

Initial Evaluation, Diagnosis and Management of Patients with Suspected Multi-System Inflammatory Syndrome in Children (MIS-C)

Authors: Members of the Divisions of Pediatric Infectious Diseases, Pediatric Cardiology, Pediatric ED, Pediatric Hospital Medicine, Pediatric Intensive Care, Pediatric Allergy and Immunology Pediatric Hematology / Oncology, Pediatric Pharmacy

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 This is a rapidly evolving situation and contents of this document may become outdated.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):

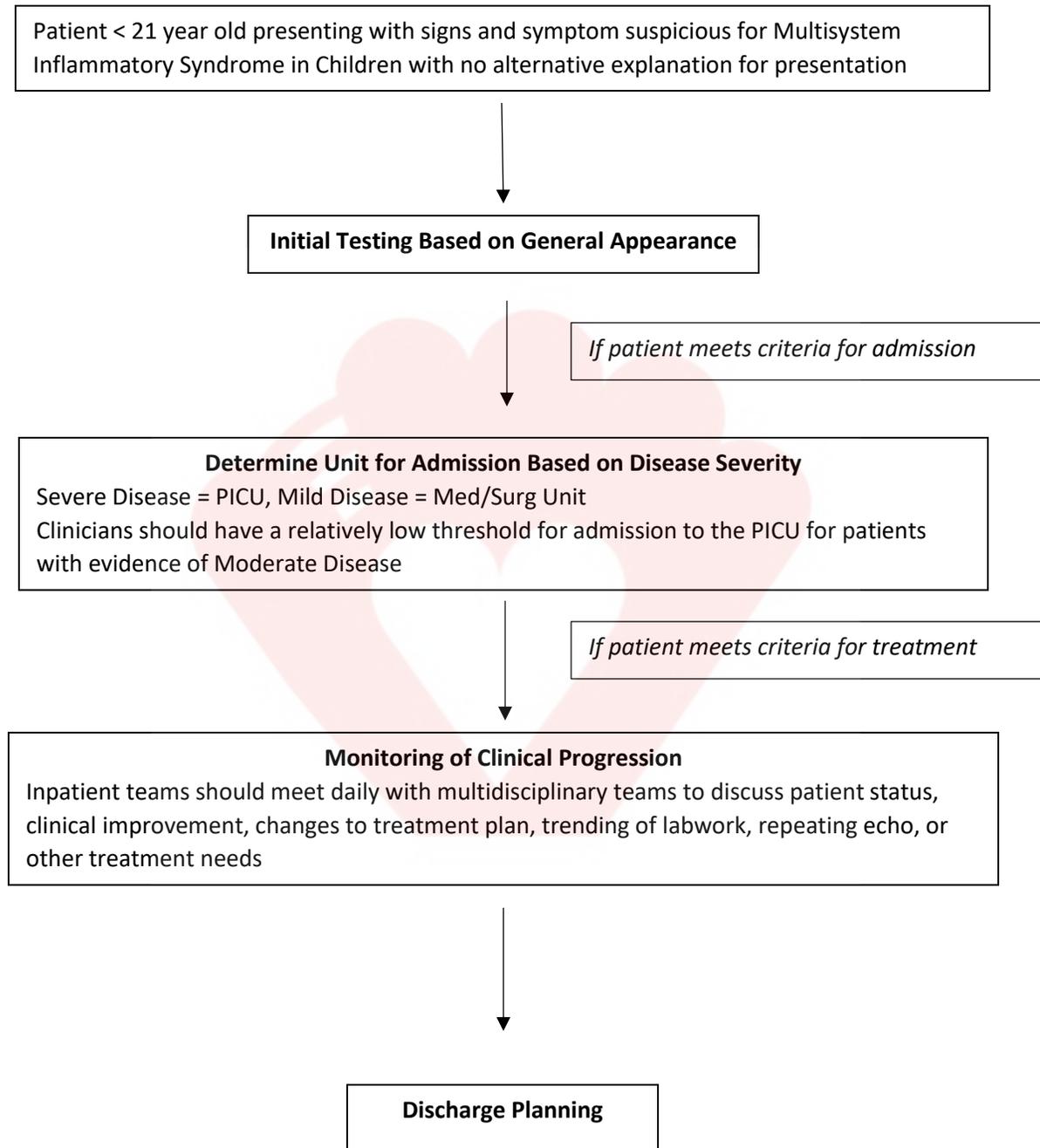
1. An individual aged < 21 years presenting with feverⁱ, laboratory evidence of inflammationⁱⁱ, and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
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

This clinical guideline is intended as an evidence-based guide for clinical care and not as a replacement for clinical decision making

Multi-system Inflammatory Syndrome in Children (MIS-C) Clinical Practice Guideline



MIS-C should be considered in the following pediatric patients:

- **Fever** - > 38.0 C for > 24 hours, though fevers typically last for at least 3 days
- **Prior history of COVID or close contact with known COVID positive case**
- **No other plausible explanation for presentation**
- **Evidence of ≥ 2 systems involved**
 - **GI:** Severe abdominal pain, vomiting, diarrhea
 - **Neuro:** headache, changes in mental status
 - **Mucocutaneous:** findings seen in Kawasaki Disease, rash, oral mucosal changes, non-purulent conjunctivitis, extremity swelling/erythema
 - **Lymphatic:** cervical adenopathy > 1.5 cm
 - **Cardiac:** evidence of cardiogenic shock/dysfunction
 - **Hematologic:** petechiae, bruising
 - **Respiratory:** respiratory distress, hypoxemia
 - **Renal:** Oliguria



Emergency Department Pathway

Patient with Clinical Features Suspicious for MIS-C without Alternative Plausible Explanation

Recommended Initial Testing Based on General Appearance

More Well Appearing

Ill Appearing with Evidence of Shock And/Or Requiring PICU Admission

- **CBC with Differential**
 - **CMP**
 - **CRP**
 - **ESR**
 - **Other testing as indicated by presentation**
- Labs concerning for MIS-C include neutrophilia, leukopenia, hyponatremia, transaminitis, hypoalbuminemia, and elevated CRP/ESR*

- **SARS-CoV2 PCR**
- **SARS-CoV2 IgG**
- **CBC with Differential**
- **CMP**
- **CRP**
- **ESR**
- **Ferritin, D-dimer, LDH, PT/PTT, Fibrinogen**
- **Pro-BNP, Troponin, EKG, echocardiogram** (based on discussion with admitting physician)
- **Blood Culture**
- **Lactate**
- **Imaging based on patient presentation**
- **Discuss with consultants as needed**

Concerning Lab Abnormalities

Results and Exam Reassuring and otherwise Meets Discharge Criteria

- **SARS-CoV2 PCR**
- **SARS-CoV2 IgG**
- **Ferritin, D-dimer, LDH, PT/PTT, Fibrinogen**
- **Pro-BNP, Troponin, EKG, echocardiogram** (based on discussion with admitting physician)
- **Blood Culture**
- **Lactate**
- **Imaging based on patient presentation**
- **Discuss with consultants as needed**

Discharge Home with Appropriate Follow-up

- **Admission to Appropriate Unit (PICU, IMCU, Med/Surg)**
- **Consult ID and cardiology on all patients treated for MIS-c**
- **Consider other consults as listed in inpatient treatment section**

Disease Severity

DISEASE SEVERITY	CRITERIA
MILD	<ul style="list-style-type: none">• No vasoactive medication requirement• No respiratory support• Normal ventricular function on echo (if have results)
MODERATE	<ul style="list-style-type: none">• Concern for hemodynamics not responding to fluid administration OR• Potential need for vasoactive therapy OR• Supplemental oxygen requirement OR• Mild ventricular dysfunction (if have results)
SEVERE	<ul style="list-style-type: none">• Requiring vasoactive therapy to maintain hemodynamics OR• Non-invasive or invasive ventilator support OR• Moderate to severe ventricular dysfunction (if have results)



MIS-C Inpatient Pathway

Admit to Hospital Medicine or ICU

Precautions:

If SARS-CoV-2 PCR positive: enhanced respiratory
 If SARS-CoV-2 PCR negative: contact/droplet

Consultants:

- Treatment decisions should be made in concert with consulting services
- All patients with concern for MIS-C:
 - Cardiology
 - Infectious Diseases
- Consult based on clinical syndrome:
 - Hematology
 - Gastroenterology
 - Nephrology
 - Allergy/Immunology
 - Rheumatology

Studies: Refer to table

Treatment: Refer to algorithm

Discharge Criteria:

- Afebrile for at least 24 hours after IVIG, improved symptoms and lab abnormalities, and otherwise meeting routine discharge criteria
- Patients with myocardial dysfunction or coronary findings, complete repeat echo prior to discharge and discuss with cardiology prior to discharging patient

Follow up

- Infectious Diseases: every 2 weeks
- Cardiology
 - Myocardial dysfunction or coronary findings on last echo: 2 weeks
 - Normal echocardiogram: 4-6 weeks and 1 year
- Hematology (if patient is on enoxaparin): 2-4 wks

All cases of MIS-C will be reported to Department of Health

DIAGNOSTIC STUDIES		
On admission (if not obtained in ED)	Daily Labs	
IgG, IgA, IgM levels	CBC with diff	
Triglycerides	CMP	
Ferritin	CRP	
Fibrinogen, PT, PTT	Ferritin	
D Dimer, Troponin, BNP	Troponin, BNP (if abnormal)	
LDH	If evidence of acute kidney injury, please refer to AKI Clinical Practice Guideline for further work up	
SARS-CoV-2 PCR and Antibody		
EKG		
Echocardiogram (once decision is made to treat)		
GUIDANCE FOR TREATMENT BASED ON DISEASE SEVERITY		
	Mild	Moderate-Severe
IVIG*	<ul style="list-style-type: none"> • 2 G/kg x 1 (Max 100 G) follow infusion guidelines from Pharmacy Department. 	
Initial Steroids (Indication: fluid refractory hypotensive shock)	<ul style="list-style-type: none"> • No steroids 	<ul style="list-style-type: none"> • Methylprednisolone 2 mg/kg/day 1-2 x per day (Max 60 mg/day), followed by taper • If necessary due to clinical status: 10-30 mg/kg/day (max 1 g/day) IV q24 h x 3 days, then 2 mg/kg/day 1-2 x per day (Max 60 mg/day)
Steroid Taper (If started on steroids)	<ul style="list-style-type: none"> • Prednisolone 2 mg/kg/DAY 1-2 x per day (Max 60 mg/day) x 1 week, then 1 mg/kg/DAY x 1 week, then 0.5 mg/kg/DAY x 3 days, then 0.25 mg/kg/DAY x 3 days 	
Anticoagulation	<ul style="list-style-type: none"> • Start Aspirin 30-50 mg/kg/day (max 975 mg/dose) q6h • Once afebrile x 24 hours OR using steroids, reduce to Aspirin 3-5 mg/kg/day (max 81mg/day) • Avoid NSAIDs while on aspirin therapy • Enoxaparin indications: see attached Hematology guideline 	
Treatment Failure (fever 36hr after IVIG completion or recrudescence fever within 7 days, clinical worsening in 24hr, escalation of respiratory support, ICU transfer)	<ul style="list-style-type: none"> • Infliximab* (biosimilar) 10 mg/kg IV x 1 (Round dose to nearest 100 mg vial size) OR • Anakinra* 2-5 mg/kg/day (Max 100 mg/dose) IV or SC (IV preferred) in 1 or 2 divided doses; frequency may increase to q6hr in certain cases. 	

*Dosing is based on ideal body weight