Clinical Guideline

This guideline should not replace clinical judgment.

Multi-system Inflammatory Syndrome in Children

Inpatient Pediatrics

Table 1: Description of presentation for patients who meet MIS-C Criteria

Presentation	Description	Isolation precautions

Mild	• No hemodynamic instability
	• No or minimal respiratory support (nasal cannula)
	• No cardiac dysfunction on ECHO
	• Minimal end organ injury
	• **Admission:** Stepdown (monitored continuously on telemetry)
		• MIS-C is an immune mediated, post-infectious process and diagnosis alone should not prompt placement on expanded precautions
		• If the SARS-CoV-2 PCR is **negative**:
		  • Admit the patient on standard precautions unless they have a requirement for transmission-based precautions for another indication (e.g. adenovirus)
		• If the SARS-CoV-2 PCR is **positive**:
		  • Admit the patient on contact/droplet precautions OR contact/airborne if requiring respiratory support or procedure that generates aerosols
		• If the SARS-CoV-2 PCR is **negative** and the COVID-19 antibody test is **pending or positive**:
		  • Admit the patient on standard precautions unless they have a requirement for transmission-based precautions for another indication (e.g. adenovirus)

Moderate-Severe	• Hemodynamic instability +/- vasoactive requirements • Significant respiratory support (HFNC, BiPAP, mechanical ventilation) • Evidence of moderate to severe end organ injury • Altered mental status • Cardiac dysfunction on ECHO • **Admission:** PICU (monitored continuously on telemetry)	

Table 2: Treatment dosing and duration for patients who meet criteria for MIS-C

Medication	Mild	Moderate-Severe

Intravenous Immunoglobulin (IVIG)[a,b]	• IVIG 2 gram/kg (max 100 g/dose) x 1 dose
	• **IVIG should be based on IBW for patients who meet the following criteria:**
	  • Patients aged 2-19 years with actual body weight >IBW by 20%
	  • Adults >19 years with BMI > 30 kg/m2
	• Consider a second dose if patient does not have clinical improvement (>24-36 hours)
	  • **NOTE:** fever is typical within the first 24 hours post completion of IVIG and should NOT prompt retreatment	

Steroids	**If patients have MILD illness, can consider therapy with IVIG alone[c]** Would recommend steroids in patients with mild illness who have persistent/high inflammatory markers after 1 round of IVIG, Kawasaki-like features with age < 12 months **AND/OR** documented coronary artery enlargement (Z-score >2.5) **Intravenous** • Methylprednisolone 2 mg/kg/day (max 60 mg/day) IV divided every 12 hours for 5 days, then taper over 2-3 weeks **Oral** • Prednisolone/prednisone 2 mg/kg/day (max 60 mg/day) PO divided BID for 5 days then taper over 2-3 weeks	• Methylprednisolone 2 mg/kg/day (max 60 mg/day) IV divided every 12 hours for 5 days, then taper over 2-3 weeks • Consider pulse dosing if severe disease: Methylprednisolone 10-30 mg/kg/day (max 1000 mg/day) divided every 12-24 hours for 1-3 days, followed by 2 mg/kg/day (max 60 mg/day) IV divided every 12 hours for 5 days then taper over 4-6 weeks or per rheumatology recommendations

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	Transition from intravenous to oral steroids when patient is clinically stable and able to tolerate oral	
	Suggested steroid taper after the initial 5 days: 1. Oral prednisone/prednisone 0.5 mg/kg/dose twice daily x 5 days (max 30 mg daily) 2. Then, oral prednisolone/prednisone 0.5 mg/kg/dose daily x 5 days (max 15 mg daily) 3. Then, off **Consider a longer taper in patients with prolonged illness**	
Stress Ulcer Prophylaxis	Consider stress ulcer prophylaxis with famotidine (0.5-1 mg/kg/day IV/PO divided BID [max 40mg daily]) for patients on steroids	
Aspirin[d]	All patients < 12 years of age, regardless of coronary artery abnormalities All patients ≥ 12 years of age and **NOT** receiving low-molecular weight heparin: Low dose aspirin: 3-5 mg/kg/day (max 81 mg/day) • **Exceptions to low-dose aspirin:** Platelets less than 80,000, active bleeding, or significant bleeding risk • **Anticipated duration:** Per pediatric cardiology but plan for a 6-week duration or longer if there is coronary involvement OR crossover with KD features	

Low molecular weight heparin (enoxaparin)[d]	• Consider prophylactic enoxaparin (factor Xa level 0.1-0.3) after consultation with pediatric hematology-oncology for risk assessment and recommendations
	• Strongly recommend if D-dimer > 5 times upper limits of normal **PLUS** one VTE risk factor **(see Table 4 below)**
	• Dosing if patient has a normal renal function (CrCl >30) and BMI <40 kg/m2:
	  • < 60 kg: 0.5 mg/kg/dose SC BID
	  • ≥ 60 kg: 30 mg/dose SC BID	

Antibiotics	Usually not indicated	• Initiate broad spectrum antibiotics for patients that present with shock and in whom there is concern for sepsis • Recommend vancomycin **PLUS** 3rd or 4th generation cephalosporin • Consider discontinuation **AFTER** 48 hours if bacterial cultures are negative and **NO** evidence of bacterial infection
Antivirals	• MIS-C is thought to be a post-infectious inflammatory process, **NOT** the direct result of SARS-CoV-2 viral replication • For most patients, **antivirals are NOT indicated**, even if the nasopharyngeal PCR test is positive	

Anakinra	• If lack of clinical response **AFTER** initiation of typical first line therapy (at least > 48 hours after IVIG and steroids), please discuss further recommendations surrounding immunomodulation (i.e. anakina) with rheumatology
	  • Usual dosing: 2-4 mg/kg/dose (max 100 mg/dose) IV or SC BID
	  • May increase to TID dosing if unresponsive	

a. NO live vaccines x 11 months if IVIG was administered

b. Cardiac function and fluid status should be assessed BEFORE IVIG is given. IVIG should be safe to give prior to echocardiogramif no clinical signs of CHF, normal EKG, BNP and troponin. May discuss with cardiology. In some patients with cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily over 2 days).

c. A recent study by Ouldali et al. JAMA. Feb 2021 evaluated IVIG **PLUS** steroids versus IVIG alone in MIS-C patients. They found that combination therapy led to a more favorable fever course. This was a retrospective study with a small sample size. The authors acknowledge that the cohort that received IVIG **PLUS** steroids had a more severe initial presentation with more frequent LV dysfunction.

d. Data suggests that patients with COVID-19 may be at higher risk for thromboembolic events during active infection and perhaps some time after. This increased risk has not been established for patients with MIS-C.

Table 3: Suggested daily labs

Lab Testing	Initial Schedule; Please re-assess daily and de-escalate as clinically indicated	Comments on Typical Lab Findings
CBC with differential	Daily, attention to platelets, lymphocyte count, neutrophil count	Platelet count may be normal or low, anemia for age Lymphopenia (ALC < 1000) has been associated with cases
CMP	Daily, attention to renal function, transaminases, albumin	Hyponatremia, increased creatinine, increased ALT/AST Normal or decreased albumin
CRP	Twice weekly	Increased, marker of systemic inflammation
ESR	Weekly	Increased, marker of systemic inflammation May remain elevated for an extended period of time and is often among the last inflammatory marker to normalize
Triglycerides	Daily if abnormal and concern for macrophage activation (MAC)	May be elevated, particularly in patients with MAC
Ferritin	Daily	Increased, marker of systemic inflammation
PT/PTT/INR	Daily if abnormal	Coagulopathy, with elevated INR
D-dimer	Daily if abnormal	Increased, marker of activated coagulation, marker of inflammation, non-specific
Fibinogen	Daily if abnormal	Increased, marker of activated coagulation, inflammation
LDH	PRN, consider daily if abnormal	Increased
Troponin	Daily until down trending	Marker of myocardial injury if elevated
Brain type natriuretic peptide	1-2 times per week or with clinical change	Marker of ventricular expansion and pressure overload, which may be elevated in heart failure; in reported MIS-C cases, often elevated to a greater extent than may be expected based on clinical/echo findings
Procalcitonin (collect if at St. Mary's)	Twice weekly	Increased, marker of inflammation (note overlap with bacterial sepsis)

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Table 4: Common risk factors for VTE prophylaxis

Risk factors
• Central line
• Mechanical ventilation
• Prolonged immobility/hospitalization (>3 days)
• Age > 12 years or post pubertal
• Obesity (> 95% BMI if ≤ 18 years of age; BMI > 30 kg/m2 for adults)
• Cardiac disease
• Oncologic disease
• Hypercoagulable states
• Personal or family history of VTE
• Estrogen containing OCP

Discharge criteria
• 48 hours afebrile
• Off all vasoactive support > 48 hours
• Improving labs
• ECHO improved/stable
• Normal EKG
• Tolerating full oral diet/medications

Outpatient follow up
• PCP 2-3 days
• Pediatric cardiology 1-2 weeks
• No sports until cleared by pediatric cardiology
• No live vaccines x11 months if IVIG was administered
• If ultimately no concern that patient has MIS-C but rather acute COVID-19: follow up with PCP in 2-3 days; PCP to determine return to play for sports if applicable

Multisystem Inflammatory Syndrome (MIS-C) Guideline
Executive Summary

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