Supplement 2

Children's Hospital of Philadelphia:
Emergency Department, ICU and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome (MIS-C)
The Children's Hospital of Philadelphia
Pathways Program, Center for Healthcare Quality and Analytics
https://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway

COVID-19 Treatment Guidance – Pediatric Patients

Currently, there are limited evidence to recommend a specific treatment regimen for patients with suspected or confirmed COVID-19 infection. The suggested approach for nearly all children is supportive care. Treatment options discussed below are under investigation at this time – decisions to use these should be made only with close attention to the patient's clinical status, comorbidities, and interacting

This guidance was developed by a multidisciplinary team at Levine Children's (Infectious Diseases, Critical Care, Cardiology, Rheumatology, Hematology, Emergency Department).

Table 1: Management of Children (< 18 years) with ACUTE COVID-19 Infection
Hospitalized patients with positive SARS-CoV-2 PCR

	Presentation	Treatment	Labs/Monitoring (refer to Table 2 for suspected MIS-C labs)
Mild to Moderate Disease	Cough, coryza, sore throat, *without shortness of breath or oxygen requirement*	Supportive care alone.	**Baseline**: • CBC with diff (evaluate absolute lymphocyte count) • CMP (evaluate LFTs) • CRP
Severe Disease	Shortness of breath or hypoxia requiring supplemental oxygen	Supportive care alone is appropriate for the majority of children. ID consult for **remdesivir** and/or **convalescent plasma** consideration.	**Baseline**: • CBC with diff • CMP • CRP • PT/PTT, D-dimer, fibrinogen, lupus anticoagulant, beta 2 glycoprotein and anticardiolipin
Critical Disease	Respiratory failure requiring non-invasive positive-pressure ventilation or intubation	ID consult to initiate **remdesivir**. See inclusion/exclusion criteria on page 4. Consider **convalescent plasma**. Consider **tocilizumab** for treatment of severe COVID-19 disease with respiratory failure (without MIS-C); must meet all criteria: • Confirmed CoV-2 by PCR • PICU admission + Infectious Diseases consultation • Radiographic infiltrates by imaging • Rapidly worsening respiratory effort (if not intubated) • $PaO_2/FiO_2 \leq 300$mmHg (when PaO_2 not available, $SpO_2/FiO_2 \leq 315$)	**Baseline and Clinical Worsening:** • CBC with diff • CMP, CRP • LDH • Ferritin • IL-6 • INR • PT/PTT, D-dimer, fibrinogen • Lupus anticoagulant, beta 2 glycoprotein and anticardiolipin • ECHO **Daily:** • CBC with diff • CMP • CRP

- **The use of antivirals for confirmed COVID-19 infection is restricted to Pediatric Infectious Diseases**. ID approval is required prior to pharmacy dispensing tocilizumab and remdesivir. Hydroxychloroquine, chloroquine, lopinavir-ritonavir are no longer recommended.
- Pediatric Infectious Diseases consultation is recommended for any hospitalized child with COVID-19 if considering treatment.
- Outpatient therapy, other than OTC symptom treatment, is not recommended.
- Utilize "COVID-19 Pediatric Diagnostic Labs and Monitoring" Powerplan

Table 2: Multisystem Inflammatory Syndrome (MIS-C): Screening and Presentation

<table>
<tr><td rowspan="3">Suspected MIS-C: Screening Labs</td><td colspan="2">Clinical/Historical Features: GI symptoms, any classic KD criteria (below), neurologic symptoms, COVID exposure or SARS-CoV-2 + PCR</td></tr>
<tr><td>Evaluation for Possible MIS-C</td><td>Fever ≥ 38°C ≥ 1 day PLUS ≥ 2 clinical/historical features: Obtain CBC, CMP, CRP, ESR, SARS-CoV-2 PCR and IgG
IF: CRP ≥ 3, ESR ≥40, WBC < 1k, Platelets < 150k, Na < 135 (and no alternative plausible diagnosis)
THEN: obtain troponin, BNP, ECG. IF all initial labs abnormal, obtain ECHO/cardiology consult and PICU consult</td></tr>
<tr><td>Suspected MIS-C with Shock</td><td>Fever ≥ 38°C ≥ 1 day PLUS ≥ 2 clinical/historical features PLUS myocardial dysfunction or hypotension:
Obtain MIS-C baseline labs/studies in Table 3 and consult PICU</td></tr>
<tr><td>CDC Case Definition for MIS-C: Reporting Purposes Only</td><td colspan="2">• Fever (≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours)
• Lab evidence of inflammation: ≥1: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, neutrophils, reduced lymphocytes or albumin
• Clinically severe illness requiring hospitalization
• Multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
• No alternative plausible diagnoses
• 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</td></tr>
<tr><td>Key Findings with MIS-C</td><td colspan="2">• High fevers (universal)
• Severe abdominal pain/diarrhea in most
• +/- rash, oral mucosal changes, conjunctivitis
• Respiratory failure uncommon
• Key lab findings:
○ ↑ CRP, D-dimer, ferritin, markedly elevated BNP
○ ↓ lymphocytes, sodium, platelets</td></tr>
<tr><td>Kawasaki Disease AHA Criteria</td><td>Typical Kawasaki:
Fever ≥ 5 days PLUS 4 of 5 of:
• Changes in lips/oral cavities
• Conjunctivitis
• Rash
• Erythema/edema of hands/feet
• Lymphadenopathy > 1.5cm</td><td>Incomplete/Atypical Kawasaki:
Fever ≥ 5 days PLUS 2-3 criteria OR infants with fever ≥ 7 days without explanation
• CRP < 3 and ESR < 40: Serial clinical and lab evaluation if fevers persist. ECHO if peeling develops.
• CRP ≥ 3 and/or ESR ≥ 40: Treat if positive ECHO OR ≥ 3 lab findings: (↓ Hgb for age, platelet ≥ 450,000 after 7th day of fever, albumin ≤ 3 g/dL, ↑ ALT, WBC ≥ 15,000/mm^3, urine ≥ 10 WBC)</td></tr>
<tr><td>Kawasaki Disease vs MIS-C</td><td colspan="2">
<table>
<tr><th>COVID-19 MIS-C Shock</th><th>KAWASAKI Shock</th></tr>
<tr><td>Lymphopenia</td><td>No lymphopenia</td></tr>
<tr><td>Majority > 5 years of age in reported cases</td><td>80% under 5 years of age</td></tr>
<tr><td>Severe abdominal pain</td><td>Some GI complaints</td></tr>
<tr><td>↑ Ferritin and CRP; ↓platelets and albumin</td><td>Same but less severe</td></tr>
<tr><td>Platelet counts normalize with recovery</td><td>Marked thrombocytosis day 10-14</td></tr>
<tr><td>African Americans appear at highest risk</td><td>Asians at highest risk of KD</td></tr>
<tr><td>Myocarditis/myocardial dysfunction/arrhythmias</td><td>Coronary aneurysms</td></tr>
<tr><td>NT-proBNP markedly ↑, D-dimer and troponin ↑</td><td>Not often reported (mycocardial dysfunction less severe) but generally normal to mildly elevated</td></tr>
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Table 3: Multisystem Inflammatory Syndrome in Children (MIS-C): Initial Management

ALL Patients:

Based on criteria/key findings in Table 2, multidisciplinary discussions with consultants will occur using guidance below. Treatment regimens are investigational.

1. **Consults**: Infectious Diseases, Critical Care, Cardiology, Hematology, Rheumatology
2. **Supportive Care**: fluid resuscitation, early use of vasopressors/inotropes, respiratory support
3. **Antiviral Therapy**: consider remdesivir in patients with positive SARS-CoV-2 PCR
4. **Anticoagulation**: consult hematology in patients with thrombosis or APLA +
   - Prophylaxis (platelets > 25k, not on high dose aspirin): enoxaparin 0.5 mg/kg SQ BID in high risk patients. High Risk= age ≥ 15 years, sickle cell disease, PICU admission, D-dimer > 500 ng/mL or APLA + (lupus anticoagulant, beta-2 glycoprotein, or anticardiolipin antibody).
   - Therapeutic anticoagulation: consider IF confirmed/suspected VTE/PE or intubated patients with sudden clinical decline or worsening coagulopathy.
5. **Antibiotics** per LCH sepsis powerplans: immunocompetent patients- ceftriaxone +/- metronidazole +/- vancomycin. Consider stop/de-escalation after 48 hours. Consider further coverage for toxic shock syndrome (clindamycin) or Rikettsia infection (doxycycline) based on presentation.
6. **GI prophylaxis**: famotidine if on steroids. Patients with severe GI symptoms have higher risk of bowel perforation with pulse steroids. Consider risk/benefit.

	Presentation	Anti-Inflammatory Treatment	Labs/Monitoring	
Mild to Moderate Disease	• No vasoactive requirement • No/minimal respiratory support	• *Consider* baseline labs and methylprednisolone 1 mg/kg every 12 hours (taper over 2 weeks) on a case by case basis	**Baseline:** • Blood culture • RPP • SARS CoV-2 PCR and IgG • CBC with diff • CMP • CRP, ESR • pro-BNP • Troponin • D-dimer • Ferritin • LDH • IL-6 • Procalcitonin • PT/INR, PTT, TEG • Fibrinogen • APLA: lupus anticoagulant, beta-2 glycoprotein, and anticardiolipin antibody • ECHO • EKG • CXR	**Daily:** • CBC • CMP • CRP • Pro-BNP • D-dimer • Ferritin • Other initial abnormal labs Space out upon clinical improvement
Severe Disease	• VIS score ≤ 10 • Significant supplemental O2 requirement	• *Consider* Methylprednisolone 10 mg/kg x1 (max 1000mg), then 1 mg/kg every 12 hours (taper over 6 weeks) • *Consider* IVIG 2 g/kg (max 70g)		
Critical Disease	• VIS score > 10 • Non-invasive positive-pressure ventilation or intubation • Moderate or severe organ injury (including moderate to severe ventricular dysfunction)	• Methylprednisolone 20-30 mg/kg (max 1000 mg) x1, then 1 mg/kg every 12 hour (taper over 6 weeks) • IVIG 2 g/kg (max 70g) • *Consider* anakinra 2-4 mg/kg/dose IV (max 100 mg/dose) every 6-12 hours (up to 8 mg/kg/day) in patients with refractory shock after steroids after excluding superimposed bacterial infection		
Kawasaki Disease	• Classic or Incomplete (see Table 2) • Meeting criteria for MIS-C	• IVIG 2 g/kg (max 70g) • Aspirin 50 mg/kg/day until afebrile, then 3-5 mg/kg/day • Methylprednisolone 1 mg/kg q12h (taper over 2 weeks) for high risk patients (CA aneurysms at diagnosis, age < 12 mo or > 8 yr, IVIG resistance) • Repeat IVIG in patients with persistent fever 36 hours after completion of first dose • Consider pulse steroids (30mg/kg x 1-3 days) or anakinra in patients refractory to 2 doses IVIG		

VIS score: dopamine dose (µg/kg/min) + dobutamine dose (µg/kg/min) + 100 x epinephrine dose (µg/kg/min) + 10 x milrinone dose (µg/kg/min) + 10,000 x vasopressin dose (U/kg/min) + 100 x norepinephrine dose (µg/kg/min)

Table 4: Agents Under Investigation for Management of COVID-19

Agent	Dosing	Criteria for Use	Additional Information
Remdesivir: Emergency Use *as of 6/24/20; information subject to change per FDA EUA EUA Fact Sheet for PROVIDERS EUA Fact Sheet for Parents/Caregivers	Pediatric Dosing: **3.5kg-40kg:** 5 mg/kg (max 200mg) IV load on day one, followed by 2.5 mg/kg (max 100mg) daily **≥ 40 kg**: 200mg IV day 1, followed by 100mg daily Duration: 5 days	*Inclusion Criteria:* • Suspected or confirmed SARS CoV-2 • SaO2 < 94% on room air, requiring supplemental oxygen, mechanical ventilation or ECMO *Exclusion Criteria*: • ALT > 5 x upper limit of normal Weigh risk/benefit in patients with AST > 5 x upper limit of normal or eGFR < 30 mL/min (or Scr > 1 mg/dL in full term nenates 7-28 days old).	Refer to "AH COVID-19 Remdesivir Protocol" on the Physician Connect COVID-19 hub for more information. Patients will be reviewed daily by an ID/ASN team during normal business hours (8:00am-4:30pm), 7 days per week. EUA requirements: **1.** Provide the EUA Fact sheet for Patients and Parents/Caregivers and document in the medical record the following: • Provided fact sheet (no signature needed) • Informed of alternatives • Informed remdesivir is an unapproved drug used under an EUA **2.** Document eGFR prior to starting (Scr in neonates) in progress note. **3.** Documented LFTs prior to starting and daily during therapy in progress note. Remdesivir should be stopped in pateints who develop ALT ≥ 5x ULN OR ALT elevation with increasing conjugated bilirubin, alk phos or INR. ****MUST complete steps 1-3 prior to ordering remdesivir**** **4.** Daily documentation of ROS and exam, including review of vitals, clinical course and relevant labs (Cr, eGFR) while on therapy. **5.** Mandatory reporting of all serious adverse effects (including death) and medication errors within 7 days via FDA MedWatch.

Preparation/Administation: only lypophilized powder remdesivir vials may be used in children < 40kg. RDV will be diluted in 25, 50 or 100mL, depending on weight with a default infusion time of 30 minutes (may be extended to 120 minutes).

Drug interactions: *in vitro*, remdesivir is a substrate for CYP2C8, CYP2D6, CYP3A4, Polypeptides 1B1 and P-glycoprotein transporters. *In vitro*, remdesivir inhibits CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance has not been established.

Example verbiage for EUA documentation in progress note: "Given ___, we have offered the patient/family treatment with remdesivir. I discussed there are no currently approved medications for COVID-19 and the option for Remdesivir as a FDA unapproved drug under an EUA. I discussed information on available alternative treatments, the significant known potential risks and benefits of remdesivir, and the extent to which such risks and benefits are unknown. The patient/caregiver has received the EUA Fact Sheet ("Fact Sheet for Patients and Parents/Caregivers"), which I have reviewed with them. He/she would like to proceed with treatment. I discussed plans with the primary team and patient's RN who are all in agreement with proceeding. His has an eGFR of __ mL/min and AST/ALT of ___"

Table 4: Agents Under Investigation for Management of COVID-19

Tocilizumab

Should only be considered in patients with severe disease

[80 mg, 200mg, 400mg vials]

Dosing

Pediatric Dosing*: 8 mg/kg
Max dose: 200mg (< 35 kg) or 800mg (> 35kg)

Duration: Single dose is recommended.

Redosing x1 dose 8-12 hours after initial dose may be considered if continued clinical decompensation.

Weight (kg)	*Dose Rounding*	*Vial size to use*
1-12	If 8 mg/kg < 80 mg, use calculated dose. If > 80 mg, round to 80 mg.	80 mg
13-22	If 8 mg/kg < 160 mg, use calculated dose. If > 160 mg, round to 160 mg.	80 mg x 2
23-35	If 8 mg/kg < 200 mg, use calculated dose. If > 200 mg, round to 200 mg.	200 mg
For weight > 35 kg, pharmacy will round to nearest vial size per adult dose rounding.		

**IV formulation ONLY **
(subcutaneous formulation should not be used)

Adverse Effects/Drug Interactions

Adverse Effects:

- **Serious and potentially fatal infections reported, avoid in patients with sepsis**
- Reactivation of latent and new TB infection
- Hepatotoxicity
- Neutropenia (caution if ANC < 2000/mm^3)
- Thrombocytopenia (caution if platelets < 100,000/mm^3)

Common Drug Interactions:

- Immunosuppressants, including tacrolimus (increased risk for immunosuppression)
- CYP3A4 substrates (decreased concentrations of CYP3A4 substrates, blockade of IL-6 enhances CYP function).
- Consult pharmacy for full review prior to initiating.

Additional Information

Baseline Labs Prior To Starting:

- HCV Ab
- HBV sAg
- HIV Ab
- Quantiferon-TB Gold
- Send out to Cincinnati Children's:
  - Soluble IL-2R
  - Plasma cytokines
  - CXCL9
  - https://www.cincinnatichildrens.org/-/media/cincinnati%20childrens/home/service/h/human-genetics/human-genetics-shared-pdfs/requisitions/dil-req-pdf.pdf

Recommended Lab Monitoring:

- CRP
- LDH
- D-dimer
- Ferritin
- ALT

Table 5: Additional Guidance	
AGENT	**COMMENTS**
Angiotensin/RAS Blocking Agents (ACEi/ARBs)	• Do not discontinue these agents for COVID-19. • At this time, there is insufficient data to recommend discontinuation of these agents to decrease the risk of more severe COVID-19. • This recommendation is supported by a joint statement from the AHA, ACC, and HFSA.
Antibiotic Therapy for Community Acquired Pneumonia	• Secondary bacterial co-infection is uncommon, even in critically ill patients. If empiric therapy is started, therapy should be assessed and discontinued once a patient is confirmed COVID positive. • Antibiotics may be indicated in critically ill patients when there is a new concern for secondary infection with worsening leukocytosis and/or hemodynamic instability. • Empiric inpatient therapy: ceftriaxone (discontinue after 48 hours if no ongoing evidence of bacterial co-infection). ○ Severe beta-lactam allergy: levofloxacin
Ascorbic Acid (Vitamin C)	• There is insufficient clinical data for the use of high-dose ascorbic acid as adjuntive therapy in COVID-19.
Baloxavir	• Due to the lack of a defined mechanism or *in vitro* data to demonstrate acivity against COVID-19 and other coronaviruses, the use of baloxavir is not recommended.
Darunavir-cobicistat	• No *in vitro* or clinical data exists to support the use in COVID-19 at this time – a clinical trial has been registered in China.
Ibuprofen/NSAIDs	• There is insufficient clinical data establishing a link between the use of ibuprofen or other NSAIDs and worsening COVID-19.
Ivermectin	• There is insufficient clinical data for the use of ivermectin in treatment of COVID-19.
Oseltamivir	• Coronaviruses do not utilize neuraminidase; there is no enzyme to be inhibited by oseltamivir. • Oseltamivir, as well as other neuraminidase inhibitors, should be avoided in COVID-19 once influenza is ruled out.
Ribavirin (oral) +/- Interferon	• These agents are not recommended for use based on poor *in vitro* activity and lack of animal or human data, along with significant risks for toxicity (hematologic, hepatoxicity, neuropsychiatric, ischemia, infection).
Zinc	• There is insufficient clinical data for the use of zinc as adjunctive therapy in COVID-19.

Further details regarding the clinical syndrome of COVID-19 infections can be found in the below reference:

World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Interim guidance. 13 March 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

REFERENCES

National guidance

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Remdesivir

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3. Goldman J, Lye D, Hui. Remdesivir for 5 or 10 days in patients with severe COVID-19. NEJM 2020 May 27

MIS-C

1. Riphagen S, Gomez X, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 6
2. Verdoni L, Mazza A, D'Antga L. An outbreak of sever Kawasaki like disease at the Italian epicentere of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020 May 13

OVERVIEW

This guidance was developed by a multi-specialty team of Boston Children's Hospital (BCH) clinicians to assist with evaluating and treating patients who present to BCH seeking care related to symptoms or complications of coronavirus disease 2019 (COVID-19), including Multisystem Inflammatory Syndrome in Children (MIS-C). As this guidance was developed for BCH patients, any use of this document by other clinicians or facilities should be based on the individual clinical circumstances of their own patients and the resources available to the patient's treating clinicians. As the evidence base for COVID-19 and MIS-C treatment and care management is evolving rapidly, this guidance will change frequently as identified by the date stamp on the document.

This guidance outlines the team approach at Boston Children's related to laboratory evaluation and subspecialty consultation (Section A), antiviral therapy (Section B), and immunomodulatory therapies (Section C), as well as other agents, including convalescent plasma (Section D), for BCH patients. The BCH Hematology service has created separate guidance on anti-coagulation in patients with COVID-19.

This treatment guidance was developed based on available in vitro and animal model data, limited clinical evidence issued in public sources, federal and state treatment guidance as issued to date, and the experiences of our treating clinicians based on our patient population. The therapies offered for consideration are hypothesized to be effective against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection or its sequelae, but they have not been proven, and definitive evidence of their benefit has not been published in a peer-reviewed journal. As of the date of this guidance, they are not FDA-approved for use in COVID-19.

Given the lack of established therapies, possibility of harm, and limited drug supply, BCH does not recommend any treatment outlined in this document for (1) prevention or post-exposure prophylaxis or (2) non-hospitalized patients with confirmed or suspected COVID-19. Any questions related to this guidance should be directed to Dr. Mari Nakamura (mari.nakamura@childrens.harvard.edu).

A. LABORATORY EVALUATION AND SUBSPECIALTY CONSULTATION

Table 1. Recommendations for Laboratory Evaluation and Subspecialty Consultation

Disease Category	Respiratory Status	Concern for MIS-C (see Section C for definition)	Diagnostic Evaluation (pre-consultation)	Subspecialty Consultation
Mild	No dyspnea	• Fever *and* • GI symptoms *and* • Kawasaki disease features (rash, conjunctivitis, extremity changes, mucositis, lymphadenopathy) *and* • Epidemiologic link to SARS CoV-2	• SARS-CoV-2 PCR and/or serologies • Consider CBC with differential, BUN, creatinine, LFTs, ESR, CRP • Consider chest x-ray	• Consult Rheumatology if concern for MIS-C • Supportive care; no antiviral or immunomodulatory treatment recommended
Moderate	Dyspnea and/or chest imaging consistent with COVID-19, but no change from pre-illness baseline respiratory support requirement	Same as mild cases *plus*: • Myocardial dysfunction (without need for vasopressors) • Significant abdominal pain, vomiting, diarrhea • Neurologic features (severe headache, meningismus, focal neurologic deficits, mental status changes)	• SARS-CoV-2 PCR and/or serologies • CBC with differential, BUN, creatinine, LFTs, LDH, ESR, CRP, PT & PTT, D-dimer, procalcitonin, ferritin[1] • Troponin and BNP • If available, cytokine panel[1] • Chest x-ray for respiratory symptoms • EKG	• Consult Immunology and Infectious Diseases (ID) for all cases • Consult Rheumatology if concern for MIS-C or Cytokine Storm • Consult Cardiology if concern for MIS-C
Severe	Dyspnea and/or chest imaging consistent with COVID-19, with new or increased supplemental O_2 and/or non-invasive ventilatory support requirement	Same as for moderate cases	Same as for moderate cases	Consult Immunology, ID, Rheumatology, and Cardiology for all cases
Critical	Respiratory failure requiring mechanical ventilation +/- acute respiratory distress syndrome (ARDS)	• Myocardial dysfunction and/or low-output heart failure requiring vasopressor support or ECMO • Systemic inflammatory response syndrome (SIRS) • Multi-organ failure • Encephalopathy	Same as for moderate cases	Same as for severe cases

[1]At BCH, order these studies using the COVID-19 Immunology Panel Plan [found within the COVID-19 (Novel Coronavirus) Evaluation Plan].

B. ANTIVIRAL THERAPY

Antiviral treatment decisions should weigh individual risks and benefits for the patient in question, taking into account considerations such as potential risk factors for disease progression, clinical trajectory, and drug contraindications or interactions. Refer to Table 2 for **proposed pediatric risk factors**; **adult risk factors** for progression to severe disease include age >60 years, immunocompromising conditions, active malignancy, structural lung disease, chronic kidney disease, hypertension, coronary artery disease, or diabetes in patients requiring admission for treatment of COVID-19 disease (Zhou et al. Lancet 11 Mar 2020).

A decision not to treat with an antiviral would be reasonable in many circumstances. ID consultation is required for all patients for whom COVID-19 treatment is being considered.

Table 2. Potential Risk Factors for COVID-19 Progression in Pediatric Patients

Subspecialty Service	Risk Factors/High-Risk Populations
Cardiology	*Principles:* 1. Evidence-based data to risk-stratify children with congenital or pediatric heart disease are extremely limited. The list below was contributed by Heart Center faculty based upon first principles, recognizing that there are few reports of severe COVID-19 to date even in children with severe CHD. 2. Cross-cutting themes across these categories include comorbidities such arrhythmias, lung disease, other end-organ dysfunction, severe hypoxemia, or immunosuppression. 3. Some categories below have overlap, but we have erred on the side of being complete. *Categories of cardiac patients presumed to be at higher risk of severe COVID-19:* • All CHD (exclude ASD/VSD/CoA) patients who test positive (or are considered PUI until rapid testing becomes widely available) and require ICU admission for supplemental oxygen or inotrope support • Early post-operative patients on mechanical ventilator therapy for >3-4 days • COVID-19-associated myocarditis • Dilated cardiomyopathy >mild (LV EF ≤45%) • Congestive heart failure for any reason based upon symptoms and signs • Single ventricle heart disease at any stage • Unrepaired cyanotic heart disease of at least moderate severity, e.g., saturations <80 at rest, or Hgb >3 SD above age-adjusted mean • Pulmonary artery hypertension with at least one of the following: ≥ systemic PA pressure, any RV dysfunction, associated lung disease, rheumatologic disorders, or chronic thromboembolic pulmonary hypertension • Multivessel pulmonary vein stenosis • Congenital or acquired heart disease with comorbidities of lung disease/history of tracheostomy/ventilator dependence • Large left-to-right shunt lesions (e.g., estimated Qp:Qs >2, symptoms, or LVEDV or RVEDV >3) • Severe heart valve dysfunction (stenosis, regurgitation, or mixed valve disease) • Right ventricular hypertension (≥70% systemic) or dysfunction (RV EF <45%). • Heterotaxy patients (asplenia or polysplenia)

	• Coronary heart disease, with or without history of myocardial infarction (e.g., Kawasaki disease, homozygous familial hyperlipidemia) • Age ≥21 years with moderate or severe CHD OR any ACHD patient with physiologic class C or D (see Appendix Tables 1, 2, and 3 for definitions) • Congenital and/or acquired pediatric heart disease not specified above but judged by the patient's cardiologist to be in a high-risk category
Gastroenterology	• Immunosuppressed patients: Those on >10 mg prednisone daily, mercaptopurine, methotrexate, or biologics such as infliximab • Patients with intestinal failure (short bowel syndrome, microvillous inclusion disease) that require parenteral nutrition • Serious chronic liver disease (e.g., biliary atresia) • Patients with central lines due to requirement for parenteral nutrition or hydration (e.g., motility disorders such as pseudo-obstruction) • Patients with ileostomies who may be prone to dehydration
HSCT	• Stem cell transplant patients with active or history of (including pre-transplant) inflammatory lung disease
Immunology	• Prior history of infections with opportunistic pathogens or severe infections requiring hospitalization • Anatomic or functional asplenia or splenic dysfunction • Documented impairment in T cell-mediated immunity, including: T cell lymphopenia prior to COVID-19, reduced lymphocyte proliferation to mitogens or antigens, reduced CD8 cytotoxicity • Documented impairment in B cell-mediated immunity, including reduced levels of IgG, IgA, or IgM, reduced antibody response to vaccines • Documented impairment in NK cell-mediated immunity: reduced NK cell number or NK cell cytotoxicity • Other defects in innate immunity, including abnormal response to Toll-like receptor stimulation • Documented immune dysregulation syndrome characterized by multiple autoimmune diseases and/or overactive immune signaling pathways, including patients on immune modulators. • Patients with allergic or immune-related disease who are on immunomodulatory agents, including high-dose inhaled corticosteroids, tacrolimus/sirolimus/cyclosporine, and biologic agents
Nephrology	• Immunosuppression with cyclophosphamide, calcineurin inhibitor therapy, azathioprine, mycophenolate mofetil, and/or chronic high dose steroids (>0.5 mg/kg/day or 20 mg/day for >1-2 months) • Immunomodulatory therapy (such as rituximab) within the last year • Active nephrotic syndrome with anticipated depressed IgG levels (ongoing losses) • Chronic kidney disease (eGFR <60 ml/min/1.73 m_2) • End-stage renal disease requiring chronic dialysis
Oncology	• Metastatic lung disease • History of lung irradiation (including irradiation to mediastinum) • Other underlying cardiopulmonary disease • Acute leukemia, not in remission (e.g., undergoing induction, reinduction, treatment for refractory disease) • AML, receiving high-dose chemotherapy cycles for new diagnosis or relapsed disease • Any patient on active therapy with low ALC (<200)
Pulmonary	*The following patients are at high risk of mortality based on poor physiologic reserve:* • Patients with a history of one or more episodes of ICU admission for respiratory decompensation, including severe asthma exacerbation, RSV or other pneumonia, hypercarbic or hypoxemic respiratory failure.

	• Any patient with supplemental home oxygen use • Any ventilator-dependent patient or patient with tracheostomy • Any patient with FEV1, TLC, or DLCO <60% predicted at baseline *The following patients have a high risk of severe disease, regardless of current level of disease severity:* • Patients on active immunosuppressive or biologic therapy • All cystic fibrosis or primary ciliary dyskinesia patients • All patients with interstitial lung disease • All patients with bronchopulmonary dysplasia • All patients with pulmonary hypertension
Rheumatology	• Current treatment with cyclophosphamide • Current treatment with chronic high-dose steroids (>0.5 mg/kg/day or >20 mg/day for >1-2 months) • Immunomodulatory drugs, including biologics, should not be stopped unless a patient has symptoms of COVID-19 and either has (1) a positive SARS-CoV-2 PCR or (2) a close contact with confirmed COVID-19.
Solid Organ Transplant	*Heart:* All heart transplant recipients
	Kidney: All kidney transplant recipients
	Liver/Intestine: All liver and intestine transplant recipients
	Lung: All lung transplant recipients

Table 3. Antiviral Dosing and Monitoring
Whether to undertake antiviral treatment will be decided for each individual patient with input from the patient (if developmentally appropriate) and family, primary team, and Infectious Diseases.

Antimicrobial	Dosage Form	Dosing	Dose Adjustments	Safety/Monitoring	Drug Interactions
Remdesivir (intravenous only) Available in limited supply at BCH for children or adults with severe or critical manifestations of confirmed (PCR-positive) COVID-19.	100-mg vials	Day 1: 5 mg/kg/dose IV x1 dose (200 mg maximum dose) infused over 30 to 60 minutes Day 2-10: 2.5 mg/kg/dose IV Q24 hours (100 mg maximum dose) infused over 30 to 60 minutes No lower age limit has been established.	No dose adjustments provided by manufacturer. Stop therapy if patient develops CrCl <30 ml/min or ALT rise to ≥5x upper limit of normal.	Daily electrolytes, renal function tests (creatinine, BUN), liver function tests (including ALT, AST, bilirubin, and alkaline phosphatase), hematology (complete blood count with differential and prothrombin time), and urinalysis Potential toxicities: Elevated liver function tests. Of note: Remdesivir preparation contains sulfobutylether β-cyclodextrin sodium (SBECD). Approved FDA medications that contain SBECD (e.g., voriconazole) should be used with caution when CrCl estimates fall below 50 ml/min.	Advisement to avoid nonsteroidal anti-inflammatory medications and other nephrotoxic medications. There are currently no data available on the interaction of remdesivir and other investigational agents. Administering remdesivir concurrent with other investigational anti-CoV agents may lead to antagonism, synergy, or have no effect.

Note: Convalescent plasma (see Table 5) is another therapeutic option for pediatric patients with critical COVID-19 or adult patients with severe or critical COVID-19, particularly those not improving with antiviral treatment.

C. MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) AND IMMUNOMODULATORY THERAPY

MIS-C CDC Case Definition:

- 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 CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin

* Some individuals may fulfill full or partial criteria for Kawasaki disease but should be considered to have MIS-C if they meet the case definition for MIS-C.

Hyperinflammation in COVID-19 *versus* MIS-C:
As defined above, MIS-C is characterized by fever, systemic inflammation, and multi-organ dysfunction that occurs in teh late phase of SARS-CoV-2 infection. Cytokine Storm Syndrome (CSS) is defined by hyperinflammation mediated by pro-inflammatory cytokines that typically develops in the acute, infectious phase of COVID-19. There may be similarities in the features of some children with MIS-C and COVID-19-associated CSS, as they share features of lymphopenia, coagulopathy, hyperferritinemia, transaminitis, elevated CRP, and elevated LDH. However, patients with CSS typically present later in the course of acute infection (often during the second week of the respiratory illness) with clinical decline, whereas the time frame of the development of MIS-C following COVID-19 exposure is 2-6 weeks, and affected patients are generally well prior to onset of symptoms. Clinical symptoms of GI involvement and evidence of myocardial dysfunction tend to be more prominent in MIS-C than in CSS. Antibody testing may help differentiate the two, but this is an area of debate.

As patients with MIS-C may have significant cardiac involvement, appropriate labs (BNP and troponin) and imaging (echocardiogram) with Cardiology input are essential for any child thought to have MIS-C, regardless of the presence or absence of features of Kawasaki disease.

In general, patients with signs of CSS in COVID-19 and the shock presentation of MIS-C are more likely to have severe disease and require ICU-level care.

PLEASE NOTE: There are no established therapies for COVID-19-associated CSS or MIS-C.

These medications are to be used only with guidance from Rheumatology, Cardiology and Infectious Diseases. Patients who are being evaluated for immunomodulatory therapy should also be considered for antiviral therapy if they are not already receiving it.

The evidence base for management of MIS-C in COVID-19 is evolving rapidly, and this guidance will change frequently. Please do not print this document.

Table 4. Immunomodulator Dosing and Monitoring
This table includes possible medications that may be recommended by Rheumatology to treat COVID-19-associated CSS or MIS-C. Treatment will be tailored to each individual patient with input from the primary team, Rheumatology, and Infectious Diseases.

Immunomodulator	Current Trials	Dosage Form	Dosing	Dosing Adjustments	Safety Monitoring	Drug Interactions
IVIG MIS-C with or without features of Kawsaki disease or signs of myocardial dysfunction OR Severe or critical COVID-19 with evidence of CSS (see Table 1)	NCT04261426	IV solution	1-2 g/kg/dose IV 2 g/kg/dose IV if Kawasaki disease stigmata	Use with caution in patients with renal impairment	Assess cardiac function and fluid status prior to giving to avoid fluid overload Baseline renal function tests, urine output, IgG level, CBC Monitor clinically for signs of hemolysis after first dose Hgb/Hct, type and screen before second dose Hgb/Hct after subsequent doses Potential adverse reactions: anaphylaxis, infusion reaction, hemolysis, transaminitis, aseptic meningitis	MMR, varicella vaccines[1]
Glucocorticoids: Methylprednisolone, prednisone, prednisolone, dexamethasone MIS-C with features of shock or coronary artery dilation/aneurysm	NCT04344288 NCT04325061 NCT04244591	Liquid, tablets, IV solution	1-2 mg/kg/day divided BID (prednisone, prednisolone, methylprednisolone) 5 mg/m$_2$ daily (dexamethasone)	None	Monitor blood pressure daily Monitor glucose and electrolytes	None

OR Severe or critical COVID-19 with evidence of CSS						
Anakinra MIS-C that has failed other therapies OR Severe or critical COVID-19 with evidence of CSS	NCT04324021 NCT04330638	100-mg syringe	2-4 mg/kg/dose (max 100 mg) BID (can increase to TID or QID if there is a lack of full response) IV/SQ Continue for up to 7 days if good response Half-life 4-6 hours Improvement in fever curve, CSS labs, clinical status expected in 1-3 days	CrCL<30mL/min, consider QOD dosing Not dialyzable	CBC w/diff, BUN, Cr, AST, ALT, ferritin, LDH, D-dimer, fibrinogen in 24-48 hours and then at least 2x/weekly Potential adverse reactions: anaphylaxis, neutropenia, eosinophilia, transaminitis, immunosuppression	Live vaccines Simultaneous treatment with more than one biologic medication is not recommended
Tocilizumab Severe or critical COVID-19 with evidence of CSS Elevated CRP and/or IL-6	NCT04310228 NCT04331795 NCT04320615	IV solution	<30 kg:12 mg/kg IV ≥30 kg: 8 mg/kg IV Max 800 mg Typically given as single dose May repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve Half-life in children up to 16 days	None	CBC w/diff, BUN, Cr, AST, ALT, ferritin, LDH, D-dimer, fibrinogen in 24-48 hours and then at least 2x/weekly Potential adverse reactions: anaphylaxis, neutropenia, thrombocytopenia, transaminitis, hyperlipidemia, immunosuppression, GI perforation CRP & IL-6 levels are no longer reliable measures of inflammation after tocilizumab treatment	Live vaccines Simultaneous treatment with more than one biologic medication is not recommended
Canakimumab		150-mg vial	5-8 mg/kg SQ Max 300 mg	None	CBC w/diff, BUN, Cr, AST, ALT, ferritin, LDH, D-	Live vaccines

Severe or critical COVID-19 with evidence of CSS Favorable response to anakinra with requirement for ongoing therapy			Typically given as single dose Half-life in children 23-26 days		dimer, fibrinogen in 24-48 hours and then at least 2x/weekly Potential adverse reactions: anaphylaxis, neutropenia, thrombocytopenia, eosinophilia, transaminitis, immunosuppression, vertigo	Simultaneous treatment with more than one biologic medication is not recommended

[1]For guidance on vaccination after IVIG, please refer to CDC recommendations: https://www.cdc.gov/vaccines/pubs/pinkbook/genrec.html

D. ADDITIONAL TREATMENT GUIDANCE

Table 5. Other Agents

Agent	Comment
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	There are hypothetical arguments for and against use. We do not recommend initiating these medications in patients with COVID-19. We do not recommend stopping them in patients already on therapy (unless they are hypotensive), per HFSA/ACC/AHA guidance.[1]
Azithromycin	Use of azithromycin in combination with hydroxychloroquine is strongly discouraged due to biological implausibility of azithromycin activity against SARS-CoV-2 and reports of additive toxicity as QTc-prolonging agents.[2]
Convalescent plasma	*Pediatric patients (<18 years):* Consider for critical COVID-19, particularly if no improvement with antiviral treatment. Available via Single Patient Emergency Investigational New Drug application to FDA,[3] which will be submitted by the ID service. Requires coordination with Dr. Steve Sloan, Blood Bank Medical Director. May be used concurrently with other COVID-19 therapies, including remdesivir. *Adult patients (≥18 years):* Consider for severe or critical COVID-19, particularly if no improvement with antiviral treatment. Available via enrollment in national Expanded Access Program,[4] which will be performed by the ID service. Requires coordination with Dr. Sloan. May be used concurrently with other COVID-19 therapies, including remdesivir.
Glucocorticoids	Do not use routinely for COVID-19 pneumonia except if treating another indication.[5] If required, use glucocorticoids at the lowest dose for the shortest duration. Possible indications include asthma, shock with history of chronic steroid use, or multi-pressor shock without history of chronic steroid use. The Society of Critical Care Medicine (SCCM) draft guidelines suggest using systemic corticosteroids for adults with COVID-19 and ARDS (weak recommendation, low-quality evidence).[6] Glucocorticoids are a potential option for treatment of COVID-19-associated cytokine storm syndrome or MIS-C with features of shock or coronary artery dilation/aneurysm (see Section C).
Hydroxychloroquine	We do not recommend use of hydroxychloroquine based on safety concerns due to potential COVID-19 cardiac involvement in children and adults.
NSAIDS	Concern has been raised that NSAIDs may worsen COVID-19 disease. As reflected in an FDA statement,[7] there is no evidence to support this concern. Patients on remdesivir therapy may not receive concomitant NSAIDS due to risk of nephrotoxicity.
Ribavirin	We do not recommend use of ribavirin for COVID-19 due to insufficient evidence of activity against SARS-CoV-2 and significant toxicity risk.

[1]HFSA/ACC/AHA guidance: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19

[2]See, for example: Chorin et al. *Nature Med* 2020 (https://www.nature.com/articles/s41591-020-0888-2) and Borba et al. *medRxiv* 2020 (https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2).

[3]Single Patient eIND for convalescent plasma: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
[4]COVID-19 Convalescent Plasma Expanded Access Program: https://www.uscovidplasma.org/
[5]WHO interim guidance: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
[6]Society of Critical Care Medicine draft guidelines: https://link.springer.com/article/10.1007/s00134-020-06022-5
[7]FDA statement on use of NSAIDs in COVID-19: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19

Suggested MIS-C Patient Management Guidelines, by Clinical Setting and Acuity

MIS-C

- CDC Definition
- Differential diagnosis
- Anti-inflammatory agents for MIS-C
- Symptom Clusters According to Age

Office

- Well appearing child

ED

- Well appearing child
- Toxic appearing child
- Triage
- BCH MIS-C Taskforce Members

Inpatient

- Acute care floor/Wards
- PICU Triage and Management
- Discharge criteria

Post-discharge

- Follow-up
  - Cardiology Outpatient follow-up
  - Rheumatology Outpatient follow-up
- Reporting
- References

Office

• Well appearing child

Fever ≥ 3 days, PLUS at least 2:

- GI symptoms (vomiting, diarrhea, abdominal pain)
- Upper or lower respiratory tract symptoms
- Rash (oral, hands, feet)
- Conjunctivitis/mucous membrane changes
- Headache, mental status changes
- Extremity changes (hand/foot swelling, erythema)
- Cervical LAD
- High potential for exposure or known COVID exposure within past 4-6 weeks

- Well appearing child
- Diagnosis unclear
- Quick turn-around lab

Initial Work-Up:

- CBCD
- CMP
- ESR
- CRP

- CRP <30 *and*
- ESR <40?
- ALC > 1000?
- Plts >150?
- Na >135?

YES → Home with f/u in 24-48h

NO → To ED if signs of inflammation

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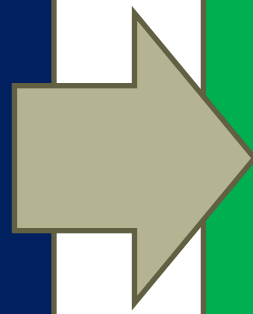
ED

• Well appearing child

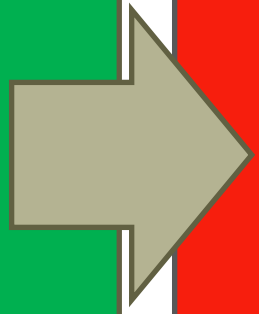
Fever ≥ 3 days, PLUS at least 2:

- GI symptoms (vomiting, diarrhea, abdominal pain)
- Upper or lower respiratory tract symptoms
- Rash (oral, hands, feet)
- Conjunctivitis/mucous membrane changes
- Headache, mental status changes
- Extremity changes (hand/foot swelling, erythema)
- Cervical LAD
- High potential for exposure or known COVID exposure within past 4-6 weeks



Primary Work-Up:

- CBCD**
- CMP**
- ESR*
- CRP*
- COVID PCR
- Blood culture
- Other testing as clinically indicated



*ESR and CRP should be primary determinates

**Clinician should use judgement with interpretation

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ED

• Well appearing child

Fever and ≥ 2 symptoms *PLUS*:

- ESR > 40*
- CRP > 30*
- Ancillary labs:**
  - ALC <1000
  - Platelets <150
  - Na <135

NO → Consider home with f/u in 24-48h??

YES →

Secondary Work-Up:

- D-dimer
- Troponin
- BNP
- PT/PTT
- Fibrinogen
- Ferritin
- SARS CoV Antibody (IgG)
- Cytokine Profile
- UA
- 12-lead EKG

→

- Transfer to hospital with or admit to pediatric COVID unit
- Obtain Peds ID consult
- Obtain Peds Rheumatology consult
- Consider Peds Cardiology consult if:
  - ↑ BNP, troponin
  - Abnormal EKG
- ECHO per cardiology

*ESR and CRP should be primary determinates
**Clinician should use judgement with interpretation

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ED

• Toxic appearing child

Fever ≥ 1 days, PLUS at least 2:

- GI symptoms (vomiting, diarrhea, abdominal pain)
- Upper or lower respiratory tract symptoms
- Rash (oral, hands, feet)
- Conjunctivitis/mucous membrane changes
- Headache, mental status changes
- Extremity changes (hand/foot swelling, erythema)
- Cervical LAD
- High potential for exposure or known COVID exposure within past 4-6 weeks
- Evidence of cardiac dysfunction, i.e. hypotension, shock

Work-Up:

- CBCD
- CMP
- ESR
- CRP
- PT/PTT/Fibrinogen
- D-dimer
- BNP
- Troponin
- Ferritin
- COVID PCR
- SARS CoV Antibody (IgG)
- Cytokine profile
- Blood culture, UA
- EKG
- STAT ECHO/POCUS
- Other testing as indicated

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- Resuscitate per 2020 Pediatric Surviving Sepsis Guidelines:
  - Recommend fluid boluses 10-20ml/kg of buffered IVF
  - Assess for fluid overload between boluses
  - Consider initiating epinephrine or norepinephrine[1] if abnormal perfusion after 40-60mL/kg
- Transfer or admit to hospital with PICU[2]

[1]Epinephrine (0.03-2 mcg/kg/min IV) recommended for cold shock and cardiogenic shock. Norepinephrine (0.05-2 mcg/kg/min IV) recommended for warm shock.

[2]Brenner Physician Access Line: 336-716-7654/800-277-7654

ED

• Triage

Consider direct admission to PICU if:

- Vasoactive infusion
- Active, ongoing fluid resuscitation
- Requiring positive pressure ventilation, including HFNC
- Obtundation
- Evidence of cardiac dysfunction
- Need for advanced hemodynamic monitoring
- Severe electrolyte or other lab derangement needing frequent monitoring
- Organ failure requiring frequent monitoring (> q4h) or intervention (e.g., AKI)

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ED

• BCH MIS-C Taskforce Members

You may contact us to discuss an MIS-C case, to help with reporting requirements, or to help facilitate testing/outpatient scheduling. To contact us, or to arrange for transport to Brenner Children's Hospital, call the Brenner Physician Access Line: 336-716-7654/800-277-7654.

- Dr. John Darby, Pediatric Hospitalist
- Dr. Cara Haberman, Pediatric Hospitalist
- Dr. Brandon Hays, Pediatric Cardiology
- Dr. Rima Jarrah, Pediatric Critical Care
- Dr. Chad McCalla, Pediatric Emergency Medicine
- Dr. Kacy Ramirez, Pediatric Infectious Disease
- Dr. Alysha Taxter, Pediatric Rheumatology

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Inpatient

• Acute care floor/Wards

Admit as PUI to unit with:

- COVID isolation
- Central telemetry

Pediatric Consultants

- Rheumatology
- Cardiology
- Infectious Disease*

*Consider such consults as indicated by level of suspicion, differential diagnoses and clinical presentation.

Monitoring

- Telemetry
- Consider daily EKGs while febrile
- Follow closely for clinical sign of progressive heart failure and/or fluid overload:
  - Edema
  - Hepatomegaly
  - Rales
  - ↑WOB/new O2 requirement

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Inpatient

• Acute care floor/Wards, cont'd

Treatment

- IVIG 2 gm/kg QD, once. Consider further dosing based on clinical response.
- Methylprednisolone 2mg/kg BID vs Pulse dosing (consult Pediatric Rheumatology)
- Consider anakinra (consult Pediatric Rheumatology)
- Consider antimicrobials:
  - Vancomycin
  - Clindamycin
  - Doxycycline
  - Metronidazole
- Consider ASA 81mg QD, unless platelets <80K if treating with IVIG, steroids
- Consider LMWH if coronary artery Z-score <10

Continue all medications in IV form until GI symptoms are resolved.

Serial Labs/Studies

- CBCd, CMP, ESR, CRP, Ferritin q24h until afebrile
- Troponin q24h unless initial abnl, then q4h until downtrending
- BNP q24 if abnl, space per Cardiology
- Trend any other initial abnl labs q24 with input from multidisciplinary team
- EKG q48h, at minimum, until discharge
- ECHO q24-48h until improving, and then as needed. If coronary artery changes noted, ECHO q2-3d until stable.
- **NOTE**: if see increase in inflammatory markers, recheck all initial labs, including BNP and Troponin.

Inpatient

• PICU Triage and Management

Consider direct admission to PICU if:

- Vasoactive infusion
- Active, ongoing fluid resuscitation
- Requiring positive pressure ventilation, including HFNC
- Obtundation
- Evidence of cardiac dysfunction
- Need for advanced hemodynamic monitoring
- Severe electrolyte or other lab derangement needing frequent monitoring
- Organ failure requiring frequent monitoring (> q4h) or intervention (e.g., AKI)

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Inpatient

• PICU Triage and Management

Admit to PICU as PUI with:

- COVID isolation
- VS per PICU routine

Pediatric Consultants*

- Rheumatology
- Cardiology
- Infectious Disease
- +/- Pediatric Surgery

*Consider such consults as indicated by level of suspicion, differential diagnoses and clinical presentation.

Assessment and Stabilization

- STAT Echocardiograph, if not done
- Placement of upper extremity, double lumen CVL
- STAT blood gas, lactate, cooximetry
- If low BP, consider
  - 10-20 ml/kg buffered IVF
  - Norepinephrine
  - Epinephrine
  - Milrinone

Consider:

- CVP monitoring
- Arterial line for NIBP, labs
- HFNC/NIMV
- Intubation/CMV
- V-A ECMO, peripheral cannulation

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Inpatient

• PICU Triage and Management

Treatment

- IVIG 2 gm/kg QD, once. Consider further dosing based on clinical response.
- Methylprednisolone 2mg/kg BID vs Pulse dosing (consult Pediatric Rheumatology)
- ASA 81mg QD, unless platelets <80K
- Consider LMWH if coronary artery Z-score <10
- IV Gastritis ppx
- Consider Anakinra with Pediatric Rheumatology input
- With Peds ID input, consider antimicrobials:
  - Vancomycin
  - Clindamycin
  - Doxycycline
  - Metronidazole

Continue all medications in IV form until GI symptoms are resolved.

Serial Lab/Studies

- CBCd, CMP, ESR, CRP, Ferritin at least q24h
- BNP q24h.
- Troponin q24h unless initial abnl, then q4h until downtrending, then space to q24h.
- Trend any other initial abnl labs q24 with input from multidisciplinary team
- ECHO q24-48h until improving, and then as needed. If coronary artery changes noted, ECHO q2-3d until stable.
- EKG q24 if abnl, then q48h
- **NOTE**: if see increase in inflammatory markers, recheck all initial labs, including BNP and Troponin.

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Inpatient

• Discharge Criteria

- Afebrile x48-72h
- Inflammatory markers downtrending x 72h
- Cardiac function improved and stable. Continue checking these throughout hospitalization, even in recovery, b/c of risk of relapse.
- GI function normalized, able to tolerate enteral feeds and absorb medications
- Resolution of severe organ dysfunction

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Post-discharge

•Follow-up

Outpatient Appointments

- Pediatric Rheumatology
- Pediatric Cardiology
  - Unclear who is at risk for coronary artery aneurysms, thus should treat all MIS-C patients similar to KD patients from a cardiac perspective
- Pediatric Infectious Disease
- Others

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Post-discharge

•Cardiology Outpatient Follow-up

Every MIS-C patient will require:

- Low dose ASA until 6 week appointment/6 weeks after initiation
- If EF is <35%, consider LMWH for two weeks post-discharge, with guidance of hematology/cardiology
- ECG and ECHO at 2 weeks & 6 weeks post-IVIG

Other considerations

- Cardiac MRI
  - at 2-6 mo if EF <50%
  - consider earlier in patients with elevated troponin
- Stress test
  - If myocarditis/elevated troponins, follow myocarditis guidelines with activity restrictions for 3-6 mo and stress testing prior to returning to full activities
- Consider more frequent long-term follow up with ECG and echo at least 3, 6 mos, 1 year

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Post-discharge

•Rheumatology Outpatient Follow-up

- Follow-up appointment with pediatric rheumatology 1-2 weeks
- Prior to discharge, rheumatologist will coordinate tapering of steroids, anakinra and determine type and timing of outpatient labs to follow.

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CDC Definition MIS-C

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, 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 exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
**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

Additional comments:

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

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Differential Diagnosis

- Includes, but not limited to, and may overlap with:
  - Kawasaki Disease/Kawasaki Shock Syndrome
  - Toxic Shock Syndrome
    - Staphylococcal
    - Streptococcal
  - Rocky Mountain Spotted Fever or other Rickettsial infections
  - Hemophagocytic lymphohistiocytosis (HLH)/ Macrophage Activating Syndrome (MAS)
  - Myocarditis
  - Bacterial or viral infection/sepsis
  - Rheumatologic disease

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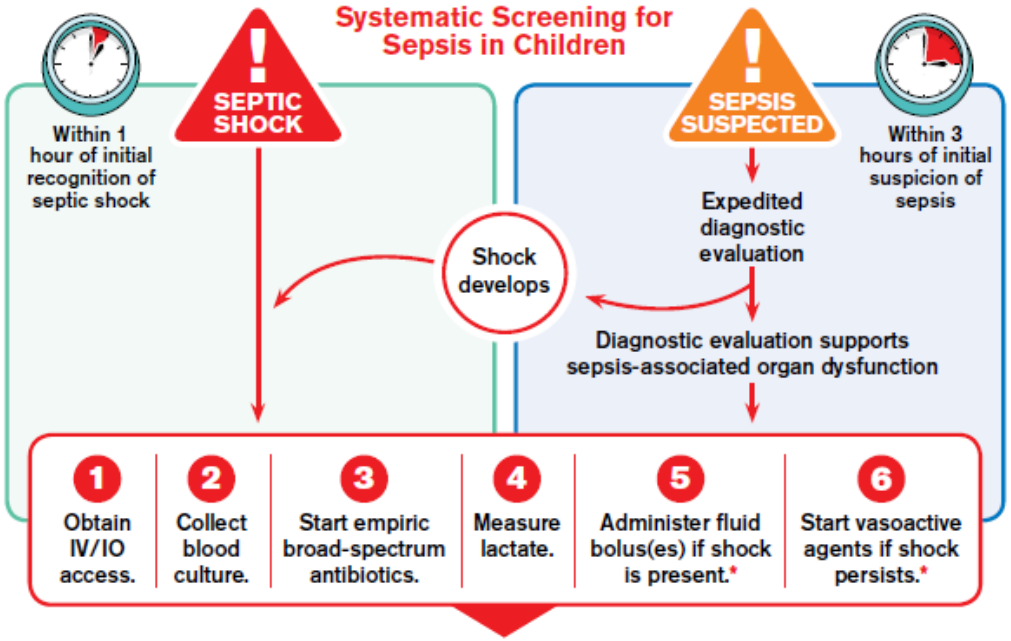
Initial Resuscitation Algorithm for Children

Surviving Sepsis Campaign



Respiratory support

Assess for Pediatric Acute Respiratory Distress Syndrome

Infectious source control — Continuous reassessment — Fluid and vasoactive titration*

Advanced hemodynamic monitoring if shock persists

- +/- hydrocortisone for refractory shock**
- Nutritional support
- Avoid hypoglycemia
- Antimicrobial stewardship

VA or VV ECLS for refractory shock or oxygenation/ventilation failure (after addressing other causes of shock and respiratory failure)

*See fluid and vasoactive algorithm. Note: Fluid bolus should be omitted from bundle if a) fluid overload is present or b) it is a low-resource setting without hypotension. Fluid in mL/kg should be dosed as ideal body weight.

**Hydrocortisone may produce benefit or harm.

www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients

Society of Critical Care Medicine

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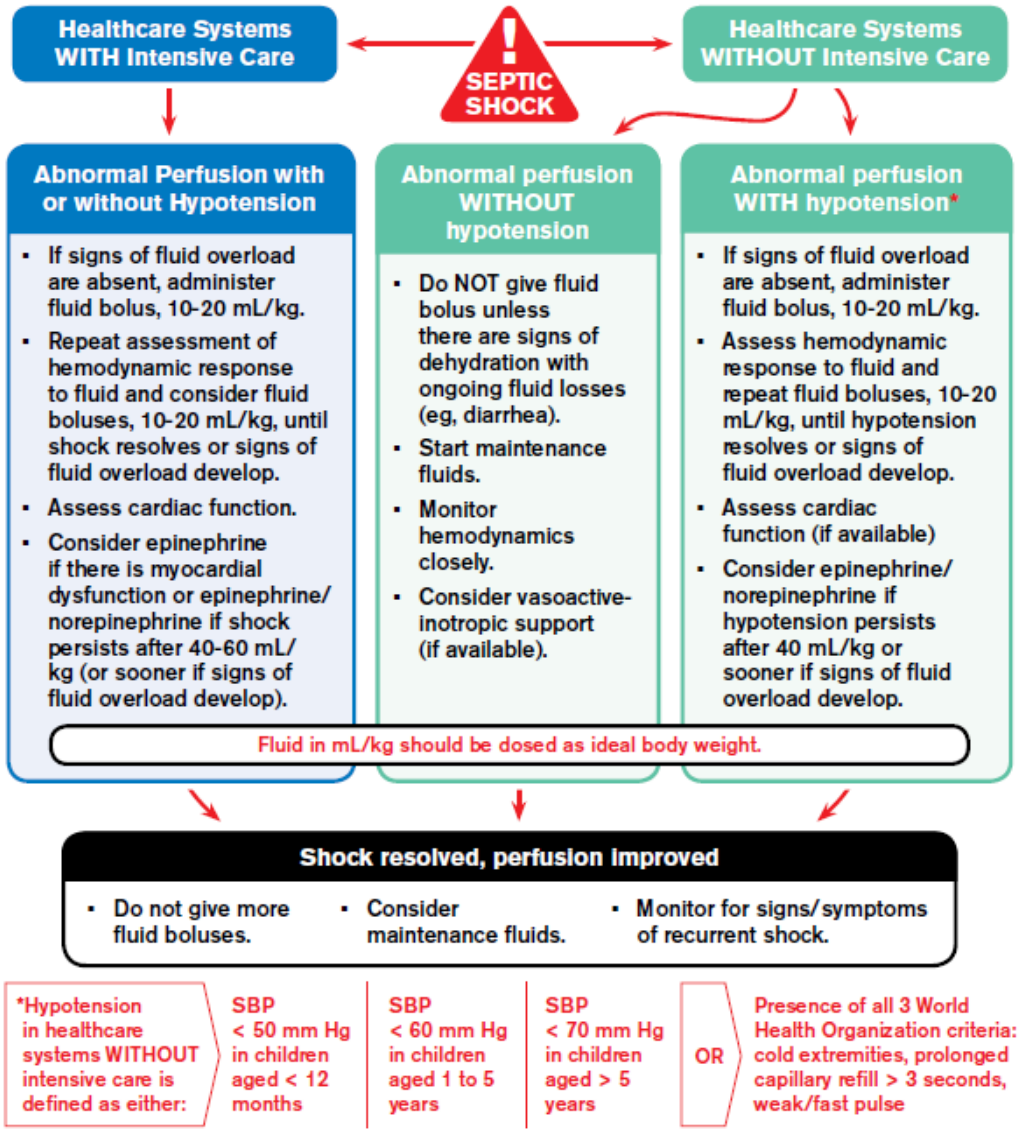
Fluid and Vasoactive-Inotrope Management Algorithm For Children

Surviving Sepsis Campaign



*Hypotension in healthcare systems WITHOUT intensive care is defined as either:

- SBP < 50 mm Hg in children aged < 12 months
- SBP < 60 mm Hg in children aged 1 to 5 years
- SBP < 70 mm Hg in children aged > 5 years

OR

- Presence of all 3 World Health Organization criteria: cold extremities, prolonged capillary refill > 3 seconds, weak/fast pulse

www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients

Society of Critical Care Medicine

Anti-Inflammatory Agents being Used for MIS-C

Intervention	Biology	Experience in hyperinflammation	When to start in MIS-C
Glucocorticoids (≤2 mg/kg/day)	Transcriptional regulation via glucocorticoid receptor	Mainstay of treatment	Early
Glucocorticoids (>250 mg/day)	Transcriptional regulation via glucocorticoid receptor	Commonly used during initiation	If low concern for infection and nonresponsive to treatment
IVIG	Unclear mechanism	Case reports	Early
Anakinra	Block IL-1 signal	Sepsis trials, MAS, HLH, sJIA	If elevated ferritin, concern for MAS, unclear etiology (infection vs MIS-C)
Tocilizumab	Block IL-6 signal	CAR-T CRS, sJIA	If nonresponsive to treatment

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Adapted from Henderson 2020

Symptom Clusters According to Age, NY State data

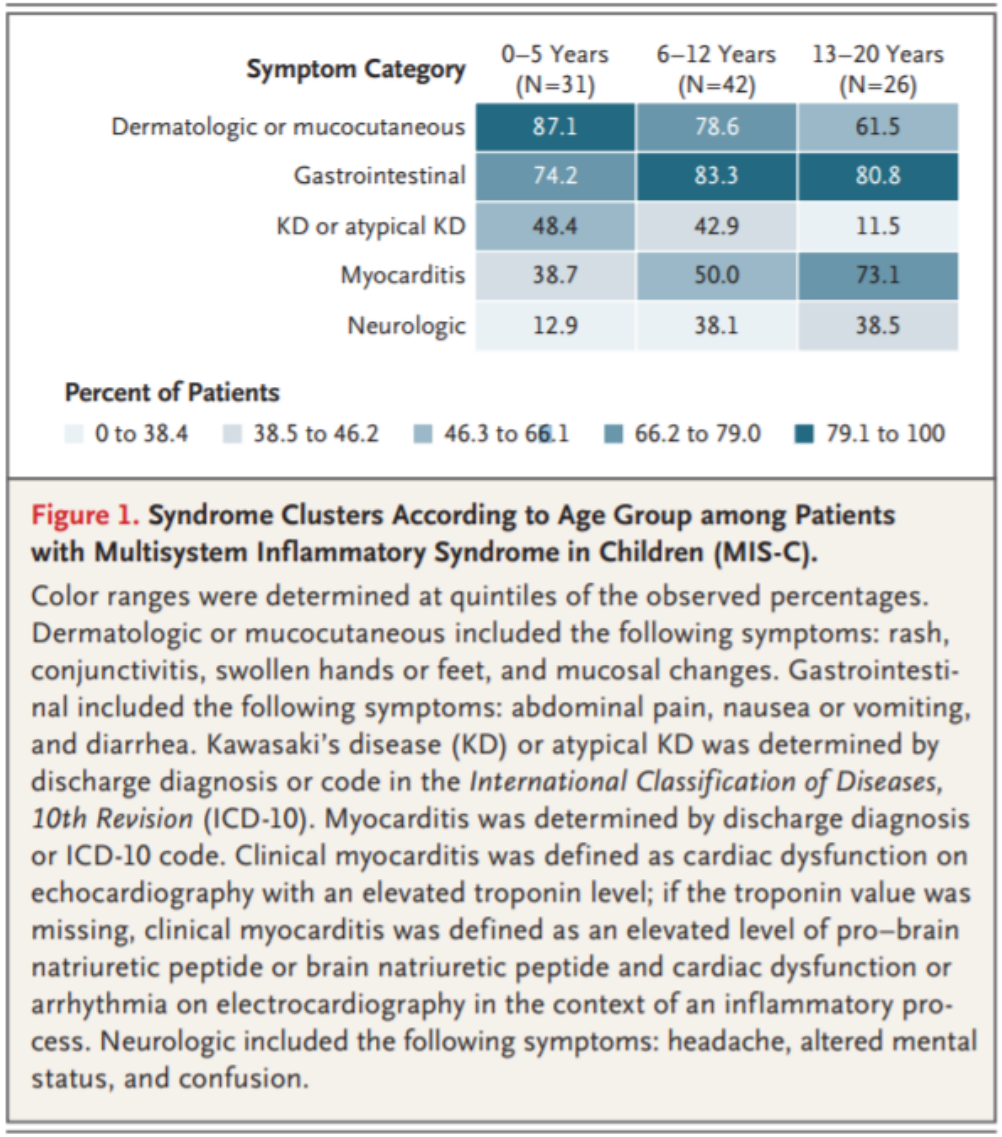

Figure 1. Syndrome Clusters According to Age Group among Patients with Multisystem Inflammatory Syndrome in Children (MIS-C).

Color ranges were determined at quintiles of the observed percentages. Dermatologic or mucocutaneous included the following symptoms: rash, conjunctivitis, swollen hands or feet, and mucosal changes. Gastrointestinal included the following symptoms: abdominal pain, nausea or vomiting, and diarrhea. Kawasaki's disease (KD) or atypical KD was determined by discharge diagnosis or code in the *International Classification of Diseases, 10th Revision* (ICD-10). Myocarditis was determined by discharge diagnosis or ICD-10 code. Clinical myocarditis was defined as cardiac dysfunction on echocardiography with an elevated troponin level; if the troponin value was missing, clinical myocarditis was defined as an elevated level of pro–brain natriuretic peptide or brain natriuretic peptide and cardiac dysfunction or arrhythmia on electrocardiography in the context of an inflammatory process. Neurologic included the following symptoms: headache, altered mental status, and confusion.

From Dufort EM et al, Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020;383:347-58.

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Reporting

According to the CDC, cases of MIS-C should be reported to local, state or territorial health departments:

- Instructions for MIS-C case report forms can be found at: : https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-instructions.pdf
- Electronic case report forms can be found at: https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-fillable.pdf

Several registries and studies are collecting data about MIS-C patients:

- World Health Organization
  - Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19
  - WHO Case report form: L'IV version 16-05-20
- The BEST Study
  - https://bestavailabletreatmentstudy.co.uk/wp-content/uploads/2020/06/Best-available-trThe BEST Studyeatment-for-paediatric-inflammatory-syndromes-associate-with-SARS_AC_ML_AC-1.pdf

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June 8, 2020 v2

Children's Healthcare of Atlanta

Emergency Department
Recommended ED Workflow for suspicion of
Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2
For ages 6 months to 21 years

Fever ≥ 3 day (subjective or ≥ 38.0°C/100.4°F)

No → Off Algorithm

Hypotension?

Yes → Initiate **ED Septic Shock guideline**
Use fluids judiciously
Assess for crackles, hepatomegaly after each bolus
Prep early for pressors if poor response to first bolus
Start **10-20 cc/kg** bolus NS

No

Gastrointestinal
- Diarrhea, abdominal pain, vomiting

Ophthalmologic
- Bulbar conjunctival injection without exudate

Dermatologic
- Erythema or edema of hands and feet
- Non vesicular rash
  - Maculopapular or polymorphic rash
  - Petechial rash

Oral Mucosa
- Erythematous, dry cracked or fissured lips
- Erythema of oral and pharyngeal mucosa
- Strawberry tongue

Lymphadenopathy
- Cervical, unilateral, > 1.5cm

Neurologic
- Headache, irritability, confusion/AMS

Other
- Edema: hands and feet, generalized, or periorbital

Consider Extended MIS-C workup
CBC, CMP, ESR, CRP, UA, [do not repeat if ED Screen done]
EKG, Troponin, BNP, if Trop/BNP abnormal→ ECHO in ER
DIC panel, Blood Culture, UA, Urine culture,
Consult Cardiology for abnormal cardiac workup
(Including refractory tachycardia, abnormal BNP, Trop, EKG, Echo)
Consider Admission for abnormal extended work up if no other plausible etiology is likely

≥ 2 clinical features → **Initiate ED Lab Screen:**
CBC, CMP, ESR, CRP, clean catch UA

ED Screen Positive if:
ESR > 40 or CRP > 3 (CRP>30 at HS ER)
AND
Any two supplemental findings
- Absolute Lymphocyte Count < 1000
- Platelets < 150
- Sodium < 135
- Elevated AST/ALT
- Elevated creatinine
- Albumin < 3
- UA WBC > 10
- Tachycardia refractory to initial bolus, pain/fever control & calming measures

Screen positive → Consider Extended MIS-C workup

< 2 clinical features

Screen negative

Discharge home if
- Tolerates fluid intake
- Reassuring vital signs & exam
- In person PCP follow up in 24 hours with full vitals with BP; advise regular follow up with PCP until fever subsides

ED MISC Screen is negative at this time
Return to ED care as appropriate

Inpatient Guide for Multisystem Inflammatory Syndrome in Children (MIS-C)

Required:
- Fever (T>38°C/100.4° for ≥ 3 days)

And ≥ 2 Clinical Symptoms
- Gastrointestinal: Diarrhea, abdominal pain, vomiting
- Ophthalmologic: Bulbar conjunctival injection without exudate
- Dermatologic: Erythema or edema of hands and feet, non vesicular rash (maculopapular, polymorphic, or petechial rash)
- Oral Mucosa: Erythematous dry cracked or fissured lips, erythema or oral and pharyngeal mucosa, strawberry tongue
- Lymphadenopathy: Cervical, unilateral, > 1.5 cm
- Neurologic: Headache, irritability, confusion/alteration mental status
- Other: Generalized edema, periorbital edema

Initial MIS-C Screening Labs

- CBC/diff
- CMP
- CRP
- ESR
- Urinalysis without reflex to culture

Extended MIS-C Workup

- Coronavirus SARS-CoV-2 ORF1ab+S RT-PCR
- Coronavirus SARS-CoV-2 IgG
- DIC Screen
- Ferritin
- Blood culture
- Urinalysis with reflex to culture
- BNP
- Troponin intact
- EKG

If BNP or Troponin is abnormal

- Echocardiogram
- Cardiology Consult

Management

Consultants

- **Infectious disease** Considering treatment for MIS-C
- **Hematology** Anticoagulation
- **Rheumatology** Refractory to IVIG
- **Cardiology** Abnormal BNP, Troponin, EKG, or Echo, all confirmed MIS-C diagnosis

Lab Monitoring

Daily
- CRP
- Ferritin
- CBC
- CMP
- BNP
- Troponin

If BNP or Troponin is trending upward

- Repeat Echocardiogram

1 First Line Therapy

IVIG: 1-2 g/kg X1

Prior To IVIG obtain the following labs *(listed in prioritized order)
- NGAL urine
- Cytokine Panel
- Soluble IL-2R
- Save Specimen (2 redtop tubes)
- ANA IgG with reflex titer and Ab ID

Anticoagulation

Aspirin chewable tablet
- Recommended 3-5 mg/kg daily [Max 325 mg]

Lovenox

Patient < 2 mo:
- 0.75 mg/kg, SubQ, BID

Patient > 2 mo and < 60 kg:
- 0.5 mg/kg SubQ, BID

Patients > 60 kg:
- 30 mg, SubQ, BID OR 40 mg SubQ Daily

Hold Lovenox if known personal or family history of bleeding disorder, platelet count < 20K, invasive procedure planning within 12 hours, active bleeding

2 Second Line Therapy

If continued fever 24 hours after IVIG

Steroids
- 2 mg/kg/day divided BID X 5 days (max of 60 mg)

Followed by
- *1 mg/kg/day for up to 5 days-then stop*

3 Third Line Therapies

Consult Rheumatology

If continued fever 24 hours after IVIG and Steroids

- Tocilizumab
- Actemra
- Anakinra

Multisystem Inflammatory Syndrome in Children (MIS-C): Clinical Guide for ID providers

Table of Contents

Summary of Rationale for Document

In the wake of the global pandemic related to infection with SARS-CoV-2 leading to widespread COVID-19 disease, pediatric patients have overall demonstrated less severe clinical manifestations with decreased incidences of admissions to the intensive care unit and death. However, recently, pediatric hospitals in Europe and North America have reported an increase in cases of children presenting with gastrointestinal symptoms, prolonged fever, hemodynamic instability, high inflammatory markers and evidence of impairment or injury of one or more organ systems. These patients have had clinical and laboratory features that overlap with other inflammatory conditions including Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Signs and symptoms that have been reported include rash, bilateral non-purulent conjunctivitis, and evidence of coronary artery dilation and aneurysms resembling Kawasaki disease. Further, other patients have developed shock that is phenotypically similar to toxic shock syndrome as well as cardiac dysfunction.

This syndrome is currently known by various names, including, “Pediatric Multisystem Inflammatory Syndrome,” “Pediatric Inflammatory Multisystem Syndrome,” “Pediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19," “Pediatric Multisystem Inflammatory Syndrome Potentially Associated with COVID-19,” and “Multisystem Inflammatory Syndrome in Children (MIS-C).”

In terms of the epidemiology, these cases have presented during the pandemic in areas of high incidence of COVID-19, and these cases usually occur several weeks following the COVID-19 peak in the geographic location. Given the emergence of these clinical cases, the severity of associated illness, and the recent plateau of COVID-19 cases in Colorado, we propose a guideline for recognition of suspected cases that includes laboratory and radiographic evaluation, and treatment. Some of these patients may warrant close monitoring or admission to the pediatric intensive care unit as well as input from subspecialists including pediatric infectious diseases, cardiology, and rheumatology.

This syndrome is newly emerging, so recommendations in this document may change as more evidence for evaluation studies, laboratory monitoring, and treatment emerge. Please ensure that you are using the most updated clinical guidance document related to MIS-C. We expect that there will be a broad spectrum of clinical disease described as this syndrome is more fully elucidated. In order to ensure consistency across the ID section with regards to recommendations for clinical evaluation, laboratory and radiographic studies, and treatment for both inpatients and outpatients.

Case definition

CONFIRMED CASES CHCO:

NOTE: This is a definition that has been compiled from the various case definitions in an attempt to capture the appropriate patient population. Other active case definitions listed below.

Children and adolescents <21 years of age with **FEVER** ≥ 3 days **AND**
TWO of the following: 1. Rash or bilateral non-purulent conjunctivitis or signs of mucocutaneous inflammation (erythema and/or swelling of hands and feet, strawberry tongue, red lips) 2. Acute gastrointestinal problems (diarrhea, vomiting, and/or abdominal pain 3. Hypotension or shock 4. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities (including echocardiogram findings or elevated troponin or NT-pro BNP 5. Evidence of coagulopathy (by PT, PTT, elevated D-dimer)
AND elevated markers of inflammation • 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
AND no other obvious microbial cause of inflammation including bacterial sepsis, local bacterial infection (e.g. urinary tract infection, osteomyelitis, etc.), or staphylococcal and streptococcal toxic shock syndromes
AND evidence of COVID-19 (RT-PCR positive, positive serologies) **OR** likely contact with patients with COVID-19

OTHER POSSIBLE CLINICAL SIGNS AND SYMPTOMS

Systemic Inflammation: • Fever >38.5°C • Myalgias • Hypotension (systolic blood pressure ≤90 mm Hg for adults or less than the fifth percentile by age for children aged less than 16 years) • Hypoperfusion or hyper-perfusion • Lymphadenopathy, lymphadenitis Gastrointestinal • Abdominal pain • Vomiting • Diarrhea • Hepatic or splenic enlargement Cardiopulmonary • Respiratory distress • Chest pain • Syncope • Tachycardia • Arrhythmia	Renal: • Evidence of acute kidney injury Hematologic: • Evidence of unprovoked thromboses Musculoskeletal: • Swollen hands and feet Mucocutaneous: • Rash (polymorphous exanthem, erythroderma, erythematous macules and/or papules) • Bilateral non-purulent conjunctivitis • Mucous membrane changes (erythematous mucous membranes, strawberry tongue) • Peeling of skin Neurologic • Headache • Altered mental status/confusion • Disorientation or alterations in consciousness when fever and hypotension are absent

CASE DEFINITIONS FROM OTHER ORGANIZATIONS

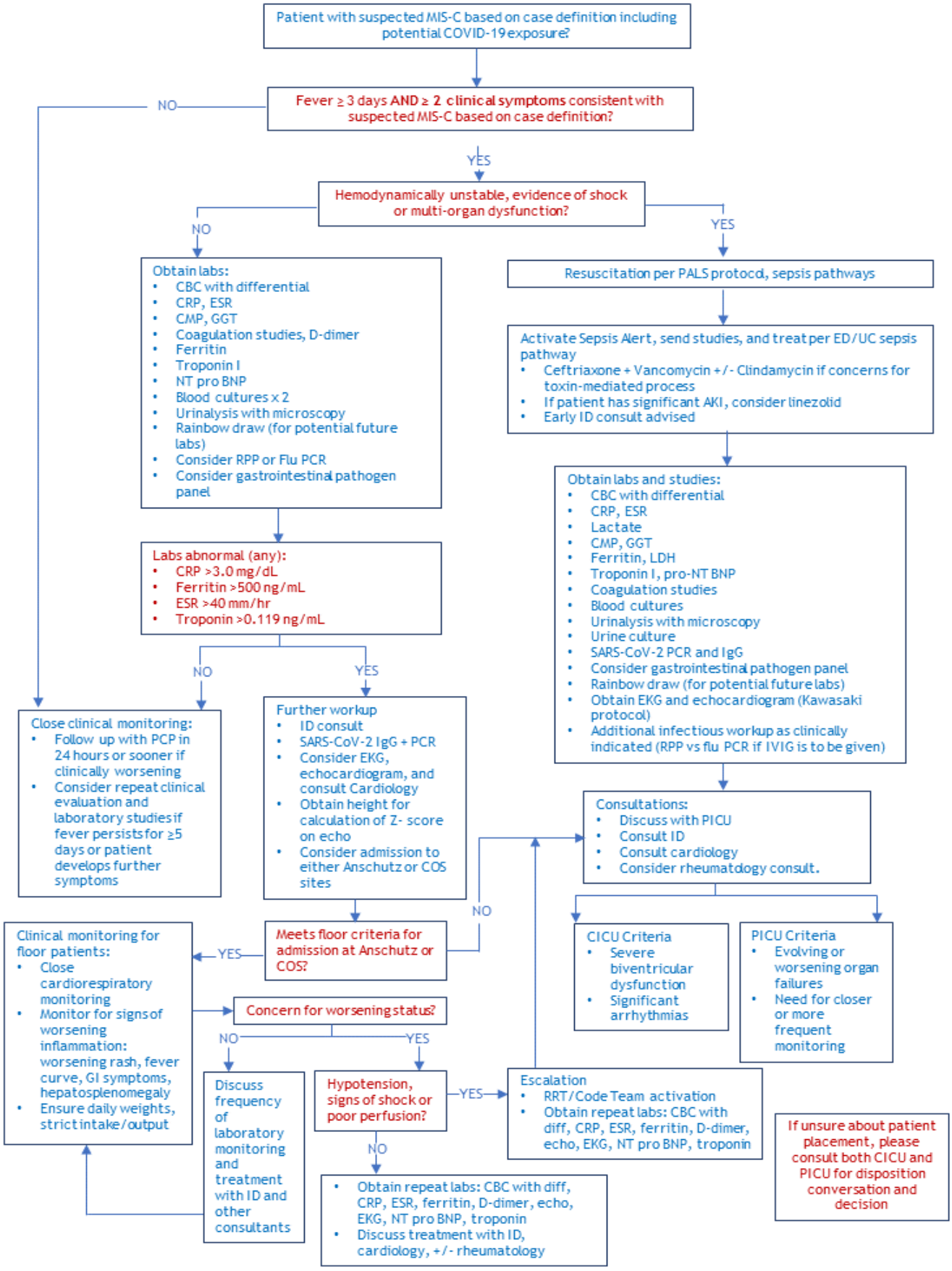
Category	Royal College of Paediatrics and Chlld Health	New York State Department of Public Health	Centers for Disease Control	World Health Organization
Name	Paediatric multisystem inflammatory syndrome temporally associated with COVID-19	Pediatric multi-system inflammatory syndrome temporally associated with COVID-19 Interim Case definition in New York state	Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)	Multisystem inflammatory syndrome in children and adolescents with COVID-19
Release date	5/1/2020	5/13/20	5/14/2020	5/15/2020
Age	"child"	<21 years	<21 years	0-19
Fever	Persistent fever >38.5ºC	A minimum one-day history of subjective OR objective fever ≥ 100.4ºF/38.0ºC **AND**	Fever >38.0ºC for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours **AND**	Fever ≥ 3 days **AND**
Clinical findings	Single or multi-organ dysfunction (shock, cardiac, respiratory, renal, GI or neurological disorder) *See resource for more details*	Hospitalization **AND** **Either**: ONE or more of the following: - Hypotension or shock (cardiogenic or vasogenic) - Features of severe cardiac illness** - Other severe end-organ involvement including but not limited to neurological or renal disease (excluding severe respiratory disease alone) **OR** TWO or more of the following: - Maculopapular rash - Bilateral non-purulent conjunctivitis - Acute GI symptoms (diarrhea, vomiting, or abdominal pain) **AND**	Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) **AND**	TWO of the following: 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities (including echo findings, elevated troponin/NT-proBNP) 4. Acute GI problems (diarrhea, vomiting, or abdominal pain) **AND**
Evidence of inflammation	Inflammation (neutrophilia, elevated CRP and lymphopenia)	***General Laboratory Criteria*: Two** or more of the following markers of inflammation: - Neutrophilia, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, D-Dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6 (IL-6), OR elevated procalcitonin	Laboratory evidence of inflammation 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 **AND**	Elevated markers of inflammation such as ESR, CRP, or PCT **AND**
Evidence of SARS-CoV-2 infection	SARS-CoV-2 PCR testing may be positive or negative	***Virologic Laboratory Criteria*: One** of the following SARS-CoV-2 laboratory results - Detection of SARS-CoV-2 RNA or antigen in a clinical specimen, at the time of presentation with this clinical picture or within the prior 4 weeks. - Detection of SARS-CoV-2 antibody ***Epidemiologic Criteria*** One or more of the following exposures in the 6 weeks prior to the onset of symptoms: - Close contact with an individual with laboratory-	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	Evidence of COVID-19 (RT-PCR, antigen test, or serology test positive) or likely contact with patients with COVID-19 **AND**

		confirmed SARS-CoV-2 infection - Close contact with an individual with illness clinically compatible with COVID-19 disease who had close contact with an individual with laboratory-confirmed SARS-CoV-2 infection. - Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2.		
Exclusion of other microbial cause	Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).	The absence of a more likely diagnosis of the illness (e.g. bacterial sepsis or other viral infection)	No alternative plausible diagnoses	No other obvious microbial cause of inflammation including bacterial sepsis, staphylococcal or streptococcal shock syndromes
Relation to KD	May include children fulfilling full or partial criteria for KD.	Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C		
Special notes:		**Case classifications**: *Confirmed*: Meets clinical, general laboratory, and virologic laboratory criteria *Suspect*: Meets clinical, general laboratory, and epidemiologic criteria	Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection	
Reference	https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19	https://health.ny.gov/press/releases/2020/docs/2020-05-13_health_advisory.pdf	https://emergency.cdc.gov/han/2020/han00432.asp	https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

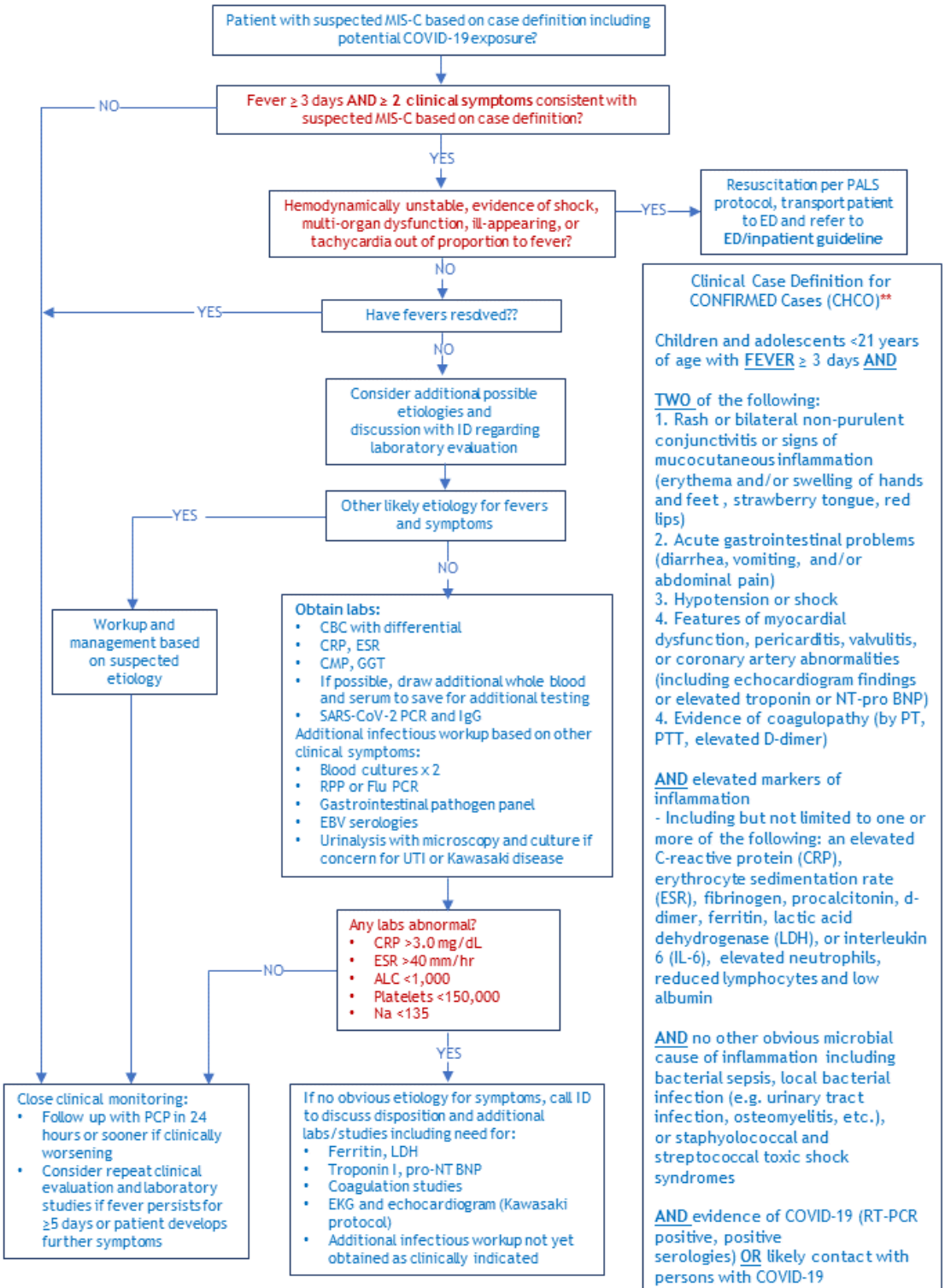
****** Severe cardiac illness: including but not limited to myocarditis, pericarditis, or valvulitis, significantly elevated troponin/pro-BNP, or coronary artery abnormalities

Algorithm for SUSPECTED Cases:

ED/Inpatient



ED/Inpatient



Consultation with subspecialty providers:

CONSULTS:

Critical Care Medicine:

- Early discussions regarding need for critical care management and monitoring for patients with concern of hypotension, poor perfusion, or multi-organ failure.

Infectious Diseases:

- Contact with suspicion of this entity for recommendations regarding additional laboratory workup, interpretation of clinical and laboratory findings to help diagnose and differentiate Pediatric Multisystem Inflammatory Syndrome versus Kawasaki Disease versus Toxic Shock syndrome versus COVID-19 infection. Will provide recommendations for management of antimicrobials, use of IVIG, use of infliximab, and laboratory monitoring. Will also facilitate reporting to appropriate state and national public health entities.
- Very young children (those less than 7 months old) can have KD without the usual signs/symptoms. We recommend discussing all of these very young, inflamed children (without a known source) with Infectious Disease to determine the diagnosis and optimal therapy.

Cardiology:

- Myocarditis (as evidenced by any apparent low/depressed ventricular function, pericardial effusion, unusual tachycardia, arrhythmia, other ECG findings, and/or troponin leak), hypotension associated with decompensated cardiogenic shock, coronary artery dilation or aneurysms, coronary artery thrombus, and significant arrhythmia, please **consult cardiology**.
- Specific inotropic support to be determined by the attending intensivist. Consideration for ECMO support as a bridge to recovery should be considered early in patients with shock with or without fulminant myocarditis. Patient with coronary artery thrombus within 72 hours will need coronary artery thrombolysis (follow the thrombolysis guideline established in the cardiac catheterization laboratory).

Rheumatology:

- Consideration for escalation to immunomodulatory therapy including anakinra and corticosteroids

Infectious Diseases Work-up Recommendations:

OVERALL RECOMMENDATIONS:

1. Providers are recommended to discuss cases early with consultants including Critical Care, Infectious Diseases, Cardiology, Rheumatology.
2. Refer to Epidemiology Alert for policy on management of COVID-19 or suspected COVID-19.
    a. Isolation precautions
    b. It is under M and then scroll down to:
    c. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)
3. Discuss initial antibiotic management pending clinical symptoms and consider substitute for vancomycin if patient has evidence of AKI.
4. Encourage provider to take full COVID-19 exposure history (".COVIDEXPOSURE" SmartText available to all ED, hospital medicine, PICU, CCBD, NICU providers)
    - International travel in the 14 days prior to symptom onset? {YES-DESCRIBE/NO/UNKNOWN}
    - Domestic travel in the 14 days prior to symptom onset? {YES-DESCRIBE/NO/UNKNOWN}
    - Contact with family member with laboratory confirmed COVID-19? {YES-DESCRIBE/NO/UNKNOWN}
    - Symptomatic household contact with fever or respiratory symptoms in the last 21 days? {YES/NO/UNKNOWN}
        - If yes, describe who: ***
    - Interval (in days) between onset of symptoms in the contact and the patient: ***
    - Community contact with laboratory confirmed COVID-19? {YES-DESCRIBE/NO/UNKNOWN}
    - Personal occupational risk factor? {Healthcare worker/first-responder/grocery employee/public transit employee/postal worker/other essential worker}
    - Household contact occupational risk factor? Healthcare worker/first-responder/grocery employee/public transit employee/postal worker/other essential worker}
    - Healthcare exposure: {Inpatient or outpatient visit in last 14 days prior to symptom onset/Actively receives home health care or nursing care/Resident of long-term care facility}
    - Social gathering (>10 people) in 14 days prior to symptom onset {YES-DESCRIBE/NO/UNKNOWN}
    - Other known community exposure: {YES-DESCRIBE/NO/UNKNOWN}
    - Household size (including the patient): ***
    - School or daycare in the 14 days prior to symptom onset: {YES-DESCRIBE/NO/UNKNOWN}

ID-SPECIFIC RECOMMENDATIONS:

1. At this time would still consider MIS-C a relative diagnosis of exclusion, so would continue to recommend additional infectious workup or consultation with rheumatology as we would pre-COVID-19.
2. **Please ensure to take exposure history for potential infectious diseases risk factors including COVID-19 exposures.**

	Fever <3 days, no MIS-C symptoms	**Fever >3 days, no MIS-C symptoms**	**Fever > 3 days + MIS-C symptoms, stable**	**Unstable Fever + MIS-C symptoms**	**"Burned out" illness**
Clinical description	Patient is well-appearing, +/- localizing symptoms	Patient is well-appearing, +/- localizing symptoms	Patient with signs and symptoms consistent with MIS-C including abdominal pain, fever, mucocutaneous inflammation	Patient with signs/symptoms of shock (hypotension, poor perfusion), altered mental status when afebrile	fevers for 3-10 days, previous symptoms, well, now afebrile
Initial lab work	None	- CRP - Rainbow top draw: consider more complete evaluation if patient has known exposure to SARS-CoV-2 or close contact with known COVID-19 patients. - Save and freeze	KD workup + ferritin + troponin - CRP, ESR - CBC with differential - CMP, GGT - UA with micro - Ferritin - Troponin - NT prop BNP - Save and freeze - Consider cytokine panel	- CRP, ESR - CBC with differential - CMP, GGT - UA with micro - Ferritin, LDH - Troponin, pro NT - Coagulation studies, D-dimer - Fibrinogen - Save and freeze - Consider cytokine panel	- CRP, ESR - CBC with differential - SARS-CoV-2 IgG - Consider SARS-CoV-2 PCR - Can repeat if this has been done earlier in the illness
Infectious Diseases workup	None	- Consider SARS-CoV-2 PCR - Consider RPP, GIP if symptoms are consistent - Consider additional ID workup based on inflammatory markers	- SARS-CoV-2 PCR + IgG (if diagnosed with MIS-C) - Consider blood cultures, urine cultures - Consider RPP to evaluate for influenza if plan to give aspirin - GIP if symptoms are consistent - Consider LP if signs/symptoms of meningitis or encephalitis - Serology/PCR for other causes of systemic inflammation based on history and physical (see ID testing below) #	- Blood cultures x 2 - Urine culture - SARS-CoV-2 PCR, IgG - Consider RPP, GIP - Consider LP if signs/symptoms of meningitis or encephalitis - Serology/PCR for other causes of systemic inflammation based on history and physical (see ID testing below) #	- If afebrile and no signs of inflammation, may not require workup - If ongoing signs of inflammation, should be seen by ID with additional workup per history including exposures.
Imaging recommendations	None	- Guided by history and presence of localizing symptoms	**KD Echocardiogram**: If patient has signs or symptoms of inflammation or syndrome that could be consistent with KD or MIS-C **Abdominal u/s**: if significant abdominal complaints **U/s extremities**: if signs of DVT **Consider CT chest/PE:** if dyspnea or chest pain	**KD Echocardiogram**: If patient has signs or symptoms of inflammation or syndrome that could be consistent with KD or MIS-C **EKG** **Abdominal u/s**: if significant abdominal complaints **U/s extremities**: if signs of DVT **CT chest/PE:** if dyspnea or chest pain	**KD Echocardiogram:** if patient has history of fever and signs and symptoms consistent with either KD or MIS-C, can be done as an outpatient within a few days (must be afebrile).
Treatment	Supportive care	Supportive care	- If KD (complete/incomplete) treat with IVIG + ASA +/- infliximab depending on presence of coronary artery lesions	- Empiric antibiotics per sepsis pathway. - If concern for TSS: IVIG, ceftriaxone, vancomycin + clindamycin (versus linezolid or ceftaroline if AKI present)	- If patient continues to have signs of inflammation, treatment with IVIG is warranted. - If coronary artery abnormalities

			- If concerns for bacterial infection, antibiotics per typical recommendations - If patient fulfills criteria for MIS-C, treat with IVIG and monitor (ensure strict Is/Os)	- If concern for tickborne illness, add doxycycline - If concern for KD shock, IVIG +/- infliximab, ASA - For MIS-C: IVIG + infliximab (if coronary artery lesions present), ASA, +/- anakinra pending response to initial therapy - Discuss steroids with rheumatology/cardiology	identified, admission for IVIG and infliximab is recommended
Disposition	Recommend follow up if fevers continue or additional symptoms develop	Recommend follow up if fevers continue or additional symptoms develop	Recommend admission for close clinical monitoring and additional workup as we would for other children with fever and high inflammatory markers	Recommend admission to the PICU if SARS-CoV-2 PCR positive, and recommend discussion between the CICU and the PICU if the patient has a negative PCR and signs of cardiac dysfunction.	Potential admission if signs of inflammation, ongoing fevers, or coronary artery lesions.
Follow up	With PCP if fevers continue	With PCP if fevers continue	- If treated for KD with coronary artery lesions, follow up in KD clinic the Tuesday after discharge - If treated for MIS-C with coronary artery lesions, discuss with cardiology follow up echo timing, KD clinic follow up the Tuesday after discharge. - If treated for KD or MIS-C and normal echo, will follow up in KD clinic 2 weeks after discharge	- If treated for KD with coronary artery lesions, follow up in KD clinic the Tuesday after discharge - If treated for MIS-C with coronary artery lesions, discuss with cardiology follow up echo timing, KD clinic follow up the Tuesday after discharge. - If treated for KD or MIS-C and normal echo, will follow up in KD clinic 2 weeks after discharge	- If coronary artery lesions seen and no lab evidence of inflammation, cardiology will determine frequency of follow up. - If treated with IVIG or other therapies, KD follow-up per our typical KD schedule

INITIAL LABORATORY/IMAGING ABNORMALITIES FOR ACTIVE DISEASE MAY INCLUDE:

- CBC with differential
    - Elevated total white blood cell count
    - Neutrophilia
    - Lymphopenia
    - Evaluate for eosinophilia as this could potentially differentiate KD from MIS-C?
    - Low hemoglobin
    - Elevated platelets
- C-reactive protein (high)
    - Note: If obtained at another hospital or lab, please check units: mg/dL used at CHCO Main and NOC; mg/L used at COS)
- ESR (high)
- Coagulation studies
    - Elevated D-dimer
    - Abnormal fibrinogen
    - PT/PTT prolonged
    - INR
- Complete metabolic panel
    - Elevated BUN/creatinine
    - Low albumin
    - Elevated AST/ALT
- Lacatate dehydrogenase (high)
- Triglycerides (high)
- Cardiac function:
    - Elevated troponin (troponin I)
    - Elevated NT pro BNP
- Ferritin (high)
- Cytokine studies including IL-1 IL-6, IL-18, CXCL9, soluble IL-2 receptor
    - In discussion with rheumatology
    - Expect some or all to be elevated

- Save and freeze of serum (in the event IVIG will be given)
- Urinalysis with microscopy:
    - Proteinuria
- Infectious workup:
    - Respiratory pathogen panel
    - SARS-CoV-2 PCR
    - SARS-CoV-2 IgG (serum SARS-CoV-2 IgG antibody test (IgM not needed) is recommended on all patients with MIS-C if the SARS-CoV-2 PCR is negative)
    - Blood cultures
- Other infectious workup guided by clinical presentation#
    - Urinalysis with microscopy and urine culture
    - Culture from any focus of infection (abscess, sinusitis, lymphadenitis, cellulitis, pneumonia)
    - Gastrointestinal pathogen panel (if diarrhea or vomiting present)
    - CSF studies (if concerning neurologic symptoms present): cell count, differential, protein, glucose, culture, meningitis encephalitis panel
    - Consider additional enterovirus testing if clinical concern for viral myocarditis, meningitis, encephalitis, or acute flaccid myelitis
- Echocardiogram: An echo is recommended on all patients with KD or MIS-C both during the acute illness and for outpatient follow-up. Coronary artery abnormalities have been reported in many series of patents with MIS-C. Currently, we do not know the rate at which patients with MIS-C will have coronary artery abnormalities (or the timeline for development), so it is prudent get a follow-up echocardiogram on these patients.

LABORATORY STUDIES TO TREND IN PATIENTS FULFILLING MIS-C CRITERIA:

Lab	Clinically stable, normal echo	Clinically stable, abnormal echo	ICU patient with signs of shock
CBC with differential	Every 24-48 hours	Every 24-48 hours	Every 24 hours
CRP	Every 24 hours	Every 24 hours	Every 24 hours
ESR	Only if worsening	Once 24 hours post IVIG	Once 24 hours post IVIG
D-dimer	Every 24-48 hours	Every 24 hours	Every 24 hours
LDH	Every 24-48 hours	Every 24 hours	Every 24 hours
Ferritin	Every 24 hours	Every 24 hours	Every 24 hours
CMP	Every 24-48 hours	Every 48-72 hours	Every 24 hours
Troponin I	Once, if normal no need to check.	Once, if abnormal, then every 6 hours and guided by cardiology	Every 6 hours, based on clinical status or guided by cardiology
NT Pro BNP	Every 24 hours, if normal no need to check	Every 24 hours	Every 24 hours
Cytokine panel	On admission	On admission	On admission

Management:

RECOMMENDATIONS FOR ED/HOSPITALISTS/PICU:

EARLY MEDICAL MANAGEMENT

Isolation precautions:

- Positive for SARS-CoV-2 PCR: Refer to COVID-19 and isolation precautions infection policy documents for guidance regarding appropriate PPE
- Negative SARS-CoV-2 PCR: can be placed on precautions related to presenting symptoms and other infectious diseases testing (contact versus droplet versus standard).

Clinical management reminders

- Standard PALS resuscitation and supportive management per CHCO Code Blue Activation and Rapid Response Team Evaluation Policy.
- Empiric antibiotics per ED/UC Sepsis Pathway or Inpatient Sepsis Resources with consideration of need for addition of protein synthesis inhibitor. If patient has evidence of significant AKI, consider potential use of ceftriaxone + linezolid -OR- ceftaroline + clindamycin
- Discussion with ICU team early for advice on management, transport, and/or placement for those who are critically ill.
- Deterioration of patients can be rapid, so recommend close cardiorespiratory monitoring in patients.
- Early 12-lead ECG and echocardiogram are indicated where it is possible to obtain them
- Ensure that Save and Freeze of serum obtained prior to immunomodulatory treatment (including IVIG) in discussion with ID, Immunology, and Rheumatology

MEDICATIONS:

- Empiric antibiotics: ceftriaxone, vancomycin (+/- clindamycin) versus linezolid versus ceftaroline + clindamycinif signs of toxin-mediated disease and presence of acute kidney injury.
- Intravenous Immunoglobulin
  - Indications: myocardial dysfunction, coronary artery dilation or aneurysms, signs of toxic shock syndrome, confirmed MIS-C
  - Dosing:2 g/kg IV over 12 hours**
  - **Discuss dosing and infusion duration with pharmacy and ID if patient has poor renal function, evidence of fluid overload, or is >50 kg
    - For patients who are >50 kg, discuss whether the dose could be split or run over a more prolonged period of time.
    - There have been discussions between pharmacy and ID/KD group about the best dosing for these patients to ensure adequate treatment but mitigate potential side effects:
      - Benefits: in KD patients, we know that receiving 1g/kg of IVIG is inferior to 2 g/kg in terms of preventing coronary artery lesions.
      - Risks: most of these patients are older and therefore weigh more than a typical KD patient, so they are getting a larger dose, which increases the risk of IVIG-related side effects including aseptic meningitis and hemolytic anemia
    - Recommend discussion with ID pharmacy and unit pharmacy about what dose to use on case-by-case basis until we have more definitive evidence that doses <2g/kg are efficacious.
    - Potential options to discuss for patients >50 kg:
      - Max out on dosing for the IVIG at 100 g
      - Split the dose up and give 2 doses of 1 g/kg over the span of 24-48 hours
  - Can repeat second dose in discussion with ID
  - Clinical monitoring:
    - Evidence of hemolytic anemia and aseptic meningitis
    - Follow renal function
    - Ensure strict intake and output, daily weights, monitor for signs of fluid overload
  - Managed in conjunction with: ID, cardiology
- **Infliximab:**
  - Indications: coronary artery dilation or aneurysms, or no response to IVIG in patients with diagnosis of KD, KD shock syndrome, or confirmed MIS-C
  - Dosing: 10mg/kg IV x 1
  - Frequency: can repeat second dose in discussion with ID and cardiology if fevers persist or evidence of worsening coronary artery involvement.
  - Clinical monitoring: need to assess for tuberculosis and Hepatitis B risk factors. If risk factors present, please obtain Quantiferon Gold, chest x-ray, and Hepatitis B surface antigen.
  - Managed in conjunction with: ID, cardiology
  - Recommend discussion between primary team, rheumatology, and ID about next line of therapy for patients who have not responded to IVIG as infliximab, anakinra, and steroids are all possibilities, and these should be considered on a case-by-case basis
- **IL-1 receptor antagonist (Anikinra)**
  - Indications: Patients with fever or systemic inflammation that is refractory to IVIG
  - Dosing: 5mg/kg IV or subcutaneous every 12 hours
  - Frequency: twice daily
  - Clinical monitoring: monitor for elevation of transaminases, will suppress fever curve
  - Managed in conjunction with: rheumatology
- **Corticosteroids**
  - Use as targeted therapy for inflammation should be discussed in conjunction with ID, cardiology, and rheumatology.
  - Per some case series, patients have responded well to administration of 2 mg/kg/day of methylprednisolone
  - Potential benefits: more broad impact on inflammation, and we don't know the specific inflammatory derangements in these patients just yet.
  - Potential risks:
    - Some evidence in KD patients with coronary artery involvement that there is an increased risk of rupture
    - Concerns about use of steroids in these patients, particularly if sepsis is still on the different.
  - Recommend discussion between the primary team, ID, and rheumatology if steroids will be considered. In a previous patient, we waited to make the decision until a repeat echo was done, and the patient ended up with coronary artery lesions, so we gave infliximab.

- **Aspirin**
  - Indications: Children who are diagnosed with Kawasaki Disease (KD) should be treated with 30-50 mg/kg/day of aspirin (in addition to IVIG)
  - Dosing: 30-50mg/kg/day
  - Frequency: divided every 6 hours
  - Clinical and laboratory monitoring:
  - Managed in conjunction with: cardiology, ID
  - Contraindications:
    - Platelet counts less than 150,000/mm3
      - Once their platelet counts normalize, consideration of low-dose aspirin (3-5 mg/kg/day) is indicated as is standard in our Kawasaki Disease practice
    - Use of other anticoagulants, (e.g. low molecular weight heparin, warfarin, etc.) whether for thrombosis, thrombosis prophylaxis or severe coronary artery abnormalities.
      - Patients on anti-coagulants should be discussed with ID and Cardiology on a case-by-case basis to decide on aspirin use. The benefit vs. risk (adverse effects from multiple anti-thrombotic agents) should be weighed, as many patients may not benefit significantly from the addition of aspirin.
  - Have a respiratory viral PCR sample positive for influenza
  - Have an allergy or contraindication to aspirin
  - Children with hyper-inflammation and ARDS
  - Patients with active or significant risk for bleeding where the addition of aspirin would pose a significant risk
  - Children that have a clear diagnosis of toxic shock do not need aspirin. Be aware that a small percentage of children with Kawasaki Disease can present with features of shock. Sometimes, it is unclear whether children have KD or toxic shock and are then treated for both. If this is the case (unable to be distinguished), the child should be treated with aspirin (as in the above guidance and cautions). It is also possible, that some patients have signs and symptoms that make toxic shock versus MIS-C indistinguishable. If that is the case, see the above guidance for treatment of those patients with aspirin (including the cautions of who not to treat).
- **For SARS-CoV-2 PCR positive patients:**
  - Discussion of application for remdesivir and/or convalescent plasma per other treatment guidelines
- **Anticoagulation for coronary artery dilation and aneurysms**
  - Discuss with cardiology

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	Type of Policy: Hospital
	POLICY TITLE: Evaluation and Management of COVID-19 Multisystem Inflammatory Syndrome in Children (MIS-C)
	Effective Date: 05/31/2020

PURPOSE: This guideline is to provide guidance in the evaluation and management of confirmed or suspected COVID-19 multisystem inflammatory syndrome in children (MIS-C). For management of primary active COVID-19 infections, please refer to the CHKD Treatment Guideline for COVID-19 in Children. This guideline is subject to change as more information becomes available

BACKGROUND: To date, critical illness due to COVID-19 is rare among pediatric patients and represents 1-2% of all COVID-19 cases with lower severity and mortality when compared to adults. As of May 2020, there have been reports worldwide of children presenting with a rare COVID-19 associated syndrome referred to as MIS-C.[1-2] MIS-C consists of persistent fever, elevated inflammatory markers (including cytokine storm), neutrophilia, lymphopenia, coagulopathy and a variety of clinical manifestations including:

- **a)** Vasodilatory shock with normal or mildly depressed systolic function
- **b)** Cardiogenic shock with ≥ moderate systolic dysfunction
- **c)** Kawasaki disease (KD) features (can be complete or incomplete KD)
- **d)** Clinical and laboratory features of cytokine storm
- **e)** Coronary artery dilation and aneurysms (up to 25% of children and teens with MIS-C[26])
- **f)** Any combination of the above

Not all patients present with respiratory symptoms and/or a (+) COVID-19 tests via RT-PCR or serology.[1-3] The CDC recommends reporting any patient who meets the case definition (see below) to local, state, and territorial health departments. If a child meets the case definition below or presents with a persistent fever (≥3 days), is moderately to severely ill, and clinical signs of organ dysfunction MIS-C should be considered.[11] Some patients may fulfill full or partial criteria for Kawasaki disease (KD); however should still be reported if they meet the case definition for MIS-C.[1-3] If a patient presents with a classic KD and incidentally found to be COVID-19 (+), treat as standard KD. Heme-Onc should be consulted on any patient who present with COVID-19 + HLH. Infectious disease should be consulted to assist with management in addition to the specific treatment and management recommendations outlined in (Figure 1). The spectrum of MIS-C has ranged from mild to severe. At this time, treatment recommendations are not clear and will continue to be changed based on emerging research.

DEFINITIONS:

1. **MIS-C Case Definition in Children**[1]

   Patients present with ALL:

   a) Age <21 years with:

   - Fever: ≥ 38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
   - Laboratory evidence of inflammation: 1 or more of the following: [1]

Increased			Decreased
CRP	LDH	Procalcitonin	Lymphocytes
D-dimer	IL-6	VBG w/ Lactate	Platelets
ESR	Neutrophils	LDH	Albumin
Ferritin		BNP	Serum Na

   - Evidence of clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement [cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic]

b) No alternative plausible diagnoses
c) Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

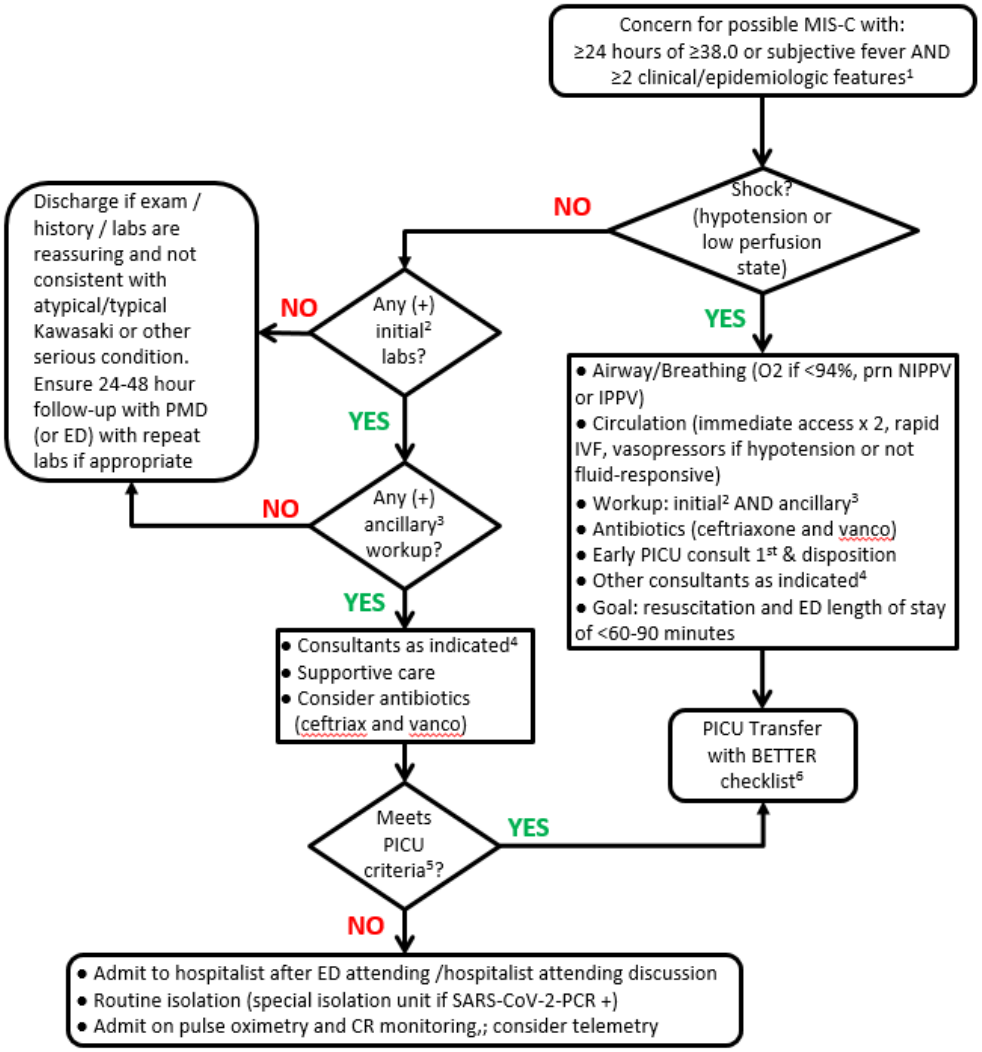
2. **COVID-19 Cytokine Storm**[1-4]
    a. A severe inflammatory condition that has been observed in adults and children with COVID-19 that is thought to be secondary to a host immune response to COVID-19
    b. Typically presents in the second week of illness with manifestations of worsening respiratory distress/failure and/or other organ dysfunction
    c. Criteria for risk high-risk of cytokine storm[8]

≥ 1	**Description**
IL-6	≥3x upper normal limit
Ferritin	>300 ug/L with doubling in 24 hr
Ferritin + LDH	>600 ug/L at presentation >250
D-dimer	Elevated

PROCEDURE:

1. **Initial Work-up for Suspected MIS-C**

CHKD ED Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway



Pathway is not a substitute for good clinical judgment; consider other differential diagnoses)

[1] **Clinical/epidemiologic features**
- GI (vomiting; abdominal pain; diarrhea)
- Rash (polymorphic, maculopapular, or petechial)
- Neurologic (headache, AMS, confusion, lethargy)
- Conjunctivitis (bilateral, bulbar, non-exudative)
- Oromucosal (erythema; not discrete lesions)
- Extremities (edema, erythema)
- Lymphadenopathy (>1.5 cm)
- Epidemiologic history (COVID history, or a COVID suspected / confirmed contact)

[2] **Initial labs**: CBC, CMP, CRP, ESR, Urinalysis; other workup as clinically indicated. Initial labs considered "positive" if: [ESR≥40 or CRP≥3] AND [ALC<1K or Plts<150k or Na<135]

[3] **Ancillary workup**: ARPP, blood culture, cardiac evaluation (ECG, BNP, Troponin, +/-ED POCUS for myocardial dysfunction or effusion), COVID IgG, COVID-PCR, d-dimer, ferritin, fibrinogen, LDH, procalcitonin, PT/INR, PTT; other workup as clinically indicated, including chest radiograph consideration.

[4] **Consultant indications**:
- Consult **cardiology** if any abnormalities on cardiac evaluation ancillary workup, hypotension, or PICU disposition
- Consult **hematology** if elevated d-dimers once coagulation profile resulted
- Consult **infectious disease** if indicated
- Consult **hospitalist/PICU attending** if considering admission

[5] **PICU criteria**: significant dyspnea, hemodynamic instability (persistent tachycardia after fluid resuscitation or hypotensive episode), significant cardiac evaluation abnormality, persistent AMS/confusion, or acute kidney injury.

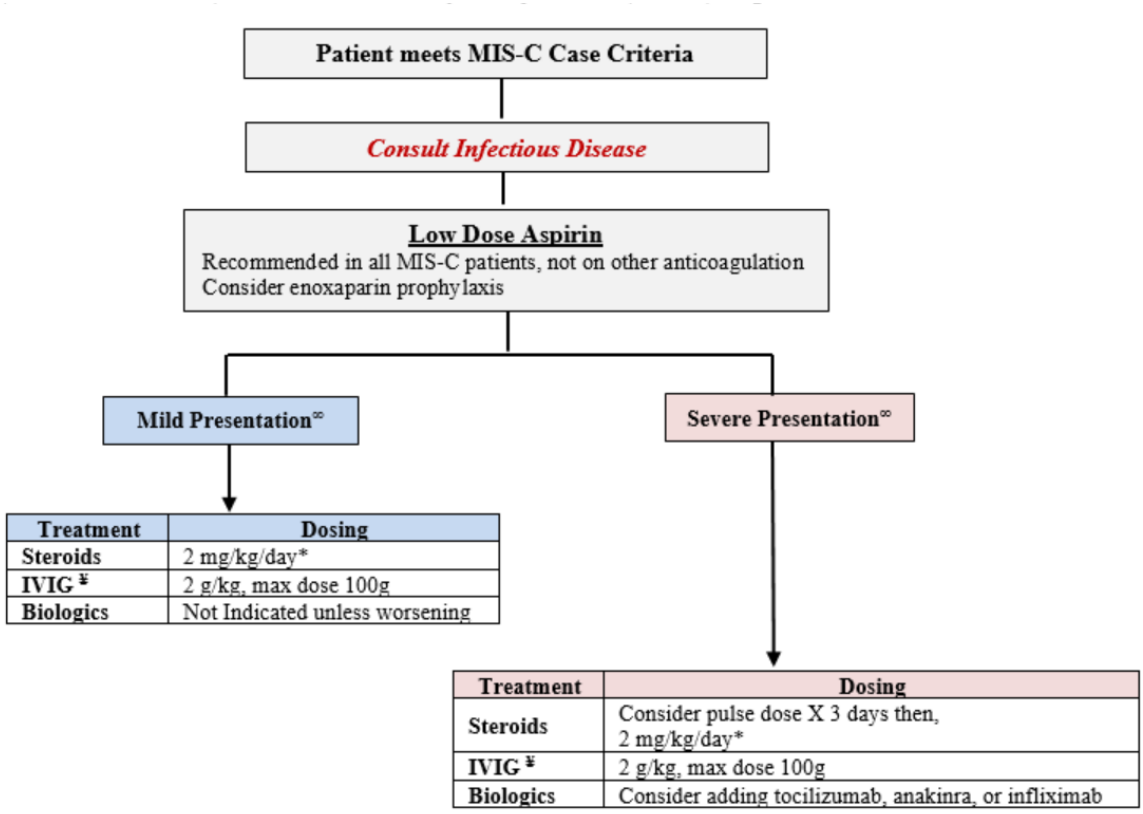
[6] **B.E.T.T.E.R. Checklist**: Briefing ED-To-ICU To Exit Ready checklist to ensure attending re-evaluation and medication/equipment preparedness prior to transport

2. Classification of MIS-C [8-9]

Presentation not well defined and may be subjective

Presentation	Description
Mild	Requires minimal to no respiratory support No vasoactive requirements Minimal to no organ injury Does not require ICU admission
Severe	Significant oxygen requirement (HFNC, BiPAP, mechanical ventilation) Mild-Severe organ injury and/or ventricular dysfunction (+/-) Vasoactive requirement ICU admission

3. MIS-C Treatment (Figure 1): For dosing see (Table 1)



¥ Caution use if overlapping features of HLH due to ↑ clotting risk

* Taper steroids

Pharmacotherapy Management of MIS-C (Table 1)[8-9]

MIS-C Specific Therapy	Dosing & Duration	Comments
IVIG (IV) • KD features and/or coronary artery changes • RT-PCR and serologic testing should be completed. Later serology may be needed if all (-) initially • *Serologic test must be sent prior to administration of IVIG*[11]	**Dosing**: • 2 g/kg, (max dose 100g)[26]	**Adverse events:** • Infusion reactions • Anaphylaxis • Transaminitis, • Aseptic meningitis • Hemolysis Cardiac function & fluid status assessed prior to avoid fluid overload
Biologics		
Anakinra (SQ/IV) • *Non-formulary-limited supply* • IL-1 Inhibitor • Consider if fevers > 24 hrs post steroids/IVIG or moderate/severe presentation ***ID Consult Required***	Discuss Dosing with ID or Rheum **Dosing:** • 2-4 mg/kg/dose (Max 100 mg/dose) SQ/IV BID [26,30], May ↑ to TID or QID if poor response • Continue for 5-7 days **Dose Adjustments:** • CrCL<30mL/min, consider QOD dosing • Not dialyzable	**Caution:** • Treatment with >1 biologic not recommended • Avoid live viral vaccines • Caution converting from tocilizumab to anakinra **Adverse Events:** • Anaphylaxis, Neutropenia, Eosinophilia, Transaminitis, Immunosuppression Short half-life (4-6 hours) –MAY convert to tocilizumab without concern Clinical improvement expected in 1-3 days
Tocilizumab • Consider for MIS-C if fevers > 24 hrs post steroids/IVIG or moderate/severe presentation	**Adult Dosing (≥18 years):** • 8 mg/kg X 1 (Max 800 mg) **Pediatric Dosing (<18 years):** • < 30 kg: 12 mg/kg X 1 (Max 800 mg) • ≥ 30 kg: 8 mg/kg X 1 (Max 800 mg) ** Round dose to nearest full vial ** **Duration:** One dose Consider additional dose 8-12 hours after if continued clinical decompensation	**Contraindications:** • Avoid in pregnancy • Breastfeeding **Caution:** • Treatment with >1 biologic is not recommended • Avoid live viral vaccines • Caution converting from tocilizumab (half-life~16 days) to anakinra • CRP & IL-6 levels not reliable measurements of inflammation post tocilizumab **Serious adverse events:** • Gastrointestinal perforation, Anemia, Hepatitis, Infusion reaction Typical response within 48-72 hrs with cessation of fevers and stabilized or improved oxygenation
Steroids		
Corticosteroids (IV/PO) prednisone, prednisolone, methylprednisolone • Consider for high-risk KD features • MIS-C • Consider for ARDS	**Dosing:** • 2 mg/kg/day divided q8-q12h **Pulse dosing:** • 10 mg/kg-30 mg/kg/day for 1-3 days followed by 2 mg/kg/day divided followed by a taper • Determine based on patient severity	**Adverse events:** • Hypertension • Hyperglycemia

4. Reporting Cases to Health Department

a. Per a recent CDC Health alert, MIS-C cases are to be reported to the health department
b. Please report case, including patient demographics and date of diagnosis

5. Recommended Follow-up

a. Outpatient pediatric cardiology follow-up starting 2 to 3 weeks after discharge[11]

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RELATED DOCUMENTS: CHKD Treatment Guideline for COVID-19 in Children: Version 2.2 June 1, 2020

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Originated: 05/29/2020	Last Revised: 07/16/2020
Revision History: 7/17/20: Updated anakinra dosing and tocilizumab notes 7/6/20:Addition of labs recommendations, addition of recommended follow, addition of MIS-C diagnosis consideration if fever ≥3 days	

MIS-C clinical pathway

June 26, 2020

Primary Care

Fever ≥3 days AND < 2 signs/symptoms*

Fever ≥2 days AND 2 or more signs/symptoms*

Fever ≥1 day AND 2 or more signs/symptoms* AND Ill appearing

Assess for alternative diagnoses to explain symptoms

Yes → OFF PATHWAY Treat as usual

No

If fever and not meeting criteria listed, then continue with usual workup for KD, FUO, infections, other causes.

Evaluate for signs and symptoms of Kawasaki Disease, including fever ≥7 days in infant < 12 months. Use KD pathway if meeting criteria.

ED

Well appearing?

No → Initial labs:
- CBC DIFF, Chem 14 ESR, CRP
- UA + micro
- SARS-CoV-2 PCR
-SARS-CoV-2 Ab
Depending on age and clinical suspicion:
- Urine culture
- Blood culture
-CXR
- FA RVP, strep, ASO, EBV

Yes → Clinical suspicion for MIS-C without clear source of fever

Yes → Initial labs

Any Labs abnormal:
- CRP ≥3 mg/dL, ESR ≥40, ALC < 1000, platelets < 150K, Na < 135

Yes → Toxic appearing
Hypotension
Signs/sx heart failure
Poor perfusion

Yes to any → PICU consult

For Septic Shock:
- Follow septic shock pathway
- If no signs of fluid overload, 10-20 ml/kg bolus over 15 minutes
- Repeat reassessment of response to bolus
- Consider fluid boluses 10-20 ml/kg until shock resolves or signs of fluid overload
- consider epinephrine for myocardial dysfunction or epinephrine/norepinephrine if shock persists after 40-60 ml/kg fluids

Labs: DIC panel, ferritin, LDH, BNP, troponin
Echocardiogram ASAP‡
EKG
Antibiotics: Ceftriaxone, add clindamycin if TSS, add vancomycin if MRSA
Consider other etiologies, eg toxic shock

No → Low threshold for PICU admission, if any signs/ symptoms/diagnostics suggest cardiac involvement

‡If SARS-CoV-2 PCR positive, then team discussion between attendings with primary service, ID, and cardiology consult to discuss need for echo and type of echo. Consider initial limited echo to assess function, with follow-up echo of coronary arteries if clinically indicated.

Inpatient Med-Surg

ADMIT to Med-Surg
Alternative diagnosis made and low suspicion for MIS-C?

Yes → Treat underlying diagnosis OFF PATHWAY

No → Secondary labs:
- DIC panel, ferritin, LDH
- BNP, troponin
- If SARS-CoV-2 NP PCR negative, send rectal swab
- Echocardiogram‡, EKG
Consults:
ID and cardiology
PRN: A/I, rheumatology¥

Echo abnormal?

Yes → - Repeat BNP, troponin
- Repeat echo, EKG in 1-2 days

No → SARS-CoV-2 Ab positive?

Yes → Repeat echo, EKG in 2-3 days

No → Clinically improved Labs downtrending

Yes → No

No → Consider Incomplete KD
Consider Repeat Echo, EKG
Consult Rheumatology
OFF PATHWAY

Consider treatment:
- IVIG 2 g/kg
- If moderate or severe illness, ADD methylprednisolone 2 mg/kg/day div Q12 x 5 days. Consider taper if prolonged course.
Treatment failure: anakinra 5 mg/kg

Upon DC:
Low dose ASA 3-5 mg/kg/day
Max 81 mg

¥ Tertiary labs if rec. by A/I or rheumatology:
- T cell subsets extended
- Cytokine panel
- Anti-phospholipid Antibodies

PICU

Admit to PICU
Secondary labs:
- Discuss with consulting teams
Consults:
Cardiology, ID, A/I and Rheum
Consider treatment:
- IVIG 2 g/kg **AND** Methylprednisolone 2 mg/kg/day div Q12 x 5 days. Consider taper if prolonged course.
- anakinra, tocilizumab

Repeat echo per cardiology recommendations

Upon DC:
Low dose ASA 3-5 mg/kg/day
Max 81 mg

Post-discharge

DC Home
Follow-up PCP with return precautions

Option → DC Home
Follow-up ID clinic

SARS-CoV-2 Ab positive AND/OR Fever >/=5 days?

No → Follow-up with PCP
Refer to ID PRN

Yes → Refer to cardiology for urgent outpatient echo and EKG
Repeat labs

Labs or echo abnormal?

Yes → Admit to hospital

No

Interim guidance:
If fever >/=5 days but now resolved, option to refer to cardiology for echo

*** SIGNS/SYMPTOMS:**
- Rash
- Non-purulent conjunctivitis
- Redness or swelling of hands or feet
- Erythema of oral mucosa
- Hypotension or shock
- Cardiovascular (lab, clinical, or echo evidence or myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities)
- Hematologic: abnormal PT, PTT, or D-Dimer
- GI (diarrhea, vomiting, or abdominal pain)
- Renal insufficiency/AKI
- Respiratory
- Neurologic (mental status changes, meningitis, headache, irritability, lethargy)

Also consider and evaluate for other manifestations of systemic inflammation

EXPOSURE:
-SARS-CoV-2 PCR positive
-SARS-CoV-2 IgG positive
-Previous household or close contact with a person with SARS-CoV-2 within 4 weeks

Protocol for the Treatment of Multisystem Inflammatory Syndrome in Children (MIS-C)
Divisions of Infectious Diseases, PICU and Pharmacy
Children's Hospital of Michigan
Detroit, Michigan

Disclaimer: Our understanding of this illness is constantly evolving. This document is subject to revision. Please look at the footnote to confirm this is the most recent Medication Guide. This protocol is intended to provide guidance on the medical management of patients with MIS-C at Children's Hospital of Michigan**.**

Currently there is no FDA approved treatment for COVID-19 (coronavirus disease 2019) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). There is interest in using several FDA approved medications, even though there is no definitive clinical evidence to show their efficacy or safety in the treatment of **Multisystem Inflammatory Syndrome in Children associated with COVID-19.** The following summarizes our approach at Children's Hospital of Michigan, Detroit, Michigan.

Infectious Diseases consultation is needed for all MIS-C cases admitted to PICU

First Line Therapy (IVIG AND Aspirin)[1]

IVIG

- Order via Caresets: PEDS MEDS – IVIG, PEDS ID – IVIG for Kawasaki
- Dosing
  - 2 gm/kg IV x 1
  - Max dosing: none
  - Obese patients, recommended to utilize dosing weight based on same percentile for height
  - Infuse over ~12 hours, see IVIG Infusion Tip Sheet for more information
  - Renal dose adjustment:
    - Use with caution – rate of infusion and concentration of solution should be minimized
- Pre-treatment Medications
  - Acetaminophen administered 30 minutes prior to infusion
  - Diphenhydramine administered 30 minutes prior to infusion
- Monitoring
  - Baseline vital signs should be obtained prior to starting infusion (Temp, HR, RR, BP)
  - Monitor vital signs every 15 minutes during first hour, then every hour for the duration
  - Monitor vital signs 15 minutes after the completion of infusion
- Other considerations
  - Due to the national shortage, pharmacy will dispense IVIG product currently available, please contact pharmacy if specific product is desired
  - For stability and to limit drug waste, pharmacy may split larger doses into two doses

Moderate-dose aspirin

- Dosing
  - 30-50 mg/kg/day, PO divided q6h
  - Max dosing: 1 gm PO q6h (4 gm/day)
  - Obese patients, consider dosing based on adjusted body weight
    - Adjusted Body Weight = Ideal Body Weight + 0.4(actual body weight – ideal body weight)

    - No liquid formulation available, round doses to nearest quarter-tab of 81 mg and/or 325 mg tabs. May combine both strengths to achieve desired dose.
    - Renal dose adjustment: no adjustment necessary, for GFR <10: avoid use
- Duration
    - Transition to low-dose aspirin therapy (3-5 mg/kg/day once daily) when afebrile for 48-72 hours, OR
    - Up to 14 days from first day of fever until fever resolves for at least 48 to 72 hours, then transition to low-dose aspirin therapy (3-5 mg/kg/day once daily)
- Other Considerations
    - GI prophylaxis with H_2RA or PPI
    - Recommended to avoid concomitant ibuprofen administration

Criteria for 2nd Line Therapy: Persistent fever, signs of inflammation, cardiac inflammation
Note: Send TB spot (do not need to wait for results); if positive, treat with INH/Rifapentine once weekly for 12 weeks (must discuss with ID)

Second Line Therapy
Infliximab [2] (or infliximab biosimilar)
- Order via Careset: Peds Rheum - Infliximab
- Dosing
    - 10 mg/kg IV x 1
    - Max dosing: none
    - Obese patients, consider dosing based on adjusted body weight
        - Adjusted Body Weight = Ideal Body Weight + 0.4(actual body weight – ideal body weight)
    - Infuse over ~2 hours, see Infliximab Infusion Guidelines for Immunology Service Patients for more information
    - Renal dose adjustment: no adjustment necessary
- Pre-treatment Medications
    - Acetaminophen administered 30 minutes prior to infusion
    - Diphenhydramine administered 30 minutes prior to infusion
- Monitoring
    - Baseline vital signs should be obtained prior to starting infusion (Temp, HR, RR, BP)
    - Monitor HR and BP every 15 minutes during the infusion
- Other Considerations
    - Infiximab is available in 100 mg vials – please try to round to a vial if possible
    - Medications for possible hypersensitivity reactions should be added to the eMAR and can be ordered via the careset

Criteria for 3rd Line Therapy: Persistent fever, signs of inflammation, cardiac inflammation

Third Line Therapy
"Pulse Dose" Methylprednisolone (Preferred) [1]
- Dosing (confirm indication – dosing varies for other indications)
    - 30 mg/kg/dose IV once daily for 1 to 3 days

- Max dosing: 1000 mg/dose

"RAISE Study Steroid Protocol" [1] (longer Course of steroids with taper- option)

- Methylprednisolone IV : 2 mg/kg/day, divided q8h x 5 days or until afebrile, then transition to oral 2 mg/kg/day prednisolone Q 8 hours until CRP normalized and continue taper over 2 weeks
  - Administer IV over 60 minutes
  - Renal dose adjustment: no adjustment necessary
- Other Considerations
  - GI prophylaxis with H_2RA or PPI

Fourth Line Therapy

Criteria for anakinra: Persistent fever, signs of inflammation, cardiac inflammation; persistent coronary artery dilation with Z score of > 2.5

***Anakinra*[3]**

- Non-formulary agent, enter under "non-formulary"
- Must be approved by ID and PICU attendings on service
- Dosing
  - Initial dose: 2 mg/kg/dose IV q12h x 2, max dose 50 mg/dose
  - Maintenance dose: 4 mg/kg/day SC or IV, max dose 100 mg/day
    - Maintenance dosing starts 24 hours after the first dose
  - Administer IV bolus over 1 to 3 minutes
  - Renal dose adjustment
    - CrCl < 30 mL/min: 50% dose reduction
- Duration
  - 2 weeks (until coronary artery dilatation resolves, Z score of <2)
  - May extend to an additional 4 weeks depending on Z score after two weeks of treatment
- Monitoring
  - Neutropenia
- Other Considerations
  - Anakinra is supplied as 100 mg/0.67 mL syringes – please try to round dosing to nearest syringe size if possible

References:

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease, a scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135:e927-e999.
2. Casteele NV, Oyamada J, Shimizu C, et al. Infliximab pharmacokinetics are influenced by intravenous immunoglobulin administration in patients with Kawasaki Disease. *Clin Pharmacokinet* 2018; 57:1593-1601.

3. Tremoulet AH, Jain S, Kim S, et al. Rationale and study design for a phase I/IIa trial of anakinra in children with Kawasaki disease and early coronary artery abnormalities (The ANAKID Trial). *Contemp Clin Trials* 2016 May; 48:70-75.
4. Wolters Kluwer Clinical Drug Information, Inc. (Lexi-Drugs). Wolters Kluwer Clinical Drug Information, Inc.; May 6, 2020.

CHAM Pediatric Multisystem Inflammatory Syndrome (PMIS) Ambulatory and Urgent Care Guidelines

Ambulatory Care:

Fever T ≥ 38C/subjective fever with 2 or more of the following:

- GI symptoms (abdominal pain, vomiting, diarrhea)
- Conjunctivitis
- Oral mucosal changes (red cracked lips/strawberry tongue)
- Rash
- Swelling of the hands and feet
- Myalgias, headache, irritability, lymphadenopathy, sore throat

Or

Any fever ≥5 days

Parent/Caregiver calls practice, CRM generated; sent to the clinical pool; LPN/CCRN sets up a video visit and routes the note to the scheduled provider; provider completes visit and if concerned re: PMIS they would call Peds ED at 718.741. 2150 and give a warm handoff and then patient instructed to go to the CHAM ED

If low concern for PMIS; would recommend follow up video visits in 1-2 days to reassess symptoms

Urgent Care:

Parent/Caregiver calls PAC; Urgent care NP screens patient; schedule for urgent care visit or telemedicine visit; provider completes visit and if concerned re: PMIS, Provider would call Peds ED at 718.741. 2150 and give a warm handoff and then patient instructed to go to the CHAM ED

If low concern for PMIS; would recommend follow up video visits in 1-2 days with PCP to reassess symptoms, urgent care provider should send staff message to PCP so they are aware of need for follow up visit.

CHAM Pediatric Multisystem Inflammatory Syndrome (PMIS) Emergency Room & Inpatient Guidelines

Fever T ≥ 38C/subjective fever with 2 or more of the following:
- GI symptoms (abdominal pain, vomiting, diarrhea)
- Conjunctivitis
- Oral mucosal changes (red cracked lips/strawberry tongue)
- Rash
- Swelling of the hands and feet
- Myalgias, headache, irritability, lymphadenopathy, sore throat

Or

Any fever ≥5 days

2017 AHA KD statement: *Classic KD* (fever ≥ 5 days with at least 4/5: rash, palm/sole swelling, bilateral limbic sparing conjunctivitis, cervical lymphadenopathy (one > 1.5cm), red crackled lips/strawberry tongue)
Atypical KD (fever ≥ 5 days with 2-3/5 sxs above or fever ≥7d in infant + at least 3/6 :anemia for age, WBC > 15,000, platelets > 450, albumin < 3 g/dL, elevated ALT, sterile pyuria >10 WBC/hpf on clean UA or a + echo
Txt: IVIG 2g/kg x 1 and ASA 100 mg/kg/day po Q6 until afebrile x 48 hrs then aspirin 3-5 mg/kg/day
IVIG resistance: Persistence or recrudescence of fever > 36 hrs after IVIG completion

PCP/ MMG teleheath visit 24-48 hrs *Return to ED : ill appearing, KD, fever ≥5d*

YES

*Well appearing **WITH OTHER plausible cause***

NO

Well appearing

SARS CoV-2 NP swab PCR , CBC diff, retic count, Chem 20, Troponin-I, BNP, CRP, ESR, ferritin, LDH, PT/PTT, d-dimer, IgA, fibrinogen, procalcitonin, LDH, TG, amylase, CK, UA, blood culture , CXR, ECG *(other tests based on sxs)*

ill appearing signs: ↓ BP, ↑ HR out of proportion to the fever, hypoxia, altered mental status, confusion, dehydration, acute abdomen, imaging (enteritis, hydrops of gall bladder) ***OR*** KD classic/atypical ***OR*** ↑ Troponin/pro-BNP

Shock /low cardiac output
↓ O2 unresponsive to NC
↓ BP unresponsive to fluid resuscitation

- PICU -> supportive txt
- Daily labs*,ID/Cards c/s
- Echo: ↓ cardiac output, ↑ Troponin/BNP, KD
- Rheum c/s: ↑ ↑ inflammatory markers
- ¥ Heme c/s
- If KD -> KD guidelines

PMIS
No KD
No shock
No ventricular dysfunction

- PHM service
- Daily labs *
- ID/Rheum c/s
- Cards c/s for ↑ Troponin/BNP/abnl ECG
- ¥ Heme c/s

KD
No shock
No ventricular dysfunction

- PHM service
- Txt: 2017 KD AHA statement
- Avoid ASA if plt < 100 K or bleeding
- Daily labs *,echo, ID/cards c/s
- ¥ *Heme c/s prior to high dose ASA (CHAM anticoag/antiplt gdlines)*
- IVIG resistance -> echo & 2nd IVIG
- Fever s/p IVIG x 2 -> Rheum c/s

Ventricular dysfunction
No shock
No low cardiac output
No KD

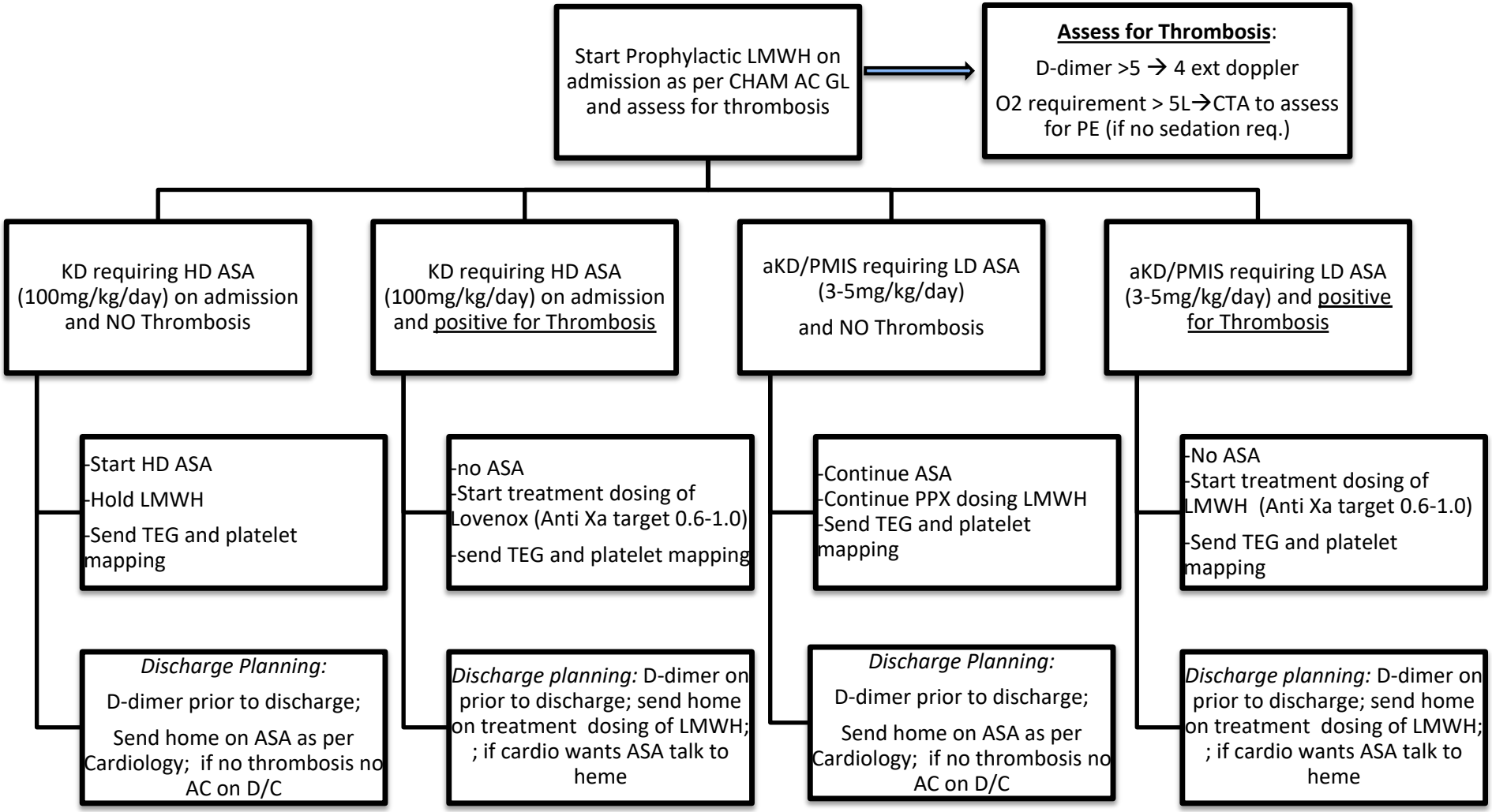
- PHM service
- Cards c/s
- Daily labs *
- ¥ Heme c/s
- ID c/s

The Children's Hospital at Montefiore

EINSTEIN

* Daily labs: CBC diff, Chem 20, Troponin, BNP, CRP, ferritin, d-dimer & other abnl labs (*ok to space out if improving)*
¥ Heme c/s prior to starting antiplatelet tx; TEG with platelet mapping and AT3 on ALL floor/ICU pts *(**inform heme if sent**)*
¥ **CHAM Anticoagulation and Antiplatelet Guidelines on ALL children on ASA**
¥ *CHAM anticoagulation protocol age < 21 yrs on ALL children NOT on ASA*

Anticoagulation and Antiplatelet Guidelines in PMIS-KD



THE UNIVERSITY OF CHICAGO | Department of Pediatrics Established 1930

Multisystem Inflammatory Syndrome in Children (MIS-C)

***__IMPORTANT:__ Care of patients with suspected MIS-C should be done in consultation with Pediatric Infectious Diseases, Pediatric Rheumatology, Pediatric Cardiology, and Pediatric Hematology-Oncology (Subspecialties should be consulted from the ED). Other services like Pediatric GI, Pulmonary, Nephrology, and Dermatology should also be considered per individual patient presentation. Due to the overlap in presenting features between MIS-C and cytokine storm due to other causes, it is essential to obtain multispecialty consultation prior to proceeding with treatment.

CASE DEFINITION (in the setting of no alternative plausible diagnosis)

Age	Age < 21 years
Fever	• Fever > 38.0°C • Report of subjective fever
Clinical findings	• Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological)
Evidence of SARS-CoV-2	• Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test
Laboratory markers	Laboratory abnormalities consistent with MIS-C, including, but not limited to ≥1 of the following: • ↑ C-reactive protein (CRP) • ↑ erythrocyte sedimentation rate (ESR) • ↑ fibrinogen • ↑ D-dimer • ↑ ferritin • ↑ neutrophils • ↑ BNP • ↓ lymphocytes • ↓ albumin • ↓ platelets

Additional comments

- Specific exposure(s) to COVID-19 should be elicited by examining clinician(s).

INITIAL EVALUATIONS:

- Initial: CMP, magnesium, phosphorus, CBC w/ diff, CRP, coagulation markers, ESR, ferritin, D-dimer, BNP, troponin, RVP, SARS-CoV-2 PCR, SARS-CoV-2 antibody, blood culture, urine culture. Frequency of labs should be discussed with consulting services after initial draw.

- Do not wait to initiate subspecialty consultation before results of SARS-CoV-2 antibody testing are available if there is high suspicion of MIS-C.
- 12 lead EKG should be performed as soon as possible to evaluate for ischemia/cardiac strain.
- Chest X-ray
- Echocardiography should be performed within the first 24 hours after admission. Exact timing should be discussed directly with Pediatric Cardiology. If elevated BNP, multiple fluid boluses required, or abnormal EKG, please call Pediatric Cardiology for urgent echocardiography.
- Please make patients NPO in the ER, as may need sedation for critical care procedures
- Fluid resuscitation: Use caution as patients may be at risk for worsening cardiac strain and/or pulmonary edema.
- Consider obtaining lymphocyte subset 3, cytokine panel, and vitamin D level.

MANAGEMENT

Initial therapy for patients with high suspicion/confirmed MIS-C:

1. **1st line therapy** Intravenous immunoglobulin (IVIG) and/or corticosteroids depending on clinical judgment of consulting team(s).
    a. Due to similarities with KD, administer 2 g/kg/day (based on ideal body weight or adjusted body weight if obese). Infusion should be administered over a prolonged duration similar to KD patients and titrated to a max of 2 mL/kg/hr
    b. Pre-medicate with diphenhydramine and acetaminophen 30 minutes prior to administration of IVIG
    c. Methylprednisolone: 1 mg/kg/dose (max 40 mg/dose) IV q12H x 5 days (may extend therapy if inflammatory/cardiac markers not improving)
        i. Methylprednisolone should be started regardless of use of other corticosteroids such as hydrocortisone which may be used for shock or adrenal insufficiency
    d. Dosing will be tapered from q12H methylprednisolone → q24H methylprednisolone → oral prednisone/prednisolone **based upon Rheumatology consult recommendations**.
    e. Patient will be discharged home on once daily prednisone/prednisolone based upon multi-disciplinary input. Outpatient doses will be tapered by Rheumatology in discussion with other subspecialties based upon trend in cardiac and inflammatory markers.

2. Anakinra: consider in patients with inadequate response to IVIG and corticosteroids based on clinical, laboratory, and/or echocardiographic evaluation. Suggest allowing at least 12h s/p 1st dose to steroids evaluate response unless clinical decline. May consider as part of combination initial treatment for patients with unusually severe/life-threatening initial presentation.

    -Anakinra Dosing: doses from 2-4mg/kg every 12 hours have been successfully used as initial dosing. May decrease from twice-daily to once-daily dosing once stability has been established, again with multispecialty input and consultation. Patients treated with

anakinra should be observed in the hospital for 24 hours off of the medication prior to discharge.

Anticoagulation and antiplatelet therapy

1. **Enoxaparin** prophylaxis (to begin at presumed/suspected diagnosis)
    a. **See Pediatric Enoxaparin Guidelines for dosing and monitoring recommendations**
    b. Goal anti-Xa level for prophylaxis is 0.1-0.5 IU/mL drawn 4-6 hours after the 3rd-4th dose of regimen; dosing and duration to be determined in consultation with pediatric hematology service.
2. **Aspirin** (round dose to nearest ½ tablet up to 81mg PO daily): 3-5 mg/kg/dose PO once daily. Use in patients with KD-like features and/or thrombocytosis (platelet count >450,000). Avoid in thrombocytopenia (platelet count <80,000/uL).
3. **SCDs**

Additional considerations

1. **Antipyretic therapy**
    a. Acetaminophen: 10-15 mg/kg/dose (max 650 mg) PO/rectal q4-6h PRN fever
    b. Avoid ibuprofen, if possible, due to potential adverse drug interaction with aspirin
2. **GI protection**
    a. Famotidine 0.5 mg/kg (max 20 mg) PO/IV q12h, or PPI depending on availability

REFERENCES:

- CDC Case Definition
- Riphagen S, et al. Hyperinflammatory shock case series. Lancet 2020
- Verdoni. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study
- Toubiana. Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France
- Belhadjer et al. Pediatric acute heart failure and SARS-CoV-2 infection. Circulation
- Licciardi. SARS-CoV-2 Induced Kawasaki-like Hyperinflammatory Syndrome: A Novel COIVD Phenotype in Children. Pediatrics

MIS-C

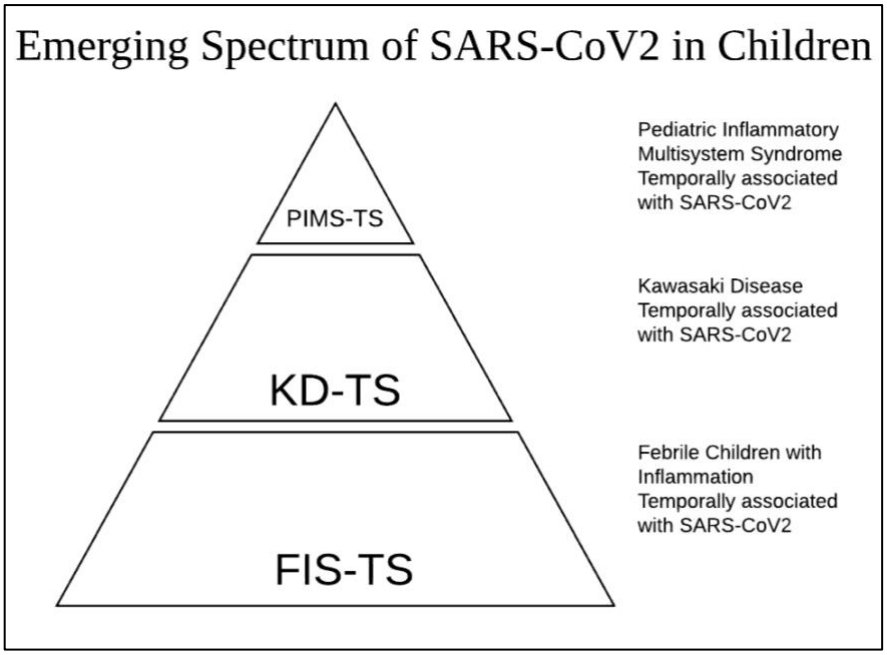
Multisystem Inflammatory Syndrome in Children

Overview

Areas hard hit by COVID-19 around the world have described a new pediatric illness that appears to follow a SARS-CoV-2 infection or exposure. Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity of uncertain etiology that involves significant hyper-inflammation, potentially leading to organ dysfunction and shock. Presentation features may overlap Kawasaki Disease or Toxic Shock Syndrome.

It is postulated that MIS-C is a post-infectious hyper-inflammatory process, rather than a manifestation of an acute infection. In case series in NYC and the UK, patients had antibodies for the virus despite negative nasopharyngeal SARS-CoV-2 PCR swabs.

As we gain experience with this new illness, it appears that MIS-C (sometimes also called Pediatric Inflammatory Multisystem Syndrome or PIMS) is on a spectrum of febrile, inflammatory illnesses associated with COVID-19. We do not know yet if they represent a single, continuous process or separate clinical entities with overlapping features, and it is unclear if that distinction is important in determining health outcomes in children with MIS-C.



Adapted from Michael Levin, "Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 –PIMS-TS," COCA Webinar, 19 May 2020

While we know that these patients are at high risk for developing cardiovascular collapse, resulting in the need for high levels of critical care support, what is less clear at this time is how these patients can be differentiated from those with more common pediatric febrile illnesses such as viral gastroenteritis or a urinary tract infection

MIS-C

Multisystem Inflammatory Syndrome in Children

This document and the associated algorithms are intended to help physicians understand the clinical presentation of MIS-C, providing a systematic framework for the evaluation and early diagnosis of patients with suspected MIS-C, when they are hopefully at lower risk of cardiovascular collapse. The algorithms are designed to be used **in addition** to your typical approach to the febrile pediatric patient.

Important Consideration

MIS-C is a very new syndrome, and little information exists in the literature regarding signs, symptoms, laboratory data, or best practices, such as basic care guidelines and treatment options. The medical community is still in the early stages of investigating this condition, and our understanding of MIS-C will surely evolve and change in the next few weeks to months.

The recommendations found here are based on the expert opinions of pediatric specialists at C.S. Mott Children's Hospital. We have taken into account published case reports of patients with MIS-C, as well as information from webinars presented by clinicians treating MIS-C patients around the world. Our goal is to identify patients who are at risk for further clinical deterioration at a point prior to cardiovascular collapse, without including every child with a common febrile illness.

Keeping in mind our goal of differentiating patients with MIS-C from patients with more typical febrile childhood illnesses, we have recommended clinical criteria for initiating a laboratory workup, and then laboratory thresholds that warrant further observation and/or investigation. The clinician's judgment is an important factor as well and should be taken into consideration.

As MIS-C becomes better understood and more data become available, we anticipate that these guidelines will be frequently updated to reflect new information.

Presentation

Children with MIS-C exhibit signs and symptoms that significantly overlap with typical pediatric febrile illnesses. It is therefore important to consider the fever curve carefully. Patients universally present with prolonged or persistent fever and often complain of fever that is resistant to antipyretics. Most patients experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea, and vomiting. Additional features include rash, conjunctivitis, headache, and sore throat.

A subset of patients present with shock and require high levels of supportive care in addition to coverage for sepsis and consideration for MIS-C.

MIS-C

Multisystem Inflammatory Syndrome in Children

Concerning presenting signs and symptoms

- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy
- Shock

Initial Workup

As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.

Initial laboratory testing

- CBCPD
- Comprehensive Panel
- CRP
- D-Dimer
- High Sensitivity Troponin
- Ferritin

Laboratory thresholds of concern:

- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- D-dimer >1 mg/L
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Please refer to the ED/Outpatient Algorithm for further decision-making guidance.

Case Definitions

Since MIS-C is such a poorly understood condition at this time, with more questions than answers, data collection is a high priority for the medical community and public health agencies around the world. The Centers for Disease Control and the World Health Organization have recently established case definitions and registries for the syndrome to allow for a more systematic approach to diagnosis, better recognition of risk factors and causality, and more standardized collection of data for subsequent research. The CDC and the WHO differ slightly in their definitions; both are included below.

MIS-C

Multisystem Inflammatory Syndrome in Children

CDC case definition:

A. Age < 21 years
B. Clinical presentation including **all** of the following:
    1. Fever >38.0C (100.4F) for ≥ 24 hours or subjective fever lasting ≥ 24 hours
    2. Laboratory evidence of inflammation, including but not limited to:
        - Elevated CRP
        - Elevated ESR
        - Elevated fibrinogen
        - Elevated procalcitonin
        - Elevated D-dimer
        - Elevated ferritin
        - Elevated LDH
        - Elevated IL-6 level
        - Neutrophilia
        - Lymphcytopenia
        - Hypoalbuminemia
    3. Severe illness requiring hospitalization
    4. Multisystem (2 or more) involvement
        - Cardiovascular
        - Renal
        - Respiratory
        - Hematologic
        - Gastrointestinal
        - Dermatologic
        - Neurologic
C. No alternative plausible diagnosis
D. Recent or current SARS-CoV-2 infection or exposure, with **any** of the following:
    - Positive SARS-CoV-2 RT-PCR
    - Positive serology
    - Positive antigen test
    - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

MIS-C

Multisystem Inflammatory Syndrome in Children

WHO case definition:

A. Age 0-19 years
B. Fever for ≥ 3 days
C. **At least 2** of the following clinical signs:
    - Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, feet)
    - Hypotension or shock
    - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP
    - Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
    - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
D. Elevated markers of inflammation, such as ESR, CRP, procalcitonin
E. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal or streptococcal toxic shock syndromes
F. Evidence of COVID-19, with any of the following:
    - Positive SARS-CoV-2 RT-PCR
    - Positive serology
    - Positive antigen test
    - Likely contact with an individual with COVID-19

MIS-C

Multisystem Inflammatory Syndrome in Children

Inpatient Considerations

Once a patient suspected of having MIS-C is admitted, further workup to look for specific areas of inflammation will be initiated. Given the high risk of cardiovascular collapse, patients admitted with a diagnosis of presumed MIS-C also warrant very close monitoring and a multidisciplinary approach to care.

Additional Workup at Admission

SARS-CoV2 swab	Procalcitonin	BNP
SARS-CoV2 serologies	PT/PTT	LDH
RPAN	Fibrinogen	Cytokine Panel
Blood culture	ESR	EKG
UA w/ reflex urine culture	CK	Echocardiogram
VBG	Triglycerides	Peripheral smear

- If ALC <0.5, order a Primary Immunodeficiency Flow Panel
- Consider obtaining IgG levels
- To order the peripheral smear:
  Order "Peripheral Smear Morphology Review Request"
  Type in "for Cellavision Review" in the additional comments box

Daily Labs

CBCPD	Ferritin	BNP, if elevated initially
CMP	PT/PTT	Troponin, if elevated initially
CRP	Fibrinogen	
ESR	D-Dimer	

Special Pathogen Isolation

Patients with MIS-C are presumed to have current or recent SARS-CoV2 infection and should be considered Persons Under Investigation and placed in special pathogen precautions initially. Patients do not need negative pressure rooms unless they are likely to undergo aerosol-generating procedures.

- To discontinue special pathogen precautions, patients will need to have two negative SARS-CoV2 PCR swabs, at least 24 hours apart. They should remain in special pathogen isolation until the 2nd swab has returned as negative.
- Once cleared for COVID-19, patients will require isolation precautions appropriate to their clinical presentation and diagnosis.
- Please refer to the Infection Prevention and Epidemiology (IPE) website for the most up-to-date recommendations regarding special pathogen precautions: http://www.med.umich.edu/i/ice/resources/clinical_guidance.html

MIS-C

Multisystem Inflammatory Syndrome in Children

Disease Reporting

MIS-C is currently a reportable disease process, but should only be reported after there is sufficient evidence to make a diagnosis of presumed MIS-C. At this time, we are using the CDC case definition.

- Notify IPE at pager 30032 or by email at UM-ICE@med.umich.edu to report the case. IPE will enter the case into the state database.
- Please document in the chart once IPE has been notified.

Vital Sign Monitoring

All patients admitted for presumed MIS-C require close and continuous monitoring to ensure hemodynamic stability.

- Place on a continuous cardiorespiratory monitor (+/- telemetry).
- Place on continuous pulse oximetry.
- Consider checking vital signs every 2 hours initially if there is increased concern for instability.

Subspecialty Consultations

The management of MIS-C requires a multidisciplinary team approach as it is a complex, multi-organ disease. Consultations should be ordered whenever there are clinical concerns, but the following services are frequently involved in the care of MIS-C patients.

- ID – Consult at the time of admission
- Hematology – Consult if there is clinical concern for coagulopathy
- Rheumatology – Consult if there are clinical concerns
- Cardiology – Consult for criteria listed below

Antibiotic Coverage

As MIS-C is not a bacterial process, patients do not require coverage with antibiotics unless there is concern for concomitant bacterial infection or sepsis. Empiric antibiotic coverage should be determined according the institutional sepsis guidelines and should be tailored if a bacterial process is identified.

- http://www.med.umich.edu/asp/pdf/pediatric_guidelines/Sepsis_PEDS.pdf

Anticoagulation

Although patients with MIS-C often have evidence of hypercoagulability, not all patients develop thromboses or require anticoagulation. Hematology should be consulted if there are clinical concerns for coagulopathy to help determine the need for anticoagulation and the appropriate medication choices. Before starting anticoagulation, please check platelet count and kidney function.

Cardiac Workup

MIS-C was first recognized due to the unexpected incidence of atypical Kawasaki Disease in pediatric COVID-19 patients. It is now recognized as a separate clinical entity, but similar to KD, patients have an increased risk of cardiovascular abnormality, ranging from myocarditis to coronary aneurysms to ventricular dysfunction.

- A cardiac workup should be initiated at the time of admission, including high-sensitivity troponin, BNP, EKG, and transthoracic echocardiogram.
- Consult cardiology for all patients with abnormal screening cardiac labs, EKG, echocardiogram or other clinical concerns for cardiac involvement.

MIS-C

Multisystem Inflammatory Syndrome in Children

- Initial echocardiogram can be a routine study, performed without sedation, unless the clinical situation warrants a more expedited evaluation.
- Note that the coronary arteries may be difficult to visualize in non-sedated patients, but the risk/benefit analysis does not currently justify sedating all patients. We suggest beginning with a non-sedated echocardiogram, and if views are suboptimal or there is a suspicion for important findings, a discussion between the inpatient and cardiology attendings should take place to decide if sedation is warranted.
- Follow-up recommendations below:

Initial cardiac workup	Clinical condition	Recommendations
Normal labs AND Normal echo	• Inflammatory markers improving • Hospitalization <72hrs	• Repeat echo 2 weeks after discharge
	• Inflammatory markers improving • >72hrs	• Repeat echo prior to discharge
	• Inflammatory markers significantly abnormal or worsening • Clinical deterioration	• Repeat echo and cardiac screening labs prior to discharge • Follow-up 2 weeks after discharge with clinic visit and repeat echo
	• Meets criteria for Kawasaki Disease or atypical KD	•Cardiology consult •Management for KD as per AHA algorithm
Abnormal labs OR Abnormal echo	• Variable	• Cardiology consult • Follow-up per consult team

Additional Considerations

Consider undertaking genetic testing to help identify underlying susceptibilities in patients with MIS-C. They may share genetic predispositions with other inflammatory syndromes. The recommended genetic test is the Blueprint Genetics Comprehensive Immune and Cytopenias panel. It is a very new test, and only certain providers (Rheumatology and Hematology) have access to order it, and they will often already be consulted.

Discharge Criteria

Patients can be considered for discharge once they have been afebrile for at least 24 hours and their lab work is returning to baseline. Naturally, discharge decisions will be dependent on the patient's condition and the provider's clinical judgment.

MIS-C

Multisystem Inflammatory Syndrome in Children

Inpatient Quick Reference

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized inflammatory syndrome presenting in pediatric patients, associated with current or recent SARS-CoV-2 infection. The pathogenesis is unclear, and the manifestations are still being clarified. At present, we know that children present with prolonged or persistent fever and a constellation of variable symptoms. They exhibit many markers of significant inflammation and are at high risk for cardiovascular collapse. This document accompanies the MIS-C protocol and is designed to be a quick reference guide when admitting these patients.

Initial evaluation criteria

T ≥ 38.5C for at least 3 days
No specific etiology identified

Concerning signs and symptoms

- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy

Initial lab testing and thresholds of concern:

- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- D-dimer >1 mg/L
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Additional Workup at Admission

SARS-CoV-2 swab	Procalcitonin	BNP
SARS-CoV-2 serologies	PT/PTT	LDH
RPAN	Fibrinogen	Cytokine Panel
Blood culture	ESR	EKG
UA w/ reflex urine culture	CK	Echocardiogram
VBG	Triglycerides	Peripheral smear

- If ALC <0.5, order a Primary Immunodeficiency Flow Panel
- Consider obtaining IgG levels
- To order the peripheral smear:
  Order “Peripheral Smear Morphology Review Request”
  Type in “For Cellavision Review” in the additional comments box

MIS-C

Multisystem Inflammatory Syndrome in Children

Daily Labs

CBCPD	Ferritin	BNP, if elevated
CMP	PT/PTT	Troponin, if elevated
CRP	Fibrinogen	
ESR	D-Dimer	

Vital Signs Monitoring

- Continuous cardiorespiratory monitor (+/- telemetry)
- Continuous pulse oximetry
- Consider checking vital signs every 2-4 hours initially if there is any concern for instability

Special Pathogen Isolation

- Place patients in special pathogen precautions
- Negative pressure rooms are not needed unless patients are likely to undergo aerosol-generating procedures
- May discontinue precautions after 2 negative SARS-CoV2 PCR swabs, at least 24 hours apart
- Most up-to-date recommendations regarding special pathogen precautions: http://www.med.umich.edu/i/ice/resources/clinical_guidance.html

Disease Reporting

- Must report disease if there is sufficient evidence to make diagnosis of presumed MIS-C, based on the CDC case definition
- Notify IPE at pager 30032 or by email at UM-ICE@med.umich.edu to report the case. IPE will enter the case into the state database
- Please document in the chart once IPE has been notified

Subspecialty Consultations

- ID – Consult at the time of admission
- Hematology – Consult if there is clinical concern for coagulopathy
- Rheumatology – Consult if there are clinical concerns
- Cardiology – Consult if abnormal cardiac screening labs, abnormal EKG, or abnormal echo, or if there is clinical concern for cardiac involvement

Antibiotic Coverage

- Only if concerned about concomitant bacterial infection or sepsis
- Empiric antibiotic coverage for sepsis per the institutional sepsis guidelines and should be tailored if a bacterial process is identified
- http://www.med.umich.edu/asp/pdf/pediatric_guidelines/Sepsis_PEDS.pdf

Increasing Level of Care

- Please have a lower threshold for calling an RRT on these patients; the PICU is aware this will occur

MIS-C

Multisystem Inflammatory Syndrome in Children

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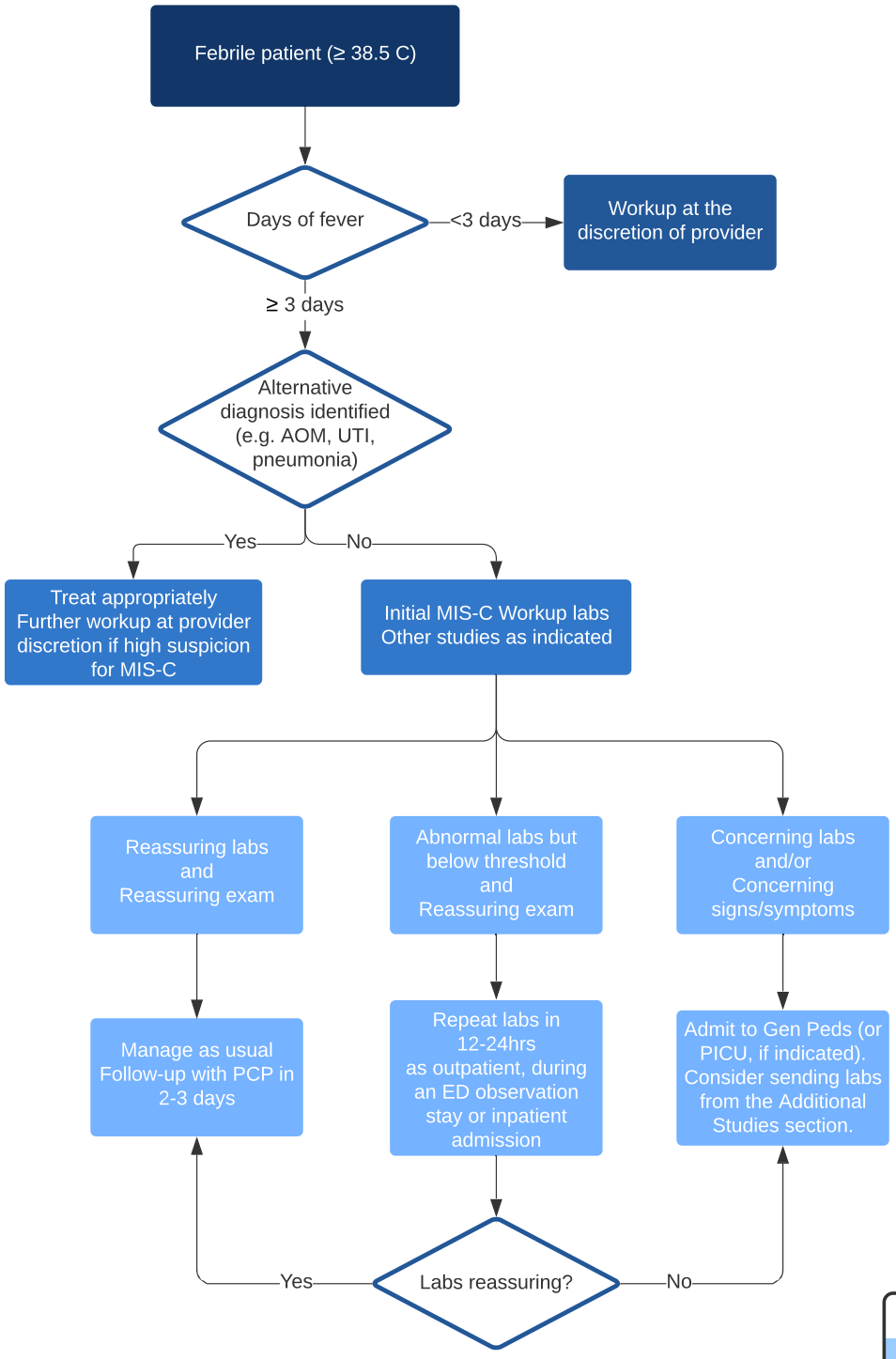
Mott ED/Inpatient MIS-C Evaluation Algorithm

C.S. Mott's Children's Hospital
June 18, 2020

This algorithm is designed to guide the initial evaluation of patients presenting with suspected Multi-system Inflammatory Syndrome in Children (MIS-C), also called Pediatric Inflammatory Multi-system Syndrome (PIMS). The Initial MIS-C Workup labs are appropriate across the ED and inpatient settings. The recommendations here should serve as a supplement to the workup for other illnesses, as indicated, and they assume that ED referral, admission/discharge criteria, and follow-up decisions will also be guided by the patient's clinical condition and alternative diagnoses.



Frequently Reported Symptoms

- Abdominal pain, diarrhea, other GI symptoms
- Rash
- Extremity changes such as edema
- Conjunctivitis
- Lymphadenopathy

Consider ordering Initial MIS-C Workup labs in any febrile patient who requires labwork for other reasons.

Disposition in the presence of an alternate etiology is beyond the scope of this algorithm and may benefit from collaborative discussion.

Initial MIS-C Workup

CBCPD
Comprehensive Panel
CRP
D-Dimer
High Sensitivity Troponin
Ferritin
EKG

Lab Thresholds of Concern

Albumin <2 g/dL
CRP >10 mg/dL
D-dimer >1 mg/L
Absolute Lymphocyte Count <0.5 K/uL
High Sensitivity Troponin >30 pg/mL
Ferritin >350 ng/mL

If Admitting the Patient

Please refer to the MIS-C Overview document for information regarding additional work up, consults and other standardized care for these patients.

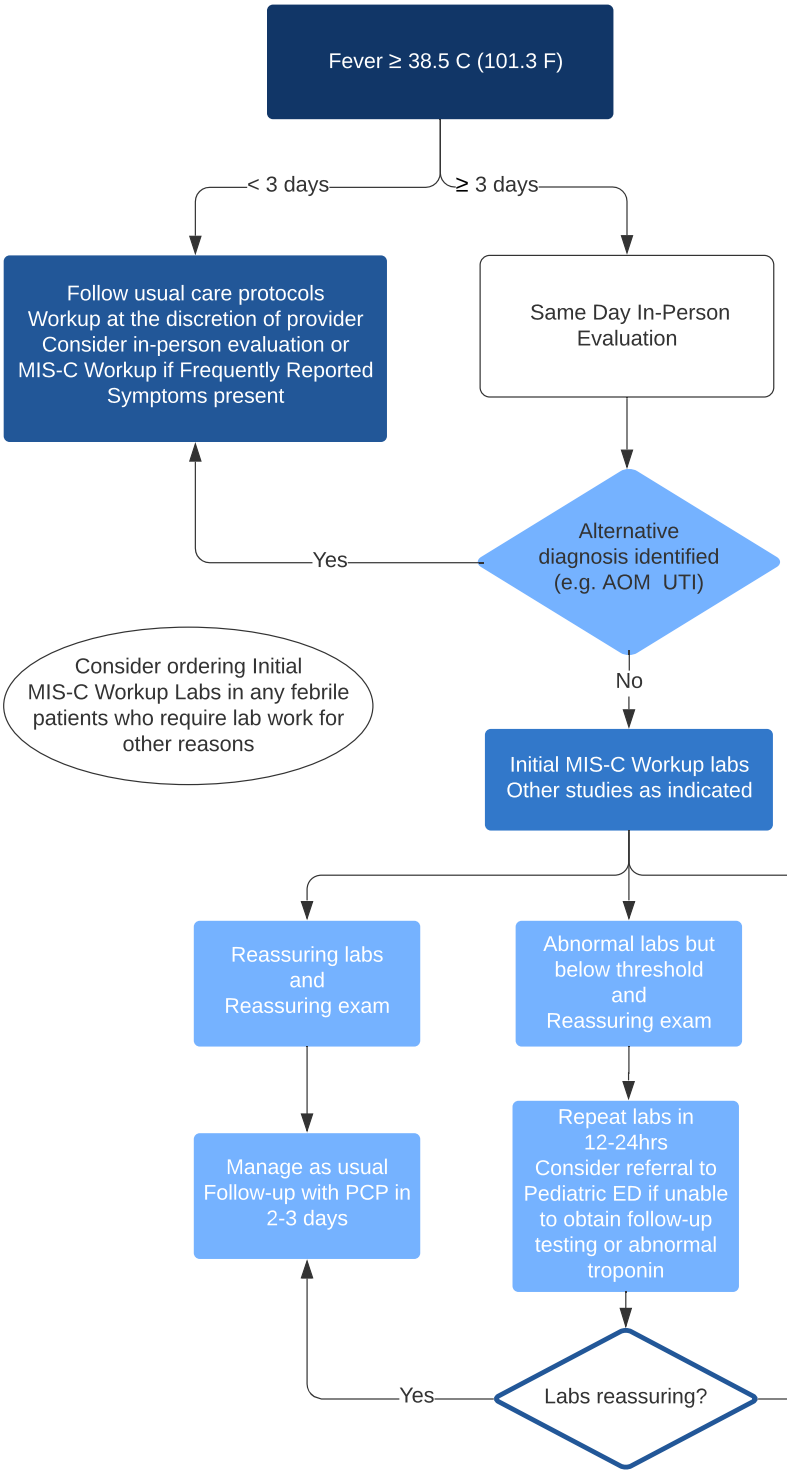
Patients should remain in special pathogen precautions as a COVID Person Under Investigation until they have 2 negative COVID-19 swabs, at least 24 hours apart. They do not require negative pressure rooms unless they are likely to undergo aerosol-generating procedures.

Additional Studies on Admission	
COVID-19 swab	ESR
RPAN	CPK
Blood culture	Triglycerides
UA & reflex culture	BNP
VBG	LDH
Procalcitonin	Cytokine panel
PT/PTT	COVID serologies
Fibrinogen	Echocardiogram

Outpatient MIS-C Evaluation Algorithm

Michigan Medicine Pediatrics/IHA Pediatrics
June 18, 2020

This is algorithm designed to guide the initial evaluation of patients for Multi-system Inflammatory Syndrome in Children (MIS-C), also called Pediatric Inflammatory Multi-system Syndrome (PIMS). The recommendations here should serve as a supplement to the workup for other illnesses, as indicated, and they assume that ED referral and follow-up decisions will also be guided by the patient's clinical condition and alternative diagnoses.



Consider sending to the Pediatric ED

Any patient who is:

- Unable to be evaluated in a timely manner
- Not well-appearing
- Unable to obtain the needed laboratory studies at an outpatient blood draw station

Frequently Reported Symptoms

- Abdominal pain, diarrhea, other GI symptoms
- Rash
- Extremity changes such as edema
- Conjunctivitis
- Lymphadenopathy

Initial MIS-C Workup Labs

ORDER STAT
CBCPD
Comprehensive Panel
CRP
D-Dimer
High Sensitivity Troponin
Ferritin

Lab Thresholds of Concern

Albumin <2 g/dL
CRP >10 mg/dL
D-dimer >1 mg/L
Absolute Lymphocyte Count <0.5 K/uL
High Sensitivity Troponin >30 pg/mL
Ferritin >350 ng/mL

What to Expect in the ED

Further testing, as indicated
COVID testing
Observation in the ED (up to 24 hours) and possible admission
Only 2 adult visitors will be allowed into the ED
Patients will be treated as COVID Persons Under Investigation

Inpatient Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

< 21 yr old with suspected MIS-C admitted based on ED MIS-C algortihm

Degree of cardiac involvement determines disposition (PC3, PICU, PCICU) based on discussion between cardiology and floor/ICU attendings

Stay in Special Airborne Contact Isolation till cleared by Infection prevention

Clinical features suggesting MIS-C	Examples of organ system dysfunction
One or more of the following: Diarrhea Abdominal pain Conjunctivitis Mucositis Rash Abnormal mental status Shock Hypoxia Joint pains /Swelling of hands and feet	Gastrointestinal (e.g. abdominal pain, diarrhea) Cardiac (e.g. shock, elevated troponin, elevated BNP, abnormal echo, new arrhythmia, ST/T wave changes on EKG) Respiratory (e.g. pneumonia, ARDS, pulmonary embolism) Renal (e.g. acute kidney injury or renal failure) Liver (e.g. elevated bilirubin or elevated liver enzymes) Neurologic (e.g. CVA, aseptic meningitis) Hematologic (e.g. coagulopathy, elevated D Dimers, thrombophilia or thrombocytopenia) Skin manifestations (e.g. polymorphic rash, petechiae, purpura)

Duke MIS-C case definition

1. **<21 yrs presenting with fever > 3 days and lab evidence of inflammation (leucocytosis/CRP) and evidence of clinically severe illness reqiring hospitalization with >/=2 organ system involvement (cardiac, resp, renal, Heme, GI, Neuro or Derm) AND**
2. **no alternative diagnosis AND**
3. **+ SARS-CoV2 PCR *or* serology *or* COVID-19 exposure within 4 weeks**

Additional work up

ECHO (if not obtained in ED)
Type and Screen
Triglycerides, Mag and Phos, SARS-CoV2 antibody IgG
ERVP if respiratory symptoms
Consider daily CBCD, CMP, DIC panel, CRP and cardiac markers

Consults

Consult infectious disease for all admitted patients.
Consult rheumatology for elevated inflammatory markers.
Consult hematology for elevated D-dimer.
Consult cardiology for elevated troponins, EKG/echo abnormalities.

Patients with MIS-C triaged to stepdown should be monitored closely for clinical deterioration. Rapid clinical deterioration has been reported. COVID RRT should be called to enable appropriate response from RRT team when appropriate

Pathway developed by the Department of Pediatrics, Duke University: Revised [June 11, 2020]
It is not a substitute for independent professional medical assessment,diagnosis, and treatment.

Incomplete/complete Kawasaki Disease	Myocarditis or depressed LV systolic function	Severe disease
1. IVIG 2 g/kg 2. Aspirin 30-50 mg/kg/d divided q6 hrs while febrile, decrease to 3-5mg/kg(max 81 mg) daily once patient defervesces 3. For high-risk KD patient (CAA at diagnosis, age < 6 months, IVIG resistance, CRP > 13 mg/dL), consider adding prednisone 1 mg/kg BID with a tapering course over ~3 weeks 4. Additional immumodulators as needed in conjunction with Rheumatology, 5. Infectious Disease, and/or Immunology and based on response to initial IVIG therapy	1. Consider IVIG 1 g/kg daily x 2 days 2. For patients with moderate or greater systolic dysfunction, consider full anticoagulation with heparin, Lovenox, or warfarin in consultation with hematology 3. Consult with rheumatology and/or infectious disease regarding additional immunosuppression options: Anakinra (interleukin-1 inhibitor), corticosteroids,Tocilizumab (interleukin-6 inhibitor)	1. Consult hematology for recommendations on anticoagulation (aspirin, lovenox or heparin) 2. Consult Infectious Disease about use of antivirals (remdesivir) 3. Consult Rheumatology/Immunology about use of immumodulating medications: Anakinra (interleukin-1 inhibitor), canakinumab (interleukin-1 inhibitor), IVIG, corticosteroids, Tocilizumab (interleukin-6 inhibitor)

For Acute COVID pediatric management guidelines please visit customid.org
https://www.customid.org/antimicrobial/guideline-therapeutic-management-pediatric-patients-confirmed-covid-19-peds

UR MEDICINE

GOLISANO CHILDREN'S HOSPITAL

GCH Algorithm for Evaluation of Multi-System Inflammatory Syndrome in Children (MIS-C) for Emergency Department and Inpatient

Patient <21yrs of age presents with fever ≥100.4°F/38°C

Does the patient have EITHER:

- **One or more** of the following:
  - Hypotension or shock (cardiogenic or vasogenic)
  - Features of severe cardiac illness/signs of cardiac dysfunction
  - Other severe end-organ involvement including but not limited to neurological or renal disease (excluding severe respiratory distress alone)

OR

- **Two or more** of the following:
  - Maculopapular rash
  - Bilateral non-purulent conjunctivitis
  - Mucocutaneous inflammatory signs (mouth, hands, or feet)
  - Acute GI symptoms (diarrhea, vomiting, or abdominal pain)

NO → **Low suspicion for MIS-C;** continue work up and management, as appropriate

YES

Proceed with the following work up:

- COVID PCR **AND** serology (SARS-CoV-2 IgG Ab)
- CBC w/ diff, CMP, CRP, ESR, fibrinogen, D-dimer, ferritin, HS Troponin T, NT-pro BNP
- EKG
- UA, urine culture, blood culture
- Imaging (e.g., CXR, abdominal imaging)/add'l testing as clinically indicated

Is the patient well appearing without evidence of hemodynamic instability?

YES

Does the patient meet criteria for admission?

NO → **Discharge home with anticipatory guidance and close PCP follow up**

YES

Do the labs demonstrate **ANY** of the following:

- **Two or more** markers of inflammation*
- Detection of SARS-CoV-2 via PCR or serology** **OR** known history of SARS-CoV-2 infection

AND

No alternative explanation (e.g., bacterial UTI, SSTI)

NO → **Consider alternative diagnoses**

YES

NO

Do the labs demonstrate **ANY** of the following:

- **Two or more** markers of inflammation*
- Detection of SARS-CoV-2 via PCR or serology** **OR** known history of SARS-CoV-2 infection

NO → **Consider alternative diagnoses**

YES

Strong suspicion for MIS-C

- Consider hold SST tube after discussion with ID
- Proceed to page 2

Neutrophilia, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated CRP, ESR, D-dimer, ferritin, fibrinogen

References:

1. https://emergency.cdc.gov/han/2020/han00432.asp
2. New York State Department of Health, Health Advisory: Pediatric Multi-System Inflammatory Syndrome Temporally Associated with COVID-19 Interim Case Definition in NYS (access pdf here)

Note: Guidance is rapidly evolving with COVID-19 and this algorithm is subject to change.

GCH Guidance for Patient Placement with Suspicion of Multi-System Inflammatory Syndrome in Children (MIS-C)

Strong Suspicion for MIS-C and Need for Hospitalization

Does the patient have ANY of the following:

- Hypotension and/or tachycardia unresponsive to fluids
- Concern for/evidence of cardiac dysfunction* (including lab elevation in HS Troponin T or NT-pro BNP)
- Concern for/evidence of end organ damage*
- Concern for/evidence of coagulation abnormalities*

YES

Consult Pediatric Intensive Care Unit (PICU) for Possible Admission

- Echocardiogram **NOT** required prior to transfer
  - Admit to PICU for ongoing evaluation and management with transfer to Pediatric Cardiac Care Center (PCCC) if significant myocardial involvement identified

NO

Admit to Pediatric Hospital Medicine (PHM) service and 8S (if bed available)

Isolation Requirements: In absence of need for COVID Quarantine based on COVID screening questions, for **ALL** patients with suspected MIS-C: Order droplet/eye/contact isolation (COVID precautions) until patient has negative COVID PCR x2 (24hrs apart)

*Definition of *concern for/evidence of* is ill defined as presentations vary and can evolve over time – PICU consultation and discussion with PHM attending is encouraged to help determine disposition for patients for whom placement is unclear

GCH Guidance for Management of Multi-System Inflammatory Syndrome in Children (MIS-C)

Consultation	Treatment Options

• Pediatric Cardiology consult and echocardiogram for all patients, subsequent cardiac studies per cardiology team
• Pediatric Infectious Disease consult for all patients
• Consider Hematology/Oncology (H/O) consult if evidence of significant coagulation abnormalities
• Consider Rheumatology consult if concern for macrophage activation syndrome (MAS) or atypical or severe presentation
• Consider PICU consult for patients with deterioration/worsening status
  • Drs. Cholette and Atallah to be contacted by PICU to assist with determining whether the patient will be admitted to the PICU or PCCC
	• Consider empiric abx coverage, if appropriate
	• Consider IVIG, especially if patient meets criteria for Kawasaki/incomplete Kawasaki.
	  • IVIG dose 2 g/kg (max 100 g)
	• Consider ASA, especially if patient meets criteria for Kawasaki/incomplete Kawasaki
	• Consideration of early steroids if refractory symptoms or concern for MAS
	• Consider prophylactic enoxaparin (dosed at 0.5mg/kg q12h) if aged >/= 18yrs **OR** critically ill **OR** at high risk for thromboembolic disease (e.g., cancer, autoimmune disease, sickle cell disease, obesity, receiving estrogen therapy, inherited thrombophilia, personal/family hx of thrombosis, decreased mobility, central lines)
	• Consideration of biologics on case by case basis with consultant

Note: Guidance is rapidly evolving with COVID-19 and this algorithm is subject to change.

Recommended Follow up for Patients with Multi-System Inflammatory Syndrome in Children (MIS-C)

SPECIALTY FOLLOW UP
• PCP: follow up within 2-3 days after discharge (in person or via video) • Cardiology: follow up 1-2 weeks (for Kawasaki-like presentation) or 1 month after discharge unless cardiac findings that require follow up sooner • Consider follow up with other specialties on case by case basis
LABORATORY FOLLOW UP*

• Consider repeat labs within 1-2 weeks after discharge pending clinical picture (e.g., Kawasaki-like presentation)
• Order the following labs to coincide with first cardiology visit:
  • CBC with diff, ESR, CRP
  • Consider repeat ferritin if concern for MAS
  • Consider repeat NT-pro BNP
  • Consider COVID serology (SARS-CoV-2 IgG Ab) if previously negative or not done (needs to be interpreted with caution in context of receipt of IVIG)
 	
* Order labs at time of discharge, if possible, and cc PCP and Cardiology and Infectious Disease physicians involved during hospitalization/at time of discharge on order

RESTRICTIONS
• Restrict physical activity until cleared by cardiology
MEDICATIONS
• Continue ASA for at least 4-6 weeks • Consider other medications on case by case basis

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Note: Guidance is rapidly evolving with COVID-19 and this algorithm is subject to change.

NYULH Multisystem Inflammatory Syndrome in Children (MIS-C) for ED and Inpatient setting.
Edited: 6/23/2020

Background

Multisystem Inflammatory Syndrome-Children (MIS-C) appears to be an inflammatory response to a prior SARS-CoV-2 infection. Cases reports have ranged in age from infancy to young adult. Most MIS-C patients present with fever, laboratory evidence of inflammation and multisystem abnormalities which are usually not respiratory in nature. Abdominal pain, vomiting, and/or diarrhea have been present in 80% of 163 children presenting in MIS-C cases in NYC and 60% had rash. Clinical features of MIS-C could resemble those seen in other diseases, including Kawasaki Disease, Hemaphagocytic Lymphohistiocytois (HLH), cardiovascular shock.

Signs and symptoms related to MIS-C can be transient. If a caregiver or another clinician has noted a sign or symptom during a patient's febrile illness that is not observed during your own evaluation, consider the previous report to be accurate and representative of an evolving illness. Children and adolescents diagnosed with MIS-C could also have bacterial (e.g., cervical lymphadenitis, urinary tract infection) or viral co-infections (e.g., Epstein–Barr virus, parvovirus). Children may have a history of a COVID-like illness, or of having exposure to a person with COVID-like illness, in the preceding 4-6 weeks. In NYC 75% of children had either positive SARS-CoV-2 PCR or antibody testing, so capturing prior infection is helpful but not necessary to make the MIS-C diagnosis.

Evaluation of MIS-C in ED and inpatient setting.

Fever and signs/symptoms of shock, evaluate for MIS-C

Stable children and young adults: Fever for 3 days and signs/symptoms from two different organ systems, evaluate for MIS-C.

- Gastrointestinal symptoms (nausea, abdominal pain, vomiting, diarrhea)
- Rash (variable in appearance, including but not limited to maculopapular, scarlatiniform)
- Conjunctivitis (bilateral bulbar conjunctival injection without exudate)
- Oral mucosal changes (erythema and cracking of lips, strawberry tongue, and/or erythema of oropharyngeal mucosa)
- Extremity changes (erythema and/or edema of the hands and feet)
- Neurologic or Psychiatric Symptoms (headache, irritability, cranial nerve palsy)
- Lymphadenitis (neck swelling causing significant pain and/or sore throat)

Work up:
Labs: CBC, chem 20 and if abdominal pain lipase, CRP, ESR, troponin, BNP, D-Dimer, ferritin, LDH, Procalcitonin, SARS-CoV 2 antibody, SARS-CoV-2 PCR

Ruling out other differentials: Blood culture, UA with reflex to Ucx, respiratory panel, focused work up depending how patient presents.
Studies in ED or once admitted: EKG and Echo

Admissions

- Admit patients with shock or markers of inflammation which are several multiples of normal. In NYC among 99 MIS-C patients, nearly all patient have elevated CRP (median 36) 90% have elevated BNP, 70% have elevated troponin.
- Patients with severe inflammation or organ dysfunction should be admitted to ICU
- Please consult Pediatric Rheumatology, Cardiology, ID and Hematology.

Treatments for MIS-C:
Treatment is tailored to patient.
NYULH has been most effective treating with IVIG, methylprednisolone and aspirin

- IVIG**:** 2 g/kg (max 100 grams) infused slowly over 8-12 hours (max at 3rd rate of titration step).
- Aspirin
    - Moderate-dose (30 mg/kg/day divided BiD) dosing of ASA.
    - Low-dose ASA (3-5 mg/kg/day ~ half baby aspirin up to 81 mg daily).
    - Possible six-week supply of ASA, until a six-week follow-up echocardiogram is normal and not revealing any signs of coronary artery dilation.

Some children have received anti-cytokine therapy and antibiotics for superinfections.

Isolation:
As this illness is suspected to occur 4-6 weeks after acute Covid infection, isolation is likely not necessary.
All SARS-CoV-2 PCR negative: no isolation
SASRS-CoV-2-positive with IgG and cycle threshold of PCR ≥35, no isolation
SARS-CoV-2-positive and IgG negative or cycle threshold <35, may isolate

Children discharged from ED

- Follow up within 24 hours either with PMD or MIS-C clinic (212 263-5490 option 3)

Multisystem Inflammatory Syndrome in Children:

an emerging condition associated with current or recent SARS-CoV-2 infection

Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity believed to follow a SARS-CoV-2 infection or exposure. The clinical presentation is accompanied by significant hyper-inflammation similar to that of Kawasaki Disease or Toxic Shock Syndrome and can lead to organ dysfunction and shock. The pathogenesis is unclear however it is thought to develop 4-6 weeks after an infection when macrophage activation and acquired immunity is occurring.

The CDC has since released a health advisory statement to alert health care providers and organize a case reporting system. Both the Centers for Disease Control and the World Health Organization have developed case definitions to guide the clinical diagnosis. See the links below and the full case definitions are copied on page 4 of this document for your reference as well.

CDC MIS-C definition

WHO MIS-C definition

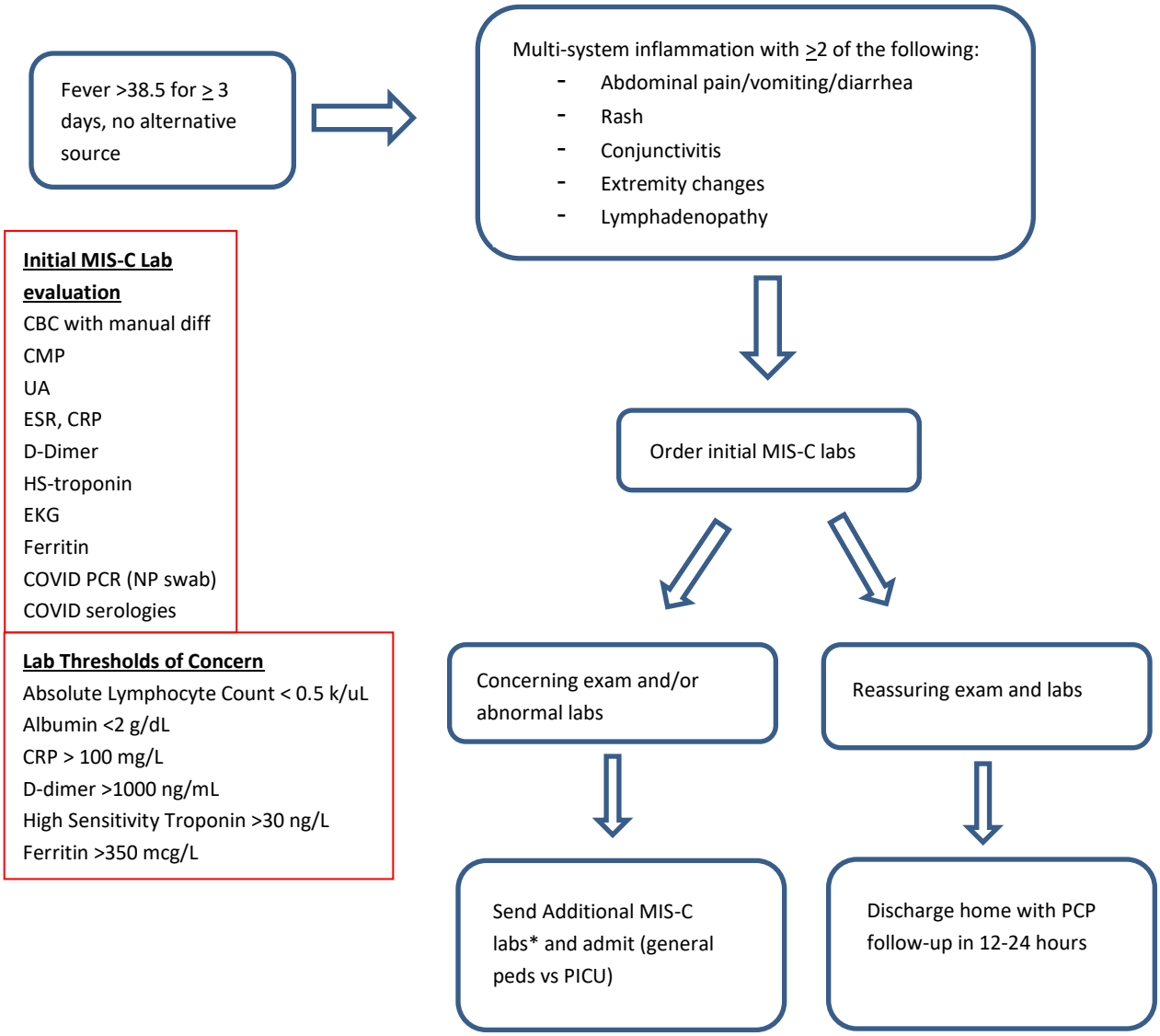
Children with MIS-C will most consistently present with prolonged fever and GI complaints (abdominal pain, vomiting, and diarrhea). Additional features include rash, extremity swelling, conjunctivitis, lymphadenopathy and appear very similar to Kawasaki Disease. The most concerning feature of MIS-C is progression to cardiovascular abnormalities (myocarditis, coronary aneurysms, ventricular dysfunction), and potentially shock. Children with MIS-C rarely exhibit respiratory complaints and death is rare.

Initial Workup/ED Evaluation

As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.

Concerning presenting signs and symptoms:

- Persistent fever, not fully responsive to antipyretics
- GI complaints such as abdominal pain (may mimic appendicitis) and/or diarrhea
- Rash
- Conjunctivitis
- Headache
- Respiratory symptoms
- Sore throat
- Lymphadenopathy
- Shock



*see next page

Inpatient Evaluation

Additional MIS-C Labs to be collected for admitted patients	
COVID PCR (NP swab x 2 total, 24 hrs apart)	PT/INR, PTT
COVID serologies if not sent	Fibrinogen
Film Array if COVID PCR negative	LDH
Blood Cx	Triglycerides
UA/UCx	BNP
VBG	Cytokine Panel
Procalcitonin	Echo
Peripheral Smear	CK

Daily lab monitoring	
CBC with manual diff	CMP
ESR, CRP	Ferritin
PT, PTT	Fibrinogen
D-dimer	BNP, troponin if original values were elevated

Vital Sign Monitoring

Continuous cardiorespiratory monitoring and continuous pulse oximetry

Isolation

Place patient in severe respiratory isolation until COVID PCR is negative x 2 (24 hours apart)

Negative pressure not needed unless pt likely to undergo aerosolizing procedures

VTE prophylaxis

Complete VTE assessment within epic on admission and reassess daily. Chemical prophylaxis with lovenox is recommended for COVID patients ≥12 years of age who are hospitalized and who do not have a contra-indication. For patients <12 years of age, VTE prophylaxis is recommended for moderate or severe COVID 19 infection or if otherwise indicated per VTE assessment. However, for MIS-C, evidence based guidelines have not been developed at this time. VTE prophylaxis should be strongly considered for any patient with suspected MIS-C, especially if D-dimer is elevated, and this should be discussed with hematology team on a case by case basis. Risks and benefits should be discussed with the patient/family.

Subspecialty consultations

ID consult if MIS-C is being considered. ID team will be responsible for reporting the disease and for outpatient follow-up (labs, echo). ID will recommend additional consultations as indicated to rheumatology, cardiology, heme/onc, immunology. Cardiology will need to be consulted if EKG, BNP/troponin or Echo are abnormal, or there are other concerns.

Disease Reporting

ID team will be responsible for reporting if there is sufficient evidence to make the diagnosis

Treatment considerations

Treatment approach will be individualized and may include supportive care, IVIG, steroids, immunomodulators as further evidence develops.

CDC case definition:

A. Age < 21 years
B. Clinical presentation including **all** of the following:
   1. Fever >38.0C (100.4F) for >/= 24 hours or subjective fever lasting >/= 24 hours
   2. Laboratory evidence of inflammation, including but not limited to:
      - Elevated CRP
      - Elevated ESR
      - Elevated fibrinogen
      - Elevated procalcitonin
      - Elevated D-dimer
      - Elevated ferritin
      - Elevated LDH
      - Elevated IL-6 level
      - Neutrophilia
      - Lymphcytopenia
      - Hypoalbuminemia
   3. Severe illness requiring hospitalization
   4. Multisystem (2 or more) involvement
      - Cardiovascular
      - Renal
      - Respiratory
      - Hematologic
      - Gastrointestinal
      - Dermatologic
      - Neurologic
C. No alternative plausible diagnosis
D. Recent or current SARS-CoV-2 infection or exposure, with **any** of the following:
   - Positive SARS-CoV-2 RT-PCR
   - Positive serology
   - Positive antigen test
   - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

WHO case definition:

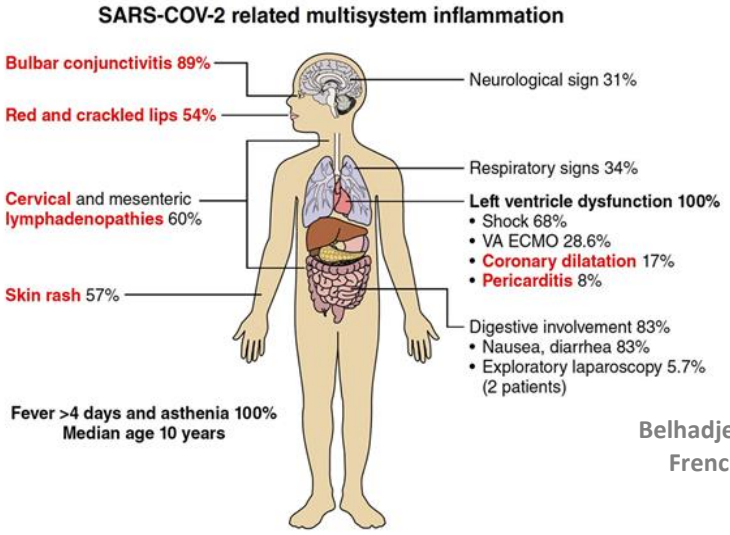
A. Age 0-19 years
B. Fever for >/= 3 days
C. **At least 2** of the following clinical signs:
   - Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, feet)
   - Hypotension or shock
   - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP
   - Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
   - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
D. Elevated markers of inflammation, such as ESR, CRP, procalcitonin
E. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal or streptococcal toxic shock syndromes
F. Evidence of COVID-19, with any of the following:
   - Positive SARS-CoV-2 RT-PCR
   - Positive serology
   - Positive antigen test
   - Likely contact with an individual with COVID-19

JOHNS HOPKINS CHILDREN'S CENTER

Multisystem Inflammatory Syndrome in Children (MIS-C) Related to SARS-CoV-2: Diagnostic and Treatment Guide

CDC Case Definition (https://emergency.cdc.gov/han/2020/han00432.asp)
• An individual aged <21 years presenting with fever[1], laboratory evidence of inflammation[2], and evidence of clinically severe illness requiring hospitalization, with multisystem (2 or more) organ involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic, neurologic) **AND** • No alternative plausible diagnosis **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 [1] fever >=38.0 C for >=24 hours, or report of subjective fever lasting >=24 hours [2] including but not limited to one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, neutrophilia, lymphopenia, hypoalbuminemia

Presentation		
Systemic • fever • myalgias • lethargy • loss of smell or taste	Cardiac/Circulation • tachycardia • conduction delay/block • hypotension • hypo/hyperperfusion • syncope	Respiratory • cough • sore throat • respiratory distress • chest pain
Neurologic • headache • altered mental status • meningismus • focal deficits • seizure	Gastrointestinal • abdominal pain (can mimic surgical abdomen) • nausea/vomiting • diarrhea • loss of appetite	Mucocutaneous • lymphadenopathy • evanescent rash (reticular, morbilliform, purpuric; blisters/erosions) • lip swelling/cracking/ erythema; strawberry tongue • conjunctivitis • swollen hands/feet • erythematous/violaceous changes of toes



Belhadjer, *Circulation*, 2020: French/Swiss series, n=35

Differential Diagnosis

- sepsis
- acute abdominal process
- Kawasaki's disease
- other vasculitides
- toxic shock syndrome
- hemophagocytic lymphohistiocytosis/macrophage activating syndrome
- tick-borne illnesses (Ehrlichiosis, Rocky Mountain Spotted Fever)
- malignancies (leukemia, lymphoma)
- myocarditis
- other infection of viral or non-viral etiology

Consultation: cardiology, GPS, hematology, infectious disease, rheumatology are mandatory; GI if abdominal exam/symptoms are prominent

Initial Resuscitation Guidelines	
Fluid resuscitation	10 cc/kg aliquots of NS if evidence of dehydration/shock; carefully assess response/tolerance of fluid (hemodynamic response, lung exam/liver edge; POCUS exam of IVC if available) as boluses are administered
Vasoactives	Shock with poor perfusion: epinephrine, 0.02-0.05 mcg/kg/min, titrate to effect; use with caution in patients with extreme tachycardia Consider addition of milrinone, 0.25 – 0.5 mcg/kg/min if oxygen delivery remains inadequate
	Shock with normal/hyperperfusion: norepinephrine, 0.02-0.05 mcg/kg/min, titrate to effect; use with caution in the setting of myocardial dysfunction Consider vasopressin, 0.1-2 mcg/kg/min if hypotension is refractory to catecholamine infusions
Hydrocortisone	If unresponsive to vasoactives, consider stress dose hydrocortisone, 25 – 50 mg/m^2/dose q6h, max dose 50 mg q6h; send spot cortisol or complete ACTH stim test prior to first dose if possible

Diagnostic Evaluation
Respiratory Viral Tests • SARS-CoV-2 NAT (NP swab) • respiratory viral panel (NP swab)
Blood • SARS-CoV-2 IgA and IgG **(send prior to IVIg administration)** • blood gas with lactate (preferably arterial) • chemistry: CMP, LDH, amylase, lipase, CPK, TG • heme/coags: CBC with diff, peripheral smear, PT/PTT, fibrinogen, d-dimer • inflammatory markers: ESR, CRP, ferritin, IL-6 • cardiac markers: troponin, BNP • rheumatology: ANA, C3, C4 • micro: blood culture • immunology **(send prior to IVIg administration)**: quantitative immunoglobulins; if myocarditis strongly suspected, send CMV/EBV/parvo/adeno PCRs; Lyme/coxsackie/CMV/EBV/parvo/adeno IgG and IgM • blood bank: type and screen

Diagnostic Evaluation (con'd)
Urine • U/A with micro • urine culture • spot urine creatinine and urine protein
Imaging Studies/Other • echo cardiogram[1] (may see decreased systolic and/or diastolic function, TR, MR, pericardial effusion, coronary artery dilation/aneurysm) A NORMAL ECHO ***DOES NOT RULE OUT*** THE DIAGNOSIS; CHANGES IN CARDIAC FUNCTION MAY OCCUR RAPIDLY • EKG (may see various types of heart block, evidence of ischemia) • abdominal imaging (U/S and/or CT) if abdominal symptoms are prominent (may see colitis, ileitis, lymphadenopathy, ascites, HSM) • head imaging if focal deficit, seizure, severe HA, meningeal signs • LP if clinical sx/sx of meningitis/encephalitis (opening pressure, cell count, glucose, protein, culture; additional studies per ID recommendations) • stool for bacterial studies in patients presenting with diarrhea

[1]include "rule out MIS-C" in the order, and a call back number for results

<table>
<tr><th colspan="4">Therapeutic Interventions
if clinical suspicion is high for MIS-C, do not wait for coronavirus testing results to initiate therapy</th></tr>
<tr><th>Therapy</th><th colspan="2">Dose</th><th>Notes</th></tr>
<tr><td>IVIg</td><td colspan="2">2 g/kg (based on IBW), max 160g; For obese patients (BMI>30), use adjusted body weight for dosing, which is [(ideal body weight + 0.4 x (actual body weight - ideal body weight)]</td><td>Dose in two aliquots if needed for fluid sparing. Watch for fluid overload, cardiac decompensation. Can repeat in 24-48 hours if not improved.</td></tr>
<tr><td>PPI (pantoprazole)</td><td colspan="2">1 mg/kg/dose IV qday</td><td>BID dosing for active GI bleed</td></tr>
<tr><td>Antibiotics[1]</td><td colspan="2">ceftriaxone, 50 mg/kg/dose q12h +/-
vancomycin (see https://intranet.insidehopkinsmedicine.org/asp/_docs/new/vancomycin.pdf [copy and paste link] for dosing information; goal trough 15-19)</td><td>Consider adding clindamycin, 10 mg/kg/dose q6h (max single dose 600 mg), if TSS likely;
additional antibiotic coverage in consultation with ID</td></tr>
<tr><td rowspan="5">Enoxaparin[2]
(VTE prophylaxis; full details in Appendix)</td><td rowspan="4">CrCl≥30 mL/min</td><td>dosing weight <40 kg</td><td>0.5 mg/kg SQ q12h</td></tr>
<tr><td>dosing weight 40-59 kg</td><td>40 mg SQ QD</td></tr>
<tr><td>dosing weight 60-119 kg</td><td>30 mg SQ q12h</td></tr>
<tr><td>dosing weight ≥120 kg</td><td>40 mg SQ q12h</td></tr>
<tr><td>CrCl<30 mL/min</td><td colspan="2">Contact clinical pharmacy specialist for assistance with enoxaparin dosing; consider UFH infusion 10 u/kg/hr, goal antiXa 0.1-0.3 IU/mL</td></tr>
<tr><td colspan="3">Monitoring:
◦ obtain peak antiXa 4 hours after 2nd or 3rd dose
◦ goal peak antiXa 0.2 – 0.5 IU/mL
◦ adjust per Appendix 1</td></tr>
</table>

[1] 48 hour rule out; continued antibiotics beyond 48 hours to be based on culture results and clinical evidence of infection in consultation with ID. If treating pneumonia/sepsis without concern for meningitis, decrease ceftriaxone dose to 75 mg/kg/day ÷ q12h or qday.
[2] indications for therapeutic anticoagulation are not clear at this time; consider extremity duplex U/S and input of hematology service in decision making

Initial Inpatient Surveillance Testing Recommendation
• routine labs per primary team • daily ESR, CRP, ferritin, LDH • daily EKG

Advanced Support Strategies	
Intubation	If intubation is required, pediatric anesthesia support (7-2777) can be requested but is not mandatory. ***Full airborne precautions (PAPR or N95/Draeger mask with face shield, gown and double gloves) are required for all intubations, regardless of COVID testing results.***
ECMO	Early consultation with the pediatric ECMO consult team is warranted for worsening hypoxemia, hypercapnia and/or hemodynamic instability despite escalation in support. If clinical status allows, obtain Doppler ultrasound of a) right neck vessels (age <4 yrs or wt < 20 kg) or b) right neck and bilateral femoral vessels (age ≥4 yrs or wt ≥20 kgs).

Additional Therapies to Consider		
Therapy	*Dose*	*Notes*
Methylprednisolone	Varies from 2 mg/kg/day ÷ q6h up to 20 mg/kg/day for 1-3 days, then 2 mg/kg/d ÷ q6h. (Max single dose 250 mg)	If initiated, an extended taper (2-8 weeks, depending on illness severity) is recommended
remdesivir	5 mg/kg (max 200 mg) x 1 on day 1; 2.5 mg/kg daily (max 100 mg) for total duration of 5-10 days	Requires ID approval and release by FDA and Gilead; see appendix 2.
aspirin	Low dose: 3-5 mg/kg/day Moderate dose: 30-50 mg/kg/day High dose: 80 mg/kg/day	Consider for patients who fulfil criteria for Kawasaki's disease; may initiate at moderate to high dose (particularly if coronary arteries changes by echo) and decrease to low dose when patient afebrile.

Additional Immunomodulators (Non-Responders)[1]	
Therapy	*Mechanism*
Anakinra (Kineret)	IL-1 receptor antagonist
Infliximab (Remicade)	TNF-alpha blocker
Tocilizumab[2]	IL-6 receptor antibody

[1] to be considered in consultation with rheumatology; require P&T approval
[2] tocilizumab has been reported to be associated with the formation of coronary artery aneurysms in Kawasaki's disease (Nozawa, *NEJM*, 2017)

Isolation and State Reporting for MIS-C

- **Patients with concern for MIS-C should be placed under COVID-19 precautions (negative pressure room, airborne + contact + face shield)**
- ***If there are no negative pressure rooms available, patients without respiratory symptoms can be housed in a regular-pressure room with COVID precautions.***
- If the first COVID-19 swab is negative, they can come off of COVID-19 precautions and resume standard precautions in a regular pressure room (mask and eye shield for all patient care, and airborne + contact precautions if doing any aerosol generating procedure). Please call HEIC to remove COVID-19 precautions.
- If there is HIGH suspicion for MIS-C as the patient's case evolves, and the diagnosis of COVID-19 may be diagnostically relevant, can consider obtaining a second COVID-19 NP Swab.
    - If the patient develops new or progressive respiratory illness, the patient should be made a PUI and retested. For intubated/trached patients, obtain a lower airway sample for COVID testing.
    - If the patient does not have respiratory symptoms or symptoms of acute COVID-19 infection, to avoid the patient getting a new EPIC isolation flag needing negative pressure isolation, the second COVID-19 test can be ordered by selecting "asymptomatic protocol" or select "no" patient does not have COVID-19 symptoms > "other" reason.
- Patients with positive SARS COV2 antibody but negative PCR test results do not need to be in COVID-19 precautions or negative pressure room.
- reporting to the Maryland State DOH
    - MIS-C is a reportable condition. The Peds infectious diseases team will notify Aaron Milstone and Anna Sick-Samuels by email of hospitalized MIS-C cases, who will help keep track of reporting of the information to the Maryland Department of Health.
    - Information to collect:
        - Patient demographic information
        - Date of symptom onset
        - Maximum temperature
        - Laboratory value(s) fulfilling the above listed laboratory evidence of inflammation
        - Hospitalization status
        - Types of organ system involvement
        - SARS-CoV-2 testing results
        - Other relevant testing results (for example, those that have been used to exclude an alternative diagnosis)
- updates can be found here: https://intranet.insidehopkinsmedicine.org/heic/novel_coronavirus/clinical_resources.html#pediatrics

****PROVIDERS: Please enter appropriate diagnostic codes to assure case reporting****

We will have a new ICD10 diagnostic codes in Epic for MIS-C in 1-2 weeks:

- **Multisystem inflammatory syndrome associated with COVID-19 in pediatric patient**
- **Multisystem inflammatory syndrome associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pediatric patient**

Until then, use

- **R6510 Systemic inflammatory response syndrome (SIRS) of non-infectious origin without acute organ dysfunction**
- **R6511 Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction**

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Diagnostic and treatment guides from the following institutions/organizations were reviewed and considered in the creation of this document (in alphabetical order): Children's National, Evelina London Children's Hospital/South Thames Retrieval Service, Hassenfeld Children's Hospital at NYU Langone, New York-Presbyterian Morgan Stanley Children's Hospital, and Royal College of Paediatrics and Child Health.

APPENDIX 1: VTE Prophylaxis Guide for Pediatric COVID Positive Patients

- **The following patients should receive VTE prophylaxis, unless presence of absolute contraindications:**
  1. All PICU COVID positive patients
     - Upon ICU discharge, assess whether high intensity dosing should be continued based on high risk criteria and inflammatory labs as outlined under non-ICU patient recommendations
  2. Non-PICU COVID Positive patients with additional risk factors including:
     - Pregnancy
     - Active malignancy Prior VTE
     - Sickle cell disease
     - Known thrombophilia
     - D-dimer > 1.5 mg/L any time during hospitalization

- **Absolute Contraindications:**
  - Active major bleeding (defined as visible signs of active bleeding, bleeding into an organ, a drop in hemoglobin of > 2 gm/dL or the need to transfuse with PRBC's)
  - Heparin induced thrombocytopenia (HIT)—requires alternate medication choice for anticoagulation
  - Platelet count < 25,000 / mm3

- **Relative Contraindications:**
  - Platelet count < 50,000 / mm3
  - Concurrent use of other anticoagulant/antiplatelet medication (e.g., NSAIDS, Aspirin, Clopidogrel)
  - Bleeding Disorder
  - Intramuscular (IM) injections
  - **LMWH only:** Avoid in patient receiving hemodialysis, renal impairment or unstable renal function when possible
    - Consider SQ or IV UFH for VTE prophylaxis for these patients
    - Dose adjustment may be required in these patients and LMWH Anti-Xa levels should be closely monitored

Table 1: VTE Prophylaxis[1]

Renal Function[2]	Dosing Weight < 40 kg	Dosing weight 40-59 kg*	Dosing weight 60-119 kg	Dosing weight ≥ 120 kg (or BMI > 40 kg/m^2)
CrCl ≥ 30 mL/min	Enoxaparin 0.5 mg/kg SQ q12h	Enoxaparin 40 mg SQ QD	Enoxaparin 30 mg SQ BID	Enoxaparin 40 mg SQ BID
CrCl < 30 mL/min	• Contact Pediatric Hematology or a Clinical Pharmacy Specialist for assistance with enoxaparin dosing • Consider initiation of a low-dose unfractionated heparin (UFH) infusion 10 unit/kg/hr (Goal 0.1 – 0.3 IU/mL) ○ Refer to (GEN109) Heparin, Management of the Pediatric Patient >> Appendix A:			

[1] A temporary Insuflon® catheter may be placed for ease of administration of enoxaparin if needed. Insuflon® catheters may be used for up to 5 days at a time for use with enoxaparin. Refer to Insuflon® Catheter for Administration of Subcutaneous Medications (GEN140) policy for additional information.

[2] Based on Bedside Schwartz Equation: [0.413 x ht (cm)] / SCr

- **Monitoring**
  - Goal peak LMWH anti-Xa 0.2 – 0.5 units/mL
  - Obtain peak LMWH Anti-Xa 4 hours after 2nd or 3rd dose

Refer to Tables 2 for recommended dose adjustments and additional anti-Xa level monitoring

Table 2: Enoxaparin Dose Adjustment

Anti-Xa LMWH Activity (IU/mL)[1]	Hold Dose?	Dose Change	Repeat Anti-Xa LMWH activity
< 0.2	No	Increase by 20 – 30%	4 hours after ≥ 2 doses
0.2 – 0.5	No	No	1 week later
0.6 – 0.7 [1]	No	Decrease 10 – 20%	4 hours after ≥ 2 doses
0.7 – 1.0 [1]	No	Decrease 30 – 40%	4 hours after ≥ 2 doses
> 1.0 [1]	YES	Decrease 40%	Obtain 24 hours after previous dose • Once Anti-Xa LMWH Activity is < 0.5 IU/mL, resume scheduled dosing at reduced dose 12 hours after level resulted [2]

[1] The renal function of patients with elevated LMWH Anti-Xa values should be accurately assessed

APPENDIX 2: Remdesivir Acquisition Guide

Acquiring Compassionate Use Remdesivir for Hospitalized Children <18 years of age with Confirmed COVID-19

Step 1: Discuss Remdesivir with Patient

- Discuss Remdesivir treatment option with patient and treating team if patient meets criteria: https://intranet.insidehopkinsmedicine.org/asp/pediatric.html
- Inform them that there will be two consent forms that will be reviewed with them prior to administering the drug, one from Gilead and one from Johns Hopkins University both available at https://intranet.insidehopkinsmedicine.org/asp/pediatric.html
    - Wait to complete consent forms after Gilead approves Remdesivir compassionate use
    - Decision as to who completes consent negotiated between ID team and primary team attending based on availability
    - Consent form signed in the room should ideally stay in the room and photographed and uploaded into Epic. If not possible, a manila envelope not brought into the room can be used to transport the consent form out of the room. All forms should be handled with gloves and a copy should be placed in the patient's chart. Email a copy of the consent to Alice Hsu (ajenh1@jhmi.edu) for IRB and pharmacy records. (ID attending will need a copy for JHU IRB [Step 5].

Step 2: Request Remdesivir from Gilead

- Infectious Diseases attending completes the Gilead Drug Request: https://rdvcu.gilead.com
- Contact Information
    - Name of Requestor: ID attending
    - Primary Treating Physician: PICU or General Pediatrics Attending
    - Pharmacy Contact: Alice Hsu, PharmD
      1800 Orleans St.
      Pediatric Inpatient Pharmacy, Bloomberg 7367
      Baltimore, MD 21287
      Work: 410-955-5926; Cell: 908-463-1148
      Email: ajenh1@jhmi.edu
- Patient information requested
    - Demographic information: Initials, DOB, gender, weight
    - Brief clinical course, current clinical status, imaging results
    - Labs: BUN, Cr, AST, ALT, AP, TBili
    - Yes/No questions: COVID Testing, pregnancy, and ICU level support (vasopressors, supplemental oxygen, intubation, ECMO, CRRT)
        - CrCl (must be entered or Gilead will not approve)
        - ALT (must be <5x upper limit of normal)
    - Past medical history
- Gilead will process the request and send "approval" email anywhere from 1-12 hours later
- Gilead will send Remdesivir to pediatric pharmacy (after they receive the eIND approval detailed below)

Step 3: Activate iMedidata Account

- ID and Primary Attending will each receive an email from Gilead to active a iMedidata account

    - Both ID and Primary Attending should create a profile (name, login, password, security question).
    - Accept the "Remdesivir_Compassionate_Use_COVID-19 study" listed under "tasks."
- Primary Attending signs Prescriber Agreement: Sign with a pen and email a scanned copy of the first 3 pages to: ClinOpsCOVID_SpecialPop@gilead.com
- ID attending enters clinical baseline assessment into iMedidata
- ID attending completes pages 4-22 of the Prescriber Agreement which are to be used for safety reporting
    - These forms are completed after Remdesivir is administered to the patient; safety reports are sent to Safety_FC@gilead.com

Step 4: Apply for eIND from the FDA (Should occur concurrently with Step 1)

- Primary attending and ID attending work together to apply for an investigator-sponsored, single-patient emergency investigational new drug (eIND) application
- ID attending will assist with completing the paperwork but the primary attending has to sign the paperwork (the same name needs to appear on the Prescriber Agreement (PA) and the eIND)
- To request an eIND from the FDA:
    - Complete FDA Form 3926, available at: https://www.fda.gov/about-fda/forms/individual-patient-expanded-access-investigational-new-drug-application-ind-pdfnote-best-form
    - eIND can be requested 24/7
    - Call (301) 796-1500 (8:00 AM-4:30 PM); (301) 796-9900 (after hours and weekends)
    - Email completed Form 3926 to cder-eind@fda.hhs.gov

- Gilead needs a copy of the initial FDA eIND authorization email with eIND number prior to sending drug; forward eIND email to: ClinOpsCOVID_SpecialPop@gilead.com
- Primary attending should email ID attending a copy of the approved eIND
- Emergency IRB (eIRB) approval for Remdesivir use at The Johns Hopkins Hospital is NOT required as JHU IRB (IRB00246242) is open for enrollment of children <18 years old receiving Remdesivir under compassionate use
    - ID attending should let Gilead know "eIRB has been approved"
    - Do not need to separately contact the JHU IRB

Step 5: Order Remdesivir

- Ensure that both consent forms are completed
- ID physician places Remdesivir order in Epic
- Dosage and duration of Remdesivir available at: https://intranet.insidehopkinsmedicine.org/asp/pediatric.html

Step 6: JHU IRB

- Pediatric ID attending submits a "Change in Research" to the IRB mentioning that a patient was "enrolled into the compassionate use study" and attaches the eIND from the FDA along with both signed patient consent forms

HMH MIS-C Initial Evaluation and Treatment

Arrival to ED with fever of >24 hours AND 2 of the following: headache, irritability, gastrointestinal symptoms (including enteritis on imaging), cough, conjunctivitis or eye swelling, mucous membrane changes, rash, or swelling of extremities

Hemodynamically Stable

Initial Labs: CBC, CMP, ESR, CRP, BNP

Normal Labs → Treat as typical fever patient with dispo as per clinical status

Labs abnormal or high

Consider further evaluation:
Ferritin, Fibrinogen, D Dimer, PT/PTT/INR, LDH, Troponin, COVID PCR, COVID Serology, Blood Culture, EKG

→ **Observation Patient:** Does not meet criteria for MIS-C, but high suspicion
Place in Observation

Suspicion for MIS-C
Fever and inflammation plus one of the following scenarios with no other plausible diagnosis

Classic Kawasaki Disease	**Incomplete Kawasaki Disease**	**Other Suspicion:**
At least 4/5: Rash, extremity changes, nonpurulent conjunctivitis, lymphadenitis/lymphadenopathy, mucous membrane changes	At least 3/6: Anemia for age, WBC >15000, Elevated AST, Plt > 450 or < 100, Albumin <3, Sterile Pyuria >10 WBC/field OR Increased troponin or BNP	Abdominal Pain, Enteritis on imaging, other suspicion

Vital sign abnormalities not responsive to hydration or out of proportion to clinical condition

Yes → Admit to ICU

No → **Admit to Floor**

Echocardiogram
Consider consultations as per clinical presentation and attached criteria

High Risk:	**Low Risk:**	**Observation:**
Echo with coronary artery dilation or < 6 months of age: Methylprednisolone 1mg/kg q 12 hr max 60mg/dose	Normal echo and > 6 months of age: Methylprednisolone 1mg/kg q 12 hr max 60mg/dose	Patient with some abnormal labs or imaging, but no full criteria met for MIS-C
Aspirin 5mg/kg daily (max 325mg) Consider prophylactic enoxaparin for plt < 100	Consider Aspirin 5mg/kg daily (max 325mg) Hold for Plt <100	Management of fluids as needed Fever Treatment Trend labs Can decide to treat if meets criteria
If meets criteria for Kawasaki or incomplete Kawasaki IVIG 2g/kg		

Hemodynamically Unstable

Send CBC, CMP, CRP, ESR, BNP, Troponin, Ferritin, D Dimer, Fibrinogen, PT/PTT/INR, LDH, COVID PCR, COVID Serology, Blood Culture, EKG, Other Fever Workup as needed

Patient stabilization as per ED (see ED pathway)
Broad Spectrum Antibiotics
Fluid resuscitation
Consider Infectious Disease and Rheumatology Consultation.
Urgent Cardiology Consultation as per attached criteria
Other consultations as needed

Admit to ICU

Consider Echocardiogram when able if not performed in ED
Blood Pressure Management

High Dose Vasoactives:	Moderate Dose Vasoactives:	Low Dose Vasoactives:	No Vasoactives:
Methylprednisolone 30mg/kg q 24 hr x 3 days (max 1gm/dose)	Methylprednisolone 10mg/kg (max 1g/dose)	Methylprednisolone 1mg/kg q 12 hours (max 60mg/dose)	Methylprednisolone 1mg/kg q 12 hours (max 60mg/dose)

If D Dimer > 10 prophylactic anticoagulation with Enoxaparin
D Dimer >2 but < 10 consider Enoxaparin or Aspirin 5mg/kg (max 325mg)
If D Dimer < 2 Aspirin 5mg/kg daily (max 325 mg)

If criteria met for typical or atypical Kawasaki disease, or abnormal echo, IVIG 2g/kg

If fever persists 24 hours after IVIG, further treatment in conjunction with Rheumatology and Infectious Disease

Hackensack Meridian *Health*

Lab Schedule

On Initial Presentation

- All patients with a diagnosis of MIS-C should have CBC, CMP, CRP, ESR, troponin, ferritin, D-Dimer, LDH, PT/PTT/INR, COVID PCR, COVID serology, blood culture
- Send blood gas with lactate if shock suspected at any point of admission
- If vomiting, amylase and lipase
- If diarrhea, consider GI Pathogen Panel (GiPP)

Consider daily labs as per patient status

- CBC, CMP, CRP
- Troponin and BNP if initially abnormal
- Ferritin, D-Dimer, PT/PTT/INR

Continued Care After Initial Treatment

Inpatient Treatment

- Continue methylprednisolone until afebrile for > 24 hours, then change to oral prednisone 1mg/kg BID
- Patient may be discharged once afebrile for 24-36 hours

Outpatient Follow Up

- Obtain CBC, CRP, ESR, and if elevated at discharge, ferritin, CBP, D-Dimer, PT/PTT/INR
- Steroid taper managed by rheumatology (for mild cases taper over 2-3 weeks, moderate to severe 6-8 weeks)

Yes

No

Cardiology Consult Indications

Urgent Echo:

- Hemodynamic compromise
- Significant dysrhythmia

Urgent Consultation

- BNP >400
- Troponin > 1

Non-Urgent Echo:

- KD Presentation without hemodynamic compromise
- Other dysrhythmia on ECG

Other Consult Indications

Hematology:

- Pancytopenia
- Hgb < 8.0
- DVT or other thrombus

Gastroenterology

- GI Bleeding
- Signs of pancreatitis
- Liver Failure

Neurology:

- Stroke
- Evidence of encephalitis
- Abnormal neurology examination

Consultations called overnight should be seen by 12pm to allow for timely team discussions

COVID Pediatric Workgroup, June 2nd, 2020

Guidance for Emergency Department evaluation of ***Multisystem Inflammatory Syndrome in Children (MIS-C),*** during COVID19 pandemic

University of Minnesota, Masonic Children's Hospital

Referrals and/or consultation, call Masonic Children's Hospital ED. (612-365-9110)

COVID19 in children may manifest as a systemic inflammatory disease, with or without positive SARS-CoV2 tests (PCR and/or serology).

Guidance is based on expert consensus derived from a small number of reported cases, and extrapolated Kawasaki Disease/Kawasaki Shock Syndrome.

Early consultation with ID, Hem/Onc, and cardiology for admitted patients.

Consider referral to COVID Clinic for suspected cases who are discharged home.

Fever ≥3 days PLUS ≥2 associated symptoms

- Irritability / headache
- Abdominal pain/diarrhea
- Rash (polymorphic)
- Oral changes
- Lymphadenopathy
- Conjunctivitis
- Redness/swelling of hands/feet
- Focal/central neurological deficits
- Arthralgia/arthritis
- Nausea/vomiting
- Urethritis
- Skin peeling

Or unexplained fever ≥5 days

Triage

- Consider MIS-C.
- Assess for COVID risk/exposure.
- Assess for Kawasaki Disease.
- Obtain labs/imaging(*).
- Assess for other etiologies (**).
- Consider empiric antibiotics(***).

- Cardiac involvement
- Dehydration
- Hypoxia (O2 support)
- Lymphocytes <1 [k/uL]
- Platelet <150 or >450 [k/uL]
- CRP≥30 [mg/L]
- ESR≥40 [mm/hr]
- Albumin≤3 [g/dL]
- Significant anemia for age
- Coagulopathy

Reassuring exam
Normal labs
(WBC/Diff/Plt+ESR+CRP+Coag+troponin)

Discharge home with PCP or COVID Clinic follow-up (24-48hrs)

COVID Clinic: 612-365-6777

Admit to Pediatric Floor
(Hospitalist / Subspecialty IP service)

Hemodynamically unstable
Poor perfusion, hypotension, cardio-pulmonary failure, altered mental status.

Suspected MIS-C with Shock (distributive, cardiogenic)

Admit to PICU

Consult ID, Hem/Onc, cards for all patients
Consult Rheumatology based on specific clinical concerns

(*) Labs / Imaging

Initial screening labs: CBC+Diff+Plt, CMP, ESR, CRP, INR/PTT, D-dimer, fibrinogen, factor VIII, AT3, troponin, NT-BNP, pro-calcitonin, urinalysis, blood/urine culture, COVID PCR/serology; EKG, CXR.

Additional labs/studies to consider (following discussion with a specialist): Ferritin, total IgG, mycoplasma PCR/serology, tick-borne PCR/serology, von-Willebrand profile,
anti-phospholipids profile, lupus anticoagulant profile, cytokine panel (IL-1, IL-6, IL-8, TNFa), LDH, uric acid, peripheral smear; **ECHO** (ordered as MIS-C eval.), CT, ultrasound (abdomen, vessels).

(**) Differential Diagnosis

- **SARS-CoV2 / COVID19.**
- **Kawasaki Disease.**
- Toxic shock syndrome.
- Septic shock.
- Other Infections: Mycoplasma, adenovirus, enterovirus, measles, tick-borne/rickettsial, leptospirosis, rheumatic fever.
- Rheum: sJIA/MAS/HLH; vasculitis/SLE.
- Others: systemic drug reaction (SJS, DRESS) malignancy, mercury poisoning.
- **Idiopathic**.

(***) Consider empiric antibiotics:

- Ceftriaxone +/- vancomycin for suspected septic shock and/or meningitis.
- Cefepime +/- vancomycin for immune-compromised or patients with central line.
- Add metronidazole for suspected abdominal pathology/perforation.
- Add clindamycin for suspected toxic shock syndrome.
- Doxycycline for suspected tick-borne infection.
- Azithromycin for suspected mycoplasma infection.

In-patient management for ***Multisystem Inflammatory Syndrome – in Children (MIS-C)***, during COVID-19 pandemic

Treatment Doses

- **IVIG: 2g/kg** (obtain serum tube to hold prior to IVIG).
- **ASA: moderate 30-50mg/kg/day; low 3-5mg/kg/day** (timing and dosing per consultation with cardiology and hematology).
- **Steroids: 2mg/kg/day divided every 12 hours [IV methylprednisolone while febrile ->**
  PO prednisolone while CRP elevation] -> 2-3 weeks taper.
- **Anakinra: 2-5 mg/kg/day** (Consult Rheumatology and Pharmacy).
- **Enoxaparin (*lovenox*): (0.5 mg/kg BID):** (Consult Hematology and Pharmacy for in- and out-patients regimens).
- **Empiric antibiotics / Remdesivir**: (Consult ID).

Daily multi-disciplinary rounds at 11:30am.

Monitor Labs and Imaging (daily for first 2-3d -> then as needed)

- CBC/plt/diff, CRP, troponin, NT-BNP, albumin, D-dimer (coag).
- **EKG:** Weekly or sooner for clinical concerns.
- **Echo** (frequency per cardiology consult).

Discharge Plans and Follow-up

- Consider repeat SARS-Cov2 PCR.
- Outpatient course of ASA 3-5 mg/kg/day.
- Virtual visit f/u within 1 week (COVID clinic, virtual visit, +/- labs).
- Cardiology f/u within 2 weeks (physical visit + ECHO +/- labs),
- For patients who are receiving *lovenox* follow-up with Hem/Onc within 2 weeks (+ labs).

Fever ≥3 days PLUS ≥2 associated symptoms

- **Irritability** / headache
- **Abdominal pain**
- Rash (polymorphic)
- Oral changes
- Lymphadenopathy
- Conjunctivitis
- Urethritis
- Skin peeling
- Arthralgia/arthritis
- Redness/swelling of hands/feet
- Focal/central neuro. deficits
- Nausea/vomiting/diarrhea

Or unexplained fever ≥5 days

Initial evaluation

- Recognize inflammatory state, multisystem involvement, and indication for floor admission.
- Recognize severe MIS-C and indication for PICU admission.
- Review labs and imaging to assess risk and indication for therapy.
- Verify a tube with serum sample is on hold and available for add-on labs.
- **Early consults with ID, Cardiology, and Hematology** to discuss urgency of therapy as well as follow-up labs and imaging.

[*For concern of evolving cardiac pathology such cardiogenic shock or high troponin – therapy, cardiology consult and ECHO are urgent*].

Pediatric Floor (Hospitalist / Subspecialty)	**PICU**
• Moderate MIS-C or KD (requiring IV therapy). • Dehydration. • Respiratory distress requiring O2 support. • Concern for clinical deterioration with normal cardiac function and hemodynamically stable.	• Hemodynamically unstable (poor perfusion, hypotension, tachycardia). • Severe MIS-C or KD with shock.

Labs / Imaging

Initial screening labs: CBC+Diff+Plt, CMP, ESR, CRP, INR/PTT, D-dimer, fibrinogen, factor VIII, AT3, troponin, NT-BNP, pro-calcitonin, urinalysis, blood/urine culture, COVID PCR/serology, EKG, CXR.

Additional labs/studies to consider: Ferritin, total IgG, mycoplasma PCR/serology, tick-borne PCR/serology, von-Willebrand profile, anti-phospholipids profile, TEG, lupus anticoagulant profile, LDH, uric acid, peripheral smear, cytokine panel (IL-1b, IL-6, IL-8, TNFa [CKCOV1]; sIL-2Ra, IL-10, IL-18, IFNg [CKCOV2]);

ECHO (ordered as MIS-C eval.), CT, ultrasound (abd., vessels).

Differential Diagnosis

- **SARS-CoV2 / COVID19.**
- **Kawasaki Disease.**
- Toxic shock syndrome.
- Septic shock.
- Other Infections: Mycoplasma, adenovirus, enterovirus, measles, tick-borne/rickettsial, leptospirosis, rheumatic fever.
- Rheum: sJIA/MAS/HLH; vasculitis/SLE.
- Others: systemic drug reaction (SJS, DRESS) malignancy, mercury poisoning.
- **Idiopathic**.

Mild MIS-C

- Normal echo **and** no KD overlap.
- Febrile, but stable and without evidence for end-organ involvement.

Consider IVIG OR steroids

Moderate MIS-C

- Abnormal echo **or** KD overlap.
- Concerning lab trends (e.g D-dimer x4nl, elevated troponin, abnormal TEG).
- Clinical concern for end-organ damage or worsening inflammation.

Kawasaki Disease

KD algorithm [2017 AHA guidelines]

Normal ECHO, no evidence of cardiac involvement.

- Age < 6 months
- CA Z-score >2.5
- Initial CRP >130

- **Shock**
- Systolic dysfunction

IVIG + ASA (+/- Steroids)

Severe MIS-C

- Cardiogenic and/or distributive **shock**.
- LV systolic dysfunction or elevated troponin
- Mental status changes.
- Respiratory failure/distress (positive pressure ventilation).

IVIG + steroids + ASA

Refractory Disease

Febrile, or without clinical improvement 24-48hr post IVIG
(**add steroids if not given and consult Rheumatology**)

Anakinra or 2nd IVIG dose
(or other immunomodulators)

Key takeaways

- Consulting services (ID, Cardiology, Hem/Onc, and Rheumatology) should be involved early when MIS-C is suspected.
- Children with persistent fever and elevated inflammatory markers may benefit from immunomodulators.
- When progressive organ involvement is suspected, IVIG should be given urgently, and ECHO done promptly.
- Based on the evidence, this approach is primarily using IVIG, steroids, and anakinra.

University of Minnesota Masonic Children's Hospital
COVID Pediatric Workgroup, June 2020

Guidance for Out-Patient Evaluation and Management of *Multisystem Inflammatory Syndrome in Children (MIS-C),* During COVID19 Pandemic

COVID Pediatric Workgroup, June 2nd, 2020

University of Minnesota, Masonic Children's Hospital

Differential Diagnosis

- **SARS-CoV2 / COVID19.**
- **Kawasaki Disease.**
- Toxic shock syndrome.
- Septic shock.
- Other Infections: Mycoplasma, adenovirus, enterovirus, measles, tick-borne/rickettsial, leptospirosis, rheumatic fever.
- Rheum: sJIA/MAS/HLH; vasculitis/SLE.
- Others: systemic drug reaction (SJS, DRESS) malignancy, mercury poisoning.
- **Idiopathic**.

Fever ≥3 days PLUS ≥2 associated symptoms

- Irritability / headache
- Abdominal pain/diarrhea
- Rash (polymorphic)
- Oral changes
- Lymphadenopathy
- Conjunctivitis
- Redness/swelling of hands/feet
- Focal/central neurological deficits
- Arthralgia/arthritis
- Nausea/vomiting
- Urethritis
- Skin peeling

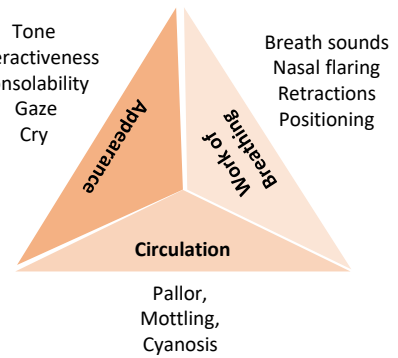
Or unexplained fever ≥5 days

Admission Criteria

SHOCK (poor perfusion), respiratory distress, dehydration, [multi]-organ dysfunction altered mental status, cardiopulmonary involvement.

Call 911
Refer to ED (612-365-9110)

Pediatric Assessment Triangle



Nursing line / Call center

0-24hr

Virtual visit

Assess child's irritability and parental concerns.
Assess reliability of temperature checks.
Assess for physical findings (alertness, breathing, rashes, eyes, lips, ambulation.
Assess for COVID risks (household exposure, travel).
Assess and verify access to care.

0-24hr

Physical exam & vitals and screening labs (per provider discretion)

Physical findings: look for **hypotension, hypoxia, dehydration**; poor perfusion; Irritability, abdominal pain, lymphadenopathy, point tenderness, organomegaly, mucus membranes.

Screening labs: CBC+diff+platelet, CMP, CRP, ESR, urinalysis, troponin, NT-BNP, INR/PTT/D-dimer, fibrinogen.
If available: COVID PCR/Serology, blood/urine culture.
[May-Oct: consider tick-borne PCR/serology].

Consult a specialist / Refer to Hospital

COVID Clinic (612-365-6777); [M-F, 8a-5p]
Hospitalist/ID IP consult (612-672-7575); [24/7]

No history of fever PLUS ≥2 associated symptoms

- Normal vitals for age.
- Playful/alert when fever down.
- Intermittent fever/response to NSAID.
- 'Typical' pattern of illness.

Normal: CBC/Diff/Plt+CRP+ESR+Albumin.

- **Consider a consult with COVID Clinic.**
- **Follow-up (virtual, in-person, referral) based on clinical concern.**
- Consider other etiologies.
- Reassurance/anticipatory guidance.

Lethargy, altered mental status, significant respiratory distress.

- Hypotension, poor perfusion, irritability, flushing, decreased urine output.
- Combination findings suggestive of Kawasaki Disease (rash, oral lesions, conjunctivitis, hands/feet changes, lymphadenopathy).

- Significantly elevated CRP and ESR
- Lymphocytes <1 [x10e3/uL]
- Neutrophils <1 or >15 [x10e3/uL]
- Platelet <150 or >450 [x10e3/uL]
- Albumin ≤3[g/dL]
- Significant anemia (for age)
- Abnormal INR/PTT/D-dimer
- Abnormal troponin, NT-BNP

Refer to ED
(Masonic ED: 612-365-9110)

Nemours. Alfred I. duPont Hospital for Children

Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Emergency Department

INCLUSION CRITERIA

Patients <21 yo presenting with

- **Fever >38°C** **AND** no alternative dx **AND** ≥2 of the following:
  - GI (pain, vomiting, diarrhea, anorexia, loss of taste)
  - Rash
  - Conjunctivitis
  - Oral inflammation
  - Altered mental status
  - Extremity swelling
  - Lymphadenopathy

OR

- One or more of the following:
  - Hypotension or shock
  - Evidence of cardiac dysfunction
  - End organ involvement

EXCLUSION CRITERIA

- Alternative plausible diagnosis

[1]MIS-C Definition

- <21 yo presenting with fever >38C (or tactile) for ≥ 24 hrs **AND**
- Clinically severe illness requiring hospitalization **AND**
- Multisystem (≥2) organ involvement: cardiac, renal, pulm, heme, GI, derm, neuro **AND**
- Lab evidence of inflammation
  - (elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, IL6, neutrophilia, lymphocytopenia, hypoalbuminemia) **AND**
- No alternative plausible dx **AND**
- Current or recent SARS-COV-2 infection by PCR or antigen test or serology; or COVID-19 exposure within 4 weeks of presentation

[2]ICU Admission Criteria

- Abnormal perfusion
- Hypotension
- Evidence of cardiac dysfunction or BNP>400 or Troponin > 0.04
- Sustained changed in mentation or perfusion
- Requiring ICU level respiratory support
- Lactate >2.5, Base deficit > -4

Initial Assessment

- Obtain and document vital signs and pulse ox
- Perform and document ED assessment
- Room to COVID screen positive zone or resuscitation bay
- Enhanced contact and droplet PPE with use of N95 for airborne generating procedures

Low Risk

- Mildly ill appearing pts presenting with fever ≥3 days **AND** ≥2 symptoms from inclusion criteria

Moderate Risk

- Ill appearing pts presenting with ≥3 days of fever **AND** ≥2 symptoms from inclusion criteria

High Risk

- Toxic appearing **OR** evidence of shock **OR** evidence of cardiac dysfunction

Screening Evaluation

- CBC, CRP, CMP, BNP, troponin
- EKG if chest pain
- **Further workup based on clinical indications**

Diagnostics Normal[Pg 3]? — No → **Complete Evaluation**

Complete Evaluation

- Screening evaluation **AND**
- VBG, lactate, ferritin, procalcitonin, UA, UCX, LDH, fibrinogen, PT/PTT, ESR, **AND**
- EKG
- CXR
- Consider blood culture
- Consider abdominal imaging if indicated
- Further workup based on clinical indications

Shock Management

- Fluid resuscitation with frequent re-evaluations (avoid fluid overload)
- Evaluate cardiac function
- Initiate Norepinephrine if refractory to fluids
- Send D-Dimer
- Initiate sepsis pathway (including antibiotics) if concern for septic shock

Treat other conditions as indicated

Meets MIS-C[1] Criteria? — No → **Off PW**; Yes → **Echo**

Echo

- Does not need to be obtained in ED
- If BNP and troponin normal, can obtain within 24 h

Further Evaluation

- Echo (if BNP and troponin normal, can obtain within 24h)
- Further workup based on clinical indications

Meets ICU admission criteria[2]?

Discharge To Home

- Ensure f/u in 24 hours
- Anticipatory Guidance
- Return to ED for repeat labs if fevers last ≥ 5 days or if new symptoms from inclusion criteria develop

Admit to Hospital

- Send rapid SARS-COV-2 PCR when available otherwise send immunology SARS-COV-2 PCR
- Admit to ICU if meets ICU criteria, otherwise admit to general inpt unit
- Consult CICU if requires VA ECMO or known underlying complex cardiac condition, otherwise, admit to PICU

See page 2

Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Inpatient

Isolation
- If SARS-COV-2 PCR positive: Enhanced contact and droplet PPE with use of N95 for airborne generating procedures
- If SARS-COV-2 PCR negative: Standard precautions

Page 1

Admission Diagnostic Evaluation
- SARS-COV-2 IGG if PCR is negative
- Labs listed on page 1 if not already completed
- To consider cytokine panel on a case by case basis
- Perform Echo if not completed in ED. If troponin and BNP normal, can obtain Echo within 24 hrs.

Ongoing Diagnostic Evaluation
- Send following labs every 24 hrs X2 then every 2-3 days as per care team's discretion
  - CBC/diff, ESR, CRP, procalcitonin, CMP, LDH, ferritin, PT/PTT, fibrinogen, D-dimer, BNP, troponin
- Troponin q6hrs if initially elevated
- EKG as needed per cardiology
- Echo
  - For pts with abnormal Echo, repeat every 1-2 days or as needed, and prior to discharge.
  - For pts with normal Echo, repeat prior to discharge. If they have prolonged fever or hemodynamic instability, obtain at discretion of cardiology

Consults
- Cardiology
- ID
- Rheumatology
- Hematology as needed

Meets diagnostic criteria from Pg 1?

Yes

Therapies
- Steroids: start early for moderate or high risk
- IVIG: start early
- High dose aspirin if Kawasaki like presentation or not treating with steroids
- Enoxaparin: start early for high risk, consider for moderate risk (discuss with Heme)
- Antivirals: may consider remdesivir for significant respiratory distress (discuss with ID)
- Proton pump inhibitor for GI prophylaxis
- Pressors as indicated
- Continue broad spectrum antibiotics as per sepsis pathway until cultures result

See page 4

Reporting
- To department of health by Infection prevention/control

Discharge Criteria
- Sats ≥ 95% on RA
- Tolerates PO
- Hemodynamically stable > 48 hrs
- Normal cardiac function
- Afebrile >48 hrs
- Inflammatory markers, troponin, BNP trending downwards

Discharge Instructions
- Continue low dose aspirin as per page 4
- Switch to low dose aspirin if on enoxaparin prophylaxis
- F/u cardiology and rheumatology in 2 weeks
- F/u hematology if anticoagulated

At Follow-up Visit
- CBC, CMP, CRP, BNP as needed
- EKG, Echo
- Consider cardiac MRI, holter if cardiac involvement was significant

No

Therapies
- Consider other diagnoses
- Treat accordingly

COVID 19 Positive
- Consider Echo in 2 weeks if recurrence of fever or inflammatory symptoms

Laboratory Test	Cut-off
Absolute Lymphocyte Count	<2000/cc
Absolute Neutrophil Count	> 8000/cc
	<2000/cc
Albumin	<2.5 gm/dL
ALT	>100 U/L
BNP	>100 pg/mL
Creatinine	>1 mg/dL
CRP	>10 mg/dL
D-Dimer	>2000 ng/mL
ESR	>40
Ferritin	>500 ng/mL
Fibrinogen	>400 mg/dL
Hemoglobin	9 gm/dL
Lactate	>2.2mml/L
Platelets	<100,000/cc
Procalcitonin	> 0.6 ng/ml
Troponin	>0.04 ng/L

Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Management by Clinical Severity			
Medication	**Mild Disease (Meets MIS-C definition and mildly ill appearing)**	**Moderate Disease (Meets MIS-C definition and Ill appearing without hemodynamic instability)**	**Severe Disease (Meets MIS-C definition and critically ill with hemodynamic instability)**
Methylprednisolone	Consider not treating with steroids and start high dose aspirin.	Start 1 mg/kg/dose BID (no max dose).	Start pulse dose regimen: 30 mg/kg/dose once daily for 3 days (max 1 g/day). Consult rheumatology for steroid taper.
Aspirin	Consider **high dose** aspirin (80 mg/kg/day divided three times daily) if not using steroids. Switch to **low dose** (3-5 mg/kg/day once daily) 48 hours after afebrile and continue at discharge.	Start low dose aspirin (3-5 mg/kg/day once daily) -OR- prophylactic enoxaparin (dosed/monitored per AIDHC protocol). If on prophylactic enoxaparin, switch to low dose aspirin at discharge.	Initiate low dose aspirin (3-5 mg/kg/day once daily) **2-3 days prior to stopping enoxaparin (refer to enoxaparin section below)** and continue at discharge.
IVIG (Privigen 10%)	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).	First dose: 2 g/kg (max 160 g). If second dose is approved, repeat 2 g/kg (max 100 g).
Enoxaparin	N/A	Start prophylactic enoxaparin (dosed/monitored per AIDHC protocol) -OR- low dose aspirin (3-5 mg/kg/day once daily). If on prophylactic enoxaparin, switch to low dose aspirin at discharge.	Start prophylactic enoxaparin (dosed/monitored per AIDHC protocol) and consult hematology for further guidance.
Anakinra/Tocilizumab	Consider if resistant to initial treatment with IVIG/steroids. Consult rheumatology for dosing guidance.		
Remdesivir	To be used on a case-by-case basis. Consult ID for medication procurement and dosing guidance.		

Ordering echocardiograms for suspected MIS-C patients	
Initial echocardiogram Please call cardiology and ensure troponin and BNP are ordered as part of lab work-up	
Mild/moderate disease patients	Can be completed within 24hrs, if hemodynamically stable, and no significant elevation of troponin or BNP. If lab values are abnormal, discuss with cardiology
Severe disease patients with shock or hemodynamic compromise	Order from the emergency department, can be completed either in the ED or in the PICU at the time of admission
Subsequent/follow-up echo	
Mild/moderate disease patients, hemodynamically stable with normal initial echocardiogram	Can repeat prior to discharge unless there is a significant change in clinical status, new elevation of troponin, BNP or persistent fever greater than 2 days
All other patients: severe disease pts with hemodynamic instability; significantly abnormal troponin, BNP; change in clinical status during admission	May be repeated in consultation with cardiology every 1 to 2 days or as needed. If remains normal, then follow low/moderate risk (hemodynamically stable) guidelines
Follow-up after discharge	
Echocardiogram in 2 weeks and 6 weeks	If any abnormal echos during admission, coordinate cardiology visit along with an echo. If echos normal throughout admission, can order echo only (let consult service know at the time of discharge)
Echocardiogram in 6-12 mos	All patient should have a f/u echo 6-12 months from initial presentation since natural history of this condition is as yet unknown.

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Introduction:
SARS CoV2 causes acute and post-acute illness in the pediatric population. One of the post-acute illnesses is Coronavirus Pediatric Multi-system Inflammatory Syndrome MIS-C. This inflammatory syndrome is not unlike other inflammatory syndromes that pediatricians and pediatric subspecialists have evaluated and diagnosed. Unfortunately, diagnostic criteria, such as available for Kawasaki Disease (KD) and atypical KD, do not exist yet. Case definitions published by states and the CDC are considered surveillance definitions for the purposes of reporting and are useful for looking back but not as helpful in making a diagnosis of MIS-C when a physician or APP is initially seeing the patient. The goal of this guideline is to provide a framework for physicians and APPs to use to guide the evaluation of patients and management of those ultimately diagnosed with MIS-C. It is not a guideline for the management of acute SARS CoV2 illness.

Synonyms:
- Pediatric Multi-system Inflammatory Syndrome (PMIS)
- Coronavirus-Pediatric Multi-system Inflammatory Syndrome (C-PMIS)

Guide for navigating this guideline
- Green boxes – steps in the algorithm
- Yellow boxes – content is presented that should caution the user to consider the box content before proceeding with next steps in the algorithm.
- Blue boxes – "Jump to" guideline sections, tables, and other content by clicking on the topic you want to review.
- Font that is a different color and underlined represent links to additional content in the guideline relevant to the evaluation of patients who might have MIS-C and management of patients diagnosed with MIS-C. To see the additional content, click on the topic you want to see.
- Red stop sign – exit guideline

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Section Title: Center for Disease Control (CDC) Surveillance Case Definition for MIS-C

An individual aged <21 years **+**

fever* **+**

lab evidence of inflammation** **+**

clinically severe illness requiring hospitalization with involvement of 2 or more organ systems

AND

No alternative plausible diagnoses

AND

Positive for current or recent SARS-CoV-2 infection

- RT-PCR
- Serology
- Antigen test

OR

COVID-19 exposure within the 4 weeks prior to the onset of symptoms

- Fever of 24 hours or more is not enough to diagnose MIS-C. To meet the CDC case definition all components must be present
- The physician and APP should explore alternative diagnoses and determine that no alternative plausible diagnosis applies
- It is preferred that laboratory testing for SARS CoV 2 is used to confirm current or recent infection. In settings where no testing is available, exposure to COVID-19 within the 4 weeks prior to the onset of the patient's symptoms may be used to meet the requirements for MIS-C

*Fever - 38.0°C or higher for 24 hours or more, or report of subjective fever lasting 24 hours or more
** 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), interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments:

- Some individuals may fulfill full or partial criteria for Kawasaki Disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

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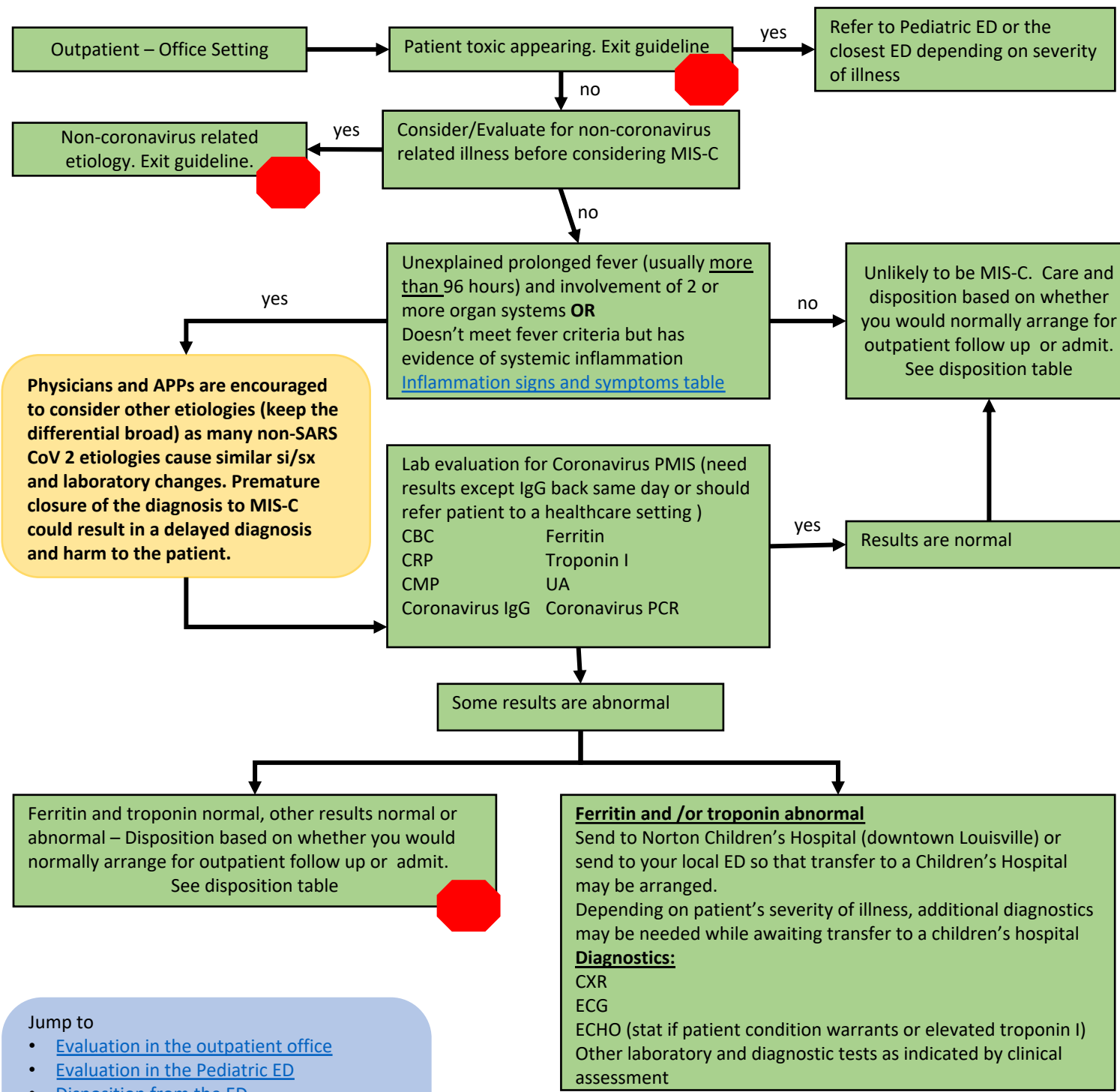
If questions about this guideline, contact evidencedbasedcollaborative@nortonhealthcare.org

Section Title: When to Consider Evaluation for MIS-C – Office Setting



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Section Title: When to Consider Evaluation for MIS-C – ED Setting

Pediatric ED

Patient toxic appearing or requires emergent interventions. Exit guideline.

yes → Stabilize. Evaluate for non-coronavirus and coronavirus etiologies.

no

Consider/Evaluate for non-coronavirus related illness before considering MIS-C

yes → Non-coronavirus related etiology. Exit guideline.

no

Unexplained prolonged fever (usually more than 96 hours) **AND** involvement of 2 or more organ systems **OR**
Doesn't meet fever criteria but has evidence of systemic inflammation

no → Unlikely to be MIS-C. Disposition based on whether you would normally discharge the patient to home or admit. See disposition table

yes

Initial lab evaluation for Coronavirus PMIS

CBC	Ferritin
CRP	Troponin I
CMP	
Coronavirus IgG	Coronavirus PCR
Blood culture	
UA	

Other laboratory and diagnostic tests as indicated by clinical assessment

Physicians and APPs are encouraged to consider other etiologies (keep the differential broad) as many non-SARS CoV 2 etiologies cause similar si/sw and laboratory changes. Premature closure of the diagnosis to MIS-C could result in a delayed diagnosis and harm to the patient.

Coronavirus available tests are still changing rapidly, listed tests current at time of publication. Use what is available in EPIC at time of patient evaluation

Some results abnormal

All available results are normal.

- Ferritin and troponin normal, other results normal or abnormal – Disposition based on whether you would normally discharge the patient to home or admit. See disposition table

Ferritin and /or troponin abnormal
Admit to care area appropriate for patient's current severity of illness. Additional evaluation may be performed in the ED or after admission based on severity of illness and/or lab results:

Lab:
BNP (even if troponin normal)
IL-6
D-dimer, fibrinogen, PT/PTT/INR

Diagnostics:
CXR
ECG
Pediatric Echo Doppler 2D M-mode Color Complete (stat if patient condition warrants or elevated troponin I, Cardiology consult)
Other laboratory and diagnostic tests as indicated by clinical assessment

Urgency of additional testing is dependent on disease severity

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Section Title: Algorithm for Evaluation and Management of Inpatient Admitted for Rule out MIS-C

ED to Inpatient OR Transfer to Inpatient for evaluation and monitoring for possible MIS-C

Physicians and APPs are encouraged to consider other etiologies (keep the differential broad) as many non-SARS CoV 2 etiologies cause similar si/sx and laboratory changes. Premature closure of the diagnosis to MIS-C could result in a delayed diagnosis and harm to the patient.

Complete laboratory and diagnostic tests for diagnosis of MIS-C

Urgency of additional testing is dependent on disease severity

Coronavirus available tests are still changing rapidly, listed tests current at time of publication. Use what is available in EPIC at time of patient evaluation

Labs
Blood culture
BNP
CBC
CRP
CMP
D-dimer, Fibrinogen
Ferritin
IL-6
PT/INR/PTT
Troponin I
UA

Coronavirus labs
Coronavirus PCR, Coronavirus IgM/IgG

Diagnostics
CXR
ECG
Pediatric Echo Doppler 2D M-mode Color Complete (Cardiology consult may be warranted at this time)
Other laboratory and diagnostic tests as indicated by clinical assessment

Unlikely to be MIS-C; other diagnosis more likely
- CR monitoring, pulse oximetry
- Repeat inflammation labs based on clinical assessment
- Continue evaluation for alternative diagnosis
- Methylprednisolone for treatment of MIS-C not indicated.
- Empiric antibiotic therapy if concern for acute bacterial infection.

Hospital course or results of labs/diagnostics suggest MIS-C

If patient meets KDPH case definition, contact IP for reporting to state.

Strong suspicion for MIS-C
- Start methylprednisolone
- Start enoxaparin – prophylaxis dose
- Start PPI
- Repeat ECHO – Day 2 hospitalization and then as indicated by unexpected change(s) in cardiovascular exam or as requested by Cardiology
- Empiric antibiotic therapy if concern for acute bacterial infection
- Consult ID, Rheumatology, and Cardiology are usually indicated
- Consult other subspecialists based on clinical assessment

Alternative diagnosis made.
- Discontinue MIS-C therapies that are no longer needed
- Exit guideline

Confirmed diagnosis of MIS-C
- Continue current MIS-C therapies and escalate based on response and clinical assessment
- See disposition for MIS-C patients

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Section Title: Signs and Symptoms of Organ Dysfunction and Inflammation

Febrile illness, hyperinflammatory response in acute illness, and post-infectious complications are not new findings for physicians and APPs. *The guideline authors remind physicians and APPs to consider alternative and additional diagnoses that are not SARS-CoV 2 related to avoid diagnostic errors.* Additional testing and monitoring may be needed to reach the correct diagnosis for a specific patient. This guideline focuses on evaluation and management of illness caused by SARS-CoV 2

Table 1: Signs and Symptoms Suggestive of Inflammation, including MIS-C

Systemic Inflammation • Fever • Myalgias • Tachycardia • Hypotension • Hypoperfusion or hyperperfusion • Lymphadenopathy/lymphadenitis	**Mucocutaneous** • Rash: reticular, morbilliform, purpuric • Lip swelling/cracking • Strawberry tongue • Extremity swelling/peeling • Conjunctivitis • Blisters or erosions
Cardiopulmonary • Respiratory distress • Chest pain	**Gastrointestinal** • Nausea/vomiting • Diarrhea • Abdominal pain
Neurologic • Headache • Altered mental status • Meningismus • Focal deficits • Seizure	

Table 2: Kawasaki Disease	Atypical Kawasaki Disease
Fever of at least 5 days duration AND 4 or more principle findings	Fever of at least 5 days duration AND 2 or more of KD principle findings AND
• Extremity changes • Polymorphous rash • Oropharyngeal changes • Bilateral, nonexudative, limbic sparing, painless bulbar conjunctival injection • Acute unilateral nonpurulent cervical lymphadenopathy with lymph node diameter greater than 1.5 cm	• Elevated ESR • Elevated CRP • Hypoalbuminemia • Anemia • Elevated ALT • Thrombocytosis • Leukocytosis • Pyuria

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Section Title: Medication Management of MIS-C

Mild MIS-C: admitted to general inpatient unit. No vasoactive requirement, minimal/no respiratory support, minimal organ injury

Moderate MIS-C: Admitted to an ICU. 0-1 cardiovascular drug infusion, significant supplemental oxygen support, mild or isolated organ injury

Severe MIS-C: Admitted to an ICU. More than 1 cardiovascular drug infusion, non-invasive or invasive ventilator support, moderate or severe organ injury including moderate to severe ventricular dysfunction

Coronavirus PMIS Severity	Medication	Dose
All patients	Consider broad spectrum antibiotics pending culture results: vancomycin + ceftriaxone. Consider addition of clindamycin (toxin mediated disease), doxycycline (tick-borne illness) or metronidazole (Flagyl) based on history, si/sx, and lab data. Gi prophylaxis with PPI. Patients with MIS-C have higher risk of bowel perforation with pulse steroids. Consider risk/benefit of high dose (I added these words) therapy in these patients	
Mild MIS-C	Methylprednisolone*	2 mg/kg/day IV divided q6h
	Enoxaparin (prophylaxis)	< 40 kg: 0.5 mg/kg SC q12h 40 kg or greater: 40 mg SC q24h
Moderate MIS-C	Methylprednisolone*	Pulse: 10 mg/kg IV x 1; followed by 2 mg/kg/day q6h starting 24 hours after pulse dose
	Anakinra (if refractory to steroids)	2-10 mg/kg/day IV for 5 – 14 days
	Enoxaparin (treatment)	1mg/kg SC q12h
	IVIG	1 g/kg IV qday x 2 days
Severe MIS-C	Methylprednisolone*	20-30 mg/kg/day (max 1000 mg) for 1-3 days; followed by 2 mg/kg/day IV q6h starting 24 hours after pulse dose.
	Anakinra	10 mg/kg/day IV for 5-15 days
	Enoxaparin (treatment)	1 mg/kg SC q12h
	IVIG	1 g/kg IV qday x 2 days
Complete or Atypical Kawasaki Disease	IVIG 2 g/kg IV Aspirin 3-5 mg/kg/day (81 – 325 mg per day) Additional immunomodulators as needed in conjunction with appropriate consultants	

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Section Title: General Inpatient Management of MIS-C

Daily Coronavirus PMIS Care	
Other Medications	IVIG 2 g/kg up to 100 g Indication: Meets criteria for Kawasaki Disease or atypical Kawasaki Disease; myocarditis; other indications may be identified during the patient's hospital course and discussion with subspecialists
	Enoxaparin increased to treatment dose if patient has evidence of clotting or DIC
Monitoring	Daily labs: CBC, CRP, troponin I, BNP, CMP until patient status improved or plateaued ESR, IL 6, fibrinogen, coagulation studies, d-dimer as needed to monitor inflammation and patient specific indications Other labs and frequency depending on organs involved and severity of illness
	Until status improved or plateaued ECHO day 2 of hospitalization and then as recommended by Cardiology or significant change in patient status ECG on day 2 of hospitalization and then as recommended by Cardiology or significant change in patient Repeat CXR as needed based on patient condition
	Enoxaparin treatment dose – anti Xa to monitor for therapeutic effect
Critical Care	Respiratory support: early proning, mechanical ventilation strategy somewhat dependent on phase of illness , especially if acute SARS-CoV-2 infection and not MIS-C
	Cardiovascular drug support as needed
	ECMO SARS CoV 2 + is not a contraindication to ECMO.. If + and arrests during cannulation, the procedure should proceed.
	ECPR SARS CoV 2 IgM and/or IgG + is not a contraindication to ECPR if respiratory [nasal (and sputum if sent] PCR negative
	Plasma exchange No specific indications. May be helpful in severe, refractory states.
	Renal replacement therapy
Consults	It is not required that hospitalists or intensivists consult others to appropriately manage the MIS-C. Services that may be helpful include: ID, Rheumatology, Cardiology, Heme/Onc, Nephrology

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evidencedbasedcollaborative@nortonhealthcare.org

Section Title: ED Disposition Guideline

Unlikely to be MIS-C	Some abnormal inflammation labs but ferritin and troponin normal	Ferritin and/or Troponin abnormal

• No indication for admission
  • Include si/sx of MIS-C and return to ED (.phrase in EPIC for AVS)
• Indication for admission
  • Admit to appropriate level of care
  • Admit patient to local hospital or refer to Norton Children's Hospital
	• No indication for admission
	  • Include si/sx of MIS-C and return to ED (.phrase in EPIC for AVS)
	• Indication for admission
	  • Admit to appropriate level of care
	  • Admit patient to local hospital or refer to Norton Children's Hospital for lab trending and monitoring
		• Admit to appropriate level of care at NCH Downtown
		• If patient in a referring hospital, transfer to Norton Children's Hospital
		  • "Just for Kids" Transport Team at 1-888-729-9111

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Section Title: Inpatient Discharge of Confirmed MIS-C or Strong Suspicion of MIS-C

Report to state	Assure NCH IP aware of case
Medications for MIS-C	Very dependent on hospital course
MIS-C Multi-disciplinary clinic	See Referral Algorithm
Discharge instructions for AVS	To be written .phrase

Inpatient at NCH with:
1) Diagnosis of COVID-PMIS
or
2) High suspicion of COVID-PMIS and treatment using COVID-PMIS pathway

COVID-PMIS Clinics:
Weekly on Monday afternoons
First clinic, Monday, May 18, 2020
Novak Center, 5th Floor (Cardiology)

Prior to Discharge:
Inpatient Team to contact COVID-PMIS Clinic Nurse Navigator
Brienne Merten, BSN
Call: 502-629-4446

Nurse Navigator will visit patient bedside, provide contact info, and schedule appointments

Each case will be reviewed to determine appropriate specialist involvement

Provider questions: contact Brian Holland, MD, call or text cell: 845-527-8441
Administrative leader questions: contact Rachel Waiz, BSN, call or text cell: 502-551-8251

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Section Title: Steroid Management

- Start with lower recommended dose in less severe MIS-C; higher dose the more severe the disease.
- Escalate dose or pulse-dose if patient continuing to deteriorate; inflammatory markers continuing to increase.
- May consider switching to enteral when patient has demonstrated improvement for 2 or more days and is tolerating enteral nutrition, and interruption of enteral nutrition isn't anticipated.
- May start tapering of steroid dose when inflammatory markers demonstrate a consistent trend of improvement, patient is improving. Slow taper is recommended even for mild disease.
    - Mild disease: taper over 14 – 21 days
    - Moderate disease: taper over 6 – 8 weeks
    - Severe disease: taper over 6 – 8 weeks and consider repulse dose at 3 – 4 weeks if unable to taper or continue taper

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- Order set pending at time of initial launch

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Section Title: Writing Team and Approvals

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Approvals		
Role	**Name**	**Initials/Date**
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Service Line Chief	Brian Holland - Cardiology	BH 5/20/2020
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Section Title: Version History

Guidelines must have a mini review by the owner every 2 years and a major review by the writing group every 4 years. If there has been attrition of members during the interval, the owner may decide to move forward with the remaining members or add new members. Is substantive changes are required, new members should be added as there may need to be a formal implementation plan to assure that the changes are incorporated into the care of patients. Any associated order sets, policies, and procedures will need to be updated.

Version	Date	Guideline Owner	Summary of Edits	Next Revision Due
1	May 19,2020	Vicki Montgomery	NA	NA

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If questions about this guideline, contact evidencedbasedcollaborative@nortonhealthcare.org

Section Title: Disclaimerand Restrictions

- Disclaimer:
  - These Guidelines are based upon a review of current medical literature, but do not mandate a course of treatment or set the standard for medical care. Departures from the Guidelines may be appropriate in the management of a particular patient or in response to changes in medical science. Individuals providing healthcare are expected to use their education, training and experience to determine what is in the best interests of the patient under the circumstances existing at the time. The clinical literature cited is not an endorsement of any article or text as authoritative.
- Restrictions:
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Jump to
- Evaluation in the outpatient office
- Evaluation in the Pediatric ED
- Disposition from the ED
- Evaluation in Inpatients
- Signs and symptoms of inflammation table
- Medication management of MIS-C
- Other management of MIS-C
- Discharge of Inpatient

Jump to
- Bibliography
- Writing Team and versions
- Disclaimer

PHOENIX CHILDREN'S | COVID-19

Multisystem Inflammatory Syndrome in Children (MIS-C)

Guidance for Practitioners

CDC is collaborating with domestic and international partners to investigate reports of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. CDC and partners are working to better understand this new syndrome, including how common it is and its risk factors, and to begin tracking cases.

Case definition for MIS-C

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic);

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 with 4 weeks prior to the onset of symptoms.

* Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

** 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

If patient is believed to meet MIS-C criteria based on the guidance above;

- **Consult the Infectious Diseases physician on call**

- **Contact Infection Prevention**
- **Consider ordering the following studies after consultation with the ID service:**

- SARS-CoV2 PCR (NP swab)-orderable in SCM
- SARS-CoV2 IgG (blood)- orderable in SCM
- CBC with differential
- Blood culture
- CMP
- Urinalysis/urine culture
- ESR
- CRP
- Procalcitonin
- Lactic Acid
- LDH
- D-Dimer
- Pro-BNP
- Troponin
- Ferritin
- Interleukin 6- orderable in SCM
- CK
- Echocardiogram to evaluate function and coronaries

Additional Comments:

•Some individuals may fulfill full or partial criteria for Kawasaki disease, but should be reported if they meet the case definition for MIS-C

•Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Multisystem Inflammatory Syndrome in Children (MIS-C) treatment options dosing

Choice of medication will be made on a case by case basis in consultation with the Infectious Diseases and Rheumatology services.

MEDICATION	DOSE
IVIG	• 2 grams/kg (Max dose 160 grams). Use ideal body weight (IBW) or actual body weight (whatever is the lower of the two) and round to the nearest vial size. • May give 1 gram/kg x 2 doses over 2 days if concerns with fluid restrictions
Aspirin (Kawasaki Disease dosing)	• Acute phase: 30 mg/kg/day div q6 • Subsequent therapy: 3-5 mg/kg/day up to 81mg daily
Methylprednisolone	30 mg/kg daily (max 1000 mg) per dose for 3-5 days.
Anakinra	4 mg/kg/day (Max dose 400 mg/day) that can be divided up to every six hours SC. Drop the dose in 3 to 5 days by 50% depending on clinical improvement.
Tocilizumab	Weight based: • < 30 kg: 12 mg/kg • ≥ 30 kg: 8 mg/kg x 1 IV • Max dose 800 mg

Inclusion Criteria: Previously healthy, age over 2 months – 21 years with fever 38°C or greater for at least 24 hours with lab and/or exam findings of severe multisystem inflammation or GI complaints^ with no other plausible explanation (1)

Exclusion criteria: Known rheumatologic disorder; alternate diagnosis confirmed or with high probability that explains presentation

Possible Multisystem Inflammatory Syndrome in Children (MIS-C) Algorithm 07.20.2020

Direct admission or CHET transported patient
Complete a history and examination (1,2)

RISK FACTORS
Positive PCR for SARS-CoV-2 infection (current or at any time in past) ***or***
Positive serology for SARS-CoV-2 ***or***
Close contact with individual with known SARS-CoV-2 diagnosis
NOTE: ⚠ *Above SARS-CoV-2 risk factors may not be known at time of initial assessment. Proceed*
with assessments even if risk factors are negative or not known. Lack of risk factors on initial
assessment therefore does not exclude a patient from this pathway.

HISTORY and EXAM (list here is not in any rank order)
Rash (any, unless clearly associated with known infectious rash such as VZV)
Swollen hands or feet
Conjunctival injection
Tongue erythema (papillary involvement may be present)
Abnormal cardiac exam (murmur, heave)
Fever to any degree, but may be greater than 40 in some cases
Diarrhea^ (non bloody)
Emesis (non bloody; note that emesis may be GI sign or instead due to other sources including cardiac)
Abdominal pain^ (non focal) or abdominal distension^
Nuchal rigidity+
Irritability, altered mental status
May not be present: shortness of breath, wheezing, rales, cough, hypoxia
Vital sign instability*: tachycardia, poor perfusion/delayed capillary refill time, hypotension

Vital sign instability* or meningeal signs+? (3)

No → History: positive Exam: positive Risk factors: positive ?

No → History: positive Exam: positive Risk factors: *negative* ?

No → History and Exam: Plausible alternate diagnosis found. Risk factors: Negative ?

Yes → OFF PATHWAY

Yes → EMERGENT STABILIZATION

CONTACT PHM (CHET) and PICU ATTENDING IMMEDIATELY

STABILIZATION AND TRANSPORT

ECHOCARDIOGRAM per PICU
Consider cardiology consult

Yes → Initiate testing *and* ADMIT to HOSPITAL

Yes → Initiate testing

ROUTINE SCREENING STUDIES (4):
COVID-19 PCR; Respiratory Viral PCR
SARS-CoV-2 Serology
CRP, ESR
COMP metabolic panel (↓Na+, albumin; ↑ AST, ALT, LDH)
CBC with differential (↓ platelets, ↓ lymphocytes, ↑ PMNs)
ROUTINE COMPLETE STUDIES (4):
D Dimer (see lab report for details; healthy patient levels are most often less than 0.5 μg/mL (FEU)
Troponin, BNP (↑ or ↑ ↑)
Ferritin (↑)
ECG 15 lead (ischemia, effusion, c/w myocarditis, other)
Urinalysis (complete)
Blood culture
CONSIDER OTHER STUDIES (based on clinical presentation) (4,5):
GI Pathogen panel, ASO, Rapid strep, NGAL (AKI concerns), EV PCR, adenovirus PCR , urine
culture, CXR (symmetric, patchy infiltrates, pleural effusion), triglycerides, procalcitonin, KUB/
abdominal sono (ascites, HSM, ileitis/coliits), Type and screen testing, VBG, lactate, PT, PTT.
Other testing as appropriate based on exam, risk factors, history.

Review differential diagnoses (examples on page 4)

Testing suggestive of MIS-C? (1)

Yes → ADMIT TO HOSPITAL

No → Testing abnormality suggests alternate diagnosis?

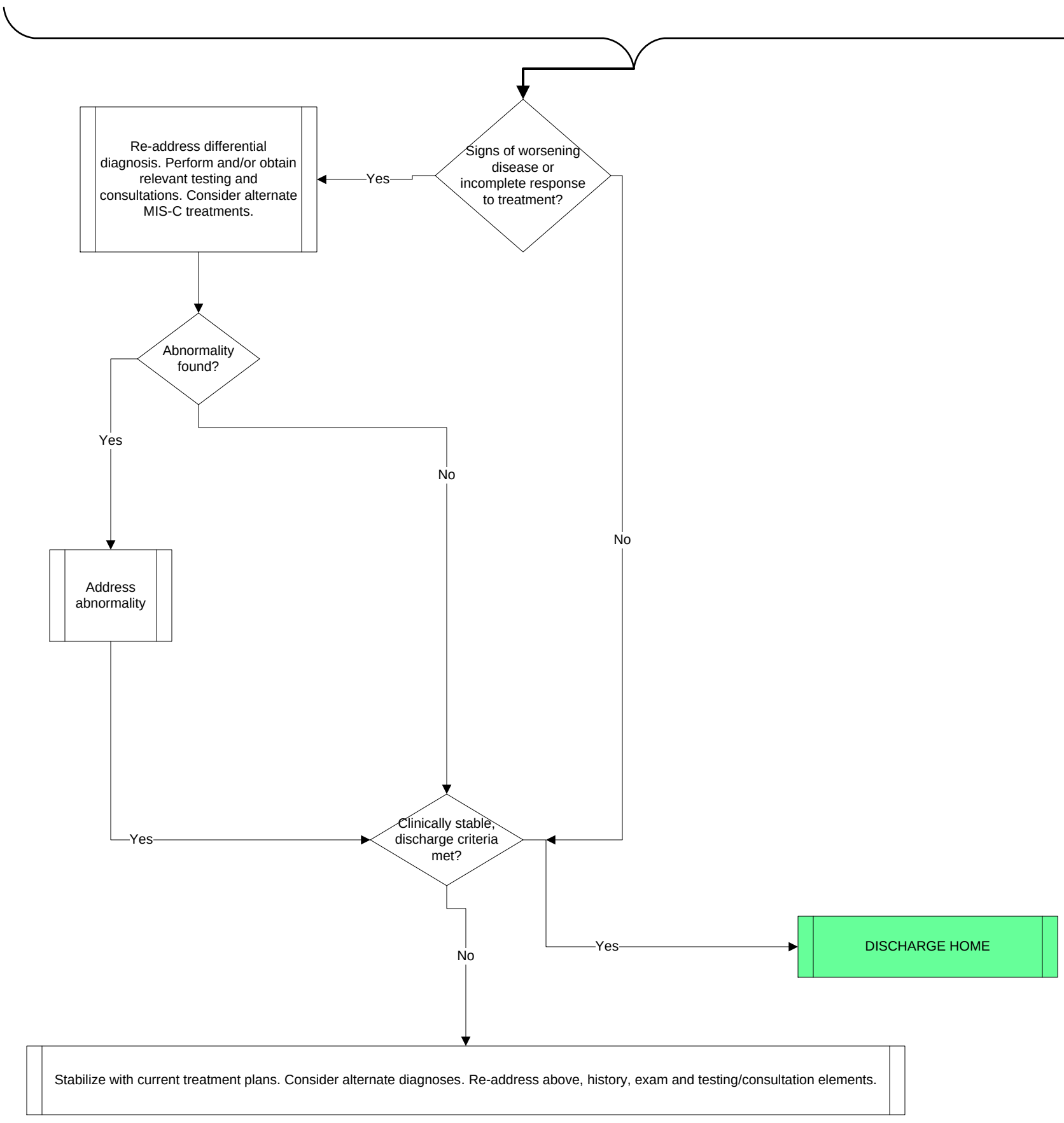
To next page

This protocol is a general guideline used at Rady Children's San Diego California, and does not represent the professional standard of care required of the health care provider. The pathway should be modified as indicated, based on the health care provider's professional judgment, to meet the needs of individual patients. Reference numbers are noted in parentheses on this algorithm.

From Page 1

ADMIT to HOSPITAL WARD
Patient may be placed in regular monitored bed (non-SIDU) if COVID-19 PCR negative, following hospital guidelines.
Complete, expand, and/or re-confirm the history and examination.
Commonly considered elements for history, exam, testing, consultations, and considerations are noted below (6,7)

OBTAIN FULL HISTORY Some history items noted below may aid in development of differential diagnosis and/or identification of potential complications. **NOTE:** This list is only an example and is not meant to be limiting. Physicians should develop their own differential diagnoses based on the patient's unique presentation and findings.	TESTING and CONSULTATION (In addition to ED/Direct Admit Phase)	MONITORING AND TREATMENT	RESPONSE TO TREATMENT **(SIGNS OF WORSENING OR INCOMPLETE RESPONSE TO TREATMENT)**
*Joint complaints (e.g. swelling, pain, stiffness)	**TESTING:**	**MONITORING:**	**Exam, clinical status:**
*Medication use in past weeks	*Echocardiogram (if hospitalist attending/consults direct)	*Continuous cardiorespiratory monitoring	*Worsening of any existing symptom or vital sign
*Tick exposure	*Repeat testing: EKG (every 2 days); trend labs	*Continuous pulse oximetry	*Persistent fever 24 hours after treatment
*Exposure to or contact with known GI infection	over time until normalized (BNP, troponin	*Strict intake and output	* New clinical problem
*Exposure to Staph or strep	recommended)	*Strict calculation of urine output (at least every 4 hrs)	* New organ system involvement (e.g. new drop in
*Travel to areas with endemic dengue fever	*Additional testing: Consider additional testing	*VTE screening per hospital protocol	urine output)
*Family history:	based on risk factors and potential differential		**Testing:**
-- cardiac disease (including cardiomyopathies)	diagnoses.	**TREATMENTS**:	*Increased CRP, AST, ALT, LDH
-- autoimmune diseases	**CONSULTS:**	**First line therapy:* IVIG	* Increased Ferritin, D Dimer, triglycerides
-- thrombophilia	*Infectious Diseases, Kawasaki, Rheumatology	**Alternate/added therapies:* Systemic steroid,	*Decreased cell counts (wbc, Hgb, platelets)
Timing, acuity/chronicity, changes, and/or	*Consider based on clinical needs: Nephrology,	Anakinra, Infliximab, Remdesivir.	*Decreasing serum sodium
progression of any history or exam finding is	Cardiology, Dermatology, Hematology	**Co-treatments: antibiotics; heparin/lovenox*	*Worsening renal function
important to note.	*Strongly consider: Social work or child life	*(See treatment page for specific indications).*	*Worsening cardiovascular status



Common medication therapies (7)

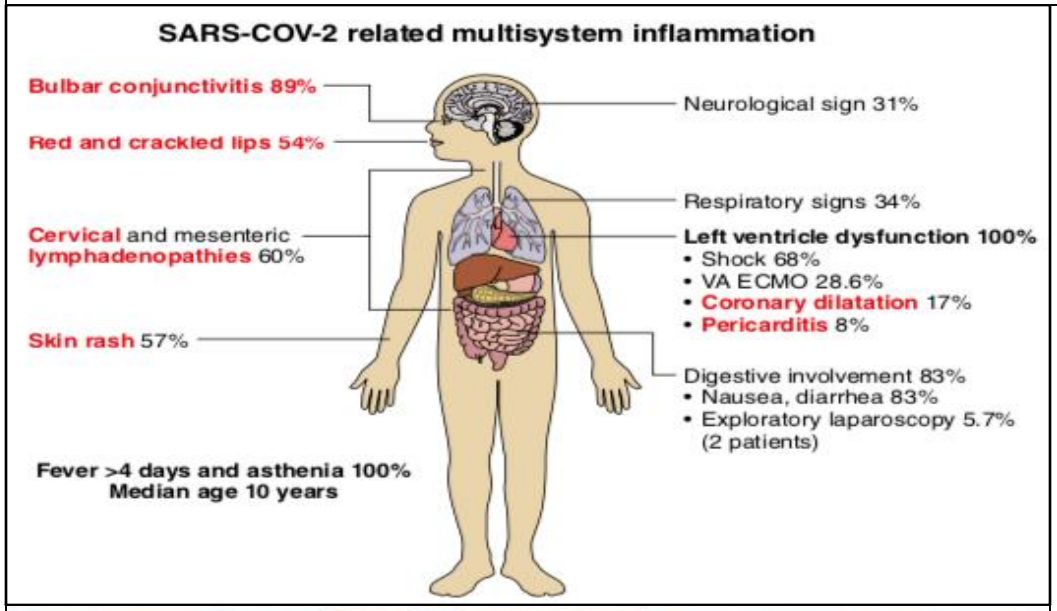
Treatment plans should be created to meet unique patient needs. Any recommendations for treatment should be agreed upon by the Hospital Medicine attending, in concert with involved subspecialists.

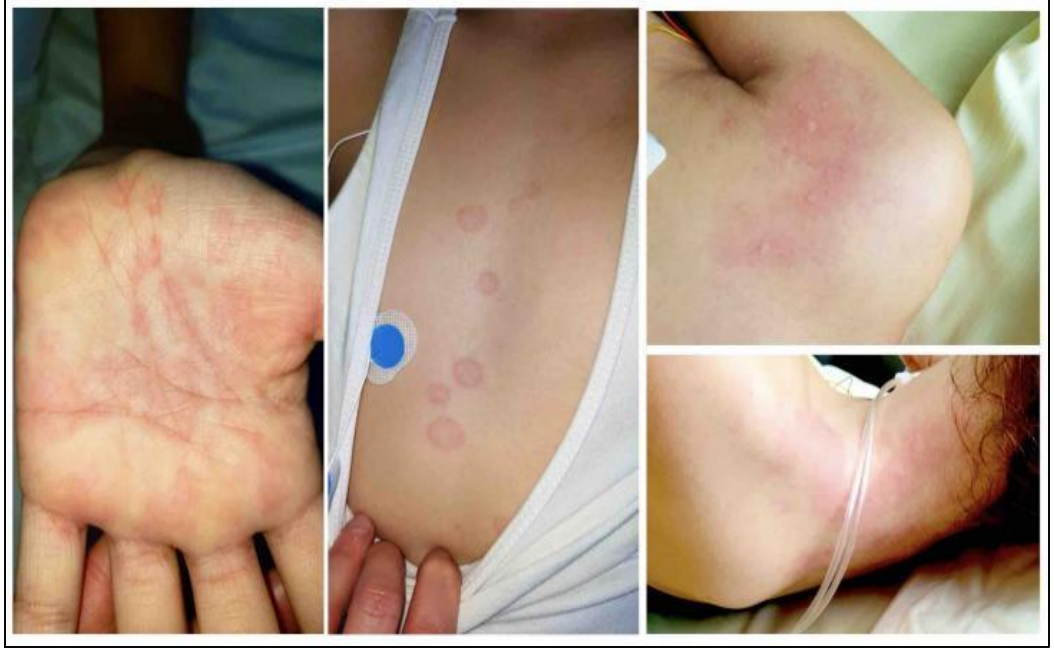
Considerations:

- **ASA:** Consider ASA especially if evidence of coronary artery involvement or abnormality on echo.
- **Immunomodulation:**
  - Consider not giving or delaying IVIG in setting of cytokine storm, shock or severe myocardial dysfunction, due to risk of fluid overload and potential inhibition of biologic drug therapy.
  - ^Use steroid with caution in patient with coronary arteritis (concern for poor vessel healing) and patients with severe GI presentation (risk of perforation). **Do not use "pulse" steroids.**
- **Antibiotics:** Broad spectrum antibiotics may be indicated in specific cases. Consider coverage for differential diagnoses such as toxic shock syndrome or Rickettsia infection depending on patient presentation.
- **Anticoagulation:** Consider prophylactic anticoagulation based on clinical picture and risk assessment. Prophylactic anticoagulation should be considered for all patients 10 years and old with High Risk VTE score or Moderate Risk VTE score with bilateral contraindications to sequential compression devices; all patients >=18 years with COVID-19; and all patients with COVID-19 in PICU and CTICU. Consider in patients with coronary artery aneursym Z score greater than 10 or with ejection fraction less that 35%. Consider full clinical presentation when deciding anticoagulation regimen and consult hematology if needed regarding choice of anticoagulant, dosing, monitoring, and duration of therapy. Most common options are heparin (IV or SQ) and enoxaparin (SQ).
- **Medication dosing**: Maintain awareness of renal function when determining medication dosing.

KD features, coronary aneurysm, without shock	**Shock, Cytokine storm, significant myocardial dysfunction**
IVIG: 2 grams/kg (max 100 grams). Note: If patient has blood type A , there may be a potential for hemolysis in some patients. Consider alternate dosing regimen. If obese, consider dosing on ideal body weight.	**Steroid**: Methylprednisolone IV 2 mg/kg x1 dose (max 80 mg) then 2 mg/kg/day divided BID (max 40 mg/dose). Steroids will be tapered slowly over 2-6 weeks.
Infliximab: 10mg/kg once (for aneurysm, coronary artery z-score over 2.5)	**IVIG**: consider delaying or slower rate due to volume
ASA: 3-5mg/kg/day max dose 81mg	**Anakinra**: 2-10mg/kg/day divided every 12 hours (max 100mg/dose).
Proton pump inhibitor: while on above therapies	**ASA**: 3-5mg/kg/day max dose 81mg/day or anti-coagulation[Per Heme recommendation in concert with other involved subspecialties]
*Steroid may be indicated; see considerations above^*	**Proton pump inhibitor**: while on above therapies
	Antibiotics: Per ID recommendations; often broad spectrum
	Infliximab: 10 mg/kg once

Common presentations and	Common differential diagnoses





Rash on the skin of a child who has COVID-19 related multi-system inflammatory syndrome (MIS-C). The image is from Damien Bonnet, M.D., Ph.D., Necker Hospital-Université, Paris, who was involved in a Circulation study published on MIS-C May 14. Image copyright Damien Bonnet, courtesy of the American Heart Association.Both figures are from the site below, accessed 06.02.2020: https://www.dicardiology.com/article/kawasaki-inflammatory-disease-affects-children-covid-19%C2%A0

Common differential diagnoses
Differential diagnoses should be considered in all cases prior to use of this clinical pathway. However, as with any patient receiving medical care, changes in a patient's clinical findings and/or test results should be appropriately incorporated into clinical decision making.
The following list of commonly encountered differential diagnoses is offered in this context. This is not a complete list, and serves only as general guidance for the clinician's medical decision-making:
* Bacterial or viral sepsis or systemic infections [ex: Adenovirus, EBV, Enteroviruses]
*Toxic Shock Syndrome (typically due to staph, strep)
*Appendicitis
*Hemophagocytic lymphohistiocytosis (HLH)
*Macrophage activation syndrome (MAS)
*Systemic lupus erythematosus; Dermatomyositis
* JIA
* Drug reactions (DRESS, SJS/TEN variants, other)
*Leukemia
*Vasculitis
*Kawasaki Disease

Discharge Criteria (8)

* Decreasing or normalized inflammatory markers
* Stable cardiac status, with stable findings by ECG and/or echocardiogram as indicated
* Stable on any new medications such as enoxaparin, with therapeutic anti_Xa level if indicated
* If patient is discharge on anti-coagulation, an appointment with hematology, KD, or cardiology services must be scheduled and testing scheduled prior to discharge per specialist recommendations
* No fever for at least 24 hours
* Able to take medications and diet orally or at baseline prior to admission
* All caregiver education completed with teachback with return precautions
* Wherever possible, have discharge medications in hand at time of discharge. For patients being sent home on steroid taper, please make sure taper is clearly detailed in both AVS and Discharge Summary. Example of a taper is noted at the bottom of this page.

Follow-up:
Patient must have a follow-up with either the PCP or a subspecialist within 1 day after discharge. This visit may be in person or telemedicine, based on unique patient needs.
* PCP in 1-2 days to assess for return precautions (below). For any concerns, call involved subspecialists.
* Specialty follow-up: per the specialty's recommendations.
* Follow-up testing to include some or all of these studies. Consider follow-up testing for any tests that have not normalized/resolved to acceptable level:
    * Convalescent SARS CoV-2 IgG
    * D Dimer, troponin, BNP
    * CBC, CMP, CRP, ferritin
    * PT, PTT, anti-Xa level as indicated
* Follow-up in 1-2 weeks with hematology clinic or other designated subspecialty clinic (with existing anti-coagulation monitoring processes) if on anti-coagulation.
* Cardiology follow-up depending on unique patient needs. Common indications for follow-up include evidence of myocarditis (by echo, ECG, or troponin) or evidence of coronary involvement as seen with Kawasaki. Follow-up with KD team at 7-14 days post discharge. Schedule as "Follow-up in KD clinic: Diagnosis MIS-C". Cardiac MRI may be indicated 2-6 months after diagnosis in patients with significant LV dysfunction. Cardiac CT may be indicated in patients with suspicion of distal coronary artery aneurysms that are not well seen on echo.

Return precautions to include but not limited to:
* Call at any time for : return of initial symptoms (e.g. rash, abdominal pain, diarrhea); intolerance of any medications; shortness of breath; headache; chest pain; easy bruising or bleeding (especially if on anti-coagulation).
* Exercise and school : NONE until cleared by all subspecialists involved in care. Home activity to be limited, e.g. no home exercising.
* Contacts: avoid contact with anyone who may be ill. Maintain all usual community and CDC guidelines for infection control.

Parent resources:
CDC website:
https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/mis-c.html
AAP website:
https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/

EXAMPLE STEROID TAPER
NOTE: This example is for a child who begins the taper on the maximal daily dose

	AM (Morning dose)	**PM (Evening dose)**	**TOTAL DAILY DOSE**
Days 1-3	40mg	40mg	80mg
Days 4-6	30mg	30mg	60mg
Days 7-10	20mg	20mg	40mg
Days 11-13	20mg	10mg	30mg
Days 14-16	10mg	10mg	20mg
Days 17-20	5mg	5mg	10mg
Days 21-24	Zero (0) mg	5mg	5mg
Day 25	OFF	OFF	OFF

RWJBarnabas HEALTH

TITLE: GUIDELINES FOR COVID-19 ASSOCIATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) IN PEDIATRIC ACUTE CARE

GUIDELINES:

These guidelines are intended as a general guide and should be applied and interpreted with caution, as they are likely to change over time. Departure from these guidelines may be appropriate and necessary in certain clinical circumstances (guidelines as of 6/1/2020).

PURPOSE:

To aid in the diagnosis, evaluation, management and follow up of pediatric patients (< 21 year-old) with confirmed or suspected COVID-19 multi-system inflammatory syndrome (MIS-C).
*These guidelines are not for the management of primary (active) COVID-19 infection. For management of primary COVID-19 infection please see **"**RWJBH Treatment Guidance for COVID-19 (SARS-CoV-2): Pediatric patients" developed on 5/4/20.

CASE DEFINITION AS PER CDC ADVISORY (5/14/20)

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

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

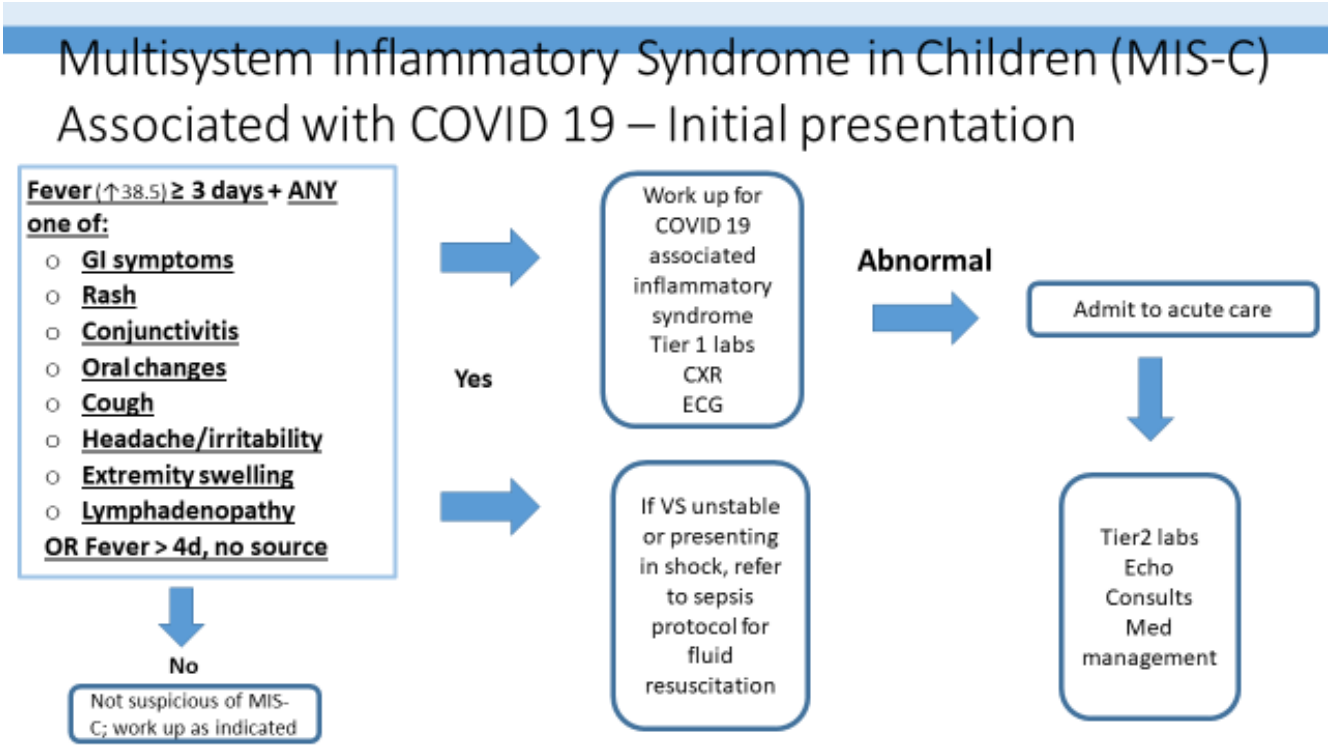
SPECTRUM OF DISEASE

Spectrum of disease — As more is learned about COVID-19 and MIS-C in children, it is becoming apparent that the spectrum of disease ranges from mild to severe. Our understanding of the full spectrum, including phenotypes, is evolving (from Son, M.B., 2020).

- **COVID-19-associated febrile inflammatory state** – Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers (especially ferritin) may be elevated, but signs of multisystem involvement are lacking.

- **COVID-19-associated KD** – Some children meet criteria for complete or incomplete KD and do not develop shock and multisystem involvement. It is unclear if the incidence of coronary artery (CA) aneurysms is higher in COVID-19-associated KD compared with classic KD.

- **COVID-19-associated MIS-C** – Children with MIS-C have a more severe presentation, with markedly elevated inflammatory markers and multisystem involvement. Cardiac involvement and shock are common.



INITIAL LAB AND IMAGING WORK-UP

• **Tier 1 labs: to be collected during initial evaluation:**
  • CBC/diff
  • CMP
  • Troponin
  • BNP
  • CPK
  • SARS-CoV- 2 PCR, Respiratory Viral Panel, Throat cx group A strep/rapid strep
  • ESR and CRP
  • Fibrinogen, PT/PTT, D-dimer
  • Ferritin
  • Procalcitonin
  • LDH
  • ABG/VBG, ionized Ca, lactate
  • Blood cx
  • UA/Urine cx
• *Save 1-2 red top tubes for additional serologies prior to IVIG administration

• **Tier 2 Labs <u>to be considered</u> after Tier 1 as indicated:**
  • SARS-CoV-2 Ab (obtain before IVIG administration)
  • ANA
  • ASLO (Anti-streptolysin O) /anti-DNase B
  • T-SPOT/QuantiFERON-TB Gold
  • Serology: EBV, CMV, HHV6, parvovirus
  • Myocarditis panel (Coxsackie Ab, echovirus Ab, influenza A, B Ab, *Chlamydophila pneumonia*e Ab)
  • Lupus Anticoagulant, Cardiolipin antibody, Beta 2 glycoprotein 1 antibody
  • EBV PCR, HHV6 PCR, parvovirus PCR, CMV PCR
  • IL-6

• **Imaging/Cardiac function:**
  ○ Initial:
  ▪ Chest X-Ray
  ▪ ECG
  ○ Subsequent:
  ▪ Echocardiogram
  ▪ Other radiologic imaging as indicated by clinical presentation may include neurological or abdominal

CLINICAL PRESENTATION	
Patients may have a preceding illness consistent with COVID-19 or had a COVID-19 sick contact	
Presenting with clinical suspicion of Kawasaki WITHOUT shock: • Patients may have typical or atypical presentation of K.D. • Patients tend to be school age rather than pre-school or younger	**Presenting with clinical suspicion of MIS-C:** • Patients have been found to most commonly present with abdominal pain, fever, and shock • EXCLUDING patients presenting with suspicion of HLH (hemophagocytic lymphohistiocytosis)
• **Inflammatory** o Fever o Myalgias o Rash o Conjunctivitis o Strawberry tongue o Extremity swelling/peeling o Blisters or erosions o Abdominal pain o Nausea o Diarrhea o Headache o Altered mental status o Meningismus	• **Symptoms on right PLUS hemodynamic response:** o Tachycardia o Hypotension o Hypoperfusion o Shortness of breath o Respiratory distress o Chest pain

↓

INPATIENT CLINICAL CONSULTS
• Cardiology • Infectious Disease • Hematology • Consider: o Rheumatology o Other specialists as indicated by clinical course and presentation

↓

SUGGESTED TREATMENT GUIDELINES*
COVID-19-associated febrile inflammatory state • Antibiotics per Pediatric Sepsis Guidelines pending diagnostic and culture results • Serial follow up of elevated inflammatory markers • Echocardiogram (baseline) • Consider watchful waiting (if no progression), OR Glucocorticoid therapy (enteral versus parenteral), and/OR IVIG • VTE prophylaxis based on risk assessment (refer to RWJUH Pediatric VTE Clinical Pathway) • Stress ulcer prophylaxis as indicated
COVID-19-associated KD (Typical or Atypical) without Shock • Management as per AHA guidelines for Kawasaki disease (echocardiogram, IVIG, ASA, etc.) • Stress ulcer prophylaxis as indicated • +/- Antibiotics if clinically indicated • VTE prophylaxis based on risk assessment (refer to RWJUH Pediatric VTE Clinical Pathway)

COVID-19-associated MIS-C
 	
• Initial resuscitation – to begin in ED and call for transport or Peds/PICU admission
• Treatment goals: decreased WOB; improvement in peripheral perfusion, blood pressure, and acidosis
• Fluid resuscitation: titrated to response and ongoing evaluations
• Vasoactive drips as indicated:
  • Initial epinephrine 0.1-0.2 mcg/kg/minute
  • Consider addition of milrinone if BP allows after consultation with cardiology
  • Consider dobutamine as a 2nd or 3rd tier agent if refractory shock
• Anti-inflammatory Medications
  o IVIG
  o Steroids
  o Biologic agents
• Antiviral therapy (e.g.Remdesivir) if indicated
• VTE prophylaxis based on risk assessment (refer to RWJUH Pediatric VTE Clinical Pathway)
• Stress ulcer prophylaxis as indicated

*For more specific medication guidelines, refer to “Management by Spectrum of Disease” chart found in appendix

FOLLOW-UP INPATIENT LAB AND IMAGING

COVID-19-associated febrile inflammatory state

- Troponin and pro BNP if abnormal
- Inflammatory markers (CRP, ESR, ferritin, d-dimer , CBC w/ diff, CMP, LDH) Q 24 x 2, then as needed
- Other laboratory follow up as clinically indicated

COVID 19 associated KD

- Troponin and pro BNP daily x 3, then if needed
- EKG on admission with repeat 48 hours, then as needed
- Echo on admission with repeat in 48 hours, then as needed
- Inflammatory markers (CRP, ESR, ferritin, d-dimer , CBC w/ diff, CMP, LDH) Q 24 x 2, then as needed
- Other laboratory follow up as clinically indicated

Moderate to Severe MIS-C

- Lactate, blood gas q 6 hours X 24 hours
- Ionized Ca, CMP q 6 hours X 24 hours and as indicated; then prn based on clinical status
- EKG daily X 3, then as needed
- Echo on admission and then 48 hours X 1, consider more often early on if clinically indicated
- Inflammatory markers (CRP, ESR, ferritin, d-dimer , CBC w/ diff, CMP, LDH) Q 24 x 2, then as needed
- Other laboratory follow up as clinically indicated

DISCHARGE PLAN

- Medications:
    - Low dose aspirin (5mg/kg/day) OR enoxaparin prophylaxis if indicated
    - Steroid taper if indicated
    - Cardiac medications and other medications as indicated by clinical course
- Follow up:
    - Cardiology within 1 week of discharge
    - ID, Rheumatology, Hematology, and others as needed

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MANAGEMENT BY SPECTRUM OF DISEASE			
Therapeutic Category	**Mild (COVID-19-associated febrile inflammatory state**	**COVID-19-associated KD**	**Moderate / Severe (COVID-19-associated MIS-C)**
IVIG*	No	IVIG 2g/Kg	IVIG 2g/Kg (if Kawasaki/shock) IVIG 1g/Kg (myocarditis/shock)
Steroids	+/- If given 2mg/kg/day taper over 2-3 weeks then taper	If indicated, 2mg/kg/day, followed by taper	**Moderate**: 10mg/kg/day x 1 dose followed by 2mg/kg/day div Q8H, then taper **Severe**: 20-30mg/kg/day pulse qday x 3 days followed by 2mg/kg/day, then taper
Other Immunomodulation	N/A	If refractory to steroids: Consult rheumatology Options: Anakinra 2-10mg/kg/day x 5-14 days OR Infliximab 10mg/kg x 1 dose	Consult rheumatology **Moderate:** Anakinra 2-10mg/kg/day Infliximab 10mg/kg x 1 dose **Severe:** Anakinra 10mg/kg/dose Q6H Other biologics can be considered
Anti-viral	As per ID	As per ID	As per ID
Anticoagulation	VTE prophylaxis based on risk assessment	Aspirin (*As per AHA guidelines for KD) OR VTE prophylaxis based on risk assessment	Enoxaparin OR low dose ASA
Stress ulcer prophylaxis	If indicated	If indicated	If indicated
Broad-spectrum antibiotics (per sepsis guidelines) pending culture or other confirmatory laboratory results	Yes	If indicated	Yes

Other medication management considerations:

*IVIG:

- If IVIG resistant, repeat IVIG and consider steroids and/or Anakinra
- In event of IVIG shortage: Consider Anakinra 2.5 mg/kg/dose (max 100 mg/dose) subcutaneous or IV Q6 hours as needed, may consider titrating up to 10 mg/kg/dose Q6 or infliximab 10mg/kg X 1
- Use IVIG with caution in patients with HLH features

Biologics:

- Caution re use of tocilizumab IL-6 inhibitor

COVID-19 v1.0: MIS-C

!

Consider differential diagnosis including acute COVID

MIS-C Case Definitions
- CDC
- WHO

Inclusion Criteria
- Fever AND critically ill OR
- Persistent fever ≥3d AND evidence of MIS-C (see box) AND ill-appearing OR
- Persistent unexplained fever ≥5 days

Clinical Features/Evidence of MIS-C
- Most patients have ≥4 organ system involvement; ≥2 required for diagnosis
- Involvement of following systems (percent of patients in case series):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Mucocutaneous (74%, 59% had rash)
  - Respiratory (70%)
  - Musculoskeletal (23%)
  - Renal (8%)
  - Neurologic (6%)
  - See definitions of organ system involvement
- Recent COVID illness OR exposure (note: not necessary to suspect MIS-C)

Lab Evidence of MIS-C

No lab criteria is diagnostic; most patients have 4 or more markers of inflammation
- **Evidence of inflammation, common values:** CRP>3 mg/dl, ESR >40mm/h, ferritin>500 ng/mL, ANC >7700, ALC <1500, platelet <150k, D-dimer >2ug/ml, fibrinogen >400 mg/dL, albumin <3 g/dL, anemia, ALT >40 U/L, INR>1.1
- **Other:** AKI, hyponatremia, high CK, high LDH, high troponin, BNP >400 pg/mL, high TG, prolonged PT or PTT; If ESR low but high ferritin and CRP, consider MAS

Percentages and values adapted from Feldstein et al, NEJM June 2020

- **Initial Labs:** CBCd, CRP, ESR, BMP, ALT, albumin, UA, COVID PCR, COVID IgG, RVP
- **Additional Labs:** BNP, troponin, ferritin, D-dimer, coags, fibrinogen, LDH, CK, triglycerides, blood culture if indicated, red top to hold prior to IVIG (freeze), further labs on consultant advice

Signs of shock?

No →
- Obtain **Initial Labs**
  *If high clinical suspicion, add **Additional Labs***
- CXR (if resp sx)

Yes →
- Obtain **Initial and Additional Labs**, EKG, CXR
- ECHO (early if signs of cardiac dysfunction)
- Consider Sepsis Pathway
  Caution with boluses; monitor for cardiac dysfunction

Lab Evidence of MIS-C?

Yes →
- Obtain **Additional Labs**
- ECHO
- EKG

No →
- Consider alternate diagnoses
- Consider discharge with close follow-up

Complete or Incomplete Kawasaki?

Yes →
- Follow Kawasaki Disease Pathway if COVID testing negative or while pending
- Monitor closely for signs of shock

No →

Evidence of MIS-C without alternate diagnosis?

No →
- Consider alternate diagnoses
- Consider discharge with close follow-up

Yes →

PCR or IgG + OR cardiac dysfunction

!

Patients with MIS-C have significant risk for developing shock

Go to MIS-C Treatment

COVID-19 v1.0: MIS-C Treatment

Approval & Citation | Summary of Version Changes | Explanation of Evidence Ratings

Suspected MIS-C: Ongoing fever, lab evidence of inflammation (most patients have 4 or more markers), multi-system involvement, and clinically seriously ill, without alternative diagnosis (review differential diagnosis)

MIS-C: Above plus confirmed SARS-CoV-2 or known exposure (see case definition links)
- ECHO if not already done; repeat as indicated
- Admit patients to ICU if any signs of shock, hypotension, or concern for cardiac dysfunction
- Consult Infectious Disease, Rheumatology, and Cardiology; goal for daily group discussion or rounds with primary team
- Antibiotics per Sepsis Pathway only if and while bacterial infection suspected
- Consider supportive care only for patients who have mild* illness; monitor for increasing severity until clearly improving

First-line treatment for all seriously* ill patients with MIS-C:
- IVIG 2 g/kg (use ideal body weight) over 12 hours
- Anti-platelet: ASA 3-5 mg/kg max of 81 mg
- Anticoagulation: SQ enoxaparin prophylaxis until discharge (barring contraindications or indications for treatment dosing)
- Early initiation of steroids and/or higher dose of steroids may be indicated for critically ill patients, such as those with persistent shock/inotropic requirement, respiratory or heart failure, or concern for MAS

Second-line: Steroids if not improving ~12 h post-IVIG
- Methylprednisolone 2 mg/kg/day divided BID, change to PO when tolerating diet
- Consider higher dose steroids (methylprednisolone 10mg/kg/day) for patients with moderately or severely depressed cardiac function, in consultation with heart failure team
- Consider H2 blocker for GI ulcer prophylaxis while on both steroids and ASA
- Wean over minimum 3 weeks due to risk of rebound with short course

Third-line: Anakinra if not improving post steroid initiation or if labs suggestive of MAS
- 4 mg/kg/dose q6 hours (or frequency per Rheumatology), max dose 100 mg/dose

Trend CBCd, CRP, LDH, ALT, Albumin, Ferritin, Creatinine, Lytes, D-Dimer, Fibrinogen and BNP (frequency dependent on clinical status and medication weaning; post-discharge labs per consultants)

Classification of illness severity is not well defined. Consider:
**Mild: Normal vital signs apart from fever, does not meet inpatient criteria other than poor PO, mild dehydration, or monitoring for worsening.*
**Serious: Definitively meets case definition and any of: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.*

Differential Diagnoses

Kawasaki Disease
- More common in younger children, if COVID testing negative, and without shock/cardiac dysfunction

Bacterial Infections/Sepsis
- Obtain cultures and evaluate for source
- Consider meningitis

Staphylococcal and streptococcal toxin-mediated diseases
- Diffuse rash and hypotension
- Obtain cultures and evaluate for source including gynecologic or scarlet fever

Staph Scalded Skin Syndrome (SSSS)
- Increasing erythema and bullae
- Younger children
- Obtain cultures

Tick-Borne Illnesses
- With epidemiologic risk factors
- Rocky Mountain Spotted Fever or Leptospirosis

Viral Infections
- Measles, adenovirus, enterovirus, active COVID infection

Myocarditis
- May overlap with MIS-C or have alternate cause

Drug Hypersensitivity Reactions
- Consider SJS, DRESS, or serum sickness like reaction
- History of recent or semi-recent exposure to drug; consider with arthralgias and diffuse mucositis

Labs to Consider with Consultants

- Quantitative immunoglobulins (IgG, IgA, IgM, red tube)
- Specimen storage, red and lavender (freeze)
- Lymphocyte subset – Full Panel with TCR
- Antiphospholipid Ab (anticardiolipin, β2 glycoprotein, lupus anticoagulant)
- Cytokine panel
- IL-1β (ARUP test code 0051536, collect 2-3mL in gold/red top, spin and freeze within 2h)
- sIL-2R (AKA sCD25)

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Definitions of Organ System Involvement

Gastrointestinal 92%
- Nausea/vomiting
- Diarrhea
- Abdominal pain
- Appendicitis
- Pancreatitis
- Hepatitis
- Gallbladder hydrops or edema

Cardiovascular 80%
- Hypotension or shock
- Cardiac dysrhythmia or arrythmia
- Ejection fraction <55%
- Pulmonary edema due to left heart failure
- Coronary artery z score ≥2.5
- Pericarditis or pericardial effusion or valvulitis
- B-type natriuretic peptide (BNP) >400 pg/mL
- Elevated troponin
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation (CPR)

Hematologic 76%
- Total white blood cell <4k
- Anemia for age
- Platelet count <150,000 /µL
- Deep vein thrombosis
- Pulmonary embolism
- Hemolysis
- Bleeding or prolonged PT/PTT
- Ischemia of an extremity

Mucocutaneous 74%
- Bilateral conjunctival injection
- Oral mucosal changes
- Rash or skin ulcers
- 'COVID' toes
- Swollen red cracked lips
- Erythema of palms or soles
- Edema of hands or feet
- Periungual (nails) desquamation

Respiratory 70% (more frequent in teens)
- Receipt of mechanical ventilation or any type of supplemental oxygen (or
- increased support for patients receiving respiratory support at baseline)
- Severe bronchospasm requiring continuous bronchodilators or
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest-tube or drainage required

Musculoskeletal 23% (more frequent in teens)
- Arthritis or arthralgia
- Myositis or myalgia

Renal 8%
- Acute kidney injury with or without dialysis

Neurologic 6%
- Stroke or acute intracranial hemorrhage
- Seizures
- Encephalitis, aseptic meningitis, or demyelinating disorder
- Altered mental status
- Suspected meningitis with negative culture

Adapted from Feldstein et al, NEJM June 2020

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CSW COVID-19 Pathway Approval & Citation

Approved by the CSW COVID-19 Pathway team for July 9, 2020, go-live

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Retrieval Website: http://www.seattlechildrens.org/pdf/covid-19-pathway.pdf

Please cite as:
Seattle Children's Hospital, Kazmier K, Albert J, de la Morena M, Eckart C, Fenstermacher S, Hartford E, Hayward K, Kemna M, Nutman S, Portman M, Sushan D, Valdivia H, Vora S, Waghmare A, Migita D, 2020 July. COVID-19 Pathway. Available from: http://www.seattlechildrens.org/pdf/covid-19-pathway.pdf

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Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children's. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are *downgraded* if studies:

- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:

- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Certainty of Evidence:

✪✪✪✪ High: The authors have a lot of confidence that the true effect is similar to the estimated effect
✪✪✪○ Moderate: The authors believe that the true effect is probably close to the estimated effect
✪✪○○ Low: The true effect might be markedly different from the estimated effect
✪○○○ Very low: The true effect is probably markedly different from the estimated effect
Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team
Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies).

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Summary of Version Changes

- **Version 1.0 (7/9/2020)**: Go live.

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Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children's Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.

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Bibliography, page 1

Methods
Both CDC and WHO case definitions were utilized in the development of this pathway. The articles cited are a representation of local and international experts' and national societies' resources that were being shared widely, some pre-publication and many that were published by the centers that were diagnosing and treating this new syndrome as the pandemic swept across the globe.

A systematic literature review is in process and may inform future versions of this document. Due to the rapidly evolving literature and the need for urgent guidance, a non-systematic review was used to guide the development of the initial version of this algorithm.

Return to Evidence Ratings

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St. Christopher's Hospital for Children
A PARTNERSHIP OF TOWER HEALTH AND DREXEL UNIVERSITY

Multisystem Inflammatory Syndrome in Children (MIS-C)
COVID-19 Ambulatory Clinical Referral & Testing Consensus Document
Updated May 29, 2020

Clinical Concern for Possible Multisystem Inflammatory Syndrome in Children (MIS-C)

↓

Refer to Emergency Department for evaluation, testing, and **consideration** of admission

↓

MISC-C Screening Test Panel

- SARS-CoV-2 PCR
- SARS-CoV-2 IgG
- CBC w/diff
- CMP
- ESR
- CRP
- PT/PTT
- Fibrinogen
- D-Dimer
- Anti-thrombin III activity
- Ferritin
- Troponin
- BNP
- LDH
- CPK
- Extended PCR panel (same swab as SARS-CoV-2)
- Blood Cx
- U/A & Urine Cx
- Staph Screen (nares, rectal, axillary swabs)

↓

CONSIDER Testing for Other Causes/ Complications

- CXR
- EKG
- Group A streptococcal throat culture
- If diarrhea: stool culture and stool PCR panel
- Enterovirus PCR (blood)
- CMV PCR (blood)
- EBV PCR (blood)
- Adenovirus PCR (blood)
- HIV Ag & Ab

Themes:
1. High index of clinical suspicion
2. ED evaluation & lab testing
3. Early engagement of consultants (Heme, ID, Rheum, Cards) PRN.

This document is an expert consensus. It has not been reviewed by the Medical Executive Committee. Given the small number of cases and evolving data it is likely to change over time.

Clinical pathways are designed to assist clinicians by providing an analytical framework for the diagnosis and treatment of specific medical problems. They are not intended to replace a physician's judgment or to establish a protocol for all patients with a particular condition. The ultimate decision regarding the care of any patient should be made in respect to the individual circumstances presented by the patient.

MIS-C Clinical Presentations
Any of below groupings (1-4)

1. Clinical concerns for any of the following:
   a. Evolving Kawasaki Disease
   b. Toxic Shock Syndrome +/- cardiogenic shock/LV dysfunction
   c. Focal neurologic symptoms or signs, encephalitis, meningitis, change in mental status
   d. Acute appendicitis, pancreatitis, or colitis
   e. Hypotension

2. Fever ≥ 24 hours AND **ONE** of the following:
   - Tachycardia beyond expected for degree of fever
   - Ill-appearing

3. Fever ≥ 24 hours AND **TWO** of the following:
   - GI symptoms (abdominal pain OR vomiting OR diarrhea)
   - Rash
   - Mucocutaneous findings (conjunctivitis, cracked lips, extremity swelling)
   - Headache, myalgias, irritability
   - Lymphadenopathy

4. Persistent fever ≥ 4 days with or without other symptoms

CDC Case Definition (MIS-C/COVID-19)

- 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

Footnotes:

[i] *fever > 38 degrees 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*

2020.05 N Apollonsky, E Souder, I Kaur, S. Lvovich, M Koncicki, B Abraham, H Kersten, D Cooperberg, Z Kassutto

St. Christopher's Hospital for Children
A PARTNERSHIP OF TOWER HEALTH AND DREXEL UNIVERSITY

COVID-19 ED Admission Testing & Consultation
St. Christopher's Hospital for Children
Updated: June 1, 2020

ED Patient Requiring Admission
AND
COVID-19 Suspected or Confirmed

↓

Perform usual Complaint/Condition specific testing and management PRN

↓

Perform COVID-19 **Baseline & Thrombotic Panel** (see sidebar)

↓

Suspected Multi-System Inflammatory Disease?
(see presentation summary below)

NO → **NO** Other COVID-19 specific Testing

YES → Perform **MIS-C Testing Panel** (see sidebar)

COVID-19 Multi-system Inflammatory Syndrome (MIS-C)

Clinical Presentations:
1. **Kawasaki** Disease-like presentation
2. **Toxic Shock** with or without cardiogenic shock/LV dysfunction
3. **GI symptoms** with evidence of inflammatory response including any of following: abd pain, diarrhea, vomiting
4. **Neurologic symptoms** including any of following: HA, altered MS, seizure, meningismus, focal neuro finding
5. **Combinations** of above

Themes:
1. High index of clinical suspicion
2. Screening labs on admission (in ED)
3. Early engagement of consultants (Heme, ID, Rheum, Cards) PRN.
4. Frequent reassessment for possible evolving cardiogenic shock
5. Low threshold for ICU admission

ED Consults
1. General COVID-19/MIS-C testing/management questions: Consult ID
2. Problem specific consultation PRN: Consult ID, Rheum, Heme, Cardiology, Critical Care, etc.

COVID-19
Baseline & Thrombotic Testing Panel

- SARS-CoV-2 PCR (as per infection prevention recommendation document)
- CBC
- CMP
- CRP
- PT/PTT
- Fibrinogen
- D-Dimer
- Antithrombin III Activity
- Ferritin
- Phosphate
- Blood Culture

COVID-19
Multi-system Inflammatory Syndrome (MIS-C) Testing Panel*

This MIS-C Panel includes all baseline tests in red box above AND the tests below

EKG
CXR

- Procalcitonin
- CPK
- LDH
- Troponin
- BNP
- Total IgG (if onc patient, transplant patient or hypogammaglobulinemia)

Infectious Disease Labs
- Extended Viral PCR panel (can use same single swab for this test & SARS-CoV-2 PCR)
- Urine culture
- Group A streptococcal throat culture
- Staph Screen (nares, rectal, axillary swabs)
- If diarrhea: stool culture and stool PCR panel
- Enterovirus PCR (blood)
- CMV PCR (blood)
- EBV PCR (blood)
- Adenovirus PCR (blood)
- HIV Ag & Ab
- SARS-CoV-2 IgG (order miscellaneous)

**consider early antibiotics if hemodynamic instability*

Diagnostic and Treatment Guidelines for Multi-system Inflammatory Syndrome in Children (MIS-C) related to SARS-CoV-2

Reviewed by: Melissa Hines, MD; Gary Beasley, MD; Cliff Takemoto, MD; Josh Wolf, MD; Ted Morton, PharmD; Shane Cross, PharmD; Terri Finkel, MD, PhD; Kim Nichols, MD; Patrick Campbell, MD; Gaby Maron, MD; Jason Goldberg, MD; Hugo Martinez, MD; Laurel Metzler, MD

General Overview

- Multi-system Inflammatory Syndrome in Children (MIS-C) is a rare hyperinflammatory syndrome affecting children and adolescents that can follow SARS-CoV-2 infection. It has been described in pediatric patients in Italy, the United Kingdom, France, Switzerland and the United States (majority of cases in New York).
- Peak occurrence is about 4 to 6 weeks from the peak of SARS-CoV-2 infection.
- Despite the severity of disease presentation, death is rare.

Table 1. CDC Case Definition

- 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 symptom

[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

- Additional comments regarding MIS-C Diagnosis per CDC recommendations
  - Some individuals may fulfill full or partial criteria for Kawasaki disease (KD) but should be reported if they meet the case definition for MIS-C
  - Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

- Based on current reports, up to 80% of MIS-C patients tested are serology-positive for SARS-CoV-2

Presentation

The syndrome represents a spectrum of inflammatory diseases with varying severity:

1. Fever and inflammation
   - Some patients present with only persistent fever and abnormal laboratory values
2. Kawasaki-like disease
   - Some patients meet KD criteria (Table 3) or atypical criteria
   - ~20% develop coronary aneurysms (unclear what proportion resolve)
   - Many (50-100%) have severe left ventricular (LV) dysfunction that improves after treatment
3. Pediatric inflammatory multisystem syndrome (PIMS)

- Associated with severe shock, vasoplegia, and end organ dysfunction
- It is unclear which patients will progress from fever and inflammation to KD-like disease or PIMS

Table 2. MIS-C Patient Presentation and Initial Laboratory Findings [1-8]	
Clinical Presentation	
• Persistent fever, myalgias • Gastrointestinal symptoms (esp. abdominal pain, nausea/vomiting, diarrhea) • Kawasaki Disease-like symptoms (cervical lymphadenopathy, rash, desquamation, conjunctivitis, etc.; Table 3) • Shock • Neurologic symptoms (headache, stiff neck, vision changes, rare reports of cerebral edema) • Hypoxia or respiratory symptoms are less common but can occur • Possible known previous SARS-CoV-2 infection or sick contact	
Laboratory Findings	
Increased WBC with neutrophilia and/or lymphopenia	Increased IL-6
Anemia	Increased pro-BNP
Thrombocytopenia	Increased troponin
Increased CRP	Increased LDH
Increased D-Dimer	Increased fibrinogen
Mildly increased ferritin	Hypoalbuminemia

Table 3. Kawasaki Disease Criteria [9]
Typical Kawasaki Disease Criteria
Fever ≥5 days plus 4 of the below criteria: • Bilateral bulbar conjunctival injection • Oral mucus membrane changes (injected or fissured lips, injected pharynx, strawberry tongue) • Peripheral extremity changes (erythema of soles/palms, swelling of hands or feet, periungual desquamation) • Polymorphous rash • Cervical lymphadenopathy
Atypical Kawasaki Disease Criteria

Fever ≥5 days plus 2 or 3 of the criteria above, plus CRP ≥3mg/dL *OR* ESR ≥40 mm/hr, then evaluate for other laboratory/imaging criteria
• Further laboratory/imaging criteria to suggest diagnosis
  ○ At least 3 laboratory criteria:
  ▪ Anemia
  ▪ Thrombocytosis (platelet count >450,000)
  ▪ Albumin ≤3g/dL
  ▪ Elevated ALT
  ▪ WBC >15,000/mm^3
  ▪ Urine WBC ≥10 cells/hpf
  ○ **OR** Echocardiogram is suggestive of diagnosis[1]

[1]Echocardiogram is considered positive if the Z-score of the left anterior descending coronary artery or right coronary artery is ≥2.5, a coronary artery aneurysm is observed, or ≥3 other suggestive features exist including decreased left ventricular function,

mitral regurgitation, pericardial effusion, or Z-scores in the left anterior descending coronary artery or right coronary artery of 2 to 2.5.

Recommended Laboratory Testing and Imaging

Testing should be sent in any patient with persistent fever (≥38.5˚C for ≥5 days; especially without another known cause) **AND** history of previous SARS-CoV-2 infection/exposure **WITH**

- any clinical findings of typical KD (see Table 3)
- **OR** GI symptoms
- **OR** concerns for new cardiac dysfunction **OR** shock

Table 4. Recommended Testing [1-8]

General Laboratory Testing and Imaging	
CBC w/smear and Pathologist Review of Slide	PT/INR
CMP	PTT
CRP	LDH
ESR	Albumin
D-Dimer	Ferritin
Fibrinogen	CPK
CXR	Reticulocyte Count

Infectious Disease Testing
1. Follow neutropenic fever or non-neutropenic fever guidelines for standard care 2. SARS-CoV-2 RT-PCR nasopharyngeal swab 3. SARS-CoV-2 Total Antibody (prior to IVIG dosing; +PCR testing is not required prior to sending this test) 4. Consider EBV, CMV, adenovirus, parvovirus, and HHV6 PCR 5. Consider LP with opening pressure and CSF studies if there are neurologic symptoms/meningeal signs; consider head CT prior to LP if any concerns for cerebral edema
Cardiac Specific Testing
1. Echocardiogram (request evaluation of coronary arteries) 2. Pro-BNP 3. Troponin 4. EKG
Additional testing to consider
1. Thromboelastography (TEG) if patient thrombocytopenic with abnormal D-Dimer or coagulation studies 2. Cytokine Panel (send out lab) 3. Assessment of endothelial damage and complement activation: Total complement level (CH50), C3, C4, C5b-9 (MAC complex) (send out labs)

Final diagnosis should be determined based on the CDC criteria (Table 1). Because many cases of SARS-CoV-2 infection are not associated with known exposure, and some individuals might not reliably make antibodies, MIS-C can be considered in even the absence of confirmed exposure or documented infection. Consider alternative diagnoses and the risks and benefits of treatment for MIS-C. Because a history of exposure to SARS-CoV-2 is increasingly common, consider alternative diagnoses in cases of presumed MIS-C without confirmed past SARS-CoV-2 infection or positive SAR-CoV2 testing (serology or PCR).

Recommended Therapy

- The current immunologic mechanism/pathophysiology for MIS-C is unclear. It is also unknown if KD therapy adequately treats KD-like disease and prevents coronary ectasias in this group of patients.
- Current treatment recommendations (Table 5) are selected according to therapies known to be effective for KD and other hyperinflammatory syndromes and from the experience of other institutions.

In addition to the below suggested therapeutic options, we recommend that care for these patients be interdisciplinary and include (in addition to their primary hematology/oncology team):

  - Cardiology
  - Infectious Diseases
  - Hematology (especially prior to starting anticoagulation with enoxaparin or antiplatelet therapy with aspirin)
  - Histiocytosis Treatment Team (if required for guidance for steroids or biologics for hyperinflammation or treatment of refractory disease)

- All patients should be assessed for need of antiplatelet/anticoagulation therapy. Overall, at least antiplatelet therapy is appropriate for patients with coronary artery abnormalities to prevent arterial thrombosis and myocardial infarction per the American Heart Association (AHA) KD guidelines; anticoagulation should be considered for prevention or treatment of venous thrombosis.
  - Anticoagulation/antiplatelet therapies are particularly complicated in our patients given that many patients have thrombocytopenia and increased bleeding risk at baseline.
- All patients should also be assessed for need for antimicrobial coverage, particularly during the initial work-up.
- Choice of anti-inflammatory therapy should follow the tiered approach below; however, simultaneous use of multiple anti-inflammatory therapies may be considered in highly unstable patients.

Table 5. Therapy Recommendations [1-9]

Therapy		Dose and Indication
Anti-Inflammatory Therapy	IVIG <u>First Tier</u>	• 2 g/kg x 1 over 10 to 12 hrs should be given to <u>*patients meeting KD and atypical KD criteria*</u> and can be considered in those not meeting KD criteria with <u>*cardiac dysfunction or shock*</u>.
	Steroids (methylprednisolone/ prednisone) <u>Second Tier</u>	• 2 mg/kg/day IV x 5 days can be considered in those with <u>*shock (i.e requiring vasopressor support) OR IVIG resistant KD*</u> (continued fever for 36 hrs after the IVIG dose or return of fever after 36 hrs). • Pulse dose steroids (30 mg/kg/day x 1-3 days), followed by low-dose steroids, 2 mg/kg/day, can be considered in patients with <u>*severe shock (Vasoactive Ionotropic Sore >10), severe LV dysfunction, or multiorgan dysfunction syndrome (MODS) or if patient has continued clinical worsening despite lower dose steroid therapy.*</u>

		• Duration of therapy will vary based on patient presentation. In patients with IVIG-resistant KD, after the initial 5 days of steroid therapy, steroids can be weaned every 5 days over 15 days (20 days total of therapy). Patients with shock alone without evidence of coronary artery dilation may require a shorter steroid course and wean can begin once patient has reached clinical stability (e.g. off vasopressor support, decreasing respiratory support, improvement of organ dysfunction, etc.).
	Biologics <u>Third Tier</u>	• Anakinra (5-10 mg/kg/day SC divided Q6H) or tocilizumab (< 30 kg, 12 mg/kg/dose X 1;<u>≥</u> 30 kg, 8 mg/kg/dose IV X 1; repeat dosing can be considered after 24 hours in consultation with ID and Histiocytosis Treatment Team) can be considered on a case-by-case basis for those with <u>*severe shock and multi-system organ failure or persistent symptoms (KD or shock/MODS) after steroid therapy or if steroids are contraindicated.*</u>

Antiplatelet and Anticoagulation Therapy	Antiplatelet	• For patients meeting typical or atypical KD criteria per the AHA KD guidelines:
		  ○ Moderate-dose aspirin 12.5 mg/kg/dose[1] Q6H until afebrile for ≥48 hrs (maintain platelet count >100,000), followed by 3-5 mg/kg/day (max 81 mg daily; maintain platelet count >20,000)
		• For patients with coronary artery dilatation:
		  ○ Low-dose aspirin (3-5 mg/kg/day; max 81 mg daily; maintain platelet count >20,000)
		• Aspirin should be continued until 4-6 weeks cardiology follow-up (per the AHA KD guidelines). Definitive length of therapy to be determined by cardiology.

	Anticoagulation Therapy	• Anticoagulation should be considered on a case-by-case basis in patients with suspected MIS-C. • Enoxaparin prophylaxis (ppx) is recommended for immobile or critically ill post-pubertal patients (generally >12 years) regardless of coronary artery findings based on standard of care venous thromboembolism (VTE) prophylaxis practices. • For prepubertal patients with abnormal coagulation profiles (including elevated D-dimer and abnormal TEG findings), consult hematology to weigh risk/benefit of enoxaparin ppx vs. treatment. Since increased VTEs have NOT been reported in patients with MIS-C, if a patient is already on low-dose aspirin,

		this may be sufficient for VTE prevention and enoxaparin ppx may not be needed. • Consider treatment dose enoxaparin in patients with LVEF <30% in consultation with cardiology team. Duration to be determined by cardiology team. • If enoxaparin ppx is started, maintain platelet count >20,000. • If enoxaparin treatment is started, maintain platelet count >30,000. Combination therapy with enoxaparin and aspirin may be needed in some patients (i.e. patients with large or giant coronary aneurysms) per the AHA KD guidelines after discussion of risk and benefit with cardiology and hematology teams.
Antimicrobial Therapy	Antibiotics	• Please follow antimicrobial guidelines for neutropenic and non-neutropenic fever; consider ID consult
	Antiviral	• Not routinely recommended; consider treatment based on COVID-19 Guidelines and results of SARS-CoV-2 testing

[1]Moderate dose was chosen due to higher risk of bleeding in our patient population, and no clear evidence that high dose aspirin is more effective than low dose aspirin

Recommendations for Follow-up

- Identification of patients at risk for developing coronary ectasias after MIS-C is currently unclear, but some patients do develop signficant coronary ectasias after resolution of MIS-C.
- All patients with a diagnosis of MIS-C should have cardiology follow-up with ECHO at 4 to 6 weeks after presentation. Depending on the severity of coronary ectasia, cardiology may recommend more robust imaging with magnetic resonance angiography.

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Appendix

Vasoactive-Ionotropic Score

VIS = dopamine dose (µg/kg/min) +
dobutamine dose (µg/kg/min) +
100 x epinephrine dose (µg/kg/min) +
10 x milrinone dose (µg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
100 x norepinephrine dose (µg/kg/min)

Stony Brook Children's

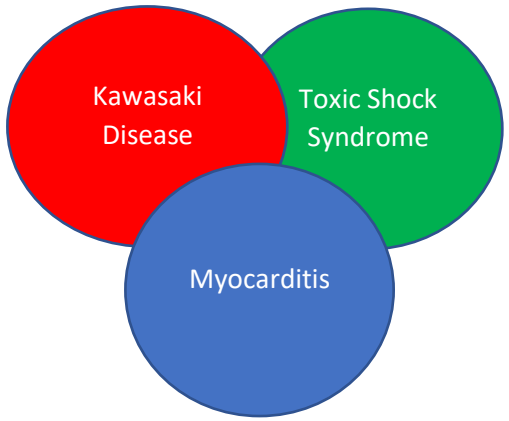
Practice Guideline: Multisystem Inflammatory Syndrome in Children (MIS-C)

Case definition[1]:

1. An individual aged <21 years presenting with fever > 1 day, lab evidence of inflammation and clinically severe illness requiring hospitalization, with multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, dermatologic or neurologic). This may include children fulfilling full or partial criteria for Kawasaki Disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. Positive for current or recent SARS-CoV-2 PCR or serology testing or exposure to suspected/confirmed COVID-19 case within 4 weeks of onset of symptoms. Negative SARS-CoV-2 testing does not rule out MIS-C due to high prevalence of disease in Suffolk County.

Clinical Presentation:

- Typical or atypical Kawasaki Disease
  - Can have coronary artery involvement or not
  - Occurs in children through adolescence
  - Can have myocardial dysfunction
- Refractory vasodilatory shock similar to Toxic Shock Syndrome
  - Normal heart function with septic (warm) shock presentation
  - Abnormal heart function/ myocarditis with "cardiogenic shock"



History/PE Findings:

- Prominent GI symptoms: vomiting, diarrhea, abdominal pain (can seem like acute abdomen), melena
- Respiratory symptoms uncommon
- Fever- at least 4 days
- Conjunctivitis
- Rash
- Lymphadenopathy
- Red cracked lips/strawberry tongue
- Headaches
- Hand/foot swelling
- Progression of symptoms can be rapid
- History of COVID-19 exposure or infection uncommon, but if positive presentation is 3-4 weeks post infection

Reported differences in lab findings (not absolute):

KD-like Presentation	TSS-like Presentation
Troponin normal	Troponin elevated
High or low platelets	Normal/low platelets
Normal/mildly low albumin	Low albumin
IL-6 and Ferritin normal	IL-6 and Ferritin high
No Lymphopenia	Lymphopenia

1. CDC Guidance for Healthcare Professionals, Multisystem Inflammatory Syndrome (MIS-C) 5/29/20.

Stony Brook Children's

Practice Guideline: Multisystem Inflammatory Syndrome in Children (MIS-C)

Kawasaki Disease-like Presentation

Toxic Shock- like Presentation

Initial Labs: CBC with diff, Chem 8, Mg, Phos, LFTs, lipase, PT/PTT, D-dimer, CRP, ESR, Ferritin, CPK, Troponin, BNP, LDH, Procalcitonin, UA, Urine Culture, Blood Culture, Procalcitonin, RVP, Sars-CoV-2 PCR, HCG on all females >11 years

Other initial studies: CXR, EKG, Abdominal imaging (for prominent GI symptoms) -consider ultrasound, AXR series or CT depending on signs/symptoms, POCUS in ED for rapid assessment

Initial Consults to call:

- Infectious Disease: help determine additional labs and initial treatment
- Cardiology: Consultation to help determine degree of cardiac involvement, timing of echocardiogram

Other Investigations to Consider:

- ABG/VBG
- Lactate
- EBV panel
- Throat Culture
- Antiphospholipid Antibodies
- Complement Levels
- Sars-CoV-2 antibody testing (if PCR neg)
- Stool for Sars-Cov-2 PCR (if possible)
- HIV screen
- TB Quantiferon gold
- IL-6 level
- Stool Guiac

If Sars-CoV-2 PCR positive, would consider Remdesivir

KD-like Presentation Initial Treatment Strategy

- Rheumatology Consultation
- IVIG 2g/kg per KD protocol (send Ig levels prior)
- High dose Aspirin 20-25mg/kg/dose q6h
- Methylprednisolone (1mg/kg/dose q12h)
- For refractory cases: consider re-dosing IVIG and Anakinra (1-2mg/kg/day q12h to a max dose 100mg q6h)
- PPI for GI prophylaxis

TSS-like Presentation Initial Treatment Strategy

- PICU admission-telemetry/hemodynamic monitoring
- Rheumatology consult
- Supportive care: Fluid resuscitation, inotropic support, management of cardiac dysfunction
- Broad spectrum ABx pending cultures: Vancomycin, Clindamycin, Ceftriaxone
- Consider Methylprednisolone, Anakinra, tocilizumab (Rheumatology input)
- Hematology Consultation: anticoagulation vs prophylaxis

1. CDC Guidance for Healthcare Professionals, Multisystem Inflammatory Syndrome (MIS-C) 5/29/20.

UCDAVIS CHILDREN'S HOSPITAL

UC Davis Children's Hospital MIS-C guidelines

Consider the diagnosis of MIS-C in the following clinical situations:

A child 0-18 years of age presenting with fever >=3 days* and:

- Multisystem (>=2) involvement, including
  - Gastrointestinal (abdominal pain, vomiting, diarrhea)
  - Cardiac (cardiogenic shock, LV dysfunction)
  - Neurologic (confusion, headache, altered mental status, irritability)
  - Renal (acute kidney injury)
  - Respiratory (respiratory distress or pulmonary infiltrates)
  - Hematologic (lymphopenia, neutrophilia, anemia, thrombocytopenia)
- Symptoms consistent with KD, including rash, conjunctivitis, cervical lymphadenopathy, extremity swelling or other changes
- Fever >=5 days with no alternative explanation

*A child who is *ill-appearing* with suspected MIS-C should be evaluated as per the diagnostic work-up below, even if fever is present <3 days

Recommended diagnostic evaluation:

1. Initial laboratory evaluation
   a. CBC with differential
   b. CMP
   c. ESR, CRP
   d. Urinalysis
   e. Blood culture
   f. Procalcitonin
   g. VBG with lactate
   h. Additional labs as clinically indicated: Resp pathogen panel, GI biofire panel, lumbar puncture
   i. Imaging:
      i. Chest X-ray
      ii. Abdominal ultrasound or CT scan if concerning symptoms/physical findings
2. If initial labs concerning for MIS-C without alternative explanation (including lymphopenia with ALC <1000, platelets <150k, albumin <=3g/dL, hyponatremia <135, ESR >=40, CRP>=3mg/dL), consider the following evaluation:
   a. Cardiac markers: troponin T and BNP
   b. Other markers of inflammation: ferritin, triglycerides, LDH, CK
   c. Coagulation panel: PT, PTT, fibrinogen, D-dimer
   d. Serology for SARS-CoV-2 (please contact Peds ID and request that order be placed)
   e. SARS-CoV-2 PCR from nasopharyngeal swab
   f. Twelve-lead electrocardiogram (EKG)
   g. Echocardiogram (transthoracic)
   h. Early consultation of specialists to assist in management (as needed), such as PICU, cardiology, rheumatology, infectious diseases, neurology, nephrology

3. Admission to PICU if any signs of impending shock (i.e. tachycardia unresponsive to fluid, etc.), need for non-invasive or invasive respiratory support (i.e. CPAP, BIPAP, mechanical ventilation), or other concerning labs suggestive of significant organ disease (i.e. elevated troponin)

Diagnosis:

Diagnosis is made as per the CDC criteria below. Even if SARS-CoV-2 testing is negative, treatment may be considered for patients with high suspicion of MIS-C, if recommended by pediatric rheumatology or infectious disease consultants.

CDC case definition for multisystem inflammatory syndrome in children (MIS-C).

(1) An individual aged < 21 years with:

(2) Clinical criteria:

- A minimum 24-hour history of subjective or objective fever ≥ 38.0°C AND
- Severe illness necessitating hospitalization AND
- Two or more organ systems affected (i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological)

(3) Laboratory evidence of inflammation

- One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin

(4) Laboratory or epidemiologic evidence of SARS-CoV-2 infection

- Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR
- COVID-19 exposure within 4 weeks prior to onset of symptoms

(5) No alternative diagnosis

Infection Prevention:

- No isolation needed if SARS-CoV PCR testing negative
- COVID isolation if SARS-CoV PCR testing positive

Treatment of MIS-C (see doses in table on page 4):

	Mild disease	Moderate-severe disease**
Steroids	Yes, see table for dosing	Yes, see table for dosing
IVIG (peds ID to write note in chart supporting its use)	Yes	Yes
Anakinra, tocilizumab, etc.	No	May be considered per peds rheumatology
Anticoagulation	Low dose aspirin	Prophylactic enoxaparin
GI protection	Yes	Yes
Empiric antibiotics	As per discretion of provider	Yes (see sepsis guidelines)

**Moderate-severe disease defined as: Need for vasoactives or inotropes, mechanical ventilation, presence of significant coronary dilation or aneurysm, significantly decreased LV function

In-hospital care

-Further tests to be considered depending on sub-specialty input: IL-6, anti-phospholipid antibody panel, quantiferon, hepatitis B panel

-Repeat CRP, CBC with diff, coagulation panel, ferritin, troponin T, BNP every 24-48 hours (do not repeat ESR as this will be affected by IVIG administration)

-If patient continues with fever or evidence of inflammation 36 hours after administration of IVIG and/or steroids, please consult peds ID or peds rheumatology (if not consulted already.)

-May consider use of anakinra or tocilizumab for severe or refractory cases

-Consider serial EKG or echocardiogram depending on initial studies, follow-up labs, and clinical status

Follow-up after hospital discharge:

-Follow up should be scheduled with pediatric cardiology for repeat echocardiography at 2 and 4-6 weeks (similar to KD follow-up)

-Follow up to be scheduled with pediatric rheumatology if receiving anakinra at time of discharge

-Follow up to be scheduled with pediatric hematology if patient is discharged home on enoxaparin or other anticoagulation

-If child is sent home on steroid wean, they should have early morning cortisol and ACTH after steroids are weaned off. If low, would consider referral to pediatric endocrinology.

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Doses for immunomodulatory agents in the treatment of MIS-C

Medication Class	Dose	Important Notes
IVIG	• 1–2 g/kg IV in a single dose or divided doses per attending discretion	Consider dividing dose or giving lower dose if fluid overload, renal dysfunction. Obtain blood for SARS-CoV-2 serology and other serologic tests (i.e.antiphospholipid antibodies) prior to administration
Corticosteroids	Mild disease: Methylprednisone 1 mg/kg/dose q12h IV for 5–7 d or until CRP normalizes followed by 14 day course of prednisolone detailed below: Days 1-5: Prednisolone (or prednisone) 1mg/kg/dose BID Days 6-10: Prednisolone 0.5mg/kg/dose BID Days 11-14: Prednisolone 0.5mg/kg/dose once a day Moderate to severe disease: Day 1: Methylprednisolone 10 mg/kg/dose q12h (maximum 500 mg) Day 2-5: Methylprednisolone 2 mg/kg/dose IV q 12h (max:50mg/day; can switch to PO sooner if response is seen) Day 6-10: Prednisolone (or prednisone) 1 mg/kg/dose BID PO (max:40mg/day) Day 11-15: Prednisolone 0.8 mg/kg/dose BID (max:40mg/day) Day 16-20: Prednisolone 0.6 mg/kg/dose BID (max:35mg/day) Day 21-25: Prednisolone 1 mg/kg/dose once a day (max:25mg/day) Day 26:29: Prednisolone 0.9 mg/kg/dose once a day (max:20mg/day) Day 30-32: Prednisolone 0.7 mg/kg/dose once a day (max:15mg/day) Day 33-35: Prednisolone 0.5 mg/kg/dose once a day (max:15mg/day) Day 36-38: Prednisolone 0.4 mg/kg/dose once a day (max:10mg/day) Day 39-41: Prednisolone 0.2 mg/kg/dose once a day (max:7.5mg/day) Day 42-44 Prednisolone 0.1 mg/kg/dose once a day (max:5mg/day) Day 45-48 Prednisolone 0.05 mg/kg/dose once a day (max:2.5mg/day) Day 49-51 Prednisolone 0.05 mg/kg/dose every other day and then stop (max:2.5mg/day)	
Anakinra	• 2-6 mg/kg/day IV/SQ, length of therapy to be decided with input from pediatric rheumatology or immunology	Safe in setting of sepsis, please send quantiferon and Hepatitis B serology prior
Tocilizumab	• < 30 Kg: 12 mg/kg IV in a single dose • > 30 Kg: 8 mg/kg IV in a single dose (max 800mg)	Trials ongoing for safety and efficacy in the setting of active coronavirus infection
Aspirin	• 3–5 mg/kg/d (max 81mg/day) until follow up with cardiology	Precaution if platelets <80,000/µL
Enoxaparin	Prophylaxis: 0.5 mg/kg/dose q 12 hours (max dosing 30mg IV q12h) Treatment: 1 to <3months: 1.8mg/kg/dose q 12 hours 3-12 months: 1.5mg/kg/dose q 12 hours 1-5 years: 1.2mg/kg/dose q 12 hours 6-18 years: 1mg/kg/dose q 12 hours	If thrombosis present or rapidly rising D-dimer, increase to treatment dosing. With treatment dosing, monitoring with anti-Xa levels is recommended.

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June 2020

Evidence Based Clinical Guideline: Multi-System Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease in 2019 (COVID-19)

PURPOSE/BACKGROUND:

Multi-system inflammatory syndrome in children (MIS-C) is a newly recognized syndrome that is being increasingly reported in both the United State and Europe and is temporally associated with the coronavirus disease in 2019 (COVID-19).[1] While the incidence of MIS-C is unknown, it appears to be a rare complication of COVID-19 in children.[1,2]

On May 14, the Centers for Disease Control and Prevention (CDC) issued a national health advisory including the following background:

> On April 26, 2020, clinicians in the United Kingdom (UK) recognized increased reports of previously healthy children presenting with a severe inflammatory syndrome with Kawasaki disease-like features. The cases occurred in children testing positive for current or recent infection by SARS-CoV-2, the novel coronavirus that causes COVID-19, based on reverse-transcriptase polymerase chain reaction (RT-PCR) or serologic assay, or who had an epidemiologic link to a COVID-19 case. Patients presented with a persistent fever and a constellation of symptoms including hypotension, multi-organ (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involvement, and elevated inflammatory markers. Respiratory symptoms were not present in all cases.
>
> During March and April, cases of COVID-19 rapidly increased in New York City and New York State. In early May 2020, the New York City Department of Health and Mental Hygiene received reports of children with multisystem inflammatory syndrome. From April 16 through May 4, 2020, 15 patients aged 2-15 years were hospitalized, many requiring admission to the intensive care unit. As of May 12, 2020, the New York State Department of Health identified 102 patients (including patients from New York City) with similar presentations, many of whom tested positive for SARS-CoV-2 infection by RT-PCR or serologic assay. New York State and New York City continue to receive additional reports of suspected cases.
>
> It is currently unknown if multisystem inflammatory syndrome is specific to children or if it also occurs in adults.[1]

Presentation in children is similar to incomplete Kawasaki disease (KD) or toxic shock syndrome. Similarities in clinical presentation from case reports include: persistent fevers, rash, conjunctivitis, peripheral edema, generalized extremity pain, and gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea. MIS-C has also been referred to as pediatric multi-system inflammatory syndrome (PMIS), pediatric inflammatory multisystem syndrome (PIMS), pediatric hyper-inflammatory syndrome, or pediatric inflammatory shock. It has been suggested that the syndrome results from an abnormal immune response to the virus.[1,2]

Healthcare providers are asked to report cases that meet the case definition of MIS-C to the Ohio Department of Health and should consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection. Contact UH Infection Control to facilitate reporting.

The after-hours epidemiologist on-call for the State of Ohio may be reached at 614-995-5599. For additional information the CDC's 24-hour Emergency Operations Center (770-488-7100) is available.

This document has been developed on the best available evidence at the time of writing and will be subject to continuous review and updating as the medical community collectively learns more about this syndrome.

INCLUSION:

Inclusion criteria is consistent with the Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C) provided by the CDC:

1. An individual aged <21 years presenting with ***fever***, **laboratory evidence of inflammation****,* and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
2. No alternative plausible diagnoses; **AND**
3. 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

****Fever*** ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

*****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

EXCLUSION:

Any other infectious cause of fever
Kawasaki Disease (not an absolute exclusion)
Toxic Shock Syndrome

TARGET USERS:

Target users include, but are not limited to:

- Clinicians caring for subject in the urgent care, emergency department, and inpatient care setting
- Attending, fellow, or resident
- Patient care staff including nurse practitioner, nurses, respiratory therapists, clinical pharmacy specialists, and clinical educators

GUIDELINE STATEMENTS:

I. Differential Diagnosis

a. Kawasaki disease
b. Toxic shock syndrome
c. Macrophage activation syndrome
d. Sepsis

II. Diagnostic Evaluation

a. In the ER, if a patient is suspected of having MIS-C then the following labs should be drawn:
    i. CBC/D
    ii. Covid PCR nasal swab
    iii. CRP
    iv. D dimer
    v. Ferritin
    vi. PT/PTT/INR
    vii. Troponin (if Troponin not available, order EKG)
    viii. BNP
    ix. CMP
    x. Fibrinogen
    xi. Consider blood and urine cultures
b. In the ED, If the patient has fever and symptoms that could be consistent with MIS-C but doesn't rise to full severity or if the full list of labs above is not able to be drawn, then order the following:
    i. COVID-19 PCR via NP swab
    ii. CBC/D
    iii. CRP
    iv. CMP
    v. Ferritin
    vi. D-dimer
c. Radiologic studies
    i. Consider Chest x-ray
    ii. Consider abdominal ultrasound
    iii. If the D-dimer is > 500 and patient has respiratory symptoms then CT angiogram of the chest should be strongly considered due to concerns of embolism
d. If a patient meets the admission criteria or CDC case definition for MIS-C, the following additional labs are recommended:
    i. Triglycerides
    ii. ESR
    iii. CK
    iv. LDH
    v. Urinalysis
    vi. ANA/ENA reflex
    vii. Immunodeficiency panel
    viii. Cytokine panel – Must order as a miscellaneous test and in comment section state: "*ARUP test code: 0051394 and serum tube*"
    ix. Radiologic studies, if not already completed in the ED:
        1. CXR
        2. EKG
        3. ECHO
        4. Abdominal ultrasound

III. Assessment

a. **Physical exam**
   i. Detailed evaluation for any evidence of inflammatory changes
      1. NOTE: see KD tool below for reference paying special attention to check for signs consistent with Kawasaki disease
   ii. Patient History
      1. Conduct detailed exposure history for the following:
         a. Known COVID-19 case in household or known exposure
         b. Other exposure that might trigger an infection that might mimic this illness (exposure to unpasteurized milk, animals, travel outside the US, etc.)
   iii. Clinical assessment tool for Kawasaki Disease:
      1. Diagnostic criteria for Kawasaki Disease published by the American Heart Association (See Table 1)

Table 1: Diagnosis Criteria for Classic Kawasaki Disease (American Heart Association)

Classic KD is diagnosed in the presence of fever for at least 5 d (the day of fever onset is taken to be the first day of fever) together with at least 4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 d of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 d of fever in rare cases (Figure 2):
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

IV. Management/Treatment Statements

b. Any patient not admitted to the hospital should have follow up within 24-48 hours
c. Any patient who is Covid-19 PCR positive who is ill enough to require hospitalization should be placed on the Covid-19 treatment algorithm and an ID consult made to consider treatment with remdesivir.
(See Anti-infective Medication Management of Pediatric Patients with COVID-19)
d. Follow Infection Control policy for guidance on unit placement and isolation orders
e. Classification of Clinical Severity
   i. Mild Disease– Patients that meet any of the following should be admitted to PCRS/Floor/PICU based on clinical judgement
      1. no vasoactive requirements; and
      2. SpO2 ≥ 92% on supplemental oxygen of ≤ 4LPM or equivalent with no more than mildly elevated work of breathing; and
      3. minimal organ injury
   ii. Moderate Disease – Patients that meet any of the following should be admitted to the PICU
      1. Vasoactive-Inotropic Score ≤ 10 or EF 45-55; or

2. HF nasal cannula needed to maintain SpO2 > 92% or to support work of breathing; or
3. Mild or isolated organ injury (e.g. creatinine 2x baseline, Glasgow coma scale 13-14, etc.)

iii. Severe Disease – Patients that meet any of the following should be admitted to the PICU
1. Vasoactive-Inotropic Score >10 or EF<45; or
2. Any positive pressure respiratory support; or
3. Moderate or severe organ injury (e.g. creatinine 3x baseline, Glasgow coma scale < 13, etc.)

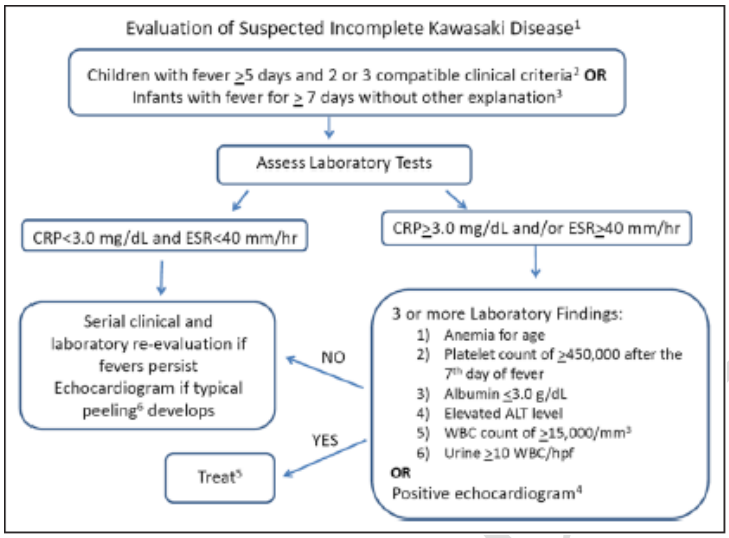
f. Recommended initial inpatient consultations include:
iv. Infectious Diseases
v. Hematology
vi. Cardiology
vii. Rheumatology (may not be applicable for mild disease)

g. Consider the following consultations if clinically indicated:
viii. Immunology
ix. Nephrology
x. Pulmonology
xi. Gastroenterology
xii. Neurology

h. Further diagnostic workup to consider following admission include the following:
xiii. ESR, CK, LDH, urinalysis, ANA with ENA reflex, Immunodeficiency profile, cytokine panel, any patient who might get IVIG should have an extra serum tube drawn and sent to lab to hold for future testing
xiv. **Infectious Disease**: extensive ID workup should be done and should include diagnostics consistent with presenting symptoms (respiratory panel if cough/rhinorrhea, stool pathogen panel if diarrhea present), also consider enterovirus, CMV, EBV, Strep, Staph, Parvovirus, Coxsackie virus
xv. **Cardiology**- extensive cardiology evaluation should be done and includes an ECHO and EKG. Follow up ECHOs will be arranged by cardiology and are dependent on initial findings
xvi. **Pulmonary**: CT angiogram of the chest should be strongly considered in any patient with a D-dimer > 500 and respiratory symptoms (tachypnea, tachycardia, hypoxemia etc). This will guide level and duration of anticoagulation. Pulmonology should be consulted on all children with suspected or confirmed PE.
xvii. **Gastroenterology**: Any patient with GI symptoms should have a fecal calprotectin and fecal occult blood sent. If either of these are positive a GI consult should be called.

i. Initial Treatment Considerations
xviii. If the patient meets criteria for atypical or classic Kawasaki (see Figure 1: Algorithm for Diagnosis of Atypical Kawasaki Disease) they should be treated accordingly with aspirin and IVIG (Table 2: Medication Management)

Figure 1: Algorithm for Diagnosis of Atypical Kawasaki Disease (published by American Heart Association)



1. For children receiving IVIG
    a. Prior to the start of IVIG therapy, order an IgG, IgA, and IgM level
    b. Prior to the start of IVIG therapy, order an extra serum tube to be held in lab for possible further diagnostics
2. For moderate and severe cases, rheumatology should be consulted and consideration given to starting steroids, anti-IL-1 therapy and/or anti-IL-6 therapy

xix. If the patient does not meet criteria for Kawasaki disease then consider the following therapies:
1. For Mild disease may start steroids or monitor depending on lab values and clinical picture
2. Steroids should be strongly considered unless concern for contraindication.
3. Rheumatology may also consider initiating anti-IL6 or IL-1 therapy either alone or together with steroids.

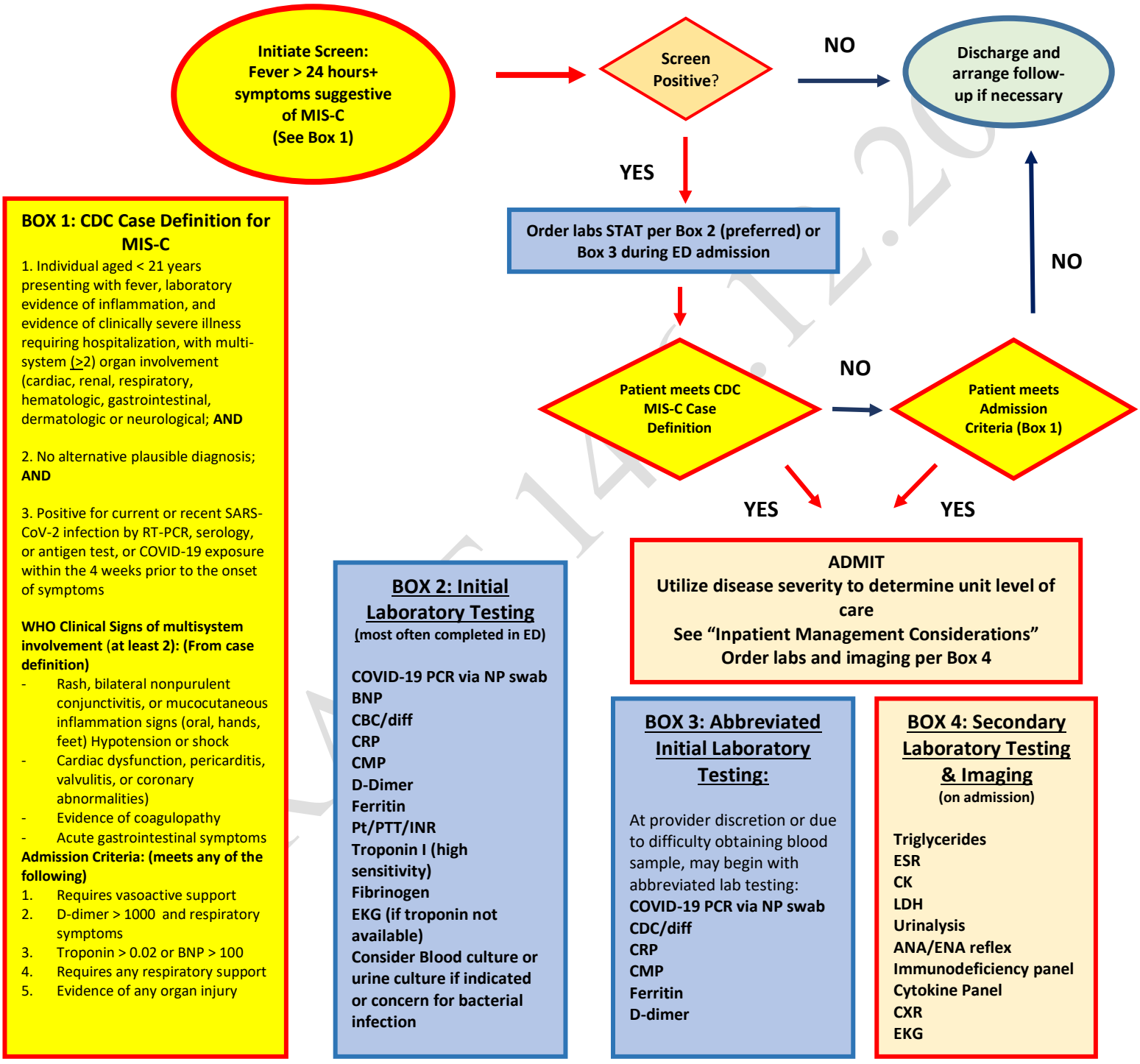
xx. All patients with coagulopathy (elevated PT/PTT/Fibrinogen/D-dimer) should have a hematology consult and be started on enoxaparin or heparin therapy

Table 2: Medication Management for MIS-C*

Medication	Role in MIS-C Management	Dose	Consultation and Monitoring
Intravenous Immune Globulin (IVIG)	All patients that meet Kawasaki Disease (KD) criteria; Coronary artery changes; Consider in patients with carditis	2g/kg x 1 dose (See Kawasaki Disease order set for dosing and administration)	Prescribed by Infectious Disease following consultation Monitor for fluid overload
Aspirin	All patients that meet KD criteria; Coronary artery changes	High dose: 80-100mg/kg/day	Prescribed by Cardiology following consultation; subsequent/step-down dosing per cardiology
Methylprednisolone	Severe KD KD at risk for IVIG resistance Moderate-severe MIS-C	Moderate: 2mg/kg x 1 (Max 125mg per dose) Severe: 10mg/kg x 1 (Max 1gm dose)	Subsequent/step-down dosing per rheumatology *(Case reports indicate that many patients with MIS-C required steroid for resolution)* *(Case reports indicate that methyprednisone doses of up to 30mg/kg/dose have been used)*
Interleukin 1 inhibitor IL-1 (Anakinra)	Severe inflammatory shock	Moderate/Severe: dosing per rheumatology	Prescribed by Rheumatology following consultation on case-by-case basis
Interleukin 6 Inhibitor IL-6 (Tociluzimab)	Severe inflammatory shock without evidence of bacterial infection	Moderate/Severe: dosing per rheumatology	Prescribed by Rheumatology following consultation on case-by-case basis
Enoxaparin	D-dimer > 500 + MIS-C or COVID-19 diagnosis	Prophylaxis Dosing: 0.5mg/kg/dose SQ q12 hours	Prescribed by Hematology following consultation; Exercise caution when administering with high-dose aspirin
Unfractionated Heparin	D-dimer > 500 + MIS-C or COVID-19 diagnosis with renal dysfunction	Prophylaxis Dosing: 10 units/kg/hour continuous infusion	Prescribed by Hematology following consultation Exercise caution when administering with high-dose aspirin
Empiric Antimicrobial Therapy Ceftriaxone + Vancomycin	Severe multisystem shock – until bacterial infection has been ruled out	Ceftriaxone: 50mg/kg/day q24h, (max 2000mg/day) Vancomycin: 15mg/kg/dose q6h (max 2000mg/dose)	Follow vancomycin dosing guidelines; adjust frequency for renal insufficiency
Clindamycin	Features consistent with toxin-mediated illness – until bacterial infection has been ruled out	40mg/kg/day divided q8 hours (Max 600mg/dose)	
Remdesivir	If meets Emergency Authorization Criteria	<40kg: Load 5mg/kg/dose once (Max 200mg/dose) Maintenance 2.5mg/kg/dose daily (Max 100mg/dose)	Prescribed by Infectious Disease following consultation under emergency authorization - (See Anti-viral Medical Management of Pediatric Patient with COVID-19)

**Medications and dosing in table are intended to serve as guidance. Prescribers may utilize clinical judgement in the medical management of MIS-C based on information available at the time of prescribing*

Figure 2: Initial Screening, Testing, and Management Considerations for Multisystem Inflammatory Syndrome in Children (MIS-C)



Evidence Summary Table

Citation	Study Design	Population	Methods	Measures/ Outcomes	Results
Belhadjer et al.; Pediatric acute heart failure and SARS-CoV-2 infection. 10.1161/CIRCULATIONAHA.120.048360	Retrospective Cohort	35 children admitted for acute heart failure in febrile patients that is temporally related to previous exposure to SARS-CoV-2	Retrospective collection of data for all children with acute left ventricular systolic dysfunction or cardiogenic shock and associated MIS-C admitted to 12 hospitals in France and 1 hospital in Switzerland from March 22-April 30. All institutions located within active COVID-19 pandemic areas in France. Inclusion Criteria: fever, cardiogenic shock or acute left ventricular dysfunction with inflammatory state (CRP > 100 mg/ml)	Demographic characteristics, clinical data, laboratory findings, results of cardiac examination, medical treatments, need for invasive or non-invasive respiratory support, need for mechanical circulatory support, and outcome of case All patients tested for SARS-CoV-2 during hospital course. A patient was considered positive if any method of test was positive.	N = 35 Median age = 10 years None had underlying cardiac disease 17% were overweight SARS-CoV2 infection confirmed in 31/35 patients. Positive antibody assays in 30/35. (Among 2 negative patients, CT features were typical of COVID pneumonia) GI symptoms in 80% of patients Clinical signs suggestive of KD – rash, cheilitis, cervical adenopathy, mengingism were frequent. 0/35 met classic KD criteria. Median delay between 1st clinical symptoms and sx HF was 6 days 29/35 admitted directly to PICU. The 6 patients that were admitted to regular pediatric ward deteriorated quickly and were later transferred to PICU 80% were in cardiogenic shock and required inotropes 10/35 required ECMO. All successfully weaned and removed. 2/3 had resp distress requiring mechanical ventilator support All patient had severe inflammatory state evidence by elevated CRP and D-dimer. IL-6 was elevated. Troponin I elevation was consistent but mild to moderate.

					BNP elevation was present in all children ECHO: EF < 30% in 10/35 EF 30-55% in 25/35 Dilation of coronary arteries in 6 patients. No coronary aneurysms observed to date (at the time this was written) 28/35 inotropic support IVIG given in 25/35 1st line. 1 pt required repeat dose 12/35 received IV steroids and considered high risk for incomplete KD. 3 received IL-1 receptor antagonist (Anakinra) for persistent inflammatory state 25/35 treated with therapeutic dose heparin Favorable outcome in 28/35 patient. 7/35 either still in hospital or with residual LV dysfunction. At time of submission all but 1 patient who was on ECMO left the hospital after median hospital stay of 8 days. None had a thrombotic or embolic event Median ICU stay = 7 days Median hospital stay = 10 days
Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Anitga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020	Retrospective observational cohort	All patients diagnosed with a Kawasaki-like disease in the past 5 years (Patient divided into 2 groups: Before (group 1) or After (group 2) the beginning of the SARS-CoV-2 epidemic	Retrospective review of notes of patients diagnosed with KD admitted to the General Pediatric Unit of Hospital Papa Giovanna XXIII (Bergama, Italy) between Jan 1, 2015-April 20, 2020. Data obtained from hospital medical	Confirmation of SARS-CoV-2 infection Incidence Kawasaki Disease Diagnosis Response to treatment Clinical presentation	Group 1 Incidence 0.3 per month Incomplete KD 6/19 (31%) Avg onset = 3 years Group 2 – Incidence 10 per month (p<0.00001) Incomplete KD 5/10 (50%) Avg onset = 7.5 years 7 boys and 3 girls NP/OP swab positive for SARS-CoV-2 in 2/10 patients; serology testing

			records: demographic data; presenting symptoms; and h/o previous treatments; contact with confirmed or suspected cases of COVID-19, vital signs, laboratory data including WBC, lymphocyte count, ESR, CRP, procalcitonin, ferritin, fibrinogen, proBNP, troponin, NK activity, IL-6. ECHO and EKG were done in all children		revealed 8/10 IgG antibody positive and 3/10 IgM positive 10 patients dx with Kawasaki Disease: 5/10 incomplete KD 5/10 met criteria for KDSS because of hypotension and clinical signs of hypoperfusion (compared to 0/19 in group 1) 5/10 met MAS (compared to 0/19 in group 1) 5/10 positive chest x-ray for mono or bilateral infiltrates Diarrhea, conjunctivitis, abnormal echocardiogram detected in majority of patients in group. Additional lab abnormalities noted: elevated ferritin, transaminases, triglycerides, fibrinogen, D-dimer and thrombocytopenia 60% abnormal echo in group 2 compared to 10% in group 1 All 10 in group 2 treated with IVIG + 8/10 (80%) required adjunct steroid treatment compared to 4/19 (16% in group 1)
Jones VG, Mills M, Suarez D et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020 (pre-publication)	Case Report	Single case report of 6 month old patient with Kawasaki Disease and co-infected with SARS-CoV-2	6-month old, full-term, previously healthy and fully immunized female presented to urgent care with 1 day of fever, fussiness, and refusal to eat. Influenza swab and urinalysis were negative. Patient was diagnosed with viral infection. On Day 2, she developed an erythematous, non-pruritic blotchy rash. On Day 4, returned to urgent care with persistent rash. Pt was mildly congested, febrile, sinus tachycardia, and tachypnea. Exam notable for conjunctivitis and dry cracked lips. Abnormal lab testing revealed left shift WBC, elevated CRP (13.3 mg/dL), ESR (118 mm/hr), hyponatremia (133 mEq/L) and hypoalbuminemia (2.8 g/dL). Chest x-ray showed faint opacity in left midlung zone. Pt sent to ED for COVID-testing prior to admit for KD evaluation. On arrival, patient met classification for classic KD and was treated with single dose of 2gm/kg IVIG and high dose ASA. ECHO was normal and pt afebrile within 24 hours of completing IVIG. Evening prior to discharge, RT-PCR testing for COVID-19 resulted positive. Pt discharged on low dose ASA with plans to				

			follow-up with pediatric cardiology.
Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020	Case Cluster Report	Cluster of 8 children in UK during mid-April 2020 with inflammatory shock presentation	Clinicians noted 8 cases of children with hyperinflammatory shock with features similar to Kawasaki Disease shock syndrome or toxic shock syndrome. 6/8 Afro-Caribbean descent 5/8 boys 4/8 had known family exposure to COVID-19 Similar clinical presentation – fever, variable rash, conjunctivitis, peripheral edema, and extremity pain with gastrointestinal symptoms. All progressed to warm shock, refractory to volume resuscitation, and required noradrenaline and milrinone for hemodynamic support Other notable features: development of small pleural, pericardial, and ascitic effusions, suggestive of diffuse inflammatory process Laboratory evidence of elevated CRP, procalcitonin, ferritin, triglycerides, and D-dimers. Common echocardiographic finding was bright coronary vessels 1/8 children died from a large cerebrovascular infarct All children treated with IVIG in the first 24 hour and empiric antibiotics 6/8 children treated with aspirin. All children discharged from PICU after 4-6 days and receiving ongoing surveillance for cardiac abnormalities
Deza Leon MP, Redzepi A, McGrath E, Abdel-Haq N, Shawaqfeh A, Sethuraman U, Tildford B, Chopra T, Arora H, Ang J, Asmar B. COVID-19 Associated Pediatric Multi-System Inflammatory Syndrome. J Pediatric Infect Dis Soc 2020. (Accepted Manuscript)	Case Report	Single case report from Children's Hospital of Michigan	6y old female initially diagnosed with strep throat in ED on Day 3 of illness and discharged on amoxicillin; Returned to ED on Day 6 with hypotension and with elevated inflammatory/cytokine release markers (CRP: 450 mg/L, LDH: 794 units/L, and ferritin 699.5 ng/ml, troponin 114 ng/L, d-dimer 4.21 mg/L, and fibrinogen 834 mg/dL. Pt also had elevated WBC. Cardiac ultrasound revealed mildly left ventricular function. Patient was started on vancomycin, clindamycin, and ceftriaxone and treated in PICU for cardiogenic shock. Patient met criteria for incomplete KD with echo findings suggestive of myocarditis. She was treated with IVIG and aspirin on Day 6. Patient required intubation, resuscitation, and placement on ECMO on Day 7. Patient found to be subsequently COVID-19 PCR positive. By Day 12, patient was removed from ECMO with downward trend in inflammatory markers and no further signs of end organ damage. Similar but less severe incomplete KD-like illness was reported in two other pediatric patients; both improved with IVIG treatment.
Balasubramanian S.; Nagendran TM.; Ramachandran B.; Ramanan AV.Hyper-inflammatory Syndrome in a Child With COVID-19 Treated Successfully With Intravenous Immunoglobulin and Tocilizumab Indian pediatrics May 2020;(): (Pre-print submitted for publication;	Case Report	Single case report from India	8-yr old boy presented with fever, cough, and throat pain. Admitted Day 4 for persistent fever spikes. Labs revealed leukocytosis, CRP 120 mg/L, and CXR positive for right upper and middle lobe infiltrates. RT-PCR for SARS-CoV-2 was negative. Pt empirically treated with ceftriaxone and azithromycin. Later (illness day not clear) referred to higher level care facility and found to have RR 50 bpm, intercostal retractions, febrile, tachycardia, hypotensive, and capillary refill time of 3 seconds. Erythematous skin rash was noted as well as bulbar

subject to edits)			conjunctivitis, cracked lips, strawberry tongue, edema of limbs, tender hepatomegaly, and abdominal distension. Labs revealed Hgb 8.9 g/dL, leukocytosis, elevated CRP (317 mg/L), raised ESR (115 mm/h), elevated ferritin (1496 ng/ml), hypoalbuminemia 2.6g/dL), hyponatremia (133 meq/L). Pt treated with fluid bolus and antimicrobials. Referred to PICU with differential diagnosis of septic shock, COVID-19 pneumonia, KD, and TSS. IVIG 2g/kg and ASA 75 mg once daily given. ECHO normal. Repeat RT-PCR for SARS-CoV-2 was positive. 72 hours after IVIG, pt was still febrile and had an elevated CRP (121 ng/dL), therefore given Tociluzimab 8 mg/kg IV over 2 hours. 12 hours later, fever spikes settled and inflammatory markers rapidly decreased to baseline.
Giacomet V, Manfredini VA, Meraviglia G, Peri CF, Sala A, Longoni E, Gasperetti A, Stracuzzi M, Mannarino S, Zuccotti GV. Acute inflammation and elevated cardiac markers in a two-month-old infant with severe acute respiratory syndrome coronavirus 2 infection presenting with cardiac symptoms. The Pediatric infectious disease journal. May 2020. Accepted for publication April 29, 2020.	Case Report	Single case report from Milan, Italy	2-month old child presented with reported history of fever, non-bloody diarrhea, and 2 episodes of vomiting. Due to recent close contact with 2 known cases of confirmed coronavirus in family members, the child was tested and found to be PCR (+) for SARS-CoV-2. At admission, child was found to have tachycardia, mottled skin, RR 40 bpm, BP 88/50, and Sat O2 96% on room air. EKG confirmed sinus tachycardia. Normal ECHO. Blood tests revealed normal CRP and PCT. WBC and Hgb were mildly decreased. Cardiac panel revealed increased troponin (103mg/L), elevated BNP (12,507 ng/L), and elevated interleukin-6 (236 ng/L). Child was admitted to PICU with suspected myocarditis and initiated on empiric cefotaxime + ampicillin diagnosed with suspected myocarditis. On Day 2 of arrival, blood tests showed increased CRP, D-dimer, and PCT with further decrease in Hgb. Repeat ECHO showed hypokinesia of inferior left ventricular wall and inferior intraventricular EF. PRBC's given and IVIG 2gm/kg in 24 hours. Between Day 3 and Day 6, decrease of cardiac and inflammatory markers was evident. Day 4 ECHO revealed EF recovery and normal EF. Mild dyskinesia of left inferior ventricular wall and inferior intraventricular septum persisted. On Day 5, HR and BP stable. (Of note – stool was negative for adenovirus and rotavirus. Search for other possible cardiotropic viral agents including coxsackievirus, Epstein-Barr virus, mumps, parvovirus B19, adenovirus, varicella zoster virus, measles morbillivirus were negative. Blood cultures were negative.)
Chiotos K, Bassiri H, Behrens EM, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series	Case Series	Six children treated in the PICU at Children's Hospital of Philadelphia	Case 1: 14 yr old presented with 5 day h/o fever, headache, diarrhea, and erythematous rash, and 1 day h/o dyspnea. Elevated inflammatory markers noted on admission; SARS-CoV-2 PCR test was negative; bilateral pulmonary infiltrates on CXR; cardiac ultrasound found diminished LVF. Treated with IVIG 2gm/kg, methylprednisolone 2mg/kg/day, and low dose aspirin. Case 2: 12 yr old male presented for OSH with 6-day h/o fever, abdominal pain, diarrhea, fissured lips, resp distress, and altered mental status. SARS-CoV-2 PCR test was negative, labs included inflammatory markers; ECHO revealed LV dysfunction; chest radiography revealed diffuse bilateral infiltrates. Required vasoactive support and non-invasive mechanical ventilation. Treated with IVIG 2gm/kg and methylprednisolone 10mg/kg/day. SARS-CoV-2 IgG positive.

			Case 3: 9 yr old female presented with fever, copious diarrhea, and intermittent periumbilical pain. SARS-CoV-2 PCR test was negative; labs notable for inflammatory markers; abdominal CT performed for possible appendicitis. Repeat SARS-CoV-2 PCR testing was positive. On Day 5 developed conjunctivitis, extremity edema, and mucosal changes. Normal ECHO. Treated with IVIG 2gm/kg, methylprednisolone 2mg/kg/day, and low dose aspirin. Cardiomegaly and pulmonary edema on chest radiography. Case 4: 5yr old female presented with fever, rah, mucosal changes, conjunctivitis, swollen hands, emesis, diarrhea, irritability, and nuchal rigidity. Notable elevated inflammatory markers, hypotensive, elevated BNP and troponin. Initial SARS-CoV-2 PCR test was negative, but repeat was positive. Pulmonary infiltrates positive and moderately diminished LV systolic function. Started on vasoactive support with epinephrine and milronone and intubated. Treated with IVIG 2gm/kg, methylprednisolone 2mg/kg/day on Day 0. IVIG 2gm/kg was repeated on Day 2 for persistent fevers. Head CT showed cerebral edema. Due to ongoing disease manifestations, given anakinra 4mg/kg/day and pulse methylprednisolone 30mg/kg/dose on Day 4. IgG testing was positive. Case 5: 5 yr old female with 5 day history of fever, conjunctivitis, irritability, lethargy, and nuchal rigidity. Hypotensive on transfer from OSH with elevated inflammatory markers. SARS-CoV-2 PCR test was negative. ECHO demonstrated left ventricular dilation and mildly diminished LV function. Treated with IVIG 2gm/kg on Day 0 and repeated on Day 2. Treated with low dose aspirin. IgG testing was positive Case 6:6 yr old female with 7 day h/o fever, abdominal pain, and bilious emesis. Transferred from OSH, intubated, and treated for shock. ECHO on Day 0 demonstrated left ventricular dilation with mildly diminished systolic shortening and low normal right ventricular systolic shortening. Cardiac support with dobutamine, milrinone, and epinephrine required. Treated with IVIG 2gm/kg, methylprednisolone 2mg/kg/day. Due to worsening disease and possible macrophage activation syndrome, treated with pulse methylprednisolone 30mg/kg/day on Day 1-3. IgG testing was positive At the time of writing this, Case 1-5 were discharged home. Case 6 remained hospitalized.

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Appendix 1: Multisystem Inflammatory Syndrome in Children Associated with Covid-19 (MIS-C)

Information for Parents and Caregivers

What is MIS-C?
Multisystem Inflammatory Syndrome in Children (MIS-C) is a condition where different organs (body parts) can become inflamed, such as: the heart, lungs, kidneys, brain, skin, eyes, or stomach. MIS-C can be serious, even deadly, but most children who have been diagnosed with this condition have gotten better with medical care.

What causes MIS-C?
Currently scientists and doctors are not yet certain what causes MIS-C. However, we know that many children with MIS-C had the virus that causes COVID-19, or had been around someone who had COVID-19.
Therefore, we currently believe there is a link between MIS-C and COVID-19, although it is not yet clear.

Is my child at risk for MIS-C?
We do not yet understand why in rare cases some children have gotten sick with MIS-C and others have not. Until we learn more, we have to assume that all children are at risk.

What symptoms should I watch out for?
The symptoms of MIS-C can vary but most patients have had a fever for more than one day plus one of these other symptoms: abdominal pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes and feeling extra tired.

Who should I call if I think my child might have MIS-C?
Call your pediatrician if you think your child might have MIS-C. The pediatrician can ask you some questions and may order a few simple tests that might help them understand if your child does have MIS-C or not.

If your child has any **emergency warning signs** such as: trouble breathing, trouble waking up, chest pain, confusion, or signs of dehydration such as peeing less or having a dry mouth, then you should take your child to the **emergency room or call 911**.

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ORIGINAL APPROVAL: June 8, 2020

Multisystem Inflammatory Syndrome in Children (MIS-C)

Associated with COVID-19

UPMC Children's Hospital of Pittsburgh Response Team Recommendations:

Background

Diagnostic Criteria & Reporting

Diagnostic Testing

Management

1. BACKGROUND

The presentation of a growing number of cases of multisystem inflammatory syndromes 4-8 weeks following the emergence and spread of SARS-CoV-2 within a given geographic region raises concern that these illnesses represent post-infectious sequelae of infection with this virus. The Centers for Disease Control and Prevention has called these illnesses Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 (MIS-C, also previously called Pediatric Multisystem Inflammatory Syndrome [PMIS] and Pediatric Inflammatory Multisystem Syndrome [PIMS]) and asked for potential cases to be reported through state departments of health. To date, it is not known whether these cases are causally related to SARS-CoV-2 and, if so, whether there is any relationship to the presence or absence of symptoms or the severity of COVID-19 in those with the inflammatory conditions. Of note, early evidence suggests that if MIS-C is indeed a post-COVID-19 sequela, it occurs very infrequently among those infected. Furthermore, an increase in clinical cases similar to Kawasaki disease and Kawasaki shock syndrome have been noted. Early descriptions of these patients show important distinctions that may confound diagnosis, challenge clinicians, and influence management strategies.

This document presents our current recommendations regarding diagnostic criteria, diagnostic testing, and management for children being evaluated for MIS-C and related conditions.

There is limited information currently available about risk factors, pathogenesis, clinical course, and treatment for MIS-C. CDC is requesting that healthcare providers report suspected cases to public health authorities to better characterize this newly recognized condition.

2. DIAGNOSTIC CRITERIA & REPORTING

- **Initial Recommendations for Reporting to the Pennsylvania Department of Health**
  - Children < 21 years of age meeting MIS-C criteria should be reported to the CHP Command Center.
  - CHP is responsible for reporting suspected cases in collaboration with the CHP MIS-C Response Team.
  - Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.
- **Multisystem Inflammatory Syndrome in Children**
  - Case Definition[1] for Multisystem Inflammatory Syndrome in Children (MIS-C) (should include all of the following):
    - An individual aged < 21 years presenting with fever*
    - Laboratory evidence of inflammation**
    - Evidence of clinically severe illness requiring hospitalization
    - 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

*Fever ≥ 38.0°C for ≥ 24 hours, or subjective fever lasting 24 hours

** 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

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease, but should be reported if they also meet the case definition for MIS-C.
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.
- If suspicion for MIS-C remains high despite negative SARS-CoV-2 testing and no identifiable exposure, consider Infectious Diseases and/or Rheumatology consult(s)

Classic Kawasaki Syndrome Case Definition

- 5 or more days of fever
- At least 4 of 5 of the following clinical criteria:
  - Non-purulent conjunctivitis
  - Mucositis (e.g., cracked lips, strawberry tongue)
  - Cervical lymphadenopathy (≥ 1.5 cm)
  - Rash (non-vesicular)
  - Swelling and/or redness of the hands and feet (primarily palmar/plantar)
- No Alternative Explanation
- Additional Criteria in response to COVID-19 Pandemic: Evidence of current or recent SARS-CoV-2 infection
  - Positive RT-PCR, serology, or antigen test
    or
  - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Incomplete Kawasaki Syndrome

- ≥ 5 days of fever (in some instances KD may considered with shorter duration of fever)
- 2 or 3 clinical criteria as above
- Definition as defined by AHA 2017
- Additional criteria in response to COVID-19 Pandemic: Evidence of current or recent SARS-CoV-2 infection as described above
- Be aware of features that are LESS like classic KD AND overlap with MIS-C including older age, GI symptoms, race, low platelet count, low lymph count, high ferritin

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3. DIAGNOSTIC EVALUATION OF SUSPECTED MIS-C

For patients meeting the diagnostic criteria for KD or MIS-C (including no plausible alternative diagnosis) without shock, features of macrophage activation syndrome (MAS) / hemophagocytic lymphohistiocytosis (HLH), or hepatitis, additional laboratory evaluation should be performed as below in accordance with CDC guidelines. For most patients, this expanded testing is not expected to alter management, but rather to help better characterize this emerging syndrome. Further infectious workup should be informed by the patient's presentation. Patients fitting one or more of the other categories should have an expanded rheumatologic/immune and infectious evaluation as listed, primarily aimed at determining whether an alternative etiology may be present.

Timing of expanded infectious and rheumatologic/immune workup

For those patients with shock, MAS/HLH, or hepatitis, it is anticipated that the infectious and rheumatologic/immune workup would be sent in the event that there is not a clear cause for a patient's presentation following initial workup. Accordingly, it is likely that some of these studies will have already been sent (such as various bacterial cultures), but these are included for the sake of completeness. Additionally, it is possible that patients could present with features of more than one category, such as cardiogenic shock and MAS.

Differentiation of shock

	Cardiogenic "cold" shock	Vasoplegic "warm" shock
Clinical features:	Delayed capillary refill, diminished pulses	Flash capillary refill, bounding pulses
Echo or point of care ultrasound	Diminished cardiac function	Preserved cardiac function
Cardiovascular support:	May require inotropic agents such as epinephrine or milrinone	May require vasopressors such as norepinephrine or vasopressin

Suggested Consults

- Infectious Diseases
- Rheumatology
- Cardiology
- Hematology

Recommended Diagnostic Tests

The table that follows is not intended to replace consultant input if MIS-C is suspected, and involvement of some or all of the above services may be needed for diagnostic or management assistance.

Initial Laboratory Work-up	Suspected MIS-C or known KD w/o shock	Cardiogenic shock	Vasoplegic shock	MAS/HLH or hepatitis
General labs				
CBC	X	X	X	X
BMP	X	X	X	X
LFTs	X	X	X	X
LDH	X	X	X	X
UA, voided	X	X	X	X
Lactate		X	X	X
CRP	X	X	X	X
PCT (unavailable if PCR+)	X	X	X	X
ESR (unavailable if PCR+)	X	X	X	X
Ferritin	X	X	X	X
D-Dimer	X	X	X	X
Coags with fibrinogen		X	X	X
CK	X	X	X	X
Troponin	X	X	X	X
BNP (delayed for PCR+)	X	X	X	X
ADAMTS13		X	X	X
Rheumatologic/Immune Labs				
C3		X	X	X
C4		X	X	X
Triglycerides		X	X	X
sIL2r		X	X	X
Infectious Studies				
SARS-CoV-2 PCR*	X	X	X	X
SARS-CoV-2 serology**	X	X	X	X
Blood culture		X	X	X
Urine culture if concerning UA		X	X	X
Respiratory culture (if intubated)		X	X	X
Adenovirus blood PCR		X	X	X
Enterovirus blood PCR		X		
EBV PCR and serology				X
CMV PCR and serology				X
HSV blood PCR				X
Ehrlichia PCR (summer/spring)		X	X	X
Anaplasma PCR (summer/spring)		X	X	X

*Patients reported to have positive PCR with MIS-C typically had high cycle thresholds, indicative of low level positivity. Thus the chance of a false negative is higher, and a second PCR should be sent if negative
**If negative, discuss retesting prior to discharge

Imaging / Other (all patients)

Due to the multisystem nature of the inflammatory response presentations affecting CNS, Cardiac, Pulmonary, GI, Renal and Hematologic systems have been seen. Additional organ specific imaging, laboratory evaluation and consultation should be obtained per clinical judgement.

- Chest x-ray for any patient with respiratory symptoms
- Echo
    - In a patient meeting diagnostic criteria for MIS-C, echo should be obtained within 24 hours of diagnosis. This does not require that all infectious testing be resulted prior to obtaining echo, but initial lab results should be available and consistent with the diagnosis, and there should be reasonably high suspicion for MIS-C.
    - A repeat echo should be obtained 10-14 days later at a minimum.
- EKG
    - While data on incidence is limited, heart block, right bundle branch block and other conduction abnormalities have been reported. May warrant serial monitoring.

- Neurologic
    - While data on incidence is limited, CSF pleocytosis, cerebral edema, cranial nerve abnormalities particularly CN VI have been reported.
    - Pathogenesis is unknown. Subsequently more complete neurologic evaluation maybe warranted on a case by case basis including but not limited to LP, MRI, EEG to differentiate ischemic versus inflammatory disease, altering empiric management.

4. MANAGEMENT OF MIS-C

The rapidly developing clinical scenario called Multisystem Inflammatory Syndrome in Children temporally related to COVID-19 (MIS-C) ***or*** Pediatric Multisystem Inflammatory Syndrome (PMIS) has raised important therapeutic questions. This section is meant to provide preliminary guidance for the management of **suspected MIS-C**.

- This guidance applies to **inpatients at UPMC Children's Hospital of Pittsburgh**
    - It assumes that MIS-C patients requiring special therapeutic consideration are ill enough to require inpatient admission.
    - **It is not meant to affect management decision-making prior to the decision to admit.**
    - It relies on testing and evaluation structures that may not generalize outside of UPMC Children's Hospital.
- These recommendations **will change** as new experience and literature becomes available.

The emerging literature on MIS-C identifies similarities with other recognized syndromes, including but not limited to, Kawasaki disease and macrophage activation syndrome[1-4]. As such, we have extrapolated from existing knowledge about these syndromes to help guide the management of MIS-C.

ALTERATIONS IN KAWASAKI DISEASE (KD) CLINICAL EFFECTIVENESS GUIDELINES (KD-CEG)

MIS-C has been linked most strongly to the clinical features of KD, and several patients have developed coronary aneurysms. Some clinical features may be more prevalent in MIS-C than KD, and the presence of these features should alter typical KD management. Currently, we recommend that first-line therapy for suspected MIS-C should include intravenous immunoglobulin (IVIg) and low-dose aspirin (ASA) according to the existing KD-CEGs, with a few alterations:

- **Initial lab testing** per MIS-C diagnostics group recommendations of ALL patients with suspected KD and MIS-C, refer to Section 3.

- Patients **without shock**, but not (yet) meeting KD-CEG criteria to receive IVIg/ASA, should be considered for such treatment if suspicion for MIS-C is high. Decisions on IVIg/ASA, and potentially other anti-inflammatory therapies in these patients, should be made in consultation with Rheumatology and other specialties as appropriate. Clinical features **beyond those typically seen in KD that may warrant IVIg/ASA** include:

    - Pronounced abdominal pain/intestinal symptoms
        - Diarrhea, abdominal pain, vomiting
    - Age > 5 years
    - Myocarditis
    - Neurologic symptoms
        - Headache, irritability, lethargy, altered mental status, focal deficit, seizures
    - Evidence of marked systemic inflammation
        - e.g., ferritin > 700, lymphopenia, hypoalbuminemia, hyponatremia, thrombocytopenia
    - Strong suspicion for prior SARS-CoV-2 infection
        - based on exposure history, PCR, or serologic testing
    - Absence of other identified pathogen or cause

- Management of all KD or MIS-C patients with concern for **IVIg resistance** should be made in consultation with Rheumatology regardless of timing after IVIg. (See adjuvant anti-inflammatory therapies below.)

<u>Alterations of Shock/Hyperinflammation guidelines</u>:

Shock and macrophage activation syndrome (MAS)-like features are known complications of KD, but may be more common/insidious in MIS-C. Patients in shock and/or with features of MAS should largely be managed using current practice guidelines and protocols. However, MIS-C carries the potential for development of coronary aneurysms in novel clinical contexts. In consultation with Rheumatology and other appropriate specialists, IVIg/ASA (at the doses indicated in KD-CEG) should be considered in the following scenarios:

- Vasoplegic Shock*
- Cardiogenic Shock*

*IVIg/ASA administration is strongly recommended. Use precautions for fluid overload. Subsequent plasma exchange (PLEX) should be reserved for children with evidence of persistent systemic inflammation with progression of organ dysfunction (MOF $\geq$ 2). Alternatively, in critically ill children, plasma exchange can be pursued aggressively, and IVIg given following PLEX course.

SPECIFIC THERAPEUTIC CONSIDERATIONS IN MIS-C

- **Supportive**
    - Supportive care should be provided under existing shock guidelines.[5]
- **Anti-Inflammatory**
    - **IVIg/ASA** - Given concern for coronary aneurysm formation, IVIg/ASA will be first-line anti-inflammatory therapy for all suspected MIS-C patients. Dosing will remain as indicated in the KD-CEG.
        - **IVIg 2g/kg (max 100g)** Modifications may be required to avoid fluid overload.

        - **ASA 3-5mg/kg daily (see KD CEG for dosing guideline, hold for platelet count <50)**
    - **Adjuvant anti-inflammatories**: Specific clinical features, severity, or chronicity could warrant the use of adjuvant anti-inflammatory therapies alongside or following IVIg/ASA, in consultation with Rheumatology and other specialties as appropriate.
    - **Glucocorticoids**: Consider whether an adequate work-up for infectious and oncologic causes has been performed prior to initiating. Limiting steroid exposure may be warranted in patients with positive PCR testing for SARS-CoV-2, particularly those with negative serology. Glucocorticoids may be given alongside IVIg/ASA in patients with shock or MAS-like features, or for persistent/refractory inflammation. May be given at **pulse** (methylprednisolone 30mg/kg/dose up to 1g) or **standard** (~2mg/kg/day) dosing. Rebound inflammation has been described; a taper over 2-4 weeks following improvement of inflammation may be required.
    - **Anakinra**: Increasing evidence in MAS/HLH[6], and case reports in MIS-C[2]. May be given SQ or IV at doses up to 2.5mg/kg/dose q6H (max starting dose of 100mg q6H)
    - **PLEX**: Increasing evidence in sepsis-related multiple organ dysfunction, particularly with evidence of MAS[7,8], thrombocytopenia associated multiple organ failure[9], IVIg refractory KD[10,11], and case reports in MIS-C[12-14].
    - **Infliximab**: Evidence for efficacy in refractory KD[15,16]. Typically given 5mg/kg/dose IV once.
    - **Tocilizumab**: Case reports of efficacy in severe COVID-19[17]. Typically given at 8-12 mg/kg/dose IV once. May be repeated. Requires approval from the UPMC System COVID-19 Therapeutics Group **AND** approval from CHP Director of Pharmacy to be ordered for each patient.
- **Anti-Microbial**
    - **Anti-viral**: Anti-viral therapies are not recommended for the treatment of SARS-CoV-2 PCR-negative MIS-C at this time[18]. Treatment of PCR+ patients should be considered in consultation with the Infectious Disease team.
    - **Empiric and Prophylactic**: Suspicion for MIS-C should not alter the current practice of empiric/prophylactic antimicrobial management. There is no evidence at this time that bacteria contribute to the pathogenesis of MIS-C.
- **Anti-Thrombotic:**
    - **Anti-platelet**: low-dose aspirin should be given in accordance with the above.
    - **Anti-coagulation**: Prophylactic unfractionated heparin continuous infusion (preferred, see CHP Lexicomp heparin dosing) or LMW heparin (enoxaparin, see CHP Lexicomp enoxaparin dosing) should be considered in all patients with shock, cardiac dysfunction, or coronary abnormalities according to existing KD-CEG ICU/shock guidelines in consultation with hematology.
    - Other patient specific factors for anticoagulation should be considered on a case by case basis and may include advance testing in discussion with hematology including: ADAMTS13, TEG, antiphospholipid antibodies, von Willebrand factor. Note that some studies may be unavailable in the setting of PCR positivity.

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Initial Evaluation, Diagnosis and Management of Patients with Suspected Multi-System Inflammatory Syndrome in Children (MIS-C)

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Version 1.2 Date: June 5, 2020

Ambulatory and Inpatient Guidelines for evaluation of patients with suspected COVID-19 are detailed in separate documents (latest versions 5/6/20 and 5/26/20, respectively).

Purpose:
To provide guidance for care of children with suspected Multi-system Inflammatory Syndrome in Children (MIS-C).

This is a rapidly evolving situation and contents of this document may become outdated. This guidance will continue to evolve as more is known about MIS-C.

Background:
On May 14, 2020 the Centers for Disease Control and Prevention (CDC) released a case definition for Multisystem Inflammatory Syndrome in Children (MIS-C) (https://emergency.cdc.gov/han/2020/han00432.asp). There is limited information currently available about risk factors, pathogenesis, clinical course and treatment for MIS-C.

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

1. 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
2. No alternative plausible diagnosis; AND
3. 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 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, low albumin.

MIS-C Ambulatory & ED Pathway

Fever ≥ 38C / Subjective fever + ≥ 2 of the following:
- GI symptoms: Abdominal pain, vomiting diarrhea
- Mucocutaneous symptoms: Conjunctivitis, rash, lymphadenopathy, oral mucosal changes, sore throat
- Swelling of hands and/or feet
- Myalgias, headache, irritability

OR

Any fever ≥ 5 days

Additional history / physical exam items to consider are in Box 1 below.

Toxic-appearing or abnormal vital signs (hypotension for age, elevated HR out of proportion to fever, hypoxia, altered mental status)?

Yes → Refer patient to ED

No → Fever/history of fever ≥ 38.0 for ≥ 3 days AND/OR multiple characteristic features (Box 1)

No → Clinical workup as indicated

Yes →

Evaluation for possible MIS-C - Initial Lab Testing
Blood: CBC with diff, CMP, CRP, ESR, Blood culture
NP Swab: SARS-CoV-2 PCR, RPP
Other testing as clinically indicated (consider abdominal ultrasound if concern for intra-abdominal pathology)

Consider ED referral if unable to obtain above labs or concern for time / space constraints.

Labs and physical exam reassuring →

Discharge
Tolerates PO
Reassuring PE
PCP follow-up 24-48 hrs

CRP ≥ 20 mg/L and/or ESR ≥ 40 mm/hr
AND
- Lymphopenia < 1k or
- Thrombocytopenia < 150k or
- Na < 135 or
- Hypoalbuminemia < 3 g/dL
- Acute abdomen or
- Abnormal imaging on abdominal ultrasound (enteritis, hydrops of gall bladder)

Consult ID - phone discussion re: need for additional testing. Consult Surgery if concern for acute abdomen.

Yes →

Further evaluation
Additional ancillary labs:
- Troponin I, BNP, D-dimer
- Additional Red Top tube to save in lab
- PT/PTT, Fibrinogen, antithrombin level
- Ferritin
- LDH
- Triglycerides
- IgG, IgA, IgM levels
- SARS-CoV-2 antibody testing
- Urinalysis
- ECG
- Echocardiogram
- CXR

Consider antibiotics

Normal echo, BNP, troponin and ECG?

Yes → **Admit to hospital medicine**

Location: COVID unit until cleared by Infection Prevention

Refer to inpatient pathway for further guidance.

No → Fluid responsive, no cardiac involvement?

Yes → Admit to hospital medicine

No → **Admit to PICU**

Location: COVID unit until cleared by Infection Prevention

Consider CICU admission:
- Severe valvular dysfunction, valvular insufficiency
- Evidence of coronary artery involvement (ectasia, aneurysms)
- Arrhythmias (ventricular ectopy, AV conduction abnormalities)
- Elevated BNP or troponin with or without cardiac dysfunction

Refer to ICU pathway for further guidance.

No → Normal echo, BNP, troponin and ECG?

Suspected MIS-C with Shock
Fever/history of fever ≥ 38 for ≥ 1 day
+
Evidence of myocardial dysfunction or Hypotension/vasopressor requirement, elevated HR out of proportion to fever, hypoxia, altered mental status, confusion,+
≥ 2 clinical / historical features

Sepsis CPG
Consult Cardiology
Diagnostic laboratory studies
- CBC with diff, CMP, CRP, ESR, Blood culture
- Troponin I, BNP, D-Dimer
- Blood gas
- Ferritin
- LDH
- PT/PTT, fibrinogen, antithrombin level
- Triglycerides
- Additional Red Top Tube to save in lab
- Quantiferon gold (Tspot)
- SARS Co-V-2 antibody testing
- SARS-CoV-2 PCR, RPP
- Urinalysis
- ECG
- Echocardiogram
- CXR

Gentle fluid resuscitation, vasopressors
Antibiotics per sepsis CPG

Multisystem Inflammatory Syndrome in Children (MIS-C) Case Definition
- An individual aged <21 years presenting with fever[1], laboratory evidence of inflammation[2], 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

1. Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
2. 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

Box 1. Clinical / Historical Features of MIS-C
- **Rash** - polymorphic, maculopapular, petechial, NOT vesicular
- **GI symptoms** - diarrhea, abdominal pain, vomiting
- **Extremity changes** - erythema and edema of hands and feet in acute phase
- **Oral mucosal changes** - erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- **Conjunctivitis** - bilateral bulbar conjunctival injection without exudate
- **Lymphadenopathy** - Cervical, ≥ 1.5 cm, unilateral
- **Neurologic symptoms** - headache, irritability, lethargy, AMS, meningismus
- **Epidemiologic link to COVID** - Patient with history of COVID or close contact with known positive COVID case in past 4 weeks, or person placed in quarantine

Version: 1 June 2020

MIS-C Inpatient Pathway

Version: 1 June 2020

Admit to Hospital Medicine for Suspected MIS-C

Precautions:
- If SARS-CoV-2 PCR positive: contact/droplet/eye protection
- If SARS-CoV-2 PCR negative: routine

Place patient on telemetry.

Consultants:
- Treatment decisions should be made in concert with consulting services
- All patients with concern for MIS-C:
  - Cardiology
  - ID
  - Rheumatology
  - Hematology
- Consult based on clinical syndrome:
  - General Surgery (acute abdomen)
  - GI (colitis)
  - Renal (AKI)

Studies: Refer to table.

Treatment: Refer to algorithm. Patients presenting with "Classic Kawasaki Disease" should be treated according to 2017 AHA Guidelines.

Discharge Criteria:
- Afebrile ≥ 36 hours from end of IVIG, abnormal labs trending towards normal, hemodynamically stable without hypoxemia, otherwise meeting routine discharge criteria.
- Follow-up in multi-disciplinary MIS-C clinic 1 week after hospital discharge. Visit to be arranged by cardiology fellow.
- Specific instructions will be given to family for monitoring at home, including potential for deterioration after discharge. Contact information will be provided should the patients' clinical status worsen after discharge. Specific instructions will be given to families to reduce risk of transmission at home to themselves as well as other family members.
- VUMC providers will contact PCP prior to patient discharge and send PCP eStar letter. We recommend that PCP follow up with patient by telephone within 1 week after discharge

Table. Diagnostic Studies

Daily Labs	Exploratory labs (send if recommended by consulting services)
CBC/diff	sIL2R
CMP	sCD163
CRP, ESR	CXCL9
Ferritin	Cytokine panel
PT/PTT/INR, Fibrinogen	Perforin
D Dimer, Troponin I, BNP	CD107a mobilization
LDH	

Treatment Algorithm

MIS-C WITHOUT Severe Hyperinflammation*
- IVIG 2g/kg (Max 80g)± AND
- ASA 50mg/kg/day divided q6h (avoid if bleeding or plt <30k)
- Consider Enoxaparin:
  - Treatment dose if coronary artery aneurysms
  - Prophylaxis dose if additional baseline thrombosis risk****

Treatment failure?** →

MIS-C WITH Severe Hyperinflammation*
- IVIG 2g/kg (Max 80g)± AND
- ASA 3-5mg/kg (avoid if bleeding or plt <30k)
- IV Methylprednisolone: 1mg/kg q12h x 5d (max 30mg/dose), followed by 2-3 wk taper
- Consider Cytokine Directed Therapy***
- Consider Enoxaparin:
  - Treatment dose if coronary artery aneurysms
  - Prophylaxis dose if additional baseline thrombosis risk****

Considerations for IVIG therapy
- Obtain red top (x2) prior to initial adminstration
- If evidence of circulatory failure, consider 1g/kg/day x 2 days
- Use with caution in patients with HLH-like features (increased thrombosis risk)

Anticoagulation considerations
- Platelet goal >30k (can transfuse to achieve goal) while on anticoagulation
- Avoid NSAIDs which counteract irreversible antiplatelet effects of ASA
- Consider risk of Reye syndrome associated with ASA use (see AHA 2017 KD guidelines)

Definitions

***Severe Hyperinflammation:** Features may include hyperferritinemia, thrombocytopenia, anemia, hepatosplenomegaly, neurologic changes (AMS, seizure), hepatic dysfunction (encephalopathy, coagulopathy, rising hepatic enzymes), vasodilatory shock

****Treatment Failiure:** Defined as fever 36hr after IVIG completion or recrudescent fever within 7 days, clinical worsening in 24hr, escalation of respiratory support, ICU transfer.

*****Cytokine Directed Therapy:** Consideration for anti-cytokine therapy will be made for those patients with persistent fever or worsening hyperinflammatory features* despite initial treatment with IVIG +/- steroids. If given, Anakinra will be preferred anti-cytokine agent due to short half life and evidence for use in both Kawasaki disease and other hyperinflammation syndromes.

******Additional Baseline Thrombosis Risk:** Known inherited thrombophilia, history of thrombosis, low antithrombin levels, nephrotic syndrome, critical illness, age ≥ 12yr

Suspected MIS-C¥ (with Shock) Guidelines

- ❑ Fever/History of Fever ≥38C for ≥1 day **AND**
- ❑ Evidence of Myocardial Dysfunction or Hypotension/Vasopressor Requirement **AND**
- ❑ ≥ 2 Clinical/Historical Features¥¥

Admit to CICU/PICU§

- ❑ **Antibiotics**
  - Broad spectrum Abx for patients presenting in shock with concerns for sepsis as per usual clinical care standards
  - Obtain cultures prior to treatment when able
- ❑ **GI Prophylaxis** with PPI

Treatment Algorithm

MIS-C WITHOUT Severe Hyperinflammation*: Initial Therapy

- ❑ IVIg¶ 2 g/kg (Max 80 g) AND
- ❑ ASA 50 mg/kg/day divided q6h§§, ¶¶
- ❑ Consider enoxaparin¶¶
  - ❑ Treatment dosing if coronary artery aneurysms§§
  - ❑ Prophylaxis dosing if additional baseline thrombosis risk****

Treatment Failure?**

MIS-C WITH Severe Hyperinflammation*: Initial Therapy

- ❑ IVIg¶ 2 g/kg (Max 80 g) AND
- ❑ ASA 3-5 mg/kg/day§§, ¶¶
- ❑ Methylpred 1mg/kg (max 30 mg/dose) IVq12h x5d
  - ❑ Follow with 2-3 week taper
- ❑ Consider cytokine directed therapy***
- ❑ Consider enoxaparin¶¶
  - ❑ Treatment dosing if evidence coronary artery aneurysms§§
  - ❑ Prophylaxis dosing if additional baseline thrombosis risk****

Consulting Services

ALL Patients meeting MIS-C Criteria

- ❑ ID
- ❑ Rheumatology
- ❑ Hematology
- ❑ Cardiology

Relevant End-Organ Considerations

- ❑ Nephrology (↑ AKI)
- ❑ Gastroenterology (↑ Colitis)
- ❑ General surgery (↑ Acute abdomen)
- ❑ ECMO/CT Surgery

Diagnostic Studies in ICU⊕

- Antithrombin (once)
- CBC c diff (daily*)
- CMP (daily)
- CRP, ESR (daily)
- TG (daily if concern for MAS)
- Ferritin (daily)
- PT/PTT/INR (daily)
- D Dimer (daily)
- Fibrinogen (daily)
- LDH (daily)
- Troponin I (daily)
- BNP (daily)
- Blood gas (PRN)
- Echocardiography (on admit and PRN)
- Electrocardiography (on admit and PRN)
- Exploratory labs per consulting services

§Consider CICU Admission

- ❑ Severe ventricular dysfunction, valvar insufficiency
- ❑ Evidence coronary artery involvement (ectasia, aneurysms)
- ❑ Arrhythmias (e.g ventricular ectopy, AV conduction abnormalities)

⊕Daily laboratory studies may be scaled back with improvement, though decisions should be individualized and made in concert with consulting services where appropriate.

§§Kawasaki Disease Considerations

Refer to 2017 AHA Kawasaki Disease Guidelines (PMID 28356445) for case definitions of KD and "atypical" KD, as well as additional treatment guidelines.

Patients presenting with "Classical Kawasaki Disease" should be treated according to 2017 AHA Guidelines.

Version 2.3 (1 June 2020)

¶Considerations for IVIg Therapy

- ❑ Obtain red top (x2) prior to initial administration.
- ❑ If evidence of circulatory failure, consider 1g/kg/day x 2 days.
- ❑ Use with caution in patients with HLH-like features (increased thrombosis risk)

¶¶Anticoagulation considerations

- ❑ Platelet goal >30K (can transfuse to achieve goal) while on anticoagulation
- ❑ Avoid NSAIDs which counteract irreversible antiplatelet effects of ASA
- ❑ Consider risk of Reye syndrome associated with ASA use (see AHA 2017 KD guidelines§§)

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******Thrombosis risk factors:** Thrombophilia, prior history of thrombosis, low AT levels, nephrotic syndrome, **critical illness, age ≥12yr**)

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

- ✓ 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

¥¥Clinical/Historical Features of MIS-C

- ❑ **Rash**
  Polymorphic, maculopapular, petechial, NOT vesicular
- ❑ **GI Symptoms**
  Diarrhea, abdominal pain, vomiting
- ❑ **Extremity changes**
  Erythema and edema of the hands and feet in acute phase
- ❑ **Oral Mucosal Changes**
  Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- ❑ **Conjunctivitis**
  Bilateral bulbar conjunctival injection without exudate
- ❑ **Lymphadenopathy**
  Cervical > 1.5 cm, unilateral
- ❑ **Neurologic Symptoms**
  Headache, irritability, lethargy, AMS, meningismus
- ❑ **Epidemiologic Link to COVID**
  Patient with history of COVID disease or close contact with known Positive COVID case in past 4 weeks, or person placed in quarantine

Supporting Diagnostic Features

- ❑ CRP ≥20 mg/L or ESR ≥40 mm/hr AND
  - ❑ Lymphopenia AND/OR
  - ❑ Thrombocytopenia AND/OR
  - ❑ Hyponatremia AND/OR
  - ❑ Hypoalbuminemia AND/OR
  - ❑ Acute abdomen or GB hydops by US

Appendix A. Pediatric cardiology management of patients admitted with MIS-C

MCJCHAV Pediatric Cardiology

For patients with suspected MIS-C - clinically stable (likely under hospitalist service)

1. Suspected Kawasaki disease
    a. Follow routine KD (complete/incomplete) protocol with cardiology consult, echocardiogram and ECG
2. No signs of KD but with CRP ≥ 3, ESR ≥ 40, lymphopenia (<1k) or thrombocytopenia (<150K)
    a. Obtain ECG, echocardiogram, troponin, BNP and cardiology consult

For patients with suspected MIS-C – shock (ICU care)

1. Obtain ECG, echocardiogram, troponin, BNP and cardiology consult
2. Additional imaging for patients with ventricular dysfunction: cardiac MRI once patient is clinically stable

Imaging:

1. At diagnosis
2. For patients with normal function and normal coronary artery dimensions:
    a. f/u 1-2 weeks post diagnosis to recheck coronary size

Pediatric cardiology follow-up of patients discharged with MIS-C

1. Routine cardiology follow-up for patients with classic KD

2. Patients to be followed in multidisciplinary clinic:

    a. Those treated with “non KD symptoms” and CRP ≥ 3, ESR ≥ 40, lymphopenia (<1k) or thrombocytopenia (<150K)
    b. MISC-shock
    c. Follow up from cardiology to include:
        i. Visit: 1 week, 4 weeks, 6 months, 1 year post discharge
        ii. Tests 1 week visit: ECG/Echo Troponin/BNP
        iii. Tests 4 week visit: ECG/Echo + any abnormal 1 week lab
        iv. Tests 6 month visit: ECG, Echo + MRI if decreased function at presentation
        v. Tests 1 year visit: ECG, Echo + MRI if abnormal at 6 month

Appendix B. Text to include for PCP on hospital discharge

Your patient was diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C), which is an inflammatory condition that is temporally associated with the SARS-CoV-2 virus. As a newly emerging syndrome there is much that remains unknown and a multidisciplinary team will continue to follow your patient after discharge. Recurrence of symptoms such as fever, rash, abdominal pain, or altered mental status within the next 2-3 weeks should prompt medical evaluation.

MIS-C is thought to be a post-infectious inflammatory process; however, some patients will test positive for SARS-CoV-2 PCR and these patients should remain in home isolation until 3 days after resolution of fever and other symptoms, and 10 days since symptoms first appeared.

Your patient will follow-up with our MIS-C multidisciplinary team within one week of discharge and will update you on any changes in clinical status or plan of care. We also recommend patients follow-up with their primary care providers by telephone within a few days of discharge.

With specific questions about the care of these patients, call 615-835-8088, which will connect you with the on-call provider for Pediatric Infectious Diseases.