5 g/L)	Lipoprotein lipase suppression by cytokines; plasminogen activator produced by macrophages	Triglyceride levels may be altered by parenteral nutrition
Hemophagocytosis	Bone marrow, other tissues	Due to macrophage activation	
Hyperferritinemia	≥ 500 ng/mL (≥ 500 µg/L)	Released from activated macrophages	Test dilution may be required
Reduced or absent natural killer-cell cytotoxicity		Due to genetic defect or transient dysfunction	CD107a assays[a] may be more valuable
Elevated soluble CD25 (soluble IL-2 receptor)	≥ 2,400 U/mL	Released by activated T-cells	Test dilution may be required
Other features			
Elevated transaminases and bilirubin		Infiltration by lymphocytes and histiocytes; viral triggers	
Elevated lactate dehydrogenase		Cell death and proliferation	
Elevated D-dimers		Hyperfibrinolysis	
Elevated CSF cells or CSF protein		Cell infiltration into the CNS	
Elevated soluble CD25/ferritin ratio (> 2)			Can suggest underlying malignant neoplasm
Hypoalbuminemia		Hypercytokinemia	
Hepatomegaly		Infiltration by lymphocytes, macrophages, and histiocytes	

HLH = hemophagocytic lymphohistiocytosis, CSF = cerebrospinal fluid.
[a]Also known as CD107a mobilization or degranulation assays.

TABLE 2.
Macrophage Activation Syndrome Diagnostic Criteria (7, 8)

2016 Classification Criteria for MAS Related to Systemic Juvenile Idiopathic Arthritis (7)	
Clinical and laboratory diagnosis	Patients must have a suspected or known diagnosis of systemic juvenile idiopathic arthritis
	Fever
	Ferritin > 684 ng/mL (> 684 µg/L)
	Any two of the below
	Platelet count ≤ 181 × 10^9/L
	Aspartate aminotransferase > 48 U/L
	Triglycerides > 156 mg/dL (> 1.76 mmol/L)
	Fibrinogen ≤ 360 mg/dL (≤ 3.60 g/L)
Classification Criteria for MAS Related to Juvenile Systemic Lupus Erythematosus (8)	
One clinical criterion and two laboratory criteria are required	
Clinical criteria	Fever (> 38°C)
	Hepatomegaly (≥ 3 cm below the costal arch)
	Splenomegaly (≥ 3 cm below the costal arch)
	Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
	CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)
Laboratory criteria	Cytopenia affecting two or more cell lineages (WBC count ≤ 4.0 × 10^9/L, hemoglobin ≤ 90 g/L, or platelet count ≤ 50 × 10^9/L)
	Increased aspartate aminotransferase > 40 units/L
	Increased lactate dehydrogenase > 567 units/L
	Hypofibrinogenemia (fibrinogen ≤ 1.5 g/L)
	Hypertriglyceridemia (triglycerides > 178 mg/L)
	Hyperferritinemia (ferritin > 500 µg/L)

MAS = macrophage activation syndrome.

biallelic genetic defects in the perforin-dependent cytotoxic pathway or mutations affecting activation of the inflammasome (1, 2). Secondary (acquired) HLH (sHLH) often results from infections, malignancies, or autoinflammatory/autoimmune diseases. HLH induced by autoinflammatory/autoimmune disease is termed macrophage activation syndrome–associated HLH (MAS-HLH) (Table 2) (9). The immune dysfunction in sHLH is characterized by reversible natural killer (NK) or CD8+ T cell dysfunction, which occurs in some viral infections or rheumatologic disorders, or by NK-cell deficiency, which can occur after chemotherapy or during sepsis (1, 10–12).

The overall frequency of HLH within the general and critical care population is unknown, but it is rare. Recently, 1.5% of patients with hyperferritinemia (> 500 µg/L) who were admitted to ICUs reportedly had HLH (13, 14). However, HLH often requires supportive care management in ICUs (> 60% in pediatric HLH cases) with high mortality rates (36–40% of pediatric cases and 41–68% of adult cases) (9, 15–18). In addition to the supportive care needed to treat HLH, intensivists also play a crucial role in the diagnosis of HLH because HLH diagnoses are frequently not established before ICU admission (19). Diagnosis remains challenging because of the relative rarity of HLH and its clinical overlap with other hyperinflammatory disorders, such as sepsis, leading to a high number of undiagnosed cases (20). In addition to the challenges in recognizing and diagnosing HLH, the advent of several new therapeutic strategies has presented new challenges in HLH management. To aid intensivists in the understanding of the pathobiology, recognition, diagnosis, and treatment of HLH, we created the following consensus guidelines, including statements specific for the ICU settings.

METHODOLOGY

The following recommendations were formed by the Group on HLH Subtypes of the Histiocyte Society, which is an interdisciplinary committee of pediatric and adult hematologists/oncologists (n = 8), immunologists (n = 2), critical care specialists (n = 4), and rheumatologists (n = 3) with HLH expertise. We based our consensus statements on relevant published studies and expert opinions. Each statement was issued the highest level of evidence represented by the National Health and Medical Research Council Evidence Design Framework (https://www.ncbi.nlm.nih.gov/books/NBK121300/table/appb.t21/). The Society of Critical Care Medicine reviewed and endorsed these guidelines. Details outlining the consensus statement definitions and processes are fully described in the **Supplementary Material** (http://links.lww.com/CCM/G882).

CONSENSUS STATEMENTS AND RECOMMENDATIONS

Statement 1

"HLH (including MAS-HLH) is often difficult to discern from other hyperinflammatory disorders, including sepsis, multiple organ dysfunction syndrome (MODS), and other cytokine storm syndromes. These entities represent varying degrees of hyperinflammation and underlying pathobiology. Patients meeting HLH criteria often have/exhibit one of the most severe forms of the critical care hyperinflammatory phenotypes (strong consensus; level IV diagnostic accuracy)."

Hyperinflammation is a phenotype commonly observed in ICUs, which occurs in association with sepsis, MODS, systemic inflammatory response syndrome, cytokine release syndrome, and autoinflammatory/autoimmune flares. These ICU-related disorders characterized by severe hyperinflammation include the newly described MAS-like sepsis or MAS-like MODS, also termed hyperferritinemic sepsis in children, in addition to HLH (21–23). More recently, immune dysregulation with cytokine storm was reported secondary to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections (24–27). Similar to the pathophysiology of HLH, the severity of the hyperinflammatory phenotypes in ICUs most likely depends on the immune dysregulation type (i.e., cytotoxic dysfunction vs deficiency), its reversibility, and the presence of persistent or new infections (2, 12, 28). As reported for patients with MAS-like MODS, SARS-CoV-2 infections, and HLH, patients with severe, persistent hyperinflammatory phenotypes can benefit from immunomodulatory therapy (see statement 9) (22, 24).

Statement 2

"HLH should be suspected in all critically ill patients with unexplained or disproportionate inflammatory responses (e.g., fever, cytopenias, hyperferritinemia, hepatomegaly, splenomegaly, or coagulopathy). The suspicion for HLH should be further increased for cases of rapidly evolving MODS and inadequate responses to appropriate empiric treatment or escalating supportive care (Strong consensus, level IV diagnostic accuracy)."

Taken together, the HLH-2004 criteria are valuable to diagnose HLH, although the individual parameters are nonspecific. Patients in critical care units who experience at least five of the HLH-2004 criteria (i.e., HLH phenotype; see statement 4) are most likely to have uncontrolled inflammation; therefore, suspicion for HLH should be raised. We define disproportionate inflammatory responses or hyperinflammation as persistent fever with one of the following criteria: marked hyperferritinemia (further discussed in statement 3), cytopenias, hepatomegaly and/or splenomegaly, or hemophagocytosis (3, 13, 19, 29). Further suspicion of HLH should be raised in patients with underlying malignant neoplasms or immunocompromised states (19, 29). Ideally, HLH should be suspected before decompensation; however, HLH should be further considered in differential diagnoses when unexpected and rapid deterioration with evolving organ failure that does not respond to appropriate therapy (e.g., vasopressors, antimicrobial treatment, and aggressive supportive care) occurs (19, 20).

Statement 3

"Testing for HLH (e.g., ferritin, soluble interleukin [IL-2] receptor [sIL-2R], or complete blood count) should be initiated promptly in all ICU patients with unexplained hyperinflammation (strong consensus; level III-3 diagnostic accuracy)."

For those who meet criteria for disproportionate inflammatory responses, as described in statement 2, an initial HLH assessment is recommended, as outlined in **Table 3** (4). Currently, no laboratory tests (except

flow cytometric studies and genetic testing for familial HLH) or physical findings specific to HLH are available. Both require interpretation according to previously published reports and consideration of the overall clinical presentation. The validity of each single criterion varies, and each is further described in detail in the Supplementary Material (http://links.lww.com/CCM/G882), including common laboratory findings (Table 1), interpretation of functional and expression testing, and indications for genetic testing.

If HLH is suspected on the basis of a focused panel of tests, early consultations with an HLH expert (e.g., hematologist, oncologist, rheumatologist, or immunologist) are recommended; however, if an HLH expert and/or final test results are not available, initiation of HLH-directed therapy must not be delayed while waiting for a final determination of an HLH diagnosis.

Statement 4

"Meeting five of the eight HLH-2004 diagnostic criteria currently serves as a practical tool for HLH diagnosis. In certain circumstances such as MAS-HLH, other sets of diagnostic criteria may be applied (strong consensus; level IV diagnostic accuracy)."

The most widely used set of criteria are established in the HLH-2004 protocol (Table 1 for criteria and mechanisms), in which HLH is defined by meeting at least five of the eight criteria. The HLH-2004 diagnostic criteria remain the standard for diagnosis of HLH and serve as a practical guide, particularly for pediatric patients, but have not yet been fully validated in adults (4). However, a recent threshold of four or more HLH-2004 criteria was found to be highly sensitive (95%) and specific (93%) for HLH diagnoses in adults admitted to ICUs, with improved

TABLE 3.
Diagnostic Tests in Hemophagocytic Lymphohistiocytosis (4, 30, 31)

Initial Recommended Test for HLH Workup	
Tests for HLH-2004 criteria	Complete blood count (with absolute neutrophil count)
	Ferritin (with dilutions)
	Triglycerides
	Fibrinogen
	Radiologic imaging for liver and spleen size, especially if not palpable on examination
	Bone marrow aspirate
	Soluble CD25 (soluble interleukin-2 receptor)[a]
Other helpful tests	Alanine aminotransferase and asparate aminotransferase levels
	Albumin
	Bilirubin (direct and indirect)
	Lactate dehydrogenase
	C-reactive protein
	Prothrombin time, activated partial thromboplastin time
	Sodium level
Confirmatory tests for primary HLH	
Screening for primary HLH	CD107a mobilization/degranulation assay[a,b]
	Perforin expression[a,b]
	Signaling lymphocytic activation molecule–associated protein and XIAP expression in male patients[a,b]
Confirmation of primary HLH	HLH genetic panel (*PRF1*, *UNC13D*, *STX11*, *STXBP2*, *LYST*, *RAB27A*, *XIAP*, *SH2D1A*, and *NLCR4*)

HLH = hemophagocytic lymphohistiocytosis, *XIAP* = X-linked inhibitor of apoptosis.

[a]May not be available at all institutions and may take several days for results. If some tests are not available, do not postpone the treatment but consider storing frozen serum and/or EDTA/heparin samples before treatment (including steroids).

[b]Results may not be available in patients with low absolute lymphocyte count but will still be accurate after given therapy.

specificity when additional criteria were met (3). In line with these findings, initiation of therapy should be considered if four or more criteria are fulfilled, particularly if worsening organ dysfunction is evident. Additional laboratory findings that are not part of the HLH-2004 criteria but are often found in cases of HLH and can further support HLH diagnoses, such as transaminitis and hyperbilirubinemia, are listed in Table 1 (3, 4, 13, 32). In some forms of HLH, such as isolated HLH with CNS involvement (CNS-HLH) (see **Statement 6**, Supplementary Material, http://links.lww.com/CCM/G882), five criteria are never met, but a diagnosis can be later verified by HLH genetic testing (33). Other sets of criteria have been suggested, particularly for adult patients, such as the HScore in which parameters of the HLH-2004 criteria (sCD25$^-$ and NK-cell cytotoxicity, plus hepatomegaly and aspartate aminotransferase) are weighed according to severity. Most importantly, the HScore in adults considers the presence of immunodeficiency/immunosuppression. The web-based HScore calculator is available at http://saintantoine.aphp.fr/score/ (29). The HScore is particularly helpful for HLH diagnoses in adult patients admitted to ICUs, with high sensitivity (100%) and specificity (94%; reported cutoff 168) (3). For patients with systemic juvenile idiopathic arthritis (sJIA), a specific set of criteria is based on data from patients with sJIA and MAS-HLH, as well as control patients (7). Levels of ferritin, platelets, aspartate aminotransferase, triglycerides, and fibrinogen were included in these criteria, however, at cutoff levels distinct from those of the HLH-2004 criteria (7). The sJIA criteria were primarily developed to differentiate between flares of autoinflammation and MAS-HLH (Table 2). Additionally, distinct criteria are proposed for patients with systemic lupus erythematosus (SLE)-related MAS, including the MAS/HLH score (8, 34). In other autoimmune and autoinflammatory conditions, no consensus guidelines on the classifying criteria for MAS are available.

Statement 5

"A thorough investigation of the underlying triggers of HLH is mandatory for the optimal treatment of HLH. Infectious triggers, predominantly viral and less commonly autoimmune or autoinflammatory triggers, span across all ages, whereas the likelihood of an underlying malignant disease increases with age (strong consensus; level III-2 etiology)."

Establishing a broad workup for triggers is nearly as important as starting HLH-directed therapy because it may strongly affect treatment and prognosis. HLH in children and adults is commonly associated with infectious, autoimmune/autoinflammatory, or malignant neoplasm triggers (5, 9). In children, other predisposing conditions, such as immunodeficiencies and inborn metabolic diseases, are also described (5, 9). In adults, infectious and malignant disease triggers are the most frequent triggers within the general and ICU populations (9, 18). Adult cancer-associated HLH should always be considered, particularly with increasing age. Occult malignant disease, particularly evidence of lymphoma, should be suspected and aggressively sought in the cases of HLH with an unknown trigger, as fully described by LaRosée et al (35) (9, 36). Evaluation must include testing for the viral infections commonly associated with HLH, including those caused by Epstein-Barr virus, cytomegalovirus, HIV, and, more recently, SARS-CoV-2, either alone or in the setting of opportunistic infections or malignant neoplasms (25, 37). Other infectious etiologies, such as bacterial, protozoal, and fungal pathogens, should also be considered (37). An evaluation for leishmaniasis and rickettsial diseases should be sought in endemic areas (35, 38). Notably, treatment of HLH in the setting of leishmaniasis is limited to liposomal amphotericin alone without the need for immunosuppression (37, 39). MAS-HLH occurs in both children and adults, predominantly in sJIA, adult-onset Still disease, SLE, and inflammatory bowel disease, and may be the initial presentation of these diseases (9, 40).

Statement 6

"CNS disease and unique pulmonary features may develop in patients with HLH/MAS-HLH. In ICU-admitted patients with hyperinflammation, CNS manifestations should promptly initiate diagnostic evaluation for HLH. Severe pulmonary involvement is increasingly recognized, particularly in MAS-HLH (strong consensus; level IV etiology)."

CNS-HLH can be life-threatening and results in severe morbidity. It is reported in 21% adults and 30–73% of children with HLH (17, 41–43). Therefore, high suspicion and rapid evaluation of possible CNS involvement important in patients with hyperinflammatory symptoms and unexplained neurologic manifestations.

Typical clinical, laboratory, and radiologic findings are further described in the Supplementary Material (http://links.lww.com/CCM/G882). The presence of neurologic symptoms, abnormal spinal fluid, and/or abnormal CNS radiology in patients with HLH is sufficient to determine CNS involvement (41–43). Early and intensive therapy consisting of systemic HLH-directed therapy (see statement 9) can halt CNS inflammation (33, 42, 44, 45). If elevated intracranial pressure is present, it should be aggressively managed per the standard of care.

Pulmonary findings in patients with HLH/MAS-HLH who are admitted to ICUs are frequent. Infectious causes are most common and should be investigated first (46). More recently, pulmonary arterial hypertension, interstitial lung disease, and pulmonary alveolar proteinosis are reported in MAS-HLH (47–49). Pulmonary involvement is a poor prognostic indicator (46, 47).

Statement 7

"Early and aggressive intensive interventions, such as broad-spectrum antibiotics, vasopressors, renal replacement therapy, mechanical ventilation, blood product replacement, and management of coagulopathy, are often required in HLH/MAS-HLH (strong consensus; level IV intervention)."

The recommended supportive care for patients with HLH is in accordance with the standard ICU guidelines for life-threatening diseases. Because patients with HLH often experience neutropenia with high fever and some may have concomitant bacterial infections at diagnosis, aggressive use of antimicrobials is indicated for the treatment of suspected or proven infections. In addition to CNS and pulmonary manifestations, the predominance of liver dysfunction, fluid overload, coagulopathy, rapid deterioration, and high risk of MODS are unique to this patient population (13, 19, 44, 50). Coagulopathy in these patients is multifactorial and secondary to thrombocytopenia, hypofibrinogenemia, hyperfibrinolysis, and disseminated intravascular coagulation that often requires multiple blood products (e.g., fresh frozen plasma, platelets, packed RBCs, and coagulation factors) (50, 51). The need for aggressive supportive therapy, including mechanical ventilation (58–89%), vasopressors (often multiple; 43–90%), renal replacement therapy (17–75%), and extracorporeal life support (ECLS; 15–25% in adult cohorts), varies in different patient populations (13, 19, 50). Although these supportive therapies are often required, they are often not curative alone. Specific immunosuppressive therapies and targeted treatments for the potential triggers are needed for adequate treatment of patients with HLH (see statement 9) (13, 19, 50).

Statement 8

"HLH itself is not a contraindication for ECLS, which can be used in select patients as a bridge therapy until a response to an HLH-specific therapy and the underlying trigger is addressed (strong consensus; level IV intervention)."

According to the current limited evidence for using ECLS in patients with HLH, HLH itself is not a contraindication for the use of ECLS because both pediatric and adult HLH ECLS outcomes are similar to those in other cohorts with immunosuppression (13, 52–56). Careful assessment of the potential reversibility of MODs and the underlying HLH etiology (i.e., oncologic diagnoses, autoimmune disorders, or infection) requires a multisubspecialty approach to determine ECLS candidacy. In this cohort, venovenous ECLS may not be adequate, and some patients placed on venovenous ECLS may require conversion to a venoarterial circuit (52). The requirement for circuit anticoagulation may pose considerable risk for bleeding in patients with HLH due to refractory thrombocytopenia and coagulopathy. Particular attention to fibrinogen repletion with the use of fibrinogen cryoprecipitates in patients with cogaulopathy is needed to reduce risk of bleeding while on ECLS (52). Hyperfibrinolysis, acquired clotting factor, and von Willebrand factor deficiencies can develop because of the extracorporeal circuit (57). Therefore, careful optimization of hemostasis and anticoagulation is mandatory to avoid excess clotting and/or bleeding. Ultimately, ECLS can serve only as a bridge, whereas the underlying causes or triggers of HLH and inflammation are treated. Importantly, HLH-directed therapies can be given to patients on an ECLS circuit, with consideration of their underlying renal function (13, 54–56, 58).

Statement 9

Our treatment recommendations are as follows:

1) Identification and treatment of the underlying etiology is a priority in the management of sHLH.
2) In treatment-naive ICU patients with sHLH and MAS-HLH that is not severe, persistent, or relapsing, steroid treatment with or without IV immunoglobulin is suggested.

3) In familial HLH and in severe, persistent, or relapsing sHLH and MAS-HLH, prompt etoposide treatment adjusted for renal function and age is recommended, particularly in the cases with CNS involvement and/or other organ failure.
4) In patients with insufficiently responding MAS-HLH, the addition of IL-1 inhibition and/or cautiously dosed cyclosporine A is recommended (strong consensus; level IV intervention).

Treatment of sHLH in critically ill patients depends on many factors, including disease severity and the underlying HLH triggering factor(s). Prompt initiation of treatment directed at the underlying trigger is essential, with immediate additional immunosuppressive or immunomodulatory HLH-directed therapy (19, 59). The following section focuses on sHLH and MAS-HLH. For treatment of familial HLH, see previous reports describing the HLH-94 and HLH-2004 treatment protocols (17, 44, 58). Treatment of inflammation specifically related to SARS-CoV2 is not discussed.

TABLE 4.

Organ Dysfunction in Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome-Hemophagocytic Lymphohistiocytosis Stratified by Severity and Response Criteria in ICUs According to Expert Consensus (19, 60, 61)

Proposed Severity of Secondary HLH in ICU-Admitted Patients		Therapy See Statement 9 Text and Supplementary Material (http://links.lww.com/CCM/G882) for Recommendations
Mild	No evidence of organ dysfunction except coagulation/hematologic system	Treat underlying trigger; consider glucocorticoid therapy in case of rapid deterioration
Moderate	Evidence of moderate organ dysfunction (SOFA or pSOFA score 2 or less per organ system excluding coagulation/hematologic system) Possible need for supplemental oxygen	Treat underlying trigger; strongly consider glucocorticoid therapy
Severe	Evidence of severe organ dysfunction (SOFA or pSOFA Score 3 or more of at least one organ system excluding coagulation/hematologic system) and/or any need for organ replacement therapy due to organ failure, including positive-pressure ventilation, renal replacement therapy, vasopressors, and extracorporeal life support	Treat underlying trigger; glucocorticoid therapy; add etoposide or additional immunomodulatory therapy based on underlying disease
Proposed Response to Therapy		**Therapy** **See Statement 9 Text and Supplementary Material (http://links.lww.com/CCM/G882) for Recommendations**
Response	Improvement in ferritin, normalization of temperature, and clinical stabilization (i.e., no worsening organ dysfunction) within 48–72 hr after start of therapy	Continue full treatment of trigger; reassess disease daily, and wean therapy as tolerated
Nonresponse	Lack of improvement in ferritin, persistent fever, and/or lack of clinical improvement > 48–72 hr after start of therapy	Reevaluate triggers to ensure they are treated; consider adding additional HLH-directed therapy
Progression	Increasing ferritin and/or persistent fever > 48–72 hr after start of therapy. Increasing need for support of organ dysfunction (i.e., positive-pressure ventilation, renal replacement therapy, increasing blood product replacement, and/or need for vasopressors and extracorporeal life support) at any point	Aggressively reevaluate triggers to ensure they are treated; highly consider the addition of other or additional HLH-directed therapies

HLH = hemophagocytic lymphohistiocytosis, pSOFA = pediatric sequential organ failure assessment, SOFA = sequential organ failure assessment.

Selecting the optimal treatment for sHLH/MAS-HLH requires careful consideration of the underlying pathobiology and triggers, which may not be immediately evident in the ICU setting. **Table 4** outlines the proposed severity of disease and response according to expert consensus. In mild sHLH cases, HLH-specific treatment is not mandatory, and the etiologic search can be prioritized. However, early treatments, such as steroids, are often valuable to stabilize the disease while further diagnostic workups are being performed and should not be delayed in the cases of moderate sHLH; however, corticosteroids may make the diagnosis of hematologic cancers and autoimmune diseases more difficult. In

TABLE 5.
Recommended Therapies for Hemophagocytic Lymphohistiocytosis

HLH Type	Severity	Therapy
Primary and familial HLH	All	Per Ehl et al (58) based on HLH-94 therapy (17, 68)
Secondary HLH	Mild	Consider addition of corticosteroid therapy (58)
	Moderate	Dexamethasone 10 mg/m^2 daily divided every 12 hr (17, 58, 68) or equivalent methylprednisolone dosing (2 mg/kg/d) (58); consider addition of anakinra 2–10 mg/kg/d, divided in two to four daily doses (subcutaneous or IV) (22, 56, 62, 64, 65)
	Severe, progressive, or refractory	Addition of etoposide with dose reduction as follows (35, 66, 67) 100 mg/m^2 once weekly in older teens 75 mg/m^2 once weekly in adults 50 mg/m^2 once weekly in the elderly Renal dose reduction is recommended, per Ehl et al (58); dose reduction for hypoalbuminemia, hyperbilirubinemia alone, other evidence of liver dysfunction, and/or cytopenias is not recommended (58)
Macrophage activation syndrome-HLH	Mild	Steroids (such as methylprednisolone 30 mg/kg/d with max 1 g/d, for 3–5 d) with or without IVIG (69)
	Moderate	Consider addition of anakinra (dosing as above) and/or cautiously dosed cyclosporine (2 mg/kg/d in two divided doses aiming for serum levels of 100–150 ng/mL) and/or consideration of tocilizumab (35, 62, 70)
	Severe, progressive, or refractory	Consider addition of etoposide or cyclophosphamide (63, 69)
Malignancy-associated HLH	HLH-triggered organ damage (e.g., cytopenias, cholestatic icterus, pulmonary infiltrates, encephalopathy, or renal failure)	Two-step approach (11, 67) Etoposide (75–100 mg/m^2), corticosteroids, and IVIG Once stabilized, start cancer-directed therapy
Additional Therapies	**Agent**	**Indication**
Adjunctive therapies	IVIG (18, 35, 56)	General anti-inflammatory and antiviral effects
	Plasmapheresis (71)	Anti-inflammatory effects; use with caution if giving a monoclonal antibody
	Cytokine adsorption columns (72)	Anti-inflammatory effects
Salvage therapies and agents under investigation	Alemtuzumab (73) Tocilizumab (74) Emapalumab (75) Ruxolitinib (76–79)	These agents have some evidence for specific use in HLH. Please see Supplementary Material (http://links.lww.com/CCM/G882) for list of current clinical trials

HLH = hemophagocytic lymphohistiocytosis, IVIG = IV immunoglobulin.

moderately severe sHLH, daily administration of dexamethasone (10 mg/m^2 divided over 12-hr periods) or methylprednisolone (2 mg/kg/d) or pulsed methylprednisolone for MAS-HLH (30 mg/kg/d, maximum 1 g/d) can suffice. In nonresponsive MAS-HLH, IL-1 blockade with anakinra and/or etoposide can be added (62, 63). IL-1 blockade with anakinra can also be used for other forms of HLH and is associated with reduced mortality in patients with sepsis and features of sHLH (22, 56, 62, 64, 65). Dosing for anakinra in these settings is variable, with doses of 2–10 mg/kg/d divided in 2–4 daily doses (subcutaneous or IV) and up to 2 mg/kg/hr given as a continuous infusion for 72 hours (22, 56, 62, 64, 65). In severe, nonresponsive, or progressive sHLH and MAS-HLH, particularly in the cases with CNS involvement and/or worsening HLH-triggered organ dysfunction, prompt addition of age-adjusted etoposide treatment is recommended. In contrast with the HLH-94 and HLH-2004 treatment protocols designed for children with primary HLH, etoposide reduction should be considered for older teenagers (100 mg/m^2 once weekly), adults (75 mg/m^2 once weekly), and elderly patients (50 mg/m^2 once weekly) with sHLH to reduce myelotoxic effects in these cohorts (35, 66, 67). Some patients may require twice weekly etoposide dosing according to the response and treatment duration. Recommendations for etoposide dose adjustments, treatment of cancer-associated HLH, use of adjunctive therapies, and a list of salvage agents and therapies under further investigation are included in **Table 5** and the Supplementary Material (http://links.lww.com/CCM/G882).

In contrast with that of patients with familial HLH, many patients with sHLH do not require a full 8-week treatment course, as described in the HLH-94 and HLH-2004 protocols. The length of therapy is, however, suggested to be evaluated weekly and tailored to the patients and underlying triggers (35). Trending ferritin levels and sIL-2R if available can help to determine disease activity (80, 81). In general, therapy should be continued for the least amount of time possible to prevent prolonged immunosuppression and secondary infections but continued until ferritin and/or sIL-2R levels have decreased and stabilized and the patients show progressive clinical improvement. Patients should be monitored closely for relapse of disease when weaning or after discontinuing therapy. Antimicrobial prophylaxis and regular screening for *Candida*, *Aspergillus*, *Pneumocystis*, and *Herpesviridae* infections, per institutional guidelines, are advised.

CONCLUSIONS

Treating HLH in the critically ill, including patients with sepsis, remains a challenge. HLH is becoming more widely recognized in ICUs, but early recognition of the disease and its diagnosis is limited, and definitions of the severity of disease need to be validated. Nevertheless, early initiation of HLH-directed immunomodulatory therapy in combination with treatment for the underlying disease can be lifesaving. Similar to sepsis, the heterogeneity of HLH has led to increased complexity in defining its therapies. Further prospective trials are needed to determine optimum therapies in different patient populations with HLH, including the use of biologics and other novel therapies.

1 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

2 *Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, and Theme of Children's Health, Karolinska University Hospital, Stockholm, Sweden.*

3 *Department for Hematology/Oncology/Stem Cell Transplantation, Hannover Medical School, Hannover, Germany.*

4 *Department of Pediatrics, Children's Cancer Research Center, Kinderklinik München Schwabing, Technical University of Munich School of Medicine, Munich, Germany.*

5 *Department of Pediatrics, Division of Hematology/Oncology, Children's Mercy Hospital, Kansas City, MO.*

6 *Department of Pediatric Hematology and Oncology, University Medical Center Eppendorf, Hamburg, Germany.*

7 *Divisions of Immunobiology and Bone Marrow Transplantation and Immune Deficiency, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

8 *Department of Internal Medicine and Immunology, Section of Clinical Immunology, Erasmus University MC, Rotterdam, The Netherlands.*

9 *Department of Anaesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, Berlin, Germany.*

10 *Division of Pediatric Stem Cell Transplantation and Immunology, Center for Obstetrics, Pediatric and Adolescent Medicine, University Medical Center Eppendorf, Hamburg, Germany.*

11 *Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warsaw, Poland.*

12 *McCaig Institute For Bone and Joint Health, University of Calgary, Calgary, AB, Canada.*

13 *Klinik für Innere Medizin II, Schwarzwald-Baar-Klinikum, Villingen-Schwenningen, Germany.*

14 *National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Immunology and Microbiology, Bethesda, MD.*

15 *Department of Pediatrics, Division of Pediatric Critical Care, University of California, San Francisco, CA.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

All authors contributed to the literature analysis and writing and editing of the article. All authors approved the final article.

Supported, in part, by grants from the Swedish Children's Cancer Foundation and the Stockholm County Council (Agreement between the Swedish state and some county councils on cooperation on basic education of doctors, medical research, and the development of health care [ALF] project) to Dr. Henter and by American Lebanese Syrian Associated Charities to Dr. Hines. Dr. Lachmann is participant of the Berlin Institute of Health Charité Clinician Scientist Program granted by the Charité–Universitätsmedizin Berlin and Berlin Institute of Health.

These guidelines have been endorsed by the Histiocyte Society and by the Society of Critical Care Medicine.

Dr. Horne serves as a speaker for Swedish Orphan Biovitrum (SOBI) and Novartis; Dr. Jordan serves as a consultant for Novimmune and SOBI; Dr. Hines receives research funding from Incyte and the Histiocytosis Association; Drs. K. Beutel, Lehmberg, and Henter serve as consultants for SOBI; Dr. La Rosée serves as a speaker and consultant for SOBI and Novartis. Dr. Hines' institution received funding from the American Lebanese Syrian Associated Charities and Incyte. Drs. Hines, Beutel, Hays, and Henter disclosed the off-label product use of extracorporeal life support, Etoposide, dexamethasone, anakinra, cyclosporine, cyclophosphamide, alemtuzumab, Tocilizumab, ruxolitinib, plasmapheresis, cytokine adsorption, IV immunoglobulin, and methylprednisolone. Drs. Beutel, Horne, Lachmann, Machowicz, La Rosée, and Henter received funding from SOBI Adboard. Dr. Beutel received funding from Biotest AG. Dr. Horne's institution received funding from Novartis. Dr. van Laar disclosed government work. Dr. Shakoory disclosed that there is a Cooperative and Development Research Agreements between her section at National Institutes of Health (NIH) and SOBI. Dr. Zinter received funding from the NIH American Thoracic Society grant (K23HL146936); he received support for article research from the NIH. Dr. Henter's institution received funding from the Swedish Children's Cancer Foundation and the Stockholm County Council (ALF project). The remaining authors have disclosed that they do not have any potential conflicts of interest. The above competing interests and Histiocyte Society involvement did not influence the content of these guidelines.

For information regarding this article, E-mail: melissa.hines@stjude.org; jan-inge.henter@ki.se

REFERENCES

1. Brisse E, Wouters CH, Matthys P: Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: Differences and similarities. *Br J Haematol* 2016; 174:203–217
2. Brisse E, Wouters CH, Matthys P: Hemophagocytic lymphohistiocytosis (HLH): A heterogeneous spectrum of cytokine-driven immune disorders. *Cytokine Growth Factor Rev* 2015; 26:263–280
3. Knaak C, Nyvlt P, Schuster FS, et al: Hemophagocytic lymphohistiocytosis in critically ill patients: Diagnostic reliability of HLH-2004 criteria and HScore. *Crit Care* 2020; 24:244
4. Henter JI, Horne A, Aricó M, et al: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48:124–131
5. Janka GE: Familial and acquired hemophagocytic lymphohistiocytosis. *Eur J Pediatr* 2007; 166:95–109
6. Tsuji T, Hirano T, Yamasaki H, et al: A high sIL-2R/ferritin ratio is a useful marker for the diagnosis of lymphoma-associated hemophagocytic syndrome. *Ann Hematol* 2014; 93:821–826
7. Ravelli A, Minoia F, Davì S, et al; Paediatric Rheumatology International Trials Organisation; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society: 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis* 2016; 75:481–489
8. Parodi A, Davì S, Pringe AB, et al; Lupus Working Group of the Paediatric Rheumatology European Society: Macrophage activation syndrome in juvenile systemic lupus erythematosus: A multinational multicenter study of thirty-eight patients. *Arthritis Rheum* 2009; 60:3388–3399
9. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al: Adult haemophagocytic syndrome. *Lancet* 2014; 383:1503–1516
10. Andaluz-Ojeda D, Iglesias V, Bobillo F, et al: Early natural killer cell counts in blood predict mortality in severe sepsis. *Crit Care* 2011; 15:R243
11. Lehmberg K, Sprekels B, Nichols KE, et al: Malignancy-associated haemophagocytic lymphohistiocytosis in children and adolescents. *Br J Haematol* 2015; 170:539–549
12. von Bahr Greenwood T, Palmkvist-Kaijser K, Chiang SC, et al: Elevated ferritin and soluble CD25 in critically ill patients are associated with parameters of (hyper) inflammation and lymphocyte cytotoxicity. *Minerva Anestesiol* 2019; 85:1289–1298
13. Knaak C, Schuster FS, Spies C, et al: Hemophagocytic lymphohistiocytosis in critically ill patients. *Shock* 2020; 53:701–709
14. Lachmann G, Knaak C, Vorderwülbecke G, et al: Hyperferritinemia in critically ill patients. *Crit Care Med* 2020; 48:459–465
15. Gupta AA, Tyrrell P, Valani R, et al: Experience with hemophagocytic lymphohistiocytosis/macrophage activation syndrome at a single institution. *J Pediatr Hematol Oncol* 2009; 31:81–84
16. Barba T, Maucort-Boulch D, Iwaz J, et al: Hemophagocytic lymphohistiocytosis in intensive care unit: A 71-case strobe-compliant retrospective study. *Medicine (Baltimore)* 2015; 94:e2318
17. Bergsten E, Horne A, Aricó M, et al: Confirmed efficacy of etoposide and dexamethasone in HLH treatment: Long-term results of the cooperative HLH-2004 study. *Blood* 2017; 130:2728–2738

18. Knaak C, Schuster FS, Nyvlt P, et al: Treatment and mortality of hemophagocytc lymphohistiocytosis in adult critically ill patients: A systematic review with pooled analysis. *Crit Care Med* 2020; 48:e1137–e1146
19. Buyse S, Teixeira L, Galicier L, et al: Critical care management of patients with hemophagocytic lymphohistiocytosis. *Intensive Care Med* 2010; 36:1695–1702
20. Lachmann G, Spies C, Schenk T, et al: Hemophagocytic lymphohistiocytosis: Potentially underdiagnosed in intensive care units. *Shock* 2018; 50:149–155
21. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A, et al; Hellenic Sepsis Study Group: Macrophage activation-like syndrome: An immunological entity associated with rapid progression to death in sepsis. *BMC Med* 2017; 15:172
22. Shakoory B, Carcillo JA, Chatham WW, et al: Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: Reanalysis of a prior phase III trial. *Crit Care Med* 2016; 44:275–281
23. Carcillo JA, Berg RA, Wessel D, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: A multicenter network assessment of three inflammation phenotypes in pediatric sepsis-induced multiple organ failure. *Pediatr Crit Care Med* 2019; 20:1137–1146
24. The RECOVERY Collaborative Group: Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med* 2021; 384:693-704
25. Mehta P, McAuley DF, Brown M, et al; HLH Across Speciality Collaboration, UK: COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395:1033–1034
26. McGonagle D, Sharif K, O'Regan A, et al: The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020; 19:102537
27. Wang D, Hu B, Hu C, et al: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323:1061–1069
28. Carcillo JA, Halstead ES, Hall MW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigators: Three hypothetical inflammation pathobiology phenotypes and pediatric sepsis-induced multiple organ failure outcome. *Pediatr Crit Care Med* 2017; 18:513–523
29. Fardet L, Galicier L, Lambotte O, et al: Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014; 66:2613–2620
30. Rubin TS, Zhang K, Gifford C, et al: Perforin and CD107a testing is superior to NK cell function testing for screening patients for genetic HLH. *Blood* 2017; 129:2993–2999
31. Marsh RA, Bleesing JJ, Filipovich AH: Using flow cytometry to screen patients for X-linked lymphoproliferative disease due to SAP deficiency and XIAP deficiency. *J Immunol Methods* 2010; 362:1–9
32. Henter JI, Elinder G, Söder O, et al: Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. *Acta Paediatr Scand* 1991; 80:428–435
33. Blincoe A, Heeg M, Campbell PK, et al: Neuroinflammatory disease as an isolated manifestation of hemophagocytic lymphohistiocytosis. *J Clin Immunol* 2020; 40:901–916
34. Minoia F, Bovis F, Davì S, et al; Pediatric Rheumatology International Trials Organization, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society: Development and initial validation of the macrophage activation syndrome/primary hemophagocytic lymphohistiocytosis score, a diagnostic tool that differentiates primary hemophagocytic lymphohistiocytosis from macrophage activation syndrome. *J Pediatr* 2017; 189:72–78.e3
35. La Rosée P, Horne A, Hines M, et al: Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019; 133:2465–2477
36. Lehmberg K, Nichols KE, Henter JI, et al; Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society: Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematologica* 2015; 100:997–1004
37. Rouphael NG, Talati NJ, Vaughan C, et al: Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; 7:814–822
38. Cascio A, Giordano S, Dones P, et al: Haemophagocytic syndrome and rickettsial diseases. *J Med Microbiol* 2011; 60:537–542
39. Singh G, Shabani-Rad MT, Vanderkooi OG, et al: Leishmania in HLH: A rare finding with significant treatment implications. *J Pediatr Hematol Oncol* 2013; 35:e127–e129
40. Ravelli A, Davì S, Minoia F, et al: Macrophage activation syndrome. *Hematol Oncol Clin North Am* 2015; 29:927–941
41. Horne A, Wickström R, Jordan MB, et al: How to treat involvement of the central nervous system in hemophagocytic lymphohistiocytosis? *Curr Treat Options Neurol* 2017; 19:3
42. Horne A, Trottestam H, Aricò M, et al; Histiocyte Society: Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. *Br J Haematol* 2008; 140:327–335
43. Song Y, Pei RJ, Wang YN, et al: Central nervous system involvement in hemophagocytic lymphohistiocytosis in adults: A retrospective analysis of 96 patients in a single center. *Chin Med J (Engl)* 2018; 131:776–783
44. Trottestam H, Horne A, Aricò M, et al; Histiocyte Society: Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: Long-term results of the HLH-94 treatment protocol. *Blood* 2011; 118:4577–4584
45. Mahlaoui N, Ouachée-Chardin M, de Saint Basile G, et al: Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: A single-center retrospective report of 38 patients. *Pediatrics* 2007; 120:e622–e628
46. Seguin A, Galicier L, Boutboul D, et al: Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016; 149:1294–1301
47. Kimura Y, Weiss JE, Haroldson KL, et al; Childhood Arthritis Rheumatology Research Alliance Carra Net Investigators: Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2013; 65:745–752
48. Schulert GS, Yasin S, Carey B, et al: Systemic juvenile idiopathic arthritis-associated lung disease: Characterization and risk factors. *Arthritis Rheumatol* 2019; 71:1943–1954
49. Saper VE, Chen G, Deutsch GH, et al; Childhood Arthritis and Rheumatology Research Alliance Registry Investigators:

Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis* 2019; 78:1722–1731
50. Leow EH, Soh SY, Tan AM, et al: Critically ill children with hemophagocytic lymphohistiocytosis: A case series of 14 patients. *J Pediatr Hematol Oncol* 2017; 39:e303–e306
51. Valade S, Azoulay E, Galicier L, et al: Coagulation disorders and bleedings in critically ill patients with hemophagocytic lymphohistiocytosis. *Medicine (Baltimore)* 2015; 94:e1692
52. Cashen K, Chu RL, Klein J, et al: Extracorporeal membrane oxygenation outcomes in children with hemophagocytic lymphohistiocytosis. *Perfusion* 2017; 32:151–156
53. Beutel G, Wiesner O, Eder M, et al: Virus-associated hemophagocytic syndrome as a major contributor to death in patients with 2009 influenza A (H1N1) infection. *Crit Care* 2011; 15:R80
54. Henter JI, Chow CB, Leung CW, et al: Cytotoxic therapy for severe avian influenza A (H5N1) infection. *Lancet* 2006; 367:870–873
55. Cheng A, Williams F, Fortenberry J, et al: Use of extracorporeal support in hemophagocytic lymphohistiocytosis secondary to ehrlichiosis. *Pediatrics* 2016; 138:e20154176
56. Wohlfarth P, Agis H, Gualdoni GA, et al: Interleukin 1 receptor antagonist anakinra, intravenous immunoglobulin, and corticosteroids in the management of critically ill adult patients with hemophagocytic lymphohistiocytosis. *J Intensive Care Med* 2017; 34:723–731
57. Kalbhenn J, Wittau N, Schmutz A, et al: Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy. *Perfusion* 2015; 30:675–682
58. Ehl S, Astigarraga I, von Bahr Greenwood T, et al: Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: Consensus statements by the HLH steering committee of the histiocyte society. *J Allergy Clin Immunol Pract* 2018; 6:1508–1517
59. Schram AM, Berliner N: How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015; 125:2908–2914
60. Matics TJ, Sanchez-Pinto LN: Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. *JAMA Pediatr* 2017; 171:e172352
61. Vincent JL, de Mendonca A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26:1793-1800
62. Miettunen PM, Narendran A, Jayanthan A, et al: Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: Case series with 12 patients. *Rheumatology (Oxford)* 2011; 50:417–419
63. Horne A, von Bahr Greenwood T, Chiang SCC, et al: Efficacy of moderately dosed etoposide in macrophage activation syndrome - hemophagocytic lymphohistiocytosis (MAS-HLH). *J Rheumatol* 2021; 48:jrheum.200941
64. Eloseily EM, Weiser P, Crayne CB, et al: Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol* 2020; 72:326–334
65. Mehta P, Cron RQ, Hartwell J, et al: Silencing the cytokine storm: The use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020; 2:e358–e367
66. Henter JI, Palmkvist-Kaijser K, Holzgraefe B, et al: Cytotoxic therapy for severe swine flu A/H1N1. *Lancet* 2010; 376:2116
67. Daver N, McClain K, Allen CE, et al: A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer* 2017; 123:3229–3240
68. Henter JI, Samuelsson-Horne A, Aricò M, et al; Histocyte Society: Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002; 100:2367–2373
69. Gavand PE, Serio I, Arnaud L, et al: Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. *Autoimmun Rev* 2017; 16:743–749
70. Zhou S, Qiao J, Bai J, et al: Biological therapy of traditional therapy-resistant adult-onset Still's disease: An evidence-based review. *Ther Clin Risk Manag* 2018; 14:167–171
71. Nusshag C, Morath C, Zeier M, et al: Hemophagocytic lymphohistiocytosis in an adult kidney transplant recipient successfully treated by plasmapheresis: A case report and review of the literature. *Medicine (Baltimore)* 2017; 96:e9283
72. Greil C, Roether F, La Rosée P, et al: Rescue of cytokine storm due to HLH by hemoadsorption in a CTLA4-deficient patient. *J Clin Immunol* 2017; 37:273–276
73. Marsh RA, Allen CE, McClain KL, et al: Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. *Pediatr Blood Cancer* 2013; 60:101–109
74. Dufranc E, Del Bello A, Belliere J, et al; TAIDI (Toulouse Acquired Immune Deficiency and Infection) study group: IL6-R blocking with tocilizumab in critically ill patients with hemophagocytic syndrome. *Crit Care* 2020; 24:166
75. Locatelli F, Jordan MB, Allen C, et al: Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med* 2020; 382:1811–1822
76. Ahmed A, Merrill SA, Alsawah F, et al: Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: An open-label, single-centre, pilot trial. *Lancet Haematol* 2019; 6:e630–e637
77. Zhao JY, Liu SN, Xu LP, et al: Ruxolitinib is an effective salvage treatment for multidrug-resistant graft-versus-host disease after haploidentical allogeneic hematopoietic stem cell transplantation without posttransplant cyclophosphamide. *Ann Hematol* 2021; 100:169–180
78. Hansen S, Alduaij W, Biggs CM, et al: Ruxolitinib as adjunctive therapy for secondary hemophagocytic lymphohistiocytosis: A case series. *Eur J Haematol* 2021; 106:654–661
79. Huang Z, Xie J: Ruxolitinib in conjunction with the HLH-94 protocol for Epstein-Barr virus-related hemophagocytic lymphohistiocytosis in the intensive care unit: A case report. *Medicine (Baltimore)* 2021; 100:e25188
80. Bleesing J, Prada A, Siegel DM, et al: The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. *Arthritis Rheum* 2007; 56:965–971
81. Komp DM, McNamara J, Buckley P: Elevated soluble interleukin-2 receptor in childhood hemophagocytic histiocytic syndromes. *Blood* 1989; 73:2128–2132