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Review

Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes

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ABSTRACT

A subset of patients with severe COVID-19 develop profound inflammation and multi-organ dysfunction consistent with a "Cytokine Storm Syndrome" (CSS). In this review we compare the clinical features, diagnosis, and pathogenesis of COVID-CSS with other hematological CSS, namely secondary hemophagocytic lymphohistiocytosis (sHLH), idiopathic multicentric Castleman disease (iMCD), and CAR-T cell therapy associated Cytokine Release Syndrome (CRS). Novel therapeutics targeting cytokines or inhibiting cell signaling pathways have now become the mainstay of treatment in these CSS. We review the evidence for cytokine blockade and attenuation in these known CSS as well as the emerging literature and clinical trials pertaining to COVID-CSS. Established markers of inflammation as well as cytokine levels are compared and contrasted between these four entities in order to establish a foundation for future diagnostic criteria of COVID-CSS.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 4 million people worldwide, resulting in a pandemic responsible for over 278,000 deaths as of May 11, 2020 [1,2]. The severity of coronavirus disease of 2019 (COVID-19) ranges from asymptomatic infection to critical illness, with up to one third of hospitalized patients requiring mechanical ventilation in an intensive care unit (ICU) [3–6]. Fatality rates vary between demographic groups, with old age and certain comorbidities (hypertension, obesity, diabetes) associated with higher risk.

In a subset of patients with severe COVID-19, rapid progression of pulmonary infiltrates and multi-organ failure coincides with dramatic increases in inflammatory cytokines and other biochemical markers of inflammation, consistent with a COVID-19 associated cytokine storm syndrome (COVID-CSS) [7–11]. The high mortality rate associated with COVID-CSS has led to the off-label use of targeted anti-cytokine therapies aimed at blocking the inflammatory cascade and improving patient outcomes. Clinical trials are being conducted to assess the safety and efficacy of cytokine blockade in COVID-19. Currently there are no standard therapies for COVID-19 or COVID-CSS, and recent National Institutes of Health (NIH) guidelines have recommended against use of investigational agents outside of clinical trials [12]. On May 1, 2020 the United States Food and Drug Administration (FDA) have granted Emergency Use Authorization for the anti-viral drug remdesivir based on the as-yet unpublished results of a National Institute of Allergy and Infectious Diseases (NIAID) sponsored randomized control trial that demonstrated reduced recovery time compared to placebo [13]. How this drug my influence cytokine storm and how the NIAID trial compares to a prior study that found no benefit of the drug are currently not known [14].

COVID-CSS has brought renewed attention to cytokine storm syndrome as a general concept [15]. In 1993, (perhaps influenced by the military operation "Desert Storm") the term "cytokine storm" was

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coined to describe the hypercytokinemia seen in graft-versus-host disease (GVHD) [16,17]. CSS has since been associated with viral infections (eg. Influenza, severe acute respiratory syndrome/SARS), autoimmune diseases (eg. systemic lupus erythematosus/SLE, systemic juvenile idiopathic arthritis/JIA), hematologic conditions (hemophagocytic lymphohistiocytosis/HLH) and medications [18–20]. Examples of the latter include the phase I clinical trial of TGN1412, an anti-CD28 monoclonal antibody that caused severe cytokine storm in healthy volunteers, and the cytokine release syndrome (CRS) following chimeric antigen receptor (CAR)-T cell therapy [21,22]. The wide heterogeneity of conditions that have been placed under this umbrella term underscore the need to better understand the pathophysiology and treatment of diseases characterized by hypercytokinemia. Recently, CSS has been defined as a condition of dysregulation and perpetuated activation of lymphocytes and macrophages resulting in secretion of large quantities of cytokines leading to overwhelming systemic inflammation and multi-organ failure with high mortality [20].

Understanding the hypercytokinemia and immune dysregulation associated with COVID-19 is urgent. Some have proposed that COVID-19 is actually a hypo-inflammatory vasculopathy rather than a cytokine storm. This hypothesis is based on one study reporting relatively low interleukin-6 (IL-6) levels (mean 25 pg/mL, normal range < 7) measured on admission to hospital in one Chinese study [23]. However, cytokine storm is generally thought to develop later in the course of this disease, and emerging data from our center and others indicates that patients with COVID-CSS have a degree of hypercytokinemia (i.e. IL-6 levels 100 to 5000 pg/mL) comparable to conditions such as CAR-T cell CRS. The overlap in clinical and biochemical features between COVID-CSS and cytokine storm syndromes associated with other conditions may allow for insight into the underlying pathologic immune dysregulation in COVID-CSS and inform strategies for therapeutic intervention. In this review, we summarize the clinical features, pathologic mechanisms, standard and investigational therapies for CSS in three well-defined hematological cytokine storm syndromes: secondary hemophagocytic lymphohistiocytosis (sHLH), idiopathic multicentic Castleman disease (iMCD), CAR-T cell CRS, in order to compare and contrast them with COVID-CSS.

2. Clinical features and diagnosis

2.1. Secondary HLH

HLH is a hyperinflammatory syndrome of fever, cytopenias, and multi-organ dysfunction caused by uncontrolled immune activation and excessive cytokine production [24]. Primary HLH is typically a pediatric condition driven by germline mutations impairing granule-mediated cytotoxicity in natural killer and cytotoxic T cells [25]. The secondary HLH syndromes observed in adults are most often driven by infection (commonly viral such as Epstein-Barr virus [EBV], Cytomegalovirus [CMV], or Human Immunodeficiency Virus [HIV]); malignancy (lymphomas), primary rheumatologic conditions (termed Macrophage Activation Syndrome-HLH subtype, MAS-HLH), or medications (immune checkpoint inhibitors, lamotrigine) [24]. The HLH-2004 diagnostic criteria (Table 1) developed for the pediatric population are recommended to guide diagnosis in adults, and include soluble interleukin-2 receptor, a marker of T cell activation, as a cytokine-related diagnostic criterion [24,26,27]. The HLH-2004 criteria may be restrictive in identifying all patients that may benefit from immunomodulation. The HScore was developed specifically for secondary, and especially malignancy associated, HLH in adults, but unfortunately does not include any cytokine-related criteria [28]. Initially named for the hemophagocytosis seen on tissue biopsy; hemophagocytosis in bone marrow aspirate is a common but non-specific feature in adults [29,30]. Clinical and laboratory features include fevers (often described as “hectic” in that they may exceed 40 °C), organomegaly, cytopenias, coagulopathy, and profound hyperferritinemia often >10,000 μg/L; which often rapidly worsen despite initial empiric anti-microbial therapy resulting in eventual multisystem organ failure [24,31]. Mortality remains high in adults, around 70% despite therapy; though patients with MAS-HLH driven by rheumatologic diseases have better prognosis with less aggressive immunosuppression than other secondary HLH syndromes [24,29].

2.2. Idiopathic MCD

Castleman disease (CD) describes a group of syndromes with shared clinical hyperinflammation and histopathological features [32]. Diagnosis requires lymph node biopsy with characteristic histopathology, as defined by consensus guidelines, residing on a spectrum of histologic patterns from regressed germinal centers and prominent vascularization to hyperplastic germinal centers with prominent plasmacytosis [32,33]. Idiopathic MCD is characterized by dysregulation of IL-6 mediated inflammation. Typically occurring in the 5th and 6th decade of life, patients present with lymphadenopathy in more than one lymph node station, constitutional symptoms, fluid accumulation, and cytopenias [32,33]. Liver or kidney dysfunction as well as the presence of secondary autoimmune phenomenon are also common [32,34]. The profound inflammation of the disease is reflected by a frequently observed polyclonal hypergammaglobulinemia in the iMCD-not otherwise specified

Table 1
Comparison of clinical characteristics.

HLH [24,29,31,114]	Post CAR-T cell therapy [36,38,40–42]		iMCD [33,34,115]	COVID-CSS [116]
	CRS	ICANS		
Fever	Fever	Headache	Fever	Fever
Hepatosplenomegaly	Malaise	Encephalopathy	Weight loss	Hypotension
Hepatobiliary dysfunction	Anorexia	Dysphasia/aphasia	Night sweats	Hypoxia
Coagulopathy	Myalgias	Delirium	Lymphadenopathy	ARDS
Neurologic symptoms	Tachycardia	Tremor	Hepatosplenomegaly	Cardiomyopathy
Headache	Widened pulse pressure	Seizures	Anasarca	Multi-organ dysfunction
Cognitive changes	Hypotension		Pleural effusion	Thrombosis
Focal neurologic deficits	Hypoxia		Ascites	
Seizure	Capillary leak syndrome		Peripheral Edema	
Associated conditions and triggers	Renal impairment		Renal impairment	
Infection [commonly EBV, CMV]	Hepatic failure		Peripheral neuropathy	
Malignancy [commonly lymphoma]	DIC		Cherry angiomata	
Rheumatologic disease			Violaceous papules	
Immunodeficiency				
Medications [such as checkpoint inhibitors and lamotrigine]				

HLH – Hemophagocytic lymphohistiocytosis; CAR-T cell – chimeric antigen receptor T cell; CRS – cytokine release syndrome; ICANS - Immune effector cell-associated neurotoxicity syndrome; iMCD – idiopathic multicentric Castleman disease; COVID-CSS – coronavirus disease of 2019 associated cytokine storm syndrome; EBV – Epstein-Barr virus; CMV – cytomegalovirus; ARDS – acute respiratory distress syndrome.

(iMCD-NOS) subgroup [35]. A subset of patients demonstrate a more aggressive clinical course with thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, and organomegaly (TAFRO) and do not exhibit the same hypergammaglobulinemia seen with iMCD-NOS [32,35].

2.3. CAR-T cell therapy CRS

The engineering of CAR T-cells to bind tumour-specific epitopes and elicit cell-mediated death of malignant cells has been a major leap forward in cancer therapy. First implemented in relapsed and refractory B-cell lymphoid malignancies, CD19 CAR-T cell therapy has demonstrated response rates of 50–90% in CD19+ B-cell acute lymphoblastic leukemia and non-Hodgkin lymphoma [36]. The activation of CAR-T cells after an encounter with target cells leads to release of granzyme and perforin, proliferation of the CAR-T cell population, and a supraphysiologic increase in cytokines such as IL-6 and interferon-γ. This cytokine release syndrome (CRS) may occur in up to 70% of patients depending on conditioning therapy and cell construct, with ICU admission rates up to 13% [36–38]. CRS is grade 1–2 in the majority of patients but may be severe in 12–47% of patients [37]. CRS typically presents within the first 6 days following CAR-T cell infusion with fever as the defining feature followed by hypotension, tachycardia, hypoalbuminemia with capillary leak and weight gain, and consumptive coagulopathy [36,38]. Immune effector cell associated neurotoxicity syndrome (ICANS) with a varied symptom profile (Table 1) may also be observed with later onset: during an episode of CRS or shortly after its resolution [36,38–40]. ICANS can also occur in patients who did not develop CRS and this observation in addition to the separate timeline of development has resulted in the separation of ICANS from CRS in the consensus grading system as a distinct toxicity [39,41,42]. CRS may be observed after other tumour-directed immune therapies, including the bi-specific T-cell engager drug, blinatumumab [37].

2.4. COVID-CSS

For most people who contract COVID-19, the clinical course is mild (and often asymptomatic) with the majority of those able to be recover from the disease at home. Individuals who require hospitalization most commonly present with fever, cough, fatigue, and dyspnea [7–9,43]. Routine laboratory investigations on admission demonstrate lymphopenia, elevated D-Dimer, and elevated CRP. Chest imaging demonstrates bilateral patchy shadows or ground glass opacities [7–9,43]. Twelve to 31% of patients admitted to hospital will eventually develop severe hypoxemic respiratory failure and require critical care support [5,6,9,43]. Severe COVID-19 disease, as per WHO-China working group definition, includes the following: respiratory frequency $\geq$ 30/min, blood oxygen saturation $\leq$ 93%, PaO2/FiO2 ratio $<$ 300, and/or lung infiltrates >50% of the lung field within 24–48 h [44]. Critical disease is defined as severe COVID-19 with any of the following: respiratory failure, septic shock, and/or multiple organ dysfunction/failure [44]. While multi-organ failure is frequently reported in this population, marked organomegaly has not been reported. One of the emerging facets of severe COVID-19 is the association with a hypercoagulable state. D-dimer elevation was recognized early on in the pandemic to be an important prognostic marker for predicting severe disease and mortality [43]. Klok et al. have reported a 31% incidence of thrombotic complications in COVID patients admitted to the ICU including demonstration of venous thromboembolism (VTE) in 27% of patients [45]. Increased thrombotic risk is seen with many inflammatory states and reflects overlap in the regulation inflammation and thrombosis [46]. The profound activation of thrombotic pathways may be a unique feature to COVID-19 compared to other CSS, but remains to be confirmed in further studies.

In the pediatric population affected with COVID-19 there have been emerging reports of a hyperinflammatory shock syndrome, sharing features with an atypical Kawasaki disease. Initial symptoms of fever, conjunctivitis, rash, and gastrointestinal symptoms progress to shock requiring vasopressor support, fluid accumulation, and cardiac injury [47]. The delayed-onset and profound rise in inflammatory markers suggest a secondary pathologic immune response that may share features with adult COVID-CSS but further study is needed to confirm these observations.

There is no consensus definition of COVID-CSS, and it is prudent to recognize that not all patients with severe or critical COVID-19 infection develop dysregulated immune response and toxic cytokine secretion [11]. The working definition of COVID-CSS at our institution used for consideration of adjunct immunomodulatory therapy is: critical COVID-19 with evidence of derangement of multiple inflammatory markers including ferritin >1000 μg/L and CRP > 100 mg/L although we are presently analyzing other clinical and laboratory parameters and immune biomarkers such as IL-1 and IL-6 to produce a more nuanced definition.

3. Pathophysiology

The recent consensus recommendations for the management of adult HLH state that: “Primary and secondary HLH, including MAS-HLH, are hyperferritinemic hyperinflammatory syndromes with a common terminal pathway but with different pathogenetic roots” [24]. This concept of a common terminal pathway resulting from diverse pathophysiological mechanisms can reasonably be extended to other cytokine storm syndromes including COVID-CSS. Marked elevation in inflammatory cytokines such as IL-1 and IL-6, and chemokines associated with a Th1 response, such as IP-10 and MCP-3, were reported in a subset of COVID patients, affirming the notion of a cytokine storm in this disease [48]. The marked elevation in IL-6 bears some resemblance to hyper-IL-6 syndromes such as CAR-T cell CRS and Castleman disease, and the hyperferritinemia and coagulopathy parallels sHLH [49]. Similarities and differences between the pathophysiology of COVID-CSS and these hematological cytokine storm syndromes are outlined below.

3.1. Secondary HLH

As the adult secondary HLH disorders result from many different etiologies and triggers, an in-depth understanding of pathophysiology is lacking. Inferring from studies of the genetic defects in primary HLH patients, the HLH syndrome results from the dysregulation and unrestrained activation of macrophages, cytotoxic T-cells and NK cells leading to the observed end-organ damage [24,25,31,50]. The inability to resolve certain infections and subsequent uncontrolled immune activation may explain the amplified inflammatory response in sHLH from viral, bacterial, and fungal infections. Aberrant, autonomous cytokine production from malignant cells of the immune system may develop into the HLH observed in lymphomas [24,25,31]. Secondary HLH can complicate auto-inflammatory conditions (SLE, Stills disease, etc) with the inappropriate response to self-antigen driving continuous activation of T-cells and macrophages [24,51]. The observed responses to IFN-γ antibody therapy suggests this may be a key factor perpetuating the pathologic feedback loop of inflammation; but murine models of primary HLH have implicated both IFN- γ dependant and independent pathways [52–54].

3.2. Idiopathic MCD

The pathogenesis of iMCD is less well understood than when the syndrome is driven by human herpesvirus 8 (HHV-8) or POEMS. Increased IL-6 is seen in the majority of patients and the response to IL-6 targeted therapy has implicated dysregulation of this pathway as the main driver of disease [32]. Elevated Vascular endothelial growth factor (VEGF) levels and dysregulated mammalian target of rapamycin (mTOR) signaling are also observed in some patients [32,55]. The cause of the elevated IL-6 levels and inappropriate inflammatory activation is

not known. Associations of iMCD and autoimmune and malignant conditions may point to shared pathophysiology, while as-yet-undiscovered infectious triggers have also been hypothesized.

3.3. CAR-T cell therapy CRS

The development and severity of CRS correlates with CAR-T cell expansion, but preclinical mouse studies have also shown monocyte and macrophage production of IL-1 and IL-6 to be the major drivers of the inflammatory response [38,56–58]. Subsequent endothelial activation results in microvascular permeability and the clinical features of capillary leak, hypotension, and reduced serum albumin levels [38]. Autopsy evidence also suggests activated endothelial cells produce additional IL-6 reinforcing the pathologic inflammatory feedback loop [59]. Eventual blood-brain barrier disruption as a result of increased IL-6 levels and endothelial activation is thought to contribute to severe ICANS [37].

3.4. COVID-CSS

Our understanding of COVID-CSS is rapidly evolving, with early clinical, biochemical, and autopsy observations supplemented by more thorough preclinical studies of the closely related SARS-CoV, responsible for the 2003 SARS outbreak. Mouse models of SARS-CoV suggest that delayed type I interferon signaling promotes accumulation of pathogenic inflammatory macrophages leading to hypercytokinemia, vascular leakage, and impaired T cell responses [60]. Deleting the IFN-gamma receptor or depleting macrophages protected mice from lethal infection without affecting viral load, supporting that the inflammatory response may contribute more to severe disease pathology than direct viral effects [60]. In a subset of patients with COVID-19, disease severity seems to correlate with inflammatory markers commonly implicated in other cytokine storm disorders including IL-2R, IL-6, IL-10, and TNF cytokines [7,8,10]. In patients with COVID-CSS, development of sepsis, need for intubation, and ARDS, are accompanied by worsening inflammatory markers and are observed between 7 and 14 days after illness onset consistent with clinical deterioration due to inflammatory sequelae [43]. An autopsy series from 6 patients who died from COVID-19 demonstrated IL-6 production by virus-infected macrophages present in lymph nodes and spleen tissue, suggesting that viral-infection leading to macrophage production of IL-6 was the initial trigger for inflammatory dysregulation [61].

4. Treatment of cytokine storm syndromes

Established and investigational therapies for sHLH, iMCD, CAR-T CRS are summarized by condition in Tables 2-4. Potential therapies and ongoing clinical trials for COVID-CSS are summarized in Table 5.

4.1. Corticosteroids (with or without chemotherapy)

Corticosteroids have been the cornerstone in managing hyperinflammatory disorders due to their broad effects leading to reduced inflammatory mediators and immune cell activity. Used alone or in combination with cytotoxic therapies, responses are frequent but often short-lived and associated with significant long-term toxicity. The HLH-94 protocol combines upfront dexamethasone with etoposide for its specific reduction of T cell activity and cytokine production [62,63]. Cyclosporine may be introduced after 8 weeks, or after 1 week as per the HLH-2004 protocol, though it is often poorly tolerated in adult patients [24,26]. Despite the demonstrated efficacy in pediatric HLH syndromes, adults treated with the HLH-94 protocol and its variations demonstrate poor long-term survival around 30% [24]. Relapses in secondary HLH occur frequently either despite standard therapy or as therapy intensity is tapered; mortality related to infectious or other complications of prolonged immunosuppression is also common.

In iMCD, corticosteroids are frequently used as adjunct therapy for disease flares, though only half of patients will demonstrate improvement with corticosteroids [32]. As high dose corticosteroid therapy is poorly tolerated in the long term, a number of lymphoma-like chemotherapy options have be used to treat patients with iMCD [32]. Steroid-

Table 2
Summary of therapies for secondary hemophagocytic lymphohistiocytosis.

Medication	Mechanism of action	Approved indications	Dose regimen	Notable toxicities	Evidence
Etoposide [26,62]	Inhibits DNA synthesis by inhibiting topoisomerase II	1. Refractory testicular tumors 2. Small cell lung cancer	150 mg/m^2 twice weekly for 2 weeks, then 150 mg/m^2 once weekly for 6 weeks	Myelosuppression Hypersensitivity reactions Secondary malignancies	Prospective trial ($N = 249$) using HLH-94 protocol found a 5 year probability of survival of 54% ± 6%
Dexamethasone [26,62]	Inhibits inflammatory cells and suppresses expression of inflammatory mediators	1. Multiple allergic, hematologic dermatologic, neoplastic, rheumatic, autoimmune, nervous system, renal, and respiratory conditions. 2. Adrenal insufficiency 3. Cerebral edema	10 mg/m^2 for 2 weeks, then 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for one week, and one week of tapering	Immunosuppression Metabolic changes Hypertension Mood alteration	Prospective trial ($N = 369$) using HLH-2004 protocol found a 5 year probability of survival of 61% (95% CI, 56% - 67%)
Cyclosporine[a] [26,62]	Inhibits calcineurin mediated lymphocyte activation	1. Solid organ transplant rejection prophylaxis 2. Rheumatoid arthritis 3. Psoriasis	3 mg/kg BID daily, adjusted for target serum trough level of 200 μg/L	Hypertension Renal failure Drug-drug interactions	
Emapalumab [69]	Monoclonal antibody directed against IFN-γ	1. Primary HLH; refractory, recurrent or progressive disease or intolerance to conventional HLH therapy	1 mg/kg every 3 to 4 days; for 8 weeks; can be increased up to 10 mg/kg	Immunosuppression Infusion reactions	Overall response rate of 64.7% (95% CI, 46% -80%; $P = .0031$) and 12-month survival of 69% (95% CI, 50% - 82%) in Phase I/II trial ($N = 34$)
Ruxolitinib [99–102]	Inhibits the JAK/STAT pathway decreasing cytokine signaling and inflammation	1. Myelofibrosis 2. Polycythemia vera 3. Acute graft versus host disease	5 to 20 mg BID	Myelosuppression Immunosuppression	Two-month overall survival of 100% (95% CI, 57% - 100%) in pilot study 5 adult patients with secondary HLH
Anakinra [91–93,117]	Il-1 receptor antagonist	1. Rheumatoid arthritis	SubQ: 100 mg once daily	Immunosuppression Injection site reaction Leukopenia Eosinophilia	Case reports/series [91,93,117] Cohort of pediatric MAS [92]

[a] Cyclosporine initiated at Week 9 in HLH-94 protocol and at Week 1 in HLH-2004 protocol.

Table 3
Summary of therapies for CAR-T cell cytokine release syndrome.

Medication	Mechanism of action	Approved indications	Dose regimen	Notable toxicities	Evidence
Corticosteroids [36,37,98]	Inhibits inflammatory cells and suppresses expression of inflammatory mediators	1. Multiple allergic, hematologic dermatologic, neoplastic, rheumatic, autoimmune, nervous system, renal, and respiratory conditions.	Grade 3 CRS: Methylprednisolone 1 mg/kg BID or dexamethasone 10 mg every 6 h Grade 4 CRS: methylprednisolone 1 g/day × 3 days, followed by a rapid taper Alternative: methlyprednisolone 2 mg/kg x 1 dose then 2 mg/kg/day divided 4 times a day[3]	Immunosuppression Metabolic changes Hypertension Mood alteration	Consensus over dose and regimen is debated Considered second line therapy after tocilizumab given potential effect on persistence and efficacy of CAR-T cells
Tocilizumab [22][36][37]	Monoclonal antibody against IL-6 receptor	1. Rheumatoid arthritis 2. Giant cell arteritis 3. Polyarticular juvenile idiopathic arthritis 4. Systemic juvenile idiopathic arthritis 5. Severe or life-threatening CAR-T induced cytokine release syndrome	Grade 2–4 CRS: 8 mg/kg x 1 dose Repeat 8 mg/kg dose within 3–5 days if lack of improvement	Immunosuppression Hepatoxicity Bowel perforation Demyelinating disorders	69% (95% CI, 53% - 82%) of patients responded to 1–2 doses within 14 days, with median time to response of 4 days in retrospective analysis of CTL019 and KTE-C19 on prospective clinical trials

Table 4
Summary of therapies for idiopathic Multicentric Castleman Disease.

Medication	Mechanism of action	Approved indications	Dose regimen	Notable toxicities	Evidence
Siltuximab[a]	Monoclonal antibody against IL-6	1. HHV-8 negative/idiopathic multicentric Castleman disease	11 mg/kg every 3 weeks	Infusion reactions Hyperkalemia Hyeruricemia URTI Edema Weight gain Rash Bowel perforation	Randomized, placebo controlled trial ($N = 79$) found durable tumour and symptomatic response with siltuximab compared to placebo (34% vs 0%; $p = .0012$) [71] Extension study of ongoing responders ($N = 19$) found 100% sustained disease control at 61 months
Tocilizumab[a]	Monoclonal antibody against IL-6 receptor	1. Rheumatoid arthritis 2. Giant cell arteritis 3. Polyarticular juvenile idiopathic arthritis 4. Systemic juvenile idiopathic arthritis 5. Severe or life-threatening CAR-T induced cytokine release syndrome	8 mg/kg every 2 weeks	Immunosuppression Hepatoxicity Bowel perforation Demyelinating disorders	Multicenter, open-label, single-arm trial ($N = 28$) found sustained improvement in symptoms and biochemical abnormalities associated with MCD over 1 year [72]
Rituximab[b] [32]	Monoclonal antibody against CD20 antigen on B-lymphocytes	1. Non-Hodgkin's Lymphoma 2. Chronic Lymphocytic Leukemia 3. Rheumatoid arthritis 4. Granulomatosis with polyangiitis 5. Microscopic polyangiitis	375 mg/m^2 weekly for 4 weeks	Infusion reactions Neutropenia Hepatitis B reactivation PML	Better evidence for use in HHV8 positive MCD. In 25 cases of iMCD, CR and PR rates with rituximab as first-line therapy were 20% and 48%, respectively, with a lower PFS compared to siltuximab [118]
Sirolimus	mTOR inhibitor	1. Post-transplant rejection prophylaxis 2. Lymphangioleiomyomatosis.	7.5 mg/m^2 loading dose 2.5 mg/m^2/day maintenance	Immunosuppression Edema Hypertension Cytopenias dyslipidemia	Case reports [32,103] Clinical trial in TAFRO subtype ongoing (NCT03933904)

UTRI – upper respiratory tract infection, PML – progressive multifocal leukoencephalopathy, HHV-8 – human herpesvirus-8, CR – complete response, PR – partial response, PFS – progression free survival.
[a] May be used in conjunction with corticosteroids.
[b] May be used in monotherapy or in conjunction with chemotherapy/corticosteroids.

containing immunomodulatory regimens with thalidomide, cyclophosphamide and prednisone has also shown promising efficacy and safety [64].

The use of corticosteroids in the management of CRS following CAR-T cells is limited by the concern of unwanted cytotoxic effects on the CAR-T product reducing overall efficacy. However, given its effectiveness for rapidly reducing the systemic inflammatory burden in this population, corticosteroids are still used second-line after directed anti-cytokine therapy [36,37]. Steroids are particularly useful as first line therapy in the treatment of ICANS, with CNS penetrating steroids such as dexamethasone preferred.

Corticosteroids were used frequently in the management of COVID-19 in the early days of the pandemic in China, with reported use in 30–79% of patients [4,7–9,43,65]. The indication for therapy is not widely reported and may be due to comorbid conditions (COPD, asthma) or as adjunct therapy for sepsis. Analysis has suggested improved outcomes in patients with ARDS treated with steroids though this has not been conclusive and ideal timing and patient selection are not known [9,43,66]. Animal models and some human data of the closely related SARS-CoV infection have demonstrated early corticosteroid use may reduce initial inflammatory response, but raise the concern of increased viral replication and shedding that could worsen clinical outcomes and increase viral transmission [67,68].

Table 5
Potential therapies for COVID cytokine storm syndrome.

Intervention	Published data in COVID-19 as of April 20, 2020	NIH treatment guidelines	Select registered trials
Corticosteroids	Case series and retrospective cohort studies found possible improved outcomes in ARDS [9,43]; but there remains concern for prolonged viral shedding [67]	*For Critically Ill Patients with COVID-19:* • The Panel recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) (AIII). • For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of systemic corticosteroids (CI). • For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids (BII).	NCT04345445, NCT04329650, NCT04344288, NCT04273321, NCT04327401, NCT04344730, NCT04325061, NCT04343729
IL-6 Blockade Tocilizumab Sarilumab Siltuximab	Case reports and case series report improvement in fever and inflammatory markers with possible improvement in cytokine storm and ARDS through inhibition of IL-6 [74–80,86,119,120]	There are insufficient clinical data to recommend either for or against the use of the following agents for the treatment of COVID-19 (AIII): • Interleukin-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab) • Interleukin-1 inhibitors (e.g., anakinra)	NCT04317092, NCT04345445, NCT04331795, NCT04332094, NCT04346355, NCT04335071, NCT04320615, NCT04339712, NCT04332913, NCT04333914, NCT04330638, NCT04322773, NCT04331808, NCT04321993, NCT04345289, NCT04324073, NCT04315298, NCT04341870, NCT04329650, NCT04322188, NCT04306705, NCT04327388
IL-1 Inhibition Anakinra	A retrospective cohort study of 29 patients with COVID-19 and moderate-to-severe ARDS, and hyperinflammation with clinical improvement in 72% of patients; improved survival compared to historical controls [94]	As above	NCT04330638, NCT04324021, NCT04339712, NCT04341584
TNF Inhibition	None published Proposed that anti-TNF inhibition may reduce lung inflammation, reducing TNF-α and other inflammatory mediators in COVID-19 [121]	No recommendation	NCT04370236
IFN-γ Inhibition Emapalumab	None published	No recommendation	NCT04324021
JAK Inhibition Baricitinib Ruxolitinib Tofacitinib	Pilot study of 12 patients has demonstrated improvement in fever, dyspnea, and hypoxia with an lower rate of ICU admission than historical control [106] Proposed to be effective against consequences of elevated cytokines observed in COVID-19 by inhibiting the JAK/STAT pathway and reducing downstream cytokine signaling [122] Baricitinib may inhibit viral entry into cells through blockade of AP2-associated protein kinase 1 (AAK1) [104]	The Panel recommends against the use of Janus kinase (JAK) inhibitors (e.g., baricitinib) for the treatment of COVID-19, except in the context of a clinical trial (AIII).	NCT04340232, NCT04346147, NCT04320277, NCT04321993, NCT04345289, NCT04334044, NCT04348071, NCT04338958, NCT04337359, NCT04331665, NCT04332042
Complement inhibition	Inhibition of complement activity to reduce inflammation and subsequent tissue injury.	No recommendation	NCT04382755
LMWH	Improves the coagulation dysfunction and exerts anti-inflammatory effects by reducing IL-6 and increasing lymphocyte percentage a retrospective cohort study [90]	No recommendation	NCT04344756, NCT04345848
IVIG	Case reports of clinical improvement when administered at the time of respiratory deterioration [123]	No recommendation	NCT04261426

NIH – National Institutes of Health (https://www.covid19treatmentguidelines.nih.gov/MAS - accessed May 11, 2020), MAS – macrophage activation syndrome, LMWH - low molecular weight heparin, IVIG – intravenous immune globulin.

4.2. Cytokine targeted therapy

4.2.1. Interferon- γ

Improved mechanistic understanding of hyperinflammatory syndromes has led to therapies targeting specific cytokines implicated in disease pathogenesis. Emapalumab is a monoclonal antibody targeting interferon-γ that has demonstrated efficacy with overall response rates over 60% in a study of pediatric HLH [69]. Based on this trial the US Food and Drug Administration (FDA) approved emapalumab for use in refractory, recurrent, or progressive primary HLH in both children and adults [22]. Though there is a concern of secondary infections, particularly from organisms responsive to IFN-gamma driven immune reactions, the medication has been well tolerated in the majority of patients including those with infectious complications prior to therapy [54,69,70]. Data are limited in the use of emapalumab for secondary HLH in adults.

4.2.2. IL-6

In iMCD the disease process is thought to be dependent on elevated IL-6 levels perpetuating the hyperinflammatory state in most patients; therefore, use of IL-6 targeted therapy is now the front-line management for patients with iMCD with or without adjunctive steroids. Siltuximab, a monoclonal antibody directed against IL-6, in a placebo controlled trial has shown reduction in tumour burden and symptomatic response in a third (34%) of patients with responders having sustained disease control up to 6 years of follow-up [71]. Tocilizumab, a monoclonal antibody directed against the IL-6 receptor, has demonstrated similar improvement in symptoms and biochemical markers of disease activity in a single arm study [72]. Anti-IL-6 therapy is well tolerated for many years in patients with disease response, though relapses may be common following cessation of therapy [32,72].

The early observation of a substantial increase in IL-6 during CRS prompted the introduction of anti-IL-6 agents for management of those receiving CAR-T therapy, with good effect [73]. Tocilizumab is now FDA approved for use in CRS with response rates of 70% following 1–2 doses with a median time to response of 4 days [22,37]. Doses can be repeated every 6 to 24 h until CRS symptoms begin to improve. As tocilizumab is only used in short courses for a limited period, there is less concern of serious adverse events that may be seen in patients taking the drug long-term for rheumatologic indications. Tocilizumab administration has been demonstrated to not affect CAR-T cell efficacy, and is thus the preferred first line agent over corticosteroids. Tocilizumab appears to be not as effective for ICANS, likely because it does not cross the blood-brain barrier and targets the IL-6 receptor with no direct IL-6 lowering effect, leading to elevated systemic IL-6 levels after therapy without CNS protection [38,40,72]. Direct targeting of IL-6 by siltuximab may have better CNS response, though this has not been studied in clinical trials.

As IL-6 levels correlate with disease severity in hospitalized COVID-19 patients, anti-IL-6 therapy has been one of the first treatment strategies explored during the pandemic [7–10]. There have been several published case reports, as a well as two larger case series from China, using tocilizumab as a treatment for severe COVID-19 demonstrating biochemical efficacy with decrease markers of inflammation, but the impact of clinical outcomes such as time in intensive care and mortality compared to supportive care, remains unknown [74–79]. A recent large series of 100 consecutive patients with severe COVID-19 demonstrated clinical stability or improvement in 77% of patients following administration of tocilizumab [80]. A press release for CORIMUNO-TOCI (NCT04331808), a multi-centre, open-label randomized controlled trial of tocilizumab in moderate and severe COVID19 has suggested positive results and with the study currently under peer-review [81]. Optimal timing of tocilizumab initiation is unknown, but there is sound rationale that earlier treatment in patients demonstrating a pathologic inflammatory response may ameliorate immune-mediated lung injury. Repeated doses of tocilizumab, similar in strategy to its use in CAR-T cell related CRS, may be reasonable for patients with refractory COVID-CSS. Serious risks of tocilizumab in the short term include a small risk of bowel perforation, acute hepatic failure, and osteonecrosis of the jaw [82,83]. Case reports of hypertriglyceridemia and candidemia following tocilizumab infusion for COVID-19 have been reported [84,85]. There is a concern that the use of tocilizumab in COVID-19 could increase the risk of secondary infections and delay viral clearance, as was postulated in the report of 2 cases of viral myocarditis following tociluzumab for COVID-19 [86]. These safety concerns should be thoroughly evaluated in future studies. Clinical trials of tocilizumab, siltuximab, and sarilumab (an IL-6 receptor blocker) are currently being conducted in patients with moderate and severe COVID-19 though trials specifically evaluating these agents in the COVID-CSS population are not yet planned.

In addition to their well-known anticoagulant properties, heparins are known to have anti-inflammatory effects with lowering of IL-6 levels specifically described [87–89]. In patients with COVID-19, a retrospective study has observed reduction of IL-6 levels in patients treated with low-molecular weight heparin (LMWH) [90]. Given the maturing evidence of increased thrombotic risk in COVID-19, LMWH may be a good adjunct therapy for COVID-CSS to reduce both IL-6 driven inflammation and thrombotic risk. Optimal dosing strategies in patients without proven thromboembolic disease is not currently known but is being investigated in upcoming clinical trials (NCT04359277).

4.2.3. IL-1

IL-1-receptor blockade with anakinra has been used in case series and retrospective studies for HLH, with a clinical trial currently ongoing [91–93]. Anakinra has been hypothesized to have utility for CAR-T CRS and neurotoxicity based on the observation that IL-1 elevations precede IL-6 spike in murine CRS models and treatment with anakinra therapy resulted in reduction of both cytokines [56,58]. Anakinra has the added benefit of having a very short half-life compared to other anti-cytokine therapies. A retrospective cohort study of 29 patients with COVID-19 and moderate-to-severe ARDS, and hyperinflammation (CRP $\geq$100 mg/L, and/or ferritin $\geq$900 ng/mL) treated with high dose anakinra demonstrated clinical improvement in 72% of patients, and improved survival compared to historical controls [94].

4.2.4. TNF

TNF inhibiting agents are available for the management of other inflammatory conditions, though at the time of this review no reports of TNF inhibition have been reported for COVID-19. The use of TNF inhibitors has some potential concern these drugs have also been thought to trigger sHLH in some case reports [95–97]. Clinical trials for TNF inhibition in COVID-19 are planned.

4.3. Signaling pathway inhibition

To implement cellular responses to cytokines, cell surface receptors must connect these external environmental signals to the nucleus to guide gene expression, cell proliferation, and activity. This “bottle-neck” of inflammatory communication through shared internal signaling molecular pathways has facilitated the creation of targeted therapies that inhibit multiple cytokine pathways simultaneously. Many cytokine and growth receptors signal through the Janus Kinase (JAK) signal transducer of activators of transcription (STAT) pathway; this has spurred the development of small molecular JAK inhibitors for the treatment of inflammatory and neoplastic conditions [98]. These agents may be advantageous for disease states in which broader inhibition of cytokine signaling is required to control inflammation compared to the targeted blockade of single cytokines.

Ruxolitinib, a JAK1/2 inhibitor already approved for the therapy of myeloproliferative neoplasm and rheumatologic disorders, has activity in murine HLH models by reducing inflammation through IFN-γ dependant and independent pathways. This results in reduced activity and tissue infiltration of T-cells and neutrophils [52,53]. Case series in

relapsed/refractory HLH, as well as a single case of upfront therapy for moderate severity HLH, have described biochemical and clinical efficacy in treatment of HLH with ruxolitinib monotherapy [99–101]. Early phase clinical trials are ongoing, but preliminary results have demonstrated biochemical, hematologic, and clinical recovery in the few patients enrolled thus far [102]. Importantly, the treatment is tolerated well with few adverse events reported, especially in contrast to standard regimens of prolonged chemotherapy combined with high dose steroids.

Patients with the TAFRO subtype of iMCD will typically have a more aggressive course and most have no substantial response to IL-6 blockade. Analysis of molecular signaling pathways active in iMCD patients refractory to anti-IL-6 agents has implicated downstream activation of the PI3K/Akt/mTOR pathway, common to signaling of the T cell receptor and VEGF pathways [103]. Use of the mTOR inhibitor sirolimus has met with early success in limited numbers of patients and a clinical trial in IL-6 blockade refractory TAFRO patients is underway [32,55,103]. Pre-clinical studies of cells obtained from patients with iMCD have also indicated that JAK inhibitors may be able to interrupt IL-6 driven mTOR pathway activation [55].

Currently there are limited reports of the use of JAK-STAT or other cell signaling pathway inhibitors in the management of COVID-CSS. The use of JAK inhibitors is attractive as the medications are well tolerated, have short half-lives, and have the potential to target numerous inflammatory cytokine signaling pathways simultaneously. While ruxolitinib has been the agent most studied in HLH other JAK inhibitors may have potential advantages. Baricitinib, an oral JAK1/2 inhibitor that is currently approved for treatment of rheumatoid arthritis, was recently identified by artificial intelligence-based technology as a potential immunomodulatory treatment strategy for SARS-CoV-2 [104]. At therapeutic doses baricitinib is predicted to inhibit clathrin-mediated endocytosis and viral entry into cells by blocking the AP2-associated protein kinase 1 (AAK1) [104]. AAK1 regulates endocytosis in numerous cell types expressing ACE2, the receptor that mediates SARS-CoV-2 viral entry, including lung AT2 alveolar epithelial cells [104]. Because any agent that dampens the inflammatory response could lead to a potential loss of immune-mediated viral control, the hypothesized anti-viral effect makes baricitinib an attractive investigational therapy over agents that target disordered inflammation alone. Of concern with baracitinib is the increased risk of thrombosis which may increase the rate of thrombotic complications already observed with COVID-19 [105]. Clinical experience with COVID-19 is limited, but a pilot study of 12 patients has demonstrated improvement in fever, dyspnea, and hypoxia with a lower rate of ICU admission than a historical control cohort [106].

5. Inflammatory biomarkers and cytokines

CSS are disorders driven and recognized by characteristic hypercytokinemia, however availability of objective cytokine profiles is limited. Clinicians are forced to evaluate and base treatment decisions on clinical signs and symptoms of inflammation, and a few widely available markers of overall systemic inflammation. Utility of cytokine levels for diagnosis and monitoring of cytokine storm syndromes are not standardized and currently limited to research settings. Published values for inflammatory markers and cytokines observed in cytokine storm conditions are summarized in Table 6. Importantly, many of these assays are not routinely performed in hospital laboratories, and as such their clinical relevance remains to be determined by future studies that address both analytical and clinical validation of these markers.

5.1. Inflammatory biomarkers

Ferritin, the iron storage protein, and C-reactive protein (CRP) are the acute phase reactants most widely available at hospitals for monitoring systemic inflammation. Hyperferritinemia is the most common feature to prompt further evaluation for secondary HLH, with levels

Table 6
Biomarkers and cytokine levels in cytokine storm syndromes.

Marker Median (range)	HLH [107,112,124,125]	MCD [34,35,71,110,126]	CAR-T CRS [38,57]		Published COVID-19 data				Vancouver COVID-CSS (unpublished data; n = 19)[a]
			Grade 1–3	Grade 4–5	[8]		[7]		
					Moderate	Severe	Survivor	Death	
Ferritin μg/L (Normal 30–400)	100% > 500 78.9% > 10,000	>90% of cases <1500 [35]	2300 (280–15,870)	10,660 (366–53,200)	337.4 (286.2–1275.4)	1598.2 (1424.6–2036.0)	481.2 (265.1–871.5)	1418.3 (915.4–2236.2)	~1200–3500
CRP mg/L (Normal <1)	135 (76–205) [124] 56 (4–236) [125]	17.6 (0.10–181.0) [71] Median 112 [35]	162 (7–565)	229 (160–371)	22.0 (14.7–119.4)	139.4 (86.9–165.1)	26.2 (8.7–55.8)	113.0 (69.1–168.4)	~100–300
D Dimer μg/mL (Normal<0.5)			4–7	20–30	0.3 (0.3–0.4)	2.6 (0.6–18.7)	0.6 (0.3–1.3)	4.6 (1.3–21.0)	~0.5–3.5
sIL2r U/mL (Normal 241–846)	100% >2400 44.7% >10,000	Raised in 20/21 cases [34]	8002 (553–109,501) pg/mL	63,022 (15,757–268,469) pg/mL	453.0 (308.5–456.0)	1270.0 (879.0–1425.0)	566.5 (448.0–858.3)	1189.0 (901.0–1781.0)	~400–1500
IL-6 pg/mL (normal <7)	51.1 (3.9–4472.6)	7.13 (0.38–50.6) [71] 24.0 (1.4–171.5) [126] 25.9 (8.6–113) [110]	122 (0.40–20,892)	8309 (580–102,476)	15.3 (6.2–29.5)	41.5 (24.8–114.2)	13.0 (4.0–26.2)	72.0 (35.6–146.8)	~100–5000
IFN-γ pg/mL (normal 6.8–13.6)	1088.5 (49.2–5000)	6.7 (0.2–139.2) [126]	34.1 (2.14–8233)	3119 (160–15,482)					Not measured
TNF pg/mL (Normal <8.1)	3.2 (1.0–27.9)	28.2 (7.9–90.8) [126]	2.58 (0.66–105)	10.3 (1.01–47.0)	7.3 (6.2–8.8)	10.5 (10.0–11.2)	7.9 (6.7–9.6)	11.8 (8.6–17.6)	~10–45

HLH–Hemophagocytic lymphohistocytosis, MCD–Multicentric Castleman Disease, CAR-T–Chimeric antigen receptor T cell, CRS–Cytokine Release Syndrome, CSS–Cytokine Storm Syndrome.
[a] Holland et al., manuscript under review.

>10,000 μg/L observed in 78.9% of adult patients and can frequently be in excess of 100,000 μg/L [27,107]. Patients with CRS also demonstrate elevated ferritin levels with most patients reaching a peak over 3000 and many in excess of 10,000 μg/L [38,57]. Patients experiencing higher grade CRS have greater median peak ferritin and CRP though with significant overlap in the observed ranges [38,57]. Similarly, ferritin and CRP levels in patients with COVID-19 are reportedly higher in patients with severe compared to moderate disease, and in patients who died compared to those that recovered [7,8,10]. In our experience with COVID-CSS patients in the ICU we have observed ferritin levels in the range of 1000–10,000 μg/L with CRP levels typically above 100 mg/L (Hoiland R et al., manuscript under review).

The measurement of D-dimer, a fibrin degradation product, is a widely available test that shows active clot formation and breakdown. Its increase in systemic inflammation reflects the overlap between the physiologic inflammatory and thrombotic pathways. Though not frequently used in the evaluation of the cytokine storm disorders, it has been correlated with severity of CRS following CAR-T [38]. D-dimer levels correlate with disease severity in COVID-19 and admission D-dimer >1 μg/mL has emerged as one of the earliest prognostic marker to identify patients with high mortality [43].

The pattern of inflammatory markers may be more useful than relying on absolute values alone in order to establish a diagnosis. In children with sJIA the ratio of ferritin to erythrocyte sedimentation rate (ESR) was useful for identifying patients with MAS [108]. In one study of Japanese HLH cases a ratio of sIL-2R to ferritin was predictive of those with lymphoma-associated rather than benign disease [109].

5.2. Cytokines

The soluble interleukin-2 receptor (sIL2R) level is integrated into the HLH-2004 diagnostic criteria [26]. In adults with secondary HLH, levels >2400 U/mL demonstrate good sensitivity and specificity for diagnosing adult HLH with an area under the curve of 0.90 (95% confidence interval, 0.83–0.97) [107]. Soluble IL-2R levels have not been widely reported on in iMCD, but one study found elevated levels in 20 of 21 cases [34]. Additionally it was observed that for patients on anti-IL-6 therapy, sIL-2R was one of the earliest markers that predicted disease relapse and failure of therapy [34,110]. In CAR-T CRS it has been observed that sIL2R levels are markedly elevated in patients with severe compared to non-severe disease [57]. Patients with COVID-19 demonstrate higher sIL2R levels in those with severe and fatal disease; though levels have thus far reported to be typically less than 2000 U/mL [7,8,10,111].

IL-6 is a key cytokine common to the pathophysiology of most CSS disorders and has important therapeutic implications. In HLH, data available in pediatric patients demonstrate moderate IL-6 elevation though it has not been useful in distinguishing HLH from sepsis or other inflammatory conditions [112]. Idiopathic MCD is conceptualized as a primarily a disorder of IL-6 elevation, though serum IL-6 levels in iMCD may be normal or only mildly elevated. Response rates to IL-6 blockade do correlate with baseline IL-6 levels in iMCD, but many patients with low IL-6 levels will improve with therapy while patients with high IL-6 levels can show no response [32,71]. IL-6 levels peak with disease flares in iMCD and can be used to monitor disease course, but once IL-6 blockade is initiated serial monitoring is not useful. Tocilizumab and sarilumab block the receptor for IL-6 leading to clinical improvement while serum IL-6 levels will remain stable or increase [72]. Similarly, IL-6 levels cannot be accurately interpreted for 12–18 months following the last dose of siltuximab. CAR-T CRS demonstrates substantial increases in IL-6 that correlates with severity of CRS and may be orders of magnitude greater the levels reported for iMCD, and HLH [38,71,112]. In COVID-19 IL-6 levels have been high for patients with more severe and fatal disease [7,8,10,111]. In our institutions experience with COVID-CSS observed levels of IL-6 have been in the range of ~100–5000 pg/mL (manuscript under review).

Interferon-γ plays a central role in the pathogenesis of HLH, and elevated serum levels can help differentiate HLH from sepsis and other inflammatory disorders in children, but routine use for diagnosis in adults has not been studied [112,113]. Following emapalumab therapy, interferon-γ levels do not correlate with disease response, but downstream targets of interferon such as CXCL9 and CXCL10 appear to have utility in monitoring disease activity and treatment response [54,70].

Use of cytokine measurements in CSS to diagnose and monitor disease activity and response to therapy is an area in need of further refinement. Monitoring response to therapy requires in depth knowledge of drug targets and expected impact on cytokine levels, laboratory testing, and downstream pathway activation. More data, research, and experience are needed in order to develop the clinical acumen in interpretation of patterns and profiles of these diseases.

6. Conclusions and future directions

COVID-CSS has many clinical and pathologic similarities with other cytokine storm disorders. Therapy for classic CSS conditions such as iMCD and secondary HLH has been hampered by low numbers of patients, lack of diagnostic clarity and incompletely understood pathophysiology. Progress has been made with the introduction of targeted therapy aimed at interrupting the positive feedback loops of inflammatory pathways. The story of CRS following CAR-T cell therapy with comparatively rapid determination of pathophysiology and use of existing medications for treatment has been a recent success. Future goals for CSS include improved access to immunophenotyping and expression profiling to inform our understanding of disease mechanisms, and enhancing diagnostic and monitoring capabilities.

Due to the lack of currently available evidence, the NIH guidelines for the management of COVID-19 do not recommend for or against cytokine inhibition with IL-1 and IL-6 blockade and specifically recommend against off-label use of JAK pathway inhibitors outside of clinical trial [12]. Current industry sponsored trials of sarilumab (NCT04327388) and tocilizumab (NCT04320615) in patients with severe-critical COVID-19 are underway. However, they exclude critically ill patients requiring vasopressors and therefore will not address the question of whether these agents will be of benefit in those who are critically unwell with evidence of CSS. Development of consensus definitions for COVID-CSS may lead to identification of patients most likely to benefit most from immune modulating therapy. We should use the lessons learned from hematologic cytokine storm syndromes to help expedite rapid identification, evaluation, and implementation of treatments urgently needed for COVID-19 CSS.

Practice points

- A subset of patients with COVID-19 develop a syndrome characterized by organ dysfunction and marked elevation of inflammatory markers dubbed cytokine storm syndrome (CSS).
- To date, there is no consensus definition of COVID-CSS. Fever, organ dysfunction, hypoalbuminemia, and capillary leak are common to COVID-19 and other cytokine storm syndromes such as sHLH, iMCD and CAR-T cell CRS.
- COVID-19 appears to be a hypercoagulable state leading to microvascular thrombosis, a feature distinct from other hypercytokinemia syndromes
- Therapies targeting specific cytokines or common inflammatory signaling pathways have demonstrated benefit in HLH, iMCD, and CAR-T CRS and are well tolerated in those contexts. Their role in COVID-19 CSS is under active investigation.
- A pragmatic definition of COVID-CSS will likely require a combination of clinical criteria (such as fever, hypotension, critical illness), widely available laboratory parameters (such as CRP, ferritin, D-dimer), as well as novel biomarkers (such as IL-1, IL-6, other cytokines, and immunophenotyping).

Research agenda

- Consensus definitions of CSS in general and COVID- CSS in particular, with particular attention to the relationship with COVID related coagulopathy and vasculopathy
- Rapid, coordinated investigations of potentially beneficial agents targeting inflammatory pathways in COVID-19 CSS with methodologically rigorous clinical trials
- Measurement of biomarkers in CSS including traditional laboratory parameters as well as genetic studies, cytokine profiles and lymphocyte immunophenotyping at presentation and through the course of disease

Declaration of Competing Interest

Kamran Shojania: Involved in investigator-initiated vasculitis study for Bristol-Myers-Squibb.

Shahin Jamal: Attended Roche advisory board for tocilizumab in giant cell arteritis and rheumatoid arthritis.

Kevin A. Hay: Attended Advisory boards and received honoraria for Celgene and Gilead related to CAR-T cell products.

James T. England, Alym Abdulla, Ryan L. Hoiland, Cheryl L. Wellington, Mypinder Sekhon, Agnes Y.Y. Lee, Catherine Biggs, Luke Chen – no conflicts of interest to declare.

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