**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 markers of inflammation
- Evidence of inflammation, common values:
  - CRP >3 mg/dL, ESR >40 mm/h, ferritin >5000 ng/mL, ANC >7700, ALC <1500, platelet <150K, D-dimer >2 ug/mL, fibrinogen >400 mg/dL, albumin <3 g/dL, anemia, ALT >40 U/L, INR >1.1
- Other: AKI, hyponatremia, high LDH, high troponin, BNP >400 pg/mL, 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
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.

Indications for therapeutic dosing of anticoagulation (heparin or enoxaparin):
- Documented thrombosis (also consult hematology)
- Moderate to severe ventricular dysfunction per cardiology
- Coronary aneurysm Z score >10
- More than one of the following:
  - Personal history of thrombosis
  - History of acquired or inherited thrombophilia
  - Sedated and muscle-relaxed
  - D-dimer >3 mcg/mL and up-trending
  - Any rhythm abnormalities: heart block, etc.
  - Inotropic infusion
  - Central venous catheter
  - Age >13 years

Contraindication to anticoagulation: Active major bleeding
Discontinue prophylactic LMWH at discharge or earlier if patients are ambulatory with near-normal inflammatory markers. Continue therapeutic dosing while indicated and formulate outpatient plan with consultants.
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)
### 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 arrhythmia
- 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)

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

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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).
Summary of Version Changes

- **Version 1.0 (7/9/2020):** Go live.
- **Version 2.0 (8/13/2020):** Removed CK and triglycerides from Labs. Added consult with Cardiology with Echo and added Indications for therapeutic dosing of anticoagulation to Treatment page.
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.
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.
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References


References (continued)

