Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Diagnosis

Inclusion Criteria:

Patients in whom MIS-C should be considered, including:

- Age < 21 years, AND
- Fever ≥ 38.0 for ≥ 3 days or ≥ 1 day if ill-appearing, AND
- Presence of ≥ 3 symptoms from any or all categories reported with MIS-C **(See Table 1),** AND
- No alternative plausible diagnosis

OR

- Patients in whom there is concern for Kawasaki disease (KD)

Exclusion Criteria:

Patients who do not meet all of the inclusion criteria

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Evaluate for other appropriate diagnosis

Table 1. MIS-C Presenting Symptoms from Case Reports

Category	Presenting Symptom
Systemic	Fever (median duration 4 days)
	Myalgia
	Lymphadenopathy
	Shock
Mucocutaneous	Rash/skin desquamation
	Conjunctivitis
	Lip redness / swelling
Respiratory	Cough
	Dyspnea
	Hypoxia
Cardiovascular	Myocardial dysfunction
Gastrointestinal	Abdominal pain
	Vomiting
	Diarrhea
Renal	Acute Kidney Injury
Neurologic	Headache
	Lethargy
	Confusion
	Stiff neck
	Vision changes
Musculoskeletal	Swollen hands & feet

Centers for Disease Control and Prevention (CDC) definition of MIS-C includes:

- ✓ Age < 21 years
- ✓ Fever ≥ 38.0 for ≥ 24 hours
- ✓ Laboratory evidence of inflammation
- ✓ Organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
- ✓ No alternative plausible diagnoses
- ✓ 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

Evaluation

Lab

- ❑ SARS CoV-2 RT-PCR NP Swab AND SARS-Co-2 antibody – IgG
- ❑ Respiratory Pathogen PCR Panel
- ❑ Tier-1: Blood work: CBCD, CMP, CRP, ESR, coagulation studies with D-dimer, blood culture
- ❑ If patient in shock, send Tier-2 labs on initial evaluation
- ❑ Tier-2: If abnormal ESR, CRP or CBCD (ALC < 1000, Plt <150 K), then send ferritin, pro-BNP, troponin
- ❑ Consider saving Mint gel top if further testing required
- ❑ Consider urinalysis and urine culture if concern for urinary tract infection
- ❑ For severe MIS-C (See Page 2, Table 2) , consider obtaining triglycerides, LDH, Cytokine levels, soluble IL-2, NK Cell function

EKG

- ❑ Obtain for all patients that meet CDC criteria for MIS-C

Echo

- ❑ Perform if there is fever and any of the following:
  - o Hemodynamic instability
  - o Elevated troponin or pro-BNP
  - o Abnormal EKG
  - o Suspicion for complete/ incomplete KD

Echo should evaluate:

- ✓ Coronaries: left main, proximal and distal left anterior descending, proximal and distal right, and posterior descending coronary arteries for dilation, course (tapering or not tapering), aneurysm, echo bright walls, thrombus
- ✓ Valvar function
- ✓ Ventricular function
- ✓ Pericardial effusion

Other

- ❑ Perform other organ specific evaluation based on patient's presenting symptoms
  - o GI: Other infectious studies, KUB, abdominal ultrasound or CT
  - o Neuro: Head imaging-CT/MRI, LP, EEG

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Associated Policies: n/a

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Disposition

Determine patient disposition based on initial presentation and work-up	
Discharge home with PCP follow up	Well appearing patient and not meeting other admission criteria
Possible hospital admission	Any of the following: ❑ ESR ≥ 40 ❑ CRP ≥3 ❑ Lymphopenia < 1K ❑ Thrombocytopenia < 150K
Hospital admission	Any of the following: ❑ Unstable vitals ❑ Requires ongoing resuscitation ❑ Meets criteria for admission: e.g. oxygen, IV fluids or IV medications ❑ Concerns for KD
Transfer to higher level of care	❑ Hospital *without* inpatient pediatric service: Transfer to LPCH upon diagnosis of MIS-C ❑ Hospital *with* inpatient pediatric service: Transfer to Children's hospital if patient with moderate to severe MIS-C and / or signs of end organ injury (See table below)

Inpatient Management

Management Strategy (See Page 3 for other management considerations)

Disease	COVID-19 associated KD-like illness	MIS-C		
		Mild	Moderate	Severe
Definition	Meets criteria for complete/incomplete KD but without shock or multisystem involvement	NO vasoactive support Minimal organ injury	*VIS ≤10 Mild or single organ injury	*VIS > 10 Severe organ injury or multi-organ involvement
Medications				
Methylpred-nisolone	NA	**Consider 2 mg/kg/day tapered over 2 weeks	2 mg/kg/day tapered over 2 -4 weeks	30 mg/kg/day (max 1,000 mg) x 3 days followed by 2 mg/kg tapered over 4-6 weeks
IVIG	2 g/kg IV over 12-18 hours (max dose 100 grams)	**Consider 2 g/kg IV over 12-18 hours (max dose 100 grams)	2 g/kg IV over 12-18 hours (max dose 100 grams)	2 g/kg IV over 12-18 hours (max dose 100 grams)
Aspirin	30-50 mg/kg/day divided q6hr until defervescence After defervescence: low dose (3-5mg/kg/day; max 81 mg/day) until confirmed normal coronary arteries at ≥4 weeks after diagnosis Hold if platelet count <50K	NA	NA	NA
Interleukin Antagonists	NA		Anakinra (IL-1 R inhibitor) 2-4 mg/kg subQ or IV daily (max 100 mg/day)	Anakinra (IL-1 R inhibitor) 10 mg/kg subQ or IV daily to q6 (max 100 mg/day) If refractory to Anakinra (persistent fever or ferritin > 1,000), change to Tocilizumab (IL-6 inhibitor) if weight < 30 kg 12 mg/kg IV, if weight > 30 kg 8 mg/kg IV (max 800mg)
Other	NA	Consider treatment for sepsis	Consider treatment for septic shock	Consider treatment for septic shock
Consults				
	▪ Required: Infectious Disease, Cardiology ▪ Rheumatology: if considering steroids or infliximab	▪ Required: Infectious Disease, Cardiology, Rheumatology ▪ Hematology: if extra-cardiac thrombosis or considering low molecular weight heparin ▪ Nephrology: for fluid-unresponsive acute kidney injury ▪ Dermatology (optional for diagnostic purposes)		

***Vasoactive-Inotropic Score (VIS)** = dopamine dose (μg/kg/min) + dobutamine dose(μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10,000 x vasopressin dose (U/kg/min) + 100 x norepinephrine dose (μg/kg/min)

** Patients who have defervesced and have improving clinical and laboratory parameters may not need either IVIG or steroids.

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Inpatient Management

Other Management Considerations

Antimicrobials

Antivirals

In consultation with Pediatric Infectious Diseases, remdesivir may be considered for patients with suspected/confirmed MIS-C on a case-by-case basis, although the role of antiviral medications is not clear in this setting.

Antibiotics

Children with suspected/confirmed MIS-C who meet the criteria for septic shock should receive broad spectrum antibiotics per the LPCH Severe Sepsis/Septic Shock Pathway. For children with features of toxic shock syndrome, the addition of clindamycin can be considered. Antibiotics should otherwise be directed towards any infectious conditions present at the time of MIS-C diagnosis (e.g., ceftriaxone and vancomycin for patients with suspected meningitis). The rate of bacterial co-infection in children with MIS-C appears to be very low. Antibiotic use should be re-evaluated daily, and, if there is no evidence of bacterial infection, antibiotics should be de-escalated or discontinued.

Anticoagulation

Prophylactic

- ≥ 14-18 years of age: Consider prophylactic anticoagulation
- > 18 years of age: Recommend prophylactic anticoagulation
- Risk factors: malignancy, critical illness, obesity, pre-existing inflammatory disease, history of thrombosis, inherited thrombophilia, sickle cell disease, immobility, indwelling central lines
- Echocardiogram findings of concern: left atrial spontaneous echo contrast ("smoke") or left ventricular noncompaction cardiomyopathy
- Contraindications: active bleeding, platelet count < 50,000

Prophylactic anticoagulation regimen:

- < 50 kg: enoxaparin 0.5 mg/kg subQ q12h
- ≥ 50 kg enoxaparin 40 mg subQ q24h

Monitoring:

Consider checking anti-Xa level with goal 0.2-0.4 IU/ml for patients with renal disease, cardiac disease, or BMI > 40 kg/m^2

Therapeutic

- From existing data, thus far MIS-C has not been associated with an increased incidence of thrombosis. We do not recommend empiric therapeutic anticoagulation in children with MIS-C.
- Consider therapeutic anticoagulation in case of:
  - Thrombosis documented, and/or
  - Large and giant coronary aneurysms (coronary dimensions adjusted for BSA (z scores) > 10)
- Contraindications: active bleeding, platelet count < 50,000

Therapeutic anticoagulation plan (use either enoxaparin or unfractionated heparin):

Enoxaparin

- 1 mg/kg subQ q12h
- anti Xa goal 0.5-1.0 IU/ml
- Anti-Xa level should be drawn 4 hours after third or fourth dose

Unfractionated Heparin

- Administer & titrate per heparin order set
- Heparin activity level (HAL) goal 0.3-0.7 U/ml

Supportive Care

Respiratory Support

- Given available adult data, early intubation is not required in COVID-19 patients. Patients appear to present as comfortably tachypneic.
- Intubation should be considered if progressive hypoxemia, altered mental status, or continued increased work of breathing is noted on NIPPV.
- Patients should have respiratory support escalated per standard of practice and as listed below:
  - Routine nasal cannula → High Flow Nasal cannula → CPAP → BiPAP → Invasive ventilation. See: Respiratory Therapies for PUI and COVID Positive Patients
- Refer to ICU guidelines for PUI/COVID+ Airway Management document for further information.
- Positive end expiratory pressure (PEEP) considerations: experience in adult COVID-19 patients in Italy does not advise the use of higher PEEP routinely which varies from previous recommendations of PEEP use in acute respiratory distress syndrome (ARDS). In the early phase of respiratory failure with COVID-19, the lung compliance is relatively maintained. Therefore, applying low PEEP and accepting lower oxygen saturations (80's to 90's) may be advised if the patient has single organ failure of the lungs. In the later phase, the pathophysiology may change to typical ARDS requiring a higher PEEP. Individualized titration of PEEP is recommended.

Shock Management

- Provide volume resuscitation: administer 10-20 ml/kg up to a maximum of 40-60 ml/kg as long as patient remains fluid responsive without signs of fluid overload; administer each bolus over 10-30 minutes. Lower volume resuscitation may prevent need for invasive ventilatory support. For patients with LV dysfunction, administer 5-10 ml/kg fluid boluses.
- Initiate inotropic support, per standard practice with epinephrine or norepinephrine, if the patient remains hypotensive.
- See ECMO Guideline for PUI & COVID-19+ patients and Code Guidelines for PUI & COVID-19+ patients available on LPCH Intranet.

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Monitoring and Discharge

Inpatient Monitoring and Follow-up

Pediatric Intensive Care Unit (PICU)

- Weekly electrocardiogram
- Weekly echocardiogram
- More frequent echocardiograms may be considered if:
  - On inotrope support
  - Worsening clinical status

Acute Care Inpatient Ward

- Bedside monitor, telemetry
- Weekly electrocardiogram
- Weekly echocardiogram until discharge
- Additional echocardiography:
  - Worsening clinical status prompting a change in management
  - Per Cardiology recommendation for patients with specific cardiac findings

PICU Discharge Criteria

Patient does not require either:

- Respiratory support above simple nasal cannula, OR
- Inotropic support

Post Discharge Follow-up

Post-Discharge Follow-up

- Primary care physician within 1 week
- Infectious Disease (case-by-case basis)
- Rheumatology (2 weeks post-discharge, if on steroid taper)
- Cardiology:
  - 2 weeks after diagnosis with clinical evaluation, electrocardiogram and echocardiogram if patient is:
    - COVID-19+ (PCR or serology) and inflammatory syndrome present with coronary ectasia/aneurysm(s)/myocardial involvement, OR
    - COVID-19+ (PCR or serology) and KD diagnosis
  - 4-6 weeks after diagnosis with clinical evaluation, electrocardiogram and echocardiogram if patient is:
    - COVID-19+ (PCR or serology) and inflammatory syndrome present, BUT with no coronary or other cardiac involvement

Hospital Discharge Criteria

Patient demonstrates all the following:

- Improved/stable respiratory symptoms without need for oxygen support
- Adequate oral/enteral fluid intake without need for IV fluids
- No need for IV medications
- Patient / family receives education on:
  1. Quarantine practices
  2. Reasons to seek medical attention
  3. Treating fevers primarily with Tylenol
  4. Assuring access to masks

Additional Names of Syndrome:

Multisystem inflammatory syndrome in children (MIS-C) is also referred to as pediatric multisystem inflammatory syndrome (PMIS), pediatric inflammatory multisystem syndrome (PIMS), pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock.

Differences between Kawasaki disease and MIS-C:

1. **Age of presentation** – MIS-C presents in older children compared with Kawasaki disease (7 years vs 3 years).
2. **Race/Ethnicity** – There is an increased incidence of MIS-C in patients of African, Afro-Caribbean, and possibly Hispanic descent, but a lower incidence in those of East Asian descent.
3. **Gastrointestinal symptoms** – Compared to Kawasaki disease patients, MIS-C patients more commonly have GI symptoms at presentation and can be severe.
4. **Cardiac dysfunction and shock** – While shock presents in 5% of Kawasaki disease, shock and myocardial dysfunction has been more common in MIS-C (30-80%).
5. **Laboratory abnormalities** – MIS-C patients have significantly elevated troponin I and brain natriuretic peptide, higher inflammatory markers (D-dimer, CRP, ESR, IL-6), lower absolute lymphocyte count, and thrombocytopenia instead of thrombocytosis compared with patients with Kawasaki disease.

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