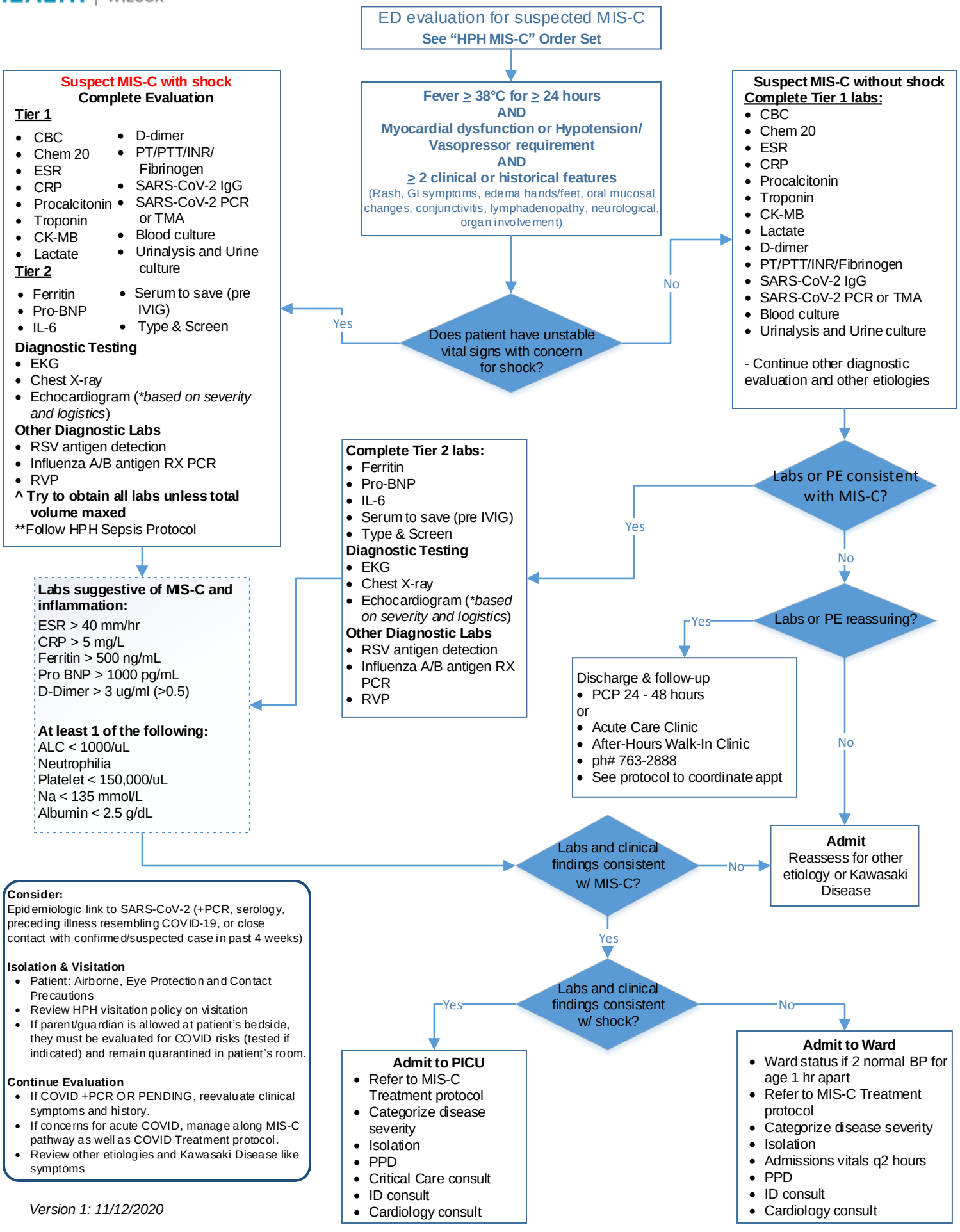
HAWAI'I PACIFIC HEALTH | KAPI'OLANI PALI MOMI STRAUB WILCOX

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated COVID-19 Evaluation Protocol



Consider:
Epidemiologic link to SARS-CoV-2 (+PCR, serology, preceding illness resembling COVID-19, or close contact with confirmed/suspected case in past 4 weeks)

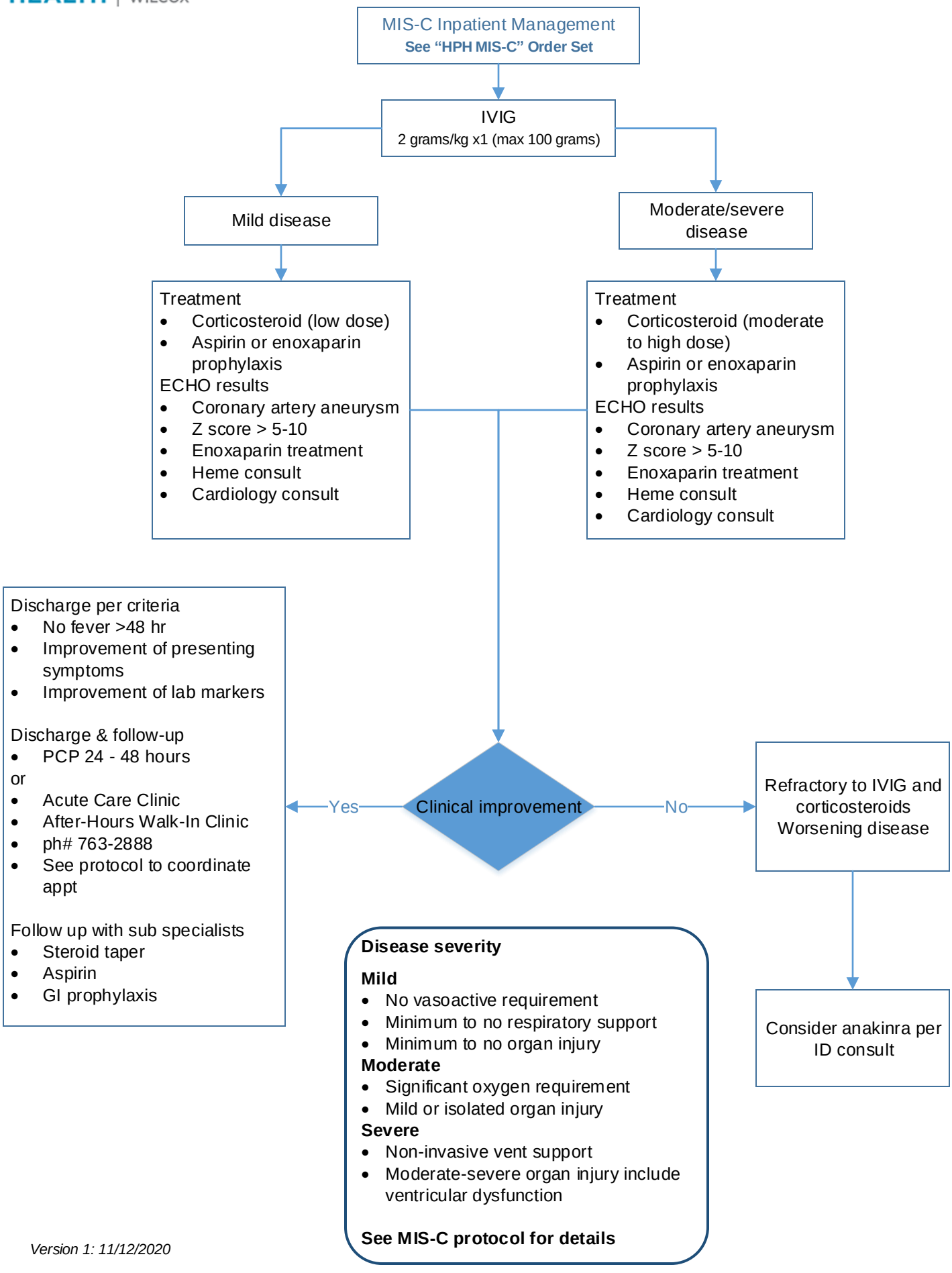
Isolation & Visitation
- Patient: Airborne, Eye Protection and Contact Precautions
- Review HPH visitation policy on visitation
- If parent/guardian is allowed at patient's bedside, they must be evaluated for COVID risks (tested if indicated) and remain quarantined in patient's room.

Continue Evaluation
- If COVID +PCR OR PENDING, reevaluate clinical symptoms and history.
- If concerns for acute COVID, manage along MIS-C pathway as well as COVID Treatment protocol.
- Review other etiologies and Kawasaki Disease like symptoms

Version 1: 11/12/2020

HAWAIʻI PACIFIC HEALTH | KAPIʻOLANI PALI MOMI STRAUB WILCOX

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated COVID-19 Treatment Algorithm



Version 1: 11/12/2020

Hawai'i Pacific Health Kapiolani Medical Center for Women & Children
Multisystem Inflammatory Syndrome in Children (MIS-C)
Associated with Coronavirus Disease 2019 (COVID-19)

CDC MIS-C Case Definition:
As described in the Health Advisory 5/14/2020
Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

Patient presents with ALL:

- Age <21 years with:
  - Fever: ≥ 38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
  - Laboratory evidence of inflammation: 1 or more of the following:

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

  - Evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement [cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic]
- No alternative plausible diagnoses
- Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

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.

CDC Clinical Manifestations may include:

- Vasodilatory shock with normal or mildly depressed systolic function
- Cardiogenic shock with > moderate systolic dysfunction
- Kawasaki Disease features – can be complete or incomplete KD
- Clinical and laboratory features of cytokine storm
- Coronary artery dilation and aneurysms (up to 25% of children and teens with MIS-C)
- Any combination above

Links:

- https://www.cdc.gov/mis-c/hcp/
- https://www.cdc.gov/mis-c/pdfs/hcp/MIS-Children-Handout-FINAL.pdf

American College of Rheumatology Differences between KD and MIS-C:

- Ethnic/racial differences (lower incidence in those of East Asian descent)
- MIS-C patients encompass a broader age range, generally older
- MIS-C patients have more prominent GI, neuro symptoms
- MIS-C patients present more frequently with shock, cardiac dysfunction
- MIS-C patients lower platelet counts, absolute lymphocyte counts, and higher CRP

Diagnostic SARS-CoV-2 Testing: ***(see HPH Multisystem Inflammatory Syndrome in Children (MIS-C) order set)***

- SARS-CoV-2 detection by RT-PCR or antigen test
- SARS-CoV-2 serology testing is suggested, even in the presence of positive RT-PCR or antigen testing.
    - Any serology testing should be performed prior to administering IVIG or any other exogenous antibody treatments.

Tier 1 Initial and Monitoring Labs:

- Complete Blood Count (CBC)
- Chem 20 (ordered as CMP, Phos, Uric acid, GGTP, Cholesterol, Triglyceride, LDH),
- Erythrocyte Sedimentation Rate (ESR)
- C-Reactive Protein (CRP)
- Procalcitonin
- Troponin
- CKMB
- Lactate
- D-dimer
- PT/PTT/INR, Fibrinogen
- SARS-CoV-2 IgG
- SARS-CoV-2 PCR or TMA nasopharyngeal
- Blood culture
- UA with Urine culture
- Testing aimed at identifying laboratory evidence of inflammation as listed in the Case Definition section is warranted.
- Testing to evaluate multisystem involvement should be directed by patient signs or symptoms.
- Testing as indicated to evaluate for other potential diagnoses should be directed by patient signs or symptoms.

Tier 2 and Monitoring Labs:

- Ferritin
- Pro B-type natriuretic peptide (BNP)
- IL-6
- KSAVE (serum to save prior to IVIG)
- Type and screen
- Vancomycin trough prior to 4th dose

Diagnostic Testing

- Echocardiogram baseline and follow up as needed (*based on severity of shock and logistics)
- Electrocardiogram
- Chest X-ray
- Cardiac MRI if needed and in follow up at 2-6 months if LVEF <50%

Other Diagnostic Labs (consider as needed):

- RSV antigen detection
- Influenza A/B antigen with reflex PCR
- Respiratory Viral Panel

Lab Monitoring during Hospitalization:

- CBC daily
- Chem 20 daily
- CRP daily
- Procalcitonin daily
- Troponin daily
- CKMB daily
- Lactate daily
- D-dimer daily
- PT/PTT/INR, Fibrinogen daily
- Ferritin daily
- Pro BNP daily
- IL-6 weekly
- Daily laboratory values are followed frequently to monitor the hyper inflammation while patients have evidence of shock and/or fever and/or persistence of symptoms (e.g., rash, conjunctivitis, diarrhea, etc).
- Daily labs can be discontinued when clinical symptoms have substantially improved, and laboratory markers are improving (but do not have to be normal) – these decisions should be individualized and considered with the primary team and multidisciplinary consultants.
- Schedule should be reassessed daily and de-escalated as clinically indicated

Table 1. MIS-C Classification of Severity – see appendix 1

Presentation	Description
Mild	• No vasoactive requirement • Minimal/no respiratory support • Minimal/no organ injury
Moderate	• Significant supplemental oxygen requirement • Mild or isolated organ injury
Severe	• Non-invasive ventilator support • Moderate or severe organ injury including moderate to severe ventricular dysfunction

Infection Control Isolation Precautions:

- Airborne isolation
- Contact isolation
- Eye protection isolation

Treatment:

There are currently no known optimal or published CDC guidelines or recommendations for the treatment of MIS-C. A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and/or glucocorticoids considered as first tier treatments.
See references/appendix for institutional protocols or publications.

Treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process.

Supportive care measures:

- Fluid resuscitation
- Inotropic support
- Respiratory support and
- In rare cases, extracorporeal membranous oxygenation (ECMO)

Antimicrobial Treatment:

Antibiotics are recommended to treat potential sepsis while awaiting bacterial cultures. Refer to Sepsis guidelines.

Table 2. MIS-C Drug Treatment by Clinical Severity – see appendix 1

Treatment	Mild	Moderate	Severe
IVIG	Yes	Yes	Yes
Corticosteroids • Methylprednisolone • Prednisone	Yes (low dose)	Yes (moderate dose)	Yes (high dose)
Anticoagulation • Aspirin • Enoxaparin	Aspirin (low dose) or enoxaparin (prophylaxis dose)	Aspirin (low dose) or enoxaparin (prophylaxis dose)	Aspirin (low dose) or enoxaparin (prophylaxis dose)
	Enoxaparin (treatment dose) • Z scores 5-10 Consider based on absolute size • Hematology and Cardiac Consultation	Enoxaparin (treatment dose) • Z scores >5-10 Consider based on absolute size • Hematology and Cardiac Consultation	Enoxaparin (treatment dose) • Z scores > 5-10 Consider based on absolute size • Hematology and Cardiac Consultation
Other Immunmodulators • Anakinra • Tocilizumab	No	Consider for disease refractory to IVIG and corticosteroids or worsening disease with multidisciplinary consultation	Consider for disease refractory to IVIG and corticosteroids or worsening disease with multidisciplinary consultation

Table 3. MIS-C Drug Treatment

Agent	Dose	Main Toxicities	Notes
IVIG	• 2 g/kg IV x 1 dose (max dose 100 g) • Round to nearest vial size if within 10% of ordered dose	• Infusion reactions • Anaphylaxis • Transaminitis • Aseptic meningitis • Hemolysis	• IVIG infusion rate per KD protocol • Assess cardiac function and fluid status in patients with shock before administration • For patients that cannot tolerate volume load, dose can be divided over 2 days
Methylprednisolone Prednisone	<u>Low dose</u> • 2 mg/kg/day (max 60 mg per day) IV divided q12h x 10 days, then • 1 mg/kg/day IV x 5 days, then • 0.5 mg/kg/day IV x 5 days <u>Moderate dose</u> • 10 mg/kg/day IV x 1 day (max 500 mg per day), then • 2 mg/kg/day IV divided q12h <u>High dose</u> • 20 mg/kg/day IV x 3 days (max 1000 mg per day), then • 2 mg/kg/day IV q12h	• Hypertension • Hyperglycemia	• Can consider equivalent oral dose if indicated
Aspirin	**<u>Low dose</u>** • < 10 kg: 40.5 mg daily • ≥ 10 kg: 81 mg daily		• Avoid platelets ≤ 80,000
Enoxaparin	**<u>Prophylaxis</u>** • < 2 months: 0.75 mg/kg/dose q12h • ≥ 2 months: 0.5 mg/kg/dose q12h **<u>Treatment</u>** • < 2 months: 1.5 mg/kg/dose q12h • ≥ 2 months: 1 mg/kg/dose q12h		• Consider Hematology screening prior to start • Consider for patients with coagulopathy • Treatment – target anti-Xa level 0.5-1 • Z scores >10 • Z scores 5-10 – consider based on absolute size

Table 4. Refractory MIS-C Drug Treatment (with Multidisciplinary Team input)

Anakinra** (IL-1 receptor antagonist) **(ID Consult)**	• 2 mg/kg/dose SQ divided q12h (max single dose 100 mg) • Can increase to q8h if clinically needed **Dose based on Boston's Children protocol	• Increased LFTs • Hematologic suppression • Increased risk of infection • Hypersensitivity reactions • Malignancies	• Short half-life: SQ: ~4-6 hours IV: ~2 hours • Established use and safety profile • Dose adjustment for mod-severe renal impairment • IV route can be considered if higher plasma conc needed • IV over 5 minutes • Avoid live viral vaccines
Tocilizumab** (IL-6 receptor antagonist) **(ID Consult)**	• < 30 kg: 12 mg/kg IV x 1 • ≥ 30 kg: 8 mg/kg IV x 1 (max 800 mg) • Round to nearest vial size if within 10% of ordered dose • Consider additional dose 12 hours later if continued clinical decompensation (Max 2 doses) **Dose based on Boston's Children protocol and extrapolated from use in CAR T cell or blinatumomab therapy	• Gastrointestinal perforation • Hypertriglyceridemia • Pancreatitis • Hepatitis • Neutropenia • Thrombocytopenia • Anemia • Increased risk of infection • Anaphylaxis • Infusion reaction	• Long half-life: ~2 weeks • Avoid live viral vaccines • Increased IL-6 levels can inhibit P450 enzymes

Discharge Criteria, Instructions and Follow-up Plan:
Discharge criteria will vary depending on the clinical scenario and severity of presenting illness, but generally include lack of fever for 48 hours without antipyretics (excluding steroids), improvement in the presenting clinical symptoms (e.g., diarrhea, rash, etc) and/or improvement in lab markers.
Criteria for discharge should be discussed with subspecialist services seeing the patient in follow up.

Discharged patients should follow-up with their PCP within 24-48 hours. If the PCP is not seeing COVID+ and/or MIS-C patients, a follow-up visit can be scheduled with the Pediatric Acute Care Clinic or the After-Hours Walk-In Clinic located in the 3rd floor Multi-Disciplinary Clinic and Pediatric Outpatient Clinic on the first floor of the shared services building, respectively. Please call 763-2888 to schedule these patients and notify the staff that the patient is a COVID+ and/or MIS-C patient requiring follow-up. The staff will also ask for a family contact number, as they will direct them where to park and will request details about their vehicle. These patients will be met outside by security and will be escorted to either clinic to minimize exposure of other patients and families. Ideally, please also send an in-basket message to the WC After Hours Walk-In Clinic Pool to notify the team that the patient needs to be seen, what they have been diagnosed with (COVID+ versus MIS-C) and any specific labs or exam findings that you would like the provider to look out for. Labs can be obtained in the clinic.

Clinic Follow-Up Summary

- Call 763-2888 to schedule an appointment. Provide family contact number to clinic.
- Please send an in-basket message to the WC After-Hours Walk-in Clinic Pool to notify the team that the patient needs to be seen and provide pertinent information.
- Pediatric Acute Care Clinic Hours
    - Monday – Friday 13:30 to 17:00
- Pediatric After-Hours Walk-In Clinic Hours
    - Monday – Friday 17:00 to 20:00
    - Saturday – Sunday 12:00 to 19:00

Follow-up Echocardiogram and EKG:
Schedule depending on severity of initial dysfunction, presence of coronary artery dilation, and clinical course, in discussion with cardiology.

- Baseline
- Prior to discharge
- 1 week
- 4 weeks
- 6-8 weeks
- 3-6 months
- 6-9 months
- 12 months and beyond

References:

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Protocol References:

1. Boston Children's PMIS COVID-19 Evaluation and Management Protocol, Accessed (5/2020)
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5. Dell Children's Mulitsystem Inflammatory Syndrome (MIS-C) Evidence-Based Outcomes Center, last updated 8/20/2020

Appendix:

CLASSIFICATION OF CLINICAL SEVERITY

- **Mild:** No vasoactive requirement, minimal/no respiratory support, minimal organ injury
- **Moderate:** Vasoactive-inotropic score** (VIS) ≤ 10, significant supplemental oxygen requirement, mild or isolated organ injury
- **Severe:** Vasoactive-inotropic score > 10, non-invasive or invasive ventilatory support, moderate or severe organ injury including moderate to severe ventricular dysfunction

**See supplement for instructions on VIS calculation

MANAGEMENT BY CLINICAL SEVERITY

Therapeutic Category	Mild	Moderate	Severe
Steroid Initial Dosing For 2mg/kg/day dosing: max 60mg/day For pulse dosing: max 1g/day	Methylprednisolone 2mg/kg/day	Methylprednisolone 10mg/kg x1, then 2mg/kg/day	Methylprednisolone 20-30mg/kg/day for 1-3 days, then 2mg/kg/day
Other Immunomodulation (see "Other Management Considerations" below for specific guidance) For Anakinra dosing: 2-10mg/kg/dose (max 100mg/dose) up to q6h frequency	Consider pulse Methylprednisolone or Anakinra if refractory illness course	Consider 1-3 days pulse Methylprednisolone, consider Anakinra if refractory to steroids	Consider Anakinra if refractory to steroids, consider other biologics if refractory to Anakinra
Anticoagulation - monitor for bleeding, thrombocytopenia, coagulopathy LMWH = low molecular-weight heparin ASA = aspirin	LMWH prophylaxis **or** low-dose ASA	LMWH prophylaxis **or** low-dose ASA	LMWH prophylaxis **or** low-dose ASA
GI prophylaxis with proton pump inhibitor	Yes	Yes	Yes
Broad-spectrum antibiotics (see "Other Management Considerations" below for specific guidance)	Yes	Yes	Yes
Steroid Taper	2-3 weeks	6-8 weeks	Steroid taper with subspecialty consultation

[i] Treatment may be deferred (if cardiac evaluation is normal) with close clinical observation and serial trending of inflammatory and cardiac biomarkers

Jonat B, et al. (in review)

Columbia University College of Physicians and Surgeons

NewYork-Presbyterian Kids Morgan Stanley Children's Hospital

Boston Children's Hospital Until every child is well

Boston Children's Hospital COVID-19 Treatment: Internal Guidance

A. LABORATORY EVALUATION AND SUBSPECIALTY CONSULTATION

Table 1. Recommendations for Laboratory Evaluation and Subspecialty Consultation

Disease Category	Respiratory Status	Concern for MIS-C (see Section C for definition)	Diagnostic Evaluation (pre-consultation)	Subspecialty Consultation
Mild	No dyspnea	• Fever *and* • GI symptoms *and* • Kawasaki disease features (rash, conjunctivitis, extremity changes, mucositis, lymphadenopathy) *and* • Epidemiologic link to SARS CoV-2	• SARS-CoV-2 PCR and/or serologies • Consider CBC with differential, BUN, creatinine, LFTs, ESR, CRP • Consider chest x-ray	• Consult Rheumatology if concern for MIS-C • Supportive care; no antiviral or immunomodulatory treatment recommended
Moderate	Dyspnea and/or chest imaging consistent with COVID-19, but no change from pre-illness baseline respiratory support requirement	Same as mild cases *plus*: • Myocardial dysfunction (without need for vasopressors) • Significant abdominal pain, vomiting, diarrhea • Neurologic features (severe headache, meningismus, focal neurologic deficits, mental status changes)	• SARS-CoV-2 PCR and/or serologies • CBC with differential, BUN, creatinine, LFTs, LDH, ESR, CRP, PT & PTT, D-dimer, procalcitonin, ferritin[1] • Troponin and BNP • If available, cytokine panel[1] • Chest x-ray for respiratory symptoms • EKG	• Consult Immunology and Infectious Diseases (ID) for all cases • Consult Rheumatology if concern for MIS-C or Cytokine Storm • Consult Cardiology if concern for MIS-C
Severe	Dyspnea and/or chest imaging consistent with COVID-19, with new or increased supplemental O_2 and/or non-invasive ventilatory support requirement	Same as for moderate cases	Same as for moderate cases	Consult Immunology, ID, Rheumatology, and Cardiology for all cases
Critical	Respiratory failure requiring mechanical ventilation +/- acute respiratory distress syndrome (ARDS)	• Myocardial dysfunction and/or low-output heart failure requiring vasopressor support or ECMO • Systemic inflammatory response syndrome (SIRS) • Multi-organ failure • Encephalopathy	Same as for moderate cases	Same as for severe cases

[1]At BCH, order these studies using the COVID-19 Immunology Panel Plan [found within the COVID-19 (Novel Coronavirus) Evaluation Plan].