GUIDELINES FOR MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED WITH CORONAVIRUS 2019 (COVID-19)

GUIDELINES:

These guidelines are intended as a general guide and should be applied and interpreted with caution and are likely to change over time. Departure from these guidelines may be appropriate and necessary in certain clinical circumstances (guidelines as of 6/5/2020).

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). These guidelines are not for the management of primary (active) SARS-CoV-2 infection. These guidelines do not address isolation precautions, transport, airway and treatment of suspected active SARS-CoV-2 infection. For management of primary COVID-19 infection please see “MSCH Pediatric Inpatient COVID-19 Management Guidelines.”
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

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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, interleukin 6, von Willebrand factor antigen, 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:**
  - Lyme IgM/IgG
- Transthoracic echocardiogram focused on ventricular function and coronary arteries - order as “COVID protocol”
- Chest X-Ray
- Electrocardiogram (ECG)
## ORGAN-SPECIFIC WORK-UP BASED ON PATIENT SYMPTOMS

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Dermatologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SARS-CoV-2 stool PCR (research)</td>
<td>• Add photographs of rash to chart</td>
</tr>
<tr>
<td>• Gastrointestinal (GI) pathogen PCR Panel</td>
<td>• Herpes Simplex Virus (HSV), Varicella, and</td>
</tr>
<tr>
<td>• Calprotectin</td>
<td>Enterovirus PCR of erosion, blister, or varicella-like lesion</td>
</tr>
<tr>
<td>• <em>Clostridium difficile</em> toxin PCR - if diarrhea</td>
<td></td>
</tr>
</tbody>
</table>

### 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
  - Additional CSF for research SARS-CoV-2 PCR - contact pediatric neurology resident on-call
  - Paraneoplastic panel (if indicated)
  - Autoimmune encephalitis panel (if indicated)

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

### 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
- The absence of a more likely diagnosis for the illness
- 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
MANAGEMENT BY CLINICAL SEVERITY

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

INTRAVENOUS IMMUNOGLOBULIN

- All patients with MIS-C 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.
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.\(^\text{10}\)
- **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**: These patients have higher risk of bowel perforation with pulse steroids. Consider risk/benefit of therapy in these patients.
- **Patients with Renal Injury**: Consult clinical pharmacy for assistance in dosing biologic medications.

FOLLOW-UP INPATIENT LAB AND IMAGING

<table>
<thead>
<tr>
<th>Pediatric Intensive Care Patients</th>
<th>General Wards Patients</th>
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<tbody>
<tr>
<td>Troponin and NT-proBNP - repeat q48h</td>
<td>Troponin and NT-proBNP - repeat weekly</td>
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<tr>
<td>ECG - repeat weekly</td>
<td>ECG - repeat weekly</td>
</tr>
<tr>
<td>Echocardiogram - repeat weekly</td>
<td>Echocardiogram - repeat every 2 weeks</td>
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</tbody>
</table>

- 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.

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 in COVID-19 multidisciplinary clinic (scheduled through cardiology) for clinical evaluation, repeat echocardiogram, and management of steroid taper.
- Additional follow-up depending on presenting symptoms and clinical indications.

GUIDELINE SUPPLEMENT:

Vasoactive-Inotropic Score Calculation

\[
VIS = \text{dopamine dose (µg/kg/min)} + \text{dobutamine dose (µg/kg/min)} + 100 \times \text{epinephrine dose (µg/kg/min)} + 10 \times \text{milrinone dose (µg/kg/min)} + 10,000 \times \text{vasopressin dose (U/kg/min)} + 100 \times \text{norepinephrine dose (µg/kg/min)}
\]
Multi-system Inflammatory Syndrome in Children management flowchart

- KD/incomplete KD criteria without suspected MIS-C
- Follow American Heart Association guidelines on KD management, do not use this algorithm

All Patients (Unless Contraindicated):
- Broad-spectrum antibiotics, GI prophylaxis, LMWH prophylaxis or low-dose ASA
- IVIG 2g/kg up to 100g – consider 2nd dose in refractory cases

- Patient with presentation consistent with Multi-system Inflammatory Syndrome in Children (MIS-C)
- Patient with suspected or confirmed HLH
- BMT consult do not use this algorithm

Mild
- No vasoactive requirement
- Minimal respiratory support
- Minimal organ injury

Moderate
- V5 > 10
- Significant O2 requirement
- Mild organ injury

Severe
- V5 > 10
- Non-invasive or invasive ventilatory support
- Moderate/severe organ injury
- Moderate/severe ventricular dysfunction

Methylprednisolone
- 2mg/kg/day
- Consider pulse
- Methylprednisolone or Anakinra if refractory illness course

Steroid Taper: 14-21 days

Methylprednisolone
- 10mg/kg x1 dose then 2mg/kg/day
- Consider 1-3 day pulse
- Methylprednisolone course
- Consider Anakinra if refractory to pulse steroids

Steroid Taper: 6-8 weeks

Methylprednisolone
- 20-30mg/kg/day for 1-3 days, then 2mg/kg/day
- Anakinra if refractory to steroids
- Consider other biologics if refractory to anakinra

Steroid taper with subspecialty consultation

-^ For Methylprednisolone 2mg/kg/day dosing, maximum dose of 60mg/day.
- For Methylprednisolone pulse dosing, maximum dose of 1g/day.
- For Anakinra, 2-10mg/kg/dose (maximum 100mg/dose) up to q6h frequency.
- **Refer to “Other Management Considerations” for specific guidance.

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References:


