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Cincinnati Children's Hospital Medical Center
COVID-19 MIS-C Algorithm
Version 2.1
July 2, 2020

COVID-19 ASSOCIATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) GUIDANCE FOR EVALUATION AND MANAGEMENT

Background:

Over the past few weeks there have been numerous reports from Europe and the USA of previously healthy children presenting with an unexplained hyperinflammatory syndrome including shock (1–3). This syndrome has been defined in several case series as pediatric multiorgan syndrome or multisystem inflammatory syndrome in children (MIS-C). These children have some similarity to incomplete/atypical Kawasaki disease (KD), but also have other clinical features including gastrointestinal involvement, and a high incidence of myocardial dysfunction and shock (4). Many (but not all) patients have tested positive for COVID-19 by PCR, have positive COVID-19 antibody, or have household exposure to COVID-19 patients. This association with COVID-19 has been increasingly featured in lay media after a national alert was issued by the Royal College of Paediatrics and Child Health on May 1 (5), followed by a Health Advisory from the CDC on May 14 (6). The purpose of this document is to provide guidance regarding patients who should be evaluated for MIS-C, the recommended initial evaluation for such patients, and management principles for patients who meet criteria for MIS-C.

Case definition[1]

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Patients to be evaluated for *suspected* COVID MIS-C:

- Patients with unexplained fever for ≥5 days OR
- Patients with unexplained fever for ≥3 days AND diarrhea, vomiting, conjunctivitis, non-vesicular rash, swelling of hands/feet or altered mental status AND moderately ill-appearing OR
- Patients with any unexplained fever and shock

Initial evaluation for *suspected* MIS-C:

- COVID PCR and serology
  - *Patients with COVID-19+ PCR should be treated per COVID treatment algorithm*
- EKG
- Echocardiogram if signs of shock, any concerns for cardiac dysfunction, or recommended per suspected Kawasaki algorithm (7).
- Consult general ID and rheumatology if not already involved.
- Labs if not already done: CBC, CMP, CRP, LDH, ferritin, procalcitonin, PT/PTT/fibrinogen, d-dimer, troponin, BNP, UA with urine protein and creatinine

Patients with suspected Kawasaki disease (complete or incomplete) but negative COVID testing and no documented COVID exposure should be evaluated and managed per AHA guidelines (7)

Evaluation and management principles for patients *meeting MIS-C Case Definition*:

- All patients should be treated as suspected COVID-19 PCR+
- Consult cardiology and echocardiogram if not already obtained; heart failure consult for any patient with significant myocardial dysfunction (EF<40%)
- Management decisions should be made by primary team (hospital medicine or critical care) in consultation with general ID, rheumatology, and cardiology
- Inpatient disposition to be discussed with primary team (hospital medicine or critical care) and cardiology:
  - Patients with shock, coronary artery dilation, or myocardial dysfunction should be transferred to PICU or CVICU via MRT
  - Patients not needing ICU care should have frequent monitoring given reports of rapid deterioration until stable >24h (watcher status w/ frequent PEWS, MRT for any concerns)
- Above labs should be trended q24-48 until clinically improving
- Repeat echocardiogram with any clinical worsening or per cardiology recommendations
- Patients meeting CDC MIS-C Case Definition will be reported by Infection Prevention & Control

Treatment

Patients without shock, myocardial dysfunction, or coronary artery changes (non-critical care):

- Low dose aspirin
- IVIG 2gm/kg up to 100gm (note: consider monitoring patients with any myocardial dysfunction in CVICU during IVIG infusion)

- Steroids: 2mg/kg/d for 2 weeks followed by taper over 2-3 weeks; consider adding PPI
- Treatment refractory patients (continued fever >36h after IVIG, worsening clinical condition, new cardiac dysfunction or shock): consider biologics in consultation with rheumatology

Patients with severe disease (Signs of shock, coronary artery dilation, or cardiac dysfunction):

- Inotropic support as needed; ECMO should be considered early in patients with refractory shock before signs of irreversible multi-organ damage.
- Low dose aspirin; discuss high-dose aspirin with cardiology for any coronary changes
- Anticoagulation as needed per cardiology and ICU team
- IVIG 2mg/kg up to 100gm
- Steroids: methylprednisolone 30mg/kg (up to 1000mg) daily for 1-3 days followed by 2mg/kg/d divided q8-q12. Continue high dose for 2 weeks (can consolidate to daily) then taper over 2-3 weeks; Consider adding PPI
- Discuss biologics in consultation with rheumatology; consider anakinra, tocilizumab, infliximab

Medication	Dosing	Notes
Aspirin	**Low dose (antiplatelet):** 3-5 mg/kg/dose once daily **High dose (anti-inflammatory):** 20-25 mg/kg/dose every 6 hours	Round aspirin dose to nearest ½ 81 mg tablet size
IVIG	2 gm/kg/dose IV (max 100 gm) for 1 dose	Retreatment may be considered if refractory (continued fever >36h or worsening clinical condition)
Methylprednisolone	**Low dose:** 2mg/kg/day for 2 weeks followed by taper over 2-3 weeks **High dose:** 30mg/kg/day (max 1000mg/day) for 1-3 days followed by 2mg/kg/day divided q8-q12. Continue high dose for 2 weeks (can consolidate to daily) then taper over 2-3 weeks	Consider adding a proton pump inhibitor for patients receiving steroids + aspirin to decrease risk for GI bleed
Biologic dosing recommendations:		
Medication	Dosing	Notes
Anakinra	2-4 mg/kg/dose (max 100mg/dose) SQ twice daily (may increase to 3 times daily) for 3 days	
Infliximab	10mg/kg/dose IV once	
Tocilizumab	<30kg: 12mg/kg IV; >30kg 8mg/kg IV, max 800mg	

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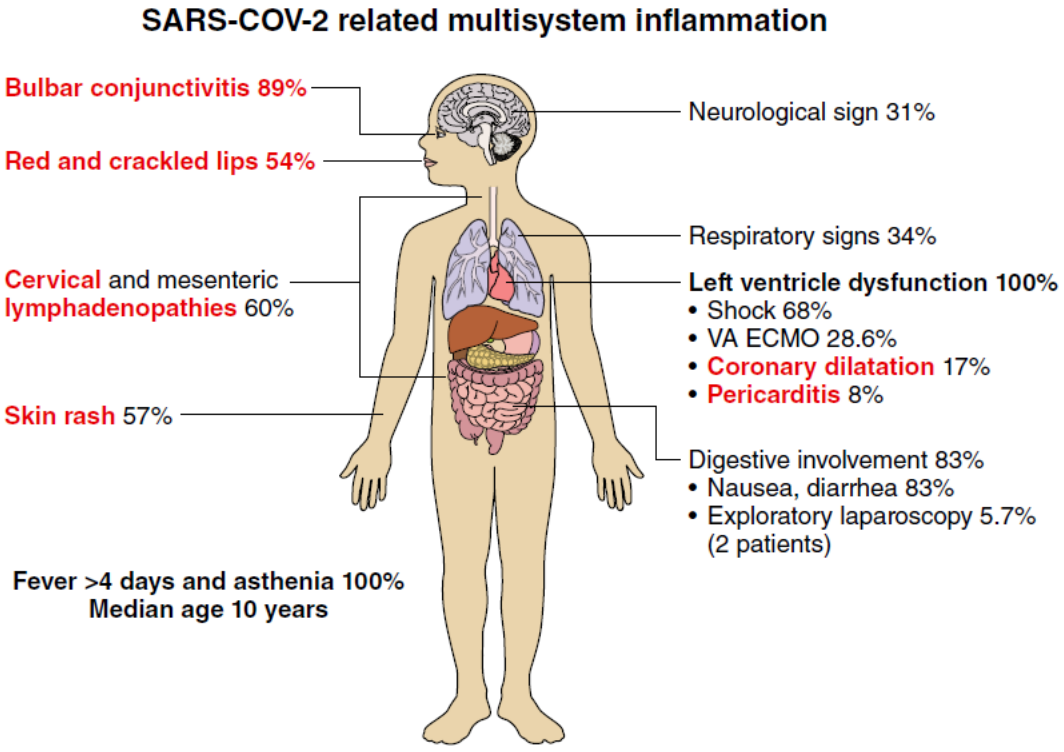
7. BW M et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association [Internet]. *Circulation* 2017;135(17). doi:10.1161/CIR.0000000000000484

Appendix I: Notes on cases and above definition:

- From *Lancet* UK series (8 patients) (1):
  - All cases had fever >39 for at least 4 days at presentation
  - 7/8 had GI symptoms of non-bloody diarrhea +/- vomiting, 5/8 had conjunctivitis
  - All COVID-19 negative by nasal swab and/or BAL; one COVID-19+ at autopsy (and 50% with positive caregivers)
- Further UK data (N=38)
  - 23/38 PCR or antibody +
  - Shock 76%, diarrhea 60%, rash 54%, vomiting 43%, conjunctivitis 32%
- From Italian series in *Lancet* (3):
  - 2/10 COVID-19+ PCR, 8/10 serology +.
  - 6/10 with diarrhea
  - 5/10 met KD criteria; remaining met incomplete KD criteria. 50% presented with shock
  - 30-fold increased incidence than historical KD in this period (10 in <2 months vs 19 in 5 years) – started about 30 days after peak of COVID outbreak
  - Vs historical KD more likely to have shock/MAS features: cytopenias, hyperferritinemia
  - All received IVIG, 80% steroids
- *Circulation* paper of French/Swiss hospitals (2):
  - 35 patients with acute heart failure; 10/30 with EF<30%, 25/35 30-50%; 10/35 required VA-ECMO (all survived)
  - 31/35 with positive COVID-19 PCR or IgG
  - 83% with GI symptoms including 2 who received emergency exploratory laparotomy prior to MIS-C diagnosis
  - 6 had coronary dilation but no aneurysms. None met classic KD criteria
  - All had elevations of troponin I (mild-moderate) and BNP (1000s pg/mL)
- Italians note referral bias – rheumatologists vs intensivists

Appendix II: (2)



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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 draft summary was approved by the ACR Board of Directors on June 17, 2020.
A full manuscript is pending journal peer review.

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.

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).

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 ≥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 possibly 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).
- 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 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/or glucocorticoids considered as first tier treatments (M/H).
- 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. (M/H).
- 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 (M/H).
- Anakinra may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments (M/H).
- 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 (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 KD-like features and/or thrombocytosis (platelet count ≥450,000/μL) 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 ≤80,000/μL (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 ≥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).

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- 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 (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, elevated lactate dehydrogenase (LDH), D-dimer, IL-6, IL-2R, and/or ferritin, and depressed lymphocyte count, albumin, and/or platelet count (M/H).
- Glucocorticoids may be considered for use as immunomodulatory therapy in patients with COVID-19 and hyperinflammation (as outlined in point above) (M).
- Anakinra appears safe in severe infections and in children with hyperinflammatory syndromes. In children with COVID-19 and hyperinflammation, anakinra (>4mg/kg/day) should be considered for immunomodulatory therapy. 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).
- 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 (M).
- 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 (M/H).
- In the absence of randomized controlled trails or comparative effectiveness studies, if immunomodulation is to be used at all, the 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 (M).

Updated June 17, 2020

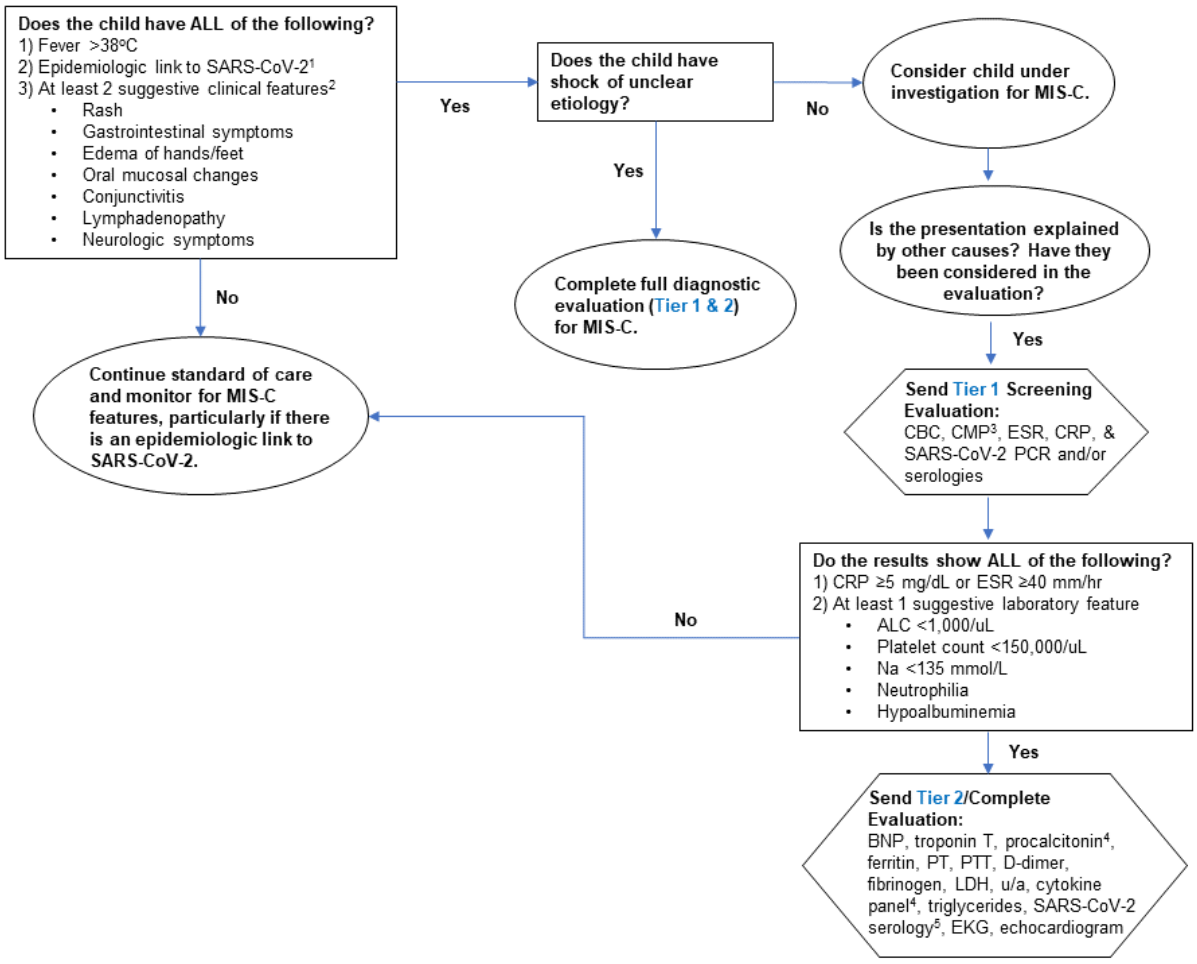

Figure 1. Diagnostic Pathway for MIS-C

[1]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 COVD-19, or close contact with confirmed or suspected COVID-19 cases in the past 4 weeks.

[2]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 metal status, encephalopathy, focal neurologic deficits, meningismus, or papilledema).

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

[4]Send procalcitonin and cytokine panel, if available.

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