COVID-19 v1.0: MIS-C

Approval & Citation | Summary of Version Changes | Explanation of Evidence Ratings

!

Consider differential diagnosis including acute COVID

MIS-C Case Definitions
- CDC
- WHO

Inclusion Criteria
- Fever AND critically ill OR
- Persistent fever ≥3d AND evidence of MIS-C (see box) AND ill-appearing OR
- Persistent unexplained fever ≥5 days

Clinical Features/Evidence of MIS-C
- Most patients have ≥4 organ system involvement; ≥2 required for diagnosis
- Involvement of following systems (percent of patients in case series):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Mucocutaneous (74%, 59% had rash)
  - Respiratory (70%)
  - Musculoskeletal (23%)
  - Renal (8%)
  - Neurologic (6%)
  - See definitions of organ system involvement
- Recent COVID illness OR exposure (note: not necessary to suspect MIS-C)

Lab Evidence of MIS-C

No lab criteria is diagnostic; most patients have 4 or more markers of inflammation
- **Evidence of inflammation, common values:** CRP>3 mg/dl, ESR >40mm/h, ferritin>500 ng/mL, ANC >7700, ALC <1500, platelet <150k, D-dimer >2ug/ml, fibrinogen >400 mg/dL, albumin <3 g/dL, anemia, ALT >40 U/L, INR>1.1
- **Other:** AKI, hyponatremia, high CK, high LDH, high troponin, BNP >400 pg/mL, high TG, prolonged PT or PTT; If ESR low but high ferritin and CRP, consider MAS

Percentages and values adapted from Feldstein et al, NEJM June 2020

- **Initial Labs:** CBCd, CRP, ESR, BMP, ALT, albumin, UA, COVID PCR, COVID IgG, RVP
- **Additional Labs:** BNP, troponin, ferritin, D-dimer, coags, fibrinogen, LDH, CK, triglycerides, blood culture if indicated, red top to hold prior to IVIG (freeze), further labs on consultant advice

Signs of shock?

No →
- Obtain **Initial Labs**
  *If high clinical suspicion, add **Additional Labs***
- CXR (if resp sx)

Yes →
- Obtain **Initial and Additional Labs**, EKG, CXR
- ECHO (early if signs of cardiac dysfunction)
- Consider Sepsis Pathway
  Caution with boluses; monitor for cardiac dysfunction

Lab Evidence of MIS-C?

Yes →
- Obtain **Additional Labs**
- ECHO
- EKG

No →
- Consider alternate diagnoses
- Consider discharge with close follow-up

Complete or Incomplete Kawasaki?

Yes →
- Follow Kawasaki Disease Pathway if COVID testing negative or while pending
- Monitor closely for signs of shock

No →

Evidence of MIS-C without alternate diagnosis?

No →
- Consider alternate diagnoses
- Consider discharge with close follow-up

Yes →

PCR or IgG + OR cardiac dysfunction

!

Patients with MIS-C have significant risk for developing shock

Go to MIS-C Treatment

COVID-19 v1.0: MIS-C Treatment

Approval & Citation | Summary of Version Changes | Explanation of Evidence Ratings

Suspected MIS-C: Ongoing fever, lab evidence of inflammation (most patients have 4 or more markers), multi-system involvement, and clinically seriously ill, without alternative diagnosis (review differential diagnosis)

MIS-C: Above plus confirmed SARS-CoV-2 or known exposure (see case definition links)
- ECHO if not already done; repeat as indicated
- Admit patients to ICU if any signs of shock, hypotension, or concern for cardiac dysfunction
- Consult Infectious Disease, Rheumatology, and Cardiology; goal for daily group discussion or rounds with primary team
- Antibiotics per Sepsis Pathway only if and while bacterial infection suspected
- Consider supportive care only for patients who have mild* illness; monitor for increasing severity until clearly improving

First-line treatment for all seriously* ill patients with MIS-C:
- IVIG 2 g/kg (use ideal body weight) over 12 hours
- Anti-platelet: ASA 3-5 mg/kg max of 81 mg
- Anticoagulation: SQ enoxaparin prophylaxis until discharge (barring contraindications or indications for treatment dosing)
- Early initiation of steroids and/or higher dose of steroids may be indicated for critically ill patients, such as those with persistent shock/inotropic requirement, respiratory or heart failure, or concern for MAS

Second-line: Steroids if not improving ~12 h post-IVIG
- Methylprednisolone 2 mg/kg/day divided BID, change to PO when tolerating diet
- Consider higher dose steroids (methylprednisolone 10mg/kg/day) for patients with moderately or severely depressed cardiac function, in consultation with heart failure team
- Consider H2 blocker for GI ulcer prophylaxis while on both steroids and ASA
- Wean over minimum 3 weeks due to risk of rebound with short course

Third-line: Anakinra if not improving post steroid initiation or if labs suggestive of MAS
- 4 mg/kg/dose q6 hours (or frequency per Rheumatology), max dose 100 mg/dose

Trend CBCd, CRP, LDH, ALT, Albumin, Ferritin, Creatinine, Lytes, D-Dimer, Fibrinogen and BNP (frequency dependent on clinical status and medication weaning; post-discharge labs per consultants)

Classification of illness severity is not well defined. Consider:
**Mild: Normal vital signs apart from fever, does not meet inpatient criteria other than poor PO, mild dehydration, or monitoring for worsening.*
**Serious: Definitively meets case definition and any of: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.*

Differential Diagnoses

Kawasaki Disease
- More common in younger children, if COVID testing negative, and without shock/cardiac dysfunction

Bacterial Infections/Sepsis
- Obtain cultures and evaluate for source
- Consider meningitis

Staphylococcal and streptococcal toxin-mediated diseases
- Diffuse rash and hypotension
- Obtain cultures and evaluate for source including gynecologic or scarlet fever

Staph Scalded Skin Syndrome (SSSS)
- Increasing erythema and bullae
- Younger children
- Obtain cultures

Tick-Borne Illnesses
- With epidemiologic risk factors
- Rocky Mountain Spotted Fever or Leptospirosis

Viral Infections
- Measles, adenovirus, enterovirus, active COVID infection

Myocarditis
- May overlap with MIS-C or have alternate cause

Drug Hypersensitivity Reactions
- Consider SJS, DRESS, or serum sickness like reaction
- History of recent or semi-recent exposure to drug; consider with arthralgias and diffuse mucositis

Labs to Consider with Consultants

- Quantitative immunoglobulins (IgG, IgA, IgM, red tube)
- Specimen storage, red and lavender (freeze)
- Lymphocyte subset – Full Panel with TCR
- Antiphospholipid Ab (anticardiolipin, β2 glycoprotein, lupus anticoagulant)
- Cytokine panel
- IL-1β (ARUP test code 0051536, collect 2-3mL in gold/red top, spin and freeze within 2h)
- sIL-2R (AKA sCD25)

Return to Home

Definitions of Organ System Involvement

Gastrointestinal 92%
- Nausea/vomiting
- Diarrhea
- Abdominal pain
- Appendicitis
- Pancreatitis
- Hepatitis
- Gallbladder hydrops or edema

Cardiovascular 80%
- Hypotension or shock
- Cardiac dysrhythmia or arrythmia
- Ejection fraction <55%
- Pulmonary edema due to left heart failure
- Coronary artery z score ≥2.5
- Pericarditis or pericardial effusion or valvulitis
- B-type natriuretic peptide (BNP) >400 pg/mL
- Elevated troponin
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation (CPR)

Hematologic 76%
- Total white blood cell <4k
- Anemia for age
- Platelet count <150,000 /µL
- Deep vein thrombosis
- Pulmonary embolism
- Hemolysis
- Bleeding or prolonged PT/PTT
- Ischemia of an extremity

Mucocutaneous 74%
- Bilateral conjunctival injection
- Oral mucosal changes
- Rash or skin ulcers
- 'COVID' toes
- Swollen red cracked lips
- Erythema of palms or soles
- Edema of hands or feet
- Periungual (nails) desquamation

Respiratory 70% (more frequent in teens)
- Receipt of mechanical ventilation or any type of supplemental oxygen (or
- increased support for patients receiving respiratory support at baseline)
- Severe bronchospasm requiring continuous bronchodilators or
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest-tube or drainage required

Musculoskeletal 23% (more frequent in teens)
- Arthritis or arthralgia
- Myositis or myalgia

Renal 8%
- Acute kidney injury with or without dialysis

Neurologic 6%
- Stroke or acute intracranial hemorrhage
- Seizures
- Encephalitis, aseptic meningitis, or demyelinating disorder
- Altered mental status
- Suspected meningitis with negative culture

Adapted from Feldstein et al, NEJM June 2020

Return to Home

CSW COVID-19 Pathway Approval & Citation

Approved by the CSW COVID-19 Pathway team for July 9, 2020, go-live

CSW COVID-19 Pathway Team:

Hospital Medicine, Owner	Katie Kazmier, MD
PICU, Stakeholder	Jesselle Albert, MD, MHA
Immunology, Stakeholder	Maite de la Morena, MD
Medical Unit, SIU, Stakeholder	Chelsea Eckart, MN, RN, CPN
Emergency Medicine, Stakeholder	Sara Fenstermacher, MSN, RN, ACCNS-P
Emergency Medicine, Stakeholder	Emily Hartford, MD, MPH
Rheumatology, Stakeholder	Kristen Hayward, MD, MS
Cardiology, Stakeholder	Mariska Kemna, MD
GME (Resident), Stakeholder	Sarah Nutman, MD
Cardiology, Stakeholder	Michael Portman, MD
Urgent Care, Stakeholder	Denise Shushan, MD
PICU, Stakeholder	Hector Valdivia, MN, ARNP, ACCNS-P, CCRN
Infectious Disease, Stakeholder	Surabhi Vora, MD, MPH
Infectious Disease, Stakeholder	Alpana Waghmare, MD

Clinical Effectiveness Team:

Consultant	Surabhi Vora, MD, MPH
Project Manager	Dawn Hoffer, SAPM
Data Analyst	Wren Haaland, MPH, Clinical Analytics
Librarian	Peggy Cruse, MLIS, Library
Program Coordinator	Kristyn Simmons

Clinical Effectiveness Leadership:

Medical Director	Darren Migita, MD
Operations Director	Karen Rancich Demmert, BS, MA

Retrieval Website: http://www.seattlechildrens.org/pdf/covid-19-pathway.pdf

Please cite as:
Seattle Children's Hospital, Kazmier K, Albert J, de la Morena M, Eckart C, Fenstermacher S, Hartford E, Hayward K, Kemna M, Nutman S, Portman M, Sushan D, Valdivia H, Vora S, Waghmare A, Migita D, 2020 July. COVID-19 Pathway. Available from: http://www.seattlechildrens.org/pdf/covid-19-pathway.pdf

Return to Home

Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children's. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are *downgraded* if studies:

- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:

- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Certainty of Evidence:

✪✪✪✪ High: The authors have a lot of confidence that the true effect is similar to the estimated effect
✪✪✪○ Moderate: The authors believe that the true effect is probably close to the estimated effect
✪✪○○ Low: The true effect might be markedly different from the estimated effect
✪○○○ Very low: The true effect is probably markedly different from the estimated effect
Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team
Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies).

To Bibliography

Return to Home

Summary of Version Changes

- **Version 1.0 (7/9/2020)**: Go live.

Return to Home

Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children's Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.

Return to Home

Bibliography, page 1

Methods

Both CDC and WHO case definitions were utilized in the development of this pathway. The articles cited are a representation of local and international experts' and national societies' resources that were being shared widely, some pre-publication and many that were published by the centers that were diagnosing and treating this new syndrome as the pandemic swept across the globe.

A systematic literature review is in process and may inform future versions of this document. Due to the rapidly evolving literature and the need for urgent guidance, a non-systematic review was used to guide the development of the initial version of this algorithm.

Return to Evidence Ratings

Return to Home

Bibliography, page 2

References

ACR MIS-C and COVID-19 Related Hyperinflammation Task Force. (2020 June 17). Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. American College of Rheumatology, A full manuscript is pending journal peer review. https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf

Bamrah Morris S, Belay E, Levin M, Marconi V, Schneider S. (2020 May 19). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) [Webinar]. Centers for Disease Control and Prevention: Clinical Outreach and Community Activity (COCA). https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp

Belhadjer Z, et al. (2020 May 18) Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation, Online ahead of print. https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.120.048360

Center for Disease Control and Prevention (2020 May 14). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). CDC Health Alert Network, CDCHAN-00432. https://emergency.cdc.gov/han/2020/han00432.asp

Cheung EW, Zachariah P, Gorelik M, et al. (published online ahead of print, 2020 Jun 8). Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA. 2020;e2010374. doi:10.1001/jama.2020.10374

Daskalakis D. (2020 May 18). 2020 Health Advisory #16: Updated Reporting Requirements for Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (Formerly Pediatric Multisystem Inflammatory Syndrome). NYC Health Department. https://www1.nyc.gov/assets/doh/downloads/pdf/han/advisory/2020/covid-19-providers-mis-c.pdf

Feldstein LR, et al.(2020 June 29) Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. doi: 10.1056/NEJMoa2021680.

Freedman S, Glaser E, Godfred-Cato S, Gorman R, Lodha R, Mofenson L, Murthy S, Rojo P, Semple C, Sigfrid L, Whittaker E. (2020 May 15). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19: Scientific Brief. World Health Organization. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

National Institutes of Health (NIH). (2020 June 11). COVID-19 Treatment Guidelines: Special Considerations in Children. NIH COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/overview/children/

Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. (2020 May 7). Hyperinflammatory shock in children during COVID-19 pandemic, The Lancet, 395(10237), 1607-1608. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31094-1.pdf

Royal College of Paediatrics and Child Health. (2020 May). Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. RCPCH. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

Return to Home

Bibliography, page 3

References (continued)

Toubiana J, et al. (preprint 2020 May 14). Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France. medRxiv [preprint]. doi: https://doi.org/10.1101/2020.05.10.20097394

Verdoni L, Ciuffreda M, Gervasoni A, Martelli L, Mazza A, Ruggeri M, et al. (2020 May 13). An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet, 395, 1771-1778. https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31103-X.pdf

Whittaker E, Bamford A, Kenny J, et al. (2020 June 8). Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. doi:10.1001/jama.2020.10369

Return to Home