

## **Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19**

**Developed by the ACR MIS-C and COVID-19 Related Hyperinflammation Task Force**

*This summary was approved by the ACR Board of Directors on June 17, 2020.*

*A full paper (Version 1) was published on July 23, 2020, then copyedited/slightly revised into its [final format](#), published in the November, 2020 issue of *Arthritis & Rheumatology*.\**

*New/edited recommendations regarding immunomodulatory treatment in MIS-C and hyperinflammation in COVID-19, as well as the use of aspirin in MIS-C, were added to or revised in this summary on November 9, 2020 and are being added to the full paper (Version 2), which will be submitted to *Arthritis & Rheumatology* for publication.*

### **Purpose**

The Task Force was convened by the ACR to provide guidance on the management of inflammatory syndromes in children (up to age 18) with recent or concurrent infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This document addresses 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. Notably, the Task Force did not attempt to create a case definition of MIS-C because several already exist. Instead, the Task Force focused on consensus building to identify the most appropriate diagnostic and therapeutic steps that providers should consider at the present time. The Task Force also provided recommendations for children with hyperinflammation during COVID-19, the acute, infectious phase of SARS-CoV-2 infection. Given that 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. The recommendations provided in this document do not replace the importance of clinical judgment tailored to the unique circumstances of an individual patient.

### **Methods**

The multidisciplinary 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. The first meeting was held on May 22, 2020, during which the Task Force was divided into 4 workgroups to address clinical questions related to MIS-C and hyperinflammation in COVID-19. Each workgroup generated preliminary statements supported by an evidence report that was shared with the entire Task Force. Subsequently, consensus was built through a modified Delphi process that involved 2 rounds of anonymous voting and 2 webinars that were leveraged to discuss voting results to achieve consensus. 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 before voting took place.

For subsequent versions of the guidance, workgroup leaders identified guidance statements that should be modified based on clinical experience and newly available evidence in the literature. These revised statements, along with the supporting literature, were provided to the panelists before a webinar was held to discuss the proposed changes. After the webinar, anonymous voting was conducted as described above.

## **MIS-C Recommendations**

### **General statements for MIS-C:**

- 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 (H).
- 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 (M).
- The approach to testing for SARS-CoV-2 infections will evolve over the course of the COVID-19 pandemic, and it is, therefore, important to consider up-to-date testing methods and the prevalence of viral transmission in the community (M).

### **Diagnostic evaluation of MIS-C:**

- 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 (H).
- See Figure 1 for guidance on the diagnostic evaluation of MIS-C (M/H).
- 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 (H).
- Outpatient evaluation for MIS-C may be appropriate for well appearing children with stable vital signs and reassuring physical exams provided close clinical follow-up can be assured (M).
- 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 (M/H):
  - Abnormal vital signs (tachycardia, tachypnea)
  - Respiratory distress of any severity
  - Neurologic deficits or change in mental status (including subtle manifestations)
  - Evidence of even mild renal or hepatic injury
  - Markedly elevated inflammatory markers (C-reactive protein  $\geq 10.00$  mg/dL)
  - Abnormal EKG, B-type natriuretic peptide (BNP), or troponin T
- Patients presenting with shock, significant respiratory distress, neurologic changes (altered mental status, 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 (H).
- 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).

### **Comparing and contrasting features of MIS-C and Kawasaki disease:**

- Patients with Kawasaki disease (KD) that is unrelated to SARS-CoV-2 will continue to require evaluation, diagnosis, and treatment during the SARS-CoV-2 pandemic (H).
- MIS-C and KD unrelated to SARS-CoV-2 infections may share overlapping clinical features, including conjunctival injection, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet, and cervical lymphadenopathy (M/H).
- Several epidemiologic, clinical, and laboratory features of MIS-C may differ from KD unrelated to SARS-CoV-2 (M).
  - 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 (M).

- 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 (M/H).
- At presentation, patients with MIS-C tend to have lower platelet counts, lower absolute lymphocyte counts, and higher CRP levels than patients with KD (M/H).
- 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 (M).
- It is unknown if the incidence of coronary artery aneurysms (CAA) is different in MIS-C compared to KD; however, MIS-C patients without KD features can develop CAA (M/H).

#### **Cardiac management of MIS-C:**

- Patients with MIS-C and abnormal BNP and/or troponin T at diagnosis should have these laboratory parameters trended over time until they normalize (H).
- 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 (M/H).
- 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 (H).
- 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 left ventricular (LV) dysfunction and/or CAA will require more frequent echocardiograms (M/H).
- 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 (ECV) quantification, and late gadolinium enhancement (H).
- Cardiac CT should be performed in patients with suspicion of distal CAAs that are not well seen on echocardiogram (M).

#### **Immunomodulatory treatment in MIS-C:**

- 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 (M).
- 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 (H).
- After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may require only close monitoring without immunomodulatory treatment (M). The panel noted uncertainty around the empiric use of intravenous immunoglobulin (IVIG) in this setting to prevent CAAs.
- A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG considered first tier therapy. Glucocorticoids should be used as adjunctive therapy in patients with severe disease or as intensification therapy in patients with refractory disease (Figure 2) (H).
  - IVIG should be given to MIS-C patients who are hospitalized and/or fulfill KD criteria (H).
  - High dose IVIG (typically 2 gm/kg, based on ideal body weight) should be used for treatment of MIS-C (H).

- 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 (H).
- In some patients with cardiac dysfunction, IVIG may be given as in divided doses (1 gm/kg daily over 2 days) (M).
- Low-moderate dose glucocorticoids (1-2 mg/kg/day) should be given with IVIG as adjunctive therapy for treatment of MIS-C in patients with shock and/or organ threatening disease (M).
- In patients who do not respond to IVIG and low-moderate dose glucocorticoids, high dose, IV pulse glucocorticoids (10-30 mg/kg/day) may be considered, especially if a patient requires high dose or multiple inotropes and/or vasopressors (M).
- 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 (H).
- Low-moderate dose steroids (1-2 mg/kg/day) may also be considered in patients with milder forms of MIS-C who are persistently febrile and symptomatic despite a single dose of IVIG (M).
- Anakinra (>4 mg/kg/day IV or SQ) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids, in patients with MIS-C and features of macrophage activation syndrome (MAS), or in patients with contraindications to long-term use of glucocorticoids (M).
- 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 (H).

#### **Antiplatelet and anticoagulation therapy in MIS-C:**

- Low dose aspirin (3-5 mg/kg/day; max 81 mg/day) should be used in patients with MIS-C and continued until normalization of platelet count and confirmed normal coronary arteries at  $\geq 4$  weeks after diagnosis. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or platelet count  $\leq 80,000/\mu\text{L}$  (M).
- 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  $\geq 10.0$  should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin (M/H).
- Patients with MIS-C and documented thrombosis or an ejection fraction (EF) <35% should receive therapeutic anticoagulation with enoxaparin until at least 2 weeks after discharge from the hospital (H).
- Indications for longer outpatient therapeutic enoxaparin dosing include: CAA with z-score >10.0 (indefinite treatment), documented thrombosis (treatment for  $\geq 3$  months pending thrombus resolution), or ongoing moderate to severe LV dysfunction (H).
- 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 (H).

#### **Hyperinflammation in COVID-19 Recommendations**

##### **General statements for children with COVID-19:**

- 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 (M/H).
- Children and adults admitted to the hospital with COVID-19 present with similar symptoms, including fever, upper respiratory tract symptoms, abdominal pain, and diarrhea (M).

##### **Immunomodulatory treatment in children with COVID-19:**

- Children with severe respiratory symptoms due to COVID-19 with any of the following should be considered for immunomodulatory therapy: acute respiratory distress syndrome (ARDS), shock/cardiac

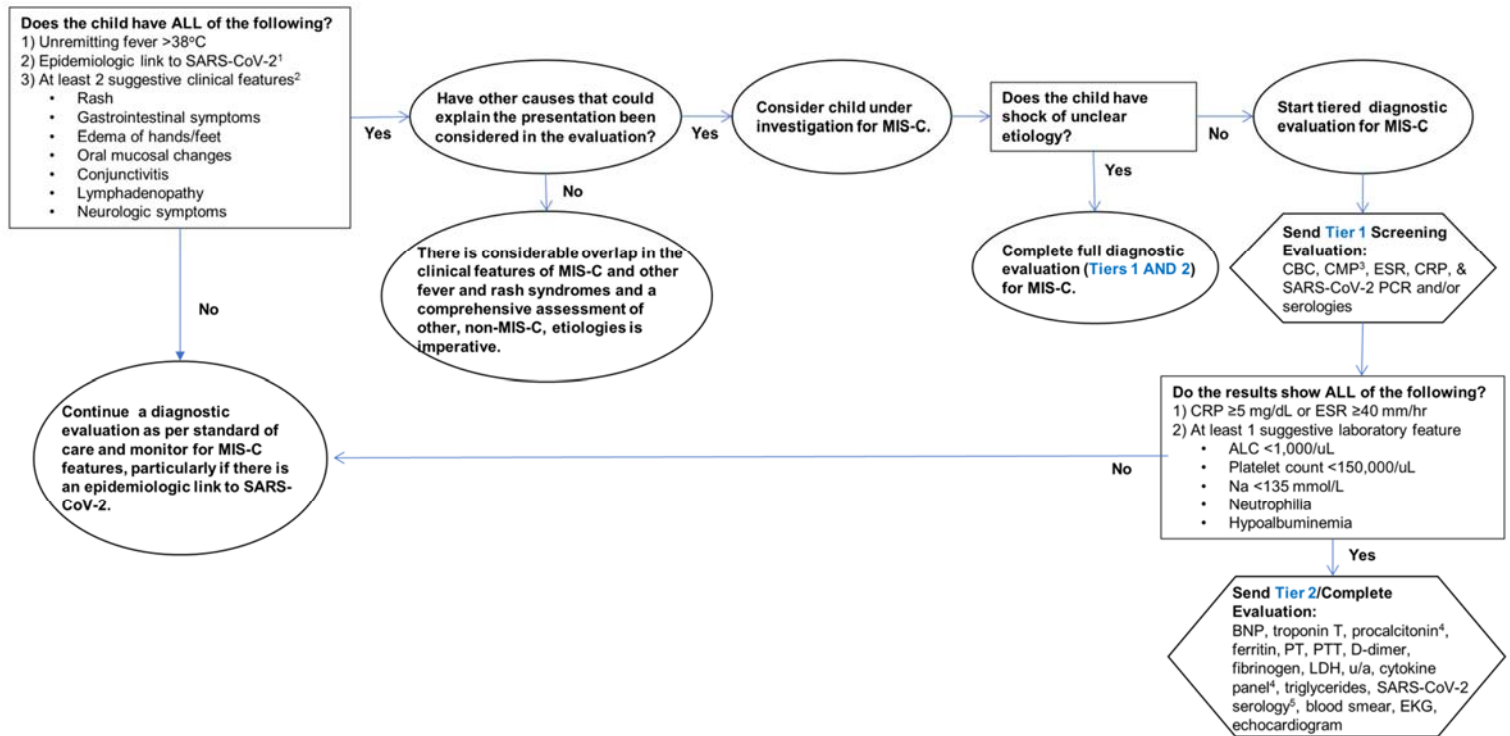
dysfunction, substantially elevated lactate dehydrogenase (LDH), D-dimer, IL-6, IL-2R, CRP, and/or ferritin, and depressed lymphocyte count, albumin, and/or platelet count (M/H).

- Glucocorticoids should be used as first tier immunomodulatory treatment in patients with COVID-19 and hyperinflammation (H).
- Anakinra appears safe in severe infections and in children with hyperinflammatory syndromes. In children with COVID-19 and hyperinflammation, anakinra (>4mg/kg/day IV or SQ) should be considered for immunomodulatory therapy in patients with refractory disease despite glucocorticoid treatment or in patients with contraindications to steroids. Initiation of anakinra before invasive mechanical ventilation may be beneficial (H).
- Children with COVID-19 treated with anakinra should be monitored for liver function test (LFT) abnormalities (M).
- Tocilizumab is not recommended for a majority of pediatric patients with COVID-19 and hyperinflammation given the lack of benefit reported in randomized, double-blind, placebo-controlled trials in adults with COVID-19 pneumonia. In addition, the effects of tocilizumab are long-lasting, which leaves little recourse if a patient does not respond favorably to the medication (M).
- There is insufficient evidence to support the use of other immunomodulatory agents unless glucocorticoids and IL-1 blocking therapies are contraindicated or have failed (M).

***Updated November 9, 2020***

***\*How to cite this article:***

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. 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. *Arthritis Rheumatol* 2020; 72; 1791-1805. doi: <https://onlinelibrary.wiley.com/doi/10.1002/art.41454>.



**Figure 1. Diagnostic Pathway for MIS-C**

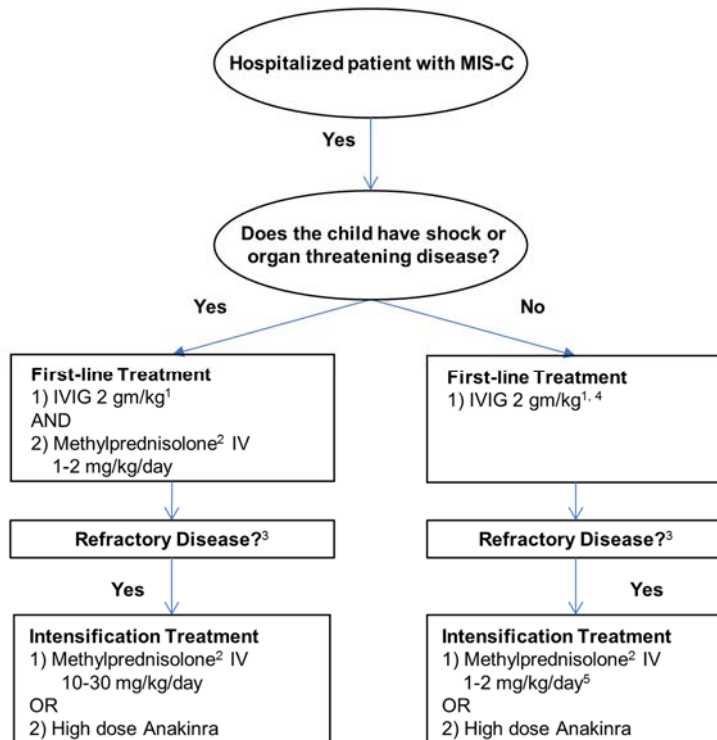
<sup>1</sup>An epidemiologic link to SARS-CoV-2 infection is defined as a child with ANY of the following criteria: positive SARS-CoV-2 polymerase chain reaction (PCR), positive SARS-CoV-2 serologies, preceding illness resembling COVID-19, or close contact with confirmed or suspected COVID-19 cases in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

<sup>2</sup>Rash, (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 injection without exudate); neurologic symptoms, (altered mental status, encephalopathy, focal neurologic deficits, meningismus, or papilledema).

<sup>3</sup>Complete metabolic panel: Na, K, CO<sub>2</sub>, Cl, BUN, Cr, glucose, Ca, albumin, total protein, AST, ALT, ALP, Bilirubin.

<sup>4</sup>Send procalcitonin and cytokine panel, if available.

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



**Figure 2. Algorithm for Initial Immunomodulatory Treatment in MIS-C**

<sup>1</sup>IVIG dosing is 2 gm/kg based on ideal body weight. Cardiac function and fluid status should be assessed before IVIG is given. In some patients with cardiac dysfunction, IVIG may be given as 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>Refractory disease is defined as persistent fevers and/or ongoing and significant end organ involvement.

<sup>4</sup>Low-moderate dose glucocorticoids (methylprednisolone 1-2 mg/kg/day) may be considered for first-line therapy in some MIS-C patients with concerning features (ill appearance, highly elevated BNP, unexplained tachycardia) who have not yet developed shock or organ threatening disease.

<sup>5</sup>If the patient was given low- moderate dose glucocorticoids as first-line therapy, methylprednisolone IV dosing should be 10-30 mg/kg/day for intensification treatment.