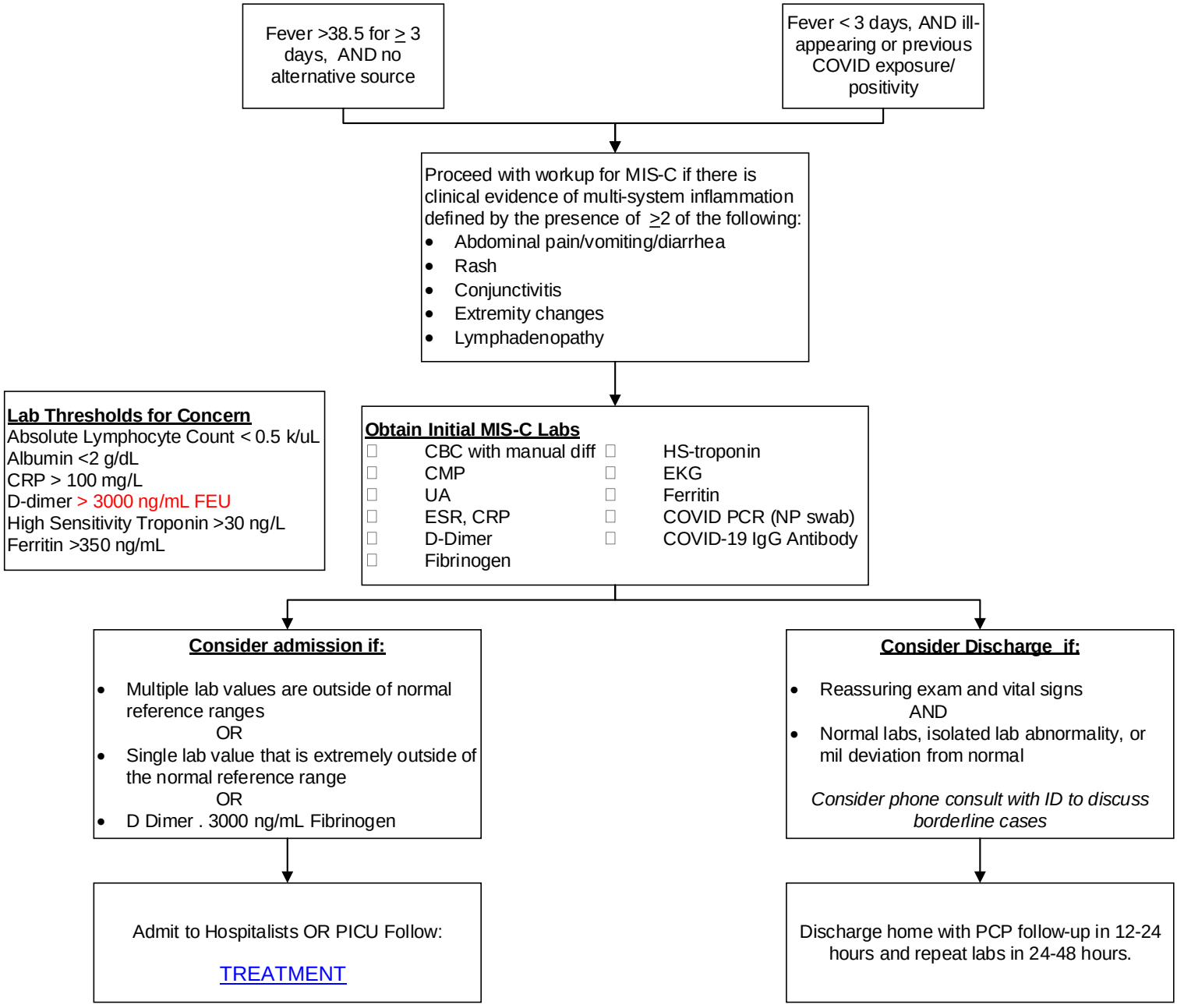
Clinical Pathways Program

Guideline: Management of Multisystem Inflammatory Syndrome in Children, INPATIENT

Spectrum Health Contact: Rosey Olivero Updated/reviewed: December 11, 2020

Clinical algorithm:



Clinical guideline summary

CLINICAL GUIDELINE NAME: Management of Multisystem Inflammatory Syndrom in Children

PATIENT POPULATION AND DIAGNOSIS: Age <21 years Multisystem Inflammatory Syndrome in Children (MIS-C)

APPLICABLE TO: All Spectrum Health Sites

BRIEF DESCRIPTION: Multisystem Inflammatory Syndrome in Children (MIS-C) is a syndrome that follows a SARS-CoV-2 infection or exposure. The clinical presentation is accompanied by significant hyper-inflammation that can have some similarities to Kawasaki Disease and Toxic Shock Syndrome and can lead to organ dysfunction and shock. The pathogenesis is unclear, but in most cases develops 2-8 weeks after a COVID-19 infection of exposure. In most cases, MIS-C is post-infectious, but occasionally occurs during acute respiratory COVID-19

OVERSIGHT TEAM LEADER(S): Andrea Hadley MD, Rosemary Olivero

OWNING EXPERT IMPROVEMENT TEAM (EIT): N/A

MANAGING CLINICAL PRACTICE COUNCIL (CPC): COVID-19 CPC

OTHER TEAM(S) IMPACTED (FOR EXAMPLE: CPCs, ANESTHESIA, NURSING, RADIOLOGY): Children's health CPC, Nursing

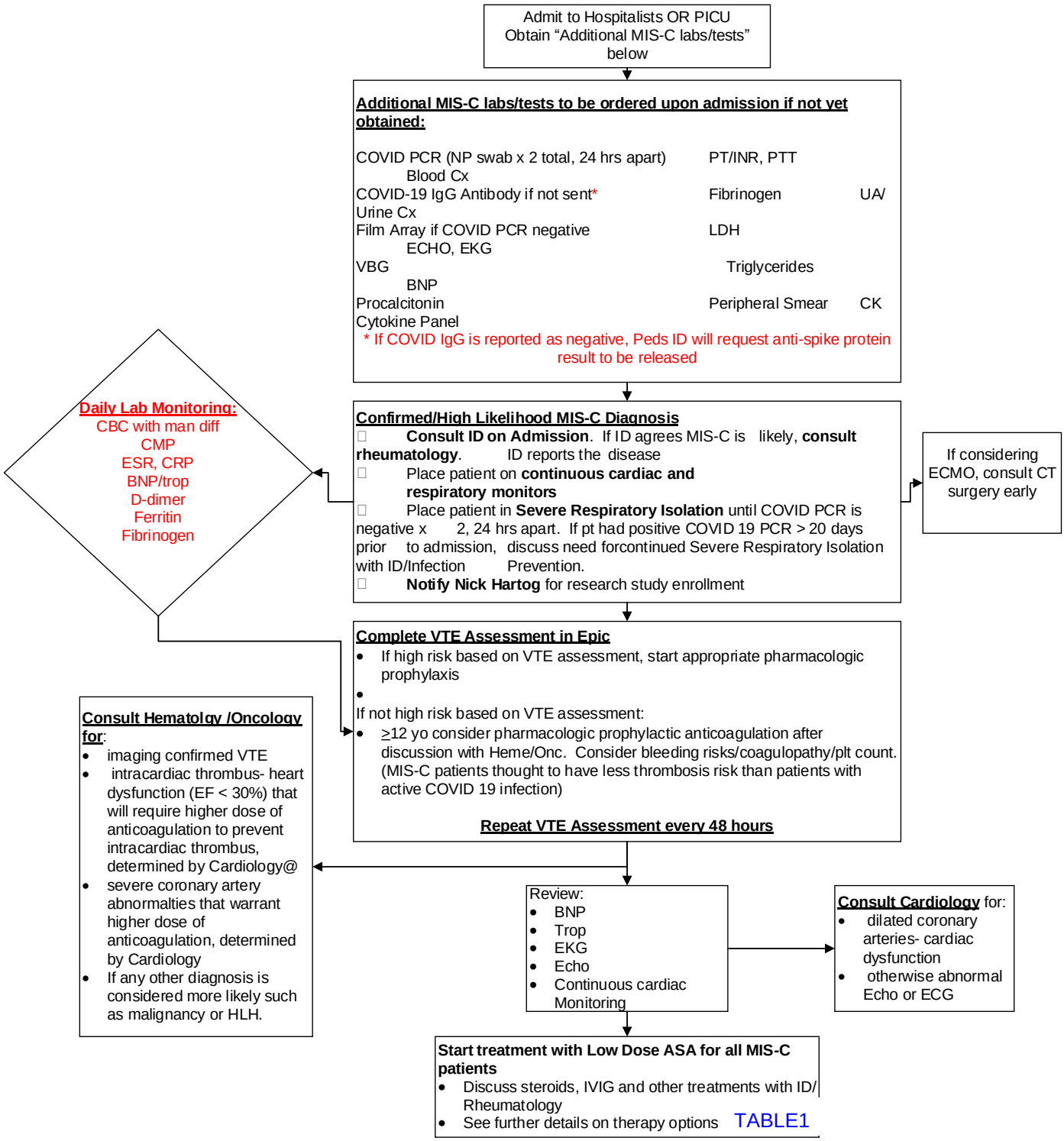
IMPLEMENTATION DATE: 6/10/2020

LAST REVISED: 12/11/2020

FOR MORE INFORMATION, CONTACT: Andrea Hadley or Rosemary Olivero

Clinical pathways clinical approach

TREATMENT AND MANAGEMENT:



The CDC has 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 this document for your reference as well.

CDC MIS-C definition
WHO MIS-C definition

Table 1. Medications

Medications	Dose	Route	Comments
Immunosuppressive Agents			
IVIG	2g/kg/dose (max = 100 grams)	IV	Infuse IVIG over 12-48 hours; consider fluid status
Steroids	Methylprednsione/Prednisone/Prednisolone 1-2 mg/kg/day divided BID, wean over 2-4 wks Consider a pulse 30 mg/kg/day once, max 1000 mg in certain severe cases	IV/PO IV	Infuse over 45 minutes, give daily for 1-3 days.
Anakinra	2-10 mg/kg once a day	SC	Dose can be escalated pending the response.
Remicade	5-7 mg/kg/day	IV	Discuss with Rheumatology
Antiplatelet / Anticoagulation			
Aspirin (ASA)	3-5mg/kg/day, max=81mg	PO	Continue approximately 4-6 weeks.
Enoxaparin (aka LMWH) (Prophylaxis dosing)	< 2months: 0.75mg/kg/dose q12 hours ≥ 2months and < 60kg: 0.5mg/kg/dose q12 hrs ≥60kg: 40mg daily (40mg q12 hours in adolescent, and critically ill	SQ	Not to be used if acute kidney injury and CrCl <30 mL/min Monitoring for prophylaxis dosing is optional. Obtain if there is new bleeding, change in liver or renal function, or in critically ill pts. If monitoring, check LMWH level 4 hours after 3rd - 5th dose. Target 0.2-0.4 units/mL
Enoxaparin (aka LMWH) (Therapeutic dosing)	< 2months 1.5 mg/kg/dose q12 hours ≥ 2months: 1 mg/kg/dose q12 hours	SQ	Not to be used in patient with acute kidney injury and CrCl <30 mL/minute Check LMWH level 4 hours after 3rd - 5th dose Target > 0.5-1.0 units/mL, Dose adjustment by Heme/Onc
Unfractionated Heparin (UFH) (Prophylaxis dosing)	Any dose ≤ 10 units/kg/hr	IV	No monitoring required unless signs or symptoms of bleeding, or patient was coagulapathic to begin with. Significant number of patients who are critically ill or with COVID have antiphospholipid antibodies. aPTT may be unreliable. If aPTT is prolonged at baseline, use Unfractionated Heparin assay (anti-Xa for UFH).

Unfractionated Heparin (UFH) (Therapeutic dosing)	Any dose > 10 units/kg/hr	IV	Baseline labs prior to initiation of heparin: aPTT, PT/INR, CBC. Significant number of patients who are critically ill or with COVID + on PCR have antiphospholipid antibodies. aPTT may be unreliable lab. If aPTT is prolonged at baseline, use Unfractionated Heparin assay (anti-Xa for UFH). Utilize age-specific UFH titration nomogram for dosing and monitoring using aPTT or Unfractionated Heparin Level Anti-Xa Assay to monitor.
Unfractionated Heparin (UFH) (Prophylaxis ONLY)	< 60kg: 75 units/kg/dose SQ every 12 hours ≥60kg: 5000 units every 12 hours >18 yrs or >125 kg: 5000 units SQ every 8 hrs	SQ	SQ UFH is used for prophylaxis only if number of lines/lumens are limited AND patient can't have LMWH.

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.

If MIS-C is diagnosed, notify Nick Hartog to consent patient for the **COVID Human Genome Effort** study. This study is an international effort to characterize genetic abnormalities that predispose otherwise healthy individuals to MIS-C and severe COVID-19 disease. Enrolled patients will have blood drawn at one time point and genetic sequencing completed and evaluated. Please contact Nick Hartog or see www.COVID-hge.com for more details on study

Treatment

If MIS-C is suspected based on the above workup, treatment approach will be individualized and multidisciplinary in nature and should involve discussion between ID, rheumatology, hematology and cardiology when indicated, and hospitalist/PICU teams.

Table 2. Discharge Coordination and Follow-up

Specialty	Instructions	Orders/ Instructions
Primary Care Physician	Hospitalist team to contact PCP prior to discharge to provide verbal handoff and summary of hospital course.	Hospital follow-up with PCP recommended within 1 week Patient/PCP to contact ID clinic with any clinical change/ fevers PCP to also monitor for side effects related to medications Annual influenza vaccination is recommended Reminder: no live vaccines for 11 months if pt received IVIG Return to School instructions per ID/rheum Return to Sports intsructions per Cardiology

Cardiology	Continue aspirin for 4-6 weeks	Cardiology Visit (new Consult or follow up) and Echo at 2 weeks and 4-6 weeks
Hematology and Oncology	Follow up required only if patient has: - documented VTE - intracardiac thrombus - cardiac dysfunction	Discuss with Chi Braunreiter or Ali Mastin via PerfectServe - LMWH level in approximately 2-4 weeks if on lovenox - Repeat imaging of confirmed VTE in approximately 4-6 weeks
Infectious Disease	Follow up at ~2 weeks and 4-6 weeks after discharge	Echos to be ordered by ID RN ID RN to report to state (if not already done) ID to coordinate labs if KD only (not MIS-C) Rheum to coordinate labs if MIS-C
Rheumatology	Follow up at about 1 week after discharge	Follow up may occur in person or via telemedicine depending on patient. Patient will have labs done (ordered by Rheum for prior to or on day of follow up).

Follow-up Details based on Patient Characteristics

MIS-C with aneurysms:

- Rheum does telemed visit and labs ~1 week out and defines the lab plan for the rest of the course
- ID does follow-up visit (in person) ~2 weeks out and carries out lab plan and Echo
- Rheum, ID and Cards does follow-up visit (in person) ~4-6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

MIS-C without aneurysms:

- Rheum does telemed visit and labs ~1 week out and defines the lab plan for the rest of the course
- Rheum does follow-up visit (in person) ~2 weeks out and carries out lab plan and Echo
- Rheum, ID and Cards does follow-up visit (in person) ~4-6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

KD (with or without aneurysms) but NOT diagnosed with MIS-C:

- ID does follow-up visit (in person) ~2 weeks out, carries out lab plan and Echo
- ID and Cards does follow-up visit (in person) ~6 weeks out, carries out lab plan and Echo
- Long term follow-up with Cards

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
    - 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

References:

Multisystem Inflammatory Syndrome in U.S. Children

Lupus Anticoagulant in Patients with Covid-19 | NEJM

American College of Rheumatology Clinical Guidance for MISC