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. Mary Bridge is using the CDC case definition https://emergency.cdc.gov/han/2020/han00432.asp which requires 1.age < 21 yrs, 2. Fever > 24h, 3. ab evidence of inflammation (usually 4 or more markers), 4. multisystem involvement (at least 2 systems, see MIS-C ED Path for definitions of system involvement) https://www.multicare.org/wp-content/uploads/Evaluation-of-Possible-COVID-Multisystem-Inflammatory-Syndrome-in-Children-Updated-08.05.20.pd ,5. seriously ill without alternative diagnosis, and 6. confirmed SARS-COV-2 infection or known exposure.

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. These children should also be monitored closely for disease progression as they may actually have MIS-C and progress quickly

-Patients meeting criteria for KD but not MIS-C 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. Cardiac dysfunction acutely is also more common in KD like MIS-C presentations

-Patients with suspected MAS 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>3 ESR>40 Ferritin >500 ANC>7700 DDIMER>2 Fibrinogen>400 ALT increased for age INR>1.1	ALC <1500 plts <150k albumin <3 Anemia for age

Other labs supportive of MIS-C: elevated TPN, BNP > 400, AKI, elevated PT or PTT

If ESR low and ferritin and CRP are high, consider MAS triggered by MIS-C

AND

No alternative plausible diagnosis.

Definitive diagnosis can be made if all of above plus positive COVID pcr or antibody testing or history of known exposure within 4 weeks prior to onset of symptoms. ***If initial pcr and ab are both negative, repeat in 24 hours. Also send stool pcr in patients with GI sx with negative ab and pcr, 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

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IPS Management MILD-MODERATE MIS-C

If patient meets classic Kawasaki Disease criteria, consider KD guideline if no other MIS-C features

. • **Echo:** obtain on admission. Followup ECHO as per Peds Cardiology. Place on CRM

- **Admission Labs**:CBC, CMP, CRP,ESR,IL-6, LD, DDIMER, Coags, ferritin, BNP, TPN, UA, BC, Covid ab and PCR, VRP, fibrinogen***, red top to freeze and hold. Stool covid pcr if diarrhea and resp pcr and ab negative.***

. • **Fluids:** resuscitate in 10 ml/kg aliquots with re-evaluation after each bolus. Maintain euvolemia.

• **Empiric antibiotics** (until cultures negative for 48 hour or as-directed by ID

. • **Consults**: **ID**: for all patients. **Cardiology**: for all patients. **Hematology**: if questions not addressed on guideline or if considering therapeutic Lovenox. **Rheumatology**: if using biologics

TREATMENT FOR MODERATE

. • **IVIG:** 2 g/kg x 1 (use ideal body weight)- See Treatment box

• **Steroids:** Methylprednisolone 2 mg/kg/day divided bid as additional first-line therapy if ill appearing, BNP > 400, unexplained tachycardia or in discussion with Peds ID. Initiate with any clinical worsening if not already started. Wean over 2-3 weeks, per Peds ID

• **Aspirin**-all patients, use low-dose (3-5 mg/kg/day with max dose of 81 mg/day) in MIS-C (including if KD features) unless plts <50k

• **GI prophylaxis** all patients; **SCDs** all patients

- **Lovenox ppx:** DDIMER > 2.5, >age 12, BMI >95%, cardiac abnormalities or other risks for thrombosis

TRENDING LABS AND EKG BY DISEASE SEVERITY

-Mild: CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x 1 day then may do PRN for clinical worsening. Repeat troponin and BNP if clinical worsening/persistent fever. EKG Q48 hr.

- **Moderate:** CBC w/ diff, CRP, BMP, d-dimer, ferritin Q day until afebrile and labs improving x 3 days then may do PRN for any clinical worsening. Repeat troponin Q6 hr until normalized and BNP Q 48 hr- repeat cardiac markers sooner if clinical worsening or persistent fever. EKG Q48 hours to monitor QT

REFRACTORY DISEASE-See Box B

Disease Severity * Not well defined in lit

Mild: Borderline or mild case. Normal VS apart from fever, no inpt criteria other than poor PO, mild dehydration, or monitoring for worsening

Moderate: Meets case definition without shock or other ICU criteria. Note-moderate can rapidly deteriorate

Severe: Meets ICU criteria

REFRACTORY DISEASE

Defined as persistent fevers and/or symptoms not improving. Timing of fever in relation to IVIG is not defined; consider if fever present 36 hours AFTER completion of IVIG.

-Discuss treatment options with PEDS ID.

-For most severely ill children, bolus Methylprednisolone 10-30 mg/kg/day IV (max dose 1g). Consider Anakinra 2-10 mg/kg/dose (max 100 mg/dose) SQ/IV (Rheum cons).

Repeating IVIG not usually indicated, unless KD-like

-Consider PICU transfer.

Discharge criteria: • CRP, ferritin, and d-dimer improving • Afebrile x 48 hours • Blood cultures without growth x 48 hours • EKG without arrhythmia • Latest echo stable/improved • Tolerating enteral diet • Not requiring oxygen • Follow-up PID,Card

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PICU Management SEVERE MIS-C

If patient meets classic Kawasaki Disease criteria, consider KD guideline if no other MIS-C features

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Initial ICU Management

• **Echo:** obtain if not already done; repeat as per Peds Cardiology

•**Admission Labs**:CBC, CMP, CRP,ESR,IL-6, LD, DDIMER, Coags, ferritin, BNP, TPN, UA, BC, Covid ab and PCR, VRP, fibrinogen, ***red top to freeze and hold. Stool covid pcr if diarrhea and resp pcr and ab negative***.

• **Empiric antibiotics** (vancomycin, ceftriaxone) until cultures negative for 48 hour or as-directed by ID.

• **Consults:** ID, Hematology and Cardiology for all ICU patients. **Rheumatology** if considering biologics

• **IVIG:** Give 2 g/kg x 1 if not already given on IPS (use ideal body weight). If not responding, see **REFRACTORY DISEASE** box

• **Steroids:** methylpred 30 mg/kg/day divided bid, with a maximum of 1 g for 1-3 days, then 2mg/kg/day divided bid. Taper over 2-3 weeks per ID

• **Aspirin-** use low-dose (3-5 mg/kg/day with max dose of 81 mg/day) in all patients unless platelet count is <50,000. Note, ok to use prophylactic Lovenox with low-dose aspirin (which adds anti-platelet and coronary artery protection).

• **VTE prophylaxis** for all patients unless contraindication with enoxaparin***. Patients with EF < 35% should be considered for treatment with THERAPEUTIC anticoagulation alone (no aspirin needed).***

• **GI prophylaxis**

Trending of Labs and EKGs in ICU patients

• 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 or sooner if clinical worsening

• Repeat other labs as indicated

• EKG Q48 hrs to monitor QT interval, or sooner if clinical worsening

REFRACTORY DISEASE-See Box B

Disease Severity * Not well defined in literature

Mild: Borderline or mild case. Normal VS apart from fever, no inpt criteria other than poor PO, mild dehydration, or monitoring for worsening

Moderate: Meets case definition without shock or other ICU criteria. Note-moderate can rapidly deteriorate

Severe: Meets ICU criteria

REFRACTORY DISEASE

Defined as persistent fevers and/or symptoms not improving. Timing of fever in relation to IVIG is not defined; consider if fever present 36 hours AFTER completion of IVIG.

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Discharge criteria: • CRP, ferritin, and d-dimer improving • Afebrile x 48 hours • Blood cultures without growth x 48 hours • EKG without arrhythmia • Latest echo stable/improved • Tolerating enteral diet • Not requiring oxygen • Follow-up PID,Card

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/dose 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) **Severe MIS-C:** - 4mg/kg/dose SQ once daily x 5 days (Max 100mg/dose) -escalate to 4mg/kg SQ Q6h 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 (moderate presentation):** - 2 mg/kg/day divided q8-q12h **Pulse dosing (severe presentation of refractory):** 30mg/kg/day divided bid for 1-3 days, max dose 1g, followed by 2 mg/kg/day divided followed by a taper over 2-3 weeks Peds ID to assist with duration and taper	**Adverse events:** -Hypertension - Hyperglycemia -PRES

DISPOSITION

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

-steroid wean in those treated over 2-3 weeks

-all patients should be seen in Ped cardiology clinic 2 weeks post discharge.

-all patients should be seen in Peds ID clinic ~ 2 weeks after discharge

Consider readmission for:

- Any recurrent fever or other recurrence of symptoms (rash, mucositis, conjunctivitis, vomiting/diarrhea, neurological changes, chest pain, etc.) should prompt urgent evaluation by primary provider. If patient is stable and can be assessed by outpatient provider within 6-12 hours that may be considered. Otherwise return to MBED

-If seen in primary clinic with recurrence of symptoms, obtain full exam + VS including BP. If unstable transfer to MBED. 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. Outpatient providers should contact PEDS ID on call to discuss,

-Worsening laboratory markers (e.g.increasing CRP) in absence of clinical signs should prompt outpatient discussion with specialists (ID, cardiology, hematology depending on the laboratory study).

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 as above
- Families should receive teaching on stress dose steroids.
-Limit exercise and strenuous activity until cleared by cardiology (may be several weeks-months)

REPORTING

Patients meeting the CDC case definition should be reported to the WA state DOH at 206-296-4774 within 24 hours. Please email Christy Robinson-Bortel, MB IP nurse to assist in reporting

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

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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.