Clinical Pathway
Multisystem Inflammatory Syndrome in Children
October 2021

Outcomes/Goals	1. Rapid identification and treatment of pediatric patients with possible MISC 2. Create a team-oriented approach to efficient and timely evaluation and work-up.
Inclusion Criteria	• Persistent unexplained fever ≥5 days OR • Fever ≥3d AND two or more organ system involvement (cardiac, renal, respiratory, GI, dermatologic, neurologic) OR • Fever AND critically ill (e.g. signs of shock, respiratory failure)
Exclusion Criteria	Patients 28 days and younger Sepsis or other explanatory illness—MIS-C is a diagnosis of exclusion
NURSE Documentation	Chief complaint. Onset of symptoms^. History of recent COVID exposure or infection. Assessment including hemodynamic status (core temp, skin changes, new rash, cap refill, urine output, pulse quality, neuro status). ^Clinical symptoms of MISC may include abdominal pain, diarrhea, vomiting, oral mucosal changes, rash, conjunctivitis, headache, meningitis, erythema or edema of the hands or feet, and lymphadenopathy, among others.
INTERVENTIONS Initiate on arrival	ESI Triage level II Full set of vitals including core temperature Apply cardiac monitor, continuous pulse oximetry Establish IV (2 if possible, largest size appropriate) Bedside CBG Oxygen for hypoxia
DIAGNOSTICS	**Initial Labs:** CBC with differential, CMP, ESR, CRP, troponin (random draw), NT pro-BNP, COVID-19 RT-PCR, COVID-19 Antibody, Blood culture, Respiratory pathogen PCR Panel **Additional Labs:** D-Dimer, PT/PTT, Fibrinogen, Ferritin, Triglycerides, LDH, CK, Blood gas with lactate, UA with microscopy **Additional Studies:** CXR, EKG, Echocardiogram
PHYSICIAN (LIP)	
Evaluation	Obtain Initial Labs. Add Additional Labs and consider additional studies if high suspicion for MIS-C or patient is critically ill Review MIS-C differential diagnosis (see pages 3 and 4)
Fluids	Normal Saline or lactated ringers to normalize perfusion (HR, BP, cap refill, pulses, mental status), with careful evaluation for fluid overload after each bolus (e.g. hepatomegaly, rales, etc.). Consider POCUS to evaluate cardiac function and IVC distensibility. ***If concern for cardiac dysfunction, exercise caution with fluid and favor early vasoactives.***
Medication Antibiotics	If concern for possible sepsis, treat with empiric antibiotics (see ED Sepsis Pathway)
Vasoactives	Epinephrine 0.05-1 mcg/kg/min (first line for 'cold' shock) Norepinephrine 0.05-1 mcg/kg/min (first line for 'warm' shock)
Dextrose	D10 5ml/kg for CBG <60
Antipyretics	Acetaminophen 12.5 mg/kg PO Ibuprofen 10mg/kg PO
ADMISSION	If exam and laboratory testing consistent with MIS-C, patient should be admitted. Admit to PICU if refractory shock, neuro deficits, respiratory failure, or cardiac dysfunction.

Clinical Pathway Decision Making Process

Multisystem Inflammatory Syndrome in Children

October 2021

Patient presents with either:
- Persistent unexplained fever ≥5 days

OR
- Fever ≥3d AND clinical concern^ for MIS-C with ≥2 organ systems involved

OR
- Fever AND critically ill (e.g. signs of shock, respiratory failure)

^Clinical features of MISC include 2 or more (common to less common):
- Gastrointestinal symptoms (abd pain, diarrhea, vomiting)
- Oral mucosal changes
- Rash
- Conjunctivitis
- Erythema or Edema of hands/feet
- Lymphadenopathy
- Neurologic symptoms

Signs of Shock?

NO → Obtain **Initial labs*** Consider **EKG, CXR, Cardiac POCUS**

YES → Obtain **Initial Labs*** AND **Additional Labs****
EKG
CXR

- **Initial Labs*:** CBC w/diff, CMP, ESR, CRP, Random Troponin, NT-Pro-BNP, COVID RT-PCR, COVID AB, Blood culture, RVP Panel
- **Additional Labs**:** D-Dimer, PT/PTT, Fibrinogen, Ferritin, Triglycerides, LDH, CK, Blood gas with lactate, UA with microscopy

1) CRP ≥30mg/L, ESR ≥ 40mm/h **AND**
2) At least 1 of the following:
   a. ALC < 1,000
   b. ANC >7,700
   c. Platelets < 150K
   d. Na < 135
   e. Albumin < 3
   f. ALT > 40
   g. NT-Pro-BNP>400
   h. Elevated troponin

NO → Reassuring exam and labs

YES → Obtain **Additional Labs****
EKG, CXR if not already done

Use ED Sepsis Pathway.
Fluid resuscitate but monitor closely for signs of cardiac dysfunction.
Vasopressors early
Antibiotics

Labs and exam consistent with MIS-C → Consult Peds ID
Consult Peds Cardiology if any e/o cardiac dysfunction

Labs or exam concerning but not consistent with MIS-C → Review Differential Diagnosis for MISC, including Kawasaki Disease

- Refractory shock or hypotension?
- E/o cardiac dysfunction or injury?
- Concern for respiratory failure?
- Altered mental status or neuro deficits?

YES → Alternative diagnosis requires admission?

YES → Admit to PICU, Tier 1 or 2 based on stability

NO → Admit to Inpatient

NO → Discharge with close follow-up

Treatment per multidisciplinary team for ***confirmed*** MIS-C may consistent of steroids, IVIG, biologics, thromboprophylaxis

Multisystem Inflammatory Syndrome in Children Rationale and Data

Goals of Clinical Pathway

1. Rapid identification and treatment of pediatric patients presenting with possible MISC.
2. Create a team-oriented approach to efficient and timely evaluation and work-up.

Definition of MIS-C

The CDC issued a Health Advisory on May 14, 2020, outlining the following 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 neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Definition and Frequency of Organ System Involvement

Organ System	Frequency	Manifestations
Gastrointestinal	92%	Nausea, vomiting, diarrhea, abdominal pain, pancreatitis, hepatitis, gall bladder hydrops or edema
Cardiovascular	80%	Hypotension or shock, BNP > 400pg/ml, elevated troponin, EF < 55%, congestive heart failure, coronary artery dilatation, pericarditis or pericardial effusion, cardiac dysrhythmia or arrhythmia, vasoactive support, CPR
Hematologic	76%	Total WBC < 4K, Neutrophilia, Lymphocytopenia, Anemia, Plts < 150K, deep vein thrombosis, pulmonary embolism, hemolysis, bleeding or coagulopathy, ischemia of extremity
Mucocutaneous	74%	Bilateral conjunctival injection, oral mucosal changes, rash, swollen red cracked lips, erythema/edema of hands, feet, periungual desquamation
Respiratory	70%	Respiratory insufficiency, severe bronchospasm, pulmonary infiltrates on radiograph, pleural effusion, pneumothorax, pulmonary hemorrhage, mechanical ventilation
Musculoskeletal	23%	Myositis or myalgias, arthritis or arthralgias
Renal	8%	Acute kidney injury
Neurologic	20-30%	Stroke or intracranial hemorrhage, seizures, encephalitis, demyelinating disorder, altered mental status, aseptic or culture-negative meningitis

Differential Diagnosis for MIS-C

Diagnosis	Differentiating features	Work-up/Management
Sepsis	Less likely to have cardiac involvement, coronary abnormalities	Antibiotics Aggressive treatment to normalize perfusion Refer to ED Sepsis pathway
Acute Covid	Loss of taste and smell Sore throat Headache Severe pulmonary involvement can occur but uncommon Myocardial dysfunction and shock less common GI symptoms less common Inflammatory markers less elevated	NSAIDs, APAP Supportive care Antiviral or glucocorticoids ***may*** be indicated in severely ill, hospitalized children—consult infectious disease Bacterial coinfection is uncommon
Kawasaki disease	Patients tend to be younger (infants and children) GI symptoms uncommon Myocardial dysfunction, shock less common (though are features of Kawasaki Disease Shock Syndrome) Usually normal or elevated platelets, ALC	Consult ID if suspicious High dose aspirin IVIG
Other viral infections (e.g. EBV, CMV, adenovirus, enterovirus, etc.)	May cause multisystem disease in immunocompromised children, rarely do so in immunocompetent ones Can uncommonly cause myocarditis	Consult ID if severe disease, uncertain diagnosis Inotropic support for myocarditis if necessary Serology or PCR to distinguish from MISC

Toxic Shock Syndrome	Rapid development of illness May be able to identify source (e.g. menstrual) Rash typically diffuse erythroderma ("sunburn rash")	Obtain cultures Antibiotics with Clindamycin AND Vancomycin
Staph Scalded Skin Syndrome	Generally children under 6 years of age Worsening erythema and bullae, painful skin	Obtain cultures Antibiotics with Oxacillin+/-Clindamycin If extensive may require burn center
Macrophage Activation Syndrome (MAS) /Hemophagocytic Lymphohistiocytosis (HLH)	Can occur in healthy children and those with underlying rheumatologic disease Can include multiorgan involvement, cytopenias, liver dysfunction Cardiac and GI involvement less common Neurological symptoms more common	Requires special immunologic testing Consult Peds Oncology
Myocarditis	May be a feature of MIS-C or have another cause (e.g. EBV, CMV, etc. as above)	Elevated troponin, elevated BNP EKG (often arrhythmias present) Echocardiogram (to identify cardiac dysfunction)
Drug Hypersensitivity Reactions	Fever, rash, arthralgias = serum sickness like reaction Fever, lymphadenopathy, eosinophilia, organ involvement (liver most common) = DRESS Erythematous macules with purpuric centers or diffuse erythema with mucosal involvement = SJS	Discontinue offending agent Treatment depends on diagnosis
Appendicitis	Overlaps with abdominal pain, vomiting, +/- diarrhea, but lacks cardiac and respiratory involvement, rash	Refer to ED Appendicitis pathway

References:

https://emergency.cdc.gov/han/2020/han00432.asp. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19).

Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. Published online ahead of print June 29, 2020. N Engl J Med. 2020;10.1056/NEJMoa2021680. doi:10.1056/NEJMoa2021680.

Children's Hospital of Philadelphia. Emergency Department, ICU and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome in Children (MIS-C).

Seattle Children's Hospital. COVID-19 Pathway v6.0

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19: Version 2. Arthritis Rheumatol 2021; 73; e13-e29

Johns Hopkins Children's Center. Peds ED MIS-C Guidelines. May 29,2020

Additional Pediatric COVID-19 and MIS-C Resources:

https://www.cdc.gov/mis/mis-c/hcp/index.html
https://pubmed.ncbi.nlm.nih.gov/33666649/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7905703/
https://pubmed.ncbi.nlm.nih.gov/34133855/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8405351/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7489842/