

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

Version 3

Revised October 19, 2021

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

*This summary was initially 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 and published in the November, 2020 issue of Arthritis & Rheumatology.\**

*New/edited recommendations regarding immunomodulatory treatment in MIS-C and hyperinflammation in COVID19, as well as the use of aspirin in MIS-C, were added to or revised in this summary on November 9, 2020 and subsequently added to the full paper ([Version 2](#)), which was published in the April, 2021 issue of Arthritis & Rheumatology.\*\**

*New/edited recommendations regarding immunomodulatory treatment in MIS-C and hyperinflammation in COVID- 19, as well as statements on thrombotic risk and anticoagulation in MIS-C, were added to or revised in this summary on October 19, 2021. These recommendations were added to the full paper (Version 3), 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 and a webinar was held to discuss the proposed changes. After the webinar, anonymous voting was conducted as described above. An additional cardiologist with expertise in thrombotic risk assessment and anticoagulation joined the TF in September 2021 for the 3<sup>rd</sup> version of the guidance.

### **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).
- 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 antibody test should prompt consideration of alternative diagnoses (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 (H):
  - Abnormal vital signs (tachycardia, tachypnea)
  - Respiratory distress of any severity
  - Neurologic deficits or change in mental status (including subtle manifestations)
  - Evidence of renal or hepatic injury (including mild injury)
  - Markedly elevated inflammatory markers
  - Abnormal EKG, B-type natriuretic peptide (BNP), or troponin T
- 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).

#### **MIS-C and Kawasaki disease phenotypes:**

- MIS-C and KD 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 (H).
- Several epidemiologic, clinical, and laboratory features of MIS-C may differ from KD (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 (ventricular dysfunction and arrhythmias) 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).
- Ventricular dysfunction is more frequently associated with MIS-C whereas KD is more frequent to manifest with coronary artery aneurysms; however, MIS-C patients without KD features can develop CAA (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).

#### **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 and low-moderate dose glucocorticoids considered first tier therapy in most hospitalized patients (Figure 2) (M).
- High dose glucocorticoids, anakinra, or infliximab should be used as intensification therapy in patients with refractory disease (Figure 2) (M).
  - 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, max 100gm) should be used for treatment of MIS-C (M).
  - 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 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 dual therapy for treatment of MIS-C in hospitalized patients (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).
- In patients who do not respond to IVIG and low-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 (M).
- High dose anakinra (>4 mg/kg/day IV or SQ) should 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).
- Infliximab (5-10 mg/kg/day IV x1 dose) may be considered as an alternative biologic agent to anakinra for treatment of MIS-C 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 (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).
- Central venous catheterization, age >12 years, malignancy, ICU admission, and D-dimer level elevated to greater than 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 (M).
- 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  $\geq 10.0$  should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) for at least 2 weeks, and then can be transitioned to vitamin K antagonist (VKA) therapy (INR 2-3) or direct-acting oral anticoagulant (DOAC) as long as CAA z-score exceeds 10 (M).
- MIS-C patients with an ejection fraction <35% should receive low dose ASA and therapeutic anticoagulation\* until EF exceeds 35% (M).  
\* Therapeutic anticoagulation =  
Enoxaparin SC with target antiXa levels of 0.5 to 1.0  
OR Warfarin/VKA (INR 2-3)  
OR DOAC
- MIS-C patients with documented thrombosis should receive low-dose ASA and therapeutic anticoagulation\* 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 (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:**

- Children, particularly infants, with medical complexity including type I diabetes, complex congenital heart disease, neurologic conditions, obesity, 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 (M).
- 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:**

- Hospitalized children requiring supplemental oxygen or respiratory support due to COVID-19 should be considered for immunomodulatory therapy. Substantial elevation of inflammatory markers\* may support this decision and prove useful in monitoring (H).  
\*LDH, D-dimer, IL-6, IL2R, CRP, and/or ferritin, and depressed lymphocytes count, albumin level, and/or platelet count
- Dexamethasone (0.15 to 0.3 mg/kg/day, max 6mg, 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 (M).
- Children with increasing oxygen requirements and elevated inflammatory markers due to COVID-19 who have not improved with glucocorticoids alone should receive secondary immunomodulatory therapy (H).
- 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, the decision of which to choose will depend on availability, patient age, and comorbidities (such as renal failure or thrombosis) (H).
- Tofacitinib can be considered as an alternative medication for secondary immunomodulatory therapy if tocilizumab and baricitinib are not available or contraindicated (M).
- 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, non-invasive ventilation, or ICU admission) (H).
- Secondary immunomodulatory therapy should be used in combination with glucocorticoids. Tocilizumab may be given at a dose of 8mg/kg IV (max 800mg) and may be redosed  $\geq$  8hr later if there is insufficient clinical response. Baricitinib may be given orally to children with normal renal function at a dose of 2mg daily in children 2 years to less than 9 years of age, and 4mg daily in children  $\geq$  9 years of age for up to 14 days (M).
- Children with COVID-19 treated with secondary immunomodulatory therapy should be monitored for secondary infections and LFT abnormalities. Children on tocilizumab should also be monitored for hypertriglyceridemia and infusion reactions. Children on baricitinib should also be monitored for thrombosis and thrombocytosis (M/H).
- 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 (M).
- 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 (M).

***Recommendations Updated November 9, 2020***

***Recommendations Updated October 19, 2021***

### **\*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

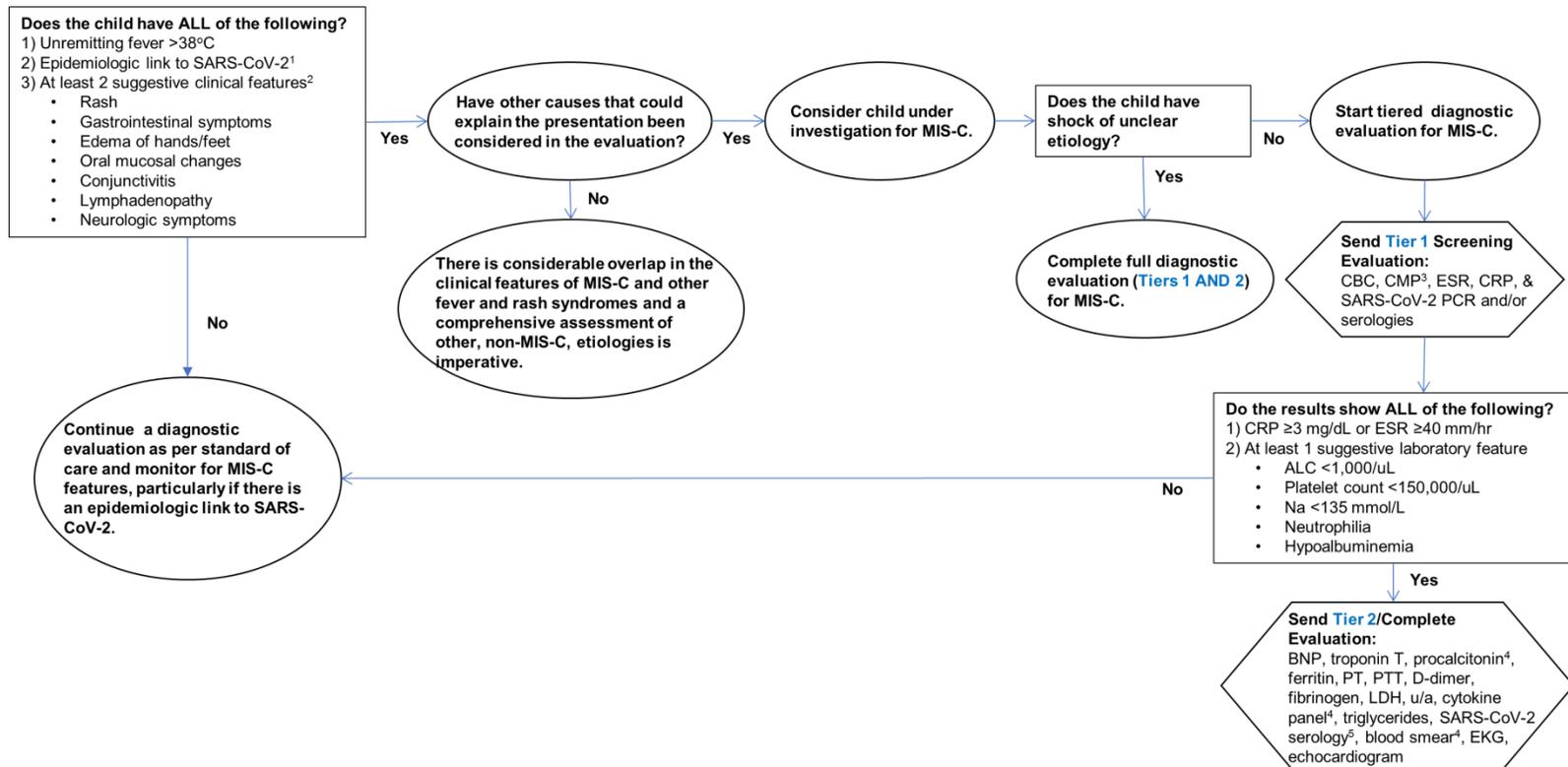
SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. *Arthritis Rheumatol* 2020; 72; 1791-1805. doi:

<https://onlinelibrary.wiley.com/doi/10.1002/art.41454>.

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<https://onlinelibrary.wiley.com/doi/10.1002/art.41616>



**Figure 1. Diagnostic Pathway for MIS-C (M/H)**

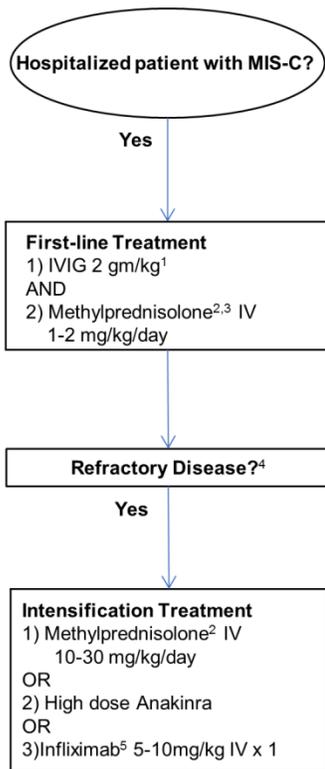
<sup>1</sup>Due to the difficulty in establishing an epidemiological linkage to a preceding SARS-CoV-2 infection given the evolving COVID-19 pandemic, the diagnosis of MIS-C must be determined based on the totality of the history, exam, and laboratory studies. Patients may have MIS-C even in the absence of preceding COVID-19-like illness or a clear exposure history to SARS-CoV-2, especially in the setting of high community prevalence.

<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 (M/H)**

<sup>1</sup>IVIG dosing is 2 gm/kg based on ideal body weight with maximum dose of 100gm. 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>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 for 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 MAS.