

# UC San Diego

## UC San Diego Previously Published Works

### Title

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3

### Permalink

<https://escholarship.org/uc/item/31g3q999>

### Journal

Arthritis & Rheumatology, 74(4)

### ISSN

2326-5191

### Authors

Henderson, Lauren A  
Canna, Scott W  
Friedman, Kevin G  
et al.

### Publication Date









2022-04-01

### DOI

10.1002/art.42062

Peer reviewed

# American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3

Lauren A. Henderson,<sup>1</sup>  Scott W. Canna,<sup>2</sup> Kevin G. Friedman,<sup>1</sup> Mark Gorelik,<sup>3</sup> Sivia K. Lapidus,<sup>4</sup>   
Hamid Bassiri,<sup>2</sup>  Edward M. Behrens,<sup>2</sup>  Kate F. Kernan,<sup>5</sup> Grant S. Schulert,<sup>6</sup>  Philip Seo,<sup>7</sup>  
Mary Beth F. Son,<sup>1</sup> Adriana H. Tremoulet,<sup>8</sup> Christina VanderPluym,<sup>1</sup> Rae S. M. Yeung,<sup>9</sup>  Amy S. Mudano,<sup>10</sup>  
Amy S. Turner,<sup>11</sup>  David R. Karp,<sup>12</sup>  and Jay J. Mehta<sup>2</sup>

*Due to the rapidly expanding information and evolving evidence related to COVID-19, which may lead to modification of some guidance statements over time, it is anticipated that updated versions of this article will be published, with the version number included in the title. Readers should ensure that they are consulting the most current version.*

*Guidance developed and/or endorsed by the American College of Rheumatology (ACR) is intended to inform particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to this guidance to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. Guidance statements are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidance developed or endorsed by the ACR is subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.*

*The American College of Rheumatology is an independent, professional medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.*

**Objective.** To provide guidance on the management of Multisystem Inflammatory Syndrome in Children (MIS-C), a condition characterized by fever, inflammation, and multiorgan dysfunction that manifests late in the course of SARS–CoV-2 infection. Recommendations are also provided for children with hyperinflammation during COVID-19, the acute, infectious phase of SARS–CoV-2 infection.

**Methods.** The Task Force is composed of 9 pediatric rheumatologists and 2 adult rheumatologists, 2 pediatric cardiologists, 2 pediatric infectious disease specialists, and 1 pediatric critical care physician. Preliminary statements addressing clinical questions related to MIS-C and hyperinflammation in COVID-19 were developed based on evidence reports. Consensus was built through a modified Delphi process that involved anonymous voting and webinar discussion. A 9-point scale was used to determine the appropriateness of each statement (median scores of 1–3 for inappropriate, 4–6 for uncertain, and 7–9 for appropriate). Consensus was rated as low, moderate, or high based on dispersion of the votes. Approved guidance statements were those that were classified as appropriate with moderate or high levels of consensus, which were prespecified before voting.

**Results.** The guidance was approved in June 2020 and updated in November 2020 and October 2021, and consists of 41 final guidance statements accompanied by flow diagrams depicting the diagnostic pathway for MIS-C and recommendations for initial immunomodulatory treatment of MIS-C.

**Conclusion.** Our understanding of SARS–CoV-2–related syndromes in the pediatric population continues to evolve. This guidance document reflects currently available evidence coupled with expert opinion, and will be revised as further evidence becomes available.

## INTRODUCTION

Since its initial description in December 2019 in Wuhan, China, COVID-19, caused by infection with SARS-CoV-2, has rapidly evolved into a worldwide pandemic affecting millions of lives (1). Unlike adults, the vast majority of children with COVID-19 have mild symptoms. However, there are children who have significant respiratory disease, and some children may develop a hyperinflammatory response similar to what has been observed in adults with COVID-19. Furthermore, in late April 2020, reports emerged of children with a different clinical syndrome resembling Kawasaki Disease (KD) and toxic shock syndrome; these patients frequently had evidence of prior exposure to SARS-CoV-2 (2,3). Subsequent to these initial reports from Italy and the United Kingdom, multiple case series from Europe and the United States have surfaced describing a similar phenomenon (4–10). While this constellation of symptoms has been given many names, for the purposes of this discussion we refer to it as multisystem inflammatory syndrome in children (MIS-C).

For a number of reasons, there is an urgent need to provide guidance to healthcare providers evaluating patients in whom MIS-C is a diagnostic consideration. These reasons include the fact that 1) there are variable case definitions for MIS-C, 2) clinical features of MIS-C may also be seen in other types of infections and malignant entities and in other rheumatic diseases in childhood, 3) suggested treatment strategies have relied on extrapolation from other inflammatory or rheumatic conditions with similar clinical presentations and comparative cohort studies, and 4) myocardial dysfunction may present insidiously but is a major source of morbidity and mortality in MIS-C. In addition, pediatric rheumatologists are often asked to recommend immunomodulatory therapy for patients with hyperinflammation as a result of acute SARS-CoV-2 infection.

Therefore, the American College of Rheumatology (ACR) convened the MIS-C and COVID-19–Related Hyperinflammation Task Force on May 22, 2020, which was charged by ACR leadership to

provide guidance to clinicians in the evaluation and management of MIS-C and COVID-19–related hyperinflammatory syndromes in children. Clinical guidance generated from this effort is intended to aid in the care of individual patients, but it is not meant to supplant clinical decision-making. Modifications to treatment plans, particularly in patients with complex conditions, are highly disease-, patient-, geography-, and time-specific, and therefore must be individualized as part of a shared decision-making process.

## METHODS

**Task force.** Panelists were selected by the Task Force leadership (LAH and JJM) based on their clinical expertise in rheumatology, infectious diseases, cardiology, cytokine storm–related syndromes, and KD, as well as their experience in managing MIS-C and hyperinflammation in acute SARS-CoV-2 infection. The multidisciplinary Task Force was composed of clinicians from the United States and Canada and included 9 pediatric rheumatologists, 2 adult rheumatologists, 2 pediatric cardiologists, 2 pediatric infectious disease specialists, and 1 pediatric critical care physician. All individuals who were approached to develop this guidance agreed to participate.

**Initial guidance.** Prior to the first meeting, Task Force members were subdivided into 4 work groups to address the following clinical topics related to MIS-C and hyperinflammation in COVID-19: 1) diagnostic evaluation of MIS-C (led by SKL); 2) cardiac management of MIS-C (led by KGF); 3) treatment of MIS-C (led by MG); and 4) management of hyperinflammation in COVID-19 (led by SWC). During the first webinar on May 22, 2020, participants agreed with the importance of addressing these 4 overarching topics and the structure of the work groups. The first webinar was used to confirm the target audience for the guidance, which focuses on clinicians in North America managing inflammatory syndromes in children related to recent or concurrent infections with SARS-CoV-2. Notably, the Task Force

Supported by the American College of Rheumatology.

<sup>1</sup>Lauren A. Henderson, MD, MMSc, Kevin G. Friedman, MD, Mary Beth F. Son, MD, Christina VanderPluym, MD: Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; <sup>2</sup>Scott W. Canna, MD, Hamid Bassiri, MD, PhD, Edward M. Behrens, MD, Jay J. Mehta, MD: Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine; <sup>3</sup>Mark Gorelik, MD: Morgan Stanley Children's Hospital and Columbia University, New York, New York; <sup>4</sup>Sivia K. Lapidus, MD: Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center and Hackensack Meridian School of Medicine, Hackensack, New Jersey; <sup>5</sup>Kate F. Kernan, MD: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; <sup>6</sup>Grant S. Schulert, MD: Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio; <sup>7</sup>Philip Seo, MD, MHS: Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>8</sup>Adriana H. Tremoulet, MD, MAS: University of California San Diego and Rady Children's Hospital, San Diego, California; <sup>9</sup>Rae S. M. Yeung, MD, PhD: The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; <sup>10</sup>Amy S. Mudano, MPH: University of Alabama at Birmingham; <sup>11</sup>Amy S. Turner: American College of Rheumatology, Atlanta, Georgia; <sup>12</sup>David R. Karp, MD, PhD: University of Texas Southwestern Medical Center, Dallas.

Dr. Henderson has received consulting fees from Sobi, Pfizer, and Adaptive Biotechnologies (less than \$10,000) and research support from the Childhood Arthritis and Rheumatology Research Alliance and research grant support from Bristol Myers Squibb. Dr. Canna has received research support from AB2 Bio and IMMvention Therapeutix. Dr. Bassiri owns stock or stock options in CSL Behring. Dr. Schulert has received consulting fees from Novartis and Sobi (less than \$10,000 each). Drs. Son and Mehta have received salary support from the Childhood Arthritis and Rheumatology Research Alliance. Dr. Yeung has received consulting fees from Novartis and Eli Lilly (less than \$10,000 each). No other disclosures relevant to this article were reported.

No part of this article may be reproduced, stored, or transmitted in any form or for any means without prior permission in writing. For permission information contact [permissions@wiley.com](mailto:permissions@wiley.com). For information about purchasing reprints contact [commercialreprints@wiley.com](mailto:commercialreprints@wiley.com).

Address correspondence to Lauren A. Henderson, MD, MMSc, Karp Family Research Building, 10th Floor, 1 Blackfan Circle, Boston, MA 02115. Email: [Lauren.Henderson@childrens.harvard.edu](mailto:Lauren.Henderson@childrens.harvard.edu).

Submitted for publication December 13, 2021; accepted in revised form December 22, 2021.

deliberately did not attempt to create a new case definition for MIS-C, as several already exist (8–10) (Table 1). Instead, the Task Force elected to leverage consensus building to identify the most appropriate diagnostic and therapeutic steps that providers should consider at the present time. All panelists agreed to develop consensus through a modified Delphi process, which involved 2 rounds of asynchronous, anonymous voting and 2 webinars to discuss voting results.

**Evidence review.** From May 22 to May 29, 2020, the work groups developed preliminary recommendation statements within their assigned topic, based on expert opinion and evidence reviewed from publications listed in PubMed, scientific briefings from the World Health Organization, health alerts from the Centers of Disease Control and Prevention, and guidance provided by the Royal College of Paediatrics and Child Health. Each work group generated an evidence report supporting the recommendations, which was shared with the entire Task Force.

**Voting. Round 1.** The Task Force voted virtually and anonymously using the RAND/University of California at Los Angeles (UCLA) Appropriateness Method (11). A 9-point scale was used by panelists to rate the appropriateness of each of the statements. A score of 9 was considered to be the highest level of appropriateness, while a score of 1 indicated that the statement was entirely inappropriate. Prior to voting, median scores of 1–3 were defined as inappropriate, 4–6 as uncertain, and 7–9 as appropriate. Consensus was prespecified as high if all 16 votes coalesced within the same tertile, while low consensus was recognized when voting was dispersed widely along the 9-point scale (with ≥5 votes in the 1–3 score range and ≥5 votes in the 7–9 score range). Moderate consensus encompassed all other scenarios. The votes of each Task Force member were counted equally and tallied. The results of the initial voting were distributed to the Task Force and reviewed during a 90-minute webinar on June 4, 2020. Statements that were rated as uncertain (median score 4–6) and/or characterized by moderate or

**Table 1.** Case definitions of MIS-C\*

Criteria	RCPCH†	CDC	WHO‡
Age	All children (age not defined)	<21 years	0–19 years
Fever	Persistent fever (≥38.5°C)	Temperature ≥38.0°C for ≥24 hours <i>or</i> subjective fever for ≥24 hours	Fever for ≥3 days
Clinical symptoms	Both of the following: 1. single or multiorgan dysfunction; <i>and</i> 2. additional features	Both of the following: 1. severe illness (hospitalized); <i>and</i> 2. ≥2 organ systems involved	At least 2 of the following: 1. rash, conjunctivitis, and mucocutaneous inflammation; 2. hypotension or shock; 3. cardiac involvement; 4. coagulopathy; 5. acute GI symptoms
Inflammation	All 3 of the following: 1. neutrophilia; <i>and</i> 2. increased CRP; <i>and</i> 3. lymphopenia	Laboratory evidence of inflammation including, but not limited to, 1 or more of the following: 1. ↑CRP; 2. ↑ESR; 3. ↑fibrinogen; 4. ↑procalcitonin; 5. ↑D-dimer; 6. ↑ferritin; 7. ↑LDH; 8. ↑IL-6; 9. neutrophilia; 10. lymphopenia; 11. hypoalbuminemia	Elevated inflammation markers, including any of the following: 1. ↑ESR; 2. ↑CRP; 3. ↑procalcitonin
Link to SARS-CoV-2	Positive or negative by PCR	Current or recent findings of the following: 1. positive by PCR; 2. positive by serology; 3. positive by antigen test; <i>or</i> 4. COVID-19 exposure within prior 4 weeks	Evidence of COVID-19 by the following: 1. positive by PCR; 2. positive by antigen test; 3. positive by serology; <i>or</i> 4. likely COVID-19 contact
Exclusion	Other infections	No alternative diagnosis	No obvious microbial cause

\* Case definitions of multisystem inflammatory syndrome in children (MIS-C) are adapted from recommendations from the World Health Organization (WHO) (8) and Centers for Disease Control and Prevention (CDC) (10) for MIS-C, as well as the Royal College of Paediatrics and Child Health (RCPCH) for pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (9). For laboratory parameters, ↑ indicates elevated levels. GI = gastrointestinal; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; IL-6 = interleukin-6; PCR = polymerase chain reaction.

† In the RCPCH case definition, additional features include abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, and vomiting.

‡ In the WHO case definition, cardiac involvement is defined as the presence of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including findings on echocardiogram or elevated levels of troponin/N-terminal pro-B-type natriuretic peptide).

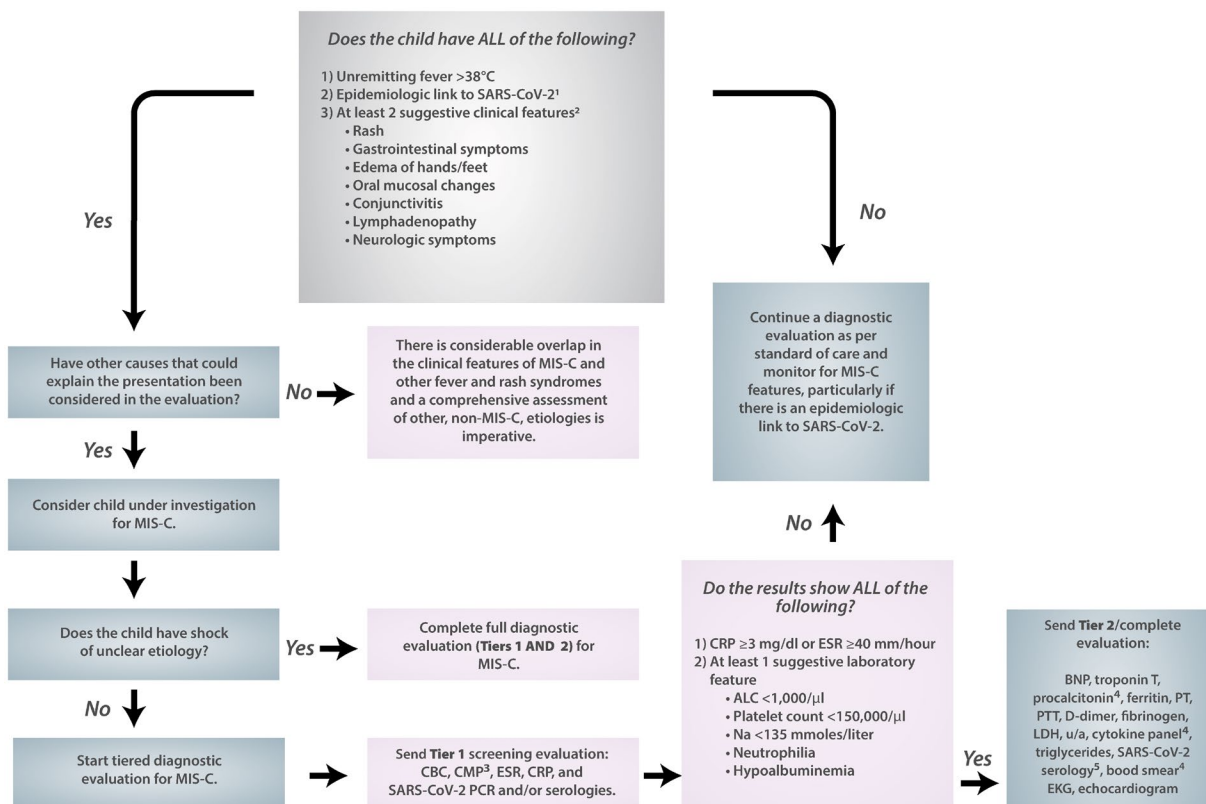
low consensus were addressed first. The panelists were then encouraged to discuss the remaining statements.

**Round 2.** Input from the initial voting and discussion was incorporated (by LAH and JJM) into the draft guidance statements, and the document was redistributed to the entire Task Force for a second round of voting. Voting in this phase was conducted in the same manner as described above, and results were reviewed at a third webinar on June 10, 2020. Guidance statements that earned a median score of 7–9 with moderate or high levels of consensus were approved by the panel.

**Guidance approval.** Following the final webinar, approved statements were refined and, in some instances, combined to reduce redundancy. A preliminary guidance document was generated, and the entire Task Force was given an opportunity to

review and edit the document. Approval was obtained from each panelist on June 14, 2020 and by the ACR Board of Directors on June 17, 2020 (12). After further review, the authors decided to include measurement of C-reactive protein (CRP) levels in the laboratory evaluation of hyperinflammation in severe COVID-19 (Table 7) and the entire Task Force then re-voted on the guidance statements and approved the modifications to this recommendation statement.

**Guidance revisions.** For subsequent versions of the guidance, work group leaders were asked to identify guidance statements that should be modified based on clinical experience and newly available evidence in the literature. Revised statements along with the supporting literature were provided to the panelists before a webinar was held on October 13, 2020 to discuss



**Figure 1.** Diagnostic pathway for multisystem inflammatory syndrome in children (MIS-C). Moderate-to-high consensus was reached by the Task Force in the development of this diagnostic pathway for MIS-C associated with SARS-CoV-2. <sup>1</sup>Due to the difficulty in establishing an epidemiologic linkage to a preceding SARS-CoV-2 infection given the evolving COVID-19 pandemic, the diagnosis of MIS-C must be determined based on the totality of the history, examination, and laboratory studies. Patients may have MIS-C even in the absence of preceding COVID-19-like illness or a clear history of exposure to SARS-CoV-2, especially in the setting of high community prevalence. <sup>2</sup>Suggestive clinical features include rash (polymorphic, maculopapular, or petechial, but not vesicular), gastrointestinal symptoms (diarrhea, abdominal pain, or vomiting), oral mucosal changes (red and/or cracked lips, strawberry tongue, or erythema of the oropharyngeal mucosa), conjunctivitis (bilateral conjunctival infection without exudate), and neurologic symptoms (altered mental status, encephalopathy, focal neurologic deficits, meningismus, or papilledema). <sup>3</sup>The complete metabolic panel (CMP) includes measurement of sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, creatinine, glucose, calcium, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin. <sup>4</sup>Procalcitonin, cytokine panel, and blood smear test results should be sent, if available. <sup>5</sup>Serologic test results should be sent if not sent in Tier 1 evaluation, and if possible, SARS-CoV-2 IgG, IgM, and IgA test results should be sent. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ALC = absolute lymphocyte count; CBC = complete blood cell count; BNP = B-type natriuretic peptide; PT = prothrombin time; PTT = partial thromboplastin time; LDH = lactate dehydrogenase; u/a = urinalysis; EKG = electrocardiogram.

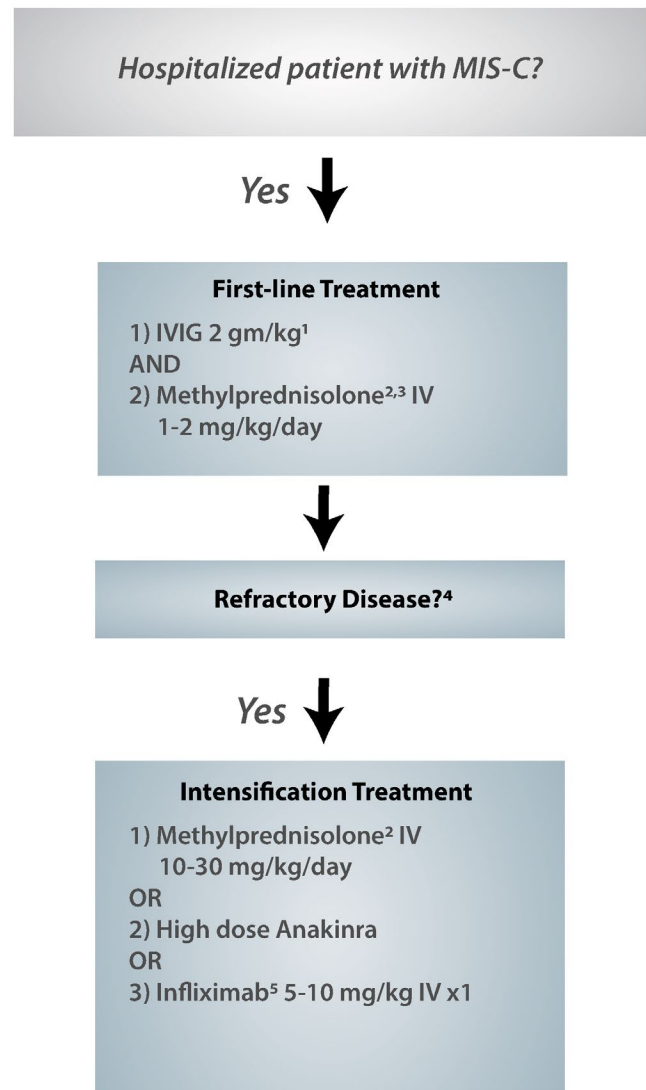
the proposed changes to the second version of the guidance. A similar process was followed in preparation for a webinar on September 9, 2021 for the third version of the guidance. Dr. Christina VanderPluym, a pediatric cardiologist with expertise in antithrombosis management, joined the Task Force in September 2021. After the webinar, anonymous voting was conducted in the same manner as described above. Revised guidance statements that were voted as being appropriate (median score of 7–9) with a moderate or high degree of consensus were approved.

## RESULTS

In the first round of voting, the Task Force evaluated a total of 125 statements that addressed the management of MIS-C and hyperinflammation in pediatric patients with COVID-19. Of these, 112 statements met the criteria for approval with a median score of 7–9 and moderate or high consensus, while 13 statements were rated as uncertain (median score of 4–6). After refining the statements based on the input from the initial phase, 128 guidance statements were approved in the second round of voting (see Supplementary Tables 1–4, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.42062/abstract>). These statements were organized into 40 final guidance statements as well as a flow diagram depicting the diagnostic pathway for MIS-C (Figure 1), which were approved by the entire Task Force and the ACR Board of Directors (12). For the second version of the guidance, the Task Force approved 22 revised statements (see Supplementary Table 5, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.42062/abstract>) as well as a second flow diagram on treatment of MIS-C (Figure 2). An additional 33 revised statements were approved by the Task Force for the third version of the guidance (see Supplementary Table 6, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41616/abstract>). Topics covered in the guidance include the following: 1) diagnostic evaluation of MIS-C (Table 2 and Figure 1); 2) MIS-C and KD phenotypes (Table 3); 3) cardiac management of MIS-C (Table 4); 4) treatment of MIS-C (Tables 5 and 6 and Figure 2); and 5) hyperinflammation in COVID-19 (Table 7).

Our understanding of SARS-CoV-2-related syndromes in the pediatric population continues to evolve. The recommendations provided by the Task Force reflect expert opinion and currently available evidence. Thus, this guidance is meant to be a “living document” and will be modified as additional data become available. The recommendations provided in the guidance document do not replace the importance of clinical judgment tailored to the unique circumstances of an individual patient.

**Diagnostic evaluation of MIS-C.** *Maintaining a broad differential diagnosis.* Multiple case definitions for MIS-C have been proposed (8–10), some of which are broader than others (Table 1). Common clinical features of MIS-C include



**Figure 2.** Algorithm for initial immunomodulatory treatment of multisystem inflammatory syndrome in children (MIS-C). Moderate-to-high consensus was reached by the Task Force in the development of this treatment algorithm for MIS-C associated with SARS-CoV-2. <sup>1</sup>Intravenous immunoglobulin (IVIG) dosing is 2 gm/kg based on ideal body weight, with maximum dose of 100 gm. Cardiac function and fluid status should be assessed before IVIG is given. In some patients with cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily over 2 days). <sup>2</sup>Methylprednisolone or another steroid at equivalent dosing may be used. <sup>3</sup>In select patients with mild disease or contraindications to glucocorticoids, IVIG alone may be appropriate as first-line treatment for MIS-C. These patients should be monitored closely and intensification therapy should be added at the first signs of clinical worsening. <sup>4</sup>Refractory disease is defined as persistent fevers and/or ongoing and significant end-organ involvement. <sup>5</sup>Infliximab should not be used in patients with MIS-C and features of macrophage activation syndrome.

fever, mucocutaneous findings (rash, conjunctivitis, edema of the hands/feet, red/cracked lips, and strawberry tongue), myocardial dysfunction, cardiac conduction abnormalities, shock, gastrointestinal symptoms, and lymphadenopathy (2,4–7,

**Table 2.** Diagnostic evaluation of MIS-C\*

Guidance statement	Level of consensus
The vast majority of children with COVID-19 present with mild symptoms and have excellent outcomes. MIS-C remains a rare complication of SARS-CoV-2 infections.	High
MIS-C is temporally associated with SARS-CoV-2 infections. Therefore, the prevalence of the virus in a given geographic location, which may change over time, should inform management decisions.	Moderate
Given the high prevalence of COVID-19 in certain communities, seropositivity to SARS-CoV-2 (nucleocapsid or spike protein) may no longer adequately distinguish between MIS-C and other overlapping syndromes, although a negative finding on antibody test should prompt consideration of alternative diagnoses.	Moderate
A child "under investigation" for MIS-C should also be evaluated for other possible infections and non-infection-related conditions (e.g., malignancy) that may explain the clinical presentation.	High
Patients "under investigation" for MIS-C may require additional diagnostic studies (not described in Figure 1), including, but not limited to, imaging of the chest, abdomen, and/or central nervous system and lumbar puncture.	High
Outpatient evaluation for MIS-C may be appropriate for assessing well-appearing children with stable vital signs and for ensuring that physical examinations provide close clinical follow-up.	Moderate
Patients "under investigation" for MIS-C should be considered for admission to the hospital for further observation while the diagnostic evaluation is completed, especially if the patient displays any of the following symptoms: <ol style="list-style-type: none"> <li>1. abnormal vital signs (tachycardia, tachypnea);</li> <li>2. respiratory distress of any severity;</li> <li>3. neurologic deficits or change in mental status (including subtle manifestations);</li> <li>4. evidence of renal or hepatic injury (including mild injury);</li> <li>5. marked elevations in inflammation markers;</li> <li>6. abnormal EKG findings or abnormal levels of BNP or troponin T.</li> </ol>	High
Children admitted to the hospital with MIS-C should be managed by a multidisciplinary team that includes pediatric rheumatologists, cardiologists, infectious disease specialists, and hematologists. Depending on the clinical manifestations, other subspecialties may need to be consulted as well; these include, but are not limited to, pediatric neurology, nephrology, hepatology, and gastroenterology.	Moderate to high

\* MIS-C = multisystem inflammatory syndrome in children; EKG = electrocardiogram; BNP = B-type natriuretic peptide; KD = Kawasaki disease.

13–22). Neurologic involvement is also reported, manifesting as severe headache, altered mental status, seizures, cranial nerve palsies, meningismus, cerebral edema, and ischemic or hemorrhagic stroke in select patients (5–7,13,14,19–23). These findings are nonspecific and can occur in other infections, as well as in non-infection-related conditions such as oncologic or inflammatory conditions (24). In the midst of the COVID-19 pandemic, there is potential for cognitive bias with anchoring on a diagnosis of MIS-C when children present with unexplained fevers. Therefore, it is imperative that a diagnostic evaluation for MIS-C include investigation for other possible causes, as deemed appropriate by the treating provider.

MIS-C is temporally associated with SARS-CoV-2 infections, and clusters of cases have been reported in geographic areas with dense COVID-19 disease burden, typically being identified within 2–6 weeks after the peak incidence of acute, infectious COVID-19 (4,13,14,17,19–21). Thus, the prevalence and chronology of SARS-CoV-2 infection in a given location, which may change over time, should also inform the diagnostic evaluation.

The incidence of MIS-C is unknown; however, it appears to be a rare complication of SARS-CoV-2 infection, with some estimates indicating that MIS-C occurs in 5.1 out of 1,000,000 person-months in individuals under the age of 21 years (20). The relative rarity of MIS-C should also be considered in the diagnostic approach (25).

**Table 3.** MIS-C and KD phenotypes\*

Guidance statement	Level of consensus
MIS-C and KD may share overlapping clinical features, including conjunctival infection, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet, and cervical lymphadenopathy.	High
Several epidemiologic, clinical, and laboratory features of MIS-C may differ from KD in the following ways: <ol style="list-style-type: none"> <li>1. There is an increased incidence of MIS-C in patients of African, Afro-Caribbean, and Hispanic descent, but a lower incidence in those of East Asian descent.</li> <li>2. Patients with MIS-C encompass a broader age range, have more prominent GI and neurologic symptoms, present more frequently in a state of shock, and are more likely to display cardiac dysfunction (ventricular dysfunction and arrhythmias) than children with KD.</li> <li>3. At presentation, patients with MIS-C tend to have lower platelet counts, lower absolute lymphocyte counts, and higher CRP levels than patients with KD.</li> <li>4. Ventricular dysfunction is more frequently associated with MIS-C whereas KD more frequently manifests with coronary artery aneurysms; however, MIS-C patients without KD features can develop CAA.</li> </ol>	Moderate to high
Epidemiologic studies of MIS-C suggest that younger children are more likely to present with KD-like features, while older children are more likely to develop myocarditis and shock.	Moderate

\* MIS-C = multisystem inflammatory syndrome in children; KD = Kawasaki disease; GI = gastrointestinal; CRP = C-reactive protein; CAAs = coronary artery aneurysms.

**Table 4.** Cardiac management of MIS-C\*

Guidance statement	Level of consensus
Patients with MIS-C and abnormal BNP and/or troponin T levels at diagnosis should have these laboratory parameters trended over time until they normalize.	High
EKGs should be performed at a minimum of every 48 hours in MIS-C patients who are hospitalized and during follow-up visits. If conduction abnormalities are present, patients should be placed on continuous telemetry while in the hospital, and Holter monitors should be considered during follow-up.	Moderate to high
Echocardiograms conducted at diagnosis and during clinical follow-up should include evaluation of ventricular/valvular function, pericardial effusion, and coronary artery dimensions with measurements indexed to body surface area using z-scores.	High
Echocardiograms should be repeated at a minimum of 7–14 days and 4–6 weeks after presentation. For those patients with cardiac abnormalities occurring in the acute phase of their illness, an echocardiogram 1 year after MIS-C diagnosis could be considered. Patients with LV dysfunction and/or CAAs will require more frequent echocardiograms.	Moderate to high
Cardiac MRI may be indicated 2–6 months after MIS-C diagnosis in patients who presented with significant transient LV dysfunction in the acute phase of illness (LV ejection fraction <50%) or persistent LV dysfunction. Cardiac MRI should focus on myocardial characterization, including functional assessment, T1/T2-weighted imaging, T1 mapping and extracellular volume quantification, and late gadolinium enhancement.	High
Cardiac CT should be performed in patients with suspected presence of distal CAAs that are not well seen on echocardiogram.	Moderate

\* MIS-C = multisystem inflammatory syndrome in children; BNP = B-type natriuretic peptide; EKGs = electrocardiograms; LV = left ventricular; CAAs = coronary artery aneurysms; MRI = magnetic resonance imaging; CT = computed tomography.

*Tier 1 screening.* Based on our review of the literature and diagnostic algorithms that are publicly available, the Task Force chose to cast a broad net with respect to the evaluation of patients with possible MIS-C, while simultaneously balancing the

need to reduce indiscriminate overtesting and to prevent unnecessary use of resources in the treatment of pediatric patients who have unrelated causes of fever (2,4,5,7,13–16,26,27). To date, there are no clear data indicating the pretest positive or

**Table 5.** Immunomodulatory treatment in MIS-C\*

Guidance statement	Level of consensus
Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infections and non-infection-related conditions before immunomodulatory treatment is initiated.	Moderate
Patients “under investigation” for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed.	High
After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may only require close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG to prevent CAAs in this setting.	Moderate
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C, with IVIG and low-to-moderate-dose glucocorticoids considered first-tier therapy in most hospitalized patients (Figure 2).	Moderate
High-dose glucocorticoids, anakinra, or infliximab should be used as intensification therapy in patients with refractory disease (Figure 2).	Moderate
IVIG should be given to MIS-C patients who are hospitalized and/or fulfill KD criteria.	High
IVIG (typically 2 gm/kg, based on ideal body weight, maximum 100 gm) should be used for treatment of MIS-C.	High
Cardiac function and fluid status should be assessed in MIS-C patients before IVIG treatment is provided. Patients with depressed cardiac function may require close monitoring and diuretics with IVIG administration.	High
In some patients with cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily over 2 days).	Moderate
Low-to-moderate-dose glucocorticoids (1–2 mg/kg/day) should be given with IVIG as dual therapy for treatment of MIS-C in hospitalized patients.	Moderate
In patients with refractory MIS-C, despite a single dose of IVIG, a second dose of IVIG is not recommended given the risk of volume overload and hemolytic anemia associated with large doses of IVIG.	High
In patients who do not respond to IVIG and low-to-moderate-dose glucocorticoids, high-dose, IV pulse glucocorticoids (10–30 mg/kg/day) should be considered, especially if a patient requires high-dose or multiple inotropes and/or vasopressors.	Moderate
High-dose anakinra (>4 mg/kg/day IV or SC) should be considered for treatment of MIS-C refractory to IVIG and glucocorticoids in patients with MIS-C and features of MAS or in patients with contraindications to long-term use of glucocorticoids.	Moderate
Infliximab (5–10 mg/kg/day IV x 1 dose) may be considered as an alternative biologic agent to anakinra for treatment of MIS-C in patients refractory to IVIG and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids. Infliximab should not be used to treat patients with MIS-C and features of MAS.	Moderate
Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering. Patients may require a 2–3-week, or even longer, taper of immunomodulatory medications.	High

\* MIS-C = multisystem inflammatory syndrome in children; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; CAAs = coronary artery aneurysms; SC = subcutaneous; MAS = macrophage activation syndrome.



**Table 6.** Antiplatelet and anticoagulation therapy in MIS-C\*

Guidance statement	Level of consensus
Low-dose aspirin (3–5 mg/kg/day; maximum 81 mg/day) should be used in patients with MIS-C and continued until the platelet count is normalized and normal coronary arteries are confirmed at ≥4 weeks after diagnosis. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or a platelet count of ≤80,000/μl.	Moderate
Central venous catheterization, age >12 years, malignancy, ICU admission, and D-dimer levels elevated to >5 times the upper limit of normal are independent risk factors for thrombosis in MIS-C. Higher-intensity anticoagulation should be considered in children with MIS-C on an individual basis, taking into consideration the presence of these risk factors balanced with the patient's risk of bleeding.	Moderate
MIS-C patients with CAAs should receive anticoagulation therapy according to the American Heart Association recommendations for KD. MIS-C patients with a maximal z-score of 2.5–10.0 should be treated with low-dose aspirin. Patients with a z-score of ≥10.0 should be treated with low-dose aspirin and therapeutic anticoagulation with enoxaparin (anti-factor Xa level 0.5–1.0) for at least 2 weeks, and then can be transitioned to VKA therapy (INR 2–3) or DOAC as long as the CAA z-score exceeds 10.	Moderate
MIS-C patients with an EF <35% should receive low-dose aspirin and therapeutic anticoagulation (defined as enoxaparin administered subcutaneously, with target anti-factor Xa levels of 0.5–1.0 or warfarin/VKA (INR 2–3) or DOAC Moderate) until EF exceeds 35%.	High
MIS-C patients with documented thrombosis should receive low-dose aspirin and therapeutic anticoagulation (see definition above) for 3 months, pending resolution of thrombosis. Repeat imaging of thrombosis at 4–6 weeks post-diagnosis should be acquired, and anticoagulation can be discontinued if resolved.	High
For MIS-C patients who do not meet the above criteria, the approach to antiplatelet and anticoagulation therapeutic management should be tailored to the patient's risk for thrombosis.	High

\* MIS-C = multisystem inflammatory syndrome in children; ICU = intensive care unit; KD = Kawasaki disease; VKA = vitamin K antagonist; DOAC = direct-acting oral anticoagulant; CAA = coronary artery aneurysm; EF = ejection fraction; LV = left ventricular.

**Table 7.** Hyperinflammation in COVID-19\*

Guidance statement	Level of consensus
Children, particularly infants, with medical complexity including type I diabetes, complex congenital heart disease, neurologic conditions, obesity, or asthma and those receiving immunosuppressive medications may be at higher risk for severe COVID-19. Racial and ethnic minorities may also be at higher risk.	Moderate
Children and adults admitted to the hospital with COVID-19 present with similar symptoms, including fever, upper respiratory tract symptoms, abdominal pain, and diarrhea.	Moderate
Hospitalized children requiring supplemental oxygen or respiratory support due to COVID-19 should be considered for immunomodulatory therapy. Substantial elevation in inflammation markers (including LDH, D-dimer, IL-6, IL-2R, CRP, and/or ferritin, and depressed lymphocyte count, albumin level, and/or platelet count) may support this decision and prove useful in monitoring.	High
Dexamethasone (0.15–0.3 mg/kg/day, maximum 6 mg, for up to 10 days) should be used as first-line immunomodulatory treatment in children with persistent oxygen requirement due to COVID-19, although other glucocorticoids may be equally effective.	Moderate
Children with increasing oxygen requirements and elevated inflammation markers due to COVID-19 who have not improved with glucocorticoids alone should receive secondary immunomodulatory therapy.	High
Tocilizumab and baricitinib have both demonstrated efficacy in clinical trials of adults with COVID-19 and should be considered as agents for secondary immunomodulatory therapy in children, and the decision of which to choose will depend on availability, patient age, and comorbidities (such as renal failure or thrombosis).	High
Tofacitinib can be considered as an alternative medication for secondary immunomodulatory therapy if tocilizumab and baricitinib are not available or contraindicated.	Moderate
The benefit of secondary immunomodulatory therapy in COVID-19 appears to be greatest when given early in the course of clinical deterioration (within 24 hours of escalation to high-flow oxygen, noninvasive ventilation, or ICU admission).	High
Secondary immunomodulatory therapy should be used in combination with glucocorticoids. Tocilizumab may be given at a dose of 8 mg/kg IV (maximum 800 mg) and may be re-dosed ≥8 hours later if there is insufficient clinical response. Baricitinib may be given orally for up to 14 days to children with normal renal function, at a dose of 2 mg daily in children age 2 years to <9 years, and 4 mg daily in children age ≥9 years.	Moderate
Children with COVID-19 treated with secondary immunomodulatory therapy should be monitored for secondary infections and LFT abnormalities. Children receiving tocilizumab should also be monitored for hypertriglyceridemia and infusion reactions. Children receiving baricitinib should also be monitored for thrombosis and thrombocytosis.	Moderate to High
There is insufficient experience in adults with COVID-19, along with extremely limited performance history in the pediatric population, to recommend for or against the use of other IL-6 or JAK inhibitors in children with COVID-19.	Moderate
Given the conflicting data from clinical trials of anakinra in adults with COVID-19 pneumonia, there is insufficient evidence to recommend for or against the use of anakinra in children with COVID-19 and hyperinflammation.	Moderate

\* LDH = lactate dehydrogenase; IL-6 = interleukin-6; IL-2R = interleukin-2 receptor; CRP = C-reactive protein; IV = intravenous; SC = subcutaneous; LFT = liver function test.

negative predictive probabilities for each clinical symptom or laboratory value in diagnosing MIS-C. It should be noted that due to the paucity of data, our recommendations reflect a multidisciplinary consensus that is likely to be revised as these data become available.

Fever is a key manifestation of MIS-C, with affected children presenting with significantly higher temperatures and longer fever duration than children with other routine pediatric illnesses (28). Thus, children with unremitting fever, an epidemiologic link to SARS-CoV-2, and suggestive clinical symptoms should be considered “under investigation” for MIS-C, while alternative diagnoses that could explain the patient’s clinical presentation are also explored (Figure 1). A tiered diagnostic approach is recommended in patients without life-threatening manifestations; this includes performing an initial screening evaluation (Tier 1), and thereafter proceeding to a complete diagnostic evaluation (Tier 2) only in patients with laboratory results from the Tier 1 screening that are concerning. Tier 1 consists of laboratory studies that are easily obtained at most clinical facilities (complete blood cell count with manual differential, complete metabolic panel, erythrocyte sedimentation rate [ESR], CRP measurement, and testing for SARS-CoV-2 by polymerase chain reaction [PCR] or serology). Among MIS-C cases reported in the literature, the overwhelming majority involve elevated levels of inflammation markers, particularly CRP, as values higher than 10 mg/dl or even 20 mg/dl are common (2,4–6,13,14,17,19–22). Thus, to enter the second stage of testing, children should have elevated ESR and/or CRP levels and at least 1 other suggestive laboratory feature: lymphopenia, neutrophilia, thrombocytopenia, hyponatremia, or hypoalbuminemia (2,4–6,13,14,17,19–22).

*Tier 2 evaluation.* Tier 2 encompasses more complex testing that typically requires additional time to complete. Reports in the literature and unpublished observations by members of the panel both note that some patients with MIS-C can decompensate rapidly (7,13). Accordingly, children with abnormal vital signs, concerning physical examination findings, or signs of cardiac involvement will need to be admitted to the hospital for supportive care while Tier 2 testing is completed. In addition, there is emerging evidence that the degree of lymphopenia, thrombocytopenia, and CRP elevation may predict severe disease, and children with these laboratory findings should be monitored closely (29,30).

The panel also noted that MIS-C appears to be a continuum of disease that encompasses milder phenotypes that have not been fully described in the published literature (31). Some patients present with fever, rash, and systemic inflammation and no other organ damage. While these children require close monitoring, they do not always need to be hospitalized. Thus, in some cases, well-appearing children with reassuring vital signs and physical examination findings may be considered suitable for outpatient diagnostic evaluations as long as close clinical follow-up can be ensured.

Prominent cardiac involvement has been reported in a proportion of MIS-C patients in every retrospective cohort study published to date (2,4–6,13,14,17,19–22,32–34). These include left ventricular (LV) dysfunction, coronary artery dilation or coronary artery aneurysm (CAA), and electrical conduction abnormalities. Valvular dysfunction and pericardial effusion are less frequently described. Among the initial descriptions of MIS-C, LV dysfunction was present in 20–55% of cases, and coronary artery dilation or CAA in ~20% (2,4,13). The early reports appear to have overestimated the incidence of cardiac features as they likely represented the most severe component of the MIS-C spectrum. In larger cohorts reported later in the course of the COVID-19 pandemic, it was observed that the rate of CAAs was closer to 13% (35). At 30 days of follow-up, most patients with MIS-C have normalization of their LV ejection fraction regardless of the degree of LV dysfunction at the initial presentation (35). Further, CAAs regress in close to 80% of patients, which is not as commonly demonstrated in pre-pandemic KD (35). While LV dysfunction and CAAs are salient and frequently described features of MIS-C, arrhythmias have been less well characterized. Recently, atrioventricular block was identified in up to 20% of children with MIS-C, including progression to second- and third-degree block in some (33).

For these reasons, EKG and echocardiogram are key components of the full diagnostic evaluation. The echocardiogram should include quantification of LV size and systolic function using end-diastolic volume (and z-score) and ejection fraction (EF) (36,37). Detailed evaluation of all coronary artery segments and normalization of coronary artery measurements to body surface area using z-scores is necessary (37,38). Cardiac laboratory values at the time of diagnosis, specifically levels of troponin T and B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP), may help identify patients with cardiac sequelae from MIS-C (4–6,13,14,17). In particular, highly elevated BNP/NT-proBNP levels may be helpful in distinguishing between MIS-C patients with and those without LV dysfunction; however, mild and transient elevations in these laboratory parameters are likely to be nonspecific, and do not necessarily indicate cardiac involvement (14,39,40). BNP, in particular, is an acute-phase reactant, and therefore may be elevated in inflammatory conditions without cardiac involvement (40).

Tier 2 testing should also include further assessment for systemic inflammation. In addition to changes in the ESR and CRP level, MIS-C patients typically demonstrate other markers of inflammation, including high D-dimer levels, moderately elevated ferritin levels (often ranging from 500 to 2,000 ng/dl), profoundly increased procalcitonin levels in the absence of bacterial infection, and increased lactate dehydrogenase (LDH) levels (5–7, 13, 14, 17). Cytokine and chemokine measurements, when available, can assist in the diagnostic evaluation, as levels of interleukin-6 (IL-6), tumor necrosis factor (TNF), or IL-10 are often increased (5,6,13,21,22,41–44). In addition, IL-18 and IFN $\gamma$ -related markers are associated with severe disease in MIS-C (45,46). However,

cytokine and chemokine levels measured in this manner should not dictate treatment choices and are not required to determine treatment plans. Along with systemic inflammation, endothelial dysfunction is a feature of MIS-C, and a peripheral blood smear can be used to identify microangiopathic changes in red blood cells, although the sensitivity and specificity of using a peripheral blood smear for the diagnosis of MIS-C is unknown (42).

Finally, a greater proportion of MIS-C patients have been found positive for SARS-CoV-2 by serologic testing (80–90%) than by PCR testing (20–40%), and both tests should be sent to evaluate the epidemiologic link to the infection (4–6,13,17,20,21). The use of serologic testing will become more complicated as the COVID-19 pandemic evolves, because seropositivity for SARS-CoV-2 IgG may not be indicative of a recent infection. Vaccination will also complicate the measurement of anti-spike antibodies. It is important to interpret serologic testing in the context of the prevalence of viral transmission in the patient's community, although a negative finding on antibody test should prompt consideration of alternative diagnoses.

**MIS-C and KD phenotypes.** In an early sentinel report from Bergamo, the Italian epicenter of the COVID-19 pandemic, KD and KD-like illnesses were observed at a rate 30 times higher than that observed in the pre-pandemic era (4). Since this observation, the clinical symptoms of MIS-C have frequently been compared to those of KD given their similarity in profiles, which includes fevers, mucocutaneous features, and cardiac sequelae (2,4–7,13–17,21,36,41,47). However, a closer examination of the literature shows that only about one-quarter to one-half of patients with a reported diagnosis of MIS-C meet the full diagnostic criteria for KD (4–6,13,14,19,20,41).

Several epidemiologic, clinical, and laboratory features of MIS-C that differ from KD unrelated to SARS-CoV-2 are worthy of mention. First, the incidence of KD is highest in Japan and East Asia. In contrast, non-Hispanic Black children are more likely to develop MIS-C when compared to pediatric patients with acute COVID-19 (2,5,6,14,19,20,35,48). It is unclear whether genetic or biologic factors could explain this racial/ethnic distribution of MIS-C or whether socioeconomic status and structural inequality are more causative.

Second, the age distribution of MIS-C is broad, ranging from infancy to adulthood, with children ages 6 to 12 years at increased risk (2,4–7,13,14,17,19–21,35,41,49). In contrast, the majority of children with KD present with symptoms before age 5 years (4,14,21,41,50,51).

Third, as discussed above, the clinical presentations of LV dysfunction and shock that are characteristic of patients with MIS-C are considerably less common in patients with KD, with fewer than 10% of KD patients presenting with KD shock syndrome (52). Close to one-quarter of untreated KD patients develop CAAs (53). Coronary artery aneurysms have been documented in ~13% of MIS-C patients and tend to regress within 30 days in

a majority of children (2,4,13,14,17,19,20,35,41). Importantly, it is clear that MIS-C patients without KD symptoms can develop CAAs, highlighting the need for cardiac evaluation in all patients with MIS-C regardless of phenotypic features, and providing support for the treatment rationale discussed below (14).

Fourth, although gastrointestinal and neurologic symptoms are reported in KD patients, the panel agreed that these findings were more frequently encountered in the MIS-C population.

Finally, the laboratory parameters that have been found to differ in retrospective cohorts of MIS-C patients compared to historical cohorts of KD patients include a lower platelet count, lower absolute lymphocyte count, and higher CRP level in MIS-C patients (4,14,21,41). There is emerging evidence that age may impact the clinical phenotype of MIS-C. Epidemiologic studies suggest that younger children are more likely to present with KD-like features, while older children are more likely to develop myocarditis and shock (19,20).

**Cardiac management of MIS-C.** Children with MIS-C will need close clinical follow-up with cardiology. Extrapolating data from KD, another condition that can be complicated by CAA, the panel recommended that repeat echocardiograms be obtained from all children with MIS-C at a minimum of 7–14 days and then 4–6 weeks after the initial presentation (36). For those patients with cardiac involvement noted during the acute phase of illness, another echocardiogram at 1 year after MIS-C diagnosis could be considered. Children with LV dysfunction and CAAs will require more frequent echocardiograms.

Although LV function improves rapidly in most MIS-C patients, the long-term complications of myocardial inflammation in this syndrome are not known and may include myocardial fibrosis and scarring, representing features that have been seen in other forms of pediatric myocarditis (6,13,54). Cardiac magnetic resonance imaging at 2–6 months post-acute illness in those patients who had moderate-to-severe LV dysfunction will allow for evaluation of fibrosis and scarring. Electrical conduction abnormalities are increasingly noted in MIS-C patients and may develop after the initial presentation; therefore, EKGs should be obtained at a minimum of every 48 hours in patients who are hospitalized and at each follow-up visit (5,6,13,14,33). If conduction abnormalities are present, the patient should be placed on telemetry while in the hospital, and may need Holter monitoring at clinical follow-up.

**Treatment of MIS-C.** *Immunomodulatory treatment in MIS-C.* Goals of treatment in the MIS-C population are to stabilize patients with life-threatening manifestations such as shock, and to prevent long-term sequelae that may include CAAs, myocardial fibrosis/scarring, and fixed cardiac conduction abnormalities. There are no randomized controlled clinical trials that directly compare therapeutic approaches in MIS-C. Recommendations approved by the Task Force are derived from experience in managing MIS-C in children, as well as from nonrandomized

comparative cohort studies and higher quality data from other pediatric conditions with similar features. Initiation of treatment will often depend on the severity of the patient's presentation. There was consensus among the panelists that patients under investigation for MIS-C without life-threatening manifestations should undergo a diagnostic evaluation for MIS-C as well as other possible infections and non-infection-related conditions before immunomodulatory treatment is initiated. This is to prevent the use of therapies that could be potentially harmful in patients who do not have MIS-C.

Further, a subgroup of patients with MIS-C will develop progressive cardiac involvement rapidly; therefore, hospital admission and sequential monitoring of inflammation markers, including BNP/NT-proBNP and troponin T levels, without instituting treatment can sometimes inform the diagnostic evaluation (7,13). Children with a life-threatening presentation such as shock will clearly require supportive care and may benefit from early initiation of immunomodulatory treatment, sometimes before a full diagnostic evaluation can be completed. In such cases, ongoing diagnostic evaluation should be pursued in parallel with treatment by a multidisciplinary team.

Finally, the current recommendations address the treatment of MIS-C that is uncomplicated by macrophage activation syndrome (MAS). Importantly, there is a subgroup of patients with MIS-C who may also develop overt MAS. The treatment of those patients may need to deviate from the recommendations presented herein (4).

*Initial immunomodulatory therapy.* A stepwise approach to immunomodulatory treatment in MIS-C is recommended, with dual therapy with intravenous immunoglobulin (IVIG) and glucocorticoids considered as first-line treatment for most hospitalized patients (Figure 2). Both IVIG and glucocorticoids are the most commonly used immunomodulatory medications in MIS-C patients reported to date (2,4–7,13–15,17,19–21,41,55). Initially, IVIG and glucocorticoids were used to treat patients with MIS-C based on their track record in KD and fulminant myocarditis, two conditions that resemble MIS-C in some aspects. IVIG at a dose of 2 gm/kg prevents CAAs in KD while the benefit of IVIG in myocarditis remains unclear; however, case reports of successful use of IVIG in coronavirus-associated myocarditis have been published (36,53,56–62). Glucocorticoids reduce rates of CAA development when used in KD patients at high risk for IVIG resistance (63,64).

Several comparative cohort studies have demonstrated favorable outcomes for children with MIS-C treated initially with IVIG in combination with glucocorticoids compared to IVIG monotherapy (65–68). This benefit was initially shown in a study by Belhadjer et al in a retrospective, single-center study that showed faster cardiac recovery in 22 MIS-C patients who received IVIG in combination with methylprednisolone (0.8 mg/kg/day for 5 days) compared to IVIG alone (n = 18) (65). Shortly thereafter, a small (n = 96) propensity score-matching analysis from a retrospective surveillance system cohort in France showed that patients

treated with IVIG and methylprednisolone (most treated with 1.6–2.0 mg/kg/day) had a lower risk of treatment failure, improved cardiac function, shorter duration of ICU stay, and reduced rates of treatment escalation compared to children who received IVIG alone (66). The larger Overcoming COVID-19 and Best Available Treatment Study (BATS) also addressed this question. Son et al showed that compared to IVIG alone, initial combination IVIG and glucocorticoid treatment (most treated with methylprednisolone 2.0 mg/kg/day) was associated with a lower risk of cardiovascular dysfunction and need for adjunctive immunomodulatory therapy on day 2 (67). In the BATS study, McArdle et al demonstrated significantly lower rates of treatment escalation with IVIG and glucocorticoids versus IVIG alone; however, there was no difference between these groups in the primary end points, a composite score of inotropic support or mechanical ventilation by day 2 or reduction in disease severity at day 2 (68). There is also some evidence to suggest that faster initiation of IVIG and glucocorticoids in MIS-C is associated with a reduction in intensive care unit (ICU) admissions and length of hospital stay (69).

There remains uncertainty about the use of glucocorticoid monotherapy as initial treatment in MIS-C. To date, BATS is the only study to compare IVIG versus glucocorticoids and showed no differences in primary outcomes between these treatment groups (68). IVIG in combination with glucocorticoids was not compared to glucocorticoids alone. Outcomes for this study were short-term and primarily measured at day 2. There is uncertainty about long-term outcomes, particularly CAAs, in MIS-C patients treated with glucocorticoids alone. In addition, a large number of children in the glucocorticoids alone group ultimately received IVIG (n = 47). Feldstein et al reported largely favorable outcomes in a large cohort of MIS-C patients, with normalization of LV dysfunction in 91% and regression of CAAs in 79.1% of patients at 30 days; however, the majority of children in this cohort received IVIG (35). Given the lack of reported longer-term outcomes in MIS-C patients treated with glucocorticoid monotherapy, the panel was unable to recommend glucocorticoids alone as initial therapy in MIS-C. The panel made this recommendation for the care of children in North America, the target audience provided by the ACR for this guidance, and recognizes that IVIG may not be as freely available in other clinical settings.

Upon review of the totality of evidence from these studies, the Task Force reached consensus that IVIG in combination with glucocorticoids should be used as first-line therapy to treat a majority of hospitalized patients with MIS-C. In a select group of patients with mild disease or contraindications to glucocorticoids, IVIG alone may be appropriate as first-line treatment for MIS-C. These patients should be monitored closely and intensification therapy should be added at the first signs of clinical worsening.

IVIG should be given at a dose of 2 gm/kg based on ideal body weight, with a maximum dose of 100 gm. Low-to-moderate-dose glucocorticoids (1–2 mg/kg/day) should be used as adjunctive

therapy with IVIG. Before IVIG is given, cardiac function and fluid status should be assessed. If abnormal, the rate of IVIG infusion may be slowed, the treatment may be given in divided doses over 2 days, and/or diuretics may be considered to avoid volume overload.

*Intensification of immunomodulatory therapy.* A patient with MIS-C is considered to have refractory disease when the child has persistent fevers and/or significant end-organ involvement despite initial immunomodulatory treatment. Typically, MIS-C patients demonstrate a response to IVIG and glucocorticoids within the first 24 hours of treatment, and intensification therapy should be strongly considered in patients who lack such clinical improvement. Compared to pre-COVID-19 pandemic KD, MIS-C patients display more cardiac dysfunction and require larger doses of IVIG due to the age and size of these patients. Thus, patients with MIS-C are at greater risk for IVIG complications such as hemolytic anemia and volume overload. Furthermore, MIS-C patients are more likely to decompensate rapidly and may benefit from faster intensification of therapy than children with non-SARS-CoV-2-related KD. Accordingly, a second dose of IVIG is not recommended in patients with refractory disease. Instead, intensification therapy is recommended with either high-dose (10–30 mg/kg/day) glucocorticoids, anakinra, or infliximab. The evidence for selecting a specific agent for intensification therapy is limited, with no available comparative studies for this clinical scenario.

Thus, recommendations from the panel are based on expert opinion, clinical experience, and available data in other pediatric hyperinflammatory syndromes. Several panelists have found that some children with shock, requiring multiple inotropes and/or vasopressors, have responded best to high doses of intravenous glucocorticoids (10–30 mg/kg/day). High-dose intravenous glucocorticoids have been used safely in patients with KD and have been used successfully in patients with MIS-C and shock (7,69–72). Adjunctive glucocorticoids have also been shown to shorten the duration of shock in patients with sepsis (73).

High-dose anakinra (recombinant human IL-1 receptor antagonist) (>4 mg/kg/day and often 5–10 mg/kg/day) can also be considered for MIS-C patients with refractory disease despite having received IVIG and steroid treatment. In addition, anakinra may also be considered as a steroid-sparing agent in patients with contraindications to long courses of glucocorticoids. These recommendations are based on the relative safety of anakinra in pediatric patients with hyperinflammatory syndromes and active infection, the experience of panel members in using anakinra to treat MIS-C patients, and case descriptions of a small number of MIS-C patients reported in the literature (13,14,17,19,21,22,41,55,74–77). In addition, anakinra has been used successfully in a small number of patients with IVIG-resistant KD (78–81).

Infliximab may also be used for intensification therapy or as a steroid-sparing agent in children with MIS-C without evidence of macrophage activation syndrome (MAS). A single-center

retrospective study comparing IVIG alone ( $n = 20$ ) with IVIG and infliximab (10 mg/kg IV  $\times$  1 dose) ( $n = 52$ ) showed that the combination treatment group was less likely to require additional immunomodulatory therapy, had a shorter length of stay in the ICU, and demonstrated less left ventricular dysfunction (82). At baseline, the IVIG and infliximab group had more severe disease, making these results even more notable. Other groups have also reported positive results for infliximab in a small number of children with MIS-C (83). Infliximab has also been shown to reduce fever in patients with IVIG-resistant KD (84,85).

*Tapering immunomodulatory therapy.* Serial laboratory testing and cardiac assessment should guide decisions to decrease immunomodulatory treatment. Children with MIS-C require a prolonged course of immunomodulatory treatment that may need to extend for 2–3 weeks, or even longer, to avoid rebound inflammation.

*Treatment of non-hospitalized patients.* Treatment with immunomodulatory agents may not always be required in MIS-C. Whittaker et al reported that 22% of MIS-C patients recovered with supportive care (14). In close coordination with specialists who have expertise in MIS-C, some patients with mild symptoms may require only close monitoring, without the use of IVIG and/or glucocorticoids. The panel noted uncertainty around the empiric use of IVIG in this setting to prevent CAAs.

*Antiplatelet and anticoagulation therapy in MIS-C.* Recommendations for antiplatelet and anticoagulation therapy in MIS-C are largely based on experience in analogous pediatric conditions, specifically KD and myocarditis, and the emerging data from adults with COVID-19. Antiplatelet agents such as aspirin (ASA) are recommended in KD due to platelet activation, thrombocytosis, altered flow dynamics in abnormal coronary arteries, and endothelial damage characteristic of this disease (36). Accordingly, low-dose ASA (3–5 mg/kg/day, up to 81 mg once daily) is recommended in all MIS-C patients without active bleeding or significant bleeding risk. ASA should be continued until normalization of the platelet count and confirmed normal coronary arteries at  $\geq 4$  weeks after diagnosis. Anti-acid treatments should be used to prevent gastrointestinal complications in MIS-C patients taking steroids and ASA.

Risk of coronary artery thrombosis is directly related to the size of the CAA, with exponentially increased probability in coronary arteries with dimensions above a z-score of 10.0 (36,86,87). Thus, MIS-C patients with a coronary artery z-score greater than or equal to 10.0 should be treated with enoxaparin (anti-factor Xa level 0.5–1.0) for at least 2 weeks, and then can be transitioned to warfarin or a direct-acting oral anticoagulant. Patients with more than mild LV dysfunction are at risk for intracardiac thrombosis (88,89). Given the lack of clarity about the exact risk of hypercoagulability in MIS-C, the Task Force recommended considering anticoagulation for MIS-C with moderate or severe LV dysfunction (EF <35%).

There is substantially more uncertainty about the use of anticoagulation in MIS-C patients without CAAs or severe LV dysfunction.

Published reports of patients with MIS-C describe marked abnormalities in the coagulation cascade, including prominent elevations in D-dimer and fibrinogen levels, a variable effect on the platelet count, and a high clot strength as determined by thromboelastography (2,4–6,13,14,19,20,22). An increased risk of thrombosis is a concern in patients with MIS-C, based on the data outlined above as well as the hypercoagulability noted in adults with COVID-19 (90–93). Thrombotic events have been reported in as many as 7–19% of adolescents with MIS-C; however, a much lower incidence of thrombosis has been reported in other case series (0–2%) (19,20,34,94). Thus, it remains unclear if MIS-C patients have a higher risk for thrombosis compared to other critically ill children with systemic inflammation. In one analysis of pediatric patients with acute COVID-19 and MIS-C, central venous catheterization, age >12 years, malignancy, ICU admission, and D-dimer levels elevated >5 times the upper limit of normal were all independent risk factors for thrombosis (94). The bleeding risk in children with MIS-C is not well understood but there have been reports of major bleeding events in MIS-C patients receiving anticoagulation (94). It remains unclear if the experience in adults with acute COVID-19 can be extrapolated to children with MIS-C; further, the data in this group are somewhat difficult to reconcile. Several clinical trials have demonstrated improved outcomes with therapeutic anticoagulation in non-critically ill adults with COVID-19, but no benefit was demonstrated in critically ill individuals (95–98). Thus, there is a high degree of uncertainty around the thrombotic and bleeding risks in children with MIS-C and the benefit of anticoagulation, be it prophylactic or therapeutic. As a result, there is wide variability in the approach to anticoagulation in this population reported in the literature and by members of the panel (99). Consensus could only be achieved in agreeing that the approach to anticoagulation management should be tailored to the patient's individual risk factors.

### **Hyperinflammation in children with COVID-19.**

*Severe COVID-19 in children.* The Task Force also addressed immunomodulatory treatment in severe COVID-19, a condition that panelists deemed to be readily distinguishable from MIS-C. A vast majority of children with COVID-19 have mild symptoms in the acute, infectious phase of the disease, but a small minority of patients become severely ill (100–105). MIS-C patients who are often previously healthy may present with fever, inflammation, and multiorgan dysfunction that manifests late in the course of SARS-CoV-2 infection (most are positive for SARS-CoV-2 IgG). In contrast, children who develop severe COVID-19 during their initial infection often have a complex medical history (101–104,106,107). Shekerdeman and colleagues reported that 40% of patients admitted to the ICU for COVID-19 had developmental delay or a genetic anomaly, or were dependent on technological support (e.g., tracheostomy) for survival (102). In addition, children with chronic medical conditions such as obesity, asthma, neurologic disorders, type I diabetes, sickle cell disease, and

complex congenital heart disease may be at higher risk for severe COVID-19 (106,107). Hospitalization rates for COVID-19 are highest in Hispanic and Black children (106,107). The reason for this disparity is not entirely clear but may be related to risk of exposure to SARS-CoV-2 due to structural inequalities in society as well as the higher rates of preexisting conditions in this population (106,107). Healthy children can develop severe illness with SARS-CoV-2 infection, particularly young infants (0–2 months of age) (106).

There is no definitive evidence suggesting that children with rheumatic diseases treated with immunosuppression are also at risk of developing poor outcomes from COVID-19. Extrapolating from adults with inflammatory bowel disease and rheumatic conditions, glucocorticoid use (>10 mg/day), rituximab, and sulfasalazine may be associated with worse outcomes in COVID-19 while treatment with TNF inhibitors may actually be protective against severe COVID-19 (108,110). Importantly, moderate-to-high disease activity in adults was associated with a higher risk of death from COVID-19, highlighting the importance of controlling inflammation in patients with rheumatic conditions (110). In addition, among cohorts of pediatric patients in this population receiving immunosuppressive medications, an increased risk of severe COVID-19 has not been identified (111–113).

*Immunomodulatory treatment in children with hyperinflammation and COVID-19.* Rheumatologists may be called upon to provide recommendations on immunomodulatory treatments for children with COVID-19. This guidance focuses on such immunomodulatory therapies and does not cover the use of antivirals, anti-SARS-CoV-2 antibodies, anticoagulation, or other modalities of treatment. Data to guide the treatment of pediatric patients with severe illness during the early phase of SARS-CoV-2 infection are limited. In adults, certain laboratory parameters associated with an exaggerated inflammatory response (hyperinflammation) portend worse outcomes in COVID-19, including elevated levels of LDH, D-dimer, IL-6, IL-2 receptor, CRP, and ferritin, and a decreased lymphocyte count, albumin level, and platelet count (87–90). In at least one case series of pediatric patients with COVID-19, increased CRP levels, elevated procalcitonin levels, and decreased platelet counts were significantly more common in children requiring ICU admission compared to those receiving floor-level hospital care; however, further studies are needed to identify laboratory parameters that could serve as predictors of poor outcomes in the pediatric population (118). These results suggest that patients with COVID-19 and hyperinflammation have poor outcomes, and that the host immune response to SARS-CoV-2 may contribute to disease severity. The panel agreed that hospitalized children with COVID-19 requiring supplemental oxygen or respiratory support should be considered for immunomodulatory therapy in addition to supportive care and antiviral medications. Substantial elevation in inflammation markers may support this decision and prove useful in monitoring.

#### *First-line immunomodulatory therapy in pediatric COVID-19.*

Glucocorticoids are a readily available and inexpensive option for immunomodulation. Results from a large randomized controlled trial (the RECOVERY trial) indicate that low-to-moderate-dose dexamethasone significantly reduced mortality in COVID-19 patients requiring mechanical ventilation (119). A meta-analysis of 7 randomized clinical trials that studied glucocorticoid treatment in adults with COVID-19 supports the results of the RECOVERY trial and also demonstrates a reduction in mortality in the treatment group (120). Based on these studies in adults, the Task Force achieved consensus in recommending that dexamethasone should be used as first-tier immunomodulatory treatment in pediatric patients with persistent oxygen requirement due to COVID-19. Dexamethasone should be given as 0.15 to 0.3 mg/kg/day (maximum 6 gm) for up to 10 days. If dexamethasone is unavailable, equivalent doses of other glucocorticoids can be used.

#### *Secondary immunomodulatory therapy in pediatric COVID-19.*

Since publication of the second version of this guidance, several randomized controlled trials in adults with COVID-19 demonstrated that a subgroup of patients with progressive respiratory involvement despite dexamethasone administration benefit from additional immunomodulatory treatment (121–125). IL-6 receptor antagonists and JAK inhibitors are the most commonly studied secondary immunomodulators in adults with COVID-19, and both drug classes have produced positive results in more than one high-quality study (121–125).

REMAP-CAP and RECOVERY are the largest published studies of tocilizumab in adults with COVID-19 pneumonia (121,122). In REMAP-CAP, patients within 24 hours of ICU admission for COVID-19 were randomized to receive an IL-6 receptor antagonist (tocilizumab,  $n = 353$ ; sarilumab,  $n = 48$ ) compared to standard of care (122). The IL-6 receptor antagonist group had significantly improved survival and increased number of organ support-free days (122). In the RECOVERY study, patients already receiving dexamethasone with ongoing hypoxia and elevated CRP levels ( $\geq 75$  mg/liter) were randomized to receive tocilizumab and had reduced mortality compared to those receiving standard of care (121).

The ACTT-2 trial compared remdesivir with and without baricitinib (patients receiving glucocorticoids were excluded) and showed that the addition of baricitinib resulted in faster recovery in adults with COVID-19 (124). In the COV-BARRIER trial, adults with COVID-19 and elevated inflammation markers who received baricitinib had reduced mortality rates at days 28 and 60 compared to standard of care (~80% of patients received glucocorticoids). In both studies of baricitinib, the effect was most pronounced in patients receiving high-flow oxygen or noninvasive ventilation. A single additional study (STOP-COVID) evaluated tofacitinib versus placebo in a smaller number of patients ( $n = 289$ ) and showed significant reduction in the primary outcome of death or respiratory failure at day 28 (125).

Upon review of the studies that support the use of IL-6 blockade or JAK inhibitors in adult COVID-19, the patients

who appeared to benefit most from such treatments were not yet mechanically ventilated and were early in the course of clinical deterioration (122–124). The COVID-19 Treatment Guidelines from the NIH recommend the addition of either baricitinib or tocilizumab to dexamethasone “for recently hospitalized patients with rapidly increasing oxygen needs and systemic inflammation.” The NIH panel states that sarilumab or tofacitinib can be used as alternatives for adults with COVID-19 if baricitinib and tocilizumab are unavailable (126).

Based on the results observed in adults, the Task Force recommends that children with increasing oxygen requirements and elevated inflammation markers due to COVID-19 who have not improved with glucocorticoids alone should receive secondary immunomodulatory therapy. As in the adult population, it is likely that children will benefit most from secondary immunomodulatory therapy when it is given early in the course of clinical deterioration and before mechanical ventilation. Both tocilizumab and baricitinib can be considered for this purpose, and the decision of which to choose will depend on availability, patient age, and comorbidities. It should be emphasized that either one of these medications should be given in combination with glucocorticoids. There are no studies in adults comparing IL-6 receptor antagonists and JAK inhibitors, and there is insufficient evidence to recommend one medication before the other. There are also no data to support the safety of using tocilizumab and baricitinib in combination.

Tocilizumab has an established track record in children with juvenile idiopathic arthritis, including FDA approval for individuals as young as 2 years of age (127–131). This medication has also been used safely in pediatric patients with cytokine storm and hyperinflammatory conditions (127,132). Several members of the panel expressed a preference to use tocilizumab in young children with COVID-19; however, shortages in the supply of tocilizumab may limit accessibility to this drug. Tocilizumab should be given at a dose of 8 mg/kg IV (maximum 800 mg) and may be re-dosed more than 8 hours later if there is an insufficient clinical response.

There is substantially less clinical experience in using baricitinib in the pediatric population. Accordingly, this medication should be given in consultation with subspecialists who have substantial experience in treating pediatric patients with immunosuppression. The emergency use authorization (EUA) from the FDA recommends that in children with normal renal function, baricitinib be given orally up to 14 days at a dose of 2 mg daily in children age 2 years to <9 years, and 4 mg daily in children age  $\geq 9$  years.

While only one trial has demonstrated efficacy for tofacitinib in adults with COVID-19, the safety and pharmacokinetics of this drug have been studied in children as young as 2 years of age (133). Tofacitinib is FDA approved for use in polyarticular juvenile idiopathic arthritis. Therefore, tofacitinib can be considered as an alternative medication for secondary immunomodulation in children with COVID-19 when tocilizumab and baricitinib are not available or contraindicated. There is insufficient experience in adults with COVID-19 and a limited performance history in the

pediatric population to recommend for or against the use of other IL-6 or JAK inhibitors in children with COVID-19.

Children receiving secondary immunomodulation should be monitored closely for secondary infections and liver function test abnormalities. Children receiving tocilizumab should also be monitored for hypertriglyceridemia and infusion reactions. Children receiving baricitinib should also be monitored for thrombosis and thrombocytosis.

Prior versions of this guidance have recommended anakinra for children with COVID-19 and hyperinflammation. Since that initial recommendation, several randomized controlled trials evaluating IL-1 inhibition in adults with COVID-19 have been published, with conflicting results. The CAN-COVID study showed no benefit of canakinumab compared to placebo in adults with COVID-19 pneumonia and systemic inflammation who were not yet mechanically ventilated (134). The CORIMUNO-ANA-1 trial evaluating anakinra for adults with mild-to-moderate COVID-19 and elevated CRP levels was stopped for futility (135). Alternately, the SAVE-MORE study showed a benefit with anakinra in patients with COVID-19 and elevated soluble urokinase plasminogen activator receptor, a laboratory parameter that is not readily available in most clinical settings. Given these conflicting data, the Task Force could not recommend for or against the use of anakinra in children with COVID-19 and elevated inflammation markers.

## DISCUSSION

There has been an evolution in our understanding of SARS-CoV-2 infections in children. Initially, it was believed that COVID-19 was almost entirely benign and of little consequence in the pediatric population. There has been a sudden reversal from this stance in the context of the emergence of MIS-C cases. The goal of this ACR Task Force was to synthesize available data and expert opinion to provide a resource for clinicians on the frontlines caring for children with inflammatory syndromes associated with recent or concurrent infections with SARS-CoV-2.

Recognizing the need to address the unique challenges facing children with inflammatory conditions triggered by SARS-CoV-2 infections, the ACR convened the Task Force to provide guidance in a short period of time. To accomplish this charge, a multidisciplinary panel was assembled that included clinicians from North America with expertise encompassing pediatric rheumatology, cardiology, infectious disease, and critical care. Well-established methodology in the form of the RAND/UCLA Appropriateness Method was used to achieve consensus.

There are limitations inherent in our approach. Given the need for expedited decision-making, we were unable to provide guidance on all topics of interest. In particular, the Task Force focused its efforts on providing diagnostic and treatment recommendations for MIS-C instead of developing a new case definition for this condition. This choice was made because several case definitions of MIS-C exist, and the data needed to develop a sensitive and

specific set of criteria are not yet available. The guidance provided in this document is targeted to clinicians with access to complex diagnostic tools and biologic treatments. Thus, some of the recommendations are not practical in less resource-rich settings. In addition, the work product of the Task Force is considered guidance, instead of formal treatment guidelines that must adhere to the strict methodology endorsed by the ACR.

The guidance provided in this document is supported by reports from the scientific literature and recommendations from public health institutions. Yet, the available data remain restricted to nonrandomized studies in children and often must be extrapolated from the experience in adults. This approach is particularly problematic when confronting clinical questions regarding MIS-C, which, to date, has been reported primarily in children. This unique manifestation of COVID-19 in children and adolescents highlights the need to prioritize and fund rigorous research in the pediatric population. For now, our understanding of pediatric SARS-CoV-2 infections is rudimentary and will continue to change as higher-quality evidence becomes available. Thus, the recommendations contained in this document should be interpreted in the setting of this shifting landscape and will be modified prospectively as our understanding of COVID-19 improves. For these reasons, this guidance does not replace the critical role of clinical judgment that is essential to address the unique needs of individual patients.

As the SARS-CoV-2 pandemic continues to unfold, the ACR will support clinicians caring for children with COVID-19 by enabling this Task Force to continue the work of reviewing evidence and providing expert opinion through revised versions of this guidance document. It is the ultimate goal of both the ACR and the Task Force panelists to disseminate knowledge quickly in an effort to improve outcomes for children with SARS-CoV-2 infections.

## ACKNOWLEDGMENTS

The Task Force thanks Dr. Anne Ferris for her contributions to the first 2 versions of this manuscript.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Henderson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Henderson, Friedman, Gorelik, Lapidus, Behrens, Seo, Turner, Mehta.

**Acquisition of data.** Henderson, Canna, Gorelik, Lapidus, Bassiri, Behrens, Kernan, Schulert, Seo, Tremoulet, VanderPluym, Yeung, Karp, Mehta.

**Analysis and interpretation of data.** Henderson, Canna, Friedman, Gorelik, Lapidus, Bassiri, Kernan, Schulert, Seo, Son, Tremoulet, VanderPluym, Yeung, Mudano, Karp, Mehta.

## REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time [letter]. *Lancet Infect Dis* 2020;20:533–4.



2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic [letter]. *Lancet* 2020;395:1607–8.
3. World Federation of Pediatric Intensive and Critical Care Societies. Statement to the media following the 2 May Pediatric Intensive Care-COVID-19 International Collaborative conference call. May 2020. URL: <http://www.wfpiccs.org/wp-content/uploads/2020/05/Media-statement-Final.pdf>.
4. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–8.
5. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourceaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 2020;369:m2094.
6. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City [letter]. *JAMA* 2020;324:294–6.
7. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc* 2020;9:393–8.
8. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. May 2020. URL: <https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>.
9. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. June 2020. URL: <https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims>.
10. Centers for Disease Control and Prevention. Emergency preparedness and response: health alert network. May 2020. URL: <https://emergency.cdc.gov/han/2020/han00432.asp>.
11. Brook R. US Agency for Health Care Policy and Research Office of the Forum for Quality and Effectiveness in Health Care clinical practice guideline development: methodology perspectives. In: McCormick K, Siegel R, editors. *The RAND/UCLA Appropriateness Method*. Rockville (MD): Agency for Healthcare Research and Quality; 1994: p. 59–70.
12. American College of Rheumatology. Clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. June 2020. URL: <https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf>.
13. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* 2020;142:429–36.
14. Whittaker E, Bamford A, Kenny J, Kafrou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;324:259–69.
15. Leon MP, Redzepi A, McGrath E, Abdel-Haq N, Shawaqfeh A, Sethuraman U, et al. COVID-19 associated pediatric multi-system inflammatory syndrome. *J Pediatric Infect Dis Soc* 2020;9:407–8.
16. Dallon C, Romano F, Siebert J, Politi S, Lacroix L, Sahyoun C. Septic shock presentation in adolescents with COVID-19 [letter]. *Lancet Child Adolescent Health* 2020;4:e211–3.
17. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory disease of childhood (MIS-C) associated with SARS-CoV-2 infection. *J Pediatr* 2020;224:141–5.
18. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. *Pediatrics* 2020;146:e20201711.
19. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in US children and adolescents. *N Engl J Med* 2020;383:334–46.
20. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med* 2020;383:347–58.
21. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis* 2020;79:999–1006.
22. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. *J Pediatr* 2020;224:24–9.
23. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol* 2021;78:536–47.
24. Roberts JE, Campbell JI, Gauvreau K, Lamb GS, Newburger J, Son MB, et al. Differentiating multisystem inflammatory syndrome in children: a single-centre retrospective cohort study. *Arch Dis Child*. doi:10.1136/archdischild-2021-322290 2021. E-pub ahead of print.
25. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open* 2021;4:e2116420.
26. Hennon TR, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, Schaefer BA, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines: a western New York approach. *Prog Pediatr Cardiol* 2020. E-pub ahead of print.
27. Children's Hospital of Philadelphia. Emergency Department, ICU, and inpatient clinical pathway for evaluation of possible multisystem inflammatory syndrome (MIS-C). May 2020. URL: <https://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway>.
28. Carlin RF, Fischer AM, Pitkowsky Z, Abel D, Sewell TB, Landau EG, et al. Discriminating MIS-C requiring treatment from common febrile conditions in outpatient settings. *J Pediatr* 2020. E-pub ahead of print.
29. Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. *J Pediatr* 2021;230:23–31.e10.
30. Dominguez-Rodriguez S, Villaverde S, Sanz-Santaefemia FJ, Grasa C, Soriano-Arandes A, Saavedra-Lozano J, et al. A Bayesian model to predict COVID-19 severity in children. *Pediatr Infect Dis J* 2021;40:e287–e93.
31. Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. *J Pediatr* 2020;226:45–54.
32. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care* 2020;10:69.

33. Dionne A, Mah DY, Son MB, Lee PY, Henderson L, Baker AL, et al. Atrioventricular block in children with multisystem inflammatory syndrome. *Pediatr* 2020;146:e2020009704.
34. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. *Circulation* 2021;143:21–32.
35. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA* 2021;325:1074–87.
36. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [review]. *Circulation* 2017;135:e927–99.
37. Colan SD. The why and how of Z scores [editorial]. *J Am Soc Echocardiogr* 2013;26:38–40.
38. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr* 2010;23:465–95.
39. Yetkin O, Hacievliyagil SS, Gunen H. Assessment of B-type natriuretic peptide in patients with pneumonia. *Int J Clin Pract* 2008;62:488–91.
40. Melendez E, Whitney JE, Norton JS, Silverman M, Monuteaux MC, Bachur RG. A pilot study of the association of amino-terminal pro-B-type natriuretic peptide and severity of illness in pediatric septic shock. *Pediatr Crit Care Med* 2019;20:e55–60.
41. Lee PY, Day-Lewis M, Henderson LA, Friedman K, Lo J, Roberts JE, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Invest* 2020;130:5942–50.
42. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase JM, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. *J Clin Invest* 2020;130:5967–75.
43. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020;26:1701–7.
44. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell* 2020;183:982–95.
45. Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumado V, Fortuny C, et al. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. *J Clin Invest* 2021;131:e144554.
46. Rodriguez-Smith JJ, Verweyen EL, Clay GM, Esteban YM, de Loizaga SR, Baker EJ, et al. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. *Lancet Rheumatol* 2021;3:e574–84.
47. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974;54:271–6.
48. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. *Pediatr Int* 2019;61:397–403.
49. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1450–6.
50. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics* 2003;112:495–501.
51. Son MB, Gauvreau K, Ma L, Baker AL, Sundel RP, Fulton DR, et al. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics* 2009;124:1–8.
52. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009;123:e783–9.
53. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341–7.
54. Banka P, Robinson JD, Uppu SC, Harris MA, Hasbani K, Lai WW, et al. Cardiovascular magnetic resonance techniques and findings in children with myocarditis: a multicenter retrospective study. *J Cardiovasc Magn Reson* 2015;17:96.
55. Dove ML, Jaggi P, Kelleman M, Abuali M, Ang JY, Ballan W, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. *J Pediatr* 2021;229:33–40.
56. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;2:1055–8.
57. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004;114:1708–33.
58. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation* 2020;141:e69–92.
59. Dennert R, Velthuis S, Schalla S, Eurlings L, van Suylen RJ, van Paassen P, et al. Intravenous immunoglobulin therapy for patients with idiopathic cardiomyopathy and endomyocardial biopsy-proven high PVB19 viral load. *Antiviral therapy* 2010;15:193–201.
60. Goland S, Czer LS, Siegel RJ, Tabak S, Jordan S, Luthringer D, et al. Intravenous immunoglobulin treatment for acute fulminant inflammatory cardiomyopathy: series of six patients and review of literature. *Can J Cardiol* 2008;24:571–4.
61. Yen CY, Hung MC, Wong YC, Chang CY, Lai CC, Wu KG. Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis. *Scientific Reports* 2019;9:10459.
62. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020;42:191.
63. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012;379:1613–20.
64. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2017;1:CD011188.
65. Belhadjer Z, Auriou J, Meot M, Oualha M, Renolleau S, Houyel L, et al. Addition of corticosteroids to immune globulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children (MIS-C). *Circulation* 2020;142:2282–4.

66. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA* 2021;325:855–64.
67. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. *New Engl J Med* 2021;385:23–34.
68. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. *New Engl J Med* 2021;385:11–22.
69. Jonat B, Gorelik M, Boneparth A, Geneslaw AS, Zachariah P, Shah A, et al. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. *Pediatr Crit Care Med* 2020. E-pub ahead of print.
70. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007;356:663–75.
71. Inoue Y, Okada Y, Shinohara M, Kobayashi T, Kobayashi T, Tomomasa T, et al. A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome. *J Pediatr* 2006;149:336–41.
72. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. *Pediatrics* 2012;129:e17–23.
73. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797–808.
74. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis* 2011;70:747–54.
75. Ter Haar NM, van Dijkhuizen EH, Swart JF, van Royen-Kerkhof A, el Idrissi A, Leek AP, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. *Arthritis Rheumatol* 2019;71:1163–73.
76. Fisher CJ Jr, Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ, et al, for the Phase III rIL-1ra Sepsis Syndrome Study Group. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome: results from a randomized, double-blind, placebo-controlled trial. *JAMA* 1994;271:1836–43.
77. Eloseily EM, Weiser P, Crayne CB, Haines H, Mannion ML, Stoll ML, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol* 2020;72:326–34.
78. Kone-Paut I, Cimaz R, Herberg J, Bates O, Carbasse A, Saulnier JP, et al. The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: a retrospective cases series. *Autoimmun Rev* 2018;17:768–74.
79. Lind-Holst M, Hartling UB, Christensen AE. High-dose anakinra as treatment for macrophage activation syndrome caused by refractory Kawasaki disease in an infant. *BMJ Case Rep* 2019;12:e229708.
80. Guillaume MP, Reuriaux H, Dubos F. Usefulness and safety of anakinra in refractory Kawasaki disease complicated by coronary artery aneurysm. *Cardiol Young* 2018;28:739–42.
81. Kone-Paut I, Tellier S, Belot A, Brochard K, Guitton C, Marie I, et al. Phase II Open Label Study of Anakinra in Intravenous Immunoglobulin-Resistant Kawasaki Disease. *Arthritis Rheumatol* 2021;73(1):151–61.
82. Cole LD, Osborne CM, Silveira LJ, Rao S, Lockwood JM, Kunkel MJ, et al. IVIG Compared to IVIG Plus Infliximab in Multisystem Inflammatory Syndrome in Children. *Pediatrics* 2021.
83. Abdel-Haq N, Asmar BI, Deza Leon MP, McGrath EJ, Arora HS, Cashen K, et al. SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment. *European journal of pediatrics* 2021;180(5):1581–91.
84. Mori M, Hara T, Kikuchi M, Shimizu H, Miyamoto T, Iwashima S, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. *Scientific reports* 2018;8:1994.
85. Yamaji N, da Silva Lopes K, Shoda T, Ishitsuka K, Kobayashi T, Ota E, et al. TNF-alpha blockers for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2019;8:CD012448.
86. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Amer Heart Assoc* 2016;5:e003289.
87. Tsuda E, Tsujii N, Hayama Y. Stenotic Lesions and the maximum diameter of coronary artery aneurysms in Kawasaki disease. *J Pediatrics* 2018;194:165–70.e2.
88. Chen K, Williams S, Chan AK, Mondal TK. Thrombosis and embolism in pediatric cardiomyopathy. *Blood Coagul Fibrinolysis* 2013;24:221–30.
89. Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation* 2013;128:2622–703.
90. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;20:1135–40.
91. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* 2020;18:1559–61.
92. Klok FA, Kruip M, van der Meer NJ, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Res* 2020;191:145–7.
93. Zhou B, She J, Wang Y, Ma X. Venous thrombosis and arteriosclerosis obliterans of lower extremities in a very severe patient with 2019 novel coronavirus disease: a case report. *J Thromb Thrombolysis* 2020;50:229–32.
94. Whitworth H, Sartain SE, Kumar R, Armstrong K, Ballester L, Betensky M, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood* 2021;138:190–8.
95. Investigators A, Investigators AC-a, Investigators R-C, Lawler PR, Goligher EC, Berger JS, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med* 2021;385:790–802.
96. Investigators R-C, Investigators AC-a, Investigators A, Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med* 2021;385:777–89.
97. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA internal medicine* 2021.
98. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Ainle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *Bmj* 2021;375:n2400.
99. Elias MD, McCrindle BW, Larios G, Choueier NF, Dahdah N, Harahsheh AS, et al. Management of Multisystem Inflammatory Syndrome in Children Associated With COVID-19: A Survey From the International Kawasaki Disease Registry. *CJC open* 2020;2:632–40.

100. Parri N, Lenge M, Buonsenso D, for the Coronavirus Infection in Pediatric Emergency Departments Research Group. Children with Covid-19 in pediatric emergency departments in Italy [letter]. *N Engl J Med* 2020;383:187–90.
101. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children [letter]. *N Engl J Med* 2020;382:1663–5.
102. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr* 2020;174:868–73.
103. Tagarro A, Epalza C, Santos M, Sanz-Santaefemia FJ, Otheo E, Moraleda C, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain [letter]. *JAMA Pediatr* 2020. E-pub ahead of print.
104. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J Pediatr* 2020;223:199–203.
105. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020;145:e20200702.
106. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 1–July 25, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1081–8.
107. Saatci D, Ranger TA, Garriga C, Clift AK, Zaccardi F, Tan PS, et al. Association between race and COVID-19 outcomes among 2.6 million children in England. *JAMA Pediatr* 2021;175:928–38.
108. Brenner EJ, Ungaro RC, Geary RB, Kaplan GG, Kissous-Hunt M, Lewis JD, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159:481–91.
109. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
110. Strangfeld A, Schafer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021;80:930–42.
111. Marlais M, Wlodkowski T, Vivarelli M, Pape L, Tonshoff B, Schaefer F, et al. The severity of COVID-19 in children on immunosuppressive medication [letter]. *Lancet Child Adolesc Health* 2020;4:e17–8.
112. Turner D, Huang Y, Martin-de-Carpi J, Aloï M, Focht G, Kang B, et al. Coronavirus disease 2019 and paediatric inflammatory bowel diseases: global experience and provisional guidance (March 2020) from the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2020;70:727–33.
113. Michelen X, Borrell H, Lopez-Corbeto M, Lopez-Lasanta M, Moreno E, Pascual-Pastor M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying antirheumatic drugs. *Semin Arthritis Rheum* 2020;50:564–70.
114. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
115. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–43.
116. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130:2620–9.
117. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
118. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. *J Pediatr* 2020;223:14–9.
119. Horby P, Lim WS, Emberson J, Matham M, Bell J, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19: preliminary report. *N Engl J Med* 2020. E-pub ahead of print.
120. Sterne JA, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al, on behalf of the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:1330–41.
121. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:637–45.
122. Investigators R-C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–502.
123. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021. E-pub ahead of print.
124. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795–807.
125. Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. *New Engl J Med* 2021;385:406–15.
126. Therapeutic management of hospitalized adults with COVID-19, NIH COVID-19 treatment guidelines. Published August 25, 2021. Accessed November 15, 2021. URL: <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/>.
127. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *New Engl J Med* 2012;367:2385–95.
128. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* 2012;64:1001–10.
129. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther* 2017;19:256.
130. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2015;74:1110–7.
131. Brunner HI, Ruperto N, Zuber Z, Cuttica R, Keltsev V, Xavier RM, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a phase III trial. *Arthritis Rheumatol* 2021;73:530–41.

132. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *New Engl J Med* 2014;371:1507–17.
133. Ruperto N, Brunner HI, Zuber Z, Tzaribachev N, Kingsbury DJ, Foeldvari I, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. *Pediatric Rheumatol (online)* 2017;15:86.
134. Caricchio R, Abbate A, Gordeev I, Meng J, Hsue PY, Neogi T, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA* 2021;326:230–9.
135. Group C-C. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med* 2021;9:295–304.