CLINICAL PATHWAY: Multi-System Inflammatory Syndrome in Children (MIS-C) Clinical Pathway

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

Clinical suspicion for Multi-System Inflammatory Syndrome in Children (MIS-C):

Fever ≥100.4 °F (≥38 °C) for ≥3 days (or fever ≥100.4 °F/≥38°C for ≥24 hours with signs of shock/critical illness), positive COVID-19 testing or exposure to probable/confirmed COVID-19 case in the prior 60 days (or detection of antibody during current illness), *no alternative plausible diagnosis,* AND any **two** of the following systems:

- Signs of shock
- **GI:** abdominal pain, diarrhea, or vomiting
- **CV:** chest pain, arrhythmia, or hypotension
- **Mucocutaneous:** rash, oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity swelling

Initial Work Up and Management:

If signs of sepsis/septic shock: follow the Septic Shock Pathway with the following caveats:

- Prompt recognition of shock is crucial. Rapid push/pull administration of 10 ml/kg aliquots of fluid as tolerated with frequent reassessment for signs of worsening heart failure, such as hepatomegaly, crackles, gallop, and other signs of fluid overload. Strong consideration should be given for early initiation of inotropic support.

1st Tier Labs/Studies (***all patients***): (see Appendix A for blood volumes and required tubes)

- CBC with differential, "hepatic function panel (no coags)", chem 10, CRP, ESR
- Extra red top and blue top tubes to hold for further studies; consider drawing and holding blood culture

2nd Tier Labs/Studies (***abnormal 1st tier labs[1], strong possibility of MIS-C based upon clinical presentation***): (see Appendix A for blood volumes and required tubes)

- *Well-appearing:* "coagulation panel" including D-dimer, troponin, NT-proBNP
- *Ill-appearing:* **add** blood gas with lactate, ferritin, cortisol, blood culture, UA (voided specimen or bag; if abnormal, obtain mid-stream or cath for urine cx)
- Obtain COVID-19 PCR via multi-viral testing LIAT, respiratory BIOFIRE
- **Consider** EKG, CXR

PPE: Full COVID-19 Special Precautions PPE until COVID-19 PCR results return

Disposition Considerations:

- Consider discharge from ED if: well appearing, no or mild elevation in labs, concrete plan in place for lab trending/follow up (may return to ED for lab follow up).
  - If mild symptoms of MIS-C (per ED and ID/Rheum), consider steroids – must have close follow up with ID and/or Rheumatology in place prior discharge.
  - For patients with normal labs and no clinical suspicion for MIS-C, f/u not necessarily required.
- Consider admission if: ill-appearing; clinical or laboratory picture strongly suggestive of MIS-C; markedly elevated inflammatory markers and/or lab or clinical evidence of end organ dysfunction; tachycardia out of proportion to clinical picture; abnormal ECG; altered mental status; meets criteria for Complete or Incomplete Kawasaki Disease; clinical need to closely monitor disease progression; if unable to arrange outpatient follow up
- Consider admission to PICU if: strongly suggestive of moderate-severe MIS-C, signs of shock and/or multisystem organ involvement

Further Work Up + Consultations During Admission

Consultations:

- If admitted: consult Infectious Diseases and Cardiology services to discuss additional work-up and management. Consider consulting Rheumatology if diagnostic question or 2nd line agents are required.
  - *Unless ED has specific questions or concerns, consults should be placed by receiving service.

Additional work up, per consultant recommendations:

- Consult Infectious Diseases for specific work up needed *prior* to IVIG administration, if feasible
- Consider Echo if NT-proBNP >800, elevated troponin, and/or clinical concern for cardiac disease
- Rheumatology to determine if cytokine studies needed (see Appendix B)
- Consider trending of labs based on consultant recommendations

Treatment and Management

Treatment may be started prior to COVID-19 PCR and serology tests result.

Mild MIS-C

(e.g., no hemodynamic instability, no cardiac dysfunction, mild abnormality in labs)

- Start oral prednisone/prednisolone taper per Rheumatology recommendations
- No indication for methylprednisolone IV and/or IVIG therapy

Moderate-Severe MIS-C

1st line agents:

- **ASA** (*avoid ASA if platelet count ≤80,000/uL*)
  - Low dose 3-5 mg/kg/day (max 81 mg/day) if diagnosed MIS-C and KD-like features and/or thrombocytosis (platelet ≥450,000/uL)
  - Continue ASA until normalization of platelet count and confirmed normal coronary arteries ≥6 weeks after diagnosis
  - *If coronary arteriopathy:* follow Kawasaki Clinical Pathway in discussion with cardiologist
  - *If other cardiac abnormalities present, or doesn't meet above criteria*: cardiology to direct antiplatelet/anticoagulation management
- **Methylprednisolone** IV 2 mg/kg x1 dose (max 80 mg); then 2 mg/kg/day IV div BID (max 40 mg/dose) – give first, then start IVIG
  - *When clinical/lab improvement:* transition to PO steroids 2mg/kg/day divided BID (max 30mg/dose)
- **IVIG** 2 g/kg x 1 (max 100 g/dose)
- If clinically indicated, consider starting antibiotics x36 hrs *(make best effort to have blood culture drawn prior to starting; modify antibiotic selection based on clinical situation, patient allergy; consider discontinuing if cultures are negative*):
  - If respiratory symptoms with concern for bacterial pneumonia: follow Community Acquired Pneumonia Clinical Pathway
  - If signs of septic shock: follow Septic Shock Clinical Pathway
- **Lansoprazole** 1 mg/kg/day PO once daily (max 30 mg/dose) or Protonix 1mg/kg/day IV once daily (max 40 mg/dose)

2nd line agents:

- *If patient without clinical improvement or develops recurrent fever*: methylprednisolone IV pulse 30 mg/kg x1. Do not repeat IVIG. Continue scheduled methylprednisolone IV 2 mg/kg/day div BID on next day.
- *If still no improvement or recurrence of fever:* high dose anakinra 10 mg/kg/day div q6hr. **Consult Rheumatology before initiation.**
- *If continues without improvement*: discuss alternative immunomodulator therapy with Rheumatology.

Other considerations:

- All MIS-C patients should follow the VTE Prophylaxis Clinical Pathway
- Any patient that meets MIS-C diagnostic criteria should be reported to the DPH Epidemiology Program at (860) 509-7994.

MIS-C CDC case definition (updated Jan 2023):

- Fever ≥100.4 °F (≥38 °C) (subjective or documented)
- Requiring hospitalization
- Positive SARS-CoV-2 nucleic acid/antigen up to 60 days prior, or detection of antibody associated with current illness, or close contact with confirmed/probable COVID-19 in 60 days prior to hospitalization
- CRP ≥3 mg/dL
- New onset manifestation in ≥2 categories:
  - Cardiac: coronary artery dilatation/aneurysm, left ventricular ejection fraction <55%, or troponin elevation above normal
  - Shock
  - Mucocutaneous: rash, oral mucosal inflammation, conjunctivitis/conjunctival injection or extremity findings (erythema, edema)
  - GI: abdominal pain, vomiting, diarrhea
  - Hematologic: platelet count <150 k/uL, ALC <1,000/uL
- No alternative plausible diagnosis

[1]Abnormal Lab Values:

- Absolute Lymphocyte Count < 1000
- Platelets < 100 or >450k
- CRP ≥3
- ESR >40
- Na < 135
- ALT >45
- NT-proBNP >800
- Elevated Troponin T, high sensitivity (if elevated, discuss significance with Cardiology)

DISCHARGE INSTRUCTIONS

- **Follow up with cardiology** for 2 and 6 weeks from discharge
- **Call Rheumatology** (or on-call) to schedule f/u in 2 weeks from discharge (5-9390)
- **For mild MIS-C**: steroid taper per Rheumatology
- **For mod-severe MIS-C**: Rx prednisolone/prednisone taper: 2mg/kg/day div BID (max 30mg/dose) x5 days; 1 mg/kg daily (max 30 mg/dose) x5 days, then 0.5 mg/kg daily (max 15 mg/dose) x5 days.
- Discharge on ASA and GI prophylaxis (if started inpatient)
- Outpatient labs to be ordered by Rheumatology within 1-2 weeks of discharge
- Other specialist appts and tests per consultants on case-by-case basis

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This pathway is subject to change, based on evolving recommendations from the CDC and CT DPH.

LAST UPDATED: 03.27.25

Appendix A: Blood Volumes and Required Tubes for Labs

Initial Work Up:

- CBC with differential: Whole blood, Lavender EDTA, Minimum 1 mL, 4mL collection tube or microtainer
- "Liver function panel" (includes GGT and coags): Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1mL plasma (liver function) AND Full Blue top sodium citrate tube (coags)
- Chem 10: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- Blood gas with lactate: 1mL of whole blood into a heparin syringe on ice or full Green Lithium Heparin tube (blood gas); Grey top or Li Heparin on ice (lactate)
- Cortisol: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- Fibrinogen: Full Blue top sodium citrate tube
- D-dimer: Full Blue top sodium citrate tube
- CRP: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- ESR: Whole blood, Lavender EDTA, Minimum 1 mL, 4mL collection tube
- Procalcitonin: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- LDH: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- Ferritin: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- Troponin: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- NT-proBNP: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- CKMB: Green top Lithium Heparin with gel-barrier, minimum 2mL whole blood, 1 mL plasma.
- Blood culture: Bactec pedi bottle (no minimum amount needed)
- Hold extra red top tube for future studies, if able

****all tubes being sent need to be full if you wish the lab to run multiple tests off of the same tube – minimum volumes added together will not suffice****

- Lavender top EDTA tube (*not the bullet)*:
  - Amount of blood: needs to be full
    - can run: CBC w diff, ESR
- Green top lithium heparin with gel barrier tube:
  - Amount of blood: needs to be full
    - Can run: liver function panel, chem 10, CRP, LDH, ferritin, triglyceride, troponin, NT-proBNP, CKMB, cortisol
- Blue top sodium citrate tube:
  - Amount of blood: needs to be full
    - Can run: coagulation tests, fibrinogen, D-dimer

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Additional Work Up:

- Type and Screen
- Triglycerides: Green top Lithium Heparin with gel-barrier, minimum 2 ml whole blood, 1 ml plasma
- Cytokine studies:
    - IL-6, Soluble IL-2, Soluble IL-2R, IL-1, IL-10 (sent as cytokine panel): Red top, preferred 1 ml serum
    - NK Function (not part of cytokine panel above): Green top, 10 ml whole blood
    - Soluble CD-163 (not part of cytokine panel above and is sent separately to Cincinnati): see **Appendix B Cytokine Studies Cincinnati Lab Requisition Form**
- CMV:
    - Serology:
        - Cytomegalovirus (CMV) Antibody, IgG: Red top serum, 1.0 mL (0.5 mL) min required
        - Cytomegalovirus (CMV) Antibody, IgM: Red top serum, 1.0 mL (0.5 mL) min required
    - PCR:
        - Cytomegalovirus DNA,QUANT,PCR: Send out to Quest, EDTA Lavender plasma, -1.0 mL
- EBV:
    - Serology:
        - All EBV serological testing: Red top serum, 1.0 mL (0.5 mL) min required
    - Molecular
        - EBV DNA, PCR, QUALITATIVE: Send out to Quest, 1 mL (0.3 mL minimum) serum from red gel barrier or red non-gel barrier tube or 1 mL Lavender EDTA plasma
        - EBV DNA, PCR, Quantitative: Send out to Quest, 1 mL (0.5 mL minimum) EDTA Lavender plasma or 1 mL (0.5 mL minimum) serum
- Parvovirus:
    - Antibodies: Send out to Quest, 2 mL (1 mL minimum) serum from a red top or SST tube
    - PCR: Send out to Quest, 1 mL (0.5 mL minimum) EDTA plasma

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CYTOKINE STUDIES

If Rheumatology determines that cytokine studies are needed, the following labs should be ordered:

- "Interleukin panel" and/or the below:
- IL-6
- Soluble IL-2
- IL-1
- IL-10
- NK Function
- Soluble CD-163
- Soluble IL-2R

Utilize **Cincinnati Children's Test Requisition Form** (next page).

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DIAGNOSTIC IMMUNOLOGY LABORATORY
Phone: 513-636-4685 • Fax: 513-636-3861
Lab Hours: Monday–Friday 8:00 AM – 5:00 PM EST
www.cincinnatichildrens.org/DIL • CBDILabs@cchmc.org

Ship First Overnight to:
CCHMC - Julie Beach
DIL - Rm R2328
3333 Burnet Avenue
Cincinnati, OH 45229-3039

DIL — TEST REQUISITION FORM

MUST BE RECEIVED MONDAY – FRIDAY WITHIN 1 DAY OF COLLECTION UNLESS OTHERWISE INDICATED

PATIENT INFORMATION (STICKER ALSO ACCEPTED)

Patient Name (Last, First, MI): _____, _____, _____ DOB (MM/DD/YYYY): _____/_____/_____

Medical Record #: _____ Collection Date (MM/DD/YYYY): _____/_____/_____ Time of Sample(HH:MM): _____

Legal Sex: ☐ Male ☐ Female BMT: ☐ Yes – Date: _____/_____/_____ ☐ No ☐ Unknown Relevant Medications: _____

Diagnosis or reason for testing: _____

TESTS OFFERED: THE MAX VOLUME LISTED IS THE PREFERRED WHOLE BLOOD VOLUME

☐ **Alemtuzumab Plasma Level**	2-3mL Sodium Heparin See #5 on page 2	☐ **Mitogen Stimulation**	See #1 on page 2
☐ **ALPS Panel by Flow** *Need CBC/Diff result*	1-3ml EDTA – See #2 on page 2	☐ **Neopterin (Circle One): Plasma or CSF**	1-3ml EDTA or 0.5-1ml CSF See #3 or #4 on page 2
☐ **Antigen Stimulation**	See #1 Below	☐ **Neutrophil Adhesion Mrkrs: CD18/11b**	1-3ml EDTA
☐ **Apoptosis (Fas, mediated)**	10-20ml ACD-A	☐ **Neutrophil Oxidative Burst (DHR)**	1-3ml EDTA
Note: Only draw Apoptosis on Wednesday for Thursday delivery		☐ **NK Function (STRICT 28 HOUR CUT-OFF)**	See #1 on page 2
☐ **B Cell Panel** *Need CBC/Diff result*	1-3ml EDTA – See #2 on page 2	☐ **Perforin/Granzyme B**	1-3ml EDTA
☐ **BAFF**	1-3ml EDTA – See #4 on page 2	☐ **pSTAT5**	1-3ml EDTA
☐ **CD40L / CD40FP / ICOS**	3-5ml Sodium Heparin	☐ **S100A8/A9 Heterodimer**	2 (0.3mL) Gold serum aliquots, frozen w/in 4 hours of collection
☐ **CD45RA/RO**	1-3ml EDTA	☐ **S100A12**	2 (0.3mL) Gold serum aliquots, frozen w/in 4 hours of collection
☐ **CD52 Expression**	1-3ml EDTA	☐ **SAP (XLP1)**	1-3ml Sodium Heparin
☐ **CD107a Mobilization (NK Cell Degran)**	See #1 on page 2	☐ **Soluble CD163**	1-2ml EDTA - See #4 on page 2
Note: Only draw CD107a Monday – Wednesday		☐ **Soluble Fas-Ligand (sFasL)**	1-3ml EDTA/Red/Gold - See #4 on page 2
☐ **CTL Function**	See #1 on page 2	☐ **Soluble IL-2R (Soluble CD25)**	1-3ml EDTA - See #4 on page 2
☐ **CXCL9**	2 (0.5ml) EDTA plasma aliquots, frozen w/in 8 hours of collection	☐ **TCR α/β TCR γ/δ**	1-3ml EDTA
☐ **Cytokines, Intracellular**	2-3ml Sodium Heparin		
☐ **Cytokines (Circle One): Plasma or CSF** *Includes: IL-1b, 2, 4, 5, 6, 8, 10, IFN-g, TNF-a, and GM-CSF*	3-5ml EDTA or 0.5-1ml CSF See #3 or #4 on page 2	☐ **T Cell Degranulation Assay**	See #1 on page 2
If sending frozen, 2 (0.5mL) EDTA plasma aliquots frozen, preferred		**Note: Only draw T Cell Degran Monday – Wednesday**	
☐ **Foxp3** *Need CBC/Diff result*	1-3ml EDTA – See #2 on page 2	☐ **TCR V Beta Repertoire**	2-3ml EDTA
☐ **GM-CSF Autoantibody (GMAb)**	1-3ml Red/Gold - See #4 on page 2	☐ **Th-17 Enumeration**	2-3ml Sodium Heparin
☐ **GM-CSF Receptor Stimulation**	1-3ml Sodium Heparin	☐ **WASP**	1-3ml Sodium Heparin
☐ **iNKT**	1-3ml EDTA	☐ **WASP Transplant Monitor**	1-3ml Sodium Heparin
☐ **Interleukin–18 (IL-18)**	3ml Red/Gold - See #4 on page 2	☐ **XIAP (XLP2)**	1-3ml EDTA
If sending frozen, 2(0.3mL) red/gold serum aliquots frozen, preferred			
☐ **Lymphocyte Activation Markers**	2-3ml Sodium Heparin	☐ **ZAP-70 (only for SCID)**	1-3ml EDTA
☐ **Lymphocyte Subsets**	1-3ml EDTA	☐ **Other:**_____	
☐ **MHC Class I & II**	1-3ml EDTA		

REFERRING PHYSICIAN

Physician Name (print): _____

Phone: (_____) _____ Fax: (_____) _____

Email: _____

_____ Date: _____/ _____/ _____

Referring Physician Signature

BILLING & REPORTING INFORMATION

We do not bill patients or their insurance. Provide billing information here or on page 2.

Institution: _____

Address: _____

City/State/ZIP: _____

Phone: (_____) _____ Fax: (_____) _____

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Patient Name: _____ Date of Birth: _____

ADDITIONAL BILLING INFORMATION – CONTINUED FROM PAGE 1

Institution: _____

Address: _____

City/State/ZIP: _____ Phone: (_____) _____ Fax: (_____)_____

Contact Name: _____

Phone: (_____) _____ Fax: (_____) _____ Email: _____

SEND ADDITIONAL REPORTS TO:

Name: _____ Name: _____

Fax Number: _____ Fax Number: _____

Laboratory Information

1. 5-10ml Sodium Heparin blood per test should be adequate for most patients unless they are lymphopenic. If you have volume constraints or an absolute lymphocyte count (ALC) of <1.0 K/uL, please see the Customized Volume Sheet on our website (www.cchmc.org/DIL) or call for adjusted volume requirements for the following tests: Antigen Stimulation, Mitogen Stimulation, CTL Function, NK Function, CD107a, or T Cell Degran.

2. Results of a concurrent CBC/Diff must accompany ALPS Panel, B Cell Panel, or Foxp3. Results will be used to calculate absolute cell counts.

3. CSF Samples: a) Fresh Specimens: Ship with frozen ice packs to keep at refrigeration temp (2-8°C/35-46°F) for receipt within 48 hours of collection.
b) Frozen Specimens: Freeze within 48 hours of collection. Ship samples frozen on dry ice.

4. Specimen Processing and Shipping Instructions **only** for tests marked with **"See #4"**.
a) Unspun whole blood: Ship as unspun whole blood at Room Temperature for receipt within 24 hours of collection.
b) Spun Specimens: See test line for acceptable specimen types. Spin and remove test-required serum or plasma from cells within 24 hours of collection. Freeze the separated plasma or serum immediately. Two aliquots per test are preferred. Ship frozen on dry ice. Once separated from cells, the serum or plasma must stay frozen until received by the DIL. Thawed samples will be rejected.

5. Specimen Processing and Shipping Instructions **only** for tests marked with **"See #5"**
a) Unspun whole blood: Ship as unspun whole blood at Room Temperature (20-25 °C) for receipt within 5 days of collection. Chilled specimens will be rejected.
b) Spun Specimens: Spin at 2000 g for 10 min and remove test-required plasma from cells in 500 µL aliquots within 5 days of collection. Freeze the separated plasma immediately. Two aliquots are preferred. Ship frozen on dry ice. Once separated from cells, the plasma must stay frozen until received by the DIL. Thawed samples will be rejected.

Visit our Clinical Lab Index at www.testmenu.com/cincinnatichildrens for detailed processing and testing information.

Additional Shipping & Handling Information

- ***Testing is not performed and samples cannot be received on Saturdays/Sundays and certain holidays.***
- Samples should be sent as whole blood at room temperature and received in our laboratory within 1 day of collection, unless otherwise indicated. We recommend using a Diagnostic Specimen pack to ensure proper processing and timely delivery of samples to the lab.
- Call with any questions or help with minimizing collection requirements.
- Package securely to avoid breakage and extreme weather conditions.
- Include a completed copy of our test requisition form with each sample.
- First Overnight shipping is strongly recommended. Please call, email or fax the tracking number so that we may better track your specimen.

Billing Information

- The institution sending the sample is responsible for payment in full.
- We do not third-party bill patient insurance.

Laboratory Information

- Hours: Monday through Friday, 8:00 AM to 5:00 PM (Eastern Standard Time). Closed on Weekends and some major holidays.
- Phone: 513-636-4685
- Fax: 513-636-3861
- Email: CBDILabs@cchmc.org

Questions?

Please call 513-636-4685 with any questions regarding collection or billing.

****THE REQUISITION MUST BE FILLED OUT COMPLETELY. INCOMPLETE FORMS MAY RESULT IN THE COMPROMISE OF THE SPECIMEN INTEGRITY WHILE THE MISSING INFORMATION IS BEING OBTAINED****