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ORIGINAL ARTICLE

Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients

Daniel E. Dulek,[1] Robert C. Fuhlbrigge,[2] Alison C. Tribble,[3] James A. Connelly,[4] Michele M. Loi,[5] Hassan El Chebib,[6] Shanmuganathan Chandrakasan,[7] William R. Otto,[8] Caroline Diorio,[9] Garrett Keim,[10] Kelly Walkovich,[11] Preeti Jaggi,[12] Jennifer E. Girotto,[6,13] April Yarbrough,[14] Edward M. Behrens,[15] Randy Q. Cron,[16] and Hamid Bassiri[8]

[1]Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]Section of Rheumatology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado, USA; [3]Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA; [4]Division of Pediatric Hematology Oncology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [5]Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado, USA; [6]Division of Infectious Diseases and Immunology, Department of Pediatrics, Connecticut Children's, Hartford, Connecticut, USA; [7]Division of Pediatric Hematology Oncology, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA; [8]Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [9]Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [10]Division of Critical Care Medicine, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [11]Division of Pediatric Hematology Oncology, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA; [12]Division of Pediatric Infectious Diseases, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA; [13]University of Connecticut School of Pharmacy, Storrs, Connecticut, USA; [14]Department of Pharmacy, Children's of Alabama, Birmingham, Alabama, USA; [15]Division of Pediatric Rheumatology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; and [16]Division of Pediatric Rheumatology, Department of Pediatrics, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama, USA

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 severe acute respiratory syndrome coronavirus 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 multiorgan 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.

Key words. COVID-19; IL-1; IL-6; immunomodulatory therapy; SARS-CoV-2.

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 multiorgan 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);

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Corresponding Author: Hamid Bassiri, MD, PhD, 3501 Civic Center Blvd, Rm 3104, Colket Translational Research Bldg, Philadelphia, PA 19104. E-mail: bassiri@email.chop.edu. Daniel E. Dulek, MD, D-7235 Medical Center North, 1161 21st Ave S, Nashville, TN 37232–2581. E-mail: daniel.dulek@vumc.org.

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in adult patients with progressive disease, extrapulmonary manifestations and evidence of multiorgan involvement are 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 multiorgan 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]. Furthermore, severe COVID-19 is associated with more significant lymphopenia, systemically elevated proinflammatory cytokine levels, and impaired $CD4^+$ T-cell interferon gamma (IFN-γ) expression compared with 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 severe acute respiratory syndrome (SARS-CoV-1; 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 (virus infections including severe [18–21]; avian influenza [22, 23]; 2009 H1N1 [24–26]; MERS [27–29]). Since the initial virus infections including severe 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 2 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 multiorgan failure [5]. In other pediatric patients, an emerging inflammatory disease has recently been described [34–36] This latter presentation has been variably called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [37], pediatric inflammatory multisystem syndrome (PMIS) [38], and multisystem inflammatory syndrome in children (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 are 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, the terms "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 rather is 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 (RCTs) 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 toward 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 3 major questions related to immunomodulatory therapy for children with COVID-19:

I. Are immunomodulatory agents indicated in children with COVID-19?
II. What criteria define the pediatric population in whom immunomodulatory therapy may be considered?
III. 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 interleukin (IL) 1 inhibitors, IL-6 inhibitors, glucocorticoids, convalescent plasma, Janus kinase inhibitors, IVIG, and interferons. Within each section we provide a guidance statement followed by rationale and an evidence summary. In vitro and animal model data are 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.

Table 1. Suggested Coronavirus Disease 2019 Illness Severity Categories

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 noninvasive/invasive mechanical ventilation.
Critical	New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, or multiorgan failure; *OR* rapidly worsening clinical trajectory that does not yet meet these criteria.

Table is modified from Chiotos et al [45]. Noninvasive mechanical ventilation includes high-flow nasal canula, continuous positive airway pressure, or bilevel positive airway pressure.

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 RCTs 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 reverse-transcription polymerase chain reaction [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 these 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 toward this category, the potential benefits of immunomodulatory therapy may offset the potential risks. In addition, given the potential risks of immunomodulatory

Table 2. Summary of Guidance Statements for Immunomodulatory Use in Pediatric Patients With Acute Coronavirus Disease 2019

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 (see 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 July 24, 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 IFNs should not be used for pediatric COVID-19 patients outside of a clinical trial.

Abbreviations: COVID-19, coronavirus disease 2019; eIND, emergency investigational new drug; FDA, Food and Drug Administration; IFN, interferon; IL, interleukin; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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 multiorgan 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, natural killer [NK] cells) and adaptive immune cells (T cells) and overproduction of proinflammatory 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

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

Hyperinflammatory Syndrome Characteristics	Familial HLH	Macrophage Activation Syndrome (MAS, Rheumatologic HLH)	Cytokine Release Syndrome (CRS, Iatrogenic HLH)	Respiratory Virus–Associated MAS/HLH	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, sIL-2Ra; low fibrinogen, albumin; hemophagocytosis	Elevated CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, triglycerides, BUN/Cr, sIL-2Ra; hemophagocytosis	Elevated CRP, ferritin, PT/PTT/D-dimer, AST/ALT, bilirubin, LDH, BUN/Cr, sIL-2Ra; 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, IL-6, IL-8, IL-10, IL-12, IL-18, TNF, CCL3, CXCL9	IFN-γ, IL-1β, IL-2, IL-6, IL-18, TNF (in SLE-MAS), CXCL9	IFN-γ, IL-6, IL-8, IL-15, GM-CSF, CCL2, CCL3, CCL4	Unclear	IFN-γ, IL-1β, IL-2, IL-6, IL-7, IL-17, TNF, G-CSF, GM-CSF, CCL2, CCL3, CCL7, CXCL9, CXCL10
Genetic predisposition	Biallelic LOF in genes critical for cytotoxic granule release and function (*PRF1*)	Pathogenic gene variants resulting in inflammasome GOF; heterozygous LOF or polymorphism in cytotoxic genes	Heterozygous *PRF1* variants (rare)	Heterozygous missense variants in *PRF1* and *LYST* identified	Unknown
Diagnostic or grading criteria	HLH-2004, MAS/HLH (MH) score	MH score, MAS/sJIA (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, IL-18-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 IL-1 or IL-18; IL-18/CXCL9 ratio used to differentiate MAS vs fHLH	IL-6 most strongly associated with severe CRS; IL-1 may also be important with murine studies suggesting role in both CRS and neurotoxicity; no hemophagocytosis	Hemophagocytosis identified in bone marrow, spleen, and/or lymph nodes in fatal cases; hyperferritinemia not always present	No HSM; hemophagocytosis seen in SARS-CoV-1

Abbreviations: ALT, alanine aminotransferase; AOSD, adult-onset Still disease; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; ASTCT, American Society for Transplantation and Cellular Therapy; BUN/Cr, blood urea nitrogen/creatinine; CAR, chimeric antigen receptor; CNS, central nervous system; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CSS, cytokine storm syndrome; ESR, erythrocyte sedimentation rate; fHLH, familial hemophagocytic lymphohistiocytosis; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; GOF, gain of function; HCT, hematopoietic cell transplant; HLH, hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; LOF, loss of function; MAS, macrophage activation syndrome; MH, MAS/HLH; MS, MAS/sJIA; PCR, polymerase chain reaction; PT, prothrombin time; PTT, partial thromboplastin time; SARS-CoV, severe acute respiratory syndrome coronavirus; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

Table 4. Clinical and Laboratory Features for Considering the Use of Immunomodulatory Therapy for Critical Coronavirus Disease 2019 in Pediatric Patients

Characteristic	Comments
Evidence for hyperinflammatory state	
Clinical signs • Sustained or recurrent fever • Hepatomegaly • Splenomegaly and/or lymphadenopathy	• 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 • Elevated ferritin and/or CRP • Decreased fibrinogen • Elevated serum IL-6 or other proinflammatory cytokines • Other CSS-associated labs (elevated sIL-2R, soluble CD163, or triglycerides)	• Very likely to be nonspecific 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 • Elevated BNP or troponin • Persistent hemodynamic instability nonresponsive to standard pressor support • Elevated lactate after appropriate fluid resuscitation • Evidence of cardiomyopathy by echocardiogram • Life-threatening arrhythmias	• Evaluation for confounding causes of organ dysfunction or failure (eg, other infections, medication effects) • 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 • Abnormal PaO_2/FiO_2 ratio or SpO_2/FiO_2 • Rapidly escalating supplemental oxygen requirement • New mechanical ventilation requirement	
Coagulopathy • Elevated D-dimer • Thrombocytopenia • Prolonged PT or PTT • Decreasing fibrinogen	
Neurologic • Altered mental status	
Hepatic • Evidence of coagulopathy (see above) • Elevated bilirubin, GGT, and/or aminotransferases	
Renal • Decreased creatinine clearance	

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; CSS, cytokine storm syndrome; FiO_2, fraction of inspired oxygen; GGT, γ-glutamyl transferase; IL, interleukin; PaO_2, partial pressure of oxygen; PT, prothrombin time; PTT, partial thromboplastin time; SpO_2, blood oxygen saturation.

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. In brief, a subset of patients progresses 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 nonpulmonary sites [49]. Laboratory evidence of markedly elevated inflammation including elevated ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate values is also noted in severe/critical COVID-19 cases [50]. Furthermore, 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, has 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 these 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 of 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 (eg, features of secondary HLH) should be limited to patients with clear evidence of critical COVID-19 disease and risk for multiorgan 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 proinflammatory cytokines, diagnostic criteria for familial HLH, MAS, and CRS should not be necessarily be used to identify COVID-19 patients who may benefit from immunosuppression or immunomodulation, 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. Furthermore, use of these therapies should be performed only with appropriate counseling and consenting of patients and families for off-label use of immunomodulatory medications according to each individual institution's policies.

III. WHICH IMMUNOMODULATORY AGENTS SHOULD BE CONSIDERED?

Guidance Statements

There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients as of July 24, 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.

Rationale

As outlined in topic-specific sections below, there are no RCTs 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 RCTs 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 (eg, anaphylaxis with tocilizumab or drug shortages). Tocilizumab is approved by the United States (US) Food and Drug Administration (FDA) (albeit not for this indication), and dosing data are extrapolated from those 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 nonhematopoietic cells and cells of myeloid origin during infections and in response to tissue injury. IL-6 binds to 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, and 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-CoV-1 or MERS coronaviruses could elicit production of IL-6 and tumor necrosis factor 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-CoV-1 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 was 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% confidence interval [CI], .33–.9) after adjusting for disease severity at tocilizumab initiation [76]. Similarly, in an Italian multicenter retrospective cohort study of 544 adults with severe COVID-19, tocilizumab treatment was associated with decreased risk of mechanical ventilation or death (adjusted HR, 0.61 [95% CI, .4–.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 (ALT) or aspartate aminotransferase (AST), in practice many patients with severe or life-threatening systemic inflammatory response syndrome experience cytopenias or elevated aminotransferases due to multisystem 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 *Mycobacterium tuberculosis*), viral reactivation (especially hepatitis B), and invasive fungal disease [67]. Notably most of these reports are from adults (eg, 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], and 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 12 mg/kg for patients with a total body weight <30 kg and 8 mg/kg for those ≥30 kg, with a maximum dose of 800 mg. Monitoring for anaphylaxis should be performed and, if noted, should be treated using standard local protocols. Additionally, periodic laboratory (eg, complete blood count, hepatic and pancreatic function testing) and clinical exam monitoring is suggested. Of note, while tocilizumab does not directly affect the cytochrome P450 (CYP) 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 8 mg/kg every 4 weeks. Most adult studies of COVID-19–associated hyperinflammation use a single dose, with some studies providing 2 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 the IL-6 level 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-CoV-1 and MERS outbreaks and early data from the current SARS-CoV-2 pandemic suggest that IL-1β may play a role in SARS-CoV-2–related immunopathology. There is 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 COVID-19 in pediatric patients,

consideration may be given to use of IL-1 inhibition in pediatric patients with severe or critical COVID-19. 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-1α and IL-1β are 2 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 proinflammatory states. IL-1β is the major biologically active and secreted form in the setting of infection and other inflammation, but IL-1α is likely released by dying endothelial cells. IL-1β exerts its effects through binding to its specific receptor subunit IL-1R1 followed by co-receptor recruitment. Biological effects of IL-1β include recruitment of endothelial adhesion molecule expression and inflammatory cell recruitment, upregulation of prostaglandins and nitric oxide, and metalloproteinase production. Systemically, IL-1β contributes to hypotension, fever, neutrophilia, and other acute phase responses. Importantly, IL-1β 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-1β signaling including anakinra, a recombinant form of IL-1 receptor antagonist (IL1-Ra) that mimics native IL-1Ra and prevents binding of IL-1α and IL-1β to IL-1R1 and thereby prevents IL-1–mediated immune effects [90]. Another IL-1–targeting drug, rilonacept, binds and neutralizes both IL-1α and IL-1β. In addition, a monoclonal antibody, canakinumab, binds IL-1β and prevents its interaction with IL-1R1 [91]. Anakinra is FDA approved for adults with rheumatoid arthritis who have failed one or more disease-modifying antirheumatic drugs and for the treatment of neonatal-onset multisystem inflammatory disease. RCTs 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 >7000 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 to 48 mg/kg/day, including use in patients with sepsis). Retrospective analysis of a large randomized clinical trial demonstrated that anakinra improved survival in patients with sepsis 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 of 12 patients treated with anakinra [100]. More recently, a retrospective report of 44 children with rheumatologic, oncologic, and infectious etiologies of CSS reported a 73% survival rate for those who received anakinra at any point during their hospitalization [101]. Furthermore, 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-1β 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-1β'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-CoV-1 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 lipopolysaccharide-primed mouse bone marrow–derived macrophages and African green monkey kidney–derived Vero cells, respectively [104–107].

Human Data

An association between IL-1β and SARS-CoV-1-associated immunopathology was made predominantly through measurement of serum/plasma IL-1β levels in SARS-CoV-1–infected patients. In general, these studies are limited by a lack of control groups and/or measurement of IL-1β at few or inconsistent time points postinfection [19, 108–110]. Immunohistochemistry of lung sections from autopsy specimens of 4 SARS-CoV-1 patients did demonstrate elevated IL-1β expression in SARS-CoV-1-infected cells [111].

Following several small case series [58, 60], 2 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 ≥100 mg/L or ferritin ≥900 ng/mL) were treated with either IV or subcutaneous anakinra [59]. 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 after treatment initiation (90% anakinra; 50% standard; $P = .09$) though mechanical ventilation–free survival differences were not statistically significant. No differences in bacteremia rates or frequency of hepatic aminotransferase elevation were noted [59]. 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 (ICU) admission for mechanical ventilation (25% vs 73%) with the difference remaining significant on multivariate

analysis (HR, 0.22 [95% CI, .1–.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 vs 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 [112, 113]. Importantly for the discussion of high-dose vs 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 rheumatoid arthritis [114].

Dosing and Practical Considerations

Though the majority of studies of anakinra have been performed using subcutaneous dosing route, IV administration is evolving as an option for the treatment of critically ill patients [99, 115, 116]. The potential utility of IV anakinra in COVID-19 patients is highlighted by the above-cited study in which low-dose subcutaneous 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 whereas the 5 mg/kg IV over 1 hour administered every 12 hours was associated with sustained clinical benefit [59]. 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 aminotransferase elevation resolves with discontinuation or lowering of dose. Complete blood count 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 [114, 117, 118]. 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 [119–121]. Glucocorticoids regulate the immune system in a broad and multimodal manner and block multiple signaling pathways that propagate inflammatory signals [122, 123]. During the early phase of the immune response, glucocorticoid-glucocorticoid receptor complexes attenuate the signaling of Toll-like receptors, inhibit the production of numerous proinflammatory cytokines [124], and dampen cytokine signaling [125]. Glucocorticoids also have a potent effect on cellular immunity, especially T-cell signaling and activation [126]. 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-CoV-1 and currently available data from COVID-19.

Data regarding the efficacy of glucocorticoids in the treatment of SARS-CoV-1 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 [127–136]. A systematic review of the treatment effects of multiple therapeutic modalities for SARS-CoV-1, including glucocorticoids, revealed that 13 of 15 studies examining the effect of steroids were inconclusive [137]. 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-CoV-1-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" [137].

Peer-reviewed data evaluating the impact of steroids on COVID-19 treatment outcomes are limited, and comparative data are lacking. Glucocorticoids have been used frequently in critically ill patients [10, 13, 138]. One retrospective cohort study of 201 adult patients with COVID-19 identified risk factors for the development of ARDS and death from ARDS [139]. 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 (HR, 0.38 [95% CI, .20–.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, 2 days postadmission [interquartile range {IQR}, 1–3 days]) compared to a standard of care cohort with later corticosteroid initiation (median time to initiation, 5 days [IQR, 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 odds ratio [OR], 0.41 [95% CI, .22–.77]) [140].

Recently, data from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, a randomized clinical trial evaluating the impact of treatment with dexamethasone in adults infected with SARS-CoV-2, were published [141]. A total of 6425 adults were enrolled, and 2104 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% vs 41%; rate ratio, 0.64 [95% CI, .51–.81]) or for those patients who received supplemental oxygen but not mechanical ventilation (23% vs 26%; rate ratio, 0.82 [95% CI, .72–.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 toward 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 1666 who did not) noncontrolled retrospective cohort comparison reported decreased mortality or mechanical ventilation (OR, 0.23 [95% CI, .08–.70]) in those with high CRP values (≥20 mg/dL) receiving glucocorticoids within 48 hours of hospital admission [142]. However, mortality or mechanical ventilation was increased in those receiving glucocorticoids if the CRP was <10 mg/dL (OR, 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 patients with severe/critical COVID-19 [143, 144]. 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-CoV-1 and MERS studies in which glucocorticoid recipients had delayed viral clearance [136, 145], 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. Moreover, 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 after onset of COVID-19 symptoms.

Guidance Statement

Diagnosis with COVID-19 does not preclude use of steroids when they are otherwise indicated (eg, 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 [146, 147]. In the critical care setting, there are limited pediatric data surrounding the efficacy of glucocorticoids in septic shock, with published studies containing small numbers of children [148–150]. 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 [151]. 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 [152]. The authors found a small reduction in 28-day mortality in the pooled analysis, though there was significant heterogeneity across trials.

There are 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 [153]. 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 on dosing ranges for the use of hydrocortisone in pediatric adrenal insufficiency [150, 154]. Prior guidelines for critically ill adults with COVID-19 have also addressed this topic [155, 156].

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 [157], and psychosis [158, 159]. 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-CoV-1 pandemic, there were reports of avascular necrosis after treatment with glucocorticoids [160–164]. In symptomatic patients, or those at increased risk of avascular necrosis, screening with plain radiographs or magnetic resonance imaging 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 [165]. In addition, several reports of adult COVID-19 patients indicate risk for invasive pulmonary aspergillosis [166, 167]. 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 CYP3A4, one of the more common hepatic isoenzymes. If this isoenzyme is inhibited by another agent (eg, macrolide, protease inhibitor), significantly increased glucocorticoid exposure can result. Alternatively, glucocorticoid exposure can also be significantly reduced by an inducer of CYP3A4 such as rifampin, requiring increased dosing to obtain the same effect [168].

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 few data supporting safety or efficacy in the use of JAK inhibitors for management of COVID-19. Moreover, data from use in other settings suggest the potential for impaired viral clearance as evidenced by herpesvirus reactivations on JAK inhibitor therapy [169]. 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 4 tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that serve as intracellular signal transducers [170]. 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 [170]. Cytokine receptor subunits bind specific JAKs, although some bind >1. 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 [171]. Emerging pediatric uses for these drugs include treatment of juvenile idiopathic arthritis [172], psoriasis [173], interferonopathies [173], and graft-vs-host disease [174,

175]. In addition to the above conditions, JAK inhibitors are also increasingly studied in the setting of CSS such as HLH and MAS [176–179]. In a small open-label series of 5 adults with secondary HLH, ruxolitinib initiation was temporally associated with improvement in cytopenias and declines in both ferritin and soluble IL-2 receptor (sIL-2R) [176].

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 evaluating the utility of JAK inhibitor therapy for COVID-19 in adults have recently been published. A single-blinded RCT of 43 adults with severe COVID-19 showed that ruxolitinib did not significantly enhance clinical improvement compared to placebo [180]. 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, 15 adult patients hospitalized with COVID-19 (with 9 requiring ICU care and 4 requiring mechanical ventilation) received baracitinib treatment [181]. Twelve of the 15 patients survived, though no comparator group was provided in this analysis. Finally, in a multicenter study from Italy, 113 baracitinib-treated patients with moderate COVID-19 were compared to 79 historical controls that did not receive baracitinib [182]. ICU admission and mortality at 2 weeks postenrollment was decreased in the baracitinib group compared with the control group (ICU: 0.88% vs 17.9%, $P = .02$; mortality: 0% vs 6.4%, $P = .01$).

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 (eg, adalimumab). However, increased risk of primary or reactivation of herpes simplex and varicella zoster virus infections has been specifically noted for JAK inhibitors [183, 184]. 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 [185]. 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 2-patient case series recently reported demonstrated adverse effects of ruxolitinib therapy for COVID-19, including anemia, thrombocytopenia, soft tissue infection, and herpes labialis [186].

Of note, baracitinib has a black box warning for potential increased risk of thrombosis that merits close attention in light of high reported incidence of thromboembolism in hospitalized COVID-19 patients [187, 188].

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 [189]. Of particular interest, care providers should use extreme caution in patients receiving potent CYP3A4 inhibitors (-azole antifungals) and potent inducers of CYP3A4 (phenobarbital and phenytoin), as this combination will likely cause subtherapeutic response or increase risks for adverse events 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 in pediatric COVID-19 may be considered as part of the recently established FDA emergency investigational new drug 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, cytomegalovirus, 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 [190]. 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-CoV-1 [191–193]. While the SARS-CoV-1 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, 2 meta-analyses of the published case series did not reveal significant harm [137, 194]. 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 [195–199]. A small RCT has also been conducted, although it was stopped early due to challenges with enrollment [200].

Human Data

Two studies demonstrate that while the patterns of development of immunoglobulin M and immunoglobulin G (IgG) can differ among different individuals, nearly all COVID-19 patients eventually do develop appreciable antibody titers [201, 202]. 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-19–afflicted adult patients with moderate to critical disease [195–199, 203, 205]. 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 CRP and inflammatory cytokine levels, and improved radiographic findings; in some cases these improvements resulted in the extubation of mechanically ventilated patients and weaning from extracorporeal membrane oxygenation 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 [204], even though the virus could no longer be detected. Although 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 [191], 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 US, 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 [205]. This study was not designed to evaluate the efficacy of convalescent plasma.

As of July 2020, a single RCT has evaluated convalescent plasma for SARS-CoV-2 [200]. 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 postinfusion.

There is a single case report of the use of convalescent plasma for a pediatric patient [206]. 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 preexisting (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 [207]. ADE is believed to occur with subneutralizing or nonneutralizing 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 [190, 208]. 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 [209]. 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 rechallenge with the same virus, as has been demonstrated with respiratory syncytial virus [210, 211].

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* species or *Trypanosoma cruzi*), and transfusion-related reactions including anaphylaxis, hemolysis, or transfusion-related acute lung injury or transfusion-related acute cardiac overload [212]. 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 FDA has provided guidance [207] 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 investigational new drug program, or under a national expanded access treatment protocol being administrated by the Mayo Clinic (Rochester, Minnesota; 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 European Union. Doses of CP administered to adults have ranged between 200 and 600 mL; it is recommended that children >40 kg be dosed with 200–500 mL and children <40 kg be dosed with 10–15 mL/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 US 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 [213].

Evidence Summary

Mechanism and Current Uses

Immunoglobulin for intravenous administration, commonly referred to as IVIG, although licensed in the US as IGIV, contains pooled IgG from the plasma of thousands of blood donors and contains more than 95% unmodified IgG, and various amounts of immunoglobulin A (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 [214], and suppression of inflammatory mediators [215]. Specific humoral effects include inhibition of B-cell differentiation, induction of B-cell apoptosis, downregulation of specific autoreactive 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 [216].

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 [217]. IVIG has also been used as an adjunct treatment in HLH along with other specific anticytokine therapy [102, 218].

In Vitro and Animal Data

Assessment of the role of IVIG in SARS-CoV-1, 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 [219]. Although no data are available regarding IVIG use in the setting of SARS-CoV-1 or MERS infection, several other viral infections (eg, human immunodeficiency virus, hepatitis C, parvovirus B19, and Zika virus) may be associated with secondary immune thrombocytopenic purpura, 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 112×10^9/L, in contrast to the median increase of 8.5×10^9/L in the 4 patients who received platelet transfusions [220].

Since severe thrombocytopenia may be associated with increased mortality in COVID-19 disease [12, 221], 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 [216]. 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 [222]. A recent publication reported IVIG dosing of 0.3–0.5 mg/kg for 5 days in a case series of COVID-19 patients [223].

INTERFERONS

Guidance Statement

Type I or type III 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 preclinical 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 show benefit. Yet, studies with IFN-λ have shown promising preclinical 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 settings.

Evidence Summary

Mechanism and Current Uses

Interferons are critical proteins involved in immune activation and regulation. There are 3 types of interferons: type I, type II, and type III. Type I IFNs include IFN-α, -β, -ε, -κ, and -ω; type II interferon is IFN-γ; and type III includes IFN-λ. While type I IFNs are produced by all cell types, plasmacytoid dendritic cells, fibroblasts, and monocytes are among the main sources [224]. Type I IFN secretion is induced by any cell type upon encountering viral signatures. In addition, type I IFNs enhance the clearance of virally infected cells by cytotoxic CD8 T cells by increasing the expression of major histocompatibility complex 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 [224]. Unlike the ubiquitously expressed IFN-α receptor, the IFN-λ receptor is expressed in epithelial cells and a subset of immune cells, including neutrophils [225, 226]. Based on its receptor expression, it is thought that type III IFN responses have critical roles in epithelial and mucosal antiviral immunity [225, 226]. When used in patients, IFN-λ, due to limited expression of its receptor in the immune compartment, results in fewer systemic side effects than type I IFN therapy [227].

Type I IFNs have 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 [228, 229]. Additionally, IFN-λ has also shown clinical efficacy similar to type 1 IFNs in the management of hepatitis C [227].

In Vitro and Animal Data

In vitro studies have shown that 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 nonhuman primates treated with IFN-β1b 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, whereas 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 an insufficient robust type I, II,

or III IFN response [54–57, 230]. This finding, along with the known antiviral properties of both type I and type III IFNs, forms the basis of its use in SARS-CoV-2 [231]. Currently, there is only one published clinical trial of IFN therapy in COVID-19 [232]. 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-β1b. 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-β1b to lopinavir-ritonavir had shorter time to complete symptom resolution and shorter time to negative nasopharyngeal swab results compared with the control group. Further studies of IFN-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 [227, 233]. Additionally, neuropsychiatric events including depression are reported [234]. Finally, neutropenia and anemia are also reported.

Additionally, there is theoretical risk for worsening disease with the use of IFN therapy. As morbidity due to COVID-19 appears to be due in large part to hyperinflammation, potential exists for IFN therapy to result in enhanced inflammation and thereby lead to worsening of the CSS [119]. 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 [235, 236].

Practical Considerations

As we do not suggest use of IFN 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 [237] 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 RCTs 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.

Notes

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