Michigan Medicine

Clinical Practice Guideline

Multisystem Inflammatory Syndrome in Children (MIS-C)

I. OVERVIEW

Recognized shortly after the start of the COVID-19 pandemic in 2020, Multisystem Inflammatory Syndrome in Children (MIS-C) is a post-infectious hyper-inflammatory process that follows a SARS-CoV-2 infection and can progress to organ dysfunction and shock. The clinical features of MIS-C may overlap with typical febrile illnesses of childhood, as well as more commonly seen inflammatory states, such as Kawasaki Disease or Toxic Shock Syndrome. MIS-C typically presents 2 to 6 weeks after an infection with SARS-CoV-2, and an increase in MIS-C cases frequently follows an increase in local SARS-CoV-2 infections. Recommendations for the management of MIS-C continue to evolve, as more information about the pathophysiology, natural history, and sequelae of the illness becomes available.

Michigan Medicine has developed a clinical practice guideline for Multisystem Inflammatory Syndrome in Children based upon current medical literature as well as expert opinion. The recommendations in our guideline are modified from the clinical guidance published by the American College of Rheumatology (ACR)(1), which has emerged as the most commonly used practice guideline at this time, after review and revision by pediatric specialists at C.S. Mott Children's Hospital. Our clinical guideline focuses on the evaluation, diagnosis, and treatment of the patient with confirmed MIS-C, but also supports the decision-making process before diagnosis, when MIS-C is merely suspected. It applies to patients who present to the Outpatient Clinics, Emergency Department, Inpatient Care and Intensive Care units.

Companion Documents:

American College of Rheumatology Care Guideline

II. PURPOSE

- Outline evidence-based diagnosis and management of patients with Multisystem Inflammatory Syndrome in Children (MIS-C)
- Provide recommendations to standardize the care of patients admitted for MIS-C, including monitoring, isolation, and physician consultations
- Establish a framework for the treatment decision-making process

III. SCOPE

This guideline provides recommendations for the care of patients with suspected MIS-C who are under the age of 21 and being managed in Michigan Medicine Primary Care Centers, as well as in the Emergency Department, Inpatient Units, and Intensive Care Units of Mott Children's Hospital. The guideline provides clinical guidance for the evaluation, diagnosis, monitoring, and treatment of MIS-C.

Clinical Specialties: General Pediatrics, Pediatric Emergency Medicine, Pediatric Hospital Medicine, Pediatric Critical Care Medicine, Respiratory Therapy, Nursing

Intended Users: Physicians, Advanced Practice Providers, Nursing, Respiratory Therapists

IV. DEFINITION

Mott Children's Hospital has adopted the case definition for MIS-C published by the CDC (2). In order to meet the case definition, patients must be under 21 years old and have:

- Fever, inflammation, and organ system involvement
  - Fever ≥ 38.0 °C for ≥ 24 hours
  - Hyperinflammatory state with one or more of the following: 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
  - Multisystem organ involvement with 2 or more systems: cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic
- No alternative diagnosis
  - MIS-C patients may also meet criteria for Kawasaki Disease; they should still be reported to the CDC as a case of MIS-C
- Recent SARS-CoV-2 infection
  - Diagnosed with nasopharyngeal PCR/antigen testing or via antibody serology

V. GUIDELINE

a) Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) was initially described in the spring of 2020 (3, 4, 5), in areas throughout the world that were hard hit by SARS-CoV-2 infection. The clinical syndrome presented with fever, hyperinflammation, and single or multiple organ dysfunction in patients who had recently had a SARS-CoV-2 infection and did not have an alternative diagnosis to explain their symptoms (6). Moreover, this apparently new illness did not fully overlap with any previously described inflammatory syndromes, such as Kawasaki Disease, Macrophage Activation Syndrome (MAS), Toxic Shock Syndrome, and Bacterial Sepsis.

Initial reports of patients with MIS-C were primarily descriptive in nature (7), without detailed guidance on screening, diagnosis, or treatment. Similar to other children's hospitals (8), Mott Children's Hospital convened a panel of experts who offered their initial opinions on which patients should undergo investigation and observation for MIS-C. Since the initial publication and subsequent revision of the Michigan Medicine MIS-C practice guideline, more information has been published regarding the diagnosis and optimal treatment of patients with MIS-C, allowing our recommendations to be further refined.

One of the most influential references that has emerged since MIS-C was recognized is the American College of Rheumatology's clinical guidance for the care of children with MIS-C. Based largely upon expert opinion, it has become the de facto standard of care in the United States. After discussion among Mott specialists taking care of MIS-C patients, Mott Children's Hospital has decided to adopt the ACR guideline as our standard. We have, however, made modifications to reflect local practice and to improve standardization of care at Mott.

b) Methodology

Methods Used to Collect/Select the Evidence:
Guideline authors and workgroup members performed searches of the medical literature including electronic databases (e.g., PUBMED) to collect evidence for review. Expert opinion and clinical experience were also considered for implementation of evidence into the guideline.

Disclaimer: This document is meant to provide a framework for patient care, and it is not meant to replace clinical judgment, nor does it intend to mandate practice for all patients. Instead, it serves as the preferred approach for most patients undergoing evaluation for MIS-C, while recognizing that some patients may fall outside the scope of this guideline. Providers caring for MIS-C patients should use this guideline to assist them in management.

c) Recommendations

The framework for our recommendations is the ACR Clinical Practice Guideline, although we have made modifications to reflect local practice and expert opinion.

(1) Inclusion Criteria
Patients included in this CPG are under 21 years of age and present to Michigan Medicine outpatient clinics, Emergency Department, Inpatient Care and Intensive Care Units.

Patients must have all of the following three criteria *or* a high index of clinical suspicion:

1. Fever ≥ 38.0 °C for ≥ 72 hours
2. Current or recent SARS-CoV-2 infection or a link to SARS-CoV-2 infection via exposure to a known infected person
3. At least 2 of the following clinical symptoms:
    - Rash
    - Gastrointestinal symptoms
    - Edema of the hands or feet
    - Oral mucosal changes
    - Conjunctivitis
    - Lymphadenopathy
    - Neurologic symptoms

(2) Exclusion Criteria
Patients who are found to have an alternative diagnosis or who do not otherwise fit the inclusion criteria.

(3) Prevention
Prevention of SARS-CoV-2 infection is the best way to prevent subsequent MIS-C. Vaccination against SARS-CoV-2 infection, masking, hand hygiene, social distancing, and contact tracing are the best methods to help prevent the spread of the virus at this time.

(4) Evaluation

(a) Step Wise Evaluation on Presentation

Please refer to Figure 1 and Table 1 for initial evaluation of MIS-C. Initial, Tier 1 laboratory investigation should be completed before deciding to proceed with subsequent, Tier 2 workup. The exception to this phased approach is the patient who is hemodynamically unstable, who should have both Tier 1 and 2 labs completed at the same time. The decision to move on to Tier 2 evaluation should be triggered by laboratory findings as noted in Table 2.

(b) Echocardiogram Timing

At this time, we do not recommend routine echocardiogram for all patients undergoing evaluation for MIS-C. An echocardiogram should be obtained for those with a clinical suspicion of decreased cardiac function, or to evaluate the coronary arteries if the clinical presentation overlaps with Kawasaki Disease. Note that there are instances in which a finding of decreased cardiac function may be too subtle to pick up on physical exam, but if seen on echocardiogram would alter the treatment plan.

(c) Daily Trending Labs

Once admitted, patients should have a daily CRP to trend for hyperinflammation. If elevated at the time of admission, BNP and Troponin should also be trended. Other laboratory values, such as CMP and CBC, do not need to be monitored daily unless there are ongoing clinical concerns.

(5) Consultation

Consultations should be based upon the index of suspicion for MIS-C and/or alternative diagnoses.

- Infectious Diseases should be consulted for patients in whom there is a high index of suspicion for MIS-C.
- Rheumatology should be consulted for patients in whom the diagnosis of MIS-C is uncertain or if the patient has refractory disease (i.e. continued fever after IVIG and steroids).
- Cardiology should be consulted if there are abnormal cardiac labs, an abnormal echocardiogram, or other cardiac concerns.
- Hematology should be consulted if the patient may require therapeutic anti-coagulation or if the patient's platelet count is less than 100,000.

(6) Admission, Monitoring, and Placement on the Floor

The decision to evaluate a patient for MIS-C in the outpatient versus inpatient setting should be based upon the clinical assessment of the care team. Please refer to Table 3 for indications that should prompt admission. Patients who appear clinically well, do not have any indications for admission listed in Table 3, and have no barriers to follow-up can continue evaluation in the outpatient setting or be discharged from the ED.

Hemodynamically stable patients undergoing evaluation for MIS-C may be admitted to the inpatient floor or moderate care, as appropriate for their clinical condition. While on the floor, patients should be monitored on a cardiorespiratory monitor with continuous pulse oximeter.

Patients who are not felt to be stable for the floor should be evaluated for possible admission/transfer to the Pediatric Intensive Care Unit.

(7) Isolation/Precautions

Patients with MIS-C are presumed to have current or recent SARS-CoV-2 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.

- In order to discontinue special pathogen precautions, patients will need a negative SARS-CoV-2 PCR swab. They should remain in special pathogen isolation until their PCR testing 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

(8) Treatment/Management

The decision to begin treatment should be based upon the clinical severity of the patient's illness, after discussion among the members of the care team. Close monitoring alone may be an option in some circumstances. Please refer to Figure 2.

(a) Immunomodulatory Treatment

(i) First-line treatment

- IVIG 2 g/kg x 1 dose (based upon ideal body weight if BMI ≥ 30kg/m^2); max dose 100 g
  - In the setting of cardiac dysfunction with concern for fluid overload, consider IVIG 1 g/kg q24h x 2 doses; max dose 50 g
- Methylprednisolone 1-2 mg/kg/DAY IV divided BID
  - In cases of clinical ambiguity, consider delaying steroids until all workup is completed.

(ii) Treatment-refractory MIS-C

- Steroid-sparing agents
  - High dose anakinra 5-10 mg/kg/DAY IV/SubQ divided q6h-q24h, in cases WITH features of MAS; max dose 100 mg IV/SubQ q6h

  OR
  - Infliximab 5-10 mg/kg x1 dose, in cases WITHOUT features of MAS
- May also consider high-dose methylprednisolone 10–30 mg/kg/DAY; max 1000 mg/DAY
- Avoid repeating IVIG

(b) Antiplatelet Therapy

(i) Low-dose aspirin (3-5 mg/kg/DAY; max dose 81 mg) for all patients

- Continue for minimum 6 weeks, until platelet count has normalized and patient is cleared by Cardiology

(c) Anticoagulation Therapy

(i) Treatment anticoagulation (must meet one of the following criteria):

- Confirmed thrombosis
- Ejection fraction less than 35%. Treatment dosing is continued until ejection

fraction is greater than 35%
- Z-score ≥ 10

(i) Prophylactic anticoagulation
- Consider in patients with MIS-C and meeting one or more of the following risk factors:
  a. Central venous catherization
  b. Age > 12 years
  c. Malignancy
  d. ICU admission
  e. D-dimer level ≥ 5 x upper limit of normal

(9) Follow Up

We recommend close follow-up of all MIS-C patients to monitor their recovery.

- Primary care: All patients with MIS-C should follow up with their primary care provider after discharge.
- Cardiology:
  - At 2 weeks, with repeat BNP, troponin, and echocardiogram
    - Decision to return to normal activity can be made depending on the results of the echocardiogram
  - At 6 weeks, with repeat echocardiogram
    - May discontinue aspirin if echocardiogram within normal limits
    - Further cardiology follow-up to be determined on an individual basis
- Other subspecialties: No routine follow-up is recommended. Rather, follow-up visits with subspecialty providers should be decided with the treatment team on an individual basis, depending upon the patient's course and medical needs at the time of discharge.

REFERENCES

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Table 1.

Tier 1, Tier 2, and Daily laboratory evaluation for patients under consideration for MIS-C. See Table 2 for parameters to initiate Tier 2 workup.

Tier 1	Tier 2	Daily
CBC CMP ESR CRP Ferritin	BNP Troponin T Procalcitonin PT, PTT, D-dimer Fibrinogen LDH Urinalysis Cytokine Panel Triglycerides Blood Smear EKG SARS-CoV-2 Serology (nucleocapsid and spike protein antibodies)	CRP BNP and Troponin if elevated in Tier 2 Consider CMP, CBC if clinically appropriate

Table 2.

Abnormal laboratory findings in Tier 1 workup that should trigger further investigation with Tier 2 workup. Both number 1 and 2 must be present. Note neutrophil and albumin levels should be compared to age-appropriate, normal lab values.

Abnormal Labs to Trigger Tier 2
1. CRP ≥ 3 mg/dL or ESR ≥40 mm/hr 2. At least one of these: • ALC <1,000/uL • Platelets <150,000/uL • Na <135 mmol/L • Neutrophilia • Hypoalbuminemia

Table 3.

Admission and Discharge criteria for patients undergoing MIS-C evaluation in the outpatient clinics or Emergency Department.

Indications for Admission
Abnormal vital signs
Ill-appearance
Neurologic deficits or change in mental status
Evidence of renal or hepatic injury
Markedly elevated inflammatory markers
Abnormal EKG, B-type natriuretic peptide (BNP), or troponin T

Criteria for Discharge
Well-appearance
No indicators for admission as listed above
Family able and comfortable continuing to monitor at home
Reliable phone and transportation
Able to follow up with PCP within 24‑48 hours
Have an identified ED within 30 minutes of home address

Table 4.

Indications for Echocardiogram
Abnormal BNP or Troponin within Tier 2 evaluation
All patients with Kawasaki-like presentation
All patients with other signs/symptoms of cardiac dysfunction
All patients being treated for MIS-C (or strongly considered for treatment)

Figure 1.

Initial phased evaluation of the patient presenting with possible MIS-C

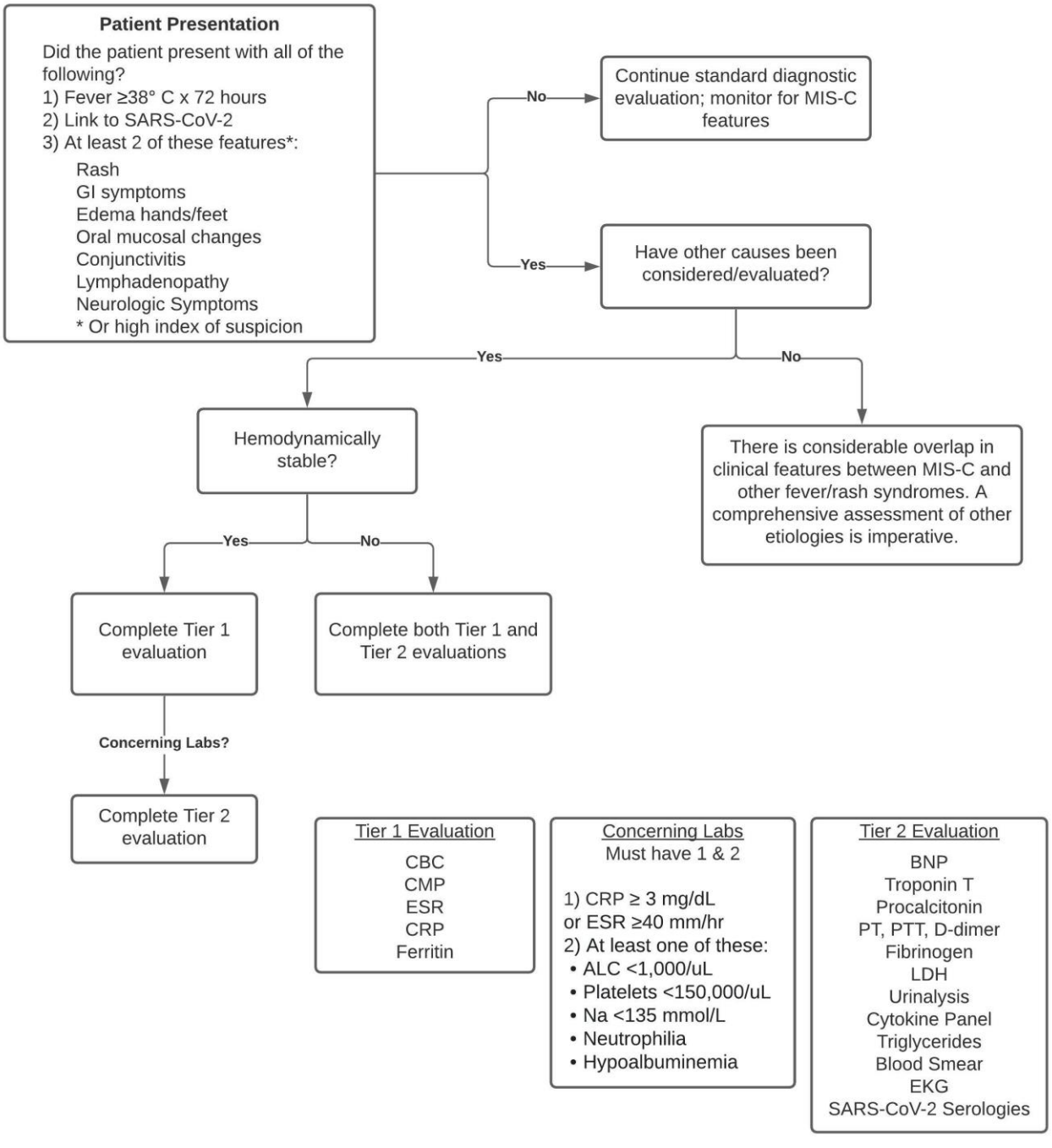
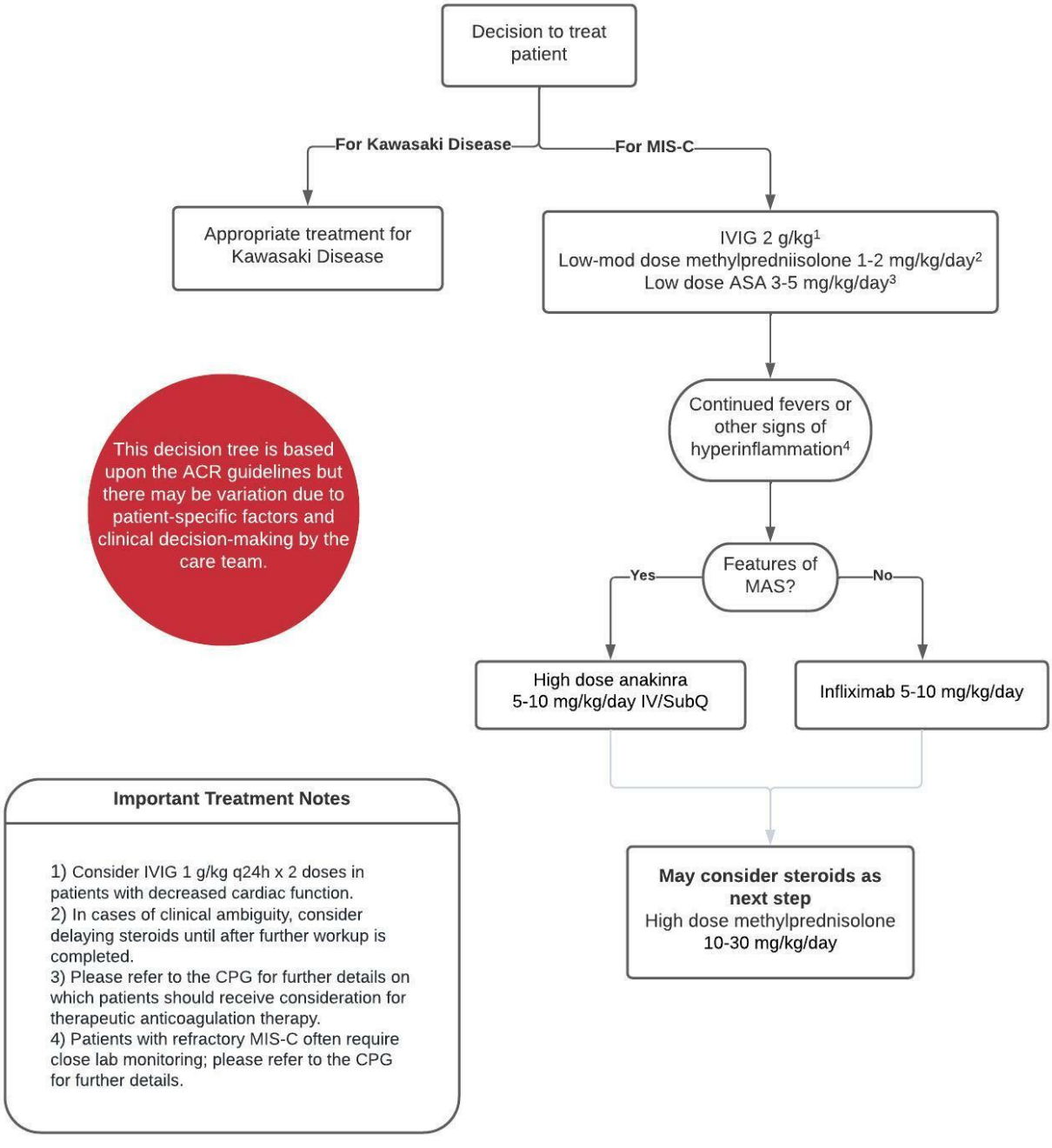


Figure 2.

Treatment algorithm for MIS-C.



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