MSH Emergency Department

Guideline for the Initial Workup & Management of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

Date Created: *05/15/2020*
Date Reviewed: 06/22/2020; 02/09/2021; 02/22/2022
Reviewed By: *L Spina, C Strother, J Sanders, A Lim*

PURPOSE:

These guidelines are meant to provide evidence based and consistent evaluation of pediatric patients presenting to the Emergency Department with suspected Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19. This guideline is not intended for the workup and management of primary COVID-19 infections.

INTRODUCTION

A number of pediatric patients presenting with a Kawasaki-like or toxic-shock-like illness have appeared in the United States since the onset of the COVID-19 pandemic. This entity has been labeled the Multisystem Inflammatory Syndrome in Children & is believed to be a post-infectious inflammatory process linked to COVID-19. A 30-fold increase in Kawasaki-like disease was reported in the Bergamo province of Italy from March through April 2020. A similar rise was noted in the first half of April 2020 in the UK. The rises in such cases have been theoretically linked to the COVID-19 pandemic & it was hypothesized that a similar increase would be seen in other areas of the world with COVID-19.

Common clinical findings include fever, conjunctivitis, oral mucous membrane changes (cracked lips, strawberry tongue), swelling of the hands and feet, lymphadenopathy, cardiac dysfunction, cardiac conduction abnormalities, GI symptoms (abdominal pain, vomiting, diarrhea), and shock. Other systems include altered mental status, focal neurologic findings and meningismus.

The incidence has been estimated to be about 316 persons per 1,000,000 COVID-19 infections in persons younger than 21 years.

GUIDELINE:

Clinician judgment should supplement and supersede any clinical guidelines or decision protocol. Departure from these guidelines may be appropriate and necessary in certain clinical situations. The use of the guideline allows for an appropriate and uniform treatment in a population that has the potential to become critically ill.

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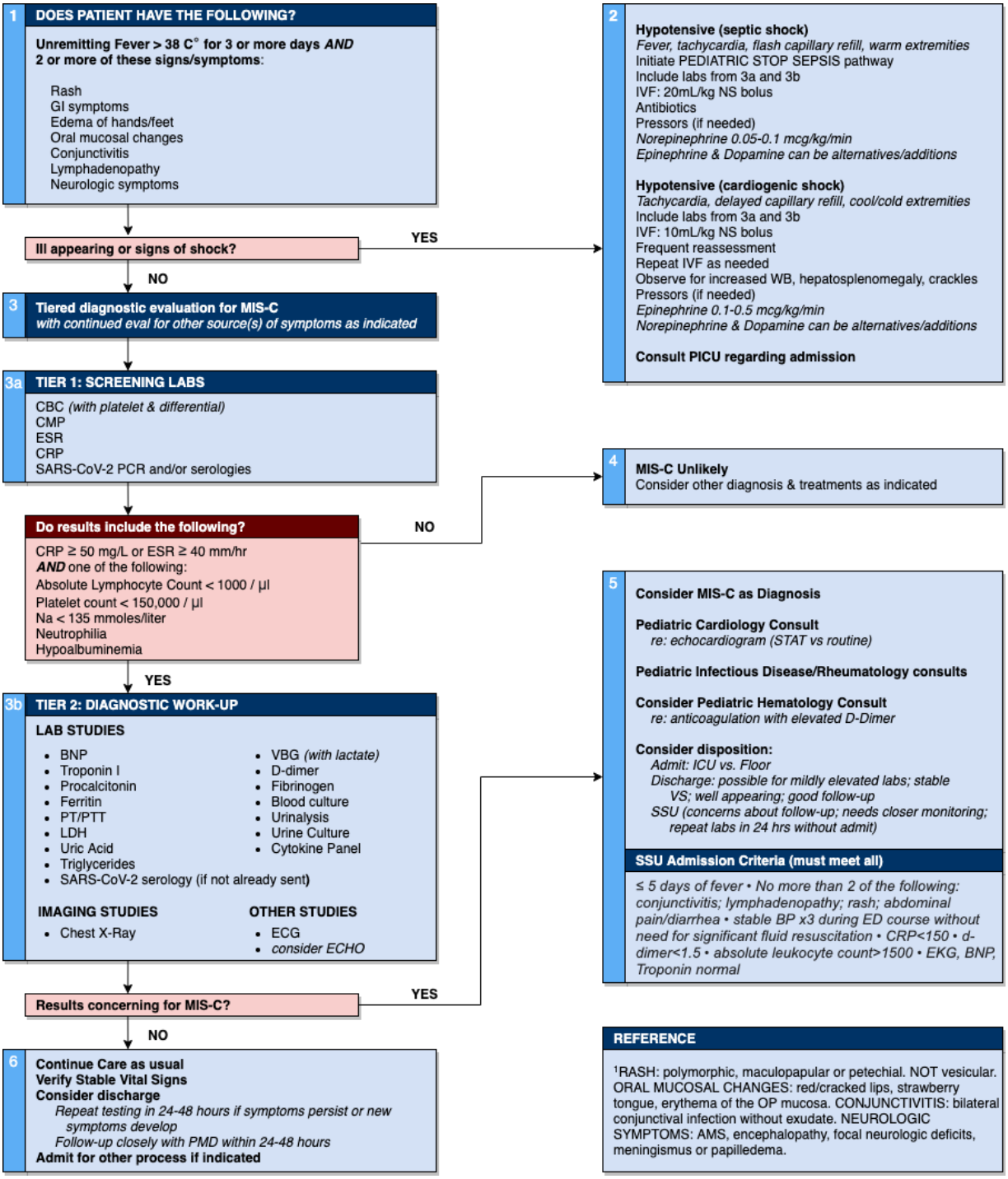

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WORKUP:

Patients being worked up for possible MIS-C can be evaluated in a tiered (step-wise) manner:

TIER 1		
Laboratory	**Imaging**	**Other**
CBC *(platelet & differential)* ESR / CRP CMP SARS-CoV2-PCR *+RVP if admission*	None	None

TIER 2		
Laboratory	**Imaging**	**Other**
LDH Troponin BNP Procalcitonin PT/PTT D-Dimer Fibrinogen VBG *(with lactate)* Ferritin Cytokine Panel Blood Culture COVID-19 Antibodies Urinalysis Urine Culture	Chest X-Ray	ECG Echocardiogram

Kawasaki-Like Illness should be evaluated when:

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A patient under the age of 21 presents with 2 or more days of fever plus any one of the following (or history of any one during the illness):

- Lymphadenopathy (usually anterior cervical & unilateral and 1.5 cm in diameter or more)
- Erythema and/or swelling of the palms and soles (or desquamation of the periungal region)
- Rash – maculopapular, erythroderma, erythema multiforme-like (or other rash)
- Red cracked lips and/or strawberry tongue
- Bilateral bulbar conjunctivitis without discharge (limbic sparing)

Any child with 3 or more days of persistent fever without an obvious source.

Any child with 2 days or more of fever plus non-specific symptoms such as fatigue, headache, cough, shortness of breath, abdominal pain, vomiting and/or diarrhea.

Any patients less than 21 years of age presenting with signs of hypotension and shock should be evaluated for MIS-C.

If the patient is thought to be suffering from sepsis or vasoactive shock (flash capillary refill, warm extremities, tachycardia and fever), intravenous fluids and antibiotics should be administered as per the stop sepsis protocol. If patient remains hypotensive after the administration of a total of 60mL/kg isotonic fluids a norepinephrine infusion at 0.05-0.1 mcg/kg/min is the vasoactive medication of choice. Epinephrine and dopamine are acceptable alternative/additional medications.

If the patient is thought to be suffering from cardiogenic shock (poor capillary refill, cool extremities, tachycardia and hypotension), intravenous fluids should be given cautiously at 10mL/kg of NS with frequent reassessment for increased work of breathing, crackles on lung exam, and hepatosplenomegaly. If present and the patient is still hypotensive, an epinephrine infusion at 0.1-0.5 mcg/kg/min can be given. Epinephrine should also be given for persistent hypotension despite the total administration of 60mL/kg. Dopamine and norepinephrine are acceptable alternative/additional medications.

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TREATMENT:

Please refer to the Kravis Children's Hospital MIS-C Treatment Guidelines

DISPOSITION:

Patients who undergo screening/workup for MIS-C in the ED and are found to have normal laboratory results, CXR and ECG with stable vital signs can be discharged home if there are no other medical concerns/issues requiring further treatment/evaluation in the emergency department. If the patient is discharged home, they should have follow-up arranged within 48 hours.

Other ongoing medical problems requiring continued emergency department care should be managed as usual.

The Pediatric Short Stay Unit at Mount Sinai Beth Israel should be considered for patients when there are concerns about follow-up or if a patient needs closer monitoring or repeat labs in 24 hours without admission.

SSU Admission Criteria

- Less than or equal to 5 days of fever
- NO more than 2 of the following
  - Conjunctivitis
  - Lymphadenopathy
  - Rash
  - Abdominal pain/diarrhea/vomiting
- Stable BPs x3 during ED course, no need for significant fluid resuscitation
- CRP <150
- D-Dimer <1.5
- Absolute Lymphocyte count >1,500
- EKG, BNP, Troponin normal

All patients with abnormal laboratory values and concern for a Kawasaki-like illness should have a pediatric infectious disease consult to determine if IVIG administration is appropriate. Any abnormal troponin or BNP levels, or abnormal ECG should prompt a pediatric cardiology consult

to determine if an emergent echocardiogram is indicated. All patients receiving IVIG should be admitted to the inpatient unit. Patients with signs of organ failure (renal failure, hepatic failure, etc) should be admitted to the inpatient unit.

Patients with possible signs of shock or hypotension, or have a need for fluid boluses, should have a PICU consult to consider admission to that unit for frequent blood pressure monitoring. Patients with clear shock or documented hypotension at any time should be admitted to the PICU. If not admitted to the PICU, the patient should be admitted to the general inpatient pediatric floor. Patients should have at least two normal blood pressures documented before transfer to the floor (non-ICU setting).

ISOLATION GUIDELINES:

What type of isolation is needed for patients with MIS-C?

SARS-CoV-2 PCR test is NEGATIVE on admission: *Varies if there are known or possible other infectious causes requiring specific isolation*

SARS-CoV-2 PCR test is POSITIVE on admission: *Special droplet and contact precautions*

*COVID-19 antibody testing is not used to determine isolation

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Internal Guidelines for Mount Sinai Health System
Guidelines for Inpatient Management of Multi-System Inflammatory Syndrome in Children Associated with COVID-19
General Floor:

	ED/Admission	Diagnosis unclear/Clinically worsening	Consistently improving	Discharge when…
Labs	• CBC/plt + diff • CMP • ESR, CRP, Procalcitonin • Ferritin • ELLA CRS cytokine panel • Fibrinogen • PT/PTT • D-dimer • Troponin • BNP • SARS-CoV-2 PCR • COVID antibody • Blood culture, UA/Urine culture • Blood gas w/lactate	Consider Daily: • CBC/plt + diff • CMP • CRP • Procalcitonin (if clinically worsening and considering bacterial infection) • Ferritin • Fibrinogen • PT/PTT • D-dimer • Troponin • BNP	Consider every 1-3 days: • CRP • Ferritin • D-Dimer • Troponin (if ≥1.0 or not trending down) • Anti-Xa (only if on treatment dose LMWH and not therapeutic) • Any other lab that has been abnormal or requires trending	• 2-3 days of ↓CRP • ↓ Troponin • Therapeutic anti-Xa (only if on treatment dose LMWH)
Other studies	• ECG • Echo • CXR if resp symptoms/hypoxia	• ECG as recommended by Cardiology • Echo if recommended by Cardiology • CXR if worsening resp status/hypoxia	• ECG as recommended by Cardiology • Echo if recommended by Cardiology	• ECG: latest w/no significant arrhythmia • Echo: - stable/improved ventricular function - stable/improved coronary artery abnormalities - stable/improved valve function
Consults	• ID, Rheumatology, Cardiology • Hematology as needed			Follow-up* arranged with PCP, Rheumatology, Hematology, Cardiology
Monitoring	• If BP down trending but not low, consider increasing BP check to Q1-2H until BP stabilizes/improves or RRT called • Consider continuous HR monitoring in patients who have cardiac findings and/or down trending BP • Pulse ox monitoring if on O2 or worsening respiratory status • Fever monitoring	• Consider RRT if: - decreasing or low BP - ↓O2 sat or worsening respiratory status	**Hypotension by SBP & Age (PALS 2015)** 0-28 days: <60 1-12 months: <70 1-10 years: <70 + (age in years x 2) >10 years: <90	• No fever x 48H • Off pressors x 48H with stable BP • Off supplemental oxygen x 48H • Eating and drinking adequately & off IV fluids
Treatment	• Anticoagulation (see MSH Pediatrics COVID-19 Associated Illness Inpatient VTE Thromboprophylaxis/Treatment Guidelines for details): - LMWH (e.g., enoxaparin) prophylaxis if high risk for VTE - Low-dose aspirin if not on prophylactic LMWH - LMWH treatment if evidence of/high suspicion for thrombosis and/or giant coronary artery aneurysm (z-score ≥10) in addition to low-dose aspirin - Consider transition to apixaban if ≥18 years - Heparin if renal failure • Fluids: Caution with boluses, especially if concern for cardiac dysfunction • Antibiotics: Consider empiric treatment with ceftriaxone, consider adding vancomycin if concern for MRSA or linezolid if concern for toxic shock; if requires transfer to PICU, consider cefepime instead of ceftriaxone; reassess need for antibiotics after 48 hours • IVIG: Consider for all (anti-inflammatory dose 2 g/kg) • IV steroids: Consider for any patient in shock and requiring RRT • Anakinra: Discuss with ID and Rheum • Tocilizumab: Discuss with ID and Rheum, up to 3 doses, 8-24 hours apart			• If going home on LMWH: - Therapeutic anti-Xa level (only if on treatment dose LMWH) - Caregiver teaching complete & supplies obtained • Heart failure symptoms, if any, well controlled with oral medications

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PICU:

	Hemodynamically Compensated/ Vasculitis only	Myocarditis	Shock
Inclusion Criteria	• Normotensive by PALS criteria above +/- coronary involvement on echo • No evidence of decreased cardiac function by echo or exam • Normal troponin • Normal ECG	• Normotensive • Increased BNP >1,000 **OR** • Elevated troponin over 1 **OR** • Evidence of decreased cardiac function by echo or exam	• Hypotensive **OR** • Evidence of impaired end organ function including altered mental status, increasing respiratory support, or worsening kidney or liver function
Evaluation/Monitoring	• Continuous telemetry monitoring • Cardiology consult in first 24 hours for possible echo • Repeat BNP, troponin, and ECG at least once within 24 hours • Evaluate for other causes of fever and elevated inflammatory markers • Consider repeat labs and ECG every 12-24 hours if no clinical improvement	• Continuous telemetry monitoring • Cardiology consult on admission • Repeat BNP, troponin, and ECG every 12-24 hours until consistent improvement	Same as for myocarditis plus: • Repeat BMP, LFTs, blood gases every 6-12 hours • Monitor urine output closely • Consider arterial line placement if no improvement in 24 hours
Consults	• Cardiology on admission or within first 24 hours depending on severity as above • Rheumatology and infectious disease within first 24 hours or if uncertain about clinical diagnosis or treatment choices • Hematology per MSH MIS-C thromboprophylaxis/treatment guidelines		
Treatment	• Consider fluid bolus if tachycardic or low urine output • Consider IVIG if no improvement in first 24 hours or any time patient meets Kawasaki criteria • Consider empiric cefepime and vancomycin or linezolid if concern for toxic shock; reassess need for antibiotics after 48-72 hours • Thromboprophylaxis/treatment per MSH MIS-C thromboprophylaxis/treatment guidelines	• IVIG on admission • Consider milrinone • Empiric cefepime and vancomycin or linezolid if concern for toxic shock; reassess need for antibiotics after 48-72 hours • Frequent re-assessment of fluid status • Thromboprophylaxis/treatment per MSH MIS-C thromboprophylaxis/treatment guidelines	Same as for myocarditis plus: • Ensure adequate fluid resuscitation • Norepinephrine for warm shock • Epinephrine for cold shock • Consider hydrocortisone or central line placement if no improvement in first 24 hours
Criteria for Transfer to General Floor	• Normal heart rate and blood pressure for age	• Normal heart rate and blood pressure for age • Evidence of improving cardiac function on clinical exam • Evidence of improving or stable cardiac function by echo if initial study is abnormal (must have 2 studies if first is abnormal) • Evidence of improving troponin if abnormal • No evidence of arrhythmias	Same as for myocarditis plus: • Normal heart rate and blood pressure for age • Evidence of adequate perfusion and improving end organ function

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*** Post-Discharge Follow-up Details:**

- Primary care physician check-in - within 3 days post-discharge
- Rheumatology (Dr. Trachtman) - 1 week post-discharge
  - Labs will be ordered by Dr. Trachtman after visit:
    - D-Dimer
    - Troponin
    - CBC
    - CMP
    - Ferritin
    - BNP
    - Fibrinogen
    - ESR/CRP
    - PT/PTT
    - Fibrinogen and LDH if abnormal at discharge
- Hematology - 2 weeks post-discharge ONLY if on anticoagulation (not if on aspirin alone)
- Cardiology
  - 1-2 weeks after diagnosis: ECG and echo
  - 4-6 weeks after diagnosis: ECG and echo; Cardiologist will determine need for 6 month follow-up
  - 6 months after diagnosis: ECG and echo; cardiac MRI in select patients
  - More frequent follow-up may be recommended to follow up specific abnormalities (e.g. depressed ventricular function, coronary aneurysms)
  - Additional testing such as Holters and/or exercise stress tests are done as clinically indicated.
  - Repeat troponin at each visit until normal (unless already sent from recent Rheumatology follow-up)

Discharge instructions to family:

- Low threshold for returning to the ED: Abdominal pain, fever, diarrhea, vomiting, chest pain, respiratory distress, severe headache, extensive bruising or bleeding
- Return slowly to normal activities
- No strenuous activity or competitive athletics until cleared by Cardiology
- No contact sports if on therapeutic anticoagulation
- Activity restrictions for at least 6 months for anyone with ventricular dysfunction, coronary abnormalities, or evidence of myocarditis & until cleared by Cardiology
- Continue infection control/handwashing even if PCR is negative. Wear a mask!

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Internal Guidelines for Mount Sinai Health System
Guidelines for Inpatient Floor Management of Multi-System Inflammatory Syndrome in Children Associated with COVID-19

Medication List/Dosing:

Treatment Type	Medication		Dosing	Notes/Restrictions
Antibiotic	Ceftriaxone		• 50 mg/kg IV q24H (max 2000 mg/dose)	
	Cefepime		• CrCl > 60 mL/min/1.73m^2: 50 mg/kg/dose IV q8h (max 2000 mg/dose) • CrCl 30 - 60 mL/min/1.73m^2: 50 mg/kg/dose IV q12h (max of 2000 mg/dose) • CrCl < 30 mL/min/1.73m^2: 50 mg/kg/dose IV q24h (max of 2000 mg/dose)	• ***RESTRICTION: Requires Pediatric ID Approval from 9 AM – 5 PM***
	Linezolid		• < 12 years: 10 mg/kg/dose IV q8h (max 600 mg/dose) • ≥ 12 years: 600 mg IV q12h	• If patient has been on SSRI antidepressant or MOAI, avoid use of linezolid due increased risk of serotonin syndrome – contact ID to discuss alternatives • ***RESTRICTION: Requires 24/7 Pediatric ID Approval***
	Vancomycin		• CrCl > 60 mL/min/1.73m^2: 15 mg/kg/dose IV q8h (initial max 1500 mg/dose) • CrCl 30 – 60 mL/min/1.73m^2: 15 mg/kg/dose IV q12h (initial max 1500 mg/dose) • CrCl < 30 mL/min/1.73m^2 or changing renal function: dose by trough - 15 mg/kg/dose x 1 (initial max 1500 mg/dose), subsequent doses based on trough values	• ***RESTRICTION: Requires Pediatric ID Approval from 9 AM – 5 PM*** • Monitor vancomycin troughs in patients expected to receive therapy > 48 hours AND/OR impaired renal function (CrCl ≤ 60 mL/min/1.73m^2) • Obtain initial trough 30 minutes prior to the 4th dose OR prior to each dose when dosing by trough • Trough goal should be individualized based on suspected source of infections
Anticoagulation	Apixaban	Prophylaxis	• 2.5 mg BID (adjust for weight ≤ 60 kg or renal impairment)	• Can consider if age ≥ 18 years (if age <18 years, but weight >60kg, discuss with Pediatric Hematology for apixaban use) • Do not give if antiphospholipid antibodies (APL Ab) are present. If patient has a normal PT but elevated PTT, send mixing studies to see if APL Ab are present before starting apixaban.
		Treatment	• 5 mg BID (adjust for weight ≤ 60 kg or renal impairment)	
	Enoxaparin If CrCl ≥ 30 mL/min/1.73m^2	Prophylaxis	• < 2 months: 0.75 mg/kg/dose SQ q12h • ≥ 2 months: 0.5 mg/kg/dose SQ q12h (initial max 30 mg/dose)	• Consider checking anti-Xa levels for weight ≥ 120 kg OR BMI ≥ 40 mg/m^2 (goal anti-Xa: 0.2 – 0.4 unit/mL for prophylaxis). Otherwise not necessary to check levels.
		Treatment	• < 2 months: 1.5 mg/kg/dose SQ q12h • ≥ 2 months: 1 mg/kg/dose SQ q12h (initial max of 150 mg/dose)	• Anti-Xa levels must be monitored (goal anti-Xa: 0.6 – 1 units/mL for treatment)

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	Heparin If CrCl < 30 mL/min/1.73m^2	Prophylaxis	• < 50 kg: limited dosing information for SQ heparin in pediatric patients for VTE prophylaxis; can consider initiating a low dose heparin infusion (ie – 10 unit/kg/hr) as an alternative • ≥ 50 kg BMI < 40 kg/m^2: 5,000 units SQ q8h BMI ≥ 40 kg/m^2: 7,500 units SQ q8h	• If on ECMO, dose per ECMO protocol
		Treatment	• Loading dose (NOT necessary unless there is concern for active thrombosis): If required, load with 75 units/kg IV over 10 minutes. • Initial IV maintenance infusion rate < 1 year: 28 units/kg/hr ≥ 1 year: 20 units/kg/hr	• Adjust dose to target a goal aPTT of 70 – 110 seconds • If on ECMO, dose per ECMO protocol
Antiplatelet	Aspirin		• 8 kg-15 kg: 40.5 mg (1/2 baby aspirin) PO daily • >15 kg: 81 mg (1 baby aspirin) PO daily	
Immunomodulator	Anakinra		• Starting dose 2 mg/kg SQ q24h (max 100 mg/dose), may titrate up to 400 mg SQ q24h in consultation with Rheumatology	• ***RESTRICTION: Requires Pediatric ID Approval for the treatment of COVID-19 and associated complications AT ALL TIMES***
	Tocilizumab		• < 30 kg: 12 mg/kg/dose • ≥ 30 kg: 8 mg/kg/dose (max of 800 mg/dose)	• For all in this category (up to 3 doses, 8-24 hours apart); dosing to be discussed between ID and Rheum • Avoid use in patients with platelets < 50,000 and those with ANC < 500 • ***RESTRICTION: HIGHLY RESTRICTED requires designated ID Attending Physician approval (Dr. Gopi Patel) AND Critical Care Attending Physician approval (Dr. Roopa Kohli-Seth) AT ALL TIMES for the treatment of COVID-19 and associated complications***
Immune globulin	IVIG		• 2 gm/kg/dose	• ***RESTRICTION: Requires Pediatric ID Approval for the treatment of COVID-19 and associated complications AT ALL TIMES***
Steroid	Hydrocortisone (for shock)		• 50 – 100 mg/m2/day IV divided q6h (max of 50 mg/dose)	• Consider avoiding if PCR+
	Methylprednisolone (for ARDS)		• 1 – 2 mg/kg/day IV divided q12h (max of 60 mg/dose)	

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Isolation Guidelines:

What type of isolation is needed for patients with MIS-C?

SARS-CoV-2 PCR test is NEGATIVE on admission	SARS-CoV-2 PCR test is POSITIVE on admission
• Standard precautions	• Special droplet and contact precautions • Airborne isolation room preferred for those patients undergoing aerosolizing procedures

***COVID-19 antibody testing is not used to determine isolation**

When can I discontinue special droplet and contact precautions on a patient with MIS-C, if they previously had a positive SARS-CoV-2 PCR test?

Inpatient	Outpatient
Test based strategy • Need two consecutive negative PCR tests separated by 24 hours AND • Improvement in symptoms AND • Afebrile x 72 hours **OR** Time based strategy • 10 days have passed from the first positive test result (14d if immunocompromised AND • Improvement in symptoms AND • Afebrile x 72 hours	Non-test based strategy • 10 days have passed from the first positive test result (14d if immunocompromised) AND • Improvement in symptoms AND • Afebrile x 72 hours

***Consult Infection Prevention to review case if you think precautions can be discontinued sooner (e.g., PCR positive in the past, presence of antibodies, high cycle threshold)**

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