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NewYork-Presbyterian Kids
Morgan Stanley Children's Hospital

CLINICAL PROTOCOL FOR MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED WITH CORONAVIRUS 2019 (COVID-19)

PROTOCOL:

This protocol is intended as a general guide and should be applied and interpreted with caution and are likely to change over time. Departure from this protocol may be appropriate and necessary in certain clinical circumstances.

PURPOSE:

To aid in the work-up, management and follow up of pediatric patients (< 21 years old) with confirmed or suspected MIS-C secondary to infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This protocol is not for the management of primary (active) SARS-CoV-2 infection. This protocol does not address isolation precautions, transport, airway and treatment of suspected active SARS-CoV-2 infection.

CASE SCREENING: PATIENT PRESENTATION WITH CLINICAL SUSPICION OF MIS-C

Patients may have a preceding illness consistent with COVID-19 or had a COVID-19 sick contact

- **Systemic Inflammation**
  - Fever*
  - Myalgias
  - Tachycardia
  - Hypotension
  - Hypoperfusion or hyperperfusion
  - Lymphadenopathy/lymphadenitis
- **Cardiopulmonary**
  - Respiratory distress
  - Chest pain
- **Neurologic**
  - Headache
  - Altered mental status
  - Meningismus
  - Focal deficits
  - Seizure
- **Mucocutaneous**
  - Rash - reticular, morbilliform, purpuric
  - Lip swelling/cracking
  - Strawberry tongue
  - Extremity swelling/peeling
  - Conjunctivitis
  - Blisters or erosions
- **Gastrointestinal**
  - Nausea/Vomiting
  - Diarrhea
  - Abdominal Pain

***This is a required symptom**

INITIAL LAB AND IMAGING WORK-UP

- SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab
- SARS-CoV-2 serology testing
  - Obtain serology sample before administration of intravenous immunoglobulin (IVIG)

- Complete blood count with differential, basic metabolic panel, liver function panel, blood gas with lactate, c-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin, D-dimer, lactate dehydrogenase, prothrombin time, partial thromboplastin time, fibrinogen, N-terminal-pro B-type natriuretic peptide (NT-proBNP), troponin, creatine phosphokinase, triglycerides, soluble interleukin-2 receptor
- Urinalysis with microscopy, urine creatinine, urine protein
- Blood culture, respiratory pathogen PCR panel, Methicillin-resistant *Staphylococcus aureus* (MRSA) PCR screen
- Quantitative immunoglobulins
- **If concern for viral co-infection or MIS-C mimic:**
  - Cytomegalovirus, Epstein-barr virus, Parvovirus, Adenovirus PCRs, Coxsackie IgM/IgG
- **If cardiac or neurologic abnormalities and risk of exposure:**
  - Lyme IgM/IgG

- Transthoracic echocardiogram focused on ventricular function and coronary arteries
- Chest X-Ray
- Electrocardiogram (ECG)

ORGAN-SPECIFIC WORK-UP BASED ON PATIENT SYMPTOMS

Gastrointestinal

- SARS-CoV-2 stool PCR (if available)
- Gastrointestinal (GI) pathogen PCR Panel
- Calprotectin
- *Clostridium difficile* toxin PCR - if diarrhea

Dermatologic

- Add photographs of rash to chart if available
- Herpes Simplex Virus (HSV), Varicella, and Enterovirus PCR of erosion, blister, or varicella-like lesion

Neurologic

- Head Imaging - consider if focal neurologic deficit, altered mental status, seizure, or severe headache with or without meningeal signs
- Cerebrospinal fluid (CSF) Studies - if lumbar puncture indicated
  - Opening pressure, cell count, glucose, protein, lactate, culture, infectious meningitis/encephalitis PCR panel
  - Paraneoplastic panel (if indicated)
  - Autoimmune encephalitis panel (if indicated)

CASE IDENTIFICATION†

Confirmed case: Meets clinical, laboratory, and virologic criteria
Suspected case: Meets clinical, laboratory, and epidemiologic criteria

Clinical Criteria

- One day of fever >38°C (or subjective fever)
- Hospitalization
- **Either:**
  - At least one sign of severe systemic inflammation or organ dysfunction including:
    - Hypotension or shock
    - Severe cardiac illness - myocarditis, elevated troponin/NT-proBNP, coronary artery abnormalities
    - Other severe organ involvement or injury (excluding isolated respiratory disease)
- **Or:**
  - Two or more signs of multi-system involvement including:
    - Rash
    - Conjunctivitis
    - Mucocutaneous inflammatory signs
    - Gastrointestinal symptoms

Laboratory Criteria

- Two or more abnormal markers of inflammation including:
  - Neutrophilia, lymphopenia, thrombocytopenia, hypoalbuminemia, elevated c-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-Dimer, ferritin, lactic acid dehydrogenase, interleukin 6, procalcitonin

Virologic Criteria

- At least one test indicating past or present SARS-CoV-2 infection including:
  - Detection of SARS-CoV-2 RNA through molecular amplification (RT-PCR) at time of illness or within 4 weeks prior
  - Detection of SARS-CoV-2 antigen in a clinical specimen at time of illness or within 4 weeks prior
  - Detection of SARS-CoV-2 antibody in serum, plasma, or whole blood

Epidemiologic Criteria

- At least one high-risk exposure in the 6 weeks prior to symptom onset:
  - Close contact with an individual with laboratory-confirmed SARS-CoV-2
  - Close contact with an individual with COVID-19 symptoms, who had close contact with an individual with laboratory confirmed SARS-CoV-2
  - Travel or residence in an area with sustained, ongoing community transmission of SARS-CoV-2

† Modified from New York State Department of Health criteria. For original case definition see https://health.ny.gov/press/releases/2020/docs/2020-05-13_health_advisory.pdf

INITIAL INPATIENT CONSULTS

- All patients (if available): Pediatric Rheumatology (or appropriate institutional subspecialty team), Pediatric Infectious Diseases, Pediatric Cardiology
- Pediatric GI and Pediatric Surgery consults - if localized abdominal pain
- **If patient has suspected hemophagocytic lymphohistiocytosis (HLH) or meets HLH criteria → do not use these management guidelines, further management with appropriate institutional subspecialty consultation**
- Additional consults based on presenting symptoms and clinical indications

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CLASSIFICATION OF CLINICAL SEVERITY

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

**See appendix for instructions on VIS calculation

SPECIAL CONSIDERATION IN MILD CASES

- In mild cases consider **deferral of treatment with serial testing** if:
  - No signs of shock
  - Minimal signs of inflammation on laboratory evaluation
  - No cardiac involvement (normal to mildly elevated troponin and/or N-terminal-pro B-type natriuretic peptide with normal ECG and echocardiogram)

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 10mg/kg/dose q6h 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

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INTRAVENOUS IMMUNOGLOBULIN

- All patients with MIS-C who undergo treatment should receive IVIG 2g/kg up to 100g. A second dose of IVIG should be considered in refractory cases. Obtain serum quantitative immunoglobulins and necessary serum serologies before administration of IVIG.
  - If IVIG indicated but unavailable, discuss with relevant subspecialty teams appropriate alternative therapy.

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OTHER MANAGEMENT CONSIDERATIONS

- **Biologics**: When considering "other biologics" for patients with severe, refractory illness would advise specialty consultation (rheumatology and/or immunology). Tocilizumab should be used with caution.
- **Antibiotics:** Ceftriaxone should be used as first-line empiric antibiotic coverage.
  - Add vancomycin if concerned for MRSA infection, including skin or soft tissue source.
  - Add metronidazole if concerned for intra-abdominal infection.
  - Reserve piperacillin-tazobactam for patients who are immunocompromised, have a history of multi-drug resistant gram-negative bacterial infections, are critically ill, or if otherwise clinically indicated.
  - Consider further coverage for toxic shock syndrome or Rickettsia infection depending on patient presentation.
- **Anticoagulation:** LMWH preferred over ASA for initial anticoagulation in patients with elevated D-dimer or fibrinogen, who are unable to tolerate ASA due to GI symptoms, or are critically ill. Consider full clinical presentation when deciding anticoagulation regimen.
- **Patients with GI Symptoms:** Treatment with high-dose steroids has been associated with GI bleeding and perforation in hospitalized patients. Consider risk/benefit of therapy, particularly in patients with GI symptoms .
- **Patients with Renal Injury:** Consult clinical pharmacy for assistance in dosing biologic medications.

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FOLLOW-UP INPATIENT LAB AND IMAGING

Pediatric Intensive Care Patients	**General Wards Patients**
• Troponin and NT-proBNP - repeat q48h • ECG - repeat weekly • Echocardiogram - repeat weekly	• Troponin and NT-proBNP - repeat weekly • ECG - repeat weekly • Echocardiogram - repeat every 2 weeks

- Clinical change or abnormal trends may warrant earlier evaluations to be determined by primary team.
- Trend of other laboratory tests and studies to be determined by primary team.

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POST-DISCHARGE FOLLOW-UP

- All patients should be discharged home on ASA 5 mg/kg/day unless contraindicated or if there is a clinical indication for other anticoagulation.
- All patients should have follow-up within 2 weeks post discharge with a pediatric cardiologist and pediatric rheumatologist (or appropriate subspecialist) for clinical evaluation, repeat echocardiogram, and management of steroid taper.
- Additional follow-up depending on presenting symptoms and clinical indications.

GUILDELINE APPENDIX:

Vasoactive-Inotropic Score Calculation

VIS = dopamine dose (μg/kg/min) +
dobutamine dose (μg/kg/min) +
100 x epinephrine dose (μg/kg/min) +
10 x milrinone dose (μg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
100 x norepinephrine dose (μg/kg/min)