Ann & Robert H. Lurie Children's Hospital of Chicago

Evaluation for Possible Multisystem Inflammatory Syndrome in Children (MIS-C)

A. MIS-C CRITERIA:

- **History & Physical Exam**
  - ✓ Fever ≥ 38.5 C for ≥ 2 days
    AND
  - ✓ Tachycardia for age
    AND
  - ✓ Presence of 2 or more Clinical/Historical Features *(See Box B)*
- **Heightened Suspicion of MIS-C if**
  - ✓ Exposure history/prior SARS-CoV-2 positivity within 8 weeks
  - ✓ History of loss of smell & taste
  - ✓ Abdominal pain

B. CLINICAL/HISTORICAL FEATURES:

GI Symptoms
Abdominal pain (mild/severe), vomiting, and/or diarrhea

Rash
Polymorphic, maculopapular, petechial, NOT vesicular

Extremity changes
Erythema and edema of the hands and feet

Oral Mucosal changes
Erythema of oropharyngeal mucosa

Conjunctivitis
Bilateral bulbar conjunctival injection without exudate

Lymphadenopathy
Cervical > 1.5 cm

Neurologic Symptoms
Headache, irritability, lethargy, altered mental status

Epidemiologic Link to SARS-CoV-2
Patient with history of COVID-19 disease or close contact with known positive SARS-CoV-2 case in past 8 weeks, or person placed in quarantine

C. CONSIDER DIFFERENTIAL DIAGNOSIS FOR MIS-C:

- Acute SARS-CoV-2
- Kawasaki Disease
- Other viral or bacterial infection
- Toxic Shock Syndrome
- Systemic Onset Juvenile Idiopathic Arthritis (JIA)
- Macrophage Activation Syndrome (MAS)
- Hemophagocytic Lymphohistiocytosis (HLHH)
- Myocarditis

Patient arrives with suspicion of MIS-C

Patient/Family Education: Link to PDF which contains QR code and link to CDC MIS-C Site

Is this suspected MIS-C? *(See Box A)*

NO → ▪ Off this algorithm ▪ Consider differential diagnosis *(See Box C)*

YES

Evidence of shock? *(Evidence: tachycardia AND myocardial dysfunction or hypotension/vasopressor requirement)*

NO

Testing to Identify cause of Fever:
- ▪ CBC
- ▪ CMP
- ▪ CRP
- ▪ ESR
- ▪ Any other testing as clinically indicated based on clinical features

▪ Physical Exam AND ▪ Labs = reassuring → ▪ Discharge home with strict return precautions ▪ PCP follow-up ▪ Contact PCP

▪ Physical Exam OR ▪ Labs = concerning (elevated CRP & ESR, but not lymphopenia or thrombocytopenia) → ▪ Consider differential *(See Box C)* ▪ Consider admission vs. PCP follow-up and further work-up

▪ CRP ≥ 3 and/or ESR ≥ 40 AND ▪ Lymphopenia < 1k OR ▪ Thrombocytopenia < 150k → Patients with abdominal pain, consider imaging and surgical consultation

▪ Consider other treatments as clinically indicated

▪ Order additional labs:
-NTproBNP
-Troponin
-Ferritin
-SARS-CoV-2 Antibody
-Coag Panel 3

Are additional labs abnormal and SARS-CoV-2 antibodies present?

NO → ▪ Admit to Floor ▪ Routine Echo ▪ Consider Cardiology Consultation & input

YES

Order:
- ▪ Consult ID
- ▪ EKG
- ▪ Cultures

Consider:
- ▪ Antibiotics
- ▪ Methylprednisolone 2mg/kg

YES → ▪ Admit to Floor ▪ Routine Echo ▪ Consider Cardiology Consultation & input

Immediate Actions:
- ▪ Notify provider
- ▪ Initiate resuscitation/sepsis huddle as clinically indicated

▪ Follow Sepsis Red Pathway: utilize order sets for fluid resuscitation and baseline labs including CMP, CBC, ESR, and CRP
**If high suspicion for myocardial dysfunction, 10-20/kg bolus and consult Cardiology
▪ Send blood cultures
▪ Start antibiotics

Clinically improved?

YES → Patients with abdominal pain, consider imaging and surgical consultation

NO

▪ Consult ID
▪ Order: SARS-CoV-2 Antibody, Troponin, NTproBNP, Coag Panel 3 (with D-dimer & Fibrinogen), Ferritin
▪ EKG (if abnormal, consult Cardiology)
▪ Patients with abdominal pain, consider imaging and surgical consultation

Shock resolved?

YES → ▪ Methylprednisolone 2mg/kg

NO → ▪ Methylprednisolone 10mg/kg ▪ Consider vasopressors → ▪ Cardiology Consultation for Echocardiogram ▪ PICU vs. CICU Admission

Last update: 03.10.21 NJS

Inpatient Care of Patient with Multisystem Inflammatory Syndrome in Children (MIS-C)

Ann & Robert H. Lurie Children's Hospital of Chicago

A. CASE DEFINITION:

- < 21 years of age
- Fever
- Lab evidence of inflammation
- Multi-system involvement
- Positive SARS-CoV-2 antibody

B. INITIAL CONSIDERATIONS FOR ALL PATIENTS:

- Appropriate antibiotic rule-out while cultures are pending (i.e. sepsis rule out or SBI rule out)
- General ID consult for treatment considerations based on clinical severity
- Use GI prophylaxis IV or PO while patient is receiving steroids
- Hematology consult to consider anti-thrombotic prophylaxis: Lovenox and/or low-dose aspirin
- Cardiology consult for abnormal echo, EKG, or troponin results
- Abdominal imaging and Pediatric Surgery consult for focal abdominal findings
- Head imaging and Neurology consult for focal neurologic findings, altered mental status, seizure, and/or severe headache with meningeal signs
- Supportive care per clinical scenario

C. CLASSIFICATION OF CLINICAL SEVERITY:

- **MILD:**
  - ✓ No vasoactive requirement
  - ✓ Minimal/no respiratory support
- **MODERATE:**
  - ✓ Single vasoactive requirement
  - ✓ Respiratory support required
- **SEVERE:**
  - ✓ High-dose or persistent vasoactive requirement
  - ✓ NIPPV or invasive respiratory support
  - ✓ Refractory to initial therapies

IMPORTANT: patients may progress and need additional therapies: frequent reassessment of clinical severity is recommended

Confirm patient meets case definition of MIS-C *(See Box A)*

Review the Initial Considerations for All Patients *(See Box B)*

Patient/Family Education: Link to PDF which contains QR code and link to CDC MIS-C Site

Which Classification of Clinical Severity does this patient meet? *(See Box C)*

	MILD	MODERATE	SEVERE
Therapeutics	▪ IVIG 2g/kg once ▪ Methylprednisolone 2mg/kg/day	▪ IVIG 2g/kg once ▪ Methylprednisolone 10mg/kg/day -If improved, 2mg/kg/day	▪ IVIG 2g/kg once ▪ Methylprednisolone 10mg/kg/day ▪ Consider Anakinra 4mg/kg/day
Anti-Coagulation Therapy	▪ Consider compression stockings (age > 12 y/o) ▪ Consideration for anti-coagulation prophylaxis should be tailored to patient's risk for thrombus	▪ Consider compression stockings (age > 12 y/o) ▪ Consideration for anti-coagulation prophylaxis should be tailored to patient's risk for thrombus	▪ Patients with documented thrombosis or an EF < 35% should receive therapeutic anticoagulation with Lovenox[1] ▪ Consider prophylactic LMWH for reduced cardiac function
Anti-Platelet Therapy	▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)[2]	▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)[2]	▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)[2]
Lab Monitoring	▪ At least Every Other Day[3]: -BMP -CRP -CBC -Troponin[4] ▪ One time & PRN: NTproBNP	▪ Daily[3]: -Troponin[4] -CMP -CBC -Coag panel 3 -CRP -Ferritin -Lactate ▪ Weekly & PRN: NTproBNP	▪ Daily[3]: -Troponin[4] -CMP -CBC -Coag panel 3 -CRP -Ferritin -Lactate ▪ Bi-weekly & PRN: NTproBNP
Cardiac Monitoring	▪ Echo twice weekly ▪ Baseline EKG	▪ Echo at least twice weekly ▪ EKG twice weekly	▪ Echo at least twice weekly ▪ EKG per Cardiology
Consulting Services	▪ ID ▪ Consider Cardiology ▪ Consider Hematology	▪ ID ▪ Cardiology ▪ Hematology	▪ ID ▪ Cardiology ▪ Hematology ▪ PrIIMe

[1] Indications for longer outpatient therapeutic dosing include: documented thrombosis, treatment for ≥ 3 months pending thrombus resolution, or ongoing moderate-to-severe LV dysfunction

[2] Platelet counts should be > 50 x 10^3/µl if patient also requires Lovenox therapy

[3] Decrease frequency of labs once clinically appropriate

[4] Troponin:
-If initial troponin abnormal, trend q12-24 hours until normalized
-If initial troponin normal, no repeat necessary unless clinical concerns

Considerations for Severe Illness and MODS
If elevated ferritin, persistent fever, and cytopenias, consider evaluating criteria for HLH/MAS with serum triglycerides, soluble IL-2 receptor, fibrinogen, NK cell function, and discussing with PrIIMe for multidisciplinary evaluation

Preparing for Discharge:

Discharge Readiness:	Medications:	Outpatient Labs:	Follow-up:
▪ Hemodynamically stable ▪ Afebrile ▪ Steadily down-trending CRP	▪ Transition to PO steroids and taper per ID - expect discharge with prednisone taper based on CRP ▪ Continue GI prophylaxis while on steroids ▪ Discontinue Lovenox at discharge ▪ Continue low-dose aspirin (if started) until seen by Cardiology at 6 week appointment or until instructed by Heme or Cardiology	▪ CRP will be trended on the 5th day of each steroid dose to determine wean schedule ▪ Other labs as needed	▪ If ventricular dysfunction, consult Cardiology for follow-up plan ▪ ID department will schedule appointment 2 weeks post-discharge along with echocardiogram ▪ Cardiology at 6 weeks post-discharge with echocardiogram ▪ Consider outpatient neurology follow-up if any significant neurologic symptoms while inpatient

Last update: 03.11.21 NJS

This guideline is developed based on the best available evidence and local expert consensus for elements of which evidence are inconclusive. Please refer to recommendation table below for further details.

MIS-C Overview

Background & Problem:
The COVID-19 pandemic was declared in March 2020. Children were initially recognized as overall having mild disease compared to adults. In April and May of 2020, reports emerged from around the world describing a new multi-system inflammatory syndrome affecting children in the post-viral period after SARS-CoV-2 infection, some with very severe illness including cardiorespiratory failure, systemic inflammation, and varied involvement of multiple organ systems. This was later termed Multisystem Inflammatory Syndrome in Children (MIS-C) by the CDC, and was thought to be temporally related to SARS-CoV-2 infection and a post-viral hyperinflammatory reaction. MIS-C has significant overlap with other syndromes including sepsis, Toxic Shock Syndrome, Kawasaki Disease, and HLH/MAS. Patient presentation and acuity is varied and subject to change rapidly. This affects resource use, time to diagnosis, and treatment planning. Given the recent development of this syndrome, data on MIS-C pathogenesis and management is limited. Little is known about clinical outcomes. This guideline is subject to change as evidence from this pandemic continues to grow.

Inclusion:
All patients in the Lurie ED or inpatient areas including intensive care units with suspected or known MIS-C.

Exclusion:
None

Outcome Measure:
- Length of stay (Observed over Expected (O:E))

Process Measures:
- MIS-C order set utilization
- Cultures or RVP sent for febrile patients
- COVID PCR and COVID antibody testing sent
- Follow up appointments made with ID and cardiology

Balancing Measures:
- Readmitted within 30 days
- Return to ED within 72 hours of discharge
- Sepsis order set utilization

*See page 4 for literature review grading details

Recommendation	Strength of recommendation	Quality of evidence
Patients meeting criteria for MIS-C[1] should be evaluated for common clinical/historical features and lab findings of MIS-C[2-5], especially if SARS-CoV-2 antibody positive which would be consistent with the timing of MIS-C occurring 4-6 weeks out from SARS-CoV-2 exposure[6].	Strong, consensus	Moderate
Other infectious or non-infectious etiologies that may explain the clinical presentation must be evaluated, including but not limited to sepsis, Kawasaki disease, or toxic shock syndrome[4-5].	Strong, consensus	Low to moderate
For patients presenting with concern for sepsis, even if also concerned for MIS-C, the sepsis guideline should be followed including drawing cultures and starting antibiotics. (link)	Strong, consensus	N/A
Patients with MIS-C usually have multiple markers of inflammation and multiple organ involvement, recommend lab evaluation similar to sepsis work-up, plus inflammatory markers CRP, ESR, and cardiac markers troponin and NTproBNP[4]. Lab markers should be repeated serially until normalized or no longer clinically applicable[8].	Strong, consensus	Moderate
For all patients with confirmed or strongly suspected MIS-C, give IVIG 2g/kg once and methylprednisolone dosing based on acuity[7-8].	Strong, consensus	Low to Moderate
Anticoagulation and anti-platelet therapy should be tailored to the patient's platelet count and coronary artery z-score[8].	Strong, consensus	Low
Anakinra is an IL-1 receptor antagonist that has been used in children with severe infections and hyperinflammatory syndromes. Anakinra may be used for severe refractory MIS-C at a dose of 4mg/kg/day[8].	Strong, consensus	Low
Until more is known about the long-term sequelae of MIS-C, recommend following outpatient evaluation similar to Kawasaki disease protocol, including cardiology follow up with echocardiogram at 2 weeks and 6 weeks post-discharge[4,8], and ID follow up to monitor resolution of symptoms and inflammation.	Strong, consensus	Low

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Rating the Quality of Evidence using GRADE

Assign priori ranking

- Randomized controlled trial (RCT): HIGH
- Observation study (OS): LOW

Determine factors for upgrade or downgrade

Downgrade for:
- Design limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

Upgrade for:
- Large consistent effect
- Dose response
- Confounders only reducing size of effect

Iterative until group consensus achieved

Assign final grade per number of upgrade or downgrade

High	• RCT • OS with 2 upgrades
Moderate	• RCT with 1 downgrade • OS with 1 upgrade
Low	• RCT with 2 downgrades • OS
Very Low	• RCT with ≥ 3 downgrades • OS with ≥ 1 downgrades • Case series/case report

Determine factors impacting recommendations

- Balance of desirable and undesirable effects
- Cost-effectiveness
- Preference of patients

Make recommendations

Strong
vs
Weak

What does our rating mean to our readers?	
High	We are very confident that the effect in the study reflects the actual effect
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different
Low	The true effect may differ significantly from the estimate
Very Low	The true effect is likely to be substantially different from the estimated effect

Design limitations

- Lack of blinding - members involved in study are aware of which arm the patient is allocated
- Lack of allocation concealment – enrolled patients are aware of which group the next enrolled patient will be allocated
- Large losses to follow up
- Incorrect analysis of Intention to treat (ITT)
- Stopped early for benefit
- Selective reporting of measured outcomes (e.g. no effect outcomes) – incomplete or absent reporting of some outcomes and not others on the basis of the results

Inconsistency of results

- Wide variation of treatment effect across studies
- Population varied
- Interventions varied
- Outcomes varied

Indirectness of evidence

- Head-to-head comparison in correct population
- Indirect comparisons
- Different populations – indirectness in population
- Different interventions – interventions delivered differently in different settings
- Different outcomes measured – time differences, use of surrogate outcomes in place of patient important outcomes
- Comparisons not applicable to questions/outcome

Imprecision

- Sample size lower than calculated optimal size
- Total # of events <300
- 95% CI includes negligible effect and appreciable benefit of harm
- Wide confidence interval
- Confidence interval not reported

Publication bias

- Studies with 'negative' findings remain unpublished

Large consistent effect

- Effect cannot be accounted for by bias common to the study; usually when relative risk are > 5 or < 2

Dose response

- when the result is proportional to the degree of exposure

Confounding only reduce size of effect

- when all possible confounders would only diminish the observed effect. It is likely that the actual effect is larger than the data suggests

References
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