NEMOURS CHILDREN'S HEALTH

# Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Ambulatory Care

**INCLUSION CRITERIA**

Patients <21 yo presenting with

- **Fever >38°C AND** no alternative dx **AND** ≥2 of the following:
  - GI (pain, vomiting, diarrhea, anorexia, loss of taste)
  - Rash
  - Conjunctivitis
  - Oral inflammation
  - Altered mental status
  - Extremity swelling
  - Lymphadenopathy

**OR**

- One or more of the following:
  - Hypotension or shock
  - Evidence of cardiac dysfunction
  - End organ involvement

**EXCLUSION CRITERIA**

- Alternative plausible diagnosis

**[1]MIS-C Definition**

- <21 yo presenting with fever >38C (or tactile) for ≥ 24 hrs **AND**
- Clinically severe illness requiring hospitalization **AND**
- Multisystem (≥2) organ involvement: cardiac, renal, pulm, heme, GI, derm, neuro **AND**
- Lab evidence of inflammation
  - (elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, IL6, neutrophilia, lymphocytopenia, hypoalbuminemia) **AND**
- No alternative plausible dx **AND**
- Current or recent SARS-COV-2 infection by PCR or antigen test or serology; or COVID-19 exposure within 8 weeks of presentation

**Nursing Assessment**

- Obtain and document vital signs and pulse ox
- Room patient per COVID Screen positive protocol
- Enhanced contact and droplet PPE with use of N95 for airborne generating procedures

**Low Risk**

- Mildly ill appearing pts presenting with ≥3 days of fever **AND** ≥2 symptoms from inclusion criteria

**Moderate Risk**

- Ill appearing pts presenting with ≥3 days of fever **AND** ≥2 symptoms from inclusion criteria

**High Risk**

- Toxic appearing **OR** evidence of shock **OR** evidence of cardiac dysfunction

Low Risk → Outpt lab capability within 12 hours?

- No → Refer to ED for complete evaluation
- Yes → Screening Evaluation

Moderate Risk / High Risk → Refer to ED for complete evaluation

**Screening Evaluation**

- CBC, CRP, CMP, BNP, troponin
- EKG if chest pain
- **Further workup based on clinical indications**

Diagnostics Normal (Pg 4)?

- No → **Refer to ED for complete evaluation**
- Yes → **Treat other conditions as indicated**

See page 2

**Follow-up**

- Ensure f/u in 1-2 days
- Anticipatory Guidance
- Repeat labs if fevers last ≥ 5 days or if new symptoms from inclusion criteria develop

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# Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Emergency Department

**INCLUSION CRITERIA**

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- **Fever >38°C** **AND** no alternative dx **AND** >2 of the following:
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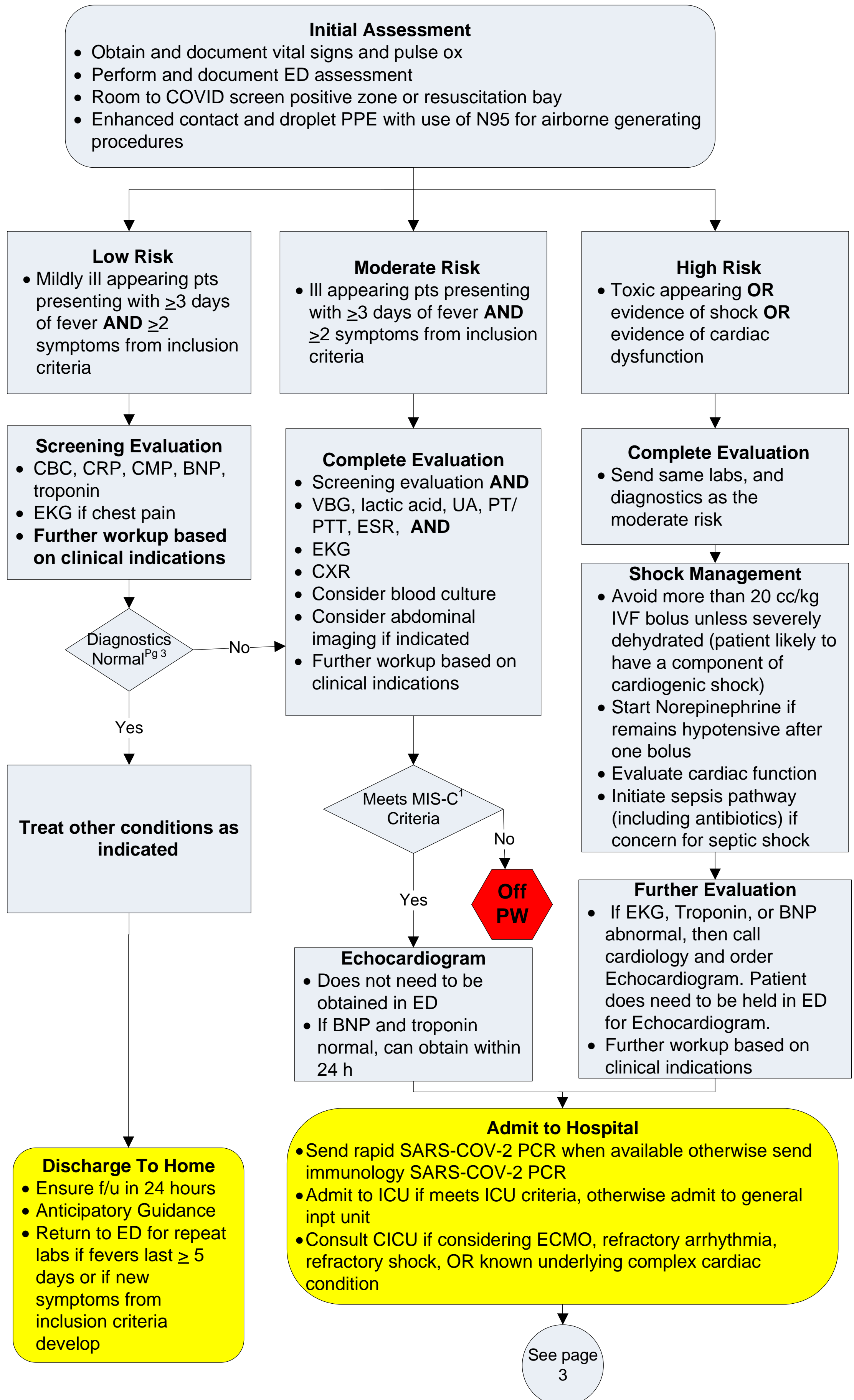
  - Rash
  - Conjunctivitis
  - Oral inflammation
  - Altered mental status
  - Extremity swelling
  - Lymphadenopathy

**OR**
- One or more of the following:
  - Hypotension or shock
  - Evidence of cardiac dysfunction
  - End organ involvement

**EXCLUSION CRITERIA**
- Alternative plausible diagnosis

**[1]MIS-C Definition**
- <21 yo presenting with fever >38C (or tactile) for > 24 hrs **AND**
- Clinically severe illness requiring hospitalization **AND**
- Multisystem (>2) organ involvement: cardiac, renal, pulm, heme, GI, derm, neuro **AND**
- Lab evidence of inflammation
  - (elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, IL6, neutrophilia, lymphocytopenia, hypoalbuminemia) **AND**
- No alternative plausible dx **AND**
- Current or recent SARS-COV-2 infection by PCR or antigen test or serology; or COVID-19 exposure within 8 weeks of presentation

**[2]ICU Admission Criteria**
- Abnormal perfusion
- Hypotension
- Evidence of cardiac dysfunction or BNP>400 or Troponin > 0.4
- Sustained changed in mentation or perfusion
- Requiring ICU level respiratory support
- Lactate >2.5, Base deficit > -4



# Multisystem Inflammatory Syndrome in Children (MIS-C) Pathway

Page 2

**Isolation**
- If SARS-COV-2 PCR positive: Enhanced contact and droplet PPE with use of N95 for airborne generating procedures
- If SARS-COV-2 PCR negative: Standard precautions

**Admission Diagnostic Evaluation**
- SARS-COV-2 IGG if PCR is negative
- Labs listed on page 1 if not already completed
- To consider cytokine panel on a case by case basis
- Perform Echo if not completed in ED. If troponin and BNP normal, can obtain Echo within 24 hrs.

**Ongoing Diagnostic Evaluation**
- Send following labs every 24 hrs X2 then every 2-3 days as per care team's discretion
  - CBC/diff, CRP, CMP, PT/PTT, BNP, troponin
- Troponin q6hrs if initially elevated
- EKG as needed per cardiology
- Echo
  - For pts with abnormal Echo, repeat every 1-2 days or as needed, and prior to discharge.
  - For pts with normal Echo, repeat prior to discharge. If they have prolonged fever or hemodynamic instability, obtain at discretion of cardiology

**Consults**
- Cardiology
- ID
- Rheumatology
- Hematology as needed

Meets diagnostic criteria from Pg 2?

Yes → Determine Disease Severity from Pg 5

**Therapies**
- Steroids: treat all illness severities with steroids
- IVIG: start early
- Consider Lasix for fluid overload
- Start Aspirin or Enoxaparin for thromboprophylaxis
- Proton pump inhibitor for GI prophylaxis
- Pressors as indicated
- Continue broad spectrum antibiotics as per sepsis pathway until cultures result
- Anakinra: consider if macrophage activation syndrom OR refractory (persistent fever, need for vasoactive agents, persistently elevated troponin, cardiac dysfunction) to initial dose of IVIG/steroids. Give pulse steroids before starting Anakinra, if not already given.

See page 5

**Reporting**
- To department of health by Infection prevention/control

**Discharge Criteria**
- Sats ≥ 95% on RA
- Tolerates PO
- Hemodynamically stable > 48 hrs
- Normal cardiac function
- Afebrile >48 hrs
- Inflammatory markers, troponin, BNP trending downwards

**Discharge Instructions**
- Continue low dose aspirin as per page 5
- Switch to low dose aspirin if on enoxaparin prophylaxis
- F/u cardiology and rheumatology in 2 weeks
- F/u hematology if anticoagulated

**At Follow-up Visit**
- CBC, CMP, CRP, BNP as needed
- EKG, Echo
- Cardiac MRI at 3-6 mos
- Holter if cardiac involvement was significant

No →

**Therapies**
- Consider other diagnoses
- Treat accordingly

**COVID 19 Positive**
- Consider Echo in 2 weeks if recurrence of fever or inflammatory symptoms

| Laboratory Test | Cut-off |
|---|---|
| Absolute Lymphocyte Count | <2000/cc |
| Absolute Neutrophil Count | > 8000/cc |
| | <2000/cc |
| Albumin | <2.5 gm/dL |
| ALT | >100 U/L |
| BNP | >100 pg/mL |
| Creatinine | >1 mg/dL |
| CRP | >10 mg/dL |
| ESR | >40 |
| Hemoglobin | 9 gm/dL |
| Lactic acid | >2.2mml/L |
| Platelets | <100,000/cc |
| Troponin | >0.04 ng/mL |

| Management by Clinical Severity | | | |
|---|---|---|---|
| **Medication** | **Mild Disease (Meets MIS-C definition and mildly ill appearing)** | **Moderate Disease (Meets MIS-C definition and Ill appearing without hemodynamic instability)** | **Severe Disease (Meets MIS-C definition and critically ill with hemodynamic instability)** |
| Methylprednisolone IV **OR** Prednisone PO | Prednisone: Start 1 mg/kg/dose BID (no max dose) | Prednisone: Start 1 mg/kg/dose BID (no max dose) | Methylprednisolone IV: Start pulse dose regimen 30 mg/kg/dose once daily for 3 days (max 1 g/day)<br>Consult rheumatology for steroid taper |
| Aspirin | Start low dose aspirin<br>(3-5 mg/kg/day once daily) | Start low dose aspirin<br>(3-5 mg/kg/day once daily)<br>**-OR-**<br>prophylactic enoxaparin<br>(Dosed per AIDHC protocol)<br>If on prophylactic enoxaparin, switch to low dose aspirin at discharge | Start low dose aspirin<br>(3-5 mg/kg/day once daily)<br>**-OR-**<br>prophylactic enoxaparin<br>(Dosed per AIDHC protocol)<br>If on prophylactic enoxaparin, switch to low dose aspirin at discharge |
| IVIG (Privigen 10%) | 2 g/kg (max 160 g) | 2 g/kg (max 160 g)<br>If refractory to IVIG then consider Anakinra | 2 g/kg (max 160 g)<br>If refractory to IVIG then consider Anakinra |
| Enoxaparin | N/A | Start prophylactic enoxaparin<br>(Dosed per AIDHC protocol)<br>(No monitoring needed unless renal dysfunction or clinical bleeding)<br>**-OR-**<br>low dose aspirin<br>(3-5 mg/kg/day once daily).<br>If on prophylactic enoxaparin, switch to low dose aspirin at discharge | Start prophylactic enoxaparin<br>(Dosed per AIDHC protocol)<br>(No monitoring needed unless renal dysfunction or clinical bleeding)<br>**-OR-**<br>low dose aspirin<br>(3-5 mg/kg/day once daily).<br>If on prophylactic enoxaparin, switch to low dose aspirin at discharge |
| Anakinra | N/A | Consider Anakinra if refractory to initial treatment with IVIG/steroids (persistent fever, need for vasoactive agents, persistently elevated troponin, cardiac dysfunction) **OR** concern for macrophage activation syndrome<br>Consult rheumatology.<br>4-10 mg/kg/day divided q12hours | Consider Anakinra if concern for macrophage activation syndrome **OR** refractory to initial treatment with IVIG/steroids. Consult rheumatology.<br>4-10 mg/kg/day divided q12hours |

| Ordering echocardiograms for suspected MIS-C patients | |
|---|---|
| **Initial echocardiogram**<br>Please call cardiology and ensure troponin and BNP are ordered as part of lab work-up | |
| **Mild/moderate disease patients** | Can be completed within 24hrs, if hemodynamically stable, and no significant elevation of troponin or BNP. If lab values are abnormal, discuss with cardiology |
| **Severe disease patients with shock or hemodynamic compromise** | Order from the emergency department, can be completed either in the ED or in the PICU at the time of admission |
| **Subsequent/follow-up echo** | |
| **Mild/moderate disease patients, hemodynamically stable with normal initial echocardiogram** | Can repeat prior to discharge unless there is a significant change in clinical status, new elevation of troponin, BNP or persistent fever greater than 2 days |
| **All other patients: severe disease pts with hemodynamic instability; significantly abnormal troponin, BNP; change in clinical status during admission** | May be repeated in consultation with cardiology every 1 to 2 days or as needed. If remains normal, then follow low/moderate risk (hemodynamically stable) guidelines |
| **Follow-up after discharge** | |
| **Echocardiogram in 2 weeks and 6 weeks** | If any abnormal echos during admission, coordinate cardiology visit along with an echo. If echos normal throughout admission, can order echo only (let consult service know at the time of discharge) |
| **Echocardiogram in 6-12 mos** | All patient should have a f/u echo 6-12 months from initial presentation since natural history of this condition is as yet unknown. |

## References – Multisystem Inflammatory Syndrome in Children

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**Legal Disclaimer:** These clinical practice guidelines are based upon the opinions of staff members of Nemours Children's Health System. Treatment should be individualized and based upon the clinical conditions of each patient.