

Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute COVID-19
in Pediatric Patients

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ABSTRACT

Background: Immune-mediated lung injury and systemic hyperinflammation are characteristic of severe and critical coronavirus disease 2019 (COVID-19) in adults. Although the majority of SARS-CoV-2 infections in pediatric populations result in minimal or mild COVID-19 in the acute phase of infection, a small subset of children develop severe and even critical disease in this phase with concomitant inflammation that may benefit from immunomodulation. Therefore, guidance is needed regarding immunomodulatory therapies in the setting of acute pediatric COVID-19. This document does not provide guidance regarding the recently emergent multisystem inflammatory syndrome in children (MIS-C).

Methods: A multidisciplinary panel of pediatric subspecialty physicians and pharmacists with expertise in infectious diseases, rheumatology, hematology/oncology, and critical care medicine was convened. Guidance statements were developed based on best available evidence and expert opinion.

Results: The panel devised a framework for considering the use of immunomodulatory therapy based on an assessment of clinical disease severity and degree of multi-organ involvement combined with evidence of hyperinflammation. Additionally, the known rationale for consideration of each immunomodulatory approach and the associated risks and benefits was summarized.

Conclusions: Immunomodulatory therapy is not recommended for the majority of pediatric patients, who typically develop mild or moderate COVID-19. For children with severe or critical illness, the use of immunomodulatory agents may be beneficial. The risks and benefits of such therapies are variable and should be evaluated on a case-by-case basis with input from appropriate specialty services. When available, the panel strongly favors immunomodulatory agent use within the context of clinical trials. The framework presented herein offers an approach to decision-making regarding immunomodulatory therapy for severe or critical pediatric COVID-19 and is informed by currently available data, while awaiting results of placebo-controlled randomized clinical trials.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emergent human pathogen that causes a variety of disease manifestations termed Coronavirus Disease 2019 (COVID-19). The spectrum of COVID-19 ranges from asymptomatic infections to severe and critical illness with multi-organ involvement that can prove fatal [1]. In adults, the most common disease presentation involves respiratory disease that either resolves or evolves into progressive pulmonary involvement and acute respiratory distress syndrome (ARDS); in adult patients with progressive disease, extrapulmonary manifestations and evidence of multi-organ involvement is common. While severe and critical COVID-19 is substantially more prevalent in adults, a small proportion of children also develop progressive respiratory disease and concomitant multi-organ dysfunction with high morbidity, but fatalities are rarely reported [2-5]. Comorbid conditions for this presentation of severe and critical COVID-19 in adults include obesity, diabetes, and underlying cardiac disease [6, 7] however, such risk factors are currently not well defined in children [3, 5, 8].

Initial descriptions of COVID-19 presentations and outcomes indicate a substantial inflammatory component to severe disease [9-11]. Inflammatory phenotypes include significant pulmonary inflammation accompanied by prolonged fevers [12] and/or a biphasic illness course characterized by initial improvement followed by rapid occurrence of respiratory failure and pulmonary inflammation [10, 13]. In addition, COVID-19-associated cardiac injury is an independent risk factor for mortality, suggesting that inflammation beyond lung parenchyma contributes to poor outcomes [14, 15]. Further, severe COVID-19 is associated with more significant lymphopenia, systemically elevated pro-inflammatory cytokine levels, and impaired CD4+ T cell IFN- γ expression compared to moderate COVID-19 [11].

These early reports of hyperinflammation are reminiscent of the cytokine storm features described in the setting of prior emergent respiratory virus infections including SARS (2002), Middle East Respiratory Syndrome (MERS), H5N1 avian influenza, and 2009 H1N1 pandemic influenza [16, 17]. In each of these viral infections, significant pulmonary and systemic inflammation was identified and, in some cases, linked to poor outcomes and mortality (SARS [18-21]; avian influenza [22, 23]; 2009 H1N1 [24-26]; MERS [27-29]). Since the initial SARS outbreak in 2002, several developments have changed the paradigm for treatment of hyperinflammation. First, detailed mechanistic knowledge of the genetics and immunopathology of macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) have led to targeted treatments for cytokine storm syndrome (CSS) [30]. In addition, new immunomodulators targeting specific cytokines, cytokine receptors, and immune pathways have been developed and studied in a wide variety of other

inflammatory and autoimmune diseases [31, 32]. Finally, the advent of chimeric antigen receptor (CAR) T cell therapy for leukemia/lymphoma and resultant cytokine release syndrome (CRS) has provided a specific example of cytokine-targeted therapy leading to rapid clinical improvement in the setting of marked and hyperacute inflammation [33].

Symptoms of severe COVID-19 in children as currently reported fall into two categories. In a small subset of pediatric patients, severe lung disease occurs and appears to mimic severe adult COVID-19 with respiratory failure, ARDS, and associated multi-organ failure [5]. In other pediatric patients, an emerging inflammatory disease has recently been described [34-36] This latter presentation has been variably called PIMS-TS [37], PMIS [38], and MIS-C [39] and manifests as acute onset of fever with multisystem involvement, frequently including hypotension and cardiac dysfunction in the absence of respiratory symptoms. Some reported cases mimic severe Kawasaki disease or Toxic Shock syndrome phenotypes. MIS-C appears to be associated with prior exposure to SARS-CoV-2. Although immune modulation with corticosteroids and intravenous immunoglobulin (IVIG) is used in severe cases of MIS-C [36], given the very limited information about the mechanisms of this disease process, in this document we do not provide specific guidance for treatment of this syndrome.

Anecdotal reports of immunomodulator use in the setting of COVID-19 have been widespread [40-44]. While numerous trials of immunomodulatory therapies for COVID-19 in adults are being launched, few clinical trials for immunomodulatory therapy in pediatric patients with COVID-19 are currently enrolling or planned. Therefore, we undertook a comprehensive review of the current state of literature regarding immunomodulatory therapy in COVID-19. The goal for this document is to provide pediatric practitioners a framework for interpreting currently available data and a rationale for considering immunomodulatory therapy in the care of pediatric acute COVID-19 patients. In the sections below, cytokine storm, CSS, and hyperinflammation are used interchangeably to refer to the pulmonary and systemic inflammation that accompanies severe and critical COVID-19. This review does not represent a final or definitive guideline for diagnosis or treatment, but a review of current knowledge, and we emphasize the importance of enrollment in clinical trials for COVID-19 immunomodulatory therapy when available.

GUIDANCE DEVELOPMENT

Approach

A multidisciplinary panel of pediatric subspecialty physicians and pharmacists with expertise in infectious diseases, rheumatology, hematology/oncology, and critical care medicine was convened. We relied on the guidance approach recently published addressing antiviral use in children with COVID-19 [45]. Guidance statements were developed based on best available evidence and expert opinion. Given the lack of currently available randomized controlled trials for the therapies considered in this document and the overall limited nature of the data, a systematic review was not performed, nor was evidence formally evaluated using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) or other methodology.

Definitions

As previously described [45], we used the following definitions and similarly assert the importance of “first do no harm” in the consideration of proposed immunomodulatory therapies with yet unknown efficacy in the setting of COVID-19. Statements using the term “**suggest**” indicate the panel’s view that currently available evidence is weighted towards risk or benefit from a proposed therapy. Guidance statements of “**consider**” reflect uncertainty by the panel with regard to risk or benefit of a proposed therapy.

Framework

The panel considered three major questions related to immunomodulatory therapy for children with COVID-19:

1. Are immunomodulatory agents indicated in children with COVID-19?
2. What criteria define the pediatric population in whom immunomodulatory therapy may be considered?
3. What agents, if any, are preferred if immunomodulatory therapy is considered for children with COVID-19?

In addressing these questions, we utilize the definitions of severe and critical COVID-19 previously published (Table 1) [45]. We provide background information for several categories of immunomodulatory therapies that have been proposed for potential use in caring for severely or critically ill COVID-19 patients. These categories include IL-1 inhibitors, IL-6 inhibitors, glucocorticoids, convalescent plasma, Janus kinase inhibitors, intravenous immunoglobulin (IVIG), and interferons. Within each section we provide a guidance statement followed by rationale and an

evidence summary. *In vitro* and animal model data is reviewed in selected sections, though we do not significantly address SARS-CoV-2 animal models given a current lack of such published data. In addition, we provide information regarding potential adverse events and practical guidance regarding dosing within each section. A summary of key guidance statements is provided in Table 2.

I. ARE IMMUNOMODULATORY AGENTS INDICATED IN CHILDREN WITH COVID-19?

Guidance statement:

We emphasize that the vast majority of children with COVID-19 will recover from the acute phase of infection with supportive care. Enrollment in clinical trials of immunomodulatory therapy for COVID-19 is preferred. In the absence of available clinical trials, use of immunomodulatory therapy for COVID-19 may be considered in compliance with local institutional policies on consent for experimental and/or off-label treatment.

Rationale:

The aforementioned antiviral guidance document provided key rationale for consideration of therapies beyond supportive care in children with COVID-19 [45]. Multiple studies and experience in a variety of settings have demonstrated that the majority of children with COVID-19 recover without immunomodulatory interventions and do not develop severe manifestations. Given the lack of available results from randomized-controlled trials of immunomodulatory therapy in children with COVID-19, the risk-benefit ratio for most pediatric patients points toward supportive care as the key management strategy. However, a subset of pediatric patients develops severe or critical illness with acute COVID-19 [5]. It is therefore possible that immunomodulation is a key part of treatment strategy for such patients.

II. WHAT CRITERIA DEFINE THE PEDIATRIC POPULATION IN WHOM IMMUNOMODULATORY USE MAY BE CONSIDERED?

Guidance statement:

We suggest that immunomodulatory therapy only be used for pediatric patients in the setting of confirmed critical COVID-19 (SARS-CoV-2 RT-PCR positive) with evidence of hyperinflammation (Table 4). In addition, pediatric COVID-19 patients with hyperinflammation whose pace of illness progression suggests imminent progression to critical COVID-19 may be considered for immunomodulatory treatment. Use of immunomodulation for pediatric COVID-19 should be performed in consultation with specialists familiar with the use of the medications.

Rationale:

Based on currently available data, very few pediatric patients with COVID-19 will become severely or critically ill [2-4, 46]. Therefore, for the majority of pediatric COVID-19 patients the risks of immunomodulatory therapy outweigh potential benefits. However, in pediatric patients with critical COVID-19 (defined previously; Table 1, [45]), or who are rapidly progressing towards this category, the potential benefits of immunomodulatory therapy may offset the potential risks. In addition, given the potential risks of immunomodulatory therapy, consideration of this therapy in the setting of severe or critical acute COVID-19 should be reserved for patients with RT-PCR-confirmed infection. We are aware that there may be a subset of patients for whom there is a high suspicion of acute COVID-19 despite negative RT-PCR testing. Given the difficulties in determining disease etiology and defining benefits of immunomodulatory therapy, we do not provide specific guidance for this scenario. In the evidence summary below, we review the current data on immunopathology in severe and critical COVID-19 and discuss potential clinical and laboratory criteria on which to base the decision to use immunotherapy.

Evidence summary:

Adult patients severely affected by COVID-19 demonstrate a variety of overlapping phenotypes of severity including features of ARDS, hypercoagulability, hyperinflammation/CSS, and multi-organ failure [9-11]. Currently published cohorts indicate that a very large percentage of COVID-19 affected children do well after infection with SARS-CoV-2. Despite these overall reassuring findings in children, reports have emerged that a small subset of pediatric patients are severely affected by COVID-19 with a presentation/severity similar to that seen in adult patients [3, 5, 8, 47].

The clinical and laboratory presentation of patients with severe acute SARS-CoV-2 infection has revealed similarities and differences with CSS. CSS is associated with dysregulated, inappropriate, and unbalanced immune responses that include enhanced production of proinflammatory cytokines (Table 3). CSS is driven by excessive activation of both innate (monocytes, macrophages, neutrophils, NK cells) and adaptive immune cells (T-cells) and overproduction of pro-inflammatory cytokines that produce a recognizable clinical and laboratory pattern of tissue pathology. In general, CSS is associated with evidence of aberrant systemic inflammation including elevated ferritin, low fibrinogen, cytopenias, hemophagocytosis, and variable occurrence of coagulopathy, NK cell dysfunction, and pulmonary, liver, spleen and/or CNS involvement [30]. Current reports of severely and critically ill COVID-19 patients indicate that aberrant and dysregulated inflammation contributes to morbidity and mortality in these patients.

However, parsing out contributions from ARDS, cytokine storm, secondary infections, and coagulopathy/hypercoagulability in the laboratory findings associated with severe/critical COVID-19 remains difficult. In addition, there is likely to be distinct pathophysiology between severe/critical COVID-19 with CSS compared to other categories of CSS. Therefore, we emphasize caution in the application of diagnostic criteria used in other CSS to the assessment of CSS in the setting of COVID-19.

Current information regarding immunopathogenesis of CSS in acute COVID-19 derives primarily from adult data. We have summarized much of this data below within each specific immunotherapeutic section. Briefly, a subset of patients progress to severe lung injury and death. Autopsy studies demonstrate exudative diffuse alveolar damage with significant capillary congestion and microthrombi [48] and an association with venous thromboembolism in non-pulmonary sites [49]. Laboratory evidence of markedly elevated inflammation including elevated ferritin, CRP, and ESR values is also noted in severe/critical COVID-19 cases [50]. Further, many patients critically ill with COVID-19 demonstrate evidence of coagulopathy including significantly elevated D-dimer [51].

Cytokine profiling of patient samples has been performed in adult and pediatric patients. Elevation in other cytokines/chemokines associated with hyperinflammation states, including CXCL-9 (MIG), CXCL-10 (IP-10), CCL-7 (MCP-3), and IL-1Ra have also been shown [52]. Single cell immune profiling demonstrates an inflammatory signature that includes significant inflammatory gene expression with classical monocytes [53]. Furthermore, several early studies have suggested a link between impaired innate interferon expression and development of excessive inflammation in COVID-19 patients [54-57]. Based on this data, several cohorts reporting use of immunomodulation in COVID-19 have been recently published [42, 58-61]. These manuscripts and related reports are reviewed in specific sections below.

The panel recommends that use of immunomodulatory therapy for the treatment COVID-19 related hyperinflammation/ cytokine storm should be conducted in the context of a clinical trial, if available. In the absence of such opportunity, and recognizing that definitive evidence is lacking, consideration for use of immunomodulatory agents in cases of SARS-CoV-2 infection with clinical and biochemical evidence of cytokine storm physiology (e.g., features of secondary HLH) should be limited to patients with clear evidence of critical COVID-19 disease and risk for multi-organ failure. In this restricted scenario, an experimental approach using immunotherapy has theoretical potential for benefit and is supported by increasing evidence, as detailed below. We propose several key categories of clinical information to consider regarding the use of immunomodulatory therapy for pediatric COVID-19 patients (Table 4). These include clinical and laboratory illness features and

take into account the pace of illness progression, evidence of organ injury/impending organ failure, and evidence of hyperinflammation. Importantly, given the current state of knowledge and lack of available clinical trial results, we are not able to provide specific cutoffs or laboratory results that indicate a definite need for immunomodulatory therapy.

Although current literature has identified proposed laboratory findings demonstrating hyperinflammation as indicators of risk for severe/critical COVID-19, these are not validated and individual values should be assessed in the context of the patient's overall status. No single feature or laboratory value is known to be sufficient to recommend immunotherapy. However, it is anticipated that timely recognition and intervention could improve outcomes, such that trends toward worsening disease and the cadence of change should be considered. Despite the overlap with CSS and noted elevations in inflammatory markers and pro-inflammatory cytokines, diagnostic criteria for familial HLH (fHLH), MAS, and CRS should not be necessarily be used to identify COVID-19 patients who may benefit from immune suppression or immune modulation, as these definitions are likely to differ for SARS-CoV-2 infections, just as they do between the different CSS categories.

Consideration for use of experimental therapies should entail discussion between the patient's primary team and appropriate consulting teams with experience in the use of immunomodulatory drug treatment in the setting of infection including infectious diseases, rheumatology, and/or hematology/oncology, critical care, and with involvement of pharmacists. Further, use of these therapies should be performed only with appropriate counseling and consenting of patients and families for off-label use of immune modulatory medications according to each individual institution's policies.

III. WHICH IMMUNOMODULATORY AGENTS SHOULD BE CONSIDERED?

Guidance statement:

There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients as of 24 July 2020. Therefore, no guidance can be provided to support the use of one immunomodulatory therapy over another.

Guidance statement:

If immunomodulators are used in the treatment of COVID-19, patients should be monitored for adverse effects.

Rationale:

As outlined in topic-specific sections below, there are no randomized, controlled trials evaluating the use of immunomodulatory therapies in pediatric COVID-19 patients. Numerous cohort studies have recently been published though many of these are limited by absence or inadequacy of a rigorous comparator group. A few randomized controlled trials have recently been published. However, none of these provides comparison between immunomodulatory agents. Therefore, the current state of evidence does not allow for selection of one immunomodulatory therapy over another. As with the decision to use or not use an immunomodulator in a pediatric COVID-19 patient, the choice of which immunomodulatory therapy to use should be driven by an individualized weighing of potential risks and potential benefits. In addition, though superseded by evidence of efficacy and adverse effects, relative drug availability and cost may play a role in immunomodulatory therapy choice. For each immunomodulatory therapy addressed below, we provide rationale, evidence summary, potential risks, and practical considerations to assist in these individualized patient care decisions. The order of discussion of immunomodulatory therapies below does not reflect any preference for one category over another.

IL-6 inhibition

Guidance statement:

IL-6 inhibition may be considered in the care of pediatric patients with critical COVID-19 with priority given to clinical trial enrollment if available.

Rationale:

The effects of IL-6 can be inhibited by blocking binding to the IL-6 receptor using monoclonal antibodies such as tocilizumab, siltuximab, and sarilumab. Notably, these are each being tested for use in COVID-19 in over a dozen clinical trials that are currently recruiting patients. Given that the pediatric experience with IL-6 inhibition has mostly been with use of tocilizumab, the panel would favor use of this agent, should this therapeutic modality be considered, although other agents may also be considered in select situations (e.g. anaphylaxis with tocilizumab or drug shortages).

Tocilizumab is FDA approved (albeit not for this indication), and dosing data are extrapolated from that used in CSS following CAR T cell or blinatumomab therapy.

Evidence summary:

Mechanism and current uses: IL-6 is a pleiotropic cytokine produced by a number of non-hematopoietic cells and cells of myeloid origin during infections and in response to tissue injury. IL-6 binds its receptor (IL-6R) and initiates a JAK/STAT-mediated signaling pathway, which results in transcription of numerous genes [62]. Increased IL-6 levels are observed in a number of viral infections, and in animal models elevated IL-6 levels favor the persistence of some of these viruses [63-66]. Tocilizumab is currently FDA approved for the treatment of CAR T cell-induced CRS in both children and adults, rheumatoid arthritis and giant cell arteritis in adults, as well as polyarticular and systemic juvenile idiopathic arthritis in children [67].

In vitro and animal data: A number of prior in vitro studies demonstrated that infection of airway epithelial cells or macrophages [68, 69] with either SARS or MERS coronaviruses could elicit production of IL-6 and TNF- α ; similar results were also observed with purified coronavirus spike (S) or nucleocapsid (N) proteins [70, 71]. In an animal model, primary infection with SARS is associated with an IL-6 gene signature and an associated self-sustaining acute phase response [72].

Human data: Several studies have examined the cytokine response to SARS-CoV-2; these have demonstrated the presence of mild to moderately elevated IL-6 in serum or plasma of adult and pediatric COVID-19 patients [11, 17, 73]. Moreover, the levels of IL-6 transcript and protein appear to correlate with the severity of COVID-19 and mortality in adults [50, 73, 74]. A proportion of pediatric COVID-19 patients were also shown to possess similarly elevated IL-6 levels [75]. While blinded and randomized clinical trial data are still needed, several recently published cohort studies have indicated mixed evidence for benefit for tocilizumab in adult COVID-19 patients. In a single center cohort study of adult COVID-19 patients requiring mechanical ventilation, treatment with tocilizumab was associated with decreased mortality with a hazard ratio (HR) for death of 0.55 (95% CI 0.33-0.9) after adjusting for disease severity at tocilizumab initiation [76]. Similarly, in an Italian multicenter retrospective cohort study of 544 severe COVID-19 adult patients, tocilizumab treatment was associated with decreased risk of mechanical ventilation or death (adjusted HR 0.61; 95% CI 0.4-0.92) [77]. These results are supported by several smaller cohorts [42, 61, 78-82]

Potential Risks:

While it is generally recommended that tocilizumab not be initiated in patients with neutropenia or thrombocytopenia or in those with elevations of alanine aminotransferase or aspartate aminotransferase, in practice many patients with severe or life-threatening systemic inflammatory response syndrome (SIRS) experience cytopenias or elevated transaminases due to multi-system organ dysfunction or the use of concurrent medications. Therefore, it may be reasonable to cautiously initiate tocilizumab therapy in such patients with close monitoring. Additionally, tocilizumab therapy may increase risk of bacterial and mycobacterial infections (especially the reactivation of *M. tuberculosis*), viral reactivation (especially hepatitis B), and invasive fungal disease [67]. Notably most of these reports are from adults (e.g. those with rheumatoid arthritis) who have received chronic IL-6 inhibition and, therefore, risk for children on shorter courses of tocilizumab may not be as significant. Interestingly, the above cited studies have shown an increase in superinfection in patients treated with tocilizumab though without clear impact on outcomes [76, 77]. Other adverse events such as pneumatosis intestinalis and intestinal perforation [83], hepatic injury and liver failure [84], hypertriglyceridemia and pancreatitis [85] have also been reported.

Dosing and practical considerations:

Note that dosing for tocilizumab in pediatric populations is largely based on use for rheumatologic indications and in CAR T cell-associated CRS [28, 32]. The suggested intravenous (iv) dosing is 12mg/kg for patients with a total body weight less than 30kg and 8mg/kg for those 30kg and above, with a maximum dose of 800mg. Monitoring for anaphylaxis should be performed and, if noted, should be treated using standard local protocols. Additionally, periodic laboratory (e.g. complete blood counts (CBCs), hepatic and pancreatic function testing, etc.) and clinical exam monitoring is suggested. Of note, while tocilizumab does not directly affect the P450 cytochrome system, elevated levels of IL-6 can inhibit these enzymes, and thus drugs that are metabolized by this system may also require monitoring. The half-life of tocilizumab is concentration dependent and is estimated to be up to 2 weeks in high-dose therapy (as suggested for use in COVID-19 hyperinflammation) of adult patients receiving chronic therapy at 8mg/kg every 4 weeks. Most adult studies of COVID-19-associated hyperinflammation use a single dose with some studies providing two doses separated by 12-24 hours if there is lack of response to the first dose. Finally, since tocilizumab blocks the IL-6 receptor, following IL-6 levels is not useful for monitoring and is not recommended.

IL-1 inhibition

Guidance statement:

IL-1 inhibition may be considered in the care of pediatric patients with critical COVID-19 with priority given to clinical trial enrollment if available. If IL-1 inhibition is used as a treatment modality for pediatric COVID-19 patients, we suggest the use of anakinra based on its safety profile and favorable pharmacokinetics.

Rationale:

Available data from the prior SARS and MERS outbreaks and early data from the current SARS-CoV-2 pandemic suggest that IL-1 β may play a role in SARS-CoV-2-related immunopathology. Evidence that inhibition of IL-1-signaling may safely improve outcomes in COVID-19 [58-60, 86]. Pediatric patients with severe COVID-19 being considered for treatment with IL-1 inhibition should be enrolled in clinical trials if available and eligible. In the absence of clinical trials for immunomodulation of COVID19 in pediatric patients, consideration may be given to use of IL-1 inhibition in pediatric patients with severe or critical COVID19. Given the established use and safety profile of anakinra in a variety of other settings as well as its short half-life allowing for rapid discontinuation of therapy in case of adverse reactions, anakinra is the preferred IL-1 inhibition agent in the setting of pediatric COVID-19. It is worth noting that a small case series has investigated canakinumab use in 10 hospitalized adult COVID-19 patients [87].

Evidence summary:

Mechanism and current uses: IL-1 α and IL-1 β are two of the 11 members (including IL-18 and IL-33) of the IL-1 cytokine family and play a critical role in a wide variety of pro-inflammatory states. IL-1 β is the major biologically active and secreted form in the setting of infection and other inflammation, but IL-1 α is likely released by dying endothelial cells. IL-1 β exerts its effects through binding to its specific receptor subunit IL-1R1 followed by co-receptor recruitment. Biological effects of IL-1 β include recruitment of endothelial adhesion molecule expression and inflammatory cell recruitment, upregulation of prostaglandins and nitric oxide, and metalloproteinase production. Systemically, IL-1 β contributes to hypotension, fever, neutrophilia, and other acute phase responses. Importantly, IL-1 β contributes to CD4⁺ Th17 differentiation by contributing to key aspects of transcriptional activation [88]. IL-1 can also act upstream to increase IL-6 expression [89].

Several targeted therapies inhibit IL-1 β signaling including anakinra, a recombinant form of IL-1 receptor antagonist (IL1-Ra) which mimics native IL-1Ra and prevents binding of IL-1 α and IL-1 β

to IL-1R1 and thereby prevent IL-1-mediated immune effects [90]. Another IL-1 targeting drug, riloncept, binds and neutralizes both IL-1 α and IL-1 β . In addition, a monoclonal antibody, canakinumab, binds IL-1 β and prevent its interaction with IL-1R1 [91]. Anakinra is FDA approved for adults with rheumatoid arthritis who have failed one or more disease modifying antirheumatic drug (DMARD) and for the treatment of Neonatal Onset Multisystem Inflammatory Disease (NOMID). Randomized controlled trials of each of the medications have demonstrated their safety with infections occurring infrequently when used in these settings [92-98].

Anakinra has been best studied in terms of treating other CSS, including macrophage activation syndrome and secondary hemophagocytic lymphohistiocytosis. It is a recombinant human protein with over 7,000 patient-years of favorable safety data. Anakinra has a short half-life of 4-6 hours, can be given intravenously or subcutaneously, and works quickly. Anakinra also has a wide therapeutic window (effective with minimal adverse effects reported from 1-48 mg/kg/day, including use in patients with sepsis). Retrospective analysis of a large randomized clinical trial demonstrated that anakinra improved survival in sepsis patients with features of CSS (hepatobiliary dysfunction and disseminated coagulopathy) from 35% (placebo) to 65% [99]. An early case series of pediatric rheumatic disease patients with refractory CSS reported resolution in 12 out of 12 patients treated with anakinra [100]. More recently, a retrospective report of 44 children with rheumatologic, oncologic, and infectious etiologies of CSS reported 73% survival rate for those who received anakinra at any point during their hospitalization [101]. Further, anakinra has also been touted to effectively treat CSS in children requiring intensive care [102].

Importantly, for interpreting results and studies summarized below, measurement of IL-1 β in peripheral blood compartments such as plasma and serum may not accurately reflect its biological activity in a variety of disease states. This is likely due in part to its short half-life and tight regulation of IL-1 β 's activity in human immune responses via soluble-IL-1 receptors and IL-1Ra, among other regulators [103].

In vitro and animal data: Several SARS proteins (E protein, Protein 3a, and ORF8b) are shown in *in vitro* studies to activate the NLRP3 inflammasome. Protein 3A and E protein each activate the NLRP3 inflammasome in LPS-primed mouse bone marrow derived macrophages and African green monkey kidney-derived vero cells, respectively [104-107].

Human data: An association between IL-1 β and SARS-associated immunopathology was made predominantly through measurement of serum/plasma IL-1 β levels in SARS-CoV-1 infected patients. In general, these studies are limited by a lack of control groups and/or measurement of IL-1 β at few or inconsistent time points post-infection [19, 108-110]. Immunohistochemistry of lung sections from autopsy specimens of four SARS patients did demonstrate elevated IL-1 β expression in SARS-infected cells [111].

Following several small case series [58, 60], two retrospective cohort studies have shown potential benefit for anakinra in the context of severe COVID-19. Adult COVID-19 patients with moderate to severe ARDS and evidence of hyperinflammation (CRP \geq 100mg/L or ferritin \geq 900ng/mL) were treated with either iv or subcutaneous anakinra [112]. Comparison between the 29 subjects in the high dose iv anakinra treatment group and historical controls indicated improved survival in the treatment group at 21 days post treatment initiation (90%, anakinra; 50% standard, $p=0.09$) though mechanical ventilation free survival differences were not statistically significant. No differences in bacteremia rates or frequency of hepatic transaminase elevation were noted [112]. In a separate study in France, 52 adult patients with severe COVID-19 treated with subcutaneous anakinra were compared to 44 historical controls [86]. Anakinra-treated subjects had significant decreased frequency of the primary composite outcome of death or intensive care unit admission for mechanical ventilation (25% versus 73%) with difference remaining significant on multivariate analysis (HR 0.22; 95% CI 0.1-0.49). Thus, anakinra appears to be safe and may provide mortality benefit in the treatment of adult COVID-19 patients. Randomized clinical trials are needed to validate these findings.

Potential risks:

Adverse effects of anakinra are difficult to distinguish versus effects of the disease processes being treated but include hematologic suppression, infections, hypersensitivity reactions, and malignancies. Those most commonly reported in pediatric studies include increased liver enzymes, which are usually self-limiting, but a few cases of acute liver failure have been reported. In addition, severe injection site reactions and cytopenias have been reported [113, 114]. Importantly for the discussion of high versus standard dose anakinra below, high dose anakinra was associated with increased risk of serious bacterial infection in a pooled analysis of studies enrolling adults with RA [115].

Dosing and practical considerations:

Though the majority of studies of anakinra have been performed using subcutaneous (SC) dosing route, iv administration is evolving as an option for the treatment of critically ill patients [99, 116, 117]. The potential utility of iv anakinra in COVID-19 patients is highlighted by the above cited study in which low dose SC anakinra (100 mg twice daily in adult patients) did not produce either significant clinical or laboratory changes in a small subset of COVID-19 patients while the 5 mg/kg IV over 1 hour administered every 12 hours was associated with sustained clinical benefit [112]. Despite these encouraging results, stability data for iv anakinra are incomplete and caution is warranted in the use of iv anakinra.

As noted above, measurement of IL-1 levels in peripheral blood is difficult and therefore not recommended during anakinra administration. For toxicity, close monitoring of AST and ALT should be performed as these can become elevated on anakinra therapy. In general, hepatic transaminase elevation resolves with discontinuation or lowering of dose. CBC with differential should be monitored to evaluate for anakinra-induced leukopenia and/or thrombocytopenia. Though increased infections are a reported risk with the use of anakinra, anakinra has a low rate of secondary infection risk and a long record of safety in clinical practice [115, 118, 119]. In the use of anakinra in COVID-19, tuberculosis screening is not needed to initiate therapy because of clinical urgency for therapy initiation.

Glucocorticoids

Guidance statement:

Given their pleiotropic effects, glucocorticoids are used in a variety of inflammatory conditions and settings. As such, it is difficult to definitively support or discourage the use of glucocorticoids in all situations. Therefore, we have provided guidance for specific situations in the following section.

Rationale:

Given the concerns over immune dysregulation associated with COVID-19, glucocorticoids have been proposed and used as a potential treatment modality [120-122]. Glucocorticoids regulate the immune system in a broad and multimodal manner and block multiple signaling pathways that propagate inflammatory signals [123, 124]. During the early phase of the immune response, glucocorticoid-glucocorticoid receptor complexes attenuate the signaling of Toll-like receptors, inhibit the production of numerous pro-inflammatory cytokines [125], and dampen cytokine signaling [126]. Glucocorticoids also have a potent effect on cellular immunity, especially T cell

signaling and activation [127]. Overall, glucocorticoids are one potential therapeutic option for the treatment of COVID-19, but benefits offered by glucocorticoids in attenuating immune dysregulation must be balanced with their inhibitory effect on the immune response needed to control viral replication as well as the risk of opportunistic infections and associated side-effects. Glucocorticoids, however, are available readily and at low cost.

Evidence summary:

Given the numerous clinical uses for glucocorticoids and mechanisms by which they impact the immune system, we have limited this evidence summary to address prior data from SARS, and currently available data from COVID-19.

Data regarding the efficacy of glucocorticoids in the treatment of SARS are difficult to interpret. Glucocorticoids were frequently used as part of many treatment protocols, each with different dosing regimens and varied times of treatment initiation; thus most studies did not contain placebo arms [128-137]. A systematic review of the treatment effects of multiple therapeutic modalities for SARS, including glucocorticoids, revealed that 13/15 studies examining the effect of steroids were inconclusive [138]. No studies showed clear benefit, and 2 studies showed possible harm. Ultimately, the authors concluded that “it is difficult to make a clear recommendation about whether [glucocorticoids] should be used to treat SARS-associated lung injury in any stage of illness, particularly as the drug is immunosuppressive and may delay viral clearance if given before viral replication is controlled” [138].

Peer-reviewed data evaluating the impact of steroids on COVID-19 treatment outcomes is limited, and comparative data is lacking. Glucocorticoids have been used frequently in critically ill patients [13, 139, 140]. One retrospective cohort study of 201 adult patients with COVID-19 identified risk factors for the development of ARDS and death from ARDS [141]. Sixty-two patients received methylprednisolone, but there were limited data on the dose and timing of initiation of therapy. For those patients with ARDS, treatment with methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% confidence interval, 0.20-0.72). However, these data should be interpreted with caution due to small sample size and risk of bias.

An additional retrospective cohort study performed in a multicenter health system in Michigan showed potential benefit of early methylprednisolone initiation (median time to initiation of 2 days post admission, IQR 1-3 days) compared to a standard of care cohort with later corticosteroid initiation (median time to initiation of 5 days with IQR of 3-7 days). In this study, early

corticosteroid initiation was associated with decreased occurrence of escalation of care to ICU, mechanical ventilation, or death (adjusted OR 0.41; 95% CI 0.22-0.77) [142].

Recently, data from the RECOVERY Trial, a randomized clinical trial evaluating the impact of treatment with dexamethasone in adults infected with SARS-CoV-2, were published [143]. A total of 6,425 adults were enrolled, and 2,104 patients received 6 mg of dexamethasone daily for up to 10 days. For the primary outcome of 28-day mortality, receipt of dexamethasone was associated with a significant decrease in mortality for those patients receiving invasive mechanical ventilation (29% versus 41%, rate ratio 0.64, 95% confidence interval 0.51 to 0.81) or for those patients who received supplemental oxygen but not mechanical ventilation (23% versus 26%, rate ratio 0.82, 95% confidence interval 0.72 to 0.94). Receipt of dexamethasone was also associated with lower risk of progression to invasive mechanical ventilation, and patients in the dexamethasone group had a shorter duration of hospitalization. There was no difference in 28-day mortality, however, for patients who were not receiving any respiratory support at the time of randomization. Conversely, there was a slight trend towards worse outcomes in those receiving no respiratory support (mortality 18% vs 14%). At time of writing, the pediatric portion of the RECOVERY trial is still enrolling patients.

Similarly, results from a large (140 received glucocorticoids vs. 1,666 who did not) non-controlled retrospective cohort comparison reported decreased mortality or mechanical ventilation (odds ratio 0.23; 95% CI, 0.08-0.70) in those with high CRP values (20 mg/dL or higher) receiving glucocorticoids within 48 hours of hospital admission [144]. However, mortality or mechanical ventilation was increased in those receiving glucocorticoids if the CRP was less than 10 mg/dL (odds ratio, 2.64; 95% CI, 1.39-5.03).

Finally, it is worth noting that some centers are reporting their experience with a combined tocilizumab plus corticosteroid strategy for severe/critical COVID-19 patients [145, 146]. Current evidence is too limited to determine whether this strategy is truly safe, effective, and/or applicable to pediatric COVID-19 patients.

Thus, there is evolving evidence to support benefit of corticosteroid treatment for critically ill adult patients with COVID-19. The degree to which findings from these studies are applicable to children with severe or critical COVID-19 is not clear at this point. Despite this uncertainty, glucocorticoid therapy could be considered in select clinical scenarios based on individualized risk-benefit assessment. Scenario-specific guidance follows. We have not provided specific dosing

recommendations beyond the below guidance statements due to the lack of COVID-19 specific evidence for dosing at present.

Scenario-Specific Guidance:

Guidance Statement:

Glucocorticoid therapy is not currently indicated for outpatients or hospitalized patients with mild or moderate COVID-19.

Rationale:

Based on currently available data, most SARS-CoV-2 infected children, even those with mild or moderate disease, will recover with supportive care. Based on SARS and MERS studies in which glucocorticoid recipients had delayed viral clearance [137, 147], administration of glucocorticoids may attenuate the immune response needed to clear viral infection. In addition, no evidence exists that glucocorticoid therapy prevents progression from mild/moderate to severe COVID-19. Therefore, the panel recommends against the use of glucocorticoids in children without symptoms or who have only mild or moderate disease.

Guidance Statement:

Glucocorticoid therapy may be considered for pediatric patients with critical COVID-19 with preference for use in the setting of clinical trials, if available.

Rationale:

As described above with regard to IL-6 and IL-1 inhibition, current evidence suggests that excessive inflammation plays a role in the immunopathology of acute critical COVID-19. Given the broad anti-inflammatory effects of glucocorticoids, their use in the setting of critical COVID-19 may impart benefit, especially for children with critical COVID-19. Further, in settings in which other immunomodulatory therapies are not readily available for pediatric patients or in the setting of monoclonal antibody shortages, glucocorticoids may be the only option for immunomodulatory therapy for acute critical COVID-19. However, there is still a lack of strong evidence for benefit in the pediatric population and given the breadth of immunosuppression associated with glucocorticoid use in this setting and the risk for impairing antiviral immunity, caution is warranted especially when early post-onset of COVID-19 symptoms.

Guidance Statement:

Diagnosis with COVID-19 does not preclude use of steroids when they are otherwise indicated (for example, in asthma or catecholamine-refractory shock).

Rationale:

Glucocorticoid therapy offers benefit in the treatment of many pediatric conditions such as asthma exacerbation or flares in inflammatory bowel disease [148, 149]. In the critical care setting, there is limited pediatric data surrounding the efficacy of glucocorticoids in septic shock, with published studies containing small numbers of children [150-152]. A recent meta-analysis evaluating the efficacy of glucocorticoids in sepsis included 42 published RCTs of which 3 enrolled only children and 1 enrolled both adults and children [153]. Pooled analysis showed that use of glucocorticoids may decrease both short-term and long-term mortality, though any effect is likely small. A recent Cochrane review included 61 RCTs, though only 8 trials included children [154]. The authors found a small reduction in 28-day mortality in the pooled analysis, though there was significant heterogeneity across trials.

There is no high-quality pediatric data to support the routine use of glucocorticoid therapy for the treatment of sepsis without shock or shock that is responsive to fluid resuscitation or vasopressors. However, if a child with COVID-19 develops circulatory shock and remains hypotensive despite fluid resuscitation and titration of vasoactive drugs, use of glucocorticoids can be considered for treatment of critical-illness related corticosteroid insufficiency. This condition is characterized by dysregulated systemic inflammation resulting from inadequate glucocorticoid-mediated anti-inflammatory activity relative to the severity of the patient's critical illness [155]. Hydrocortisone is the synthetic form of cortisol, and there is significant experience with its use in the treatment of circulatory shock. Published dosing regimens in this setting are based dosing ranges for the use of hydrocortisone in pediatric adrenal insufficiency [152, 156]. Prior guidelines for critically ill adults with COVID-19 have also addressed this topic [157, 158].

Potential Risks:

Short-term use of glucocorticoids is associated with significant adverse effects, including hypertension and fluid retention, hyperglycemia, adrenal suppression, gastritis and gastrointestinal bleeding, posterior reversible encephalopathy syndrome [159], and psychosis [160, 161]. We recommend routine screening for electrolyte abnormalities, hyperglycemia and hypertension in hospitalized children receiving steroids. These studies are often part of routine care. After the 2003 SARS pandemic, there were reports of avascular necrosis after treatment with glucocorticoids [162-

166]. In symptomatic patients, or those at increased risk of avascular necrosis, screening with plain radiographs or MRI should be considered.

Glucocorticoid therapy is also associated with immunosuppression and potentially increases the risk of secondary infection. In one recent meta-analysis of the use of glucocorticoids as adjunctive treatment for influenza, adults treated with glucocorticoids had increased odds of hospital-acquired infection, though the overall quality of evidence was low [167]. In addition, several reports of adult COVID-19 patients indicate risk for invasive pulmonary aspergillosis [168, 169]. Whether this risk is similarly present in children with COVID-19 remains unclear. Regardless, monitoring for secondary infection should occur for all patients receiving glucocorticoids.

Monitoring for drug-drug interactions is essential with glucocorticoid use. Glucocorticoids are metabolized through cytochrome P450, 3A4, one of the more common hepatic isoenzymes. If this isoenzyme is inhibited by another agent (e.g. macrolide, protease inhibitor), significantly increased glucocorticoid exposure can result. Alternatively, glucocorticoid exposure can also be significantly reduced by an inducer of CYP 3A4 such as rifampin requiring increased dosing to obtain the same effect [170].

JAK inhibition

Guidance statement:

JAK inhibitors should not be used for children with COVID-19 outside of clinical trials.

Rationale:

While there exists a theoretical rationale for the use of JAK inhibitors in severe COVID-19, the exact clinical impact of these drugs is difficult to predict, and it is unclear whether treatment with these agents would prove beneficial or harmful. Additionally, there are very little data supporting safety or efficacy in the use of JAK inhibitors for management of COVID-19. Moreover, data from use in other settings suggests the potential for impaired viral clearance as evidenced by herpesvirus reactivations on JAK inhibitor therapy [171]. Therefore, currently, we recommend against the use of these drugs for children with COVID-19 outside of clinical trials.

Evidence summary:

Mechanism and current uses: The Janus kinases (JAKs) are a family of four tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that serve as intracellular signal transducers [172]. Following the binding of cytokines to types 1 and 2 cytokine receptors on the cell surface, JAKs initiate a cascade of intracellular signaling that leads to activation or suppression of gene transcription. More than 50 cytokines signal via the JAK/STAT pathway to coordinate hematopoiesis, induce inflammation and control the immune response [172]. Cytokine receptor subunits bind specific JAKs, although some bind more than one. Complete receptors are thus associated with a pair of JAKs, and individual cytokines signal through a variety of JAK combinations.

Given the key role played by JAKs in hematopoiesis and immune signaling, these enzymes are an important target for pharmacologic inhibition. Several oral small molecule JAK inhibitors have been recently developed, and these drugs have efficacy in treating a number of neoplastic and inflammatory conditions [173]. Emerging pediatric uses for these drugs include treatment of juvenile idiopathic arthritis [174], psoriasis [175], interferonopathies [175], and graft versus host disease [176, 177]. In addition to the above conditions, JAK inhibitors are also increasingly studied in the setting of CSS such as HLH and MAS [178-181]. In a small open-label series of five adults with secondary HLH, ruxolitinib initiation was temporally associated with improvement in cytopenias and declines in both ferritin and soluble-IL-2 receptor (sIL2R) [178].

In vitro and animal data: Data summarizing key cytokines and pathways relevant for JAK inhibitors are discussed in other sections.

Human data: A few small studies have evaluated the utility of JAK inhibitor therapy for COVID-19 in adults have recently been published. A single-blinded, randomized controlled trial of 43 adults with severe COVID-19 showed that ruxolitinib did not significantly enhance clinical improvement compared to placebo [182]. Ruxolitinib-treated patients in this study did show more rapid radiographic and more rapid recovery from lymphopenia as well as decrease in peripheral blood cytokine expression.

In a small cohort study, fifteen adult patients hospitalized with COVID-19 (with 9 requiring ICU care and 4 requiring mechanical ventilation) received baricitinib treatment [183]. Twelve of the fifteen patients survived though no comparator group was provided in this analysis. Finally, in a multicenter study from Italy, 113 baricitinib-treated patients with moderate COVID-19 were compared to 79 historical controls that did not receive baricitinib [184]. ICU admission and mortality

at 2 weeks post-enrollment was decreased in the baracitinib versus control groups (ICU: 0.88% vs. 17.9%, $p=0.02$; Mortality: 0% vs. 6.4%, $p=0.01$).

Thus, clinical evidence is lacking to strongly support the use of JAK inhibitors for COVID-19 patients at this point. However, large prospective studies assessing both efficacy and adverse effects are needed prior to consideration for use of these medications in children.

Potential risks:

When studied for treatment of rheumatoid arthritis, JAK inhibitors have been shown to have a similar increased risk of infection compared to placebo as with biologic agents (e.g. adalimumab). However, increased risk of primary or reactivation of herpes simplex and varicella zoster virus infections has been specifically noted for JAK inhibitors [185, 186]. These agents have also been associated with anemia, lymphopenia or neutropenia (and thrombocytopenia in patients with myelofibrosis treated with ruxolitinib), and with elevated cholesterol and abnormal liver function tests [187]. These effects are generally mild but occasionally require drug dosage decrease, and in cases of moderate to severe lymphopenia or neutropenia, discontinuation of the drug. Indeed, a two-patient case series recently reported demonstrated adverse effects of ruxolitinib therapy for COVID-19, including anemia, thrombocytopenia, soft tissue infection, and herpes labialis [188].

Of note, baracitinib has a black box warning for potential increased risk of thrombosis which merits close attention in light of high reported incidence of thromboembolism in hospitalized COVID-19 patients [189, 190].

Finally, several JAK inhibitor agents (fedratinib, ruxolitinib and tofacitinib, specifically) are considered strong substrates of CYP3A4, and therefore put patients at risk for multiple clinically relevant drug interactions including with –azole antifungals [191]. Of particular interest, care providers should use extreme caution in patient receiving potent CYP3A4 inhibitors (-azole antifungals) and potent inducers of 3A4 (phenobarbital and phenytoin) as this combination will likely cause subtherapeutic response or increase risks for adverse event with even single dose therapy.

Dosing and practical considerations:

There are no current FDA approved indications for JAK inhibitors in pediatric patients and pediatric doses are not well established. Although there are some pharmacokinetic data for ruxolitinib and tofacitinib, we do not suggest their use outside of clinical trials and therefore potential dosing and other considerations are not provided.

Convalescent plasma therapy

Guidance statement:

Use of convalescent plasma (CP) in pediatric COVID-19 may be considered as part of the recently established FDA eIND program if in the United States or as part of a clinical trial.

Rationale:

There is a large body of literature spanning over a century describing the use of passive immunization in the treatment of influenza, poliomyelitis, measles, hepatitis B, CMV, Ebola and other viral illnesses. An additional body of literature from animal studies provides supportive rationale for this approach. The efficacy of passive transfer of convalescent plasma (CP) is thought to be mediated primarily through viral neutralization, although other mechanisms such as stimulation of antibody-dependent cellular cytotoxicity and enhanced phagocytosis have also been posited [192]. While the passive transfer of polyclonal antibodies via convalescent plasma may be of benefit, no SARS-CoV-2-specific monoclonal antibody therapies have yet been clinically tested.

Evidence summary:

With respect to coronaviruses, use of CP was trialed in MERS and more extensively in SARS [193-195]. While the SARS case series suggested possible benefit from CP for patients (especially those treated before day 14 of illness), the true efficacy of this approach remains difficult to ascertain due to lack of control groups, study biases, and use of concomitant therapeutics, all of which confound the interpretations; nonetheless, two meta-analyses of the published case series did not reveal significant harm [138, 196]. With respect to SARS-CoV-2, plasma collected from patients in the convalescent phase of infection has been used as an empirical treatment in small numbers of patients with severe COVID-19 disease, with some laboratory improvements and disease mitigation observed [197-201]. A small randomized controlled trial has also been conducted, although, was stopped early due to challenges with enrollment [202].

Human data: Two studies demonstrate that while the patterns of development of IgM and IgG can differ among different individuals, nearly all COVID-19 patients eventually do develop appreciable antibody titers [203, 204]. These and other studies collectively show that the titers of SARS-CoV-2-specific antibodies appear to be stable over the few ensuing weeks and that the majority of the neutralizing antibodies are directed against the spike protein, and specifically the portions of this protein that are responsible for the binding of virus to the ACE2 receptor. As such, these studies

suggest that the CP of many COVID-19 patients may contain sufficient quantities of neutralizing antibodies for therapeutic utility.

There have been several case reports and series examining passive transfer of CP to COVID-afflicted adult patients with moderate to critical disease [197-201, 205, 206]. Not all of these case series reported the titers of SARS-CoV-2 antibodies in the transferred plasma. Most of these case series reported that subsequent to CP, most patients displayed stabilization or improvement of disease, as evidenced by resolution of fever, decreases in C-reactive protein and inflammatory cytokine levels, and improved radiographic findings; in some cases these improvements resulted in the extubation of mechanically ventilated patients and weaning from ECMO support. However, in one case series, in which patients were treated with CP at a median time of 21.5 days from detection of SARS-CoV-2, 5 of 6 patients eventually died [206], even though the virus could no longer be detected. While the numbers of patients reported to have been treated with CP to date are too small to draw any definitive conclusions, similarly to the use of CP in SARS-CoV-1 [193], these reports do suggest that if CP is to be effective, it may need to be used earlier in the course of disease. The largest case series to date, including 5000 hospitalized adults at several centers across the United States, demonstrated only 36 severe adverse events, with only 2 of these severe adverse events judged to be definitively related to the infusion of convalescent plasma (Joyner et al JCI). This study was not designed to evaluate the efficacy of convalescent plasma.

As of July 2020, a single randomized controlled trial has evaluated convalescent plasma for SARS-CoV-2 [202]. This trial enrolled 103 patients with severe or life-threatening COVID-19 but was discontinued early due to poor accrual and thus was not powered sufficiently to answer questions of efficacy. There was no clinically significant difference found in the primary measure of time to clinical improvement. Similarly, no significant difference was identified in 28-day mortality or time to discharge. However, convalescent plasma infusion was associated with a statistically significant negative conversion rate of viral RT-PCR at 72 hours post infusion.

There is a single case report of the use of convalescent plasma for a pediatric patient [207]. A 6-year-old child with severe aplastic anemia and SARS-CoV-2 was treated with convalescent plasma without adverse effects and with improvement of SARS-CoV-2 related symptoms.

It is encouraging that none of the studies to date have revealed significant adverse effects, or evidence of antibody-dependent enhancement (ADE) of infection. Unfortunately, the use of this therapeutic approach has yet to be systematically evaluated in pediatric populations.

Potential Risks: There are a number of potential risks associated with the use of convalescent plasma therapy, including those that may result from the transfer of immunoglobulins, and those that may ensue from transfusion of human blood products. As noted above, current reports indicate that CP-infusion is generally safe. Therefore, we focus below on immunoglobulin-dependent risks including ADE and exacerbation of deleterious immune responses, as well as the potential for inhibiting the development of effective humoral immunity.

ADE is a phenomenon in which complement pre-existing (or transferred) virus-specific antibodies could increase the entry of virus into cells expressing Fc receptors; ADE has been demonstrated to occur in a variety of viruses in vitro and in animal studies, and postulated to occur with coronaviruses [208]. ADE is believed to occur with sub-neutralizing or non-neutralizing antibodies and higher viral titers. Notably, ADE has not been demonstrated in the passive transfer of convalescent plasma in patients infected with SARS-CoV-1 and MERS. Yet, the risk of ADE still remains a concern since some patients who have recovered from mild COVID-19 may have delayed development of significant titers of neutralizing antibody titers against SARS-CoV-2, and since not all current convalescent plasma protocols mandate the use of cutoffs for neutralizing antibody titers [192, 209]. In addition to ADE, transfer of virus-specific antibodies may also exacerbate the inflammatory response and lead to further lung injury; this was demonstrated in vitro and in a SARS-CoV-1 macaque infection model [210]. Another theoretical concern is that use of exogenous immunoglobulins may inhibit endogenous development of adequate titers of high affinity antibodies that could protect the patient from re-challenge with the same virus, as has been demonstrated with respiratory syncytial virus [211, 212].

In addition to the antibody-mediated concerns, there are risks associated with transfer of human blood products. These include transmission of infectious pathogens (SARS-CoV-2 and other viruses, as well as parasites such as *Babesia* spp. or *Trypanosoma cruzi*), and transfusion-related reactions including anaphylaxis, hemolysis, or transfusion-related acute lung injury (TRALI) or transfusion related acute cardiac overload (TACO) [213]. While passive immunotherapy protocols all include measures to minimize the possibility of such harm, some cannot be predicted or prevented, thus necessitating close monitoring in the days to weeks following therapy.

Dosing and practical considerations:

The United States Food and Drug administration has provided guidance [209] for the use of CP as an investigational product. CP is currently being employed in the US either under the auspices of a clinical trial, via single patient emergency IND, or under a national Expanded Access Treatment Protocol being administered by the Mayo clinic (Rochester, MN; uscovidplasma.org). Donors are eligible if they are otherwise of good health, free of other chronic viral or parasitic diseases (as stated above), and have prior documentation of positive SARS-CoV-2 RT-PCR test and have recovered (without symptoms for 4 weeks, or in the absence of symptoms for 2 weeks but with documented negative SARS-CoV-2 RT-PCR testing). The plasma of donors with history of prior pregnancies or prior transfusions of blood products must test negative for anti-HLA or -platelet or -neutrophil antibodies. In the US, the American Red Cross provides detailed guidance for potential donors, and similar guidance is provided by the European Commission for health and food safety in the EU. Doses of CP administered to adults have ranged between 200-600mL; it is recommended that children over 40kg be dosed with 200-500mL and children under 40kg be dosed with 10-15mL/kg, while being cognizant of volume overload – especially in children with cardiac dysfunction.

IVIG

Guidance statement:

We do not currently recommend use of IVIG for treatment of acute COVID-19 in pediatric patients with the exception of specific clinical scenarios in which IVIG is typically used. Importantly, our recommendations do not apply to the use of IVIG in the treatment of MIS-C.

Rationale:

Studies to suggest a benefit for IVIG treatment in COVID-19 are not available. Therefore, IVIG is not indicated in the majority of pediatric cases. A recent study, however, has shown that lots available from the USA and other parts of the world may variably contain antibodies to SARS-CoV-2. Whether these are neutralizing antibodies or are clinically insignificant is difficult to discern at this time and future clinical trials are needed to prove any potential benefit for their use in patients with COVID-19 [214].

Evidence Summary:

Mechanism and current uses: Immunoglobulin (IG) for intravenous (IV) administration, commonly referred to as IVIG, although licensed in the US as IGIV, contains pooled immunoglobulin G (IgG) from the plasma of thousands of blood donors and contains more than 95% unmodified IgG, and various amounts of IgA depending on the formulation. IVIG is an immunomodulating agent that produces effects on many components of the innate and adaptive immune system including the following: inhibition of complement activation, saturation of Fc receptors on macrophages [215] and suppression of inflammatory mediators [216]. Specific humoral effects include inhibition of B-cell differentiation, induction of B-cell apoptosis, down-regulation of specific auto-reactive B-cells, and overall inhibition of antibody production. IVIG also induces the expansion of regulatory T cells (Tregs) and downregulates the expansion of Th17 cells [217].

Currently, the FDA has approved the use of IVIG in different clinical conditions: replacement of IgG in primary and secondary immunodeficiency disorders; prevention of coronary aneurysms in Kawasaki disease; chronic inflammatory demyelinating polyneuropathies and multifocal motor neuropathy to improve neuromuscular disability; and to improve platelet counts in immune-mediated thrombocytopenia [218]. IVIG has also been used as an adjunct treatment in HLH along with other specific anti-cytokine therapy [102, 219].

In vitro and animal data: Assessment of the role of IVIG in SARS, MERS, or COVID-19 has not been evaluated through *in vitro* or animal model studies.

Human data: In the SARS-CoV-1 outbreak, thrombocytopenia was reported to occur in up to 55% of patients and was identified as a significant risk factor for mortality. The etiology of this thrombocytopenia was likely multifactorial, but may have been immune complex mediated [220]. While no data is available regarding IVIG use in the setting of SARS-CoV-1 or MERS infection, several other viral infections (e.g., HIV, hepatitis C, parvovirus B19 and Zika virus) may be associated with secondary ITP and IVIG has been used as therapy in these settings. Among 5 patients with severe thrombocytopenia with Zika virus who received IVIG, the median platelet count increase was $112 \times 10^9/L$, in contrast to the median increase of $8.5 \times 10^9/L$ in the 4 patients who received platelet transfusions [221].

Since severe thrombocytopenia may be associated with increased mortality in COVID-19 disease [12, 222], there may be a role for IVIG in treatment regimens for pediatric COVID-19 patients with thrombocytopenia. However, a causal relationship between thrombocytopenia and COVID-19-

associated mortality is not established and the mechanisms for COVID-associated thrombocytopenia are not known. Therefore, benefit of IVIG in the care of pediatric COVID-19 patients is not defined.

Potential Risks:

Given the nature of the product and its source, immediate hypersensitivity and infusion related reactions such as headaches, flushing of the face, malaise, chest tightness, fever, chills, myalgia, dyspnea, nausea, vomiting, diarrhea, change in blood pressure, and tachycardia may occur and may be more likely in IgA-deficient patients who are receiving products that contain IgA [218]. Most of these reactions can be managed or resolved by appropriate premedication regimens and slowing rates of infusion. Renal injury may be more likely in those with preexisting renal disease, volume depletion, sepsis and concomitant nephrotoxic drug usage, and may also be specific to the IVIG product used. Other specific considerations should include thromboembolism and volume considerations with administration of IVIG, especially in patients with underlying cardiac disease.

Dosing and Practical Considerations:

Dosing recommendations for IVIG vary by indication. Therefore, we do not provide extensive dosing guidance here. In pediatric patients with macrophage activation syndrome-related CSS an IVIG dose of 2 g/kg has been used [223]. A recent publication reported IVIG dosing of 0.3-0.5 mg/kg x5 days in a case series of COVID-19 patients [224].

Interferons

Guidance statement:

Type I or type III interferon (IFN) should not be used for pediatric COVID-19 patients outside of a clinical trial.

Rationale:

Type I IFNs have been used in the management of coronaviruses such as MERS-CoV and SARS-CoV-1. Although there are some compelling in-vitro and pre-clinical animal model work to show potential benefit, human studies using type I IFNs in MERS-CoV and SARS-CoV-1 were either inconclusive or did not shown benefit. Yet, studies with IFN- λ have shown promising pre-clinical data, and better tolerability and safety profile. Currently, for SARS-CoV-2, there are several ongoing clinical trials to evaluate the efficacy of both type I and type III IFNs in therapeutic and prophylactic setting.

Evidence summary:

Mechanism and current uses: Interferons are critical proteins involved in immune activation and regulation. There are three types of interferons: type I, type II and type III. Type I IFN includes IFN- α , β , ϵ , κ , and ω , Type II interferon is IFN- γ and Type III includes IFN- λ . While type I interferon is produced by all cell types, plasmacytoid dendritic cells, fibroblasts, and monocytes are among the main sources [225]. Type I IFN secretion is induced by any cell type upon encountering viral signatures. In addition, type I IFNs enhances the clearance of virally infected cells by cytotoxic CD8 T cells by increasing the expression of MHC class I. Other effects that further enhance antiviral responses include the activation of dendritic cells, macrophages and NK cells, and the induction of the production of chemokines such as CXCL9, -10, and -11 [225]. Unlike the ubiquitously expressed IFN- α receptor, the IFN- λ receptor is expressed in epithelial cells and a subset of immune cells, including neutrophils [226, 227]. Based on its receptor expression, it is thought that type III IFN responses have critical roles in epithelial and mucosal antiviral immunity [226, 227]. When used in patients, IFN- λ due to limited expression of its receptor in the immune compartment results in less systemic side effects than type I IFN therapy [228].

Type I IFN has been extensively used in the management of Hepatitis B and C infections. Due to side effects, modest efficacy, and the advent of effective antivirals, the use of IFN- α has decreased in the management of hepatitis B [229, 230]. Additionally, IFN- λ has also shown clinical efficacy similar to Type 1 IFN in the management of hepatitis C [228].

In vitro and animal data: In vitro studies have shown IFN- α and β have antiviral activity. However, IFN- β has a more potent coronavirus suppression activity than IFN- α [11-13]. Studies in murine models have shown that IFN- β in combination with antivirals improves pulmonary function but does not reduce viral replication or severe lung pathology [14]. Similar reduction in mortality was also noted in non-human primates treated with IFN- β 1b following MERS-CoV infection [15].

Though there are no corresponding coronavirus murine model studies with IFN- λ , murine models of influenza A virus (IAV) infection showed promising results. IFN- λ treatment resulted in enhanced epithelial barrier function and suppressed initial viral spread without activating the systemic effects seen with IFN- α therapy [16, 17]. Importantly, while IFN- λ treatment of IAV-infected mice lowered the viral load and protected from disease, treatment with IFN- α decreased the viral load but exacerbated disease [16].

Human data: It was recently suggested that one component of SARS-CoV-2-related immunopathology is insufficient robust type I, II or III IFN response [54-57, 231]. This finding along with the known antiviral properties of both type I and type III IFN form the basis of its use in SARS-

CoV-2 [232]. Currently, there is only one published clinical trial of IFN therapy in COVID-19 [233]. In this multicenter, open-label randomized study in Hong Kong, 41 control subjects received lopinavir-ritonavir and 86 adult subjects received intervention therapy with lopinavir-ritonavir as well as oral ribavirin and subcutaneous IFN- β 1b. Subjects were comparable with regard to clinical and laboratory characteristics and underwent treatment initiation a median of 5 days after symptom onset. Subjects in the group receiving the addition of ribavirin and IFN- β 1b to lopinavir-ritonavir had shorter time to complete symptom resolution and shorter time to negative nasopharyngeal swab compared to the control group. Further studies of interferon- β are ongoing, including with administration via inhalation which may decrease systemic side effects (NCT04385095).

Potential Risks:

Therapy with Type I or Type III IFN is associated with a variety of common adverse effects including fatigue, anorexia, nausea, diarrhea, alopecia, fever, rigors, headache, and myalgia [228, 234]. Additionally, neuropsychiatric events including depression are reported [235]. Finally, neutropenia and anemia are also reported.

Additionally, there is theoretical risk for worsening disease with the use of interferon therapy. As morbidity due to COVID-19 appears to be due in large part to hyperinflammation, potential exists for interferon therapy to result in enhanced inflammation and thereby lead to worsening of the CSS[120]. Further, there is a concern that Type I and III IFNs may impair successful antibacterial immune responses and thereby contribute to increased susceptibility to secondary bacterial infections [236, 237].

Practical Considerations:

As we do not suggest use of interferon therapy in pediatric COVID-19 patients, potential dosing and other considerations are not provided.

Other/Emerging Therapies

In addition to the above described immunomodulatory therapies, a number of other agents and immune pathways are being evaluated for treatment of COVID-19. These include immunosuppressive medications traditionally used in the setting of solid organ or hematopoietic cell transplantation, such as tacrolimus (NCT04341038), sirolimus (NCT04341675, NCT04371640), and CTLA4-Fc fusion molecules. The anti-IFN- γ antibody, emapalumab, has recently been demonstrated to have efficacy in the treatment of pediatric primary HLH [238] and is also being evaluated in the treatment of COVID-19 (NCT04324021).

Conclusions

Current data demonstrate that the vast majority of pediatric patients with acute COVID-19 recover from their initial illness without significant morbidity or mortality. However, a subset of pediatric patients progresses to severe or critical acute COVID-19 and may benefit from the use of immunomodulatory therapies that are currently being evaluated in adult COVID-19 patients. Given the paucity of randomized controlled trials of immunomodulatory therapies for COVID-19 in pediatric patients, we have provided the above guidance to support pediatric subspecialists caring for severely and critically ill pediatric COVID-19 patients. Randomized controlled trials of immunomodulatory therapies for pediatric acute COVID-19 are needed.

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References

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* **2020**; 382(13): 1199-207.
2. Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in Children in Early January 2020 in Wuhan, China. *N Engl J Med* **2020**; 382(14): 1370-1.
3. Team CC-R. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep* **2020**; 69(14): 422-6.
4. Wu Q, Xing Y, Shi L, et al. Co-infection and Other Clinical Characteristics of COVID-19 in Children. *Pediatrics* **2020**.
5. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr* **2020**.
6. Team CC-R. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* **2020**; 69(12): 343-6.
7. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J* **2020**.
8. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr* **2020**.
9. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* **2020**; 382(8): 727-33.
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**; 395(10223): 497-506.
11. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* **2020**.
12. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* **2020**.
13. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**.
14. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* **2020**.
15. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* **2020**.
16. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* **2012**; 76(1): 16-32.
17. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* **2017**; 39(5): 529-39.
18. Huang KJ, Su IJ, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. *J Med Virol* **2005**; 75(2): 185-94.
19. Zhang Y, Li J, Zhan Y, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Immun* **2004**; 72(8): 4410-5.
20. Nicholls JM, Poon LL, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* **2003**; 361(9371): 1773-8.
21. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* **2005**; 202(3): 415-24.
22. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* **2006**; 12(10): 1203-7.

23. Huang R, Zhang L, Gu Q, et al. Profiles of acute cytokine and antibody responses in patients infected with avian influenza A H7N9. *PLoS One* **2014**; 9(7): e101788.
24. Arankalle VA, Lole KS, Arya RP, et al. Role of host immune response and viral load in the differential outcome of pandemic H1N1 (2009) influenza virus infection in Indian patients. *PLoS One* **2010**; 5(10).
25. Lee N, Wong CK, Chan PK, et al. Cytokine response patterns in severe pandemic 2009 H1N1 and seasonal influenza among hospitalized adults. *PLoS One* **2011**; 6(10): e26050.
26. Schulert GS, Zhang M, Fall N, et al. Whole-Exome Sequencing Reveals Mutations in Genes Linked to Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome in Fatal Cases of H1N1 Influenza. *J Infect Dis* **2016**; 213(7): 1180-8.
27. Baseler LJ, Falzarano D, Scott DP, et al. An Acute Immune Response to Middle East Respiratory Syndrome Coronavirus Replication Contributes to Viral Pathogenicity. *Am J Pathol* **2016**; 186(3): 630-8.
28. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* **2014**; 160(6): 389-97.
29. Ng DL, Al Hosani F, Keating MK, et al. Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. *Am J Pathol* **2016**; 186(3): 652-8.
30. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. *Nat Rev Rheumatol* **2016**; 12(5): 259-68.
31. Carlisle JW, Ramalingam SS. A banner year for immunotherapy and targeted therapy. *Nat Rev Clin Oncol* **2019**; 16(2): 79-80.
32. Kumar S, Ward BR, Irani AM. Future Prospects of Biologic Therapies for Immunologic Diseases. *Immunol Allergy Clin North Am* **2017**; 37(2): 431-48.
33. Frey N, Porter D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. *Biol Blood Marrow Transplant* **2019**; 25(4): e123-e7.
34. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* **2020**.
35. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hosp Pediatr* **2020**.
36. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* **2020**.
37. Control ECfDPa. Rapid risk assessment: Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children Available at: <https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment>. Accessed May 26.
38. Deza Leon MP, Redzepi A, McGrath E, et al. COVID-19 Associated Pediatric Multi-System Inflammatory Syndrome. *J Pediatric Infect Dis Soc* **2020**.
39. Prevention CfDCa. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: <https://emergency.cdc.gov/han/2020/han00432.asp>. Accessed May 18.
40. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* **2020**; 4(7): 1307-10.
41. Michot JM, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. *Ann Oncol* **2020**.
42. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* **2020**.
43. De Luna G, Habibi A, Deux JF, et al. Rapid and Severe Covid-19 Pneumonia with Severe Acute Chest Syndrome in a Sickle Cell Patient Successfully Treated with Tocilizumab. *Am J Hematol* **2020**.

44. Di Giambenedetto S, Ciccullo A, Borghetti A, et al. Off-label Use of Tocilizumab in Patients with SARS-CoV-2 Infection. *J Med Virol* **2020**.
45. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc* **2020**.
46. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* **2020**.
47. Derespina KR, Kaushik S, Plichta A, et al. Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with COVID-19 in New York City. *J Pediatr* **2020**.
48. Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology* **2020**.
49. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann Intern Med* **2020**.
50. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* **2020**.
51. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* **2020**.
52. Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J Allergy Clin Immunol* **2020**.
53. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov* **2020**; 6: 31.
54. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* **2020**.
55. Trouillet-Assant S, Viel S, Gaymard A, et al. Type I IFN immunoprofiling in COVID-19 patients. *J Allergy Clin Immunol* **2020**.
56. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* **2020**.
57. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe* **2016**; 19(2): 181-93.
58. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis* **2020**.
59. Cavalli G DLG, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* **2020**.
60. Dimopoulos G, de Mast Q, Markou N, et al. Favorable Anakinra Responses in Severe Covid-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis. *Cell Host Microbe* **2020**.
61. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* **2020**.
62. Uciechowski P, Dempke WCM. Interleukin-6: A Masterplayer in the Cytokine Network. *Oncology* **2020**; 98(3): 131-7.
63. Kopf M, Baumann H, Freer G, et al. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* **1994**; 368(6469): 339-42.
64. Harker JA, Lewis GM, Mack L, Zuniga EI. Late interleukin-6 escalates T follicular helper cell responses and controls a chronic viral infection. *Science* **2011**; 334(6057): 825-9.
65. Kuo TM, Hu CP, Chen YL, et al. HBV replication is significantly reduced by IL-6. *J Biomed Sci* **2009**; 16: 41.
66. Lauder SN, Jones E, Smart K, et al. Interleukin-6 limits influenza-induced inflammation and protects against fatal lung pathology. *Eur J Immunol* **2013**; 43(10): 2613-25.

67. Administration FD. Actemra Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf. Accessed May 14.
68. Lau SKP, Lau CCY, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. *J Gen Virol* **2013**; 94(Pt 12): 2679-90.
69. Zhou J, Chu H, Li C, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. *J Infect Dis* **2014**; 209(9): 1331-42.
70. Wang W, Ye L, Ye L, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. *Virus Res* **2007**; 128(1-2): 1-8.
71. Zhang X, Wu K, Wang D, et al. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF-kappaB. *Virology* **2007**; 365(2): 324-35.
72. Cameron MJ, Kelvin AA, Leon AJ, et al. Lack of innate interferon responses during SARS coronavirus infection in a vaccination and reinfection ferret model. *PLoS One* **2012**; 7(9): e45842.
73. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis* **2020**.
74. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* **2020**; 46(5): 846-8.
75. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* **2020**; 26(4): 502-5.
76. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin Infect Dis* **2020**.
77. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* **2020**.
78. Price CC, Altice FL, Shyr Y, et al. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients: Survival and Clinical Outcomes. *Chest* **2020**.
79. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* **2020**.
80. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* **2020**; 76: 43-9.
81. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* **2020**.
82. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* **2020**: 102568.
83. Jacobs B, Jawad A, Fattah Z. Pneumatosis Intestinalis and Intestinal Perforation in a Patient Receiving Tocilizumab. *Arch Rheumatol* **2018**; 33(3): 372-5.
84. Genovese MC, Kremer JM, van Vollenhoven RF, et al. Transaminase Levels and Hepatic Events During Tocilizumab Treatment: Pooled Analysis of Long-Term Clinical Trial Safety Data in Rheumatoid Arthritis. *Arthritis Rheumatol* **2017**; 69(9): 1751-61.
85. Morrison AR, Johnson JM, Ramesh M, Bradley P, Jennings J, Smith ZR. Letter to the Editor: Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab. *J Med Virol* **2020**.
86. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* **2020**; 2(7): e393-e400.

87. Ucciferri C, Auricchio A, Di Nicola M, et al. Canakinumab in a subgroup of patients with COVID-19. *Lancet Rheumatol* **2020**.
88. Chung Y, Chang SH, Martinez GJ, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* **2009**; 30(4): 576-87.
89. Cahill CM, Rogers JT. Interleukin (IL) 1 β induction of IL-6 is mediated by a novel phosphatidylinositol 3-kinase-dependent AKT/I κ B kinase α pathway targeting activator protein-1. *J Biol Chem* **2008**; 283(38): 25900-12.
90. Cavalli G, Dinarello CA. Anakinra Therapy for Non-cancer Inflammatory Diseases. *Front Pharmacol* **2018**; 9: 1157.
91. Dubois EA, Rissmann R, Cohen AF. Rilonacept and canakinumab. *Br J Clin Pharmacol* **2011**; 71(5): 639-41.
92. Nuki G, Bresnihan B, Bear MB, McCabe D, European Group Of Clinical I. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* **2002**; 46(11): 2838-46.
93. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis* **2004**; 63(9): 1062-8.
94. Ilowite NT, Prather K, Lokhnygina Y, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol* **2014**; 66(9): 2570-9.
95. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum* **2008**; 58(8): 2443-52.
96. Kone-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. *Arthritis Res Ther* **2011**; 13(6): R202.
97. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. *N Engl J Med* **2018**; 378(20): 1908-19.
98. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* **2012**; 367(25): 2396-406.
99. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med* **2016**; 44(2): 275-81.
100. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. *Rheumatology (Oxford)* **2011**; 50(2): 417-9.
101. Eloiseily EM, Weiser P, Crayne CB, et al. Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis. *Arthritis Rheumatol* **2020**; 72(2): 326-34.
102. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children*. *Pediatr Crit Care Med* **2014**; 15(5): 401-8.
103. Heney D, Whicher JT. Factors affecting the measurement of cytokines in biological fluids: implications for their clinical measurement. *Ann Clin Biochem* **1995**; 32 (Pt 4): 358-68.
104. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe Acute Respiratory Syndrome Coronavirus Viroprotein 3a Activates the NLRP3 Inflammasome. *Front Microbiol* **2019**; 10: 50.

105. Nieto-Torres JL, Verdia-Baguena C, Jimenez-Guardeno JM, et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology* **2015**; 485: 330-9.
106. Siu KL, Yuen KS, Castano-Rodriguez C, et al. Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J* **2019**; 33(8): 8865-77.
107. Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. *Cell Death Discov* **2019**; 5: 101.
108. Duan ZP, Chen Y, Zhang J, et al. [Clinical characteristics and mechanism of liver injury in patients with severe acute respiratory syndrome]. *Zhonghua Gan Zang Bing Za Zhi* **2003**; 11(8): 493-6.
109. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* **2004**; 136(1): 95-103.
110. Ng PC, Lam CW, Li AM, et al. Inflammatory cytokine profile in children with severe acute respiratory syndrome. *Pediatrics* **2004**; 113(1 Pt 1): e7-14.
111. He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J Pathol* **2006**; 210(3): 288-97.
112. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* **2020**; 2(6): e325-e31.
113. Saccomanno B, Tibaldi J, Minoia F, et al. Predictors of Effectiveness of Anakinra in Systemic Juvenile Idiopathic Arthritis. *J Rheumatol* **2019**; 46(4): 416-21.
114. Sonmez HE, Demir S, Bilginer Y, Ozen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol* **2018**; 37(12): 3329-35.
115. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* **2009**; 68(1): 25-32.
116. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* **2020**.
117. Monteagudo LA, Boothby A, Gertner E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. *ACR Open Rheumatol* **2020**; 2(5): 276-82.
118. Kullenberg T, Lofqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. *Rheumatology (Oxford)* **2016**; 55(8): 1499-506.
119. Klein A, Klotsche J, Hugle B, et al. Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. *Rheumatology (Oxford)* **2019**.
120. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **2020**; 395(10229): 1033-4.
121. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet* **2020**; 395(10225): 683-4.
122. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* **2020**; 395(10223): 473-5.
123. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* **2017**; 17(4): 233-47.

124. Ratman D, Vanden Berghe W, Dejager L, et al. How glucocorticoid receptors modulate the activity of other transcription factors: a scope beyond tethering. *Mol Cell Endocrinol* **2013**; 380(1-2): 41-54.
125. Newton R, Shah S, Altonsy MO, Gerber AN. Glucocorticoid and cytokine crosstalk: Feedback, feedforward, and co-regulatory interactions determine repression or resistance. *J Biol Chem* **2017**; 292(17): 7163-72.
126. Rogatsky I, Ivashkiv LB. Glucocorticoid modulation of cytokine signaling. *Tissue Antigens* **2006**; 68(1): 1-12.
127. Herold MJ, McPherson KG, Reichardt HM. Glucocorticoids in T cell apoptosis and function. *Cell Mol Life Sci* **2006**; 63(1): 60-72.
128. Lee N, Hui D, Wu A, et al. A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong. *N Engl J Med* **2003**.
129. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* **2003**; 289(21): 2801-9.
130. Lew TW, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* **2003**; 290(3): 374-80.
131. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *The Lancet* **2003**; 361(9371): 1767-72.
132. Lau AC, So LK, Miu FP, et al. Outcome of coronavirus-associated severe acute respiratory syndrome using a standard treatment protocol. *Respirology* **2004**; 9: 173-83.
133. Sung JJ, Wu A, Joynt GM, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* **2004**; 59(5): 414-20.
134. Yam LY, Lau AC, Lai FY, et al. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. *J Infect* **2007**; 54(1): 28-39.
135. Ho JC, Ooi GC, Mok TY, et al. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med* **2003**; 168(12): 1449-56.
136. Chen RC, Tang XP, Tan SY, et al. Treatment of severe acute respiratory syndrome with glucocorticoids: the Guangzhou experience. *Chest* **2006**; 129(6): 1441-52.
137. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol* **2004**; 31(4): 304-9.
138. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* **2006**; 3(9): e343.
139. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* **2020**; 395(10223): 497-506.
140. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* **2020**.
141. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* **2020**.
142. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* **2020**.
143. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* **2020**.
144. Keller MJ, Kitsis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. *J Hosp Med* **2020**.
145. Hazbun ME, Faust AC, Ortegón AL, et al. The Combination of Tocilizumab and Methylprednisolone Along With Initial Lung Recruitment Strategy in Coronavirus Disease 2019 Patients Requiring Mechanical Ventilation: A Series of 21 Consecutive Cases. *Crit Care Explor* **2020**; 2(6): e0145.

146. Callejas Rubio JL, Luna Del Castillo JD, de la Hera Fernandez J, Guirao Arrabal E, Colmenero Ruiz M, Ortego Centeno N. Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. *Med Clin (Barc)* **2020**.
147. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* **2018**; 197(6): 757-67.
148. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* **2007**; (3): CD000195.
149. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* **2008**; (2): CD006792.
150. El-Nawawy A, Khater D, Omar H, Wali Y. Evaluation of Early Corticosteroid Therapy in Management of Pediatric Septic Shock in Pediatric Intensive Care Patients: A Randomized Clinical Study. *Pediatr Infect Dis J* **2017**; 36(2): 155-9.
151. Valoor HT, Singhi S, Jayashree M. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. *Pediatr Crit Care Med* **2009**; 10(1): 121-5.
152. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatr Crit Care Med* **2020**; 21(2): e52-e106.
153. Rochweg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Crit Care Med* **2018**; 46(9): 1411-20.
154. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev* **2019**; 12: CD002243.
155. Annane D, Pastores SM, Rochweg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* **2017**; 45(12): 2078-88.
156. Hegenbarth MA, American Academy of Pediatrics Committee on D. Preparing for pediatric emergencies: drugs to consider. *Pediatrics* **2008**; 121(2): 433-43.
157. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* **2020**.
158. Organization WH. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Accessed March 31.
159. Parikh NS, Schweitzer AD, Young RJ, et al. Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. *Journal of the neurological sciences* **2017**; 380: 11-5.
160. Hodgins GE, Saltz SB, Gibbs EP, Gonzalez R, Regan J, Nemeroff C. Steroid-Induced Psychosis in the Pediatric Population: A New Case and Review of the Literature. *Journal of child and adolescent psychopharmacology* **2018**; 28(5): 354-9.
161. Lee DTS, Wing YK, Leung HCM, et al. Factors Associated with Psychosis among Patients with Severe Acute Respiratory Syndrome: A Case-Control Study. *Clin Infect Dis* **2004**; 39: 1247-9.
162. Hong N, Du XK. Avascular necrosis of bone in severe acute respiratory syndrome. *Clin Radiol* **2004**; 59(7): 602-8.
163. Lv H, de Vlas SJ, Liu W, et al. Avascular osteonecrosis after treatment of SARS: a 3-year longitudinal study. *Trop Med Int Health* **2009**; 14 Suppl 1: 79-84.
164. Zhao R, Wang H, Wang X, Feng F. Steroid therapy and the risk of osteonecrosis in SARS patients: a dose-response meta-analysis. *Osteoporos Int* **2017**; 28(3): 1027-34.
165. Liu T, Ma J, Su B, Wang H, Wang Q, Ma X. A 12-year follow-up study of combined treatment of post-severe acute respiratory syndrome patients with femoral head necrosis. *Ther Clin Risk Manag* **2017**; 13: 1449-54.

166. Chan CW, Chiu WK, Chan CC, Chow EY, Cheung HM, Ip PL. Osteonecrosis in children with severe acute respiratory syndrome. *Pediatr Infect Dis J* **2004**; 23(9): 888-90.
167. Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as Adjunctive Therapy in the Treatment of Influenza: An Updated Cochrane Systematic Review and Meta-analysis. *Crit Care Med* **2020**; 48(2): e98-e106.
168. Rutsaert L, Steinfart N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* **2020**; 10(1): 71.
169. Koehler P, Cornely OA, Bottiger BW, et al. COVID-19 associated pulmonary aspergillosis. *Mycoses* **2020**; 63(6): 528-34.
170. Thijs E, Wierckx K, Vandecasteele S, Van den Bruel A. Adrenal insufficiency, be aware of drug interactions! *Endocrinol Diabetes Metab Case Rep* **2019**; 2019.
171. Bechman K, Subesinghe S, Norton S, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* **2019**; 58(10): 1755-66.
172. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. *Protein Sci* **2018**; 27(12): 1984-2009.
173. O'Shea JJ, Laurence A, McInnes IB. Back to the future: oral targeted therapy for RA and other autoimmune diseases. *Nat Rev Rheumatol* **2013**; 9(3): 173-82.
174. Huang Z, Lee PY, Yao X, Zheng S, Li T. Tofacitinib Treatment of Refractory Systemic Juvenile Idiopathic Arthritis. *Pediatrics* **2019**; 143(5).
175. Kerrigan SA, McInnes IB. JAK Inhibitors in Rheumatology: Implications for Paediatric Syndromes? *Curr Rheumatol Rep* **2018**; 20(12): 83.
176. Gonzalez Vicent M, Molina B, Gonzalez de Pablo J, Castillo A, Diaz MA. Ruxolitinib treatment for steroid refractory acute and chronic graft vs host disease in children: Clinical and immunological results. *Am J Hematol* **2019**; 94(3): 319-26.
177. Khandelwal P, Teusink-Cross A, Davies SM, et al. Ruxolitinib as Salvage Therapy in Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Hematopoietic Stem Cell Transplant Patients. *Biol Blood Marrow Transplant* **2017**; 23(7): 1122-7.
178. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol* **2019**; 6(12): e630-e7.
179. Sin JH, Zangardi ML. Ruxolitinib for secondary hemophagocytic lymphohistiocytosis: First case report. *Hematol Oncol Stem Cell Ther* **2019**; 12(3): 166-70.
180. Broglie L, Pommert L, Rao S, et al. Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis. *Blood Adv* **2017**; 1(19): 1533-6.
181. Trantham T, Auten J, Muluneh B, Van Deventer H. Ruxolitinib for the treatment of lymphoma-associated hemophagocytic lymphohistiocytosis: A cautionary tale. *J Oncol Pharm Pract* **2019**: 1078155219878774.
182. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* **2020**; 146(1): 137-46 e3.
183. Titanji BK, Farley MM, Mehta A, et al. Use of Baricitinib in Patients with Moderate and Severe COVID-19. *Clin Infect Dis* **2020**.
184. Cantini F, Niccoli L, Nannini C, et al. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. *J Infect* **2020**.
185. Colombel JF. Herpes Zoster in Patients Receiving JAK Inhibitors For Ulcerative Colitis: Mechanism, Epidemiology, Management, and Prevention. *Inflamm Bowel Dis* **2018**; 24(10): 2173-82.
186. Richardson PJ, Corbellino M, Stebbing J. Baricitinib for COVID-19: a suitable treatment? - Authors' reply. *Lancet Infect Dis* **2020**.

187. He Y, Wong AY, Chan EW, et al. Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *BMC Musculoskelet Disord* **2013**; 14: 298.
188. Gaspari V, Zengarini C, Greco S, Vangeli V, Mastroianni A. Side effects of ruxolitinib in patients with SARS-CoV-2 infection: two case reports. *Int J Antimicrob Agents* **2020**: 106023.
189. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* **2020**.
190. Administration UFD. OLUMIANT: Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf Accessed May 27.
191. Veeravalli V, Dash RP, Thomas JA, Babu RJ, Madgula LMV, Srinivas NR. Critical Assessment of Pharmacokinetic Drug-Drug Interaction Potential of Tofacitinib, Baricitinib and Upadacitinib, the Three Approved Janus Kinase Inhibitors for Rheumatoid Arthritis Treatment. *Drug Saf* **2020**.
192. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* **2020**; 130(4): 1545-8.
193. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* **2005**; 24(1): 44-6.
194. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* **2004**; 10(7): 676-8.
195. Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther* **2018**; 23(7): 617-22.
196. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* **2015**; 211(1): 80-90.
197. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* **2020**.
198. Zhang B, Liu S, Tan T, et al. Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection. *Chest* **2020**.
199. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* **2020**.
200. Ahn JY, Sohn Y, Lee SH, et al. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. *J Korean Med Sci* **2020**; 35(14): e149.
201. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* **2020**.
202. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA* **2020**.
203. Qu J, Wu C, Li X, et al. Profile of IgG and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* **2020**.
204. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med* **2020**.
205. Zhang L, Pang R, Xue X, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. *Aging (Albany NY)* **2020**; 12(8): 6536-42.
206. Zeng QL, Yu ZJ, Gou JJ, et al. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. *J Infect Dis* **2020**.
207. Figlerowicz M, Mania A, Lubarski K, et al. First case of convalescent plasma transfusion in a child with COVID-19-associated severe aplastic anemia. *Transfus Apher Sci* **2020**: 102866.

208. Wan Y, Shang J, Sun S, et al. Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. *J Virol* **2020**; 94(5).
209. Administration FaD. Recommendations for Investigational COVID-19 Convalescent Plasma. Available at: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma#Collection%20of%20COVID-19>. Accessed May 15.
210. Liu L, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* **2019**; 4(4).
211. Crowe JE, Jr., Firestone CY, Murphy BR. Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. *J Immunol* **2001**; 167(7): 3910-8.
212. Murphy BR, Graham BS, Prince GA, et al. Serum and nasal-wash immunoglobulin G and A antibody response of infants and children to respiratory syncytial virus F and G glycoproteins following primary infection. *J Clin Microbiol* **1986**; 23(6): 1009-14.
213. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* **2020**.
214. Diez JM, Romero C, Gajardo R. Currently available intravenous immunoglobulin contains antibodies reacting against severe acute respiratory syndrome coronavirus 2 antigens. *Immunotherapy* **2020**.
215. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* **2001**; 291(5503): 484-6.
216. Siedlar M, Strach M, Bukowska-Strakova K, et al. Preparations of intravenous immunoglobulins diminish the number and proinflammatory response of CD14+CD16++ monocytes in common variable immunodeficiency (CVID) patients. *Clin Immunol* **2011**; 139(2): 122-32.
217. Othy S, Hegde P, Topcu S, et al. Intravenous gammaglobulin inhibits encephalitogenic potential of pathogenic T cells and interferes with their trafficking to the central nervous system, implicating sphingosine-1 phosphate receptor 1-mammalian target of rapamycin axis. *J Immunol* **2013**; 190(9): 4535-41.
218. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol* **2017**; 139(3S): S1-S46.
219. Wohlfarth P, Agis H, Gualdoni GA, et al. Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis. *J Intensive Care Med* **2019**; 34(9): 723-31.
220. Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review). *Hematology* **2005**; 10(2): 101-5.
221. Van Dyne EA, Neaterour P, Rivera A, et al. Incidence and Outcome of Severe and Nonsevere Thrombocytopenia Associated With Zika Virus Infection-Puerto Rico, 2016. *Open Forum Infect Dis* **2019**; 6(1): ofy325.
222. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* **2020**; 506: 145-8.
223. Sen ES, Clarke SL, Ramanan AV. Macrophage Activation Syndrome. *Indian J Pediatr* **2016**; 83(3): 248-53.
224. Cao W, Liu X, Bai T, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. *Open Forum Infect Dis* **2020**; 7(3): ofaa102.
225. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. *Nat Rev Immunol* **2015**; 15(2): 87-103.
226. Ye L, Schnepf D, Staeheli P. Interferon-lambda orchestrates innate and adaptive mucosal immune responses. *Nat Rev Immunol* **2019**; 19(10): 614-25.

227. Prokunina-Olsson L, Alphonse N, Dickenson RE, et al. COVID-19 and emerging viral infections: The case for interferon lambda. *J Exp Med* **2020**; 217(5).
228. Muir AJ, Arora S, Everson G, et al. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J Hepatol* **2014**; 61(6): 1238-46.
229. Agarwal K, Brunetto M, Seto WK, et al. 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* **2018**; 68(4): 672-81.
230. Korean Association for the Study of the L. KASL clinical practice guidelines for management of chronic hepatitis B. *Clin Mol Hepatol* **2019**; 25(2): 93-159.
231. Chu H, Chan JF, Wang Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. *Clin Infect Dis* **2020**.
232. O'Brien TR, Thomas DL, Jackson SS, Prokunina-Olsson L, Donnelly RP, Hartmann R. Weak Induction of Interferon Expression by SARS-CoV-2 Supports Clinical Trials of Interferon Lambda to Treat Early COVID-19. *Clin Infect Dis* **2020**.
233. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* **2020**.
234. Gaeta GB, Precone DF, Felaco FM, et al. Premature discontinuation of interferon plus ribavirin for adverse effects: a multicentre survey in 'real world' patients with chronic hepatitis C. *Aliment Pharmacol Ther* **2002**; 16(9): 1633-9.
235. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* **2005**; 19(2): 105-23.
236. Planet PJ, Parker D, Cohen TS, et al. Lambda Interferon Restructures the Nasal Microbiome and Increases Susceptibility to *Staphylococcus aureus* Superinfection. *mBio* **2016**; 7(1): e01939-15.
237. Davidson S, Maini MK, Wack A. Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. *J Interferon Cytokine Res* **2015**; 35(4): 252-64.
238. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. *N Engl J Med* **2020**; 382(19): 1811-22.

Table 1. Suggested COVID-19 illness severity categories (modified from [45])

Disease category	Clinical support requirement
Mild/Moderate	No new or increased supplemental oxygen requirement.
Severe	New or increase from baseline supplemental oxygen requirement without need for new or increase in baseline non-invasive/invasive mechanical ventilation.
Critical	New or increased requirement for invasive or non-invasive mechanical ventilation, sepsis, or multi-organ failure; OR rapidly worsening clinical trajectory that does not yet meet these criteria.
Comments: Non-invasive mechanical ventilation includes high-flow nasal canula, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP).	

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Table 2: Summary of Guidance Statements for Immunomodulatory Use in Acute COVID-19 Pediatric Patients

I. ARE IMMUNOMODULATORY AGENTS INDICATED IN CHILDREN WITH COVID-19?

We emphasize that the vast majority of children with COVID-19 will recover from the acute phase of infection with supportive care. Enrollment in clinical trials of immunomodulatory therapy for COVID-19 is preferred. In the absence of available clinical trials, use of immunomodulatory therapy for COVID-19 may be considered in compliance with local institutional policies on consent for experimental and/or off-label treatment.

II. WHAT CRITERIA DEFINE THE PEDIATRIC POPULATION IN WHOM IMMUNOMODULATORY USE MAY BE CONSIDERED?

We suggest that immunomodulatory therapy only be used for pediatric patients in the setting of confirmed critical COVID-19 (SARS-CoV-2 PCR positive) **with** evidence of hyperinflammation (Table 4). In addition, pediatric COVID-19 patients with hyperinflammation whose pace of illness progression suggests imminent progression to critical COVID-19 may be considered for immunomodulatory treatment. Use of immunomodulation for pediatric COVID-19 should be performed in consultation with specialists familiar with these medications.

III. WHICH IMMUNOMODULATORY AGENTS SHOULD BE CONSIDERED?

- There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients as of 24 July 2020. Therefore, no guidance can be provided to support the use of one immunomodulatory therapy over another.
- If immunomodulators are used in the treatment of COVID-19, patients should be monitored for adverse effects.

Note: The order of discussion of each category below does not denote an order of preference.

A. IL-6 inhibition

IL-6 inhibition may be considered in the care of pediatric patients with critical COVID-19 with priority given to clinical trial enrollment if available.

B. IL-1 inhibition

IL-1 inhibition may be considered in the care of pediatric patients with critical COVID-19 with priority given to clinical trial enrollment if available. If IL-1 inhibition is used as a treatment modality for pediatric COVID-19 patients, we suggest the use of anakinra based on its safety profile and favorable pharmacokinetics.

C. Glucocorticoids

Given their pleiotropic effects, glucocorticoids are used in a variety of inflammatory conditions and settings. As such, it is difficult to definitively support or discourage the use of glucocorticoids in all situations. Therefore, we have provided guidance for specific situations in the following section.

- Glucocorticoid therapy is not currently indicated for outpatients or hospitalized patients with mild or moderate COVID-19.
- Glucocorticoid therapy may be considered for pediatric patients with critical COVID-19 with preference for use in the setting of clinical trials, if available.
- Diagnosis with COVID-19 does not preclude use of steroids when they are otherwise indicated (for example, in asthma or catecholamine-refractory shock).

D. JAK inhibition

JAK inhibitors should not be used for children with COVID-19 outside of clinical trials.

E. Convalescent plasma therapy

Use of convalescent plasma in pediatric COVID, may be considered as part of the recently established FDA eIND program if in the United States or as part of a clinical trial.

F. IVIG

We do not currently recommend use of IVIG for treatment of acute COVID-19 in pediatric patients with the exception of specific clinical scenarios in which IVIG is typically used. Importantly, our recommendations do not apply to the use of IVIG in the treatment of MIS-C.

G. Interferons

Type I or type III IFN should not be used for pediatric COVID-19 patients outside of a clinical trial.

Table 3: Comparison of Clinical, Laboratory, and Treatment Features of Hyperinflammatory Syndromes

Hyperinflammatory Syndrome Characteristics	Familial Hemophagocytic Lymphohistiocytosis (fHLH)	Macrophage Activation Syndrome (MAS, Rheumatologic HLH)	Cytokine Release Syndrome (CRS, Iatrogenic HLH)	Respiratory Virus associated MAS/HLH (RV-HLH)	Cytokine Storm Syndrome (CSS) in the context of acute COVID-19
Clinical Settings	Genetic defects in cytotoxicity	Underlying rheumatologic condition (sJIA, AOSD, SLE)	Administration of chimeric antigen receptor T-cells (CAR-T cells)	Respiratory viruses (including influenza, adenovirus)	Infection with SARS-CoV-2
Clinical Features	Early age of onset, fever, HSM, CNS disease, rash, hypoxia and ARDS	Fever, HSM, lymphadenopathy, CNS disease, rash, hypoxia and ARDS, cardiac disease Rare: Kawasaki disease	Fevers, vasodilatory shock, capillary leak, hypoxia and ARDS, neurotoxicity, heart failure and arrhythmias, HSM (occasionally)	Fevers, hypoxia and ARDS, HSM	Fever, ARDS, heart failure and arrhythmias, blood clots, stroke, CNS disease
Laboratory Features	Pancytopenia; elevated CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, triglycerides, BUN/Cr, sIL2Ra; low fibrinogen, albumin; hemophagocytosis	Elevated CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, triglycerides, BUN/Cr, sIL2Ra; hemophagocytosis	Elevated CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, BUN/Cr, sIL2Ra; low fibrinogen, albumin; delayed hematopoiesis	Elevated CRP, ferritin, PT/PTT, AST/ALT, bilirubin	Lymphopenia, thrombocytopenia; pancytopenia (rare); elevated neutrophil %, CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, BUN/Cr, cardiac troponin I; low fibrinogen, albumin; RNAemia
Pathogenic Cytokines and Chemokines Associated with Hyperinflammation	IFN γ , IL6, IL8, IL-10, IL12, IL18, TNF, CCL3, CXCL9	IFN γ , IL1 β , IL2, IL6, IL18, TNF (in SLE-MAS), CXCL9	IFN γ , IL6, IL8, IL15, GM-CSF, CCL2, CCL3, CCL4	Unclear	IFN γ , IL1 β , IL2, IL6, IL7, IL17, TNF, G-CSF, GM-CSF, CCL2, CCL3, CCL7, CXCL9, CXCL10
Genetic Predisposition	Biallelic LOF in genes critical for cytotoxic granule release and function (<i>PRF1</i>)	Pathogenic gene variants resulting in inflammasome GOF; Heterozygous LOF or polymorphism in cytotoxic genes	Heterozygous <i>PRF1</i> variants (rare)	Heterozygous missense variants in <i>PRF1</i> and <i>LYST</i> identified	Unknown
Diagnostic or Grading Criteria	HLH-2004, MH score (MAS vs HLH)	MH score, MS score and ferritin:ESR ratio (MAS vs active sJIA)	ASTCT Consensus Grading for CRS	No consensus, some diagnosed with HLH-2004	Unknown; difficult to differentiate from COVID-19 ARDS
Treatment	Glucocorticosteroids, etoposide, emapalumab, ruxolitinib, HCT	Anakinra, glucocorticosteroids, ruxolitinib, IL18-BP	Tocilizumab, glucocorticosteroids	Unknown, cases improved with glucocorticosteroids	Unknown
Comments	fHLH driven by IFN γ production by cytotoxic cells; Requires HCT for cure	MAS distinguished and driven by IL1 or IL18; IL18/CXCL9 ratio used to	IL6 most strongly associated with severe CRS, IL1 may also be important with	Hemophagocytosis is identified in bone marrow, spleen, and/or lymph nodes in	No HSM; hemophagocytosis seen in SARS-CoV-1

		differentiate MAS vs fHLH	murine studies suggesting role in both CRS and neurotoxicity; no hemophagocytosis	fatal cases; hyperferritinemia not always present	
<p>Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; HCT, Hematopoietic Cell Transplant; HSM, hepatosplenomegaly; fHLH, familial HLH; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; CSS, cytokine storm syndrome, soJIA, systemic-onset juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; AOSD, adult-onset Still's disease; ARDS, acute respiratory distress syndrome; LOF, loss of function; GOF, gain of function; CNS, central nervous system</p>					

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Table 4: Clinical and Laboratory Features for Considering the Use of Immunomodulatory Therapy for Critical COVID-19 in Pediatric Patients

Characteristic	Comments
Evidence for Hyperinflammatory State	
Clinical Signs <ul style="list-style-type: none"> • Sustained or Recurrent fever • Hepatomegaly • Splenomegaly and/or Lymphadenopathy 	<ul style="list-style-type: none"> • Fever is likely most informative in the setting of other features of hyperinflammation described below • Consider evaluation for concurrent viral, bacterial, or fungal infection
Laboratory <ul style="list-style-type: none"> • Elevated ferritin and/or CRP • Decreased fibrinogen • Elevated serum IL-6 or other pro-inflammatory cytokines • Other CSS associated labs (elevated sIL2R, sCD163, or Triglycerides) 	<ul style="list-style-type: none"> • Very likely to be non-specific in isolation • Specific values indicating need for immunomodulation are not currently known • Many labs will not have clinically actionable turnaround time for serum cytokines and some CSS associated labs
Rapid Deterioration and/or Presence of or risk for Organ Failure	
Cardiac <ul style="list-style-type: none"> • Elevated BNP or troponin • Persistent hemodynamic instability non-responsive to standard pressor support • Elevated lactate after appropriate fluid resuscitation • Evidence of cardiomyopathy by echocardiogram • Life-threatening arrhythmias 	<ul style="list-style-type: none"> • Evaluation for confounding causes of organ dysfunction or failure (e.g. other infections, medication effects, etc.) • Attention should be given to the pace of clinical worsening. Patients progressing rapidly to severe COVID-19 may be at risk for further progression to critical COVID-19.
Respiratory <ul style="list-style-type: none"> • Abnormal PaO₂/FiO₂ ratio or SpO₂/FiO₂ • Rapidly escalating supplemental oxygen requirement • New mechanical ventilation requirement 	
Coagulopathy <ul style="list-style-type: none"> • Elevated D-dimer • Thrombocytopenia • Prolonged PT or PTT • Decreasing fibrinogen 	
Neurologic <ul style="list-style-type: none"> • Altered mental status 	
Hepatic <ul style="list-style-type: none"> • Evidence of coagulopathy (see above) • Elevated bilirubin, GGT, and/or transaminases 	
Renal <ul style="list-style-type: none"> • Decreased creatinine clearance 	
Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; CSS, cytokine storm syndrome; PT, prothrombin time; PTT, partial thromboplastin time; GGT, gamma-glutamyl transferase	