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REVIEW ARTICLE

COVID-19 and cytokine storm syndrome: are there lessons from macrophage activation syndrome?



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Although interest in “cytokine storms” has surged over the past decade, it was massively amplified in 2020 when it was suggested that a subset of patients with COVID-19 developed a form of cytokine storm. The concept of cytokine storm syndromes (CSS) encompasses diverse conditions or circumstances that coalesce around potentially lethal hyperinflammation with hemodynamic compromise and multiple organ dysfunction syndrome. Macrophage activation syndrome (MAS) is a prototypic form of CSS that develops in the context of rheumatic diseases, particularly systemic juvenile idiopathic arthritis. The treatment of MAS relies heavily upon corticosteroids and cytokine inhibitors, which have proven to be lifesaving therapies in MAS, as well as in other forms of CSS. Within months of the recognition of SARS-CoV2 as a human pathogen, descriptions of COVID-19 patients with hyperinflammation emerged. Physicians immediately grappled with identifying optimal therapeutic strategies for these patients, and despite clinical distinctions such as marked coagulopathy with endothelial injury associated with COVID-19, borrowed from the experiences with MAS and other CSS. Initial reports of patients treated with anti-cytokine agents in COVID-19 were promising, but recent large, better-controlled studies of these agents have had mixed results suggesting a more complex pathophysiology. Here, we discuss how the comparison of clinical features, immunologic parameters and therapeutic response data between MAS and hyperinflammation in COVID-19 can provide new insight into the pathophysiology of CSS. (*Translational Research* 2021; 232:1 – 12)

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Submitted for Publication February 12, 2021; received submitted March 1, 2021; accepted for publication March 1, 2021.

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1931-5244/\$ - see front matter

Published by Elsevier Inc.

<https://doi.org/10.1016/j.trsl.2021.03.002>

COVID-19 AND THE CYTOKINE STORM HYPOTHESIS

The global COVID-19 pandemic has presented an urgent challenge to translational scientists internationally, to define the pathogenesis of SARS-CoV-2 infection and direct rationally designed therapeutic approaches. The earliest clinical reports from Wuhan^{1,2} suggested that patients with life-threatening COVID-19 shared clinical features which partially overlapped with macrophage activation syndrome (MAS), cytokine-release syndrome (CRS) and acute respiratory distress syndrome (ARDS), suggesting that a dysregulated host immune response may drive aspects of disease pathogenesis (reviewed in³). The hypothesis of a cytokine storm syndrome in severe COVID-19 increased in visibility with an initial case series suggesting dramatic

clinical improvements in patients treated with the anti-IL-6 biologic tocilizumab⁴ (a mainstay of CRS management). As COVID-19 spread across the globe, further uncontrolled case series of anti-cytokine therapy (largely anti-IL-6 and IL-1) continued to show promise,^{5–8} and large-scale controlled trials of corticosteroids found clear benefit.^{9,10} The promise of immunomodulatory therapies was in stark contrast to other agents such as hydroxychloroquine with initial excitement that failed in rigorous study,^{11–13} and antivirals which showed relatively small improvements without change in overall mortality.¹⁴ However, continued basic and translational research into SARS-CoV-2 pathogenesis has found conflicting evidence as to the existence of a prominent cytokine storm in COVID-19, with clear differences from the pathogenesis of conditions such as MAS. More recently, randomized trials of anti-IL-1 and IL-6 agents have found little evidence of overall benefit (and in some cases concern for harm).^{15–17} Given this, should the idea of a cytokine storm syndrome in COVID-19 be reevaluated? In particular, what can we learn from prototypical cytokine storm syndromes such as MAS regarding the pathogenesis of a cytokine storm, how such conditions can be detected, and how best to utilize immunomodulatory therapies?

WHAT IS CYTOKINE STORM?

Cytokine storm is a descriptive term that, through evocative imagery of severe meteorological phenomena, seeks to convey the severity and potential power of hyperinflammatory states to wreak immune-mediated havoc on an individual. Cytokine storm syndromes refers to a diverse set of conditions that collectively manifest a clinical phenotype of hyperinflammation, hyperferritinemia, and multiorgan failure resulting from the excessive and often self-perpetuating production of cytokines through unencumbered and amplified immune activation.¹⁸ The spectrum of cytokine storm syndromes spans wide ranging conditions with distinct underlying triggers that can include infectious, genetic, oncologic, rheumatic and iatrogenic etiologies. The CSS nomenclature provides a useful framework that highlights common clinical features and shared elements of their immune-mediated pathophysiology, despite their disparate underpinnings. At the same time, one must be cautious to avoid oversimplification and remain mindful of the important differences that exist between the CSSs, such as the degree of hyperferritinemia or the responsiveness to treatment with IL-6 directed therapies. Moreover, a genetically defined CSS, like familial hemophagocytic lymphohistiocytosis (fHLH), requires a different therapeutic

attitude than an intrinsically self-limited CSS, such as the CRS that often follows the administration of chimeric antigen receptor-T cell therapy for leukemia. Despite these limitations the CSS paradigm can serve as a useful approach in the recognition of hyperinflammatory states, understanding drives of inflammation, and considering treatment strategies.

MACROPHAGE ACTIVATION SYNDROME, A PROTOTYPIC FORM OF CYTOKINE STORM

MAS is a prototypic form of CSS that develops in the context of many rheumatic diseases, most commonly the Still's disease spectrum (systemic juvenile idiopathic arthritis [sJIA] and adult-onset Still's disease)¹⁹ but also including systemic lupus erythematosus²⁰ and Kawasaki disease.²¹ Formerly considered to be a form of secondary HLH, MAS is a systemic CSS that involves excessive activation and proliferation of T cells and well-differentiated, non-neoplastic macrophages with hemophagocytic activity.²² Clinically, it is marked by extreme hyperferritinemia, hematocytopenias, hepatic dysfunction and coagulopathy. Because of the critical importance of distinguishing MAS from inflammation related to the underlying sJIA disease activity, criteria for the classification of MAS in the setting of sJIA have been developed and refined.^{23,24} In the most widely used criteria, an expert consensus process was combined with comprehensive multivariate regression analyses of clinical and laboratory data from actual patients in an effort to bring greater objectivity to the classification of MAS in sJIA.²³ The model most predictive of the presence of MAS in febrile children with known or suspected sJIA included hyperferritinemia (>684 ng/mL), together with any 2 of the following additional criteria: platelet count $\leq 181 \times 10^9$ /liter, aspartate aminotransferase >48 units/liter, triglycerides >156 mg/dl and fibrinogen ≤ 360 mg/dl. Among the variables included in the final model, univariate analysis of hyperferritinemia (>684 ng/mL) and platelet count $\leq 181 \times 10^9$ /liter each showed very strong association with the presence of MAS.

The pathogenic factors that underlie sJIA and the development of MAS remain unclear, but most cases of MAS develop in the context of either high disease activity or an intercurrent infection.²⁵ Current evidence supports a model of MAS that involves the interplay of excessive production of the interleukin (IL)-1 superfamily member, IL-18, the overproduction of IFN γ , and the situational failure of cell-mediated cytotoxicity²² (Fig 1). It has been suggested that IL-18 plays a central role in the pathophysiology of MAS, perpetuating and amplifying innate immune activation. Elevated

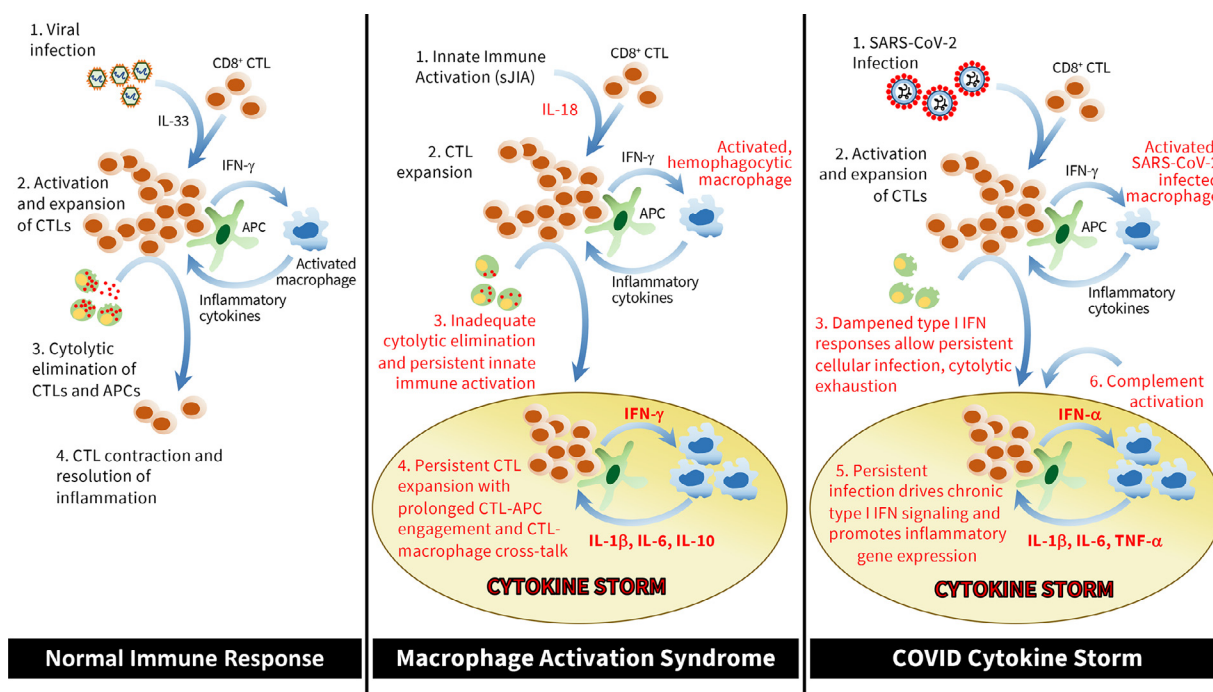


Fig 1. Comparison of macrophage activation syndrome and COVID-cytokine storm syndrome. Typical antiviral responses (left panel) produce expansion of virus-specific cytotoxic T lymphocytes (CTL), which interact with antigen presenting cells (APC) and macrophages to limit and eliminate the infection. After clearing the infection, the expanded population of activated immune cells are eliminated by cytolytic cells and the immune system returns to its typical basal level of surveillance. In macrophage activation syndrome (MAS; middle panel), innate immune activation and IL-18 drive the expansion of CTLs, their engagement with APCs and their cross-talk with macrophages. The combined persistence of innate immune activation and an inadequate cytolytic capacity to eliminate activated immune cells leads to prolonged CTL-APC engagement and continued production of inflammatory mediators, amplified CTL-macrophage cross-talk, and the cytokine storm of MAS. In COVID-19 (right panel), infection with SARS-CoV-2 stimulates these same anti-viral immune pathways with CTL expansion. Dampened type I interferon responses allow prolonged persistence of infection of the lungs and activation of type II interferon responses contribute to persistent immune activation. Failure to clear the virus lead to prolonged type I interferon signaling, driving proinflammatory cytokine production. As was the case in MAS, it is possible that inadequate cytolytic capacity due to immune exhaustion and/or defective antiviral responses leads to prolonged cross-talk between CTL, APCs and alveolar macrophages, contributing to COVID-CS. Beyond the proinflammatory mechanisms implicated in other cytokine storm syndromes, activation of the complement cascade has been observed in severe COVID-19 patients and its specific contribution to pathophysiology are not yet known.

levels of circulating IL-18 distinguish sJIA from other monogenic hereditary periodic fever syndromes.²⁶ Similarly, elevation of IL-18 is observed in the subset of sJIA patients at risk for developing MAS, ultimately differentiating MAS from disease flare.²⁷ Importantly, IL-18 is naturally counter-regulated by a circulating antagonist, the IL-18 binding protein (IL-18BP), which renders IL-18 biologically inactive through high-affinity binding.²⁸ Although both IL-18 and IL-18BP are induced by inflammatory cytokines, an imbalance between IL-18 and its antagonist exists in sJIA and MAS, resulting in elevated levels of bioactive or “free” IL-18.²⁶ This elevation of free IL-18 was shown to be a unique feature of sJIA/MAS that was not observed in other situations with IL-18 elevation, including viral

infection or fHLH.^{26,29} It is the abnormal elevation of free IL-18 that is thought to drive pathologic IFN γ production, leading to MAS in sJIA. Indeed activation of IFN γ pathways has been associated with emergence of MAS,^{30,31} and drives the proinflammatory activation of macrophages to further sustain hyperinflammation.³² These observations are recapitulated in a monogenic form of HLH/MAS caused by gain-of-function mutations in *NLRC4*.^{33,34} Mice or humans bearing gain-of-function mutations in *NLRC4* demonstrate persistent elevation of IL-18 and recurrent episodes of MAS.^{26,33,34} Beyond IL-18, defective cell-mediated cytotoxicity may also contribute to MAS. Several studies have reported an enrichment of heterozygous mutations in fHLH genes, suggesting a genetic contribution

to MAS risk.^{35–37} Indeed, the cytotoxicity defects observed in MAS are partial, but in situations where cytotoxic capacity is exceeded, the result is reduced killing by NK and cytotoxic T lymphocytes, prolonged engagement of CTLs with antigen presenting cells, hypersecretion of inflammatory cytokines, and failure to contract and resolve the inflammatory response^{38,39} (Fig 1). While there remain significant gaps in the understanding of MAS, it broadly represents a well-defined and characterized CSS that can be compared and contrasted with similar hyperinflammatory states.

CYTOKINE STORM IN SEVERE COVID-19

During the first wave of COVID-19 disease in China, early reports noted that patients with poor outcomes after SARS-CoV-2 infection had clinical and laboratory features that overlapped with those seen in CSS such as MAS. Zhou and colleagues reported that in a large cohort of hospitalized patients, those who died from COVID-19 demonstrated cytopenias including lymphopenia, anemia, and thrombocytopenia; significantly elevated AST, d-dimer, and LDH; and significant hyperferritinemia (median 1435 vs 503 ng/mL in survivors).² Similarly, patients with COVID-19 pneumonia who progressed to ARDS and death had high fevers, neutrophilia, elevated LDH and d-dimer, and hyperferritinemia (median 1029 vs 545 ng/mL).⁴⁰ In a small cohort from Wuhan, patients with severe COVID-19 had lymphopenia with neutrophilia, elevated LDH, d-dimer, transaminases, and CRP, and hyperferritinemia (median 1598 vs 337 ng/mL in moderate cases).¹ This study also performed cytokine profiling, which demonstrated elevations in IL-6, IL-10, TNF, and sIL2-R in severe patients. Together, these laboratory findings suggested that patients with severe COVID-19 pneumonia had biochemical features reflecting that seen in CSS including cytopenias, liver dysfunction, coagulopathy, and hyperferritinemia.

While the immunopathogenesis of SARS-CoV-2 infection is covered in much greater detail elsewhere in this issue, several studies characterizing the systemic inflammatory response in COVID-19 have similarly linked cytokine elevations to progression to severe disease. Del Valle et al reported evidence of a proinflammatory cytokine environment in severe COVID-19, examining nearly 2000 serum samples from more than 1400 patients hospitalized in New York City. Serum IL-6, IL-8, and TNF were all significantly elevated compared to both healthy donors and CAR T patients without signs of CRS. Interestingly, while IL-6 levels were overall higher in CAR T patients with CRS compared to COVID-19, levels in COVID-19 varied greatly. Further

examination of IL-6 levels showed that IL-6 was associated with an increased risk of death (OR = 2.47). IL-6 was positively associated with inflammatory markers including CRP, d-dimer, and ferritin, as well as fever, but even adjusting for inflammatory markers, disease severity, and comorbidities, IL-6 was independently associated with COVID-19 mortality.

Hadjadj et al further examined the peripheral immune response in 50 patients across a spectrum of COVID-19 severity.⁴¹ Whole blood transcriptional profiling found patients with high disease severity had a progressive increase in expression of a large gene set highly enriched in inflammatory and innate immune response genes. In particular, both cytokine and chemokine related genes and NF- κ B pathway genes, as well as circulating protein levels of IL-6 and TNF, were significantly increased as a function of disease activity. Interestingly, genes reflecting IFN activation were most upregulated in mild disease and reduced in more severe disease, and low IFN α plasma levels preceded clinical deterioration. Together, this points to excessive NF- κ B-driven inflammation, along with impaired IFN viral control responses, in severe hyperinflammatory COVID-19.⁴¹

Inadequate type I IFN signaling was further implicated in severe COVID-19 when 2 different host factors that dampen type I IFN responses were discovered among subjects with severe COVID-19. Loss of function mutations in genes of the type-I IFN pathway⁴² and autoantibodies directed against type I IFNs (IFN- α and/or IFN- ω)⁴³ were independently strongly enriched among subjects with severe COVID-19, relative to subjects with a mild disease course. The mutations involved 7 type I IFN pathway genes, and *in vitro* investigations of the mutated proteins (and of the neutralizing effect of the autoantibodies) confirmed their negative effect on IFN signaling and/or the induction of the interferon-regulated gene-expression signature.^{42,43} The link between severe disease and deficient IFN signaling was further bolstered by a study that compared whole blood single cell transcriptomic profiles of patients with mild-moderate COVID-19 to those of patients with severe disease. In stark contrast to the 11 subjects with mild-moderate COVID-19, in whom the interferon stimulated gene (ISG) signature was upregulated as expected, the 10 severe COVID-19 patients displayed a complete absence of ISG signature in every cell population examined; instead, there was prominent upregulation of a proinflammatory cytokine signature.⁴⁴ It is possible that in COVID-19, the reduced IFN-I signaling may acutely produce an impotent antiviral effect, but that this evolves into a chronic IFN response that contributes to the proinflammatory amplification loop observed in severe COVID-19^{45,46} (Fig 2). Taken together, these

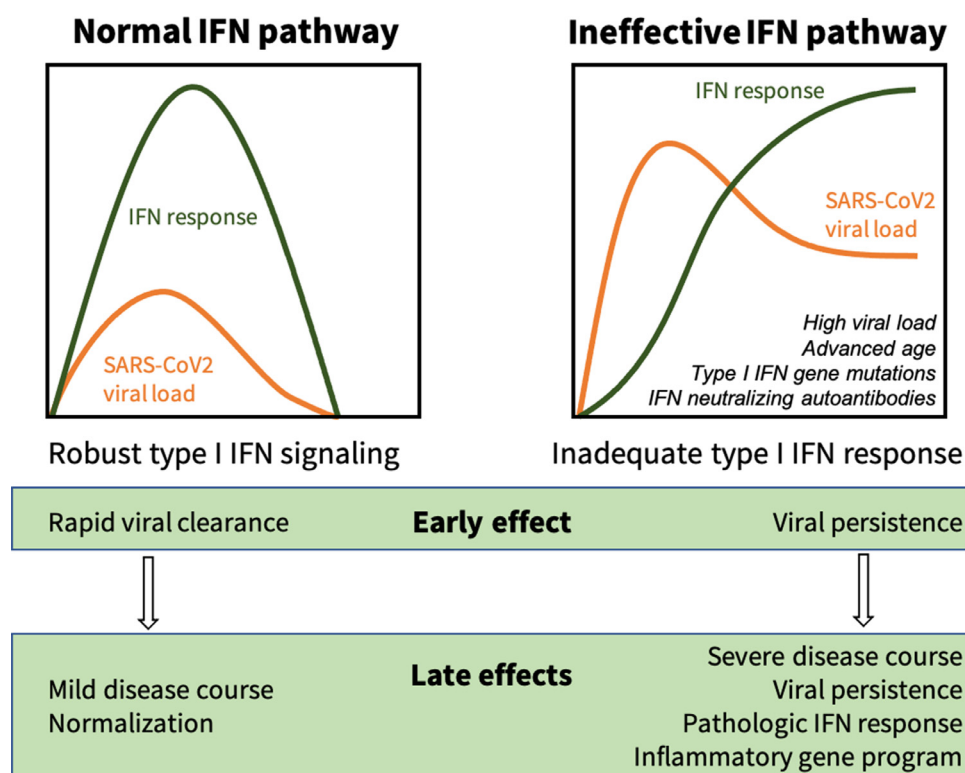


Fig 2. Timing and strength of Type I IFN responses in COVID-19. Clearance of SARS-CoV2 is uniquely dependent on type I IFN signaling. Most healthy individuals with COVID-19 are capable of activating type I IFN pathways, clearing the viral infection and normalizing the host environment with only mild symptoms. In the context of large viral loads or impaired IFN signaling pathways, dampened or inadequate IFN responses may lead to failure of antiviral responses and viral persistence. Persistent viral infection leads to chronic and pathologic elevation of type I IFN signaling which that propagates the proinflammatory amplification loop that is indicative of severe COVID-19. Adapted from Park A, Iwasaki A. Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19. *Cell Host Microbe*. 2020;27:870-878.

data suggest that both the strength and timing of type I IFN responses are important variables that influence host responses to COVID-19.⁴⁵

Although impaired type I IFNs and IL-6 levels have been closely investigated in severe COVID-19, other cytokines have also been proposed to have key roles in COVID-19 hyperinflammation. Karki and colleagues have proposed a model that the synergy between high levels of TNF and IFN γ (both found in severe COVID-19 and produced by COVID-infected PBMC) can drive proinflammatory cell death.⁴⁷ Co-administration of these cytokines in a mouse model led to hyperinflammation, multiorgan dysfunction, shock, and death. This also caused a proinflammatory form of cell death with features of pyroptosis, apoptosis, and necroptosis they termed “PANoptosis.” Inhibition of this cell death was protective against mortality in several models of cytokine storm as well as a murine model of SARS-CoV-2 infection. This is notable in that, as discussed above, IFN γ plays a central role in driving both primary HLH and MAS, further supporting a key role for this

cytokine in cytokine storms. Another recent article proposed a key role in COVID-19 for IL-33, an IL-1 family cytokine that could serve to both dampen IFN responses and sustain hyperinflammation.⁴⁸ Interestingly, IL-33 has been shown to have prominent roles in the cytokine storm caused by HLH.⁴⁹

Despite these findings, several recent authors have questioned whether severe COVID truly represents a cytokine storm, but rather is a typical inflammatory response to a life-threatening infection. First, COVID-19 has other clinical features that are not seen in CSS such as MAS, such as marked coagulopathy with endothelial injury and microthrombosis.⁵⁰ Indeed, some patients with severe COVID-19 show evidence of catastrophic microvascular injury with complement activation,⁵¹ which could suggest a phenotype similar to thrombotic microangiopathy.⁵² More broadly, the model of cytokine storm implies that the inflammatory response (and cytokines in particular) are deleterious to the host, and fails to distinguish between an appropriate vs dysregulated immune response.^{53–55} For example,

Sinha and colleagues note that while IL-6 levels are elevated in severe COVID-19, these levels are more than 10-fold lower than those typically seen in hyperinflammatory forms of ARDS.⁵³ Similar work from Kox et al demonstrated that IL-6 levels even in COVID-19 patients with ARDS were less than those seen in sepsis patients with ARDS, and comparable to levels seen in other severe disease states such as major trauma and out-of-hospital cardiac arrest.⁵⁴ Finally, while the majority of patients with severe COVID-19 have serum ferritin above defined cut-offs for cytokine storms such as MAS and HLH,^{56,57} COVID-19 patients rarely exhibit the marked elevations associated with increasing mortality in hyperferritinemic syndromes.⁵⁸ The counter-argument to this however is that while the paradigm of cytokine storm has been largely drawn from entities such as MAS, HLH, and CRS, it is not synonymous with a hyperferritinemic syndrome or an “IL-6-opathy”. Rather, the cytokine storm model describes disease states where inflammatory responses become dysregulated and create feed-forward loops of hyperinflammation that become deleterious to the host, and where targeted immunomodulatory therapy can improve outcomes. In severe COVID-19 particularly, this hyperinflammatory loop may largely operate in the lungs rather than in the circulation (Fig 1). As discussed above, the impaired type I interferon responses caused by genetic mutations or autoantibodies^{42,43} can lead to a failure to control primary SARS-CoV-2 infection in the lungs, including infection of alveolar macrophages driving persistent immune activation.^{59,60} Indeed, immune profiling of the pulmonary inflammatory response in severe COVID-19 shows expansion and IFN-driven activation of alveolar macrophages, IFN γ -producing T cells, and increased pulmonary levels of proinflammatory mediators (IL-6, IL-8, IL-1 β) and IFN-induced chemokines.^{59,61,62} This supports a model of a lung-centric, self-sustaining inflammatory loop leading to cytokine storm, but with variable circulating levels of specific mediators. It is therefore critically important to identify such patients early who could benefit from targeted therapies.

DIAGNOSIS AND MANAGING COVID-ASSOCIATED HYPERINFLAMMATION – LESSONS FROM MAS

Given the above data suggesting that extreme immune dysregulation and cytokine storm occurs in only a subset of severe SARS-CoV-2 infection, it may be beneficial to apply previously designed diagnostic and classification criteria for disorders such as HLH and MAS to COVID-19 patients. Webb and colleagues approached this question systematically, performing a

literature review to identify candidate criteria for other CSS, and then examining existing published data on COVID-19 to identify clinical and laboratory features of poor outcomes.⁶³ Using the results of these searches, they developed a classification framework called cHIS (COVID-19 associated hyperinflammatory syndrome) with 6 core features of CSS that were also reported in severe SARS-CoV-2 infections including: fever, macrophage activation, liver inflammation, hematologic dysfunction, coagulopathy, and hypercytokinemia (Table I). These criteria were then applied retrospectively to a large cohort of COVID-19 patients admitted to a regional, multisite healthcare system in the western USA. Overall, 54% of patients had a daily cHIS score of 2 or greater at some point during their hospitalization. Scores of ≥ 2 vs < 2 were associated with significantly increased length of stay, need for ICU care, mechanical ventilation, or death. Most interestingly, using the cHIS score as a time-dependent variable, they showed that a daily cHIS score of ≥ 2 was associated with significantly increased risk of clinical deterioration later in the hospitalization, potentially identifying patients who could benefit from immunomodulatory therapy before progression to respiratory failure.

Other authors have similarly used the cytokine storm paradigm to define criteria for COVID-19 patients at risk for severe disease. Caricchio and colleagues examined a large cohort of patients admitted to Temple University Hospital and diagnosed as suspected COVID-19 cytokine storm by consensus between treating pulmonologists and rheumatologists based on presence of hypoxia and elevated ferritin, CRP, d-dimer, LDH, and troponin.⁶⁴ Notably, very few of these patients fulfilled established HLH criteria such as HLH-2004⁵⁷, 2016 MAS Criteria, or the H-score⁶⁵ (Table I). Rather, using logistic regression and principle component analysis they identified 12 laboratory variables in 3 related clusters that could predict development of cytokine storm. These included several variables included in criteria for other cytokine storms, but also many that were peculiar to COVID-19 such as altered blood chemistry and troponin elevation. These criteria were highly sensitive and specific for patients clinically diagnosed as cytokine storm, and classified patients at significantly increased risk for longer hospitalization and death. Manson and colleagues suggested a simpler approach of using more direct measures of systemic inflammation.⁶⁶ These authors classified patients as having COVID hyperinflammation (COV-HI) with ferritin $> 1500 \mu\text{g/L}$, or CRP $> 15 \text{ mg/dL}$ or doubling in 24h. In their retrospective cohort of patients admitted to 2 UK hospitals, 33% met COV-HI on admission, and were associated with worse clinical outcomes including

Table I. Diagnostic and classification criteria for HLH and MAS, and proposed criteria for COVID-19 associated hyperinflammation

Criteria	HLH and MAS			COVID-19 hyperinflammation		
	HLH-2004	HScore	2016 MAS criteria	cHIS	COV-HI	Temple criteria
Fever	≥38.5 C	0 (<38.4), 33 (38.4–39.4), OR 49 (>39.4)	Fever	>38.0 C		
Hyperferritinemia	≥500 ng/mL	0 (<2000), 35 (2000–6000), OR 50 (>6000)	≥684 ng/mL	≥700 ng/mL	>1500 ng/mL	>250 ng/mL
Organomegaly	Splenomegaly	0 (no), 23 (H or SM), OR 38 (HSM)				
Cytopenia	2 or more: Hg <9.0 g/dL OR Platelets <100 ⁹ /L OR PMN <10 ³ /mL	0 (1 line), 24 (2 lines), OR 34 (3 lines)	Platelets ≤181 ⁹ /L	N:L ≥10 or both Hg ≤9.2 g/dL & Platelets ≤110 ⁹ /L		L <10.2% N >11.4 ³ /mL
Hypertriglyceridemia/ hypercytokinemia	Trig. ≥265 mg/dL OR Fibrin. ≤150 mg/dL	0 (<1.5), 44 (1.5–4.0), OR 64 (>4.0)	>156 mg/dL	Trig. ≥150 mg/dL OR IL-6 ≥15 pg/mL OR CRP ≥15 mg/dL	CRP >15 mg/dL OR doubling in 24h from >5 mg/dL	CRP >4.6 mg/dL
Hypofibrinogenemia		0 (>250), OR 30 (≤250)	≤360 mg/dL			
Elevated AST or LDH		0 (<30), or 19 (≥30)	AST >48U/mL	AST ≥100 U/L or LDH ≥400 U/L		AST >60 U/L ALT >87 U/L LDH >416 U/L
Immunosuppression Hemophagocytosis	Marrow, spleen, or lymph node	0 (no), OR 18 (yes) 0 (no), OR 35 (yes)				
NK cell function	Low or absent					
Elevated sCD25	≥2400 U/mL					
Elevated D-dimer				≥1.5 μg/mL		>4.93 μg/mL
Hypoalbuminemia						<2.8 g/dL
Cardiac enzymes						Troponin I >1.09 ng/mL
Blood chemistry						Anion gap <6.8 mmol/L Cl >106 mmol/L K >4.9 mmol/L BUN/Cr >29
Diagnosis	5 of 8 criteria met	Sum of parameters ≥169	Known or suspected sJIA + fever + ele- vated ferritin + ≥2 of 4 remaining criteria	≥2 criteria – increased risk of mechanical ventila- tion and mortality		Ferritin AND CRP AND 1 from each cluster: I: albumen, lympho- cytes, neutrophils II: AST, ALT, d-dimer, LDH, troponin III: Blood chemistry

higher mortality. Most interestingly, meeting COV-HI criteria was associated with next-day clinical deterioration or death, again suggesting a patient population for targeted interventions for developing or worsening cytokine storm.

If it is possible to identify COVID-19 patients with features of cytokine storm, what are the most appropriate treatment approaches to reduce inflammation and improve clinical outcomes? Once again, the experience managing CSS such as MAS offers several possible approaches. The longstanding therapy for MAS has been high-dose steroids (up to 30mg/kg/d methylprednisolone), with calcinurin inhibitors such as cyclosporine for patients with refractory disease, and approaches used in HLH such as etoposide in life-threatening situations.⁶⁷ The introduction of cytokine-directed biologic therapy in rheumatic diseases such as SJIA with high risk for MAS has altered this treatment landscape. Despite several early case reports suggesting that initiation of biologic therapy could trigger MAS,⁶⁸ long-term experience has suggested that overall rates of MAS during biologic treatment is similar, though with somewhat altered clinical and laboratory features.^{69–72} In contrast, there is increasing evidence that treatment with high-dose anakinra (recombinant IL-1 receptor antagonist) is effective for treating MAS,^{73,74} and is often used early after initiation of corticosteroids.⁷⁵ While anti-IL-6 treatment has proven very effective in CRS triggered by CAR-T therapy,⁷⁶ there is less experience with this treatment in other cytokine storms. Finally the anti-IFN γ monoclonal antibody emapalumab was recently FDA approved for treatment of HLH,⁷⁷ and there are ongoing clinical trials of this in MAS in children with SJIA with promising early results.⁷⁸

Despite this promising landscape, the overall experience of cytokine-directed therapy in severe COVID-19 has been mixed. Given the above findings regarding high levels of IL-6 in patients with severe SARS-CoV-2 infection, an early report of dramatic response in patients treated with the anti-IL-6 agent tocilizumab⁴ generated great enthusiasm and launched multiple randomized-clinical trials. While several further cohort studies reported promising results compared to historical or nonrandomly selected controls,^{5–7,79,80} results of randomized trials have been somewhat contradictory. The CORIMUNO-19 open label trial of tocilizumab showed a potential decrease in need for noninvasive ventilation, intubation, or death at 14 days but no difference in mortality at 28 days.⁸¹ Several other trials of tocilizumab or the IL-6 inhibitor sarilumab either failed to meet their primary endpoints or were suspended for futility.^{15,17,82} There have also been several small case series of anakinra in severe COVID-19 showing decreased mortality^{8,83,84} and one larger cohort study finding

higher rates of clinical improvement in patients treated with high dose anakinra (10mg/kg/d IV) compared to low-dose (100mg twice daily subcutaneously).⁸⁵ However, a randomized controlled trial of anakinra did not show any improvement and was stopped early for futility.¹⁶ Further randomized controlled trials of anakinra, along with other biologic agents including emapalumab, are ongoing. Finally, approaches with broader cytokine blockade such as JAK inhibitors have also been considered for severe COVID-19. A small study found that baricitinib treatment significantly reduced serum levels of a broad range of cytokines including TNF, IL-1 β , and IL-6, and associated with clinical improvement,⁸⁶ and led to the recent emergency-use authorization for baricitinib in combination with remdesivir for children and adults with severe COVID-19.

With these underwhelming results, the most effective therapy for severe COVID-19 may remain corticosteroids. Several large studies have shown that corticosteroid treatment can reduce mortality in severe COVID-19, most notably in the RECOVERY Trial. Here, dexamethasone for up to 10 days significantly reduced 28-day mortality, with the most pronounced responses in those requiring mechanical ventilation (age-adjusted rate ratio 0.65) or receiving oxygen without invasive ventilation (rate ratio 0.82).⁹ A similar large study found improved survival with hydrocortisone treatment, although this trial was stopped before reaching statistical significance,¹⁰ and a recent metaanalysis confirmed the overall benefit of corticosteroids in severe COVID-19.⁸⁷ Given this experience, corticosteroid treatment is now widely recommended for adults and children hospitalized with severe COVID-19 infection.⁸⁸ Interestingly recent new findings from the RECOVERY Trial examined use of tocilizumab in patients with and without concurrent steroid treatment.⁸⁹ These preliminary findings showed that the greatest reduction in 28-day mortality was in those receiving both tocilizumab and dexamethasone (27% vs 33% steroids alone) with no significant improvement in those without concomitant steroids. These findings were also notable in showing a trend toward greater benefit of tocilizumab in patients not requiring ventilator support, which could suggest cytokine blockade and corticosteroids work best at distinct phases of severe COVID-19. Further work is urgently needed to determine how and when to best utilize other immunomodulatory therapy as an adjuvant to in steroid-refractory or contraindicated patients.

CONCLUSIONS

While the paradigm of CSS remains new and somewhat ill-defined, it can be a useful framework to

consider disorders where the dysregulated host inflammatory response becomes itself pathologic, such as in MAS. Although the precise nature and drivers of a CSS associated with SARS-CoV-2 infection remains to be defined, it is clear that increased systemic inflammation is associated with worse outcomes in COVID-19. It has also been shown with high-quality clinical trial data that patients with severe and critical COVID-19 benefit from immunomodulatory therapy with corticosteroids. Using the CSS framework in MAS as a guide, the critical questions remaining include: How can clinicians best identify COVID-19 patients progressing to cytokine storm? Are there particular genetic or other host factors that can predispose to a CSS during or after SARS-CoV-2 infection? And most importantly, how and when can therapeutic interventions for COVID-19 CSS be utilized, including corticosteroids and cytokine-directed biologic therapy? Given the continued global spread of SARS-CoV-2 pandemic, borrowing approaches from more well-defined disorders such as MAS may provide a helpful blueprint to approach these questions.

ACKNOWLEDGEMENTS

Conflicts of Interest: Dr. Ombrello has no conflicts of interest to disclose. Dr. Schulert has received consulting fees from Novartis and SOBI of <\$10,000.

Dr. Ombrello is supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Z01-AR0411989) of the National Institutes of Health. Dr. Schulert is supported by the National Institute of Arthritis, Musculoskeletal, and Skin Disorders at the National Institutes of Health K08-AR072075.

Drs. Ombrello and Schulert have read and agree with the authorship agreement.

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