CLINICAL GUIDELINE

MIS-C: Clinic-Diagnostic/Dispo recs for *Suspected* Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 (Age <21 years)

Children's MINNESOTA

Aim: To standardize interim MIS-C management.

Symptoms of possible MIS-C[a]:

- **MUST have fever ≥24 hr) AND clinical suspicion for MIS-C with at least 2 of the following:**
- ***GI*** (abdominal pain, vomiting/diarrhea)
- ***CV*** (Chest pain, tachycardia)
- ***Heme*** (cell line abnormalities)
- ***Resp*** (SOB, cough, tachypnea)
- ***Mucocutaneous*** (strawberry tongue, cracked lips, sore throat, polymorphic rash)
- ***Extremity*** (hand/foot redness or swelling)
- ***Lymphadenopathy***
- ***Neuro***: (headache, irritable, altered mental status, CN palsy)

- History, exam + vital signs (VS) including BP
- O2 to keep sats > 90

Categorize patient

EXCLUSION GUIDELINES
Patients with alternate suspected etiology of illness. Differential Diagnosis for MIS-C: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease, appendicitis, HLH/MAS, rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, SLE, vasculitis and other diseases.

Patient stable:
- Reassuring VS for age
- Tolerating PO
- Well-appearing

Any instability including:
- Low BP, tachycardia, or tachypnea for age
- increased work of breathing
- O2 sat < 90%
- Poor perfusion or altered mental status
- Ill-appearing
- Unable to maintain hydration by PO

- **Obtain Tier 1 labs:** SARS CoV-2 PCR and serology, CBC w/ diff, CRP, ESR, procalcitonin, CMP, IgG, blood culture, UA/Ucx. Additional tests if indicated per symptoms (e.g. strep swab).

Labs[a] + exam consistent with MIS-C (without other explanation)?
≥2 results indicating systemic inflammation including:
- **Low**: Lymphocytes (ALC<1000 if older than 8 months age; <2500 if younger than 8 months age), Hgb <9, Platelets <150, Albumin <2.5
- **High**: Neutrophils >10K, CRP >5 mg/dL, (median CRP in MIS-C is ~20 mg/dL), ESR >40, Procalcitonin >0.5

Yes

Transfer to MPLS ED (unless already on STP campus) for possible MIS-C 866-755-2121

No

MIS-C not suspected
Manage off-guideline, re-evaluate if symptoms do not improve in 1-2 days

[a]Approximately 70% of patients with MIS-C have lab evidence of current or past COVID-19 (PCR or serology). Patients may have suspected exposure to COVID-19 case 3-4 weeks prior to MIS-C illness. Maintain higher index of suspicion in patients with higher risks for COVID-19 in the household.

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ED GUIDELINE

MIS-C: ED-Diagnostic/Dispo recs for *Suspected* Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 (Age <21 years)

Children's MINNESOTA

Aim: To standardize interim MIS-C management.

Symptoms of possible MIS-C:

- **MUST have fever ≥24 hr) AND clinical suspicion for MIS-C with at least 2 of the following:**
- ***GI*** (abdominal pain, vomiting/diarrhea)
- ***CV*** (Chest pain, tachycardia)
- ***Heme*** (cell line abnormalities)
- ***Resp*** (SOB, cough, tachypnea)
- ***Mucocutaneous*** (strawberry tongue, cracked lips, sore throat, polymorphic rash)
- ***Extremity*** (hand/foot redness or swelling)
- ***Lymphadenopathy***
- ***Neuro***: (headache, irritable, altered mental status, CN palsy)

- History, exam + vital signs (VS) including BP
- O2 to keep sats > 90
- PIV, fluid resuscitate

Categorize patient

EXCLUSION GUIDELINES

Patients with alternate suspected etiology of illness. Differential Diagnosis for MIS-C: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease, appendicitis, HLH/MAS, rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), bacterial enteritis, SLE, vasculitis and other diseases.

[a]Laboratory Tiers

Workup other potential etiologies as indicated.

- **Tier 1:** SARS CoV-2 PCR and serology, CBC w/ diff, CRP, ESR, procalcitonin, CMP, IgG, blood culture, UA/Ucx,
- **Tier 2:** Serum to save, lactate, blood gas, BNP, troponin, LDH, CPK, D Dimer, PT, PTT, Fibrinogen, ferritin, TG, type and cross, cytokine storm 4 plex, IgA, IgM, MRSA nasal swab. Throat swab for Group A Strep DNA PCR if sore throat.
- **Tier 3:** ASO and anti-DnaseB antibodies, vaginal swab for Group A Strep and Staph aureus (order "Genital culture"). Wound cultures as applicable.

Patient well-appearing with reassuring VS

- **Obtain Tier 1 labs[a] (use ED suspected MIS-C orderset). Discuss with consultants and obtain Tier 2 labs if Tier 1 labs result abnormal.**

Patient ill-appearing, hypotension, poor perfusion, signs of sepsis, toxidrome/toxic shock,and/ or with Kawaski Disease criteria

- **Obtain in all (use ED suspected MIS-C orderset): Tier 1 & 2 labs. Add Tier 3 labs if toxin-mediated suspected.[a]**

Labs + exam consistent with MIS-C (without other explanation)?

≥2 abnormal inflammatory markers including:

- **Low**: Lymphocytes (ALC<1000 if older than 8 months age; <2500 if younger than 8 months age), Hgb <9, Platelets <150, Albumin <2.5
- **High**: Neutrophils >10K, CRP >5 mg/dL, (median CRP in MIS-C is ~20 mg/dL), ESR >40, Procalcitonin >0.5, Ferritin (>500), troponin, BNP (>400pg/ml), Fibrinogen (>400mg/dl), D-Dimer (>3000ng/ml FEU)

Yes

MIS-C Suspected, Complete additional workup:

- CXR, Echo, EKG, Doppler Abd US
- Immunology, ID, Heme, Cards (call from ED if unstable)

Assess Severity Level for Hospital Unit Placement:

Any cardiac dysfunction (e.g. abnormal echo, EKG, or troponin, etc.), and/or shock/hypotension, high resp support, or concern for rapid progression?

No → **Admit to MPLS Med-Surg**

Yes → **Admit to ICU**

No

MIS-C not suspected

Manage off-guideline, re-evaluate if symptoms do not improve in 1-2 days

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CLINICIAL GUIDELINE

MIS-C: Inpatient/ICU Management recs (Age <21 years)

Children's MINNESOTA

Aim: To standardize interim MIS-C management.

All Patients with MIS-C

- Frequent VS including BP
- O2 to keep sats > 90
- Telemetry 72 hours or until cardiology discontinues
- Fluid resuscitate in 10 ml/kg aliquots with re-evaluation after each bolus. Maintain euvolemia
- GI prophylaxis if indicated
- VTE chemical prophylaxis unless contraindication (see VTE guideline)
- IVIG (2g/kg) x 1 (use actual body if <6 yo, use IBW if ≥ 6 yo)
- Low-dose (3-5 mg/kg/day) aspirin (as guided by heme/Cardiology)
- Empiric antibiotics (vancomycin, ceftriaxone, and clindamycin for community-acquired shock presentation) until cultures negative for 48 hour
- Consider other treatments (e.g. anakinra, steroids, anti-virals) with ID and immunology. See medication doses on page 5.

Patients meeting ICU criteria (any cardiac dysfunction [e.g. abnormal echo, EKG or troponin] or shock and/or sepsis)

- Vasopressors as indicated (Norepinephrine or Epinephrine)
- CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x 3 days
- Troponin Q6 hr, decrease as indicated
- BNP Q48 hr
- Repeat other labs as indicated
- EKG Q week to monitor QT interval
- Repeat Echos (Note 1)
- Transfer to Med-Surg unit once meeting criteria

Patients meeting Med-Surg criteria (no ongoing cardiac dysfunction or shock, normalized troponin, clinically stable)

- CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile x 48 hr and labs improving x 3 days
- Repeat Echos (Note 1)
- Continue low-dose (3-5 mg/kg/day) aspirin

Discharge criteria:

- 3 days of decreasing CRP, ferritin, and d-dimer
- Afebrile x 48 hours
- Most recent blood cultures without growth x 48 hours
- EKG without arrhythmia
- Latest echo stable/improved
- Tolerating enteral diet with home feeding plan
- Not requiring oxygen x 24 hours
- Follow-up coordinated

D/C to home

- Follow-up with PCP in 2-3 days with repeat CBC w/ diff, CRP, BMP
- Follow-up with cardiology 1-2 weeks after discharge with repeat EKG & Echo
- Follow-up 4-6 weeks with cardiology & echo, consider cardiac MRI 1-3 months
- Discharge mediations: steroid taper if indicated, low-dose aspirin until Cardiology discontinues, gastritis prophylaxis and Calcium/Vit D supplement until off steroids.

Note 1. Repeat Echo Frequency

- Initial normal: 1-2 weeks and 4-6 weeks
- Initial abnormal with CA z-score >2.5: repeat Q 2-3 days until CA aneurysm stable, then weekly until discharge. All:
- All: Repeat 1-2 weeks after discharge and again at 4-6 weeks. Consider cardiac MRI at ~ 1 to 3 months post-discharge to evaluate for ventricular function, edema, fibrosis, and scar by myocardial delayed enhancement.

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CLINICAL GUIDELINE

MIS-C: Post-Hospital Care (Age <21 years)

Children's MINNESOTA

Aim: To standardize interim MIS-C management.

Initial Follow-up Plan

- Follow-up with PCP in 2-3 days with exam, full vital signs (including BP) and repeat CBC w/ diff, CRP, BMP. Repeat labs 1-2 times per week until normalized.
- Follow-up with cardiology 1-2 weeks after discharge with repeat EKG and Echo
- Follow-up 4-6 weeks with cardiology with Echo, consider cardiac MRI 1-3 months
- Discharge mediations: steroid taper if indicated, low-dose aspirin until Cardiology discontinues, gastritis prophylaxis and Calcium/Vit D supplement until off steroids.

When to consider readmission?

- Any recurrent fever or other recurrence of symptoms (rash, mucositis, conjunctivitis, vomiting/diarrhea, neurological changes, chest pain, etc.) should prompt urgent evaluation. If patient is stable and can be assessed by outpatient provider within 6-12 hours that may be considered. Otherwise refer patient to local ED (if > 60 minutes away) or to MPLS ED.
- If seen in clinic with recurrence of symptoms, obtain full exam + VS including BP. If unstable transfer to MPLS ED. If stable and no alternate source of illness is suspected, may obtain labs: CBC w/ diff, CRP, ESR, ferritin, procalcitonin, CMP. Consider: troponin, d-dimer, UA, Urine Culture, Blood Culture, Rapid Strep. If labs abnormal discuss with outpatient specialists and refer for admission if recommended. Worsening laboratory markers (e.g. increasing CRP) in absence of clinical signs should prompt outpatient discussion with specialists (ID, immunology, cardiology, hematology depending on the laboratory study).
- Call Children's Minnesota Physician's Access 866-755-2121 to be connected with specialists on call and/or ED.

Education for Family

- Avoid NSAIDs while on aspirin
- No live-virus vaccines x 11 months if IVIG was given *(pts at high risk of exposure may receive sooner and be reimmunized after 11 months if they have an inadequate serological response)*.
- Risks of IVIG including: hemolytic anemia, aseptic meningitis
- Discuss plan for recurrent fever or other KD symptoms (rash, mucositis) with family — recommend any symptoms within 7 days of discharge be evaluated by PCP or ED ASAP.

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MIS-C: Additional Notes

A good history and exam is crucial: Talk about family risk factors or known symptoms in past month, exposure to high risk situations (e.g. meat-packer, nursing home employee, large group gatherings), etc.

A case series by Feldstein et. al (NEJM) of 186 patients with MIS-C in 26 states found:
median age 8.3 years, 62% were male, 73% were previously healthy, 70% were positive for SARS-CoV-2 by PCR or antibody.
Organ-systems affected included GI (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%) as well as others.
Some hospitals are reporting higher incidence of MIS-C in non-Hispanic Black, Asian, and Hispanic populations.

Differential Diagnosis for MIS-C: Bacterial sepsis, toxic shock syndrome, Kawasaki Disease, appendicitis, HLH/MAS, rickettsia, viral syndrome (CMV, EBV, Adenovirus, Coxsackie, varicella, etc.), SLE, vasculitis and other diseases. Maintain high index of suspicion for other etiologies.

Ordersets: ED-fever, ED-COVID, ED Suspected MIS-C, Inpatient Suspected MIS-C

Medication Dosing Suggestions (Discuss with consultants and pharmacist)

- Anakinra range: 2-10 mg/kg/dose (max 100 mg/dose) SQ/IV q6-12h
- **Steroid range:** For **mild** (e.g. med-surg)-**moderate** cases consider methylprednisolone 2 mg/kg/day (max of 40-60 mg per day) then taper over 2-3 weeks. For **moderate** cases (e.g. ill on med-surg or in ICU) consider methylprednisolone 10 mg/kg x 1 followed by 2 mg/kg/day with 2-3 week taper. For **severe** cases (e.g. ICU) consider methylprednisolone 20-30 mg/kg/day for 1-3 days, then 2 mg/kg/day and taper over 6-8 weeks with consultation from Endocrinology). Maximum dosing for pulse methylprednisolone is 1000 mg (1 g) per day.

The purpose of the prolonged steroid taper in MIS-C is prevention of rebound inflammation. General guidance:

- Initiate taper when patient has clinically improved (e.g. off pressors, off respiratory support, afebrile, downtrending CRP)
- Reduce steroid dose by 10-15% every 3 days while inpatient
- Reduce steroid dose by 15-25% every 3-5 days while outpatient
- Taper should be guided by clinical response and inflammatory markers (e.g. fever, CRP)

References/Resources:

CDC's 24-hour Emergency Operations Center: 770-488-7100.
American College of Rheumatology Guideline
Evelina London Clinical Guideline
Royal College of Paediatricsand Child Health**:** https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf
CDC: Health Alert Network (HAN) No. 432 –Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)05/14/2020
https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
Viner and Whittaker. "Kawasaki-like disease: emerging complication during the COVID-19 pandemic." *Lancet*May 13, 2020
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Toubianaet al., "Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France." medrix
Riphagenet al., "Hyperinflammatoryshock in children during COVID-19 pandemic." *Lancet*May 7, 2020
DeBiasiet al., "Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region" *JPeds*May 12, 2020
CHOP PathwayCDC COCA webinar 5-19-2020: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp
NY Presbyterian Kids Clinical Guideline
Mayo Clinic Clinical Guideline
Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32598831
Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA [Internet]. 2020 Jun 8 [cited 2020 Jun 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2767209
Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA [Internet]. 2020 Jun 8 [cited 2020 Jun 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2767207

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