










NOTES FROM THE FIELD

On the Alert for Cytokine Storm: Immunopathology in COVID-19

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Poor outcomes in COVID-19 correlate with clinical and laboratory features of cytokine storm syndrome. Broad screening for cytokine storm and early, targeted antiinflammatory therapy may prevent immunopathology and could help conserve limited health care resources. While studies are ongoing, extrapolating from clinical experience in cytokine storm syndromes may benefit the multidisciplinary teams caring for patients with severe COVID-19.

COVID-19 (coronavirus disease 2019) is sweeping across the globe. Most patients have mild-to-moderate symptoms, but a subgroup will become severely ill. Sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS) are common complications of the disease (1). Factors associated with admission to the intensive care unit and death include older age,

comorbid conditions, elevated body mass index, lymphopenia, and elevated blood levels of transaminases, lactate dehydrogenase (LDH), D-dimer, ferritin, and soluble interleukin-2 receptor (sIL-2R) (1–4).

This constellation of features is reminiscent of a family of syndromes broadly gathered under the umbrella of cytokine

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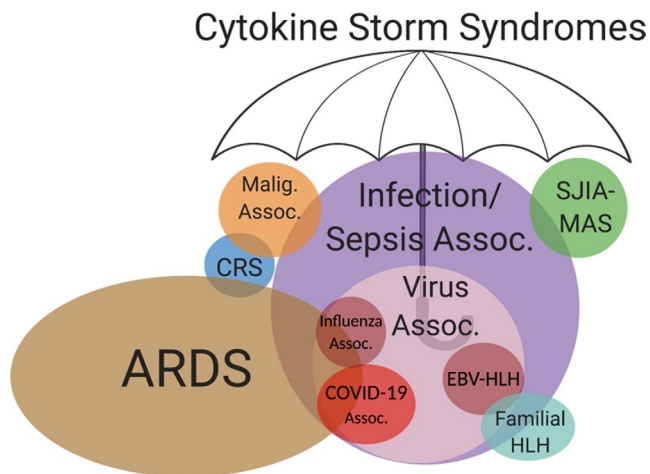


Figure 1. The family of conditions characterized by cytokine storm. Malig. = malignancy; Assoc. = associations; SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CRS = cytokine release syndrome; ARDS = acute respiratory distress syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.

storm syndrome, in which hyperinflammation and multiorgan disease arise through excessive cytokine release from uncontrolled immune activation (Figure 1). Rheumatologists face this foe regularly in systemic juvenile idiopathic arthritis (JIA), adult-onset Still's disease, and systemic lupus erythematosus, among other diseases. Macrophage activation syndrome (MAS), one form of cytokine storm syndrome, develops in at least 10% of patients with systemic JIA. Compared to systemic JIA patients without MAS, those with this complication are more likely to carry heterozygous variants in genes mediating the release of cytotoxic granules from natural killer (NK) cells and CD8+ T cells; biallelic mutations of these genes cause an inherited form of cytokine storm syndrome termed familial hemophagocytic lymphohistiocytosis (HLH). Reduced cytotoxicity impairs clearance of infected cells and elimination of activated macrophages, leading to massive release of proinflammatory mediators. One of these mediators, IL-6, further impairs NK cell function. Patients present with rapid onset of fever, cytopenias, coagulopathy, elevated transaminase levels, hyperferritinemia, and multiorgan

Table 1. Biomarkers of cytokine storm syndrome (CSS)*

Biomarker	Biology	Status in hyperinflammation	Status in COVID-19	Test availability
CRP	Hepatic release in response to IL-6	Nonspecific, useful for monitoring, blunted by IL-6 blockade	Associated with severity, ARDS	A
Complete blood cell count	Multifactorial cytopenias	May be indicative of CSS (especially thrombocytopenia)	Associated with severity, ARDS	A
↑ D-dimer, ↓ fibrinogen	Fibrin degradation product, reflective of DIC	May be indicative of active CSS	Associated with severity, ARDS	A
LDH, AST, ALT	Tissue injury, hepatitis	May be indicative of active CSS	Associated with severity, ARDS	A
Ferritin	Macrophage/hepatocyte activation	Integral part of CSS diagnosis, predictive of sepsis mortality	Associated with severity, ARDS	A
Ferritin:ESR ratio	ESR falls with fibrinogen consumption	Higher specificity than ferritin alone	Not assessed	A
Procalcitonin	Adipokine	Nonspecific, useful for monitoring	Variably associated with severity, ARDS	A, S
IL-2Ra (CD25)	Cleaved from T cells by inflammatory proteases	Part of HLH diagnostic criteria, useful for monitoring	Associated with severity	S
IL-6	Pleiotropic inflammatory cytokine	Elevated, nonspecific	Associated with severity	S
Neopterin	Metabolite of GTP induced by IFN γ	Elevated in blood and CSF	Not assessed	S
IFN γ	Classic type 1/Th1 cytokine	Elevated, but poor dynamic range	Elevated compared with healthy control	S, R
CXCL9	Chemokine induced by IFN γ	Elevated in most CSS, useful for monitoring	Not assessed	S
IL-1 β	Inflammasome-activated	Elevated, but poor dynamic range	Variably elevated with severity	S, R
IL-18	Inflammasome-activated, IFN γ inducing	Very high levels may indicate MAS, not useful for monitoring	Not assessed	S
ADA-2	Released by IFN γ -activated monocytes	Elevated in most CSS, useful for monitoring	Not assessed	S, R
S100 proteins	Neutrophil/monocyte activation	Elevated in active systemic JIA and MAS, and in some ARDS	Not assessed	S, R
CD163	Cleaved from tissue macrophages	Elevated in active systemic JIA and MAS, and in ARDS	Not assessed	S, R

* Relevant citations are provided in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.41285/abstract>). COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; IL-6 = interleukin-6; ARDS = acute respiratory distress syndrome; A = widely available; DIC = disseminated intravascular coagulation; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ESR = erythrocyte sedimentation rate; S = typically send-out; IL-2Ra = IL-2 receptor antagonist; HLH = hemophagocytic lymphohistiocytosis; IFN γ = interferon- γ ; CSF = cerebrospinal fluid; R = may be available only on a research basis; MAS = macrophage activation syndrome; ADA-2 = adenosine deaminase 2; JIA = juvenile idiopathic arthritis.

dysfunction. Historically, the cornerstones of treatment were glucocorticoids, intravenous immunoglobulin (IVIG), and cyclosporine. Despite these interventions, mortality was as high as 20%. Identification of key mediators driving MAS—including IL-1 β , IL-6, IL-18, and interferon- γ (IFN γ)—have inaugurated a new era of cytokine neutralization, potentially enabling a marked reduction in mortality (5,6).

Herpes family viruses (e.g., Epstein-Barr virus) and influenza are major triggers of cytokine storm, both in systemic JIA and in patients without a preexisting immunologic diagnosis. As in systemic JIA-related MAS, the inflammatory cytokines IFN γ and IL-18 are key mediators of hyperinflammation in a murine model of repeated Toll-like receptor 9 stimulation, which mimics severe viral infection (6). In one study of patients without underlying rheumatic disease who died of H1N1 influenza, 81% displayed fea-

tures of cytokine storm, and 36% carried pathologic variants in the cytolytic pathway (7). Treatments effective in systemic JIA-related MAS can benefit patients with cytokine storm triggered by infections (8,9). Post hoc analysis of a phase III randomized controlled trial of anakinra (recombinant IL-1 receptor antagonist) in sepsis showed that patients with coagulopathy and elevated transaminase levels exhibited better survival with IL-1 blockade than with standard of care (65% versus 35%; hazard ratio for death 0.28, $P = 0.007$) (10). Similarly, IL-6 blockade is effective in treating the related cytokine release syndrome from chimeric antigen receptor T cell (CAR-T) therapy (11).

Hyperinflammation in COVID-19 is not MAS, and it may even be distinct from other forms of viral-induced cytokine storm, in that ferritin elevation is modest and severe end-organ disease is focused on the lung. Some patients with

Table 2. Treatments for cytokine storm syndrome of potential utility in severe COVID-19*

Intervention	Biology	Experience in hyperinflammation	Experience in COVID-19	Potential likelihood of impairing viral suppression/clearance†	Concerns
Glucocorticoids (<2 mg/kg/day)‡	Transcriptional regulation via glucocorticoid receptor	Mainstay of treatment	May improve outcomes in ARDS (ChiCTR2000 029386)§	++	Hypertension, immunosuppression, metabolic changes, mood alterations
Glucocorticoids (>250 mg/day)‡	Transcriptional regulation via glucocorticoid receptor	Commonly used during initiation	May improve outcomes in ARDS (ChiCTR2000 029386)§	++	Hypertension, immunosuppression, metabolic changes, mood alterations
Cyclosporine, tacrolimus	Inhibit calcineurin-mediated lymphocyte activation	Case reports/small series in MAS, part of HLH treatment protocol	Theoretical	++	Hypertension, renal failure, immunosuppression
Anakinra	Block IL-1 signaling	Re-analysis of sepsis trials, large series in MAS and HLH (NCT02780583)	NCT04324021	+	Rare transaminitis, neutropenia, eosinophilia
Sarilumab, tocilizumab	Block IL-6 signaling	CAR-T cytokine release syndrome, case reports, ongoing clinical trials¶	NCT04322773, NCT04317092, NCT04320615, NCT04306705, NCT04324073, NCT04315298	+	Cytopenias, immunosuppression
Emapalumab	Neutralize IFN γ	Refractory familial HLH, other case reports, ongoing trials¶	NCT04324021	+	Immunosuppression
JAK inhibitors	Inhibit JAK/STAT pathway cytokines	Case reports, ongoing clinical trials	NCT04320277, NCT04321993	+++	Cytopenias, immunosuppression
Cytokine adsorption	Remove from circulation	Case reports	NCT04324528	Minimal	Central line access
IVIG	Unclear mechanism	Case reports	Theoretical	Minimal	Hypertension, hemolysis
Therapeutic plasma exchange	Remove cytokines/chemokines/DAMPs, replace factors	Case reports	Theoretical	Minimal	Central line access

* Relevant citations are provided in Supplementary Table 2 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.41285/abstract>). COVID-19 = coronavirus disease 2019; ARDS = acute respiratory distress syndrome; MAS = macrophage activation syndrome; HLH = hemophagocytic lymphohistiocytosis; IL-1 = interleukin-1; CAR-T = chimeric antigen receptor T cell therapy; IFN γ = interferon- γ ; IVIG = intravenous immunoglobulin; DAMPs = damage-associated molecular patterns.

† +, ++, and +++ indicate low, moderate, and high likelihood of impairment.

‡ In methylprednisolone equivalent doses.

§ Dosage unclear.

¶ Approved by the US Food and Drug Administration.

COVID-19 may simply have “garden-variety” ARDS associated with the tropism of the virus for the lung. However, critically ill patients with COVID-19 often demonstrate features suggestive of cytokine storm, including fever, characteristic changes in laboratory study findings, and ARDS. Lung tissue from patients with severe acute respiratory syndrome (SARS), the etiology of which has been attributed to a related coronavirus, showed hemophagocytosis—a central pathologic feature of cytokine storm—in 2 of 6 patients who succumbed to the disease (12). Patients with SARS also exhibited high levels of IFN γ and IL-18, which are particularly important in cytokine storm syndrome (13). Thus, the host’s immune response and development of tissue-focused inflammation in the lung likely plays an important role in COVID-19.

These considerations suggest that, beyond antiviral therapy and supportive care, it will be important to monitor hospitalized patients with COVID-19 for evidence of cytokine storm. Impending hyperinflammation can manifest as cytopenias (thrombocytopenia and lymphopenia), coagulopathy (low platelet and fibrinogen levels, and elevated D-dimer levels), tissue damage/hepatitis (elevated LDH, aspartate aminotransferase, and alanine aminotransferase levels), and macrophage/hepatocyte activation (elevated ferritin levels) (Table 1 and Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.41285/abstract>). Cytokine measurement is a theoretically appealing approach, but IFN γ and IL-1 β are not easily assessed in the peripheral blood and IL-6 levels have not yet been proven consistently predictive of poor outcomes. CXCL9, a stable chemokine, is a useful surrogate for IFN γ activity in MAS, as is adenosine deaminase 2 (ADA-2); however, real-time measurement of CXCL9 is not commonly available and ADA-2 testing remains available largely on a research basis. Experience suggests that trends in laboratory test findings, rather than threshold values, will be most informative. In a patient with COVID-19 who develops lymphopenia, worsening coagulopathy, hepatitis, and rising ferritin levels, it may make sense to target immune hyperactivity before end-organ manifestations, such as ARDS, ensue.

The US Centers for Disease Control and Prevention provided an unqualified recommendation against the use of glucocorticoids for the treatment of COVID-19, based on prior experience with influenza, SARS, and coronavirus-induced Middle East respiratory syndrome (MERS) (14). However, a Cochrane review of glucocorticoids as adjunctive therapy in influenza found that the evidence was of low quality, largely because of confounding by indication (15). The literature with regard to glucocorticoids in patients with MERS and SARS has reported similar findings, although some data suggest that glucocorticoids could delay viral clearance (16). Importantly, these data reflect treatment of “all comers” with influenza, MERS, or SARS, rather than therapy

targeted to patients with evidence of hyperinflammation. Of note, in one COVID-19 case series, the mortality rate was lower in patients with ARDS who were treated with methylprednisolone compared with those who did not receive glucocorticoids (46% versus 62%; hazard ratio for death 0.38, $P = 0.003$), although, again, the possibility of confounding by indication is difficult to exclude (2).

Experience from hyperinflammation in HLH, MAS, and cytokine release syndrome suggests that early intervention is essential to avoiding life-threatening tissue damage. In patients with COVID-19 who exhibit evidence of cytokine storm, treatment with glucocorticoids, IVIG, and/or anticytokine therapies should be considered, with the aim of reverting hyperinflammation before ARDS occurs (Table 2 and Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.41285/abstract>) (8,17). Glucocorticoids remain a key first-line option, and clinical trials are urgently needed to test their efficacy and to identify optimal dosing, especially given the clear advantage of glucocorticoids in worldwide availability and cost. IL-1 blockade has shown particular promise as a treatment for cytokine storm syndrome, and high-dose regimens are safe even in the context of overt sepsis (5,10). Tocilizumab (anti-IL-6 receptor) is effective in cytokine release syndrome associated with CAR-T therapy, a syndrome notably reminiscent of COVID-19 in that many patients develop ARDS (11). Emapalumab (anti-IFN γ) is approved by the US Food and Drug Administration for the treatment of HLH and may be effective in MAS. JAK inhibition appears promising; however, the safety of these medications in severe viral infection remains unknown.

Clinical trials are currently enrolling patients with COVID-19 to study the safety and efficacy of glucocorticoids and cytokine blockade strategies utilizing neutralization of IL-1, IL-6, and IFN γ (Table 2). Absent the opportunity to enroll patients in one of these studies, we would consider immunosuppression in patients with COVID-19 who have incipient cytokine storm. Ideally, treatment decisions will be undertaken with the help of a multidisciplinary team familiar with the triggers, manifestations, and treatments of cytokine storm (17). Glucocorticoids will likely be useful. Cytokine blockers may play an important role as well, while we must remain cognizant of the ongoing need for these medications in patients with chronic rheumatologic conditions. Unfortunately, many patients with COVID-19 will become critically ill before high-quality evidence of treatment efficacy is available, leaving us to extrapolate as best we can from the available evidence and from current clinical experience in cytokine storm syndromes.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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