PEDIATRIC GUIDELINES FOR MULTISYSTEM INFLAMMATORY SYNDROME in CHILDREN (MIS-C) ASSOCIATED with COVID-19

PURPOSE: The purpose of this guideline is to aid in the recognition, reporting, evaluation and management of this syndrome. Please note this guideline is not for children presenting with primary COVID-19 pneumonia/respiratory distress. Refer to the Multicare Pediatric COVID-19 guidelines for those patients.

There are currently no standardized recommendations for either evaluation or management of MIS-C, and it is likely that the guideline will frequently be updated as new information emerges.

CASE DEFINITIONS

The case definitions from the CDC versus the American College of Cardiology are slightly different. WHO has a third definition which is similar to the CDC version. See Appendix for the three case definitions.

Be aware that MIS-C can resemble Kawasaki disease and Toxic Shock syndrome. It can also present as an acute abdomen or concerning for meningitis or encephalopathy

-Other pediatric presentations that could represent inflammation due to COVID-19 will not meet the definitions, but should be evaluated for COVID-19. This includes 1) children with unexplained fevers and elevated inflammatory markers and 2) all children with Kawasaki Disease not meeting multisystem organ involvement or shock syndrome. These children should also be monitored closely for disease progression as they may progress quickly

-Patients meeting criteria for KD without shock syndrome should be managed as usual with IVIG + aspirin, but monitor closely for evolution to KDSS/MIS-C. Recommend adding BNP, ferritin and troponin to initial labs. Of note is that lymphopenia, elevated ferritin, markedly elevated CRP, marked hypoalbuminemia, and especially elevated BNP (mean peaks around 7500) are significantly more common in MIS-c vs KD.

-Patients with suspected HLH should be managed according to recommendations by Peds Heme-Onc, not this treatment guideline.

ENTER PATHWAY IF:

1) Fever ≥ 38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

AND

2) At least 2 of following organ systems involved:

a)cardiac (failure, dysrhythmia, ECHO abnormalities)

b)Renal (oliguria, failure, insufficiency)

c)Respiratory (distress, hypoxemia)

d)hematologic (DIC)

e)Circulatory (shock)

f)dermatologic (rash, conjunctivitis, mucosal changes)

g)GI (diarrhea, emesis, acute abdominal pain)

h) neurologic (mental status changes, headache, meningismus, seizures)

AND

Evidence of inflammation with 1 or more of the following:

Increased			Decreased
CRP	LDH	VBG w/ Lactate	Lymphocytes
ESR	IL-6	LDH	Albumin
Ferritin	Neutrophils	Coagulation panel	
Procalcitonin	Troponin		

AND

No alternative plausible diagnosis.

Definitive diagnosis can be made with positive COVID pcr or antibody testing or history of known exposure within 4 weeks prior to onset of symptoms. ***If initial pcr is negative, repeat in 24 hours. Also send stool pcr in patients with GI sx using a specimen cup and sending to UW virology lab using misc test.***

Elicit history of any exposures to known COVID-19 cases within past 4 weeks. Consider testing family members and close contacts for COVID-19 with pcr and antibody tests

Patient meets MIS-C Definition

CONSULT: Peds ID, Peds Cardiology, Peds Rheum, Peds H-O

MIS-C specific Lab Orders:

CBC CRP Troponin COVID pcr and antibody

CMP ESR BNP D-Dimer IL-6 fibrinogen

Ferritin PCT LDH CKP Serum tube to hold

UA Blood Cultures

MIS-C specific imaging:

EKG, ECHO, CXR

Treatment for all patients:

GI PPX, low dose aspirin OR lovenox

Lovenox suggested in patients with central lines

Mild Presentation

Moderate Presentation

Severe Presentation

Treatment	Dosing
Steroids	2 mg/kg/day
IVIG	2 g/kg,
Biologics	Not Indicated

Treatment	Dosing
Steroids	Pulse dose X 1 then, 2 mg/kg/day
IVIG	2 g/kg,
Biologics	Consider adding anakinra if not improving

Treatment	Dosing
Steroids	Pulse dose X 3 days then, 2 mg/kg/day
IVIG	2 g/kg,
Biologics	Consider adding anakinra, or tocilizumab

Presentation	Definition
Mild	Requires no respiratory support or pressors Not in ICU
Moderate	Significant oxygen requirement OR Pressors
Severe	Ventilator support OR Moderate to severe organ injury OR moderate

MIS-C Specific Therapy	Dosing & Duration	Comments
IVIG (IV) - KD features and/or coronary artery changes	**Dosing:** - 2 g/kg	**Adverse events:** - Infusion reactions - Anaphylaxis -Transaminitis, - Aseptic meningitis - Hemolysis -counsel about need to avoid live vaccines for 11 months
Anakinra (SQ/IV) - IL-1 Inhibitor - Consider if fevers > 24 hrs post steroids/IVIG or moderate/severe presentation ***Rheum Consult Required***	4 mg/kg/day SQ (Max 100 mg/dose or 10 mg/kg/day) **Mild MIS-C:** - Not Indicated **Moderate MIS-C:** - 4mg/kg/dose SQ once daily x 5 days (Max 100mg/dose) -escalate to 4mg/kg SQ bid if no response **Severe MIS-C:** - 4mg/kg/dose SQ once daily x 5 days (Max 100mg/dose) -escalate to 4mg/kg SQ bid if no response	**Preferred Biologic** -Treatment with >1 biologic is not recommended -Avoid live viral vaccines -Short half-life –may convert to tocilizumab without concern -obtain quantiferon prior to giving, but do not delay giving waiting for result -Caution converting from tocilizumab(longer half-life) to anakinra
Tocilizumab - Consider for MIS-C if fevers > 24 hrs post steroids/IVIG or moderate/severe presentation ***Rheum Consult Required***	-12 mg/kg for children <30 kg -8mg/kg for children >30kg; max dose 800mg Give x1, IV, over 1 hour. Could be repeated x 1 after 2 days if no improvement	**Tocilizumab** -Discuss with Peds Rheum before ordering; Anakinra is preferred biologic -obtain quantiferon prior to giving but do not delay giving waiting for result -(max 800) IV once, round to nearest vial size (80 mg, 200 mg, 400 mg vials).
Corticosteroids (IV/PO) prednisone, prednisolone, methylprednisolone -Consider also for high-risk KD features such as shock syndrome	**Dosing (mild presentation):** - 2 mg/kg/day divided q8-q12h **Pulse dosing:** 10 mg/kg-15mg/kg/day for 1-3 days followed by 2 mg/kg/day divided followed by a taper Determine based on patient severity	**Adverse events:** -Hypertension - Hyperglycemia -PRES

FOLLOWUP LABS

1)MIS-C shock syndrome patients in PICU should have troponin and BNP every 48 hours. Daily CRP, CBC, CMP, until stable. Close monitoring for abrupt deterioration

2)MISC-C patients on ward should have CBC, CRP, CMP, troponin and BNP daily until stable. Close monitoring for deterioration

FOLLOWUP CARDIAC MONITORING

1) Normal initial ECHO and EKG and no clinical changes—repeat at 2 and 4 weeks
2) Abnormal initial EKG or ECHO -repeat every 2-3 days until stable or as per cardiology, then weekly

DISPOSITION

-all patients with MIS-C should be discharged home on low dose ASA unless contraindicated

-all patients should be seen in Ped cardiology clinic 2 weeks post discharge. Additional subspecialty follow-up as individually warranted

REPORTING

Patients meeting the CDC case definition should be reported to the WA state DOH at 206-296-4774 within 24 hours

Peds ID will consider entering patients into the BATS registry at bestavailabletreatmentstudy@gmail.com

REFERENCES

1. Centers for Disease Control. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) health advisory published online on May 14,2020 available at https://emergency.cdc.gov/han/2020/han00432.asp?deliveryName=USCDC_511-DM28431
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5. New York Presbyterian Kids. Pediatric guidelines for COVID-19 multisystem inflammatory syndrome published May9, 2020
6. Verdani L, Mazza A, Gervasoni A et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet published online May 13,2020 available at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/fulltext
7. Riphagen S, Gomez X, Gonzales-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020. Advance online publication, doi: 10.1016/S0140-6736(20)31094 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31094-1/fulltext

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APPENDIX

CDC Case Definition (May 14,2020)

1. An individual aged <21 years presenting with fever (1), laboratory evidence of inflammation (2), and evidence of clinically severe illness requiring hospitalization, with multisystem ***(>2)*** organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) ***AND***
2. No alternative plausible diagnoses ***AND***
3. ***Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms***.

1.Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours;
2. Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

Notes:

- ***Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C***
- ***Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection***

AMERICAN COLLEGE OF CARDIOLOGY Case Definition (May 15, 2020)

-Adopted the case definition put out by the Royal College of Pediatrics and Child Health

1. Any child (age undefined) presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and ***evidence of single or multiorgan*** dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of other microbial causes including bacterial sepsis, Strep or Staph TSS, infectious myocarditis. Do not wait for results before evaluation for MIS-C

3. SARS-CoV-2 PCR testing ***may be positive or negative***

WORLD HEALTH ORGANIZATION Case Definition (May 15,2020)

1. Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

1.Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).

2.Hypotension or shock.

3.Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),

4.Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).

5.Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.