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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. Version 1.

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Innovation and Significance

- A modified Delphi approach was used by a multidisciplinary Task Force to develop guidance on the management of MIS-C associated with SARS-CoV-2 and hyperinflammation in COVID-19.
- 40 guidance statements were approved by the Task Force that address the management of these inflammatory syndromes in children with SARS-CoV-2 infections.
- The guidance provided in this “living document” will be revised as further evidence becomes available.

Abstract

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. The Task Force also provided recommendations for children with hyperinflammation during COVID-19, the acute, infectious phase of SARS-CoV-2 infection.

Methods: The Task Force was composed of 9 pediatric rheumatologists, 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 2 rounds of anonymous voting and 2 webinars. A 9-point scale was used to determine the appropriateness of each statement (1-3, inappropriate; 4-6, uncertain; 7-9, appropriate), and consensus was rated as low (L), moderate (M), or high (H) based on dispersion of the votes along the numeric scale. Approved guidance statements had to be classified as appropriate with moderate or high levels of consensus, which were pre-specified prior to voting.

Results: A total of 128 statements were approved by the Task Force, which were refined into 40 final guidance statements accompanied by a flow diagram depicting the diagnostic pathway for 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 but is meant to be modified as additional data become available.

Since its initial description in December 2019 in Wuhan China, coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (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 will use "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: 1) Variable case definitions for MIS-C; 2) The clinical description of MIS-C is limited to case series; 3) MIS-C clinical features may also be seen in infectious, malignant, and other rheumatologic entities; 4) Suggested treatment strategies have relied on extrapolation from other inflammatory or rheumatologic conditions presenting similarly; 5) 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 a hyperinflammatory state due to 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, charged by ACR leadership to provide guidance to clinicians in the evaluation and management of MIS-C and COVID-19-related hyperinflammatory syndromes. 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, JJM) based on their clinical expertise in rheumatology, infectious diseases, cardiology, cytokine storm related syndromes, and KD as well as experience in managing patients with 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. Prior to the first meeting, Task Force members were subdivided into 4 workgroups to address the following clinical topics related to MIS-C and hyperinflammation in COVID-19: 1) Diagnostic evaluation of MIS-C (Lead, SKL); 2) Cardiac management of MIS-C (Lead, KGF); 3) Treatment of MIS-C (Lead, MG); and 4) Management of hyperinflammation in COVID-19 (Lead SWC). During the first webinar on May 22, 2020, participants agreed with the importance of addressing these 4 overarching topics as well as the structure of the workgroups. The first webinar was used to confirm the target audience for the guidance, which focuses on clinicians in North America managing pediatric patients with inflammatory syndromes related to recent or concurrent infections with SARS-CoV-2. Notably, the Task Force deliberately did not attempt to create a new case definition for MIS-C as several already exist (Table 1)(4-6). 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 that involved 2 rounds of asynchronous, anonymous voting and 2 webinars to discuss voting results.

Evidence Review. From May 22-May 29, 2020, the workgroups 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 (WHO), health alerts from the Centers of Disease Control and Prevention (CDC), and guidance provided by the Royal College of Paediatrics and Child Health (RCPCH). Each workgroup generated an evidence report supporting the recommendations that was shared with the entire Task Force.

Round 1 Voting. 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 each of the statements. A score of 9 was considered to be the highest level of appropriateness while a score of 1 indicated 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 pre-specified as high (H) if all 16 votes coalesced within the same tertile while low (L) consensus occurred when voting was dispersed along the 9-point scale (when ≥ 5 votes fell in the 1-3 range and ≥ 5 votes fell in the 7-9 range). Moderate (M) 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 low consensus were addressed first. The panelists were then encouraged to discuss the remaining statements.

Round 2 Voting. Input from the initial voting and discussion was incorporated into the draft guidance statements (LAH, JM), and the document was re-distributed 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 review of the manuscript, the authors decided to include CRP in the laboratory evaluation for severe COVID-19 (Table 7) and the entire Task Force re-voted and approved the modifications to this recommendation statement.

Results

The Task Force evaluated a total of 125 statements in the first round of voting 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 4-6). After refining the statements based on the input from the initial phase, 128 guidance statements were approved in round 2 voting (Supplemental Table 1-4). These statements were organized into 40 final guidance statements accompanied by 1 figure, which were approved by the entire Task Force and the ACR Board of Directors.(12) Topics covered in the guidance include: 1) Diagnostic evaluation of MIS-C (Table 2, Figure 1); 2) Comparing and contrasting features of MIS-C and KD (Table 3); 3) Cardiac management of MIS-C (Table 4); 4) Treatment of MIS-C (Tables 5, 6); 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, which is of low quality and based on a limited number of case series and retrospective cohort studies. 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, some of which are broader than others (Table 1).(4-6) Common clinical features of MIS-C include 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, 7-10, 13-18) There are also increasing reports of neurologic involvement, manifesting as severe headache, altered mental status, cranial nerve palsies, or meningismus, in select patients.(8-10, 13, 14) These findings are non-specific and can occur in other infections as well as non-infectious etiologies such as oncologic or inflammatory conditions. 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 2-6 weeks after the peak incidence of acute, infectious COVID-19 cases.(7, 13, 14, 17) 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 infections with some estimating that MIS-C occurs in 2 out of 200,000 individuals under the age of 21 years.(19) The relative rarity of MIS-C should also be considered in the diagnostic approach.

Tier 1 Screening Evaluation for MIS-C. 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 over-testing and unnecessary use of resources on pediatric patients who have unrelated causes for fever.(2, 7, 8, 10, 13-16, 20, 21) To date, there are no clear data indicating the pre-test positive or 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. Children with 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 proceeding to a complete diagnostic work-up (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), C-reactive protein (CRP), and testing for SARS-CoV-2 by PCR or serology). The overwhelming majority of MIS-C cases reported in the literature have elevated inflammatory markers, particularly CRP, as values higher than 10 mg/dL or even 20 mg/dL are common.(2, 7-9, 13, 14, 17) Thus, to enter the second stage of testing, children should have elevated ESR and/or CRP and at least 1 other suggestive laboratory feature: lymphopenia, neutrophilia, thrombocytopenia, hyponatremia, or hypoalbuminemia.(2, 7-9, 13, 14, 17)

Tier 2 Evaluation for MIS-C. 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; however, the risk factors that predispose patients to such severe and progressive illness have not been identified.(10, 13) Accordingly, children with abnormal vital signs, concerning physical examination findings, significantly elevated inflammatory markers, or signs of cardiac involvement will need to be admitted to the hospital for supportive care while Tier 2 testing is completed. The panel also noted that MIS-C appears to be a continuum of disease that encompasses milder phenotypes that have not been fully represented in the published literature. 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 examinations may be suitable for outpatient diagnostic evaluations as long as close clinical follow-up can be assured.

Prominent cardiac involvement has been reported in a proportion of MIS-C patients in every retrospective cohort study published to date.(2, 7-9, 13, 14, 17) These include left ventricular (LV) dysfunction, coronary artery dilation or coronary artery aneurysms (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, 7, 13) Although the early reports may overestimate the incidence of cardiac features as they likely represent the most severe component of the MIS-C spectrum, these numbers nonetheless highlight the significant risk of cardiac involvement in MIS-C. 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).(22, 23) Detailed evaluation of all coronary artery segments and normalization of coronary artery measurements to body surface area using z-scores is necessary.(23, 24) Cardiac laboratory values at the time of diagnosis, specifically troponin T and B-type natriuretic peptide (BNP)/N-terminal-proBNP, may help identify patients with cardiac sequelae from MIS-C.(7-9, 13, 14, 17) In particular, highly elevated BNP/NT-proBNP may be helpful in distinguishing between MIS-C patient with and without LV dysfunction; however, mild and transient elevations in these laboratory parameters are likely non-specific and do not necessarily indicate

cardiac involvement.(14, 25, 26) BNP, in particular, is an acute phase reactant and, therefore, may be elevated in inflammatory conditions without cardiac involvement.(25)

Tier 2 testing should also include further assessment for systemic inflammation. In addition to ESR and CRP, MIS-C patients typically demonstrate other markers of inflammation including high D-dimer levels, moderately elevated ferritin (often ranging from 500-2,000 ng/dL), profoundly increased procalcitonin levels in the absence of bacterial infection, and increased lactate dehydrogenase (LDH).(8-10, 13, 14, 17) Cytokine panels, when available, can assist in the diagnostic evaluation as IL-6, tumor necrosis factor (TNF), or IL-10 are often increased; however, cytokine levels measured in this manner should not dictate treatment choices and are not required to determine treatment plans.(8, 9, 13) Finally, SARS-CoV-2 serologies have been reported positive in a greater proportion (80-90%) of MIS-C patients than PCR testing (20-40%) and both should be sent to evaluate the epidemiologic link to the infection.(7-9, 13, 17)

Comparing and Contrasting Features of MIS-C and KD

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 the pre-pandemic era.(7) Since this observation, the clinical symptomatology of MIS-C has frequently been compared to KD given the similar profile of fevers, mucocutaneous features, cardiac sequelae.(2, 7-10, 13-17, 22, 27) However, a closer examination of the literature shows that only a quarter to about one half of reported MIS-C patients meet the full diagnostic criteria for KD.(7-9, 13, 14) Several epidemiologic, clinical, and laboratory features of MIS-C that differ from KD unrelated to SARS-CoV-2 are worthy of mention. First, while the incidence of KD is highest in Japan, MIS-C appears to be frequent in patients of African and possibly Hispanic descent.(2, 8, 9, 14, 28) It is unclear if genetic or biological factors explain this racial/ethnic distribution or if socioeconomic status and risk of SARS-CoV-2 exposure are more causative. Second, the age distribution of MIS-C is broad with reports ranging from 3 months to 17 years of age.(2, 7-10, 13, 14, 17) By contrast, the majority of children with KD present before 5 years of age.(7, 14, 29, 30) Third, as discussed above, LV dysfunction and presentation in shock that are characteristic of MIS-C are considerably less common in KD, with less than 10% of KD patients presenting with KD Shock Syndrome.(31) Close to one quarter of untreated KD patients develop CAAs.(32) Coronary artery dilations or CAAs have been documented in up to

20% of MIS-C patients and at least 3 patients have developed giant CAAs.(2, 7, 13, 14, 17) It is unknown if the incidence or progression of CAAs differ in MIS-C as compared to KD. 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, the panel felt that these findings were more frequently encountered in the MIS-C population. Finally, laboratory parameters that differ in retrospective MIS-C cohorts compared to historical KD cohorts include lower platelet counts and absolute lymphocyte counts and higher CRP levels.(7, 14)

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 all children with MIS-C undergo repeat echocardiograms at a minimum of 7-14 days and then 4-6 weeks after the initial presentation.(22) 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 that has been seen in other forms of pediatric myocarditis.(9, 13, 33) 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 performed at a minimum of every 48 hours in patients who are hospitalized and at each follow-up visit.(8, 9, 13, 14) 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 prevent long term sequelae

that may include CAAs, myocardial fibrosis/scarring, and fixed cardiac conduction abnormalities. There is no available literature that directly compares therapeutic approaches in MIS-C. Recommendations approved by the Task Force are derived from experience in managing MIS-C patients and higher quality data in 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 infectious and non-infectious etiologies 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 inflammatory markers, BNP/ NT-proBNP, and troponin T without instituting treatment can sometimes inform the diagnostic evaluation.(10, 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 with a multidisciplinary team in parallel with treatment. 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 and the treatment of those patients may need to deviate from the recommendations presented in this document.(7)

A stepwise approach to immunomodulatory treatment in MIS-C is recommended, with intravenous immunoglobulin (IVIG) and/or glucocorticoids considered first tier agents. Both IVIG and glucocorticoids, either alone or in combination, are the most commonly used immunomodulatory medications in MIS-C patients reported to date.(2, 7-10, 13-15, 17) There is insufficient data available to compare the efficacy of IVIG vs. glucocorticoids in MIS-C or to determine if these treatments should be provided individually or as dual therapy. Accordingly, the Task Force recommended that IVIG and glucocorticoids could be used alone or in combination to treat MIS-C. Evidence for IVIG and glucocorticoids in MIS-C is also based on their use 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.(22, 32, 34-40) Before IVIG is given, cardiac function and fluid status should be assessed. If abnormal, the rate of

IVIG infusion may be slowed or treatment delayed until cardiac function is restored. Glucocorticoids reduce rates of CAA development when used in KD patients at high risk for IVIG resistance.(41, 42) Compared to a historic KD cohort, Verdoni and colleagues reported a high rate of IVIG resistance in KD patients who presented during the COVID-19 pandemic, which may suggest a role for glucocorticoids in MIS-C.(7) Panelists reported that low to moderate doses (1-2 mg/kg/day) of glucocorticoids were sufficient to treat many MIS-C patients. Some children with shock, requiring multiple inotropes and/or vasopressors, have responded best to high doses of intravenous glucocorticoids. High dose intravenous glucocorticoids have been used safely in patients with KD and have been used successfully in small numbers of patients with MIS-C and shock.(10, 43-45) Adjunctive glucocorticoids has also been shown to shorten the duration of shock in patients with sepsis.(46) There was agreement that MIS-C patients treated with steroids, regardless of the dose, often require a 2-3 week taper to avoid rebound inflammation.

Anakinra is recommended for MIS-C patients who are refractory to IVIG and/or glucocorticoids. This recommendation is 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 a small number of MIS-C patients reported in the literature.(13, 14, 17, 47-50) In addition, anakinra has been used successfully in a small number of patients with IVIG resistant KD.(51-53)

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 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. Published reports of patients with MIS-C describe marked abnormalities in the coagulation cascade, including prominent elevations in D-dimer and fibrinogen, a variable effect on platelet count, and a high clot strength by thromboelastography.(2, 7-9, 13, 14) There is concern for an increased risk of thrombosis in MIS-C based on these data as well as the hypercoagulability noted in adults with COVID-19.(54-57). A recent publication also described a small number of MIS-C patients with deep vein thrombosis or

pulmonary embolism but the overall risk of thrombosis in this population is not known.(58) Therefore, these recommendations are 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.(22) Accordingly, low dose ASA (3-5 mg/kg/day up to 81 mg once daily) is recommended in all MIS-C patients with KD features, CAAs, and thrombocytosis. Anti-acid treatments should be used to prevent GI complications in MIS-C patients on steroids and aspirin. Risk of coronary artery thrombosis is directly related to size of the CAA with exponentially increased probability in coronary arteries with dimensions above a z-score of 10.0.(22, 59, 60) Thus, anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin in MIS-C patients with a coronary artery z-score greater than 10.0 is advised. Patients with more than mild LV dysfunction are at risk for intracardiac thrombosis.(61, 62) 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%).

Hyperinflammation in Children with COVID-19

Severe COVID-19 in Children. The Task Force also addressed immunomodulatory treatment in severe COVID-19, which panelists felt (given current information) was 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 becomes severely ill.(63-68) MIS-C patients are often previously healthy and present with fever, inflammation, and multiorgan dysfunction that manifest late in the course of SARS-CoV-2 infection (most are SARS-CoV-2 IgG positive). By contrast, children who develop severe COVID-19 during their initial infection often have a complex previous medical history.(64-67) Shekerdemian and colleagues reported that 40% of patients admitted to the intensive care unit (ICU) for COVID-19 had developmental delay, a genetic anomaly, or were dependent on technological support for survival (e.g. tracheostomy).(65) There is no definitive evidence suggesting that children with rheumatologic diseases treated with immunosuppression are also at risk for poor outcomes from COVID-19. Shekerdemian et al. also observed that 23% of pediatric patients with COVID-19 who were admitted to the ICU were either immunosuppressed or had cancer but did not specify if any of these patients had a rheumatologic condition.(65) Extrapolating from adults with inflammatory bowel disease and rheumatologic conditions,

glucocorticoid use may be associated with worse outcomes in COVID-19 while treatment with tumor necrosis factor (TNF) inhibitors may actually be protective against severe COVID-19.(69, 70) In addition, cohorts of pediatric patients on immunosuppressive medications have not identified an increased risk of severe COVID-19 in this population.(71-73)

Immunomodulatory Treatment in Children with Hyperinflammation and COVID-19. Data are limited to guide the treatment of pediatric patients with severe illness during the early phase of SARS-CoV-2 infection. In adults, certain laboratory parameters associated with an exaggerated inflammatory response (hyperinflammation) portend worse outcomes in COVID-19, including elevated LDH, D-dimer, IL-6, IL-2 receptor (IL-2R), CRP, and ferritin, and decreased lymphocyte count, albumin, and platelet count.(74-77) In at least one case series of pediatric patients with COVID-19, increased CRP, elevated procalcitonin, and decreased platelet counts were significantly more common in children requiring ICU vs. floor level care; however, further studies are needed to identify laboratory parameters that predict poor outcomes in the pediatric population.(78) 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 children with severe COVID-19, manifesting as acute respiratory distress syndrome (ARDS), shock, or signs of hyperinflammation as measured by the laboratory parameters discussed above, should be considered for immunomodulatory therapy in addition to supportive care and antiviral medications.

Glucocorticoids are a readily available and inexpensive option for immunomodulation; however, their use in adults with COVID-19 is controversial. Prior experience with adjunctive glucocorticoid therapy in ARDS unrelated to COVID-19 has been equivocal.(79-81) Observational studies evaluating glucocorticoid treatment in other respiratory viral infections, such as influenza, suggest increased mortality; however, these studies are difficult to interpret due to confounding by indication.(82, 83) There are concerns that glucocorticoids given at high doses or early in the course of infection delay viral clearance.(84, 85) Glucocorticoid use in critically ill patients is also associated with increased neuropathy and myopathy.(86) In SARS-CoV-2 infections, there is conflicting evidence about the impact of glucocorticoids on viral clearance.(87, 88) A small number of cohort studies suggest a benefit in patients with severe COVID-19 pneumonia who are treated with glucocorticoids.(75, 89) Importantly, preliminary results from a large, randomized controlled trial (the

RECOVERY trial) report that low to moderate dose dexamethasone significantly reduced mortality in COVID-19 patients requiring mechanical ventilation; but was reported after voting had occurred.(90, 91) Based on these studies that suggest that patients with severe COVID-19 pneumonia may benefit from immunomodulation with glucocorticoids, the Task Force achieved moderate consensus that glucocorticoid treatment could be considered in pediatric patients with severe COVID-19 and signs of hyperinflammation.

Targeted neutralization of inflammatory cytokines is another approach that can be employed to reduce pathologic inflammation in COVID-19. In contrast to glucocorticoids, the panel was able to achieve high consensus on considering anakinra (recombinant human IL-1 receptor antagonist) for pediatric patients with COVID-19 and hyperinflammation. Anakinra appears to be safe in severe infections based on results of a randomized controlled trial in sepsis that showed no difference in adverse events in the anakinra arm compared to the placebo group.(49) Further, a re-analysis of data from this trial in sepsis showed increased survival in patients treated with anakinra who also had excessive inflammation manifested as hepatobiliary dysfunction and coagulopathy, which is commonly seen in COVID-19.(92) IL-1 blockade has also been used safely in children with inflammatory syndromes including systemic juvenile idiopathic arthritis and macrophage activation syndrome.(47, 48, 50) In COVID-19, case series imply safety and efficacy for anakinra in patients with elevated inflammatory markers and moderate to severe disease; however, most publications do not have a comparison group.(93-97) In one retrospective cohort of patients with COVID-19 related moderate to severe ARDS, treatment with anakinra in addition to usual care significantly reduced mortality when compared to patients treated at the same center a week prior.(98) The patients in this cohort received high dose anakinra (10 mg/kg/day) and were not yet mechanically ventilated, suggesting that treatment before intubation is beneficial.

Given the association between increased IL-6 levels and negative outcomes in COVID-19, IL-6 neutralization with tocilizumab has been appealing.(74, 75, 77) Some case series reported without a comparison group have claimed clinical improvement with tocilizumab treatment while others have not or have noted a high rate of bacterial and fungal infections.(99-102) Cohort studies with comparison groups have demonstrated conflicting results with one study reporting safety and efficacy with tocilizumab while another found no improvement in clinical outcomes.(103, 104) In the

study by Capra and colleagues that showed benefit with tocilizumab, COVID-19 patients were not yet mechanically ventilated.(103)

Our group agreed that the features of severe COVID-19 were sufficiently similar between the described adult and pediatric cases to cautiously extrapolate from adult studies. Overall, the consensus among panelists was that immunomodulatory treatment should be considered in pediatric patients with hyperinflammation and severe symptoms in the acute phase of illness. While the data are still too sparse to make definitive recommendations based on high quality evidence, the panel favored the use of anakinra in this setting.

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 goals of this ACR Task Force were to synthesize available data and expert opinion to provide a resource for clinicians on the frontlines caring for children with inflammatory syndromes due to 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 methods 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 for 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. The Task Force recognizes the need to provide support to our international colleagues and

plans to provide additional recommendations for developing countries in subsequent versions of this guidance. 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, available data remains restricted to low quality evidence that 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 panelists to disseminate knowledge quickly in an effort to improve outcomes for children with SARS-CoV-2 infections.

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Figure 1. Diagnostic Pathway for 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.

MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus; CBC, complete blood cell count; CMP, complete metabolic panel; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALC, absolute lymphocyte count; NA, sodium; BNP, B-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; LDH, lactate dehydrogenase; u/a, urinalysis; EKG, electrocardiogram

¹An epidemiologic link to SARS-CoV-2 infection is defined as a child with ANY of the following criteria: positive SARS-CoV-2 polymerase chain reaction (PCR), positive SARS-CoV-2 serologies, preceding illness resembling COVID-19, or close contact with confirmed or suspected COVID-19 cases in the past 4 weeks.

²Rash, (polymorphic, maculopapular, or petechial, but not vesicular); GI 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); neurologic symptoms, (altered mental status, encephalopathy, focal neurologic deficits, meningismus, or papilledema).

³Complete metabolic panel: Na, K, CO₂, Cl, BUN, Cr, glucose, Ca, albumin, total protein, AST, ALT, ALP, bilirubin.

⁴Send procalcitonin and cytokine panel, if available.

⁵If not sent in tier 1 evaluation. If possible, send SARS-CoV-2 IgG, IgM, IgA.

Table 1. Case Definitions of MIS-C.

Criteria	RCPCH⁵ PIMS-TS	CDC⁶ MIS-C	WHO⁴ MIS-C
Age	All children (age not defined)	<21 years	0-19 years
Fever	Persistent fever $\geq 38.5^{\circ}\text{C}$	$\geq 38.0^{\circ}\text{C}$ for ≥ 24 hrs OR Subjective fever ≥ 24 hrs	Fever ≥ 3 days
Clinical Symptoms	1) Single or multi-organ dysfunction AND 2) Additional features*	1) Severe illness (hospitalized) AND 2) ≥ 2 organ systems involved	Two of the following: 1) Rash, conjunctivitis, mucocutaneous inflammation 2) Hypotension or shock 3) Cardiac involvement** 4) Coagulopathy 5) Acute GI symptoms
Inflammation	1) Neutrophilia 2) $\uparrow$ CRP AND 3) Lymphopenia	Laboratory evidence of inflammation not limited to 1 or more of the following: 1) $\uparrow$ CRP 2) $\uparrow$ ESR 3) $\uparrow$ Fibrinogen 4) $\uparrow$ Procalcitonin 5) $\uparrow$ D-dimer	Elevated inflammatory markers such as: 1) $\uparrow$ ESR 2) $\uparrow$ CRP 3) $\uparrow$ Procalcitonin

		6) ↑Ferritin 7) ↑LDH 8) ↑IL-6 9) Neutrophilia 10) Lymphopenia 11) Hypoalbuminemia	
Link to SARS-CoV-2	PCR + or -	Current or recent: 1) +PCR 2) +Serology 3) +Antigen test OR 4) COVID-19 exposure within prior 4 weeks	Evidence of COVID-19: 1) +PCR 2) +Antigen test 3) +Serology OR 4) Likely COVID-19 contact
Exclusion	Exclusion of other infections	No alternative diagnosis	No obvious microbial cause

Adapted from⁴⁻⁶

RCPCH, Royal College of Paediatrics and Child Health; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children; WHO, world health organization; CRP, C-reactive protein; PCR, polymerase chain reaction; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; COVID-19, coronavirus disease 2019; GI, gastrointestinal symptoms

*Additional features for the RCPCH case definition: abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting.

**Cardiac involvement defined by the WHO MIS-C case definition: features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP)

Table 2. Diagnostic Evaluation of MIS-C.

Recommendation Statement	Consensus Level
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
A child under investigation for MIS-C should also be evaluated for other infectious and non-infectious (e.g., malignancy) etiologies 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 well appearing children with stable vital signs and reassuring physical examinations provided close clinical follow-up can be assured.	Moderate
Patients under investigation for MIS-C should be considered for admission to the hospital for further observation while completing the diagnostic evaluation, especially if they display the following: 1) Abnormal vital signs (tachycardia, tachypnea) 2) Respiratory distress of any severity 3) Neurologic deficits or change in MS (including subtle manifestations) 4) Evidence of even mild renal or hepatic injury 5) Markedly elevated inflammatory markers (CRP ≥ 10.00 mg/dL) 6) Abnormal EKG, BNP, or troponin T	Moderate to High
Patients presenting with shock, significant respiratory distress, neurologic changes (altered MS, encephalopathy, focal neurologic deficits, meningismus, papilledema), dehydration, or features of KD should be admitted for further work-up, regardless of MIS-C status, per standard of care.	High

Children admitted to the hospital with MIS-C should be managed by a multi-disciplinary team including pediatric rheumatologists, cardiologists, infectious disease specialists, and hematologists. Depending on clinical manifestations, other subspecialties may also need to be consulted; these include but are not limited to pediatric neurology, nephrology, hepatology, gastroenterology (H/M).	Moderate to High
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COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome in children; MS, mental status; CRP, C-reactive protein; EKG, electrocardiogram; BNP, B-type natriuretic peptide; KD, Kawasaki disease.

Table 3. Comparing and Contrasting Features of MIS-C and KD.

Recommendation Statement	Consensus Level
Patients with KD that is unrelated to SARS-CoV-2 will continue to require evaluation, diagnosis, and treatment during the SARS-CoV-2 pandemic.	High
MIS-C and KD unrelated to SARS-CoV-2 infections 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.	Moderate to High
Several epidemiologic, clinical, and laboratory features of MIS-C may differ from KD unrelated to SARS-CoV-2. 1) There is an increased incidence of MIS-C in patients of African, Afro-Caribbean, and possibly Hispanic descent, but a lower incidence in those of East Asian descent. 2) Patients with MIS-C encompass a broader age range, have more prominent GI and neurologic symptoms, present more frequently in shock, and are more likely to display cardiac dysfunction (arrhythmias and ventricular dysfunction) than children with KD. 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.	Moderate to High
It is unknown if the incidence of CAA is different in MIS-C compared to KD; however, MIS-C patients without KD features can develop CAA.	Moderate to High

KD, Kawasaki disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome in children; GI, gastrointestinal; CRP, C-reactive protein; CAA, coronary artery aneurysms

Table 4. Cardiac Management of MIS-C.

Recommendation Statement	Consensus Level
Patients with MIS-C and abnormal BNP and/or troponin T 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/valvar 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 CAA 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 suspicion of distal CAAs that are not well seen on echocardiogram.	Moderate

MIS-C, multisystem inflammatory syndrome in children; BNP, B-type natriuretic peptide; EKG, electrocardiogram; LV, left ventricular; CAA, coronary artery aneurysms; MRI, magnetic resonance imaging; CT, computed tomography

Table 5. Immunomodulatory Treatment in MIS-C.

Recommendation Statement	Consensus Level
Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infectious and non-infectious etiologies 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 require only close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG in this setting to prevent CAAs.	Moderate
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and/or glucocorticoids considered as first tier treatments.	Moderate to High
High dose IVIG (typically 1-2 gm/kg) may be considered for treatment of MIS-C. Cardiac function and fluid status should be assessed in MIS-C patients with shock before IVIG treatment is provided, and IVIG should be administered when cardiac function is restored.	Moderate to High
Low-moderate dose glucocorticoids may be considered for treatment of MIS-C. High dose, IV pulse glucocorticoids may be considered to treat patients with life-threatening complications, such as shock, and specifically, if a patient requires high dose or multiple inotropes and/or vasopressors.	Moderate to High
Anakinra (IV or SQ) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments.	Moderate to High
Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering. Patients will often require a 2-3-week taper of immunomodulatory medications.	High

MIS-C, multisystem inflammatory syndrome in children; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysms

Table 6. Antiplatelet and Anticoagulation Therapy in MIS-C.

Recommendation Statement	Consensus Level
Low dose aspirin (3-5 mg/kg/day; max 81 mg/day) should be used in patients with MIS-C and KD-like features and/or thrombocytosis (platelet count $\geq 450,000/\mu\text{L}$) and continued until normalization of platelet count and confirmed normal coronary arteries at ≥ 4 weeks after diagnosis. Treatment with aspirin should be avoided in patients with a platelet count $\leq 80,000/\mu\text{L}$.	Moderate
MIS-C patients with CAAs and a maximal z-score of 2.5-10.0 should be treated with low dose aspirin. Patients with a z-score ≥ 10.0 should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin.	Moderate to High
Patients with MIS-C and documented thrombosis or an EF $< 35\%$ should receive therapeutic anticoagulation with enoxaparin until at least 2 weeks after discharge from the hospital.	High
Indications for longer outpatient therapeutic enoxaparin dosing include: CAA with z-score > 10.0 (indefinite treatment), documented thrombosis (treatment for ≥ 3 months pending thrombus resolution), or ongoing moderate to severe LV dysfunction.	High
For MIS-C patients who do not meet the above criteria, the approach to antiplatelet and anticoagulation management should be tailored to the patient's risk for thrombosis.	High

MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; CAA, coronary artery aneurysms; EF, ejection fraction; LV, left ventricular

Table 7. Hyperinflammation in COVID-19.

Recommendation Statement	Consensus Level
Medically complex children and those on immunosuppressive medications, including moderate to high dose glucocorticoids, may be at higher risk for severe outcomes in COVID-19.	Moderate to High
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
Children with severe respiratory symptoms due to COVID-19 with any of the following should be considered for immunomodulatory therapy: ARDS, shock/cardiac dysfunction, substantially elevated LDH, D-dimer, IL-6, IL-2R, CRP, and/or ferritin, and depressed lymphocyte count, albumin, and/or platelet count.	Moderate to High
Glucocorticoids may be considered for use as immunomodulatory therapy in patients with COVID-19 and hyperinflammation (as outlined in point above).	Moderate
Anakinra appears safe in severe infections and in children with hyperinflammatory syndromes. In children with COVID-19 and hyperinflammation, anakinra (>4 mg/kg/day IV or SQ) should be considered for immunomodulatory therapy. Initiation of anakinra before invasive mechanical ventilation may be beneficial.	High
Children with COVID-19 treated with anakinra should be monitored for LFT abnormalities.	Moderate
Compared to standard care, tocilizumab may be effective in reducing mortality and ICU admission in patients with severe COVID-19 pneumonia and signs of hyperinflammation; however, patients treated with tocilizumab may be at higher risk for bacterial and fungal infections.	Moderate
When tocilizumab is used to treat children with COVID-19, weight-based dosing should be employed (<30kg: 12mg/kg IV; ≥30kg: 8mg/kg IV, max 800mg). Children treated with tocilizumab should be monitored for LFT abnormalities and elevated triglycerides.	Moderate to High
In the absence of randomized controlled trials or comparative effectiveness studies, if immunomodulation is to be used at all, the	Moderate

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balance of risks and benefits suggests anakinra as first-line immunomodulatory treatment of children with COVID-19 and hyperinflammation. There is insufficient evidence to support the use of other immunomodulatory agents unless glucocorticoids, IL-1 blocking, and/or IL-6 blocking therapies are contraindicated or have failed.	
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COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; LDH, lactate dehydrogenase; IL-6, interleukin 6; IL-2R, interleukin 2 receptor; CRP, C-reactive protein; LFT, liver function test; ICU, intensive care unit

Does the child have ALL of the following?

- 1) Fever >38°C
- 2) Epidemiologic link to SARS-CoV-2¹
- 3) At least 2 suggestive clinical features²
 - Rash
 - Gastrointestinal symptoms
 - Edema of hands/feet
 - Oral mucosal changes
 - Conjunctivitis
 - Lymphadenopathy
 - Neurologic symptoms

Yes

Have other causes that could explain the presentation been considered in the evaluation?

Yes

Consider child under investigation for MIS-C.

Does the child have shock of unclear etiology?

No

Start tiered diagnostic evaluation for MIS-C

Yes

Complete full diagnostic evaluation (Tier 1 & 2) for MIS-C.

Send Tier 1 Screening Evaluation:
CBC, CMP³, ESR, CRP, & SARS-CoV-2 PCR and/or serologies

No

Do the results show ALL of the following?

- 1) CRP ≥5 mg/dL or ESR ≥40 mm/hr
- 2) At least 1 suggestive laboratory feature
 - ALC <1,000/uL
 - Platelet count <150,000/uL
 - Na <135 mmol/L
 - Neutrophilia
 - Hypoalbuminemia

Yes

Send Tier 2/Complete Evaluation:
BNP, troponin T, procalcitonin⁴, ferritin, PT, PTT, D-dimer, fibrinogen, LDH, u/a, cytokine panel⁴, triglycerides, SARS-CoV-2 serology⁵, EKG, echocardiogram

No

Continue a diagnostic evaluation as per standard of care and monitor for MIS-C features, particularly if there is an epidemiologic link to SARS-CoV-2.