



Macrophage Activation Syndrome

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Abbreviations

AIDS	Acquired immunodeficiency syndrome	HS	HScore
APC	Antigen-presenting cell	HSCT	Hematopoietic stem cell transplant
CsA	Cyclosporine A	ICU	Intensive care unit
CTL	Cytotoxic T lymphocyte	IFN- γ	interferon-gamma
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4	IL	Interleukin
DIC	Disseminated intravascular coagulopathy	IL-18BP	Interleukin-18-binding protein
EBV	Epstein-Barr virus	IL-1Ra	Interleukin-1 receptor antagonist
fHLH	Familial hemophagocytic lymphohistiocytosis	IVIg	Intravenous immunoglobulin
FSTL-1	Follistatin-like 1	MAS	Macrophage activation syndrome
G-CSF	Granulocyte colony-stimulating factor	NK cell	Natural killer cell
GM-CSF	Granulocyte-macrophage colony-stimulating factor	sCD163	Soluble haptoglobin receptor
HAV	Hepatitis A virus	sCD25	Soluble interleukin-2 receptor alpha chain
HBV	Hepatitis B virus	sHLH	Secondary hemophagocytic lymphohistiocytosis
HCV	Hepatitis C virus	sJIA	Systemic juvenile idiopathic arthritis
HIV	Human immunodeficiency virus	SLE	Systemic lupus erythematosus
HLH	Hemophagocytic lymphohistiocytosis	Th1	T-helper 1
		TLR	Toll-like receptor
		TNF	Tumor necrosis factor
		USA	United States of America
		XLP	X-linked lymphoproliferative disease

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Introduction

HLH/MAS is thought to be a multisystem inflammatory disorder resulting from a pro-inflammatory “cytokine storm” from excessively activated

lymphocytes and macrophages [1]. Hemophagocytic syndromes are divided into primary and secondary forms. Primary cases are rare (1 in 50,000 live births), commonly present in the first year of life, and are often triggered by infection [2]. They include familial, or primary, forms of hemophagocytic lymphohistiocytosis (fHLH) that have specific genetic homozygous or compound heterozygous loss-of-function mutations in perforin-mediated cytolytic pathway proteins (e.g., *PRF1*, *STX11*, *UNC13D*, *UNC18-2*) employed by CD8 T cells and natural killer (NK) cells [3–6]. Children with certain immunodeficiency syndromes, such as Chédiak-Higashi syndrome, type II Hermansky-Pudlak syndrome, and type II Griscelli syndrome [7], have associated genetic defects in cytolysis and are also at risk for developing fHLH. Specific X-linked immunodeficiencies (signaling-lymphocytic-activation-molecule-associated protein (SAP) and X-linked inhibitor of apoptosis (XIAP) deficiencies) are also associated with Epstein-Barr virus (EBV) triggered HLH [8–10].

Acquired or secondary forms of HLH (sHLH) are usually associated with conditions that cause chronic immune dysregulation, such as rheumatologic diseases [e.g., systemic juvenile idiopathic arthritis (sJIA), systemic lupus erythematosus (SLE)] and certain malignancies (e.g., leukemias, lymphomas). Infectious agents, particularly EBV and other herpesvirus family members, may be the sHLH trigger, although identifiable infections are not always present [7]. In addition, up to 40% of sHLH and macrophage activation syndrome (MAS) patients have been found to possess heterozygous (some dominant negative) mutations in known fHLH genes. Thus, some investigators consider MAS, sHLH, and fHLH to lie on a spectrum of disease [11].

In the clinical setting, the distinction between primary and secondary forms of HLH is less clear and even considered artificial by some. It was initially used to differentiate the primary, more fatal, infantile presentations from the secondary forms, which were considered to present later in life and to have better prognoses. However, it is now known that primary genetic

forms can present later in life, even during adulthood [12, 13]. Furthermore, in some studies, only 40% of primary HLH cases are found to have recognized genetic mutations. Moreover, both primary and secondary HLH are known to be precipitated by infections [14, 15]. Finally, as mentioned previously, many patients with sHLH have heterozygous mutations in known fHLH-associated genes, thus blurring the distinction between fHLH and sHLH. Regardless of terminology, the individual patient needs to be treated appropriately. At present, most clinicians would agree that clear-cut infantile cases of fHLH will need bone marrow transplantation, typically preceded by an aggressive chemotherapeutic regimen which includes etoposide and corticosteroids. In addition, identified infectious triggers should also be treated appropriately. For all other children and adults with HLH, the most appropriate treatment remains unclear. Etoposide is quite toxic, often leading to pancytopenia itself and increasing the risk of secondary sepsis as well as increased risk of secondary malignancies [14, 16]. Novel approaches have been anecdotally reported to dampen the overly exuberant immune response and control the cytokine storm and associated multiorgan dysfunction. Most notably, targeting of specific pro-inflammatory cytokines [e.g., interleukin-1 (IL-1) and interferon-gamma (IFN- γ)] seems promising and lacks the toxicity associated with traditional chemotherapeutic approaches [17, 18].

Despite advances in the current treatment protocols, the cure rate for HLH is low. Untreated cases of fHLH have a median survival of less than 2–6 months after diagnosis [19]. In a nationwide registry of pediatric patients with HLH in Korea, the 5-year overall survival rate was 68% (38% in the familial group and 81% in the presumed secondary group) [20]. The prognosis for cases of sHLH varies depending on the underlying etiology, for example, the mortality rate is reported to be lower in cases associated with rheumatic diseases (8–22%) and greater when it is associated with malignancy. The median overall survival is about 36–67% [21–23].

Pathophysiology and Cytokine Storm

MAS/HLH develops as a “cytokine storm” which is often triggered by infectious, rheumatologic, and oncologic diseases [24]. Although not well defined, the pro-inflammatory cytokines associated with MAS/HLH likely include IL-1, IL-6, IL-12, IL-18, IFN- γ , and tumor necrosis factor (TNF) [25, 26] (Table 14.1). Also IL-27, macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) may be increased [27–29]. Furthermore, chemokines, such as IL-8/CXCL8, MIG/CXCL9, IP10/CXCL10, I-TAC/CXCL11, MCP-1/CCL2, MIP-1 α /CCL3, and MIP-1 β /CCL4, have been reported to be increased [26, 30–32]. Both cytokines and chemokines activate the immune system, perpetuating the ongoing

cytokine storm. On the other arm, levels of anti-inflammatory cytokines, such as IL-10 and IL-18-binding protein (IL-18BP), are also increased but might not be sufficient to terminate the ongoing inflammation [33, 34]. Mazodier et al. described a discrepancy between the increase in IL-18 and its antagonist IL-18BP that lead to abnormally high levels of free IL-18 [33]. Similarly, the natural antagonist to IL-1, IL-1 receptor antagonist (IL-1Ra), has been noted to be elevated during MAS/HLH, and a recombinant form of IL-1Ra has been reported by several groups to be an effective therapy for MAS/HLH/cytokine storm syndrome [35–37].

The etiology of the cytokine storm is not entirely clear. Since fHLH is associated with biallelic defects in gene products involved in the perforin-mediated cytolytic pathway used by NK cells and CD8 T lymphocytes [48, 49], the inability to clear the antigenic stimulus and thus turn off the inflammatory response has been hypothesized to result in hypercytokinemia [50]. Recently, the inability of CD8 T cells and NK cells to lyse antigen-presenting cells (APCs) via the perforin-mediated cytolytic pathway was shown to prolong (by fivefold) the engagement time between the lytic lymphocyte and the APC. This prolonged interaction resulted in increased levels of pro-inflammatory cytokines. For up to 40% of sHLH cases, single-copy mutations in these same perforin pathway genes have been reported. Some of the mutants have been demonstrated to act as complete or partial dominant-negative mutants [51–53], resulting in sHLH in older children and adults [53, 54], the oldest reported case being a 62-year-old patient [55]. One heterozygous mutation in *RAB27A* identified in two unrelated sHLH patients was shown to act in a partial dominant-negative fashion and delayed cytolytic granule polarization to the immunologic synapse between NK cells and their target cells. This was also associated with an increase in IFN- γ production, mimicking the situation described for homozygous defects in perforin or granzyme B. Moreover, increased IL-6 production has been shown to decrease cytolytic activity of NK cells, further exacerbating the lytic defect and resultant production of pro-inflammatory cytokines.

Table 14.1 Cytokines in HLH and their potential roles [38–47]

Cytokine/chemokine	Related features of HLH
TNF	Fever, cachexia, neurological symptoms, depression of hematopoiesis, elevated transaminases, hypoalbuminemia, hypofibrinogenemia, hypertriglyceridemia, disseminated intravascular coagulopathy (DIC), suppression of natural killer (NK) cell activity
IL-1	Fever, depression of hematopoiesis, coagulopathy due to plasminogen activation, hyperferritinemia, acute phase proteins, T-cell activation
IFN- γ	Fever, hemophagocytosis, depression of hematopoiesis, DIC, hypoalbuminemia, liver damage, hypertriglyceridemia, macrophage activation, stimulation of antigen presentation, stimulation of CD4 T-helper 1 (Th1) response
IL-18	Liver pathology, prolonged exposure suppression of NK cell activity
IL-10	Suppression of T-cell activation, inhibition of Th1 cytokine production, regulation of hemophagocytosis, modulation of immune-mediating pathology
IL-6	Fever, anemia, acute phase proteins, renal impairment, T-cell activation and infiltration, suppression of NK cell activity

In a healthy individual, exposure of most cells to many intracellular pathogens will normally initiate an inflammatory cascade, frequently leading to release of Th1 cytokines (IFN- γ , TNF) that will activate macrophages, NK cells, and cytolytic T cells. NK and cytolytic T cells release granules that contain perforin and granzymes [49]. Perforin is a key cytolytic protein that causes osmotic lysis of the target cell [56] and is also necessary for the uptake of granzymes by the target cell that will then catalyze cleavage of multiple protein substrates, including caspases which then trigger cell apoptosis. All the genetic defects described in fHLH involve either inadequate levels of perforin itself or improper granule exocytosis leading to impaired apoptosis of the target cell, improper removal of the stimulating antigen, and ultimately ongoing inflammation.

However, other pathways lacking cytolytic pathway gene defects can lead to the final endpoint of HLH or MAS. In a murine model of MAS, it was shown that repeated stimulation of toll-like receptor 9 (TLR9) produced MAS on a normal genetic background, without exogenous antigen. Interestingly, the TLR9-induced MAS model was IFN- γ dependent in some aspects of disease; however, lymphocytes were not required for the pathogenesis [57]. On the other hand, a state of inflammation may also reduce the lytic capacity of NK cells and CD8 T cells [58–60], resulting in cytokine storm due to frustrated phagocytosis. This was illustrated in a study where T-cell-directed immunotherapy for refractory leukemia resulted in cytokine storm and an MAS-like presentation [61]. All the aforementioned pathways have led to the proposal that MAS is due to a combination of genetic predisposition and a hyperinflammatory state reducing cytolytic function, put into action by a trigger (e.g., infection, cancer, immunodeficiency, autoimmunity, and autoinflammation) [19, 53, 62–64]. At some point a threshold level of hypercytokinemia is reached at which the body is incapable of balancing the cytokine storm with anti-inflammatory products, such as IL-10, IL-1Ra, IL-18BP, and others. This is then believed to trigger the multiorgan dysfunction resulting in clinical HLH.

Clinical Picture

Initial symptoms of HLH/MAS are usually non-specific. The cardinal feature is unremitting high fever. However, therapeutic targeting of pro-inflammatory cytokines (e.g., IL-1, IL-6) to treat underlying rheumatic diseases that often result in MAS (e.g., sJIA) makes fever not an absolute finding in all cases. This is attributed to the powerful antipyretic effect of biologics such as inhibitors of IL-1, IL-6, and TNF. On examination, many patients have hepatomegaly, splenomegaly, or both, and up to 50% of MAS/HLH patients have central nervous system involvement ranging from mild confusion to seizures or frank coma [65]. Different forms of rash can occur, often erythematous or purpuric. Patients can have progressive hepatic dysfunction and ultimately multiorgan failure. DIC-like features are often present and are partly explained by liver dysfunction, fibrinogen consumption, and thrombocytopenia [66]. This highlights the challenges in distinguishing microbial sepsis-induced DIC from HLH in the intensive care unit (ICU). Despite the similarities these two conditions share in clinical presentations, they are frequently treated differently: broad spectrum antibiotics (sepsis) versus immunosuppression (HLH), respectively [67]. As HLH is not a diagnosis of exclusion, and infections are common triggers of HLH, it is important to treat both infection and, if present, the associated cytokine storm of HLH.

Classification Criteria

MAS/HLH can be difficult to diagnose, especially in the early stages where it can be easily misdiagnosed as shock or multiorgan dysfunction due to sepsis. In addition, MAS may be confused with an underlying disease flare, as in the case of sJIA. Because MAS can have a high mortality rate in children with sJIA (~8–22%) [68–70], sensitive diagnostic criteria are needed to assist with early detection, allowing for appropriate and timely therapy. Because of the different diseases associated with MAS/HLH, different diagnostic and classification criteria have been proposed

over the years, such as HLH-04, SLE-MAS criteria, the HScore, and the novel 2016 criteria for MAS complicating sJIA (Table 14.2). Some of these criteria are disease specific (e.g., sJIA, SLE)

and can be both sensitive and specific, whereas others encompass all potential HLH-associated diagnoses, but tend to have lower sensitivities overall. Clinically, and outside of clinical trials,

Table 14.2 Published criteria for MAS and HLH

HLH-2004 diagnostic	2009 preliminary diagnostic guidelines for MAS complicating cSLE	2005 preliminary diagnostic guidelines for MAS complicating sJIA	2016 classification criteria for MAS complicating sJIA
a. Molecular diagnosis b. Diagnostic criteria <ul style="list-style-type: none"> • Fever • Splenomegaly • Cytopenia (at least two of three lineages: <ul style="list-style-type: none"> • Hemoglobin <90 gm/l, • Platelets <100 × 10⁹/l, • Neutrophils <1.0 × 10⁹/l • Hypertriglyceridemia and/or • Hypofibrinogenemia (triglycerides ≥265 mg/dl, fibrinogen ≤1.5 gm/l) • Hemophagocytosis BM, spleen, or lymph nodes • Low or absent NK cell activity • Ferritin ≥500 ng/ml • Soluble CD25 ≥ 2400 units 	a. Clinical criteria <ul style="list-style-type: none"> • Fever (>38 C) • Hepatomegaly (≥3 cm below the costal arch) • Splenomegaly (≥3 cm below the costal arch) • Hemorrhagic manifestations • Central nervous system dysfunction b. Laboratory criteria <ul style="list-style-type: none"> • Cytopenia affecting two or more cell lineages (WBC ≤4.0 × 10⁹/l, hemoglobin ≤90 gm/l or platelet count ≤150 × 10⁹/l) • Increased AST (>40 units/l) • Increased LDH (>567 units/l) • Hypofibrinogenemia (fibrinogen ≤1.5 gm/l) • Hypertriglyceridemia (triglycerides >178 mg/dl) • Hyperferritinemia (ferritin >500 mg/l) 	a. Laboratory criteria <ul style="list-style-type: none"> • Decreased platelet count (≤262 × 10⁹/l) • Elevated levels of AST (>59 U/l) • Decreased WBC count (≤4.0 × 10⁹/l) • Hypofibrinogenemia (≤2.5 g/l) b. Clinical criteria <ul style="list-style-type: none"> • Central nervous system dysfunction • Hemorrhages • Hepatomegaly (≥3 cm below the costal arch) 	A febrile patient with known or suspected sJIA is classified as having MAS if the following criteria are met: Ferritin >684 ng/ml and any two of the following: <ul style="list-style-type: none"> • Platelet count ≤181 × 10⁹/l • AST >48 U/l • Triglycerides >156 mg/dl • Fibrinogen ≤360 mg/dl
Implementation			
The diagnosis of HLH can be established in the presence of a molecular diagnosis consistent with HLH or by meeting five of eight clinical and laboratory diagnostic criteria	The diagnosis of MAS requires the simultaneous presence of at least one clinical criterion and at least two laboratory criteria. Bone marrow aspiration for evidence of macrophage hemophagocytosis may be required only in doubtful cases	The diagnosis of MAS requires the presence of at least two laboratory criteria or the presence of at least one laboratory criterion and one clinical criterion. Bone marrow aspiration for evidence of macrophage hemophagocytosis may be required only in doubtful cases	See above <i>Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidemia</i>

Adapted from Henter et al. [11], Ravelli et al. [71], Parodi et al. [72], Ravelli et al. [73]

AST aspartate aminotransferase, BM bone marrow, HLH hemophagocytic lymphohistiocytosis, JSLE juvenile systemic lupus erythematosus, LDH lactate dehydrogenase, MAS macrophage activation syndrome, NK natural killer, sJIA systemic juvenile idiopathic arthritis, WBC white blood cells

the various criteria are useful for clinicians to strongly consider MAS/HLH diagnostically so that appropriate therapy can be initiated as soon as possible to result in optimal outcomes.

MAS as a Part of sJIA (sJIA-MAS)

HLH-2004 Diagnostic Guidelines

Due to the fact that MAS resembles fHLH in its clinical presentation, HLH-2004 diagnostic guidelines were initially used to diagnose MAS. Those guidelines were developed to diagnose genetic homozygous/compound heterozygous cases of fHLH [11]. The main deficiencies regarding the HLH-2004 criteria for diagnosing MAS in patients with sJIA are due to the underlying inflammatory nature of sJIA versus fHLH. In active sJIA, one would expect elevated levels of white blood cell counts, platelets, and fibrinogen as part of the inflammatory process. Accordingly, a drop in their levels, which could still be in the normal limits as regards to the HLH-2004 criteria, should raise the suspicion of MAS. Also the underlying inflammatory process leads to elevated levels of ferritin [74]; therefore, the cutoff of ferritin >500 ng/ml in the HLH-2004 guidelines makes it difficult to distinguish MAS complicating sJIA from an sJIA flare. Adding to the shortcomings of HLH-2004 guidelines overall are the lack of availability and timely results of certain criteria, such as NK cell activity or sCD25 levels in many centers [25, 75, 76].

Preliminary Diagnostic Criteria for MAS Complicating sJIA

Eventually, preliminary diagnostic criteria were introduced for sJIA-MAS comparing it to sJIA flare [71], which yielded better results in identifying MAS among sJIA patients when compared to HLH-2004 diagnostic guidelines [77]. However, these new criteria had their own shortcomings. The study that led to the criteria development was lacking in some important laboratory parameters, including some of the important MAS markers such as ferritin, lactate dehydrogenase, and triglycerides [25, 75, 76]. Moreover,

they were based on a relatively small sampling of patients, and they were not validated. These shortcomings were an impetus to develop new sJIA-specific MAS criteria.

2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis

The deficiencies in the previous guidelines have pushed for the development of more accurate criteria for sJIA-MAS. Recently, novel classification criteria have been introduced. These were the result of an international collaborative effort combining expert consensus, evidence compiled from the medical literature, and analysis of real patients. The development of the 2016 criteria was conducted under the auspices of the European League Against Rheumatism, the American College of Rheumatology, and the Paediatric Rheumatology International Trials Organization [73]. Based on the common consensus that clinical criteria of MAS are often delayed and/or difficult to distinguish from an underlying disease flare, the 2016 sJIA-MAS criteria are based primarily on laboratory parameters with fever as the only clinical criterion [76]. These criteria are relatively simple yet proved to be both highly sensitive and specific. However, the criteria are not ideal in the setting of children with sJIA who are being actively treated with IL-1 or IL-6 blockade. Ultimately, simple criteria that are not necessarily disease specific but maintain high sensitivity and specificity for establishing an MAS/HLH diagnosis are needed.

MAS as Part of Systemic Lupus Erythematosus (SLE-MAS)

Childhood SLE (cSLE) cases complicated by MAS have been reported with increasing frequency in the recent years. As an SLE disease flare itself often results in pancytopenia, diagnostic criteria for MAS in the setting of SLE are complicated. Accordingly, it has been suggested that cSLE-MAS may be under-recognized [78]. Preliminary guidelines for SLE-MAS were

proposed in 2009. A study was conducted based on a multinational survey and data analyzing 38 patients with cSLE-MAS [72]. Patients who had evidence of macrophage hemophagocytosis on bone marrow aspiration were considered to have definite MAS, and those who did not were considered to have probable MAS. The sensitivity, specificity, and the area under the receiver operating characteristic curve of various clinical and laboratory parameters were compared in SLE patients with MAS versus patients with active juvenile SLE without MAS. The best diagnostic performance was obtained using the simultaneous presence of any one or more clinical criteria and any two or more laboratory criteria, which had a sensitivity of 92.1% and a specificity of 90.9% (Table 14.2). The demonstration of macrophage hemophagocytosis in the bone marrow aspirate was considered necessary for confirmation of doubtful cases only. Those results have led to the practical recommendation that in the clinical setting, MAS should be suspected in a patient with cSLE presenting with unexplained fever and cytopenia associated with hyperferritinemia. Both HLH-2004 criteria and preliminary diagnostic guidelines for sJIA-MAS were tested in the study but were found to be inaccurate for detecting cSLE-MAS. Interestingly, about two-thirds of the patients with cSLE-MAS developed it within 1 month of SLE diagnosis. The frequency of ICU admission was 43.7%, and the mortality rate was 11.4%.

Generic MAS Criteria/HScore

In 2014, Fardet et al. developed and partially validated a diagnostic score for the broader category of reactive hemophagocytic syndrome (HS), called the HScore [79], which can be used to estimate an individual's risk of having reactive hemophagocytic syndrome, or HLH. This score was created and tested using a multicenter retrospective cohort of 312 patients scrutinizing 10 explanatory variables that were issued from a previous Delphi survey involving 24 HLH experts from 13 countries [80]. After showing

positive associations of each variable with an HLH diagnosis, multivariate logistic regression was used to assess their independent contributions to the outcome. Following calculating each variable's threshold value, the coefficients resulting from multiple logistic regression analysis were used to assign score points to each one. The performance of the score was assessed using developmental and validation data sets. The HScore revealed excellent diagnostic performance and discriminative ability in both developmental and validation data sets. The probability of having HLH ranged from <1% with an HScore of ≤ 90 to >99% with an HScore of ≥ 250 .

The HScore has some limitations including the heterogeneity of the underlying diseases (a high proportion had cancer-associated HLH), the retrospective manner of the data collection, and the small sample size (only 10% of the entire study population) of the validation data set. As the study included only adults with reactive HLH, the applicability in children, particularly those with sJIA-MAS, is questionable. Adding to its limitations in pediatric cases, some of the criteria in the HScore might not be practically applicable in children. For example, the definition of the item, "Known underlying immunosuppression," lists some medications that are used infrequently in children with sJIA, such as cyclosporine A and azathioprine, and at the same time it does not mention the newer more widely used cytokine antagonists that have been associated with the occurrence of MAS [25, 81, 82]. Moreover, bone marrow aspirates in a search for hemophagocytosis are not frequently performed in children with sJIA-MAS, as it is not considered mandatory in either the HLH-2004 guidelines [11] or the preliminary MAS guidelines [71]. In fact, absence of hemophagocytosis does not rule out MAS, and the procedure should not delay appropriate therapy. Furthermore, the underlying inflammatory nature of sJIA that is associated with marked thrombocytosis makes the threshold level for the platelet count ($110,000/\text{mm}^3$) too low for identifying MAS in the setting of sJIA. It is the relative drop in platelets count, rather than an

absolute decrease below a certain threshold, that is more useful to make an early diagnosis [77]. Thus, the HScore is likely more valuable in diagnosing adults with HLH, particularly those with associated leukemias and lymphomas.

New Biomarkers

A new promising laboratory marker of MAS is soluble CD163 (sCD163). Its expression is restricted to the macrophage/monocyte lineage only, unlike ferritin and soluble CD25 (IL-2 receptor α -chain), which are produced by a number of tissues and cell types, including the liver, spleen, heart, kidney, and T cells under a variety of nonspecific inflammatory conditions. sCD163 has been mainly evaluated in MAS, where combination testing of sCD25 and sCD163 identified patients with subclinical MAS [83]. Further studies to evaluate its role in HLH not associated with autoimmune diseases are required. Moreover, like sCD25, the testing is not currently available in a timely fashion in most centers around the world.

Another novel biomarker, follistatin-related protein 1 (FSTL-1) was reported by Gorelik et al. to be elevated in active sJIA with higher levels during MAS. FSTL-1 levels correlated with sCD25 and ferritin levels, and FSTL-1 normalized after treatment. Perhaps more importantly, Gorelik et al. also reported that in their small cohort (28 sJIA patients) a ferritin to ESR ratio > 80 had the highest sensitivity and specificity (100% and 100%, respectively) in distinguishing between MAS and new-onset sJIA disease flare [84]. As ferritin rises due to inflammation in MAS/HLH, and the ESR tends to drop as fibrinogen (an important driver of high ESRs) is consumed during coagulopathy, a simple ratio of ferritin to ESR may prove to be a simple and valuable tool in getting clinicians to consider a diagnosis of MAS/HLH in their febrile hospitalized patients.

Although the serum IL-18 level is also not routinely available clinically, it may also serve as a distinguishing biomarker for sJIA patients who develop MAS. Comparing cytokine patterns between sJIA-MAS patients, EBV-HLH, Kawasaki disease, and healthy age-matched

controls, Shimizu et al. reported that IL-18 concentrations during sJIA-MAS were significantly higher compared to the others, and they correlated with measures of disease activity (CRP, ferritin, LDH, and other cytokines). In addition, serum neopterin and sTNF-RII levels were significantly higher during MAS compared to sJIA flares [85]. Other reports also showed that IL-18 levels were significantly elevated in sJIA [86, 87] and the patients with high levels were more likely to develop MAS [88]. Furthermore, sphingomyelinase was found to be elevated in HLH cases [89]. Thus, a variety of new biomarkers may help identify MAS among sJIA patients.

Genetic Associations

Genetic HLH has been commonly classified into two groups: fHLH which are a group of autosomal recessive disorders, and immunodeficiency syndromes related HLH. Of the immunodeficiency syndromes, Chediak-Higashi, Griscelli, and Hermansky-Pudlak are associated with a variable degree of albinism/hypopigmentation of the skin or hair and platelet dysfunction which can assist in identifying potential cases of HLH (Table 14.3) [2, 90–92]. Interestingly, up to 40% of sHLH cases possess heterozygous mutations in these same fHLH-associated gene products. Thus, the overall underlying genetic risk for sHLH may be rather striking.

In addition to underlying inflammatory states (e.g., sJIA, leukemia) and genetic predispositions (e.g., perforin deficiency), infections (some from the commensal human microbiome) are frequently significant contributing factors in lowering the threshold required to develop a cytokine storm syndrome capable of resulting in HLH/MAS (Table 14.4). HLH has been associated with a vast variety of infections, with EBV as the most commonly reported trigger. Both familial (fHLH) and sporadic or secondary (sHLH) cases of HLH are often precipitated by acute infections. It is also important to note that an underlying precipitating infection for HLH can be masked, as the HLH clinical picture can mimic an infectious process or

Table 14.3 Genetic associations with HLH

HLH type	Chromosome	Gene	Protein	Function
<i>Familial HLH</i>				
fHLH1	9q21.3–22	Unknown	Unknown	Unknown
fHLH2	10q22	PRF1	Perforin	Apoptosis and cytotoxicity
fHLH3	17q25.1	UNC13D	Mammalian uncoordinated-13–4 (Munc13–4)	Exocytosis of granules
fHLH4	6q24	STX11	Syntaxin11	Generation of granules with SNAP23
fHLH5	19p13.3–2	STXBP2	Mammalian uncoordinated-18–2 (Munc18–2)	Vesicle fusion
<i>Immunodeficiency</i>				
CD27 deficiency	12p13	CD27	TNF receptor superfamily 7 (TNFRSF7)	Lymphocyte costimulatory molecule
Chediak-Higashi	1q42.1–2	LYST	Lysosomal trafficking regulator	Transport of lysosomes
GrisCELLI, type 2	15q21	RAB27A	Ras-related protein Rab-27A	Granule exocytosis
Hermansky-Pudlak, type 2	5q14.1	AP3B1	AP-3 complex subunit beta-1	AP3 β chain: traffic from Golgi to granules
Hermansky-Pudlak, type 9	15q21.1	BLOC1S6	Biogenesis of lysosome-related organelles complex 1 subunit 6	Intracellular vesicle trafficking
ITK deficiency	5q33.3	ITK	IL-2-inducible T-cell kinase	T-cell development, proliferation, and differentiation
NLRC4 mutation (autoinflammation with recurrent MAS)	2p22.3	NLRC4	NOD-like receptor family, caspase recruitment domain-containing 4	Caspase recruitment and innate immune response
IL-2R-gamma deficiency	10p15–14	IL2RA	IL-2R	T-cell activation and regulation
SCID (common γ chain def)	Xq13	IL-2RG	IL-2R	T-cell activation and regulation
Wiskott-Aldrich	Xp11.23–22	WAS	Wiskott-Aldrich syndrome protein (WASp)	Cytoskeleton
X-linked lymphoproliferative (XLP) type 1	Xq25	SH2D1A	SH2 domain-containing protein 1A(SAP)	Activation of lymphocytes
X-linked lymphoproliferative (XLP) type 2	Xq25	XIAP	Baculoviral IAP repeat-containing protein 4 (BIRC4)	Inhibition of apoptosis
ADA deficiency	20q13.11	ADA	Adenosine deaminase	Metabolism of purine nucleosides
PNP deficiency	14q13.1	PNP	Purine nucleoside phosphorylase	Metabolism of purine nucleosides
DiGeorge syndrome	22q11.2	DCGR	Unknown	Various
XL-O-EDA-ID	Xq28	NEMO	NEMO protein	Inflammation, immunity, cell survival, and signaling pathways
XLA	Xq21.3-q22	BTK	BTK protein	B-cell maturation and proliferation

(continued)

Table 14.3 (continued)

HLH type	Chromosome	Gene	Protein	Function
Hyper-IgD syndrome	12q24	MVK	Mevalonate kinase	Isoprenoid and sterol synthesis
Lysinuric protein intolerance	14q11.2	SLC7A7	Light subunit of a cationic amino acid transporter	Transport of amino acid
Multiple sulfatase def.	3p26	SUMF1	FGE	Transcriptional activation of sulfatase
Methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria	1p34.1	MMACHC	Methylmalonic aciduria and homocystinuria type C protein	Binding and intracellular trafficking of cobalamin
Holt-Oram syndrome	12q24.1	TBX5	T-box 5 protein	Promotes cardiomyocyte differentiation
XMEN syndrome	Xq21.1	MAGT1	Magnesium transporter 1	T-cell activation via T-cell receptor
<i>Others</i>				
IRF5 polymorphisms	7q32.1	IRF5	Interferon regulatory factor 5	Role in the toll-like receptor signaling pathway and activation of pro-inflammatory cytokine genes

Table 14.4 Infectious triggers of MAS/HLH

Infectious triggers	Virus nucleic acid	Examples
Viral	DNA	EBV [93], CMV [94–97], HHV6 [98], HHV-8 [99–101], varicella zoster [102], HSV1 [103], HSV2 [104], adenovirus [105, 106], herpes simplex [107, 108], parvovirus B19 [109, 110], HBV [111]
	RNA	Hepatitis A [112, 113]/C [111, 114–116], HIV-1 [117–119], influenza H1N1 [54, 120–126], parainfluenza [127], mumps [128], measles [129], measles vaccine [130], rubella [131], enterovirus [132], human T-lymphotropic virus [133], rotavirus [134]
Zoonotic viruses	RNA	Flavivirus (dengue fever) [135–138], Crimean-Congo hemorrhagic fever virus [139], hantaviruses [140, 141], bunyavirus [142], hepatitis E virus [143], influenza A virus H5N1 subtype [144], SARS coronavirus [145]
Bacterial		<i>Mycoplasma pneumoniae</i> [146, 147], <i>Salmonella typhi</i> [148], <i>Staphylococcus aureus</i> [149, 150], <i>Klebsiella pneumoniae</i> [151], <i>Aeromonas hydrophila</i> [151], <i>Fusobacterium</i> sp. [152], <i>Chlamydia pneumoniae</i> [153], <i>Legionella pneumophila</i> [152], <i>Mycobacterium tuberculosis</i> [154, 155], <i>Mycobacterium bovis</i> —weakened form (bacillus Calmette-Guérin) [156, 157], intravesical BCG [158], <i>Acinetobacter baumannii</i> [159], <i>Escherichia coli</i> [160], <i>M. leprae</i> [161], <i>Abiotrophia defectiva</i> in endocarditis patient [162]
Zoonotic bacteria		<i>Anaplasma phagocytophilum</i> [163], <i>Bartonella henselae</i> [164], <i>Borrelia burgdorferi</i> (Lyme disease) [165], <i>Brucella</i> sp. [166–168], <i>Campylobacter</i> sp. [169], <i>Capnocytophaga</i> sp. [170], <i>Clostridium</i> sp. [171, 172], <i>Coxiella burnetii</i> [173, 174], <i>Ehrlichia chaffeensis</i> and <i>Ehrlichia ewingii</i> [175–177], <i>Leptospira</i> sp. [178, 179], <i>Listeria monocytogenes</i> [180], <i>Mycobacterium avium complex</i> [181, 182], <i>Orientia tsutsugamushi</i> [183], <i>Rickettsia</i> spp. [184], <i>Salmonella</i> sp. (excluding <i>S. typhi</i>) [185]
Protozoal/zoonotic protozoa		<i>Leishmania</i> sp. [186–188], <i>Toxoplasma gondii</i> [189, 190], <i>Babesia</i> sp. [191], <i>Plasmodium falciparum</i> [192], <i>Plasmodium vivax</i> [193, 194], <i>Strongyloides stercoralis</i> [152]
Fungal		<i>Pneumocystis jiroveci</i> [62], <i>Candida</i> sp. [195], <i>Aspergillus</i> sp. [62], <i>Fusarium verticillioides</i> [62]
Zoonotic fungi		<i>Cryptococcus neoformans</i> [196], <i>Histoplasma capsulatum</i> [197–199], <i>Penicillium marneffeii</i> [23, 200, 201]

an overwhelming septicemia. It is important nonetheless to detect and remedy any underlying treatable infection in the setting of HLH.

Virus-Associated Hemophagocytic Syndrome

EBV

Epidemiology As previously mentioned, EBV is the most commonly reported trigger of HLH [93], with the highest incidence in East Asia [202]. This could be explained by the more pathogenic strains of EBV in this part of the world [203] and also by the higher prevalence of EBV and EBV-infected T cells in Asians [204]. EBV-associated HLH (EBV-HLH) cases have also been described in the USA and Europe [205]. Most EBV-HLH cases occur in apparently immunocompetent children and adolescents [206]; however, it can also occur in the setting of primary/genetic forms (fHLH) [207], immunodeficiency disorders (e.g., XLP) [208], and secondary forms, including acute infections (e.g., infectious mononucleosis) [209] and lymphoproliferative disorders (e.g., NK cell and T-cell leukemias and lymphomas) [210].

Pathophysiology The mechanism by which EBV induces HLH has not been fully explained. During primary infection, EBV typically infects and replicates in B cells, whereas a function of EBV-specific cytotoxic T cells is the regulation of the infected B cells and the production of memory cells. On rare occasions, EBV may infect T cells and NK cells via CD21. CD21 is expressed on the surface of these cells and induces persistent EBV infection, with monoclonal or oligoclonal proliferation resulting in chronic active EBV infection, lymphoproliferative disorders, and fulminant EBV-HLH [211–213]. Infection of CD8 T cells with EBV results in a cytokine storm with the release of pro-inflammatory and Th1-type cytokines [214], including TNF and IFN- γ , leading to widespread lymphohistiocytic activation [215]. The resultant cytokine storm tends to be more prominent than those observed in non-EBV-HLH

[216]. In addition, impaired function of T cells or NK cells is thought to provide a phenotypic presentation of HLH resulting from EBV via any genetic mutation involved in the T-cell and/or NK cell activation pathways [217, 218].

Diagnosis Serologic testing can help differentiate primary EBV infection from a reactivation process, although they have limitations such as delay in positivity and difficulty in result interpretation. Real-time PCR is used to measure the EBV viral load which can help predict prognosis and response to treatment [219]. EBV PCR levels are usually higher than those seen in uncomplicated cases of EBV infectious mononucleosis [220]. Other techniques are available to determine the involvement of T cells or NK cells in helping to confirm the diagnosis. T-cell receptor (TCR) gene rearrangement is detectable in half of the patients with EBV-HLH using Southern blotting and/or PCR analyses. It is hypothesized that the presence and change of TCR gene clonality probably plays a prognostic role for EBV-HLH [90]. Sandberg et al. [221] recently reported that Southern blot analysis could be replaced by BIOMED-2 multiplex PCR in routine testing of T-cell clonality. The EuroClonality (BIOMED-2) consortium developed a uniform reporting system for the description of the results and conclusions of Ig/TCR clonality assays to help improve the general performance level of clonality assessment and interpretation in cases with suspected lymphoproliferations [222]. It was reported that TCR gene clonality with BIOMED-2 multiplex PCR [223] is highly sensitive for detecting T-cell clonality and is useful in predicting response to treatment in EBV-HLH cases [223]. Interestingly, it was found that male patients with EBV-HLH may have mutations in the *SH2D1A* gene which is classically associated with X-linked lymphoproliferative syndrome (XLPS). XLPS is a syndrome of immunodeficiency to EBV virus. Therefore, it is recommended to test for XLPS in male patients with EBV-HLH [224]. It is also recommended to test for other genetic conditions such as fHLH, especially in male patients under

1 year of age, and in those with HLH in a sibling or with consanguineous parents, or when HLH is recurrent or unresponsive to treatment.

Prognosis Of all the viruses associated with HLH, EBV-HLH carries one of the worst prognoses. In a nationwide survey in Japan to identify prognostic factors in children with EBV-HLH, Kogawa et al. [225] found that most of the clinical and laboratory parameters including EBV load, NK cell activity against EBV-infected cells, and the presence of clonality at the onset of disease were not associated with a poor outcome. Nevertheless, Matsuda et al. showed that change of clonality can be a good marker of disease activity in childhood EBV-HLH [223]. It is also reported that hyperbilirubinemia and hyperferritinemia at the time of diagnosis were significantly associated with a poor outcome. Henter et al. also reported that hyperbilirubinemia and hyperferritinemia at diagnosis, and thrombocytopenia and hyperferritinemia 2 weeks after the initiation of treatment, adversely affect the outcome of HLH [226]. Better outcome is speculated to be associated with going into remission within 8 weeks of treatment initiation [225]. Huang et al. reported that hypoalbuminemia is an independent predictor for HLH in childhood EBV-associated disease [227].

Treatment Antiviral therapy with acyclovir, ganciclovir, or cidofovir is generally ineffective as monotherapy in infectious mononucleosis and EBV-HLH [228]. However, aggressive therapy including immunochemotherapy and allogeneic stem cell transplantation has radically improved the prognosis. The optimal treatment strategy [229] for EBV-HLH consists of immunosuppressive medications that inhibit overactive T-cell and NK cell responses [i.e., corticosteroids, cyclosporine A, intravenous immunoglobulin (IVIg), antithymocyte globulins, etoposide, and plasma or blood exchange transfusions] [229, 230]. Hematopoietic stem cell transplantation (HSCT) is the last treatment resort for refractory forms of EBV-HLH, and in the case of EBV infection

occurring in genetic forms of HLH [231]. Despite the fact that reports have shown that HSCT is effective in treating patients with refractory EBV-HLH [232], it should be compared to immunochemotherapy in a randomized study to provide evidence for which approach is superior and/or safer [233].

In 2007, Balamuth et al. [230] reported that adding rituximab to the HLH-2004 treatment protocol improves its efficacy. Rituximab is a monoclonal antibody against CD20 on the surface of B cells. Because EBV targets B cells in the initial phase of the disease, rituximab's elimination of B cells is thought to inhibit the extent of the infection. In addition, B cells may be a target in EBV-HLH, and rituximab may reduce morbidity and mortality by reducing the circulating B-cell population and the EBV load [234]. Rituximab seems to be most effective in the setting of XLPS patients infected with EBV but is likely less effective when EBV is capable of infecting the T-cell pool. Nonetheless, the addition of rituximab to the treatment repertoire of EBV-HLH provides an opportunity to tailor therapy specific to the patient (personalized medicine approach).

Other Herpes Viruses

Following EBV, cytomegalovirus (CMV) and human herpes virus (HHV) 8 are the next most common of the herpesviruses to be associated with HLH. CMV infection has been associated with HLH in otherwise healthy patients [96, 235], premature infants [97], patients with inflammatory bowel disease [236, 237], rheumatological diseases [238, 239], cancer [240], and in transplant recipients [241, 242]. In a series of 171 patients undergoing HSCT, HLH was observed in 7 (4%) of them and was triggered by CMV in 3 cases [243]. In a Japanese registry with CMV-HLH diagnosed at less than a year of age (1986–2002), four of the five infants died, suggesting that younger age may be associated with a worse prognosis [244]. The use of specific anti-CMV therapy, such as CMV hyperimmune globulin,

foscarnet, or ganciclovir, has been associated with recovery in selected cases [96, 236–238, 242].

Human Herpes Virus 8

HHV-8 has been associated with HLH, mostly in the setting of Kaposi sarcoma [245], multicentric Castleman disease [246], or lymphoproliferative disorder [247], as well as in immunocompromised hosts (HIV) [99], transplant recipients [248], and, rarely, in immunocompetent hosts [100, 101]. In a prospective cohort of 44 patients with Castleman disease and human immunodeficiency virus (HIV), 4 (9%) had HLH [246]. Intriguingly, in this series, the levels of IL-8 and IFN- γ were increased, though the cytokine levels of many known inflammatory markers were not. In this study, all patients recovered after treatment with splenectomy, etoposide, and rituximab [249]. Ganciclovir and foscarnet have also been associated with recovery in some HHV8-HPS cases. Finally, all other herpes viruses [102–104, 250] with the exception of HHV-7 have been associated with HLH.

Neonatal Infection-Associated HLH

Due to the lack of disease awareness among many physicians, HLH presenting within the first 4 weeks of life is rarely recognized. It could either pass undiagnosed or be diagnosed late in the course, or even at autopsy. Neonatal HLH differs from HLH in older children in etiology, manifestations, and laboratory findings. In a nationwide survey in Japan published in 2009, 20 neonates were diagnosed with HLH within 4 weeks after birth; 6 (30%) of them were diagnosed with fHLH, and 6 (30%) were diagnosed with herpes simplex virus-associated HLH (HSV-HLH) [251]. The overall survival rate of these 20 patients was 28.6% for fHLH and severe combined immunodeficiency (SCID)-HLH, and 33.3% for HSV-HLH, despite acyclovir treatment. Although uncommon in HLH of older children, enterovirus (echovirus and coxsackievirus) and HSV have been associated with fatal or fulminant neonatal HLH [252, 253]. This mandates early treatment with high-dose acyclovir in suspected cases without awaiting viral studies results.

HIV

HLH can be associated with HIV [117] infection [the etiology of acquired immunodeficiency syndrome (AIDS)] in different settings. HLH can occur either with HIV alone or with a variety of underlying associated disorders. HLH has been reported in acute or late stages of HIV infection, in the setting of immune reconstitution inflammatory syndromes (IRIS), and in association with HIV-associated malignancies or infections (both opportunistic and non-opportunistic) [254]. HLH has even been reported as the initial presentation of HIV infection [118], which suggests a direct role for HIV in triggering HLH [195].

Due to the fact that both HIV and HLH share many similar clinical and biological findings, it is likely that this association is also underdiagnosed. In one study, hemophagocytosis was observed in 20% of 56 autopsy cases of HIV-positive patients [255]. Around 10% of bone marrow biopsies in HIV patients before highly active antiretroviral therapy (HAART) initiation revealed hemophagocytosis [256]. In adult cases with acute HIV infection, HLH was associated with low CD4 T-cell counts (<200 cells/ μ L) in almost two-thirds of the cases. In addition, a lower CD4 T-cell count was associated with a worse prognosis [257].

Influenza

The association of HLH with influenza has been described with seasonal [122, 258–262], avian [263, 264], and swine (non-pandemic) influenza [265]. It has also been associated with both immunocompromised [258–261] and otherwise healthy children [122, 266]. In a prospective pediatric study, which included 32 children hospitalized with seasonal influenza, one case had a fatal outcome [262]. Interestingly, patients with severe H5N1 avian influenza have clinical pictures and laboratory findings similar to HLH; these consist mainly of encephalitis [267], organ dysfunction with hemophagocytosis [268], bone marrow suppression [268, 269], and cytokine storm [270, 271]. The most common characteristic pathological picture seen on autopsy and biopsy in such cases is hemophagocytosis [264, 271, 272].

Clinical studies have found that mutations in some viral genes (NS1, PB2, HA, and NA) are significantly related to cytokine release, and it has been shown that recombinant hemagglutinin (H5) from H5N1 virus may suppress perforin expression and reduce the cytotoxicity of CD8 T cells, including their ability to kill H5-bearing cells leading to marked lymphoproliferation and IFN- γ hyperproduction with macrophage overactivation [273]. Considering the high mortality caused by H5N1-HLH, the resistance to many antivirals by H5N1, and the similarity between HLH and severe flu infections have led some to suggest the use of a modified HLH-94 protocol [274] with a shorter course of etoposide and dexamethasone in such cases. However, in a randomized study from Vietnam, all patients with H5N1-HLH died despite receiving corticosteroids [275].

Recently, a study was done on 16 cases of fatal influenza A (H1N1) infection who met 44 and 81% of modified HLH-2004 and MAS criteria, respectively. Five subjects (36%) carried one of three different heterozygous *LYST* mutations, two of whom also possessed the relatively common p.A91V *PRFI* mutation, which was shown to mildly decrease NK cell cytolytic function. Several patients also carried rare variants in other genes previously observed in patients with MAS. The high percentage of HLH gene mutations suggests they are risk factors for mortality among individuals with influenza A (H1N1) infection [276].

Parvovirus

HLH has been reported in approximately 30 cases of parvovirus B19 infection; most of them had hereditary spherocytosis as the underlying disease, and less than 50% were children [106, 109, 110, 277, 278]. Of these patients, 22 survived, of whom 16 did not receive any treatment. This suggests a better prognosis of parvovirus-HLH than that with other viral infections.

Hepatitis Viruses

Fulminant viral hepatitis may mimic and even cause HLH. Hepatitis A virus (HAV) is more frequently associated with HLH than other hepato-

tropic viruses, including HBV and HCV. Fifteen cases (including children) have been described in the literature, mainly in Asia; three of these patients also had a concurrent rheumatological disease (sJIA or the related adult onset Still disease), and two also had hepatitis C. Four patients survived without specific treatment. The others received corticosteroids with or without IVIg. Overall, 11 of the 15 had a good outcome [112, 113, 279].

Enterovirus

Twelve cases of pediatric enterovirus-related HLH have been described. Four patients had an underlying disease (Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia, JIA) and had a higher mortality rate (75%). Ten patients received IVIg (six in combination with corticosteroids), but only seven patients survived [132]. Other viruses associated have been associated with HLH (Table 14.4), for most of which varying courses of corticosteroids and IVIg have been used. Interestingly, HLH may contribute to the high mortality rate associated with certain hemorrhagic fever viruses, such as those causing Dengue fever and Ebola.

Bacteria-Associated Hemophagocytic Syndrome

Of the bacterial pathogens, intracellular organisms have most commonly been the precipitating bacterial agents of HLH. The pathophysiology is probably related to the host lymphocytes and monocytes producing high levels of activating cytokines. Defective NK cell and cytotoxic T-cell function is also hypothesized to play a role in the pathophysiology [2].

HLH has been reported with disseminated *Mycobacterium tuberculosis* (TB) infection. It can occur in otherwise healthy patients [280], in end-stage renal disease patients receiving hemodialysis [281], in those who had undergone renal transplantation [164], or who had malignancy [282], HIV/AIDS [283], or sarcoidosis [284]. In a review of 36 cases by Brastianos et al., 83% of cases had evidence of extrapulmonary tuberculo-

sis. The mortality rate was approximately 50% which portrays the poor outcome of TB-HLH, although antituberculous and immunomodulatory therapy (consisting of high-dose corticosteroids, IVIg, antithymocyte globulin, cyclosporine A, epipodophyllotoxin, or plasma exchange) may lead to better outcomes [155]. Early diagnosis and timely administration of antituberculous treatment are crucial in these patients. Moreover, one reported case of HLH occurred after childhood vaccination with the bacillus Calmette-Guérin [157].

HLH has also been described in association with brucellosis, with *Brucella melitensis* being the most frequently isolated species [168]. Leptospirosis has been reported with HLH and has required treatment with corticosteroids, IVIg, or etoposide, in addition to antibiotic treatment [179]. Reports have also related *Rickettsia* and *Ehrlichia* to HLH, and the prognosis seems to be influenced by the specific *Rickettsia* species, patient's immunologic status, and delay in antibiotic therapy or corticosteroid therapy [184]. Also, MAS following urinary tract infection with *Acinetobacter baumannii* was reported for the first time in a previously healthy 3-year-old child; recovery occurred without any cytotoxic treatment or immunotherapy, using only multiple doses of GCSF and red blood cell/platelet transfusions [159]. Just like viruses, a large array of additional bacterial infections has been associated with HLH (Table 14.4), but a propensity for intracellular invasion is a common theme to many of these triggers.

Parasitic and Fungal Infection-Associated Hemophagocytic Syndrome

Leishmania infection has been associated with HLH (particularly *Leishmania donovani* and *Leishmania infantum*), but considering that it presents with organomegaly and pancytopenia, it can also just mimic the syndrome of HLH. This is of importance in non-endemic areas, where visceral leishmaniasis is unlikely considered as a differential diagnosis, and repeated bone marrow smears are often required to identify *Leishmania* species by means of PCR with species-specific probes [285]. While

specific treatment with amphotericin B is usually sufficient to control HLH, fatal outcomes have been seen with undiagnosed *Leishmania* cases treated as HLH [188]. History of travel to endemic areas is also of utmost importance for suspecting HLH secondary to certain parasitic infections such as malaria, toxoplasma, babesia, and strongyloides.

Yeast infections (*Candida* sp., *Cryptococcus* sp., and *Pneumocystis* sp.) and molds (*Histoplasma* sp., *Aspergillus* sp., and *Fusarium* sp.) have been associated with HLH, most commonly during HIV infection, malignancy, prolonged corticosteroid administration, and transplantation [196, 286, 287]. Disseminated *Penicillium marneffeii* infection is common among HIV-infected patients in Southeast Asia. The first case of penicilliosis-HLH was reported in a Thai HIV-infected child in 2001, with complete recovery after antifungal and IVIg therapy [200].

Treatment Options for MAS/HLH

In addition to treating any underlying infection, treatment designed to dampen the cytokine storm associated with MAS/HLH is critical for improving survival (Table 14.5). Some researchers reported the success of high-dose corticosteroids alone [25, 288] in treating sJIA-MAS. While the fundamental role of corticosteroids in the therapy of this disease is not doubted [25, 69, 70], current regimens usually add more aggressive treatment to corticosteroids including cyclophosphamide [289], which has not gained wide use in this condition; cyclosporine A (CsA), which is currently the most commonly added medicine to corticosteroids [290, 291]; and etoposide-based regimens, such as HLH-94 and HLH-2004 [11], which have their not insignificant mortality rates during the pre- and post-bone marrow transplant periods [292]. Of the biologics, IVIg has been used, particularly for infection-associated sHLH, but IVIg must be given early in disease to be effective [293]. Furthermore, IVIg has been shown to be ineffective in some reports [17]. Antithymocyte

Table 14.5 Treatment options for HLH

<i>Antimicrobials</i>	Conventional treatment	Biological therapies	Future targets
Antivirals Antibiotics Antimycotics Amphotericin B	Corticosteroids Cyclosporine-A HSCT Etoposide Cyclophosphamide Methotrexate <i>Others:</i> Plasmapheresis	<i>Intravenous immunoglobulins</i> <i>Cytokine-targeting drugs:</i> • IL-1 blockade Anakinra Rilonacept Canakinumab • IL-6 blockade Tocilizumab • TNF- α blockade Etanercept Infliximab Adalimumab • IFN- γ blockade <i>Anti-CD20:</i> • Rituximab <i>T-cell-targeting drugs:</i> • Antithymocyte globulins • Alemtuzumab (anti-CD52) • Daclizumab (anti-CD25)	JAK inhibition TLR blockade Administration of IL-10 or IL-18BP PPAR- γ or PD-1 agonists Targeting DCs or Ag presentation Blocking alarmins (HMGB1, IL-33, etc.)

globulin has been used successfully in two patients with probable MAS [294], but it carries a significant risk of serious infections and mortality.

Recently, newer more targeted biologic therapies have provided a more targeted and effective option in treating sJIA-MAS. While there was some initial excitement about TNF blockers with reports on their success in treating many cases of MAS including several children with sJIA [295–303], reports of TNF inhibitors triggering MAS diminished enthusiasm for this therapy [304–310]. Knowing that cause and effect is certainly difficult to prove in these situations, the fact that MAS did develop in the setting of TNF inhibition is concerning [311, 312]. This has led to focusing on therapy directed at two other pro-inflammatory cytokines, IL-1 and IL-6.

The IL-1 receptor antagonist anakinra was shown to be highly effective for sJIA [313, 314]. MAS and sJIA flare share many clinical and laboratory features. Moreover in addition to the 10% risk of developing overt MAS as part of sJIA, another 30–40% of sJIA patients may have occult or subclinical MAS during flare that can eventually lead to overt MAS [68, 83]. This suggested that anakinra would also be a valuable treatment for sJIA-MAS. There are several reports of dramatically successful use of anakinra in cases of

sJIA-MAS after failing to respond to corticosteroids and CsA [313, 315–317].

Anakinra is regarded as a generally safe drug because it is a recombinant human protein with a short half-life (approximately 4 h) [318] and a wide therapeutic window (1–48 mg/kg/day) [35, 317]. However, cases of hepatitis attributed to anakinra in children with sJIA have been reported [319]. Moreover, though cause and effect are difficult to establish, there has been a suggestion that anakinra triggered MAS in two children with sJIA [320, 321]. In a large case series of 46 sJIA patients treated with anakinra at disease onset, anakinra was a potential MAS trigger in five children at doses of 1–2 mg/kg/day [313]. However, dose escalation of anakinra often seemed to help control MAS, and none of the children had to permanently stop the anakinra [313]. More research is needed to define the role of anakinra in sJIA-MAS and other forms of sHLH.

IL-6 blockade, via an anti-IL-6 receptor monoclonal antibody (tocilizumab), has also proven successful in treating sJIA [322]. However, a case report of MAS attributed to IL-6 blockade [323] underscores the need for further studies to define its role in the treatment of sJIA-MAS. IL-6 blockade, however, has been successfully used in treating cytokine storm syndrome associated with chimeric antigen receptor

(CAR) T-cell-directed therapy against resistant leukemia [324]. Other biologic therapies are being explored. Co-stimulatory blockade with cytotoxic T-lymphocyte-associated protein 4-immunoglobulin (CTLA-4-Ig) has been anecdotally beneficial in children with severe sJIA [317], but its role in treating MAS is unknown. Nevertheless, there is building evidence that biologic therapies, particularly IL-1 inhibitors, are a welcome addition to corticosteroids and CsA in treating MAS associated with sJIA [17]. Finally, rituximab has recently been reported to lead to remission in a sizable percentage of children with refractory sJIA [325], in addition to its effectiveness in treating EBV-HLH [230, 326].

HSCT

The first report of successful HSCT in HLH was reported in 1986 [327]. HSCT tends to be more frequently used in familial cases of HLH, but it is used in secondary cases as well. While several studies have shown that HSCT is the best option for permanent disease control or cure [328–332], the overall transplant morbidity and mortality is still high (~45%) and it is not uncommon for patients to develop recurrence of HLH before a suitable donor is identified. Moreover, autologous and allogeneic HSCT have been reported to induce HLH in transplanted patients, probably due to the increased risk of infection imposed by the immunosuppressive conditioning regimen with an estimated risk of 4% in a recent cohort [333]. This risk appeared to be reduced in etoposide-containing conditioning regimens [333]. The current era of biologic therapies has reduced the need for HSCT.

In the future, autologous HSCT combined with gene therapy to correct the genetic defects might be applicable. Carmo et al. have shown that transfer of a functional perforin gene (Prf1) into autologous hematopoietic stem cells from perforin-deficient mice restored perforin expression, partially repaired the cytotoxic defect, and attenuated HLH symptoms after viral challenge, provided that at least 30% engraftment was attained [334]. Similarly, Rivat et al. showed that in a mouse model of XLP, gene transfer also restored SAP expression and normalized cytotoxic function [335].

IFN- γ Blockade

IFN- γ has been shown to play a pivotal role in several HLH models. Its neutralization has substantially improved survival in HLH animal models [336, 337] and an MAS model using IL-6 transgenic mice [338]. Levels of both IFN- γ and IFN- γ -induced chemokines such as CXCL10 and CXCL9 are elevated in children with HLH [339]. Moreover, sJIA-MAS is commonly triggered by viral infections which are known to activate IFN- γ -associated pathways. Furthermore, numerous IFN- γ -producing T cells were found in close proximity to activated hemophagocytic histiocytes in a study of inflammatory infiltrates in tissues affected by MAS [340], and children with MAS show increased levels of neopterin, which is known to be released by interferon-stimulated macrophages [26]. A longitudinal study of the cytokine changes in patients with sJIA showed that levels of IFN- γ and IFN- γ -induced chemokines (particularly, CXCL9) markedly increased with the beginning of clinical MAS and returned to normal with its resolution. Furthermore, they were strongly correlated with many laboratory features associated with MAS [338]. These findings highlighted IFN- γ as an appealing targeted and potentially less toxic therapeutic option in HLH, and a clinical trial evaluating NI-0501, which is an anti-IFN- γ monoclonal antibody that binds to and neutralizes human IFN- γ , is underway [341]. Recently, a report on this trial showed promising results [18].

However, some recent studies question the potential of IFN- γ blocking therapy in MAS. First, Tesi et al. reported two cases of HLH in children with novel IFN- γ receptor mutations associated with IFN- γ deficiency, findings which highlight the significance of IFN- γ -independent mechanisms in the immune pathology of HLH and warrant that other novel therapies, beside anti-IFN- γ therapy, be investigated [342]. Additionally, sJIA patients were found to have normal levels of IFN- γ independent of disease activity [343], which suggests that this cytokine does not always play an essential role in disease pathogenesis.

Janus Kinase Inhibition

Because targeting individual cytokines might be insufficient during severe hypercytokinemia,

cytokine signaling pathways can be targeted to avoid an imbalance in the cytokine network. Janus kinases control the signaling of many cytokines, notably IFN- γ , IL-2, and IL-6. Thus, inhibition of Janus kinases via ruxolitinib for example may serve this purpose. Das et al. reported that in rodent models of primary and secondary HLH, treatment with the JAK1/2 inhibitor ruxolitinib significantly lessened the clinical and laboratory manifestations, including weight loss, organomegaly, anemia, thrombocytopenia, hypercytopenia, and tissue inflammation. Importantly, ruxolitinib treatment also significantly improved survival in this model [344]. Similarly, Maschalidi et al. reported that JAK1/2 inhibition in Prf1^{-/-} and Rab27a^{-/-} mice with full-blown HLH syndrome has led to recovery in both models [345].

Other Targets

Peroxisome proliferator-activated receptor- γ agonists have also been presented as potential agents. They interfere with the activation of the NF κ B pathway and exert both a broad anti-inflammatory effect and antiviral capacities [346, 347]. Based on research in HLH animal models, other targets for future therapy have been proposed. These include the induction of T-cell exhaustion through the stimulation of inhibitory receptors like programmed cell death 1 (PDCD1/PD-1), restoring cytokine balances by the anti-inflammatory IL-10 or IL-18BP, halting chronic TLR activation by TLR antagonists or blocking TLR signaling pathways, and targeting dendritic cells as the main drivers of ongoing antigen stimulation or suppressing antigen presentation itself [348, 349].

Over the past few years, more has been revealed about the role of IL-18 in the pathogenesis of sJIA and MAS. It has been shown that patients with sJIA have significantly higher levels of IL-18 [85–87] as opposed to other rheumatic diseases such as SLE or rheumatoid arthritis [350, 351]. sJIA patients with high levels of IL-18 are more likely to develop systemic features of the disease and are more prone to develop MAS [85]. Interestingly, the development of MAS in these patients is associated with a further rise in IL-18 levels [85]. IL-18 has also been

found to correlate with ferritin in adult onset Still disease [86]. Therefore, IL-18 has been suggested as a promising biomarker for MAS. Another interesting field of growing research is in the role of IL-18-binding protein (IL-18BP) which is a naturally occurring protein that counter-regulates the activity of IL-18. Imbalance between IL-18 and IL-18BP, leading to higher levels of unbound IL-18, has been found in patients with increased disease severity [33, 86, 352]. The administration of synthetic IL-18BP in perforin-deficient mice infected with murine CMV ameliorated liver damage but has not shown an effect on the pro-inflammatory cytokine levels or on the overall survival [353]. Based on these findings, further work is needed to demonstrate the role of IL-18 and IL-18BP in MAS. Along these lines, IL-18BP was shown to be beneficial in treating refractory MAS in a child with an NLRC4 mutation [354].

Recently, neutralizing antibodies and antagonists targeting the alarmin HMGB1 (high mobility group box 1) were proposed as potential therapeutic options, aiming to reduce the immunostimulatory load of necrosis- and pyroptosis-derived danger signals. Models of systemic sterile and infectious inflammation have demonstrated the efficacy of this strategy [355]. Moreover, blocking the alarmin IL-33, via its receptor ST2/IL-1RL1, is also a potential therapy [356] [43]. Overall, the future is looking brighter for a variety of potential therapeutics to treat HLH/MAS in a patient-specific fashion.

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