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Weathering the storm: Improving therapeutic interventions for cytokine storm syndromes by targeting disease pathogenesis

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Opinion Statement

Cytokine storm syndromes require rapid diagnosis and treatment to limit the morbidity and mortality caused by the hyperinflammatory state that characterizes these devastating conditions. Herein, we discuss the current knowledge that guides our therapeutic decision-making and personalization of treatment for patients with cytokine storm syndromes. Firstly, ICU-level supportive care is often required to stabilize patients with fulminant disease while additional diagnostic evaluations proceed to determine the underlying cause of cytokine storm. Pharmacologic interventions should be focused on removing the inciting trigger of inflammation and initiation of an individualized immunosuppressive regimen when immune activation is central to the underlying disease pathophysiology. Monitoring for a clinical response is required to ensure that changes in the therapeutic regimen can be made as clinically warranted. Escalation of immunosuppression may be required if patients respond poorly to the initial therapeutic interventions, while a slow wean of immunosuppression in patients who improve can limit medication-related toxicities. In certain scenarios, a decision must be made whether an individual patient requires hematopoietic cell transplantation to prevent recurrence of disease. Despite these interventions, significant morbidity and mortality remains for cytokine storm patients. Therefore, we use this review to propose a clinical schema to guide current and future attempts to design rational therapeutic interventions for patients suffering from these devastating conditions, which we believe speeds the diagnosis of disease, limits medication-related toxicities, and improves clinical outcomes by targeting the heterogeneous and dynamic mechanisms driving disease in each individual patient.

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Conflict of Interest

Lehn K. Weaver declares no conflicts of interest. Dr. Behrens reports personal fees from AB2Bio, during the conduct of the study; In addition, Dr. Behrens has a patent Compositions and Methods for Treating Hemophagocytic Lymphohistiocytosis pending to The Children's Hospital of Philadelphia.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Keywords

Hyperinflammation; macrophage activation syndrome; hemophagocytic lymphohistiocytosis; personalized medicine; cytokine storm

Introduction

Cytokine storm syndromes are a clinically heterogeneous set of life-threatening conditions manifested by immune dysregulation and uncontrolled inflammation that can lead to unremitting fevers, cytopenias, splenomegaly, hepatitis, coagulopathy, multisystem organ dysfunction, and death in their most severe form (1). The largest umbrella term used to categorize these conditions is sepsis (Figure 1), which was recently redefined as life-threatening organ dysfunction caused by a maladaptive host response to an infectious trigger (2). Although not classically defined as sepsis, familial hemophagocytic lymphohistiocytosis (FHL) is an example of a precisely defined subcategory of sepsis whereby an infection triggers an uncontrolled systemic inflammatory response in a host that has defective cytotoxicity (1). However, not all cytokine storm syndromes are triggered by infection, as inflammation from active rheumatic diseases can cause Macrophage Activation Syndrome (MAS) and certain malignancies are known to trigger Malignancy-Associated Syndrome of Hyperinflammation (MASH) (1). To aid in the management of these disparate cytokine storm syndromes, we outline a therapeutic approach that can be generalized across all forms of cytokine storm, as outlined in Figure 2. We frame how use of this approach can be personalized to the unique drivers of disease pathogenesis for each type of cytokine storm.

To further aid our therapeutic decision-making for patients suffering from cytokine storm, we propose a model of disease pathogenesis based on three targetable factors that impact cytokine storm outcomes, as outlined in Figure 3. Firstly, disease pathogenesis is initiated by a specific cytokine storm trigger. Triggers of cytokine storm are diverse and include a wide spectrum of infectious agents (bacterial, fungal, protozoan, and viral), malignancies and their treatment, and autoimmune or autoinflammatory rheumatic diseases (1). Depending on the inciting trigger, widely divergent clinical outcomes are possible for identical hosts (Figure 3A). However, the diversity of triggers alone cannot explain why certain individuals succumb to cytokine storm while others remain asymptomatic or are minimally affected by the same trigger. Therefore, we adapt two terms previously used to define host fitness strategies used to survive infection, disease resistance and disease tolerance (3), and apply them to cytokine storm syndromes. Patients who are susceptible to cytokine storm are unable to prevent a cytokine storm trigger from initiating disease (Figure 3B) and can be said to have reduced disease resistance (3). Alternatively, a host can preserve fitness by limiting the damage caused by the cytokine storm syndrome without affecting disease burden (Figure 3C), a phenomenon termed disease tolerance (3). Intriguingly, disease resistance and tolerance mechanisms have been described across diverse kingdoms of life, are basally active or inducible, and can be influenced by both genetic and environmental factors (3–5), albeit their contributions to cytokine storm syndromes are only beginning to be understood. Herein, we argue that use of this schema can guide our current and future

attempts to design rational therapeutic interventions for patients suffering from cytokine storm syndromes.

Treatment

Therapies to improve disease tolerance

Disease tolerance is the ability of the host to resist perturbations from homeostasis that impair host fitness without affecting disease burden (3). Therefore, therapeutic interventions to increase disease tolerance are likely to have profound benefits for patients with cytokine storm. In fact, modern ICUs are the epitome of increasing disease tolerance by providing care that supports failing organs and allows a host to survive otherwise lethal perturbations from homeostasis. As patients with cytokine storm physiology present acutely with severe organ dysfunction, prompt clinical stabilization with ICU-level supportive care is the appropriate first step in treating patients with cytokine storm. Intensivist level clinical management has provided significant benefit for patients with sepsis and include measures to maintain cardiac output and organ perfusion, oxygenation and ventilation, fluid balance, electrolyte and pH homeostasis, and filtration of metabolic waste products (6, 7). However, such supportive measures are unlikely to be sufficient to reestablish homeostasis without addressing the other pathogenic drivers of cytokine storm.

Improvements in our understanding of disease tolerance mechanisms will likely lead to the development of interventions that provide additional therapeutic benefit in cytokine storm syndromes. Furthermore, it will be important to consider how our current medical interventions may already positively or negatively impact disease tolerance mechanisms. For example, recent evidence suggests that glucose metabolism and nutritional supplementation have divergent effects on disease tolerance in models of bacterial and viral infection, whereby nutritional supplementation was detrimental to bacterial-induced pathology, but protected against viral-induced pathology without affecting the infectious burden (8). Future studies will be needed to translate these intriguing results into clinical practice and suggest that different metabolic interventions will need to be adjusted for the underlying infection that triggers disease. Alternative approaches to manipulate disease tolerance may involve mechanisms to prevent damage to specific cell types or tissues that are predisposed to the cytokine storm hyperinflammatory response. For example, widespread damage to the vascular endothelium in cytokine storm causes widespread organ dysfunction by facilitating tissue infiltration by immune cells, increasing vascular leak, reducing tissue oxygenation, and initiating a consumptive coagulopathy (9). Prevention of endothelial damage caused by cytokine storm is therefore an attractive therapeutic target. In a proof-of-concept study, London *et al* use a soluble protein inhibitor of endothelial cell activation to prevent endothelial dysfunction and improve survival in multiple preclinical models of cytokine storm (10). Although these examples demonstrate how disease tolerance can be manipulated in cytokine storm, future efforts will be needed to translate these intriguing findings into therapies that benefit patients with cytokine storm.

Therapeutic targeting of the cytokine storm trigger

The inciting trigger is an important factor in driving cytokine storm pathophysiology, as preclinical models and clinical examples suggest that individuals with high susceptibility to cytokine storm will not develop overt symptoms of cytokine storm in the absence of an initiating trigger. For example, perforin-deficient C57BL/6 mice are healthy until they are challenged with LCMV, which promotes a fatal CD8 T cell and interferon (IFN)- γ dependent hyperinflammatory response modeling FHL (11). Likewise, FHL patients who have a genetic predisposition to cytokine storm and are the most severely susceptible to disease are healthy until they are exposed to a viral trigger that initiates a fatal cytokine storm in the absence of medical intervention (12). Therefore, identification of the inciting trigger of cytokine storm is critically important, as it can present a target for therapeutic intervention.

The most common trigger of cytokine storm is infection. The diversity of pathogen triggers is broad as cytokine storm occurs after infection with bacterial, fungal, protozoan, and viral pathogens (13). Alternatively, MAS arises in the context of uncontrolled disease activity and/or infection in patients with rheumatic diseases including systemic juvenile idiopathic arthritis (SJIA), adult onset Still's disease, systemic lupus erythematosus, and Kawasaki disease most commonly. Furthermore, certain malignancies serve as a trigger of cytokine storm (14).

As the trigger for cytokine storm varies greatly between individual patients, therapeutic intervention can be personalized to the inciting trigger of disease. For example, early recognition of sepsis and administration of antibiotics has demonstrated clinical benefits for septic patients (6). Targeting EBV-infected B cells for elimination using Rituximab has been used to treat patients with EBV-induced cases of FHL and MASH (14, 15) (Level of Evidence 4). Similarly, malignancies that trigger MASH can be treated by targeting the underlying malignancy with cytoreductive chemotherapy, which is often sufficient to ameliorate manifestations of cytokine storm (14) (Level of Evidence 5). Alternatively, high-dose steroids target disease activity from the underlying rheumatic disease, which is thought to initiate cytokine storm in MAS patients (Level of Evidence 5). These examples highlight the importance of identifying triggers of cytokine storm and directing therapy to remove the specific trigger of disease for each individual patient.

In addition to targeting the primary trigger of cytokine storm, it is critically important to consider treatments to prevent secondary infections. Broad-spectrum immunosuppression leaves many cytokine storm patients susceptible to infection, and secondary infections can trigger reactivation of the underlying hyperinflammatory response leading to additional morbidity and mortality. Therefore, appropriate prophylaxis for *Pneumocystis jirovecii* pneumonia and fungal infections, intravenous immunoglobulin supplementation for hypogammaglobulinemia, and neutropenic precautions should be considered during the treatment of patients with cytokine storm (12) (Level of Evidence 5).

In summary, the ability to curtail the symptoms of cytokine storm by removing the underlying trigger highlights important pathophysiologic mechanisms of disease and makes identification of the underlying trigger an important consideration in the management of

patients with cytokine storm. However, this strategy can be complicated by the fact that not every patient has an identifiable trigger and not all triggers can be sufficiently treated to ameliorate disease. Therefore, additional therapeutic strategies are necessary to treat patients with cytokine storm syndromes.

Personalizing treatment to the underlying defect in disease resistance

The clinical features of cytokine storm syndromes are believed to represent the same end-stage pathophysiologic state reached by disparate initiating triggers that lead to uncontrolled inflammation (1). However, clinical heterogeneity in disease arises from vastly different mechanisms leading to defective disease resistance in patients suffering from cytokine storm. Therefore, the success of targeting the ensuing hyperinflammatory response with specific therapeutic interventions varies between individual types of cytokine storm and between individual patients. Herein, we emphasize how targeting the underlying pathogenic mechanisms of immune dysregulation provides a rational approach for the treatment of each type of cytokine storm syndrome.

Familial Hemophagocytic Lymphohistiocytosis (FHL)—The impact of defective host resistance on the pathogenesis of cytokine storm is best described in FHL, whereby defective cytotoxicity and/or viral clearance results in an excessive inflammatory response to infection (1). In FHL, patients lack disease resistance due to genetic defects leading to defective cytotoxicity. This leads to a state of immunodeficiency whereby a typically well-controlled viral infection in an immunocompetent host turns into a vicious hyperinflammatory response leading to fulminant cytokine storm and death if medical intervention is not initiated. Intriguingly, this is one of the few scenarios in modern medicine whereby massive immunosuppression is the main treatment for a disease initiated by an infection. This apparent paradox can be reconciled by the fact that the infection itself is not the driver of organ damage in FHL, but rather the hyperinflammatory immune response to the infection, unchecked by normal immunoregulatory mechanisms, is the major driver of disease.

Patients with FHL often present within their first year of life with their initial exposure to a virus and succumb to the ensuing immunopathology within ~2 months without medical intervention (12). Therefore, initiation of empiric therapy must be prompt and is often necessary before confirmatory genetic and diagnostic studies have resulted (12). Empiric therapy for FHL focuses on removing the infectious trigger in combination with cytoablative chemotherapy and broad-spectrum immunosuppression targeting T cell activation and proliferation (16, 17) (Level of evidence 1c). The first international treatment protocol for FHL was organized by the Histiocyte Society in 1994 (HLH-94) and consisted of an 8-week induction therapy using dexamethasone, etoposide, and intrathecal methotrexate (the latter of which is used for CNS involvement only) resulting in survival of 51% of FHL patients with a median follow-up of 3.1 years, and considered as a therapeutic bridge to HCT (17). An alternative approach with comparable survival was published from a single-center's experience using corticosteroids and antithymocyte globulin (ATG) followed by HCT (18). Patients who do not achieve remission using standard induction therapy have been successfully treated with alemtuzumab targeted depletion of CD52-expressing leukocytes to

induce remission (19). Although FHL-related induction therapies can lead to disease remission, relapses in the hyperinflammatory response is exceedingly common making HCT the only curative treatment (12). HCT for FHL is most effective when patients have achieved complete remission in disease activity prior to initiation of the conditioning therapy for HCT (16, 20). Therefore, HLA typing should be initiated early in the course of treatment to ensure HCT can be initiated as quickly as possible once disease remission is achieved because of the high risk for disease recurrence, ongoing risk of secondary infections, and the long-term risk of leukemia and myelodysplastic syndrome from etoposide (12). Reduced intensity conditioning regimens have resulted in improvements in 5-year survival of FHL patients undergoing HCT compared to conventional myeloablative conditioning regimens (20). A full discussion of the complexities in diagnosis and treatment of FHL is outside the scope of this review, and we point interested readers to recent reviews on these topics (12, 13, 16, 21).

Although treatment of FHL has been largely standardized for fulminant disease presentations, not all patients present early in life or with severe disease manifestations. In fact, the initial presentation of FHL has been reported as late as the 8th decade of life (22). Intriguingly, patients with less severe FHL and late onset disease harbor hypomorphic, monoallelic, or heterozygous biallelic mutations resulting in less severe defects in cytotoxicity (22–30). Recent reports also indicate that IL-2 can “rescue” NK cell cytotoxicity defects in FHL patients with mutations in *STXBP2* or *STX11* indicating that exposure to IL-2 may result in retained cytotoxicity function *in vivo* in certain patients (25, 31, 32). Therefore, the severity of the cytotoxicity defect seen in each individual patient helps to explain the clinical heterogeneity of FHL. However, this clinical heterogeneity complicates management of FHL patients, as not all patients require aggressive induction therapy or HCT. Therefore, the risks of treatment must be weighed against the risk of uncontrolled disease, and future studies will be necessary to determine the appropriate management strategies for individuals with less severe FHL phenotypes.

Despite recent advances in the management of FHL, refractory disease is quite common as only 50% of patients achieve a complete response and only 80% of patients survive to HCT (16). Therefore, novel therapeutic interventions are critically needed. The most promising emerging therapeutic target for the treatment of FHL is interferon (IFN) γ . This cytokine has been demonstrated to be a key driver of end-organ damage in cytokine storm syndromes, and was initially reported to correlate with FHL disease activity and relapse in the early 1990's (33, 34). Preclinical studies support the pathogenic role of IFN γ in FHL, as IFN γ -neutralizing antibodies offer complete protection from LCMV-induced hyperinflammation in perforin- and Rab27a- deficient mouse models without affecting the infectious burden (11, 35). IFN γ 's role in the pathogenesis of FHL is also supported by the use of JAK inhibitors to block signaling downstream of the IFN γ receptor, which ameliorates disease in LCMV-infected perforin- and Rab27a- deficient mice (36, 37). Finally, recent preclinical evidence suggests that IFN γ production in FHL is dependent on IL-33, as IL-33 neutralization reduces IFN γ production and ameliorates immunopathology in LCMV-infected perforin-deficient mice (38). Therefore, multiple different approaches to target IFN γ in patients with FHL may be of benefit, and a clinical trial studying the safety and efficacy of the IFN γ

neutralizing drug, NI-0501, is currently underway (ClinicalTrials.gov Identifier: NCT01818492).

Macrophage Activation Syndrome (MAS)—Macrophage activation syndrome is a cytokine storm syndrome that arises in patients with underlying autoimmune or autoinflammatory rheumatic conditions (1). The classification of patients with MAS is blurred with other categories of cytokine storm, as patients with MAS can present with nonspecific symptoms of cytokine storm before they have been diagnosed with an underlying rheumatic disease. In these scenarios, the diagnosis of MAS can be difficult, and further complicates therapeutic decision making, as MAS is treated differently than other types of cytokine storm.

The difficulties in diagnosis and treatment of MAS arise from an inadequate understanding of the mechanisms contributing to disease susceptibility. Murine models of MAS recapitulate disease manifestations including hepatosplenomegaly, cytopenias, hyperferritinemia, and hypercytokinemia, and indicate that chronic or exaggerated Toll-like receptor (TLR) stimulation is sufficient for the development of disease (39–41). The involvement of TLRs in the pathogenesis of MAS is further supported by clinical data that identified an interleukin (IL)-1 and TLR gene expression signature in the peripheral blood mononuclear cells isolated from patients with new-onset systemic JIA, the rheumatic disease with the greatest predisposition to the development of MAS (42). Furthermore, polymorphisms in IRF5, a signaling molecule downstream of TLRs, are associated with a 4-fold higher risk of MAS in known SJIA patients (43). TLRs are not the only innate immune receptor implicated in the development of MAS, as patients with activating mutations in the gene encoding NLRC4 spontaneously develop an autoinflammatory syndrome with a predisposition to the development of MAS, termed NLRC4-MAS (44, 45). NLRC4 can direct the assembly of inflammasomes leading to the activation of the proinflammatory cytokines IL-1 and IL-18, which have been implicated in the pathogenesis of MAS and are produced by cells of the innate immune system (46). These preclinical and clinical data suggest that heightened innate immune responses are sufficient to drive MAS in certain scenarios.

Despite the emerging evidence linking innate immunity to MAS disease pathogenesis, a large body of literature suggests an associated expansion of IFN γ -producing lymphocytes as a main driver of MAS (47). To reconcile these differing views of disease pathogenesis, we propose that MAS susceptibility is driven by the underlying cytokine milieu produced during chronic uncontrolled inflammation in certain rheumatic diseases. This may explain why some patients are more susceptible to MAS than others, as the cytokine milieu differs between different types of rheumatic diseases and between individual patients with the same rheumatic disease. Using SJIA as an example, Shimizu *et al* performed cytokine analysis on SJIA patient sera and found two subsets of SJIA based on levels of IL-6 and IL-18 (48). The IL-6 predominant group was more prone to the development of arthritis, while the IL-18 predominant group was more susceptible to MAS (48). IL-18 is produced by innate immune cells and stimulates IFN γ production from lymphocytes, which may explain why both innate immune cells and lymphocytes have been implicated in the pathogenesis of MAS. This possibility is supported by Bracaglia *et al* who demonstrate a strong connection

between levels of IFN γ and IFN γ -induced chemokines in SJIA patients with MAS, but not with active SJIA alone (49). However, IL-18-driven IFN γ production cannot be the only determinant in driving MAS, as some patients with active SJIA without features of MAS have high levels of IL-18 without increased levels of IFN γ (48–52), and patients with lupus-associated MAS do not have markedly elevated IL-18 levels (53). To reconcile these contradictory data, Put *et al*/describe defective IL-18-induced IFN γ production and defective IL-18 signaling in NK cells isolated from patients with SJIA without evidence of MAS (52). These data suggest that SJIA patients may be protected from the development of MAS by defective IL-18 signaling in lymphocytes, which would explain how high levels of IL-18 in some patients with active SJIA are not driving aberrant IFN γ production and MAS. However, additional translational studies will be needed to clarify whether SJIA patients who develop MAS regain NK cell responsiveness to IL-18 leading to robust IFN γ production and fulminant MAS (54). Additional evidence suggesting a link between IL-18 and IFN γ as drivers of MAS comes from treatment of 2 patients with NLRC4-MAS: one patient was successfully treated with IL-1 and IL-18 blockade and another patient responded to IFN γ neutralization (55, 56). Therefore, not only are IL-18 and IFN γ likely pathogenic mediators of MAS, but neutralization of these cytokines has therapeutic potential for the treatment of MAS. Future studies will be needed to define whether IL-18-driven IFN γ production is specific to SJIA-mediated MAS, or whether this aberrant cytokine milieu is common to MAS driven by other rheumatic diseases too.

Interestingly, targeting cytokines known to be critical drivers of active SJIA may not be beneficial in the treatment of MAS. A recent report indicates that the rate of MAS in SJIA patients was not altered by IL-1 β neutralization using canakinumab (57), and SJIA patients treated with either canakinumab or tocilizumab (a monoclonal antibody targeting the IL-6 receptor) still developed MAS despite marked improvements in SJIA-related symptoms overall (58, 59). Despite these sobering data, case series have demonstrated benefit of the recombinant IL-1 receptor antagonist anakinra that blocks IL-1 α and IL-1 β in patients refractory to standard MAS therapies with the evidence supporting this notion recently reviewed (60). Therefore, anakinra may have a limited role in the treatment of refractory MAS, while blockade of IL-1 β or IL-6 using canakinumab and tocilizumab, respectively, do not appear to be sufficient to ameliorate manifestations of MAS as monotherapy.

The mechanisms leading to MAS susceptibility and disease pathogenesis are important to consider when designing therapeutic interventions for patients with MAS. Treatment of MAS should focus on reducing both lymphocyte and innate immune cell responses that contribute to the underlying pathogenic cytokine milieu driving MAS. Not surprisingly, the medications most frequently used to treat patients with MAS target both lymphocytes and innate immune cells. Intravenous methylprednisolone 30 mg/kg (max dose 1 g), is first-line therapy for patients with MAS (Level of Evidence 5) and is used in the majority of patients diagnosed with MAS (61). Corticosteroids offer anti-inflammatory properties by reducing lymphocyte proliferation, inducing lymphocyte apoptosis, and limiting cytokine production by innate immune cells and lymphocytes. For patients with severe MAS or cases of MAS not responsive to intravenous corticosteroids, cyclosporine A is second-line therapy and leads to further reductions in lymphocyte activation and proliferation (62–64) (Level of Evidence 4). Therefore, the cornerstone of therapy for MAS directly targets the immune

mechanisms that drive the hyperinflammatory response in MAS. Intriguingly, intravenous immunoglobulin is the most commonly used therapy for MAS other than corticosteroids and cyclosporine (61), although evidence for its benefit is limited to observational studies in a heterogeneous population of cytokine storm syndrome patients not limited to MAS (65, 66) (Level of Evidence 4). Anakinra may be of benefit to patients with refractory MAS (60) (Level of evidence 4), although other biologic therapies including canakinumab and tocilizumab have not demonstrated benefit in MAS, as detailed above (57–59). Rituximab may be useful in EBV-associated MAS, as it directly targets infected B cells for destruction, and has shown efficacy in other cytokine storm syndromes (15). MAS patients who are unstable or are clinically deteriorating despite intravenous corticosteroids and cyclosporine may require cytoablative therapies that are used to treat FHL (12). However, as we continue to improve our understanding of MAS disease pathogenesis, rational design of therapeutic interventions will likely lead to more efficacious and less toxic interventions for refractory disease.

Malignancy-associated syndrome of hyperinflammation (MASH)—There is a paucity of published literature on the occurrence MASH making diagnostic and treatment recommendations difficult (14). A recent review highlights that MASH occurs more frequently in adults with presentations primarily restricted to specific types of leukemias and lymphomas (14). These disease associations raise the suspicion that the cytokine milieu produced by specific types of hematologic malignancies initiates a hyperinflammatory response leading to cytokine storm physiology. A special case of MASH arises in patients with cytokine release syndrome (CRS), a clinical syndrome accompanying novel immunotherapy treatment of B-precursor leukemia (14). Intriguingly, patients that develop CRS have been successfully treated with tocilizumab (67). Furthermore, preclinical studies demonstrate that the tyrosine kinase inhibitor ibrutinib can block cytokine production by activated immune cells and/or cytokine-releasing cancer cells (68). Whether CRS is a specific type of MASH only associated with the treatment of specific malignancies using rapidly cytoablative immunotherapies and whether its pathogenesis and treatment approach can be broadly applied to other causes of MASH remain largely unknown.

The best approach to treating patients with MASH remains unclear, as data is lacking as to whether therapeutic intervention should be directed at the underlying malignancy or to rely on therapeutic approaches that are successful for FHL (14). Currently, use of anti-neoplastic agents targeting the underlying cancer with or without etoposide combined with corticosteroids is commonly used for the treatment of MASH (14). As this treatment approach is based on very limited clinical evidence, research efforts should be focused on developing our understanding of the basic pathogenesis of MASH to inform the design of rational prospective clinical studies moving forward. This bedside to bench and back approach will likely be needed to improve our treatment of MASH.

Sepsis—Sepsis is a devastating clinical condition that contributes to high levels of morbidity and mortality worldwide (2). A new consensus definition for the term sepsis was introduced in 2016 that describes sepsis as life-threatening organ dysfunction caused by a maladaptive host response to infection (2). Severe manifestations of sepsis can lead to

circulatory, cellular and/or metabolic dysfunction, which is associated with a mortality rate greater than 40% (2). To date, the cornerstone of medical management for patients with sepsis involves early identification of disease, prompt initiation of antibiotics, appropriate hemodynamic resuscitation, and ICU level supportive care (6, 7).

Despite major improvements in the supportive care provided to patients with sepsis in the past 20 years, little progress has been made in the development of effective pharmacologic interventions. This is not for lack of effort, as numerous clinical trials have enrolled over 15,000 patients in sepsis trials testing a diverse range of interventions that demonstrated promising results in preclinical models, but failed to show a benefit in the clinic (69). The reasons for these failures are multifactorial and beyond the scope of this review, but interested readers are directed to recent reviews on this topic (69, 70). Hope for the development of pharmacologic intervention for sepsis remains high despite past failures. Recent evidence suggests that blood purification methods (71), corticosteroids (70, 72), or use of anakinra (73, 74) in select patient populations may be beneficial in sepsis. Future studies will be required to define how patients with sepsis can be categorized into subsets with similar mechanisms of disease pathogenesis.

Additional understanding of the dynamic immune dysregulation of sepsis from an initial hyperinflammatory response to immunoparalysis is necessary to provide rationale for the timing of specific therapeutic interventions (75). Finally, mechanisms of host susceptibility to sepsis are diverse and include age, sex, race, and chronic disease with additional genetic, epigenetic, and environmental factors likely to influence disease pathogenesis and severity (76). It will only be with a concerted effort to understand these contributions to disease pathogenesis that the design of rational therapeutic interventions for sepsis can be achieved.

Conclusion

Cytokine storm syndromes are challenging for clinicians and devastating for patients. Diagnosis is difficult given the clinical heterogeneity in disease and the diversity of triggers that initiate cytokine storm physiology. The need to rapidly initiate supportive measures to combat an evolving spectrum of end-organ damage can delay appropriate diagnostic evaluation. The diverse mechanisms of disease pathogenesis make therapeutic decision-making difficult. We hope that our conceptual approach to the management of cytokine storm syndromes helps to reduce these bottlenecks and provides direction for clinical management of these complex conditions. Furthermore, our model of cytokine storm pathogenesis provides a schema to direct our current and future attempts to rationally target the pathogenic mechanisms of cytokine storm. With continued efforts to understand the pathogenic drivers of disease, we believe that clinical outcomes and rational therapeutic strategies for the treatment of cytokine storm syndromes will continue to improve.

References

1. Weaver LK, Behrens EM. Hyperinflammation, rather than hemophagocytosis, is the common link between macrophage activation syndrome and hemophagocytic lymphohistiocytosis. *Curr Opin Rheumatol*. 2014; 26(5):562–9. [PubMed: 25022357]

- 2**. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315(8):801–10. This article provides an updated definition of sepsis that will facilitate rapid diagnosis of disease and improve consistency for future epidemiologic and clinical trials. [PubMed: 26903338]
3. Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. *Science*. 2012; 335(6071):936–41. [PubMed: 22363001]
4. Schieber AM, Lee YM, Chang MW, Leblanc M, Collins B, Downes M, et al. Disease tolerance mediated by microbiome *E. coli* involves inflammasome and IGF-1 signaling. *Science*. 2015; 350(6260):558–63. [PubMed: 26516283]
5. Marraffini LA, Sontheimer EJ. CRISPR interference: RNA-directed adaptive immunity in bacteria and archaea. *Nat Rev Genet*. 2010; 11(3):181–90. [PubMed: 20125085]
- 6**. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41(2):580–637. This study provides guidelines for the medical management of patients with sepsis based on supportive care that is known to improve outcomes. [PubMed: 23353941]
7. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med*. 2015; 43(1):3–12. [PubMed: 25275252]
- 8**. Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD, et al. Opposing Effects of Fasting Metabolism on Tissue Tolerance in Bacterial and Viral Inflammation. *Cell*. 2016; 166(6):1512–25. e12. This preclinical study emphasizes how host metabolism can divergently affect disease outcome depending on whether the infectious trigger was viral or bacterial. [PubMed: 27610573]
9. Hawiger J, Veach RA, Zienkiewicz J. New paradigms in sepsis: from prevention to protection of failing microcirculation. *J Thromb Haemost*. 2015; 13(10):1743–56. [PubMed: 26190521]
10. London NR, Zhu W, Bozza FA, Smith MC, Greif DM, Sorensen LK, et al. Targeting Robo4-dependent Slit signaling to survive the cytokine storm in sepsis and influenza. *Sci Transl Med*. 2010; 2(23):23ra19.
11. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. *Blood*. 2004; 104(3):735–43. [PubMed: 15069016]
12. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011; 118(15):4041–52. [PubMed: 21828139]
13. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014; 383(9927):1503–16. [PubMed: 24290661]
14. Lehmborg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematologica*. 2015; 100(8):997–1004. [PubMed: 26314082]
15. Balamuth NJ, Nichols KE, Paessler M, Teachey DT. Use of rituximab in conjunction with immunosuppressive chemotherapy as a novel therapy for Epstein Barr virus-associated hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol*. 2007; 29(8):569–73. [PubMed: 17762500]
16. Filipovich AH, Chandrakasan S. Pathogenesis of Hemophagocytic Lymphohistiocytosis. *Hematol Oncol Clin North Am*. 2015; 29(5):895–902. [PubMed: 26461149]
17. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002; 100(7):2367–73. [PubMed: 12239144]
18. Mahlaoui M, Ouachee-Chardin M, de Saint Basile G, Neven B, Picard C, Blanche S, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. *Pediatrics*. 2007; 120(3):e622–8. [PubMed: 17698967]

19. Marsh RA, Allen CE, McClain KL, Weinstein JL, Kanter J, Skiles J, et al. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. *Pediatr Blood Cancer*. 2013; 60(1):101–9. [PubMed: 22522603]
20. Seo JJ. Hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis: recent advances and controversies. *Blood Res*. 2015; 50(3):131–9. [PubMed: 26457279]
21. Janka GE, Lehmborg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program*. 2013; 2013:605–11. [PubMed: 24319239]
22. Zhang K, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. *Blood*. 2011; 118(22):5794–8. [PubMed: 21881043]
23. Wang Y, Wang Z, Zhang J, Wei Q, Tang R, Qi J, et al. Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood. *PLoS One*. 2014; 9(9):e107386. [PubMed: 25233452]
24. Meeths M, Bryceson YT, Rudd E, Zheng C, Wood SM, Ramme K, et al. Clinical presentation of Griscelli syndrome type 2 and spectrum of RAB27A mutations. *Pediatr Blood Cancer*. 2010; 54(4):563–72. [PubMed: 19953648]
25. Pagel J, Beutel K, Lehmborg K, Koch F, Maul-Pavicic A, Rohlf AK, et al. Distinct mutations in STXBP2 are associated with variable clinical presentations in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL5). *Blood*. 2012; 119(25):6016–24. [PubMed: 22451424]
26. Marsh RA, Satake N, Biroschak J, Jacobs T, Johnson J, Jordan MB, et al. STX11 mutations and clinical phenotypes of familial hemophagocytic lymphohistiocytosis in North America. *Pediatr Blood Cancer*. 2010; 55(1):134–40. [PubMed: 20486178]
27. Jessen B, Maul-Pavicic A, Ufheil H, Vraetz T, Enders A, Lehmborg K, et al. Subtle differences in CTL cytotoxicity determine susceptibility to hemophagocytic lymphohistiocytosis in mice and humans with Chediak-Higashi syndrome. *Blood*. 2011; 118(17):4620–9. [PubMed: 21878672]
28. Jessen B, Kogl T, Sepulveda FE, de Saint Basile G, Aichele P, Ehl S. Graded defects in cytotoxicity determine severity of hemophagocytic lymphohistiocytosis in humans and mice. *Front Immunol*. 2013; 4:448. [PubMed: 24379813]
29. Jessen B, Bode SF, Ammann S, Chakravorty S, Davies G, Diestelhorst J, et al. The risk of hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type 2. *Blood*. 2013; 121(15):2943–51. [PubMed: 23403622]
30. Sepulveda FE, Debeurme F, Menasche G, Kurowska M, Cote M, Pachlopnik Schmid J, et al. Distinct severity of HLH in both human and murine mutants with complete loss of cytotoxic effector PRF1, RAB27A, and STX11. *Blood*. 2013; 121(4):595–603. [PubMed: 23160464]
31. Meeths M, Entesarian M, Al-Herz W, Chiang SC, Wood SM, Al-Ateeqi W, et al. Spectrum of clinical presentations in familial hemophagocytic lymphohistiocytosis type 5 patients with mutations in STXBP2. *Blood*. 2010; 116(15):2635–43. [PubMed: 20558610]
32. Hackmann Y, Graham SC, Ehl S, Honing S, Lehmborg K, Arico M, et al. Syntaxin binding mechanism and disease-causing mutations in Munc18-2. *Proc Natl Acad Sci U S A*. 2013; 110(47):E4482–91. [PubMed: 24194549]
33. Ohga S, Matsuzaki A, Nishizaki M, Nagashima T, Kai T, Suda M, et al. Inflammatory cytokines in virus-associated hemophagocytic syndrome. Interferon-gamma as a sensitive indicator of disease activity. *Am J Pediatr Hematol Oncol*. 1993; 15(3):291–8. [PubMed: 8328642]
34. Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood*. 1991; 78(11):2918–22. [PubMed: 1954380]
35. Pachlopnik Schmid J, Ho CH, Chretien F, Lefebvre JM, Pivert G, Kosco-Vilbois M, et al. Neutralization of IFNgamma defeats haemophagocytosis in LCMV-infected perforin- and Rab27a-deficient mice. *EMBO Mol Med*. 2009; 1(2):112–24. [PubMed: 20049711]
36. Das R, Guan P, Sprague L, Verbist K, Tedrick P, An QA, et al. Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis. *Blood*. 2016; 127(13):1666–75. [PubMed: 26825707]

37. Maschalidi S, Sepulveda FE, Garrigue A, Fischer A, de Saint Basile G. Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. *Blood*. 2016; 128(1):60–71. [PubMed: 27222478]
38. Rood JE, Rao S, Paessler M, Kreiger PA, Chu N, Stelekati E, et al. ST2 contributes to T-cell hyperactivation and fatal hemophagocytic lymphohistiocytosis in mice. *Blood*. 2016; 127(4):426–35. [PubMed: 26518437]
39. Avau A, Mitera T, Put S, Put K, Brisse E, Filtjens J, et al. Systemic juvenile idiopathic arthritis-like syndrome in mice following stimulation of the immune system with Freund's complete adjuvant: regulation by interferon-gamma. *Arthritis Rheumatol*. 2014; 66(5):1340–51. [PubMed: 24470407]
40. Behrens EM, Canna SW, Slade K, Rao S, Kreiger PA, Paessler M, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. *J Clin Invest*. 2011; 121(6):2264–77. [PubMed: 21576823]
41. Strippoli R, Carvello F, Scianaro R, De Pasquale L, Vivarelli M, Petrini S, et al. Amplification of the response to Toll-like receptor ligands by prolonged exposure to interleukin-6 in mice: implication for the pathogenesis of macrophage activation syndrome. *Arthritis Rheum*. 2012; 64(5):1680–8. [PubMed: 22108837]
42. Fall N, Barnes M, Thornton S, Luyrink L, Olson J, Ilowite NT, et al. Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals molecular heterogeneity that may predict macrophage activation syndrome. *Arthritis Rheum*. 2007; 56(11):3793–804. [PubMed: 17968951]
43. Yanagimachi M, Naruto T, Miyamae T, Hara T, Kikuchi M, Hara R, et al. Association of IRF5 polymorphisms with susceptibility to macrophage activation syndrome in patients with juvenile idiopathic arthritis. *J Rheumatol*. 2011; 38(4):769–74. [PubMed: 21239750]
- 44*. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet*. 2014; 46(10):1140–6. This study provides evidence for a monogenic disease predisposing to the development of MAS. [PubMed: 25217959]
- 45*. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, Choi M, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat Genet*. 2014; 46(10):1135–9. This study provides evidence for a monogenic disease predisposing to the development of MAS. [PubMed: 25217960]
46. Canna SW, Goldbach-Mansky R. New monogenic autoinflammatory diseases--a clinical overview. *Semin Immunopathol*. 2015; 37(4):387–94. [PubMed: 25963521]
47. Schuler G, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. *Annu Rev Med*. 2015; 66:145–59. [PubMed: 25386930]
- 48*. Shimizu M, Nakagishi Y, Yachie A. Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles. *Cytokine*. 2013; 61(2):345–8. This article describes a subset of SJIA patients with an IL-18 predominant serum cytokine signature that predisposes patients to MAS. [PubMed: 23276493]
- 49*. Bracaglia C, de Graaf K, Pires Marafon D, Guilhot F, Ferlin W, Prencipe G, et al. Elevated circulating levels of interferon-gamma and interferon-gamma-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Ann Rheum Dis*. 2016 This article demonstrates a strong IFN γ signature in the peripheral blood of SJIA patients with MAS that tracks with disease onset and severity.
50. Shimizu M, Yokoyama T, Yamada K, Kaneda H, Wada H, Wada T, et al. Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis-associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis. *Rheumatology (Oxford)*. 2010; 49(9):1645–53. [PubMed: 20472718]
51. Shimizu M, Nakagishi Y, Kasai K, Yamasaki Y, Miyoshi M, Takei S, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: the diagnostic significance of interleukin-18 and interleukin-6. *Cytokine*. 2012; 58(2):287–94. [PubMed: 22398373]
- 52*. Put K, Vandenhaute J, Avau A, Van Nieuwenhuijze A, Brisse E, Dierckx T, et al. Inflammatory gene expression profile and defective IFN-gamma and granzyme K in natural killer cells of systemic juvenile idiopathic arthritis patients. *Arthritis Rheumatol*. 2016 This article suggests

that defective IL-18-induced NK cell production of IFN γ may protect SJIA patients from developing MAS.

53. Maruyama J, Inokuma S. Cytokine profiles of macrophage activation syndrome associated with rheumatic diseases. *J Rheumatol.* 2010; 37(5):967–73. [PubMed: 20231207]
54. Behrens EM. Caught in the act: Dissecting natural killer cell function in systemic JIA. *Arthritis Rheumatol.* 2016
55. Bracaglia, CPG.Gatto, A.Pardeo, M.Lapeyre, G.Raganelli, L.Marasco, E.Insalaco, A.Ferlin, W.Nelson, R.de Min, C., De Benedetti, F., editors. Anti Interferon-Gamma (IFN γ) Monoclonal Antibody Treatment in a Child with NLRC4-Related Disease and Severe Hemophagocytic Lymphohistiocytosis (HLH) [abstract]. 2015 ACR/ARHP Annual Meeting; 2015; San Francisco, CA.
56. Canna SW, Girard C, Malle L, de Jesus A, Romberg N, Kelsen J, et al. Life-threatening NLRC4-associated hyperinflammation successfully treated with Interleukin-18 inhibition. *J Allergy Clin Immunol.* 2016
- 57*. Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell D, et al. Rate and Clinical Presentation of Macrophage Activation Syndrome in Patients With Systemic Juvenile Idiopathic Arthritis Treated With Canakinumab. *Arthritis Rheumatol.* 2016; 68(1):218–28. This study demonstrates that canakinumab treatment does not alter the rate that MAS occurs in patients with SJIA. [PubMed: 26314396]
58. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012; 367(25):2385–95. [PubMed: 23252525]
59. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012; 367(25):2396–406. [PubMed: 23252526]
60. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. *Genes Immun.* 2012; 13(4):289–98. [PubMed: 22418018]
61. Minoia F, Davi S, Horne A, Bovis F, Demirkaya E, Akikusa J, et al. Dissecting the heterogeneity of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Rheumatol.* 2015; 42(6):994–1001. [PubMed: 25877504]
62. Quesnel B, Catteau B, Aznar V, Bauters F, Fenaux P. Successful treatment of juvenile rheumatoid arthritis associated haemophagocytic syndrome by cyclosporin A with transient exacerbation by conventional-dose G-CSF. *Br J Haematol.* 1997; 97(2):508–10. [PubMed: 9163630]
63. Mouy R, Stephan JL, Pillet P, Haddad E, Hubert P, Prieur AM. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. *J Pediatr.* 1996; 129(5):750–4. [PubMed: 8917244]
64. Ravelli A, De Benedetti F, Viola S, Martini A. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis successfully treated with cyclosporine. *J Pediatr.* 1996; 128(2):275–8. [PubMed: 8636829]
65. Emmenegger U, Frey U, Reimers A, Fux C, Semela D, Cottagnoud P, et al. Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. *Am J Hematol.* 2001; 68(1):4–10. [PubMed: 11559930]
66. Seidel MG, Kastner U, Minkov M, Gadner H. IVIG treatment of adenovirus infection-associated macrophage activation syndrome in a two-year-old boy: case report and review of the literature. *Pediatr Hematol Oncol.* 2003; 20(6):445–51. [PubMed: 14631618]
67. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J.* 2014; 20(2):119–22. [PubMed: 24667956]
68. Ruella M, Kenderian SS, Shestova O, Klichinsky M, Melenhorst JJ, Wasik MA, et al. Kinase inhibitor ibrutinib to prevent cytokine-release syndrome after anti-CD19 chimeric antigen receptor T cells (CART) for B cell neoplasms. *Leukemia.* 2016
69. Giamarellos-Bourboulis EJ. Failure of treatments based on the cytokine storm theory of sepsis: time for a novel approach. *Immunotherapy.* 2013; 5(3):207–9. [PubMed: 23444949]

70. Salluh JJ, Povoas P. Corticosteroids in Severe Sepsis and Septic Shock: A Concise Review. *Shock*. 2016
71. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA*. 2009; 301(23):2445–52. [PubMed: 19531784]
72. Annane D. The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update. *Front Endocrinol (Lausanne)*. 2016; 7:70. [PubMed: 27379022]
73. Shakoori B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med*. 2016; 44(2):275–81. [PubMed: 26584195]
74. Rajasekaran S, Kruse K, Kovey K, Davis AT, Hassan NE, Ndika AN, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children*. *Pediatr Crit Care Med*. 2014; 15(5):401–8. [PubMed: 24583503]
75. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013; 369(9):840–51. [PubMed: 23984731]
76. Kempker JA, Martin GS. The Changing Epidemiology and Definitions of Sepsis. *Clin Chest Med*. 2016; 37(2):165–79. [PubMed: 27229635]

Figure 1. A Venn diagram of cytokine storm syndromes

This diagram highlights the overlapping clinical entities that make up the cytokine storm syndromes discussed in this review. Sepsis is the largest category of cytokine storm syndromes and is defined as life-threatening organ dysfunction caused by a maladaptive host response to infection. As this definition of sepsis can also be used to describe FHL, we categorize FHL as a specific subset of sepsis for the purposes of this review. However, not all cytokine storm syndromes are triggered by infection. Therefore, MAS and MASH are separate entities from sepsis when they are triggered by an underlying rheumatic disease or malignancy, respectively. However, both MAS and MASH can also be triggered by infection in certain scenarios, which is denoted by the partial overlap of these conditions with sepsis.

Figure 2. Conceptual approach to the management of cytokine storm syndrome patients

We identify 5 key steps in the approach to treating patients with cytokine storm syndromes. As patients with cytokine storm are often clinically unstable at presentation, the initial step in management is to stabilize the patient with supportive care (Step #1). Next, a major hurdle in the management of patients with cytokine storm is to recognize that hyperinflammation is a major cause of the underlying disease pathogenesis. Therefore, we have highlighted the key clinical parameters that help to identify patients suffering from a hyperinflammatory response (Step #2). Step #3 is to determine the underlying cause of the dysregulated hyperinflammatory response by categorizing patients into specific subtypes of cytokine storm syndrome and treating known triggers of disease. Step #4 is to determine whether initiation of immunosuppression would be of benefit for a patient with cytokine storm and to direct therapy to the underlying pathogenic mechanisms of disease. Finally, the response to therapy must be closely monitored with titration of any immunosuppressive therapies and medical management personalized to the individual cytokine storm syndrome patient (Step #5).

Figure 3. Conceptual paradigm of the factors contributing to disease pathogenesis in cytokine storm syndromes

Light can pass through glass, but the light output will be affected by the light input, the shape of the glass, and the opacity of the glass. This analogy can be applied to cytokine storm syndromes, whereby disease is affected by the inciting trigger, defects in host resistance to disease, and the ability of the host to ‘tolerate’ the presence of cytokine storm without sustaining tissue damage or decreased fitness. A) This is an example of how two different infectious triggers can result in vastly different disease outcomes regardless of the fitness of the host. B) This example demonstrates how the same trigger can result in vastly different disease outcomes based on the presence or absence of host disease resistance mechanisms. C) This example demonstrates how the same trigger can cause vastly different disease outcomes based on the ability of the host to ‘tolerate’ the presence of a pathogen or not. These proposed mechanisms of disease pathogenesis can explain the clinical spectrum of disease seen in patients with cytokine storm syndromes, as each of these examples results in divergent clinical manifestations of cytokine storm represented by differences in the bolded colors emerging from each prism. Using this paradigm of cytokine storm pathogenesis, we conceptualize within this review how current and future clinical interventions can rationally target these specific mechanisms of disease pathogenesis for therapeutic benefit.