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Cytokine Storm Syndrome

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Abstract

Cytokine storm syndrome (CSS), which is frequently fatal, has garnered increased attention with the ongoing coronavirus pandemic. A variety of hyperinflammatory conditions associated with multiorgan system failure can be lumped under the CSS umbrella, including familial hemophagocytic lymphohistiocytosis (HLH) and secondary HLH associated with infections, hematologic malignancies, and autoimmune and autoinflammatory disorders, in which case CSS is termed macrophage activation syndrome (MAS). Various classification and diagnostic CSS criteria exist and include clinical, laboratory, pathologic, and genetic features. Familial HLH results from cytolytic homozygous genetic defects in the perforin pathway employed by cytotoxic CD8 T lymphocytes and natural killer (NK) cells. Similarly, NK cell dysfunction is often present in secondary HLH and MAS, and heterozygous mutations in familial HLH genes are frequently present. Targeting overly active lymphocytes and macrophages with etoposide and glucocorticoids is the standard for treating HLH; however, more targeted and safer anticytokine (e.g., anti-interleukin-1, -6) approaches are gaining traction as effective alternatives.

INTRODUCTION

CSS: cytokine storm syndrome

GC: glucocorticoid

HLH: hemophagocytic lymphohistiocytosis

MAS: macrophage activation syndrome

sJIA: systemic juvenile idiopathic arthritis

AOSD: adult-onset Still disease

SLE: systemic lupus erythematosus

Cytokine storm syndrome (CSS) is an umbrella term covering a broad spectrum of related but not identical hyperinflammatory states (1). One definition of CSS is a life-threatening systemic inflammatory state characterized by elevated levels of circulating cytokines and immune cell hyperactivation that can be triggered by infectious pathogens, malignancies, and autoimmune and autoinflammatory conditions (2). The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reminded us that infections can trigger fatal CSS in susceptible hosts (1). In addition to treating the underlying trigger (e.g., infection), it is critical to treat the overly exuberant immune response with both broad [e.g., glucocorticoid (GC)] and targeted (e.g., anticytokine) approaches to help lower CSS mortality (3).

Clinically, CSS presents with fever, cytopenias, hemophagocytosis, liver dysfunction, coagulopathy, central nervous system (CNS) derangement, and multiorgan system failure requiring intensive care (2, 4). A silver lining of the COVID-19 pandemic is clinicians' increased awareness of the broad spectrum of CSS triggers, which has resulted in earlier diagnosis and treatment that in turn have led to improved outcomes of this frequently fatal condition. Physicians in most pediatric and adult specialties of clinical care need to be aware of the number of CSS conditions, both broad and disease-specific CSS criteria, and the ever-growing array of therapeutic approaches to treat CSS. CSS is a relative newcomer to medicine, but basic, translational, and clinical research efforts are beginning to tame this beast.

TERMINOLOGY AND DIAGNOSIS

It is important to recognize that CSS is not a diagnosis of exclusion but rather a condition that can complicate a variety of inflammatory disease states, ranging from infections to rheumatic illnesses to hematologic malignancies. Because various underlying conditions are associated with CSS, there are numerous classification and diagnostic criteria for the many different entities under the CSS umbrella. First and foremost are the HLH-04 criteria established for the familial form of CSS, hemophagocytic lymphohistiocytosis (HLH) (5) (**Table 1**). These criteria were developed for diagnosing infants with homozygous defects in the perforin-mediated cytolytic pathway employed by cytotoxic CD8 T lymphocytes and natural killer (NK) cells. Although the HLH-04 criteria are frequently used for secondary forms of HLH, they often are not sensitive enough diagnostically. Thus, individual sets of criteria have been developed for some of the more common rheumatic disease associations with CSS, which rheumatologists refer to as macrophage activation syndrome (MAS).

MAS is a form of CSS and a frequent complication of systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still disease (AOSD). The 2016 MAS criteria (6) as well as the 2019 MAS/sJIA (MS) score (7) were created to identify MAS in the setting of sJIA (**Table 1**). Similarly, Gerstein et al. (8) have proposed a decision rule that has been proposed to recognize MAS in the setting of another commonly associated rheumatic disease, systemic lupus erythematosus (SLE). One feature critical to all of the various CSS criteria is the presence of hyperferritinemia. Indeed, hyperferritinemia alone, or a high ratio of serum ferritin to the erythrocyte sedimentation rate, is a reasonable surrogate for CSS in the setting of hospitalized febrile children (9).

The HScore was developed to reflect that both children and adults can develop CSS (10) (**Table 1**). It is based primarily on adults who have CSS associated with hematologic malignancies (e.g., leukemia and lymphoma) and, like many CSS criteria, is dependent on the availability of unique data elements (clinical, laboratory, pathologic) to assist in diagnosis. While the HScore was intended to broadly encompass various types of CSS, it relies on the availability of all the data

Table 1 Various cytokine storm syndrome criteria

Criteria	HLH-04[a]	HScore[b]	2016 sJIA MAS	MS score
Fever (°C)	≥38.5	0 (<38.4), 33 (38.4–39.4), 49 (>39.4)	Degree not specified	NA
Ferritin (ng/mL)	≥500	0 (<2,000), 35 (2,000–6,000), 50 (>6,000)	>684	0.0001 × serum level
Organomegaly	Splenomegaly	0 (no), 23 (hepato- or splenomegaly), 38 (both)	NA	NA
Hematologic	Two or three out of three lineages	0 (one lineage), 24 (two lineages), 34 (three lineages)	Platelets ≤ 181 × 10^9/L	–0.003 × platelet count
Hemorrhagic	NA	NA	NA	1.54 (yes) or 0 (no)
Triglyceride	≥265 mg/dL[c]	0 (<1.5 mmol/L), 44 (1.5–4 mmol/L), 64 (>4 mmol/L)	>156 mg/dL	NA
Fibrinogen	≤1.5 g/L[c]	0 (>2.5 g/L), 30 (≤2.5 g/L)	≤360 mg/dL	–0.004 × serum level
LDH	NA	NA	NA	0.001 × serum level
AST	NA	0 (<30 IU/L), 19 (≥30 IU/L)	>48 units/mL	NA
CNS involved	NA	NA	NA	2.44 (yes) or 0 (no)
Arthritis active	NA	NA	NA	–1.3 (yes) or 0 (no)
Known immunosuppression	NA	0 (no), 18 (yes)	NA	NA
Pathology	Hemophagocytosis	Hemophagocytosis: 0 (no), 35 (yes)	NA	NA
NK cell activity	Low or absent	NA	NA	NA
sCD25	≥2,400 units/mL	NA	NA	NA
Diagnosis	Five of eight criteria	Sum of scores > 169	Fever + sJIA + elevated ferritin + two of four criteria	Sum ≥ –2.1

[a]Hemoglobin < 90 g/L, platelets < 100 × 10^9/L, neutrophils < 1.0 × 10^9/L.
[b]Hemoglobin < 92 g/L, platelets < 110 × 10^9/L, leukocytes < 5.0 × 10^9/L.
[c]Either high triglyceride and/or low fibrinogen (counts as one criterion).
Abbreviations: AST, aspartate aminotransferase; CNS, central nervous system; HLH, hemophagocytic lymphohistiocytosis; IU, international units; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; MS, MAS/systemic juvenile idiopathic arthritis; NA, not applicable; NK, natural killer; sCD25, soluble interleukin-2 receptor α chain; sJIA, systemic juvenile idiopathic arthritis.

elements to help establish the probability of a hemophagocytic syndrome. In addition, chimeric antigen receptor T cell (CAR-T) and related therapies for refractory hematologic malignancies can also cause CSS, a condition referred to as cytokine release syndrome (CRS) (2, 11). Various grading systems for assessing the severity and neurologic toxicity associated with CRS have been proposed (12).

Among the millions of individuals infected with SARS-CoV-2 worldwide, the most severe forms of COVID-19 require hospitalization and are associated with a hyperinflammatory state resembling CSS (1). In many ways, the CSS associated with COVID-19 is unique, with a predilection for early acute respiratory distress syndrome and less elevated levels of inflammatory markers (e.g., ferritin) than are associated with other types of CSS. As a result, there have been attempts to define the CSS associated with COVID-19 (13). While children are much less prone than adults to develop severe COVID-19, they are at risk for a novel SARS-CoV-2-related postinfectious CSS termed multisystem inflammatory syndrome in children (MIS-C) (14). While MIS-C shares features with Kawasaki disease (KD)-associated MAS, the various CSS criteria do not capture the full breadth of the disease processes underlying MIS-C or COVID-19 in children (13).

CAR-T: chimeric antigen receptor T cell

CRS: cytokine release syndrome

KD: Kawasaki disease

MIS-C: multisystem inflammatory syndrome in children

Table 2 Conditions associated with cytokine storm syndrome

Type	Condition
Primary or genetic	Familial HLH (e.g., *PRF1*, *UNC13D*, *STX11*, *SXTBP2*)
	Related perforin pathway genes (e.g., *RAB27A*, *LYST*, *AP3B1*)
	X-linked lymphoproliferative disease (e.g., deficiencies in *XLP1* or *XLP2/XIAP*)
	Immunodeficiencies (e.g., *PIK3CD*, *ITK*)
	Autoinflammatory/inflammasomopathies (e.g., *NLRC4*, *CDC42*)
Infectious	Viral [herpesvirus family (e.g., EBV, CMV, HHV6, HSV1/2), influenza strains (e.g., H1N1, H5N1), hemorrhagic fever viruses (e.g., dengue, Crimean–Congo), SARS-CoV-2 (e.g., COVID-19, MIS-C), HIV (AIDS infection and secondary infections/malignancies)]
	Bacterial [*Rickettsia*, *Ehrlichia*, mycobacteria (e.g., tuberculosis)]
	Parasitic (e.g., *Leishmania*)
	Fungal (e.g., histoplasmosis)
	Septic (various organisms)
Rheumatologic/autoimmune	sJIA/Still disease
	Systemic lupus erythematosus
	Kawasaki disease
	Others (e.g., spondyloarthropathy, dermatomyositis, inflammatory bowel disease)
Malignant	Hematologic (e.g., leukemia, lymphoma)
	Therapy for refractory disease (e.g., CAR-T, BiTE)
Other	Cardiac bypass/ECMO circuit
	Pregnancy
	Others (e.g., drug-induced, graft-versus-host disease, posttransplant, Castleman disease, metabolic disorders)

Abbreviations: AIDS, acquired immunodeficiency syndrome; BiTE, bispecific T cell engagers; CAR-T, chimeric antigen receptor T cell; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; EBV, Epstein–Barr virus; ECMO, extracorporeal membrane oxygenation; HHV, human herpesvirus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sJIA, systemic juvenile idiopathic arthritis.

CATEGORIES OF CYTOKINE STORM SYNDROME

Familial Hemophagocytic Lymphohistiocytosis

As the CSS umbrella is broad (1), there are many categories of illness associated with severe hyperinflammation, with familial HLH as the prototype and the best-defined and -analyzed CSS (5) (**Table 2**). Familial HLH is a rare genetic disorder affecting approximately 1 in 50,000 live births; it typically presents within days, weeks, or months of birth. Affected infants are severely ill with fever, cytopenias, coagulopathy, CNS derangement, and multiorgan system failure. Untreated, familial HLH is uniformly fatal. Until recently it was treated exclusively with chemotherapy (etoposide) to quiet the CSS and bridge the infant to hematopoietic stem cell transplantation (HSCT) (5). Even at the most experienced medical centers, mortality from familial HLH is still roughly 40%.

HSCT: hematopoietic stem cell transplantation

Familial HLH results from biallelic defects in one of several genes critical for cytolytic CD8 T cells and NK cells to effectively lyse target cells, typically virally infected antigen-presenting cells (APCs), through the perforin-mediated cytolytic pathway (5, 15). Perforin is contained in cytolytic granules, along with apoptosis-inducing granzymes, and upon recognition of the target cell it is trafficked along the actin cytoskeleton to the immunologic synapse between the lytic lymphocyte and the APC (**Figure 1**). Various other gene products (**Table 3**) are critical for granule sorting, polarization/trafficking, docking, priming, and fusing of the perforin-containing cytolytic granules

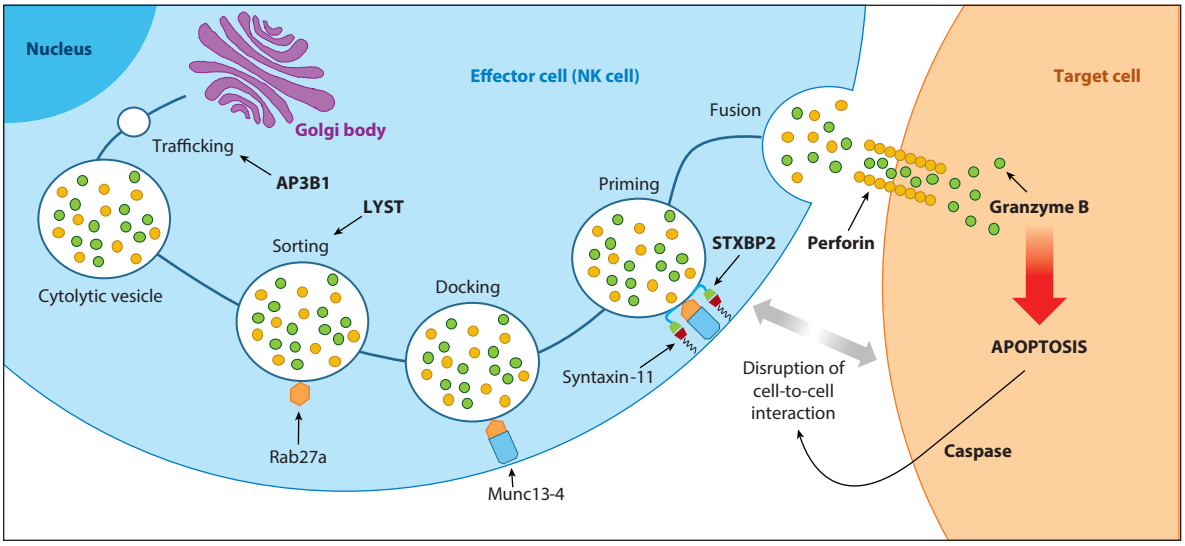

Figure 1

Familial HLH genes involved in perforin-mediated cytolysis. Upon recognition of a target cell (*orange*, *right*), the cytolytic NK cell (*blue*, *left*) polarizes preformed perforin- and granzyme-containing lytic vesicles to the immunologic synapse, enabling the release of perforin to form a pore and deliver granzyme B to the target cell. Familial HLH gene products (e.g., Munc13-4, STXBP2) are critical for trafficking, sorting, docking, priming, and fusing the cytolytic vesicles at the cell membrane. Upon apoptotic cell death triggered by granzyme B, the target cell signals via a caspase-dependent mechanism to disrupt the interaction between the lytic lymphocyte and the target cell. When the lytic pathway is disturbed, prolonged engagement between the lymphocyte and target cell results in increased production of inflammatory cytokines (e.g., interferon-γ) by the cells. Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NK, natural killer. Adapted from figure created by Dr. Daniel D. Reiff (University of Alabama at Birmingham).

to the lytic cell membrane. This process allows perforin to be released into the synapse in order to form a channel/pore between the lytic lymphocyte and its target cell and deliver the death blow of apoptosis via entry of granzyme B into the target cell (15).

A murine model of familial HLH (i.e., perforin-deficient mice) recapitulated the phenotype and uniform mortality of HLH when triggered by the lymphocytic choriomeningitis virus (16). Unlike the wild-type mice, the perforin-deficient animals were unable to clear the virus, but they survived if either the CD8 T cells were depleted or the proinflammatory cytokine interferon-γ (IFN-γ) was blocked (16). This result drove home the concept that, although the virus triggered the CSS, it was the overly exuberant immune response that killed the host. A later study elegantly demonstrated

Table 3 Familial hemophagocytic lymphohistiocytosis genes affecting perforin cytolytic pathway

Designation	Gene	Protein	Role
FHL1	9q21.3–22	Unknown	Unknown
FHL2	*PRF1*	Perforin	Pore formation
FHL3	*UNC13-D*	Munc13-4	Vesicle priming/tethering
FHL4	*STX11*	Syntaxin-11	Vesicle transport
FHL5	*UNC18-2*	Syntaxin-binding protein 2	Vesicle membrane fusing
Griscelli syndrome type 2	*RAB27A*	Ras-related protein Rab-27A	Vesicle docking
Chediak–Higashi syndrome	*LYST*	Lysosomal trafficking regulator	Vesicle sorting
Hermansky–Pudlak syndrome	*AP3B1*	Adapter related protein complex 3 subunit β1	Vesicle trafficking

Table 4 Therapeutics for cytokine storm syndrome

Type	Example
Cytotoxic agents	Etoposide
	Cyclophosphamide
Glucocorticoids	Dexamethasone
	Methylprednisolone
Calcineurin inhibitors	Cyclosporin A
	Tacrolimus
Cytokine blockade	IL-1 (e.g., anakinra, a recombinant IL-1 receptor antagonist)
	IL-6 (e.g., tocilizumab, an anti-IL-6 receptor monoclonal antibody)
	IL-18 (e.g., tadekinig alfa, a recombinant IL-18 binding protein)
	IFN-γ (e.g., emapalumab, an anti-IFN-γ monoclonal antibody)
	Janus kinase inhibitor (e.g., ruxolitinib, which blocks signaling of multiple cytokines, such as IFN-γ, TNF, and IL-6)
Filtering	Plasmapheresis
	Cytokine-absorbing filter technologies
B cell depletion	Anti-CD20 monoclonal antibody (e.g., rituximab)

Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

that perforin-deficient lytic lymphocytes, while unable to kill target cells upon recognition, remained engaged with target cells five times longer than cells that were capable of killing through the perforin pathway (17). This prolonged engagement and cross talk between the lymphocyte and APC resulted in substantially increased production of proinflammatory cytokines, including IFN-γ, that are believed to be responsible for the ensuing CSS (17). More recently, the story has come full circle with a clinical trial demonstrating survival benefit of infants with familial HLH treated with a neutralizing anti-IFN-γ monoclonal antibody (mAb) (**Table 4**) (18).

Similar increases in IFN-γ have been reported in vitro when heterozygous partial dominant-negative mutations in familial HLH genes from patients with secondary HLH (MAS) led to decreased perforin-mediated cytolysis in lymphocytes as a result of delayed cytolytic granule polarization to the immunologic synapse (19). The identification of heterozygous defects in familial HLH genes resulting in secondary HLH later in life has blurred the distinction between familial and secondary HLH (20). These heterozygous genetic defects in familial HLH genes are typically tolerated by the host until an increasingly inflammatory setting develops (e.g., in sJIA) and/or an environmental trigger (frequently intracellular pathogens) causes CSS, which is best understood using a threshold model of disease (21). Thus, many individuals may harbor heterozygous functional defects in familial HLH genes but not experience CSS until the wrong pathogen crosses their path (22).

Infection-Associated Cytokine Storm Syndrome: Triggering Pathogens

mAb: monoclonal antibody

Prior to the COVID-19 pandemic, herpesviruses including Epstein–Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus were the viral pathogens most commonly identified as triggers for CSS (**Table 2**). Infections caused by these viruses occur in the presence as well as the absence of underlying rheumatic disease. Common clinical features include hyperferritinemia, C-reactive protein (CRP) elevation, hepatobiliary dysfunction, and coagulopathy with thrombocytopenia in association with elevations in lactate dehydrogenase and d-dimer. A more extensive characterization of host responses during the 2000 outbreak of Ebola virus disease highlighted the similarities between responses to hemorrhagic fever viruses and to CSS

observed in the setting of either herpesvirus or influenza infection (23, 24). Likely due in part to the heightened recognition of virus-triggered hyperinflammation that had evolved over the preceding decade, researchers recognized the features of CSS during the initial outbreaks of SARS-CoV-2 and undertook immunomodulatory efforts to mitigate the high mortality associated with infection.

Although the clinical features of CSS are quite similar in severe cases of SARS-CoV-2-associated CSS, in comparison to other viral triggers of CSS the hyperinflammatory syndrome most commonly observed in SARS-CoV-2 is distinct in its predictable 7–14-day lag time between the onset of initial respiratory or intestinal symptoms of infection and development of CSS features, modest elevations in serum ferritin (uncommonly exceeding 2,000 ng/mL), frequent absence of fever, and significant lymphopenia. Moreover, coagulopathy with high d-dimer levels and very high CRP levels can occur in relatively asymptomatic patients. Notably, cytokine profiling in SARS-CoV-2-infected patients yields elevated serum levels of interleukin (IL)-1β, IFN-γ, monocyte chemoattractant protein 1 (MCP-1), and IP-10, as well as IL-4 and IL-10. Elevated levels of IL-6, tumor necrosis factor (TNF), MCP-1, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein 1α (MIP-1α), and soluble IL-2 receptor α (sIL2-Rα, or sCD25) are also observed in more severely affected patients (those who require intensive care compared with those who do not), supporting the concept that CSS underlies severe complications of SARS-CoV-2 (25, 26). A delayed multisystem inflammatory syndrome (i.e., MIS-C) may occur in children 2–6 weeks following infection with SARS-CoV-2, in either the presence or absence of symptomatic antecedent viral illness. MIS-C shares many clinical and laboratory features with KD- and sJIA-associated CSS, including fever; pericardial, endocardial, or myocardial inflammation; coronary aneurysm; enteritis; hepatitis; high CRP levels; coagulopathy with elevated d-dimer; and hyperferritinemia (27).

Nonviral (primarily intracellular) pathogens are increasingly being reported as triggers for CSS. These include *Mycobacterium*, *Ehrlichia*, *Histoplasma*, and *Rickettsia* species (28–30) (**Table 2**). Protozoal parasites such as *Leishmania* are also increasingly recognized as infectious triggers (31) (**Table 2**). In the majority of reported cases, patients have clinical and laboratory features meeting at least five of eight HLH-04 (Henter) criteria. In addition to appropriate antimicrobial therapy, adjuvant corticosteroid or anticytokine therapy targeting IL-1 or IL-6 may expedite recovery and/or improve survival. CSS triggered by these infections has been reported in both the absence and the presence of rheumatic disorders associated with CSS, emphasizing the importance of looking for infectious triggers in disorders associated with CSS risk.

Rheumatic Disease–Associated Cytokine Storm Syndrome

The CSSs associated with sJIA and AOSD (**Table 2**) are essentially identical, consistent with the increasing recognition of these disorders as a single entity extending across age groups. Hyperinflammation is driven primarily by a dysregulated IL-1 inflammasome, resulting in excess release of both IL-1 and IL-18; gain-of-function inflammasome mutations are becoming more widely recognized in affected patients with sJIA or AOSD (32). CSS in AOSD is characterized by high levels of IL-1α, IL-1β, IL-1 receptor antagonist, sCD25, IL-6, IL-10, IL-17A, IFN-γ, G-CSF, MCP-1, MIP-1α, and stem cell factor; higher levels of ferritin, IFN-γ, and IL-10 best distinguish CSS/MAS in patients with active AOSD or sJIA (33). Elevated levels of IL-18 may distinguish AOSD- or sJIA-related CSS from other types of CSS (34).

Features of CSS may be observed in the setting of severe flares of SLE (**Table 2**), particularly among SLE patients with antiphospholipid antibodies and SLE Disease Activity Index scores above 13 (35). Among SLE patients with signs of disease flare, the combination of fever, hyperferritinemia, leukopenia, and hepatobiliary dysfunction may best identify those developing CSS (36). Patients with KD may develop clinical features of CSS (**Table 2**) with a presentation

that, excepting the presence of coronary lesions, may be indistinguishable from that of patients with sJIA-associated CSS (37). While CSS has been reported in patients with other preexisting rheumatic disorders, including rheumatoid arthritis, seronegative spondyloarthropathy, sarcoidosis, and vasculitis syndromes (**Table 2**), the vast majority of these observations occur in the setting of infection with known infectious triggers of CSS.

Malignancy-Associated Hemophagocytic Lymphohistiocytosis

Malignancy-associated HLH (M-HLH) is a unique type of CSS observed in approximately 1% of adults with hematologic malignancies (38). According to various reports, to date M-HLH constitutes 40–70% of all cases of HLH in adults (39–41). M-HLH is most commonly found in association with lymphomas (2.8% incidence rate) (42), specifically T cell lymphomas, followed by diffuse large B cell lymphoma and Hodgkin lymphoma (43). The distribution of etiologies of M-HLH varies by geographic region; EBV-driven lymphoproliferative disorders predominate in East Asia (44). M-HLH has also been reported in the context of inherited immune defects (X-linked lymphoproliferative disorder, *MAGT1* deficiency, *HAVCR2* mutations, etc.) that can predispose patients to HLH and lymphoma (45–47). Furthermore, hypomorphic mutations in *PRF1* and related genes in the familial HLH spectrum have been reported in fewer than 5% of patients with lymphoma and HLH (48, 49). However, the pathogenesis of most of the remaining M-HLH cases has not been fully elucidated. It is thought to be related to persistent antigen stimulation and hypersecretion of proinflammatory cytokines by neoplastic cells (50).

Anticancer therapies are also a known cause of HLH in patients with hematologic or solid organ malignancies. A study of patients with acute myeloid leukemia undergoing induction chemotherapy found that HLH occurred in 9% of cases, mostly in relation to invasive fungal infections (51). HLH has also been reported after allogeneic HSCT and is associated with poor prognosis (52). In the last decade, the use of immune checkpoint inhibitors has led to reports of HLH due to T cell activation. HLH has been associated with the use of anti-PD-1, anti-PD-L1, or CTLA-4 antibodies or hybrids for various solid organ and hematologic malignancies (53). Similarly, novel cellular therapies like CAR-T therapies have also been linked with an HLH-like manifestation, which is somewhat distinct from the classic IL-6-driven CRS and typically occurs after 5–6 days of CAR-T infusion (54). CAR-T-associated HLH is characterized by profound hyperferritinemia (>100,000 ng/mL) and is associated with renal/hepatic dysfunction (50). Bispecific T cell–engaging antibodies such as blinatumomab have also been reported to cause HLH, potentially though secretion of IFN-γ from activated T cells (55).

For adults with suspected HLH, clinicians must make every attempt to search for an underlying hematologic malignancy, especially lymphoma, because of the implications for management. In some cases, splenectomy can lead to an otherwise elusive diagnosis (56). Note that the presence of EBV viremia does not exclude M-HLH, as EBV can cause lymphoma and HLH (50). The diagnosis of M-HLH can be challenging, as many of the markers listed in the HLH-04 criteria (e.g., fever, splenomegaly, bicytopenia) may be abnormal in patients with hematologic malignancies. Morphologic evidence for hemophagocytosis on bone marrow biopsy is neither a sensitive nor a specific marker for HLH (40, 57). Moreover, hyperferritinemia and elevated sCD25 can also be observed in hematologic malignancies. In one study, only 17% of adult patients with ferritin above 50,000 ng/mL had HLH, while 32% had a hematologic malignancy (58). A recent large multicenter study found that sCD25 levels were above 3,600 U/mL in 36% of patients with hematologic malignancy who did not fulfill the HLH-04 diagnostic criteria (43). The investigators found that a combination of sCD25 above 3,900 U/mL and ferritin above 1,000 ng/mL, which they called the optimized HLH inflammatory (OHI) index, identified M-HLH with 84% sensitivity and 82% specificity. Additionally, the OHI index was independently associated with mortality

among patients with hematologic malignancies, regardless of whether they met the HLH-04 criteria. Therefore, it may not be critical for management to strictly diagnose HLH using the HLH-04 criteria among patients with hematologic malignancy if they exhibit the OHI markers.

Randomized controlled clinical trials to define the management of M-HLH are lacking, as a result of the difficulty of arriving at the diagnosis, the disease heterogeneity, and the level of organ dysfunction that precludes timely enrollment in studies. Therefore, most treatment paradigms are based on expert consensus opinions (59). The HLH-94 regimen, consisting of 8 weeks of etoposide and dexamethasone (**Table 4**), plays an established role in primary HLH and may not be efficacious in M-HLH due to insufficient tumor-directed therapy. In a phase 2 single-arm trial utilizing the dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with or without rituximab among patients with non-Hodgkin lymphoma and HLH, the 5-year overall survival rate was 73.1% for B cell lymphoma, but the outcomes for T/NK cell lymphoma were dismal (1-year survival rate of 3.4%) (60).

If an underlying hematologic malignancy is known, the general principle is to apply tumor-directed therapy, preferably incorporating etoposide. However, treatment of acutely ill patients in cytokine storm with full-dose combination chemotherapy may be unsuccessful and even fatal in some instances (61, 62). Therefore, guidelines recommend considering a "prephase" treatment that aims to calm the cytokine storm through anti–T cell therapies such as corticosteroids and etoposide (59). Given the advanced age and comorbidities of patients with M-HLH, it is advisable to administer reduced-dose etoposide (50–100 mg/m^2) (59). Upon improvement of clinical condition and organ response (improvement of fevers, cytopenias, liver dysfunction), specific disease-directed therapy can be incorporated. This two-step approach can be particularly helpful in cases where the diagnosis of malignancy is not yet established, and it can stabilize the patient in order to conduct the necessary investigations. Among cases that do not respond to the prephase therapy, the DEP (doxorubicin, etoposide, methylprednisolone) regimen (62, 63) or additional cytokine-directed therapies may be utilized. The prognosis of patients who do not respond to initial treatments is poor, with high 30-day mortality (63). Although rituximab has been successfully used in cases with EBV-HLH (64), its role in M-HLH in the presence of viremia is unclear, especially when the underlying malignancy is a T-cell lymphoma. Nevertheless, it can be considered an adjunctive therapy along with monitoring of the viral load (59). The role of HSCT in M-HLH is uncertain, but autologous HSCT can be considered in first remission for T cell lymphoma per the standard of care.

The prognosis of refractory M-HLH is poor, and treatment options are mostly borrowed from non-malignancy-related HLH studies. Ruxolitinib, a Janus kinase 1/2 (JAK1/2) inhibitor (JAKi), is efficacious in other forms of secondary HLH (especially EBV-HLH) as a single agent (65) and in M-HLH when combined with doxorubicin, etoposide, and dexamethasone (66); for these reasons, it may be a reasonable next treatment option. The activity of anticytokine therapy targeting IL-1, IL-6, IL-18, and IFN-γ in M-HLH is unknown, but IL-1 blockade with the IL-1 receptor antagonist anakinra may benefit some patients with M-HLH (67). In cases of refractory M-HLH that are able to achieve a partial or complete response, allogeneic HSCT is strongly recommended.

Our knowledge of CAR-T therapy–related HLH is evolving. Most of these patients develop HLH after receipt of anti-IL-6-based therapy, and recent studies have reported responses to anakinra and corticosteroids (68), although in some instances etoposide may be added.

Other Associated Conditions

In addition to the more common triggers and disease associations, such as intracellular pathogens, rheumatic diseases, and hematologic malignancies, various other conditions are accompanied by

CSS. These conditions include pregnancy, iatrogenic or drug-induced CSS, cardiopulmonary bypass procedures, and transplantation-related CSS. The pathophysiology of many of these conditions is less well understood than in the case of familial HLH, autoimmune, or autoinflammatory disorders.

CSS (or HLH) as a complication of pregnancy can appear at any time during gestation. Known CSS risk factors (e.g., CMV, SLE) are often identified, but there are also many cases where the association is unknown (69). CSS during pregnancy shares features with HELLP (hemolysis, elevated liver enzymes, low platelet count) and thus may go unrecognized. Even when CSS is diagnosed during pregnancy, mortality for both mother and fetus remains high. Treatment typically includes GCs and intravenous immunoglobulin but sometimes requires calcineurin inhibitors, which cross the placenta, or even etoposide, which is toxic to the fetus, particularly in the first trimester (**Table 4**) (69). The risk of CSS is hypothesized to be due to the regulatory immune state during pregnancy. Moreover, maternal T cells may be activated by "foreign" material/antigens, thereby contributing to CSS. This antigen-triggered immune activation also might explain why termination of pregnancy alleviates CSS. No matter what the trigger is, pregnancy is an inopportune time to develop CSS.

Aside from T cell therapies for refractory leukemia/lymphoma that trigger CRS, other medicines have been linked to HLH, including the antiseizure medicine lamotrigine (70). Hypersensitivity reactions, including drug reaction and eosinophilia with systemic symptoms (DRESS), can overlap with HLH, and various drugs (e.g., trimethoprim-sulfa) have been linked to DRESS/HLH. Recently, concerns have arisen that biologic agents targeting IL-1 and IL-6 for treatment of sJIA can trigger DRESS in patients with MAS (71). Even before MAS was a recognized condition, children with sJIA developed CSS when treated with intramuscular gold (72). More recently, TNF inhibitors have been implicated as both triggers and effective therapies for MAS (73). While cause and effect can often be difficult to establish when identifying a drug as the etiology of CSS, removing the inciting trigger is critical for treatment.

Whether triggered by drugs, infections, rheumatic diseases, or malignancy, when CSS is severe, extracorporeal membrane oxygenation (ECMO) may be required to bypass the failing heart and/or lungs. Ironically, the circuitry involved with ECMO and other forms of cardiopulmonary bypass can trigger a dangerous cytokine release with multiorgan dysfunction (74). The inflammatory response associated with cardiopulmonary bypass is being explored (75), and xenotransplantation of porcine heart transplants is under consideration. As noted above in the context of familial HLH, another transplantation-related scenario where CSS develops is following HSCT (76). Additionally, graft-versus-host disease resulting from HSCT can trigger CSS and may be responsive to JAKi (77). While the differential diagnosis of etiologies triggering CSS is broad, including rare metabolic disorders and Castleman disease, general anti-inflammatory approaches to treatment exist (2, 11).

THERAPEUTIC APPROACHES

Chemotherapy and Transplantation

A broadly immunosuppressive approach to treating familial HLH and M-HLH is the HLH-04 protocol, which includes the topoisomerase II–inhibiting chemotherapeutic etoposide and the CNS-penetrating GC dexamethasone, followed by HSCT (**Table 4**) (5). At the most experienced medical centers, the 5-year survival rate for children with both familial and secondary HLH is approximately 60% (5). The lymphocyte-targeting calcineurin inhibitor cyclosporine A was previously part of the protocol but has fallen out of favor because it does not improve survival and presents a risk of side effects, including infection, hypertension, and risk of posterior

reversible encephalopathy syndrome. Detailed recommendations for the treatment of HLH using etoposide-based protocols and transplantation are detailed elsewhere (78).

Glucocorticoids

Although not nearly as cytotoxic as etoposide, GCs are broadly immunosuppressive and widely employed in the setting of CSS. The GC dexamethasone is integral to the HLH-04 treatment protocol with the rationale that it has good CNS penetration (5). Alternatively, rheumatologists routinely employ methylprednisolone at a GC equivalent five times the daily dose of dexamethasone as part of HLH-04. GCs pose numerous potential complications, including secondary infections, diabetes mellitus, and hypertension. Nevertheless, GCs are a powerful tool for the treatment of CSS of most etiologies. GCs were one of the first lifesaving therapies for severe COVID-19 CSS, but timing of administration and patient selection are critical to their benefit (3).

Cytokine Targeting

While rheumatologists have targeted cytokines broadly with cyclosporine A (79), the availability of less toxic and more targeted approaches to treating CSS has changed the treatment landscape (4). Regarding COVID-19 CSS, IL-6 inhibition has garnered a great deal of attention on the basis of its early use in China. While the data for improved COVID-19 survival are less compelling than for GCs, meta-analyses do reveal benefit, particularly in the setting of GC coadministration (80). Nevertheless, IL-6 blockade has received US Food and Drug Administration approval for treating iatrogenic CRS associated with treatment for refractory hematologic malignancies (81) (**Figure 2**). More recently, however, the use of IL-1 inhibition has been championed for refractory CRS, particularly CRS with CNS involvement (68).

IL-1 inhibition with anakinra has also been explored for COVID-19 CSS, and studies have shown some evidence for survival benefit in select patient populations (82). Prior to COVID-19,

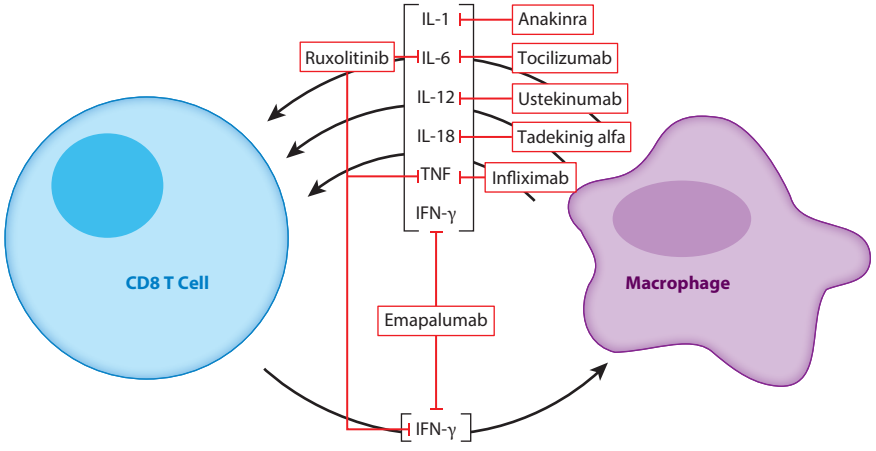

Figure 2

Potential therapeutics for blocking cytokines in CSS. The prolonged interaction between a lytic lymphocyte (e.g., CD8 T cell) and an antigen-presenting cell (e.g., macrophage) results in increased production of proinflammatory cytokines. Targeted approaches to various cytokines are clinically available; some (e.g., tocilizumab, anakinra) are more routinely used for various CSSs. Abbreviations: CSS, cytokine storm syndrome; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. Adapted from figure created by Dr. Daniel D. Reiff (University of Alabama at Birmingham).

CSS treatment with anakinra was reported to benefit a wide array of CSSs (67, 83) (**Figure 2**). The benefits of anakinra include its large therapeutic window, safety profile, and timely effectiveness in blocking signaling of both IL-1α and IL-1β. IL-1 is the prototypic product of inflammasome activation, but recently another IL-1 family member activated via the inflammasome, IL-18, was shown to be highly elevated in MAS (11). Anecdotal reports indicate that blockade of IL-18 benefits CRS associated with autoinflammation (84) (**Figure 2**), and researchers are exploring treatments of a broader array of CSS conditions with IL-18 inhibition.

While IL-1 blockade has greatly benefited children with MAS associated with the autoinflammatory disease sJIA (83), recent clinical trials have also been exploring IFN-γ blockade for sJIA MAS. These studies have built on the benefit demonstrated by the anti-IFN-γ mAb emapalumab, which improves survival of patients with untreated and refractory primary HLH (18) (**Figure 2**). Emapalumab is not associated with organ toxicity and is likely to be much less toxic than etoposide-based approaches (18). Another approach to blocking IFN-γ is JAK inhibition (85) (**Figure 2**). Many inhibitors target different JAKs associated with various receptor components common to multiple cytokines associated with CSS, including IFN-γ, IL-6, and TNF (86). Because JAKi inhibit the signaling of multiple cytokines, this treatment is intermediate between broadly immunosuppressive GCs and individually targeted cytokine approaches. JAK inhibition is also proving beneficial for COVID-19 CSS (87). Other intermediate approaches to cytokine removal, such as plasmapheresis and cytokine-absorbing filter technologies, are also being explored for CSS, including in COVID-19 (88). The future offers hope for a precision medicine approach to treating patients afflicted with CSS (89).

CONCLUSION

Clinicians and scientists have made substantial progress in understanding the breadth, clinical features, genetic risk factors, pathophysiology, and treatments of CSS. While familial HLH is rare, much has been learned from the study of these disorders. Beyond infantile familial CSS, hospitalized febrile older children and adults affected by certain infectious diseases (including COVID-19), rheumatologic diseases, and malignant disorders are increasingly being recognized as suffering CSS, particularly in the setting of multiorgan dysfunction. While broadly immunosuppressive treatment (e.g., GCs) and chemotherapeutics (e.g., etoposide) serve as traditional therapies, more targeted, less toxic approaches to inhibiting proinflammatory cytokines are gaining acceptance as effective CSS treatments. The future looks bright for this relatively young, evolving field of medicine, with the hope of broader recognition of, and precision medicine treatments for, CSS in the time to come.

SUMMARY POINTS

1. Frequently fatal cytokine storm syndrome (CSS) is increasingly recognized as a complication of a variety of etiologies, including severe cases of COVID-19.
2. Several disease-specific and broad criteria for diagnosing CSS are available; they share the feature of hyperferritinemia in the setting of fever and multiorgan dysfunction. No criterion is ideally specific or sensitive diagnostically but should alert the clinician to the potential of CSS in hospitalized febrile patients.
3. The rare condition familial hemophagocytic lymphohistiocytosis (HLH) is an assortment of largely autosomal recessive mutations in genes critical for perforin-mediated cytolysis of target cells by natural killer cells and CD8 T lymphocytes.

4. Secondary HLH presenting beyond infancy often shares features with familial HLH, including decreased lymphocyte cytolytic function that is sometimes associated with heterozygous hypomorphic or dominant-negative defects in familial HLH genes.
5. There is a broad range of infectious triggers of CSS, largely intracellular pathogens, among which the herpesvirus family (e.g., EBV, CMV) is notorious.
6. Many rheumatologic conditions can be complicated by CSS (termed macrophage activation syndrome in this setting) and are particularly prevalent among patients with Still disease and systemic lupus erythematosus.
7. CSS is associated with hematologic malignancies (termed secondary or malignancy HLH in this setting) as well as with therapeutics (e.g., chimeric antigen receptor T cells) for refractory leukemias and lymphomas that cause cytokine release syndrome.
8. Novel approaches to targeting proinflammatory cytokines (e.g., IL-1, IL-6, IFN-γ) are proving effective at treating CSS, with relatively few adverse events.

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81. Reports that IL-6 blockade is FDA approved to treat CRS following CAR-T therapy for refractory cancer.

83. Reveals that IL-1 blockade increased survival in patients with CSS.

87. Demonstrates JAKi increased survival of COVID-19 patients with CSS features.

RELATED RESOURCES

1. HScore online calculator. **https://www.mdcalc.com/hscore-reactive-hemophagocytic-syndrome#next-steps**
2. Centers for Disease Control and Prevention MIS-C webpage. **https://www.cdc.gov/mis/index.html**