Evaluation and Management of COVID-19 and Related Syndromes at UNC Children's

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Inclusions
-Children between 3 months and 22 years of age

Note: for children under 3 months of age with COVID-19, recommend management as per routine with a viral infection in this age group.

COVID-19 Suspected or Confirmed → Special Airborne and Contact Precautions → Assess Disease Type

	Acute COVID-19	MIS-C	Asymptomatic Infection
	-Prominent respiratory symptoms -PCR (+), IgG (+) or (-) -No features of MIS-C	-MIS-C findings below: often GI, derm, cardiac; may resemble Kawasaki. -**Consider differential diagnosis**, including sepsis! -PCR (+) or (-); IgG *usually* (+) -MOST have known COVID-19 history	-Patient presented for another reason (e.g., trauma, planned procedure) -NO consistent symptoms at time of screening
Initial Diagnostic Tests	-CBC/diff, CMP, LDH, CRP, ESR, DIC panel, troponin, pro-BNP -CXR -EKG -COVID-19 IgG -Consider CTA chest if PE suspected	-CBC/diff, CMP, LDH, CRP, ESR, troponin, pro-BNP, blood culture -COVID-19 PCR AND IgG -CXR, EKG -Consider echocardiogram early -Activate Code Sepsis when appropriate!	-Consider CXR -Consider labs as for acute COVID-19 and MIS-C as indicated -Consider COVID-19 IgG -Evaluation of underlying condition as indicated
Admission Criteria	-Oxygen requirement -Signs/symptoms of sepsis -Felt to be at high risk of decompensation and further monitoring needed	Admit ALL patients with suspected MIS-C Refer to Pediatric ED MIS-C pathway for more details.	As indicated based on presenting condition
Consults	Required -Pulmonary (in-person) -Infectious Diseases (in-person) -Hematology (virtual OK) As needed -Cardiology, Rheumatology -Others as indicated	Required -Rheumatology (in-person) -Infectious Diseases (in-person) If cardiac involvement -Cardiology (in-person) -Others as needed	-Consults only as indicated for underlying condition -Consider discussing with or consulting ID, Rheum, Pulm, or others if diagnosis is in doubt
Supportive Care and Monitoring	-Monitors, cont pulse ox -Oxygen support as needed -NPO/IV fluids as indicated Labs (daily, can space if improving) -CBC/diff, CMP, CRP -BNP, troponin (if initial abnormal) -DIC panel, anticoagulation labs as indicated	-Monitors, cont pulse ox -Telemetry if cardiac involvement -Echocardiogram Labs (daily, space as appropriate) -CBC/diff, CMP, CRP -BNP, troponin (if initial abnormal) -F/u EKG, echo as indicated	As appropriate for underlying condition
Treatment Considerations	-Thromboprophylaxis for most patients (see page 6) If SpO2 <94% in RA -Remdesivir (all) -Dexamethasone (most) -Convalescent plasma (some)	Commonly used -IVIG -Methylprednisolone -Aspirin Selection and dosing per Rheumatology	Treatment not indicated unless determined to be symptomatic

Table 1: Tiered approach to evaluating hospitalized pediatric patients with acute COVID-19

1. **Afebrile patients:**
   a. Vital signs per unit routine, including pulse oximetry
   b. Daily physical exam including mental status evaluation and palpation of the liver/spleen
   c. CXR if not already done
   d. Avoid scheduled antipyretics

2. **Patients with fever and normal mental status:**
   a. Continue evaluations from Section 1
   b. CBC/D q24 hours and CMP q48 hours
   c. LDH, CRP, ESR, DIC panel q24-48 hours (more frequently if indicated)
   d. Consider thromboprophylaxis and pediatric hematology consult **(see Figure 1)**

3. **Patients with hypoxemia**
   a. Continue evaluations from Sections 1 and 2; consider increasing the frequency of laboratory evaluations
   b. Start low-flow oxygen to maintain O2 sat ≥95%; if >2L/min requires transfer to PICU; trial of prone positioning
   c. Chest imaging if not already done
   d. Consult pediatric pulmonology
   e. Consider PTE evaluation if risk factors present; consider CTA if increasing hypoxemia (>5 lpm; scheduled end of day per radiology protocol)

4. **Patients with altered mental status/coma or lymphopenia or >1 cytopenia in other lineages or transaminase elevation or hepatosplenomegaly or respiratory failure:**
   a. Continue evaluations from Sections 1 and 2; consider increasing the frequency of laboratory and mental status evaluations
   b. Ferritin q24 hours, triglycerides q48 hours (more frequently if indicated)
   c. Send cytokine panel (expect >1 week turnaround time), which also contains sCD25
   d. Consult pediatric rheumatology; consult pediatric neurology with altered mental status or other focal neurologic features
   e. Consider initiation of immunosuppressive therapy after discussion with primary and consulting services **(see Table 3)**
   f. If suspicion for airway fibrin plugs or PTE, consider thrombolytics via ETT or systemically

5. **Patients meeting clinical criteria for HLH**
   a. Continue evaluations from Section 1, 2, and 4
   b. Send NK function assays (expect >1 week turnaround time) and genetic screening for familial HLH mutations
   c. Consider PCR screening for Epstein-Barr virus coinfection
   d. Consult pediatric hematology, pediatric allergy/immunology, and pediatric rheumatology
   e. Consider initiation of immunosuppressive therapy after discussion with primary and consulting services **(see Table 3)**

Table 2: Tiered approach to evaluating hospitalized pediatric patients with suspected multisystem inflammatory syndrome in children (MIS-C)

EVALUATION OF PEDIATRIC PATIENTS SUSPECTED TO HAVE MISC-C

1. Vital signs per unit routine
2. CBC/D, CMP, LDH, CRP, ESR, DIC panel, troponin, pro-BNP
3. COVID PCR and COVID IgG if not already done
4. EKG and consider telemetry
5. Baseline CXR if not already done
6. If abnormal troponin and/or pro-BNP and/or EKG, consult pediatric cardiology and consider ordering an echocardiogram
7. If considering initiation of immunosuppressive therapy, consult pediatric rheumatology **(see Table 3)**

MIS-C CASE DEFINITION

1. Individual <21-years-old presenting with fever >24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic); **AND**
2. No alternative plausible diagnosis; **AND**
3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to onset of symptoms

EXAMPLES OF ORGAN SYSTEM INVOLVEMENT

Cardiac: shock, elevated troponin, elevated pro-BNP, coronary arteritis, abnormal echocardiogram, arrhythmia

Gastrointestinal: severe abdominal pain, vomiting, diarrhea, elevated transaminases

Hematologic: elevated d-dimers, coagulopathy, lymphopenia, thrombocytosis or thrombocytopenia

Mucocutaneous: petechia or purpura, polymorphous rash, mucositis, conjunctivitis

Neurologic: headache/irritability, altered mental status, seizures, focal neurologic deficits

Respiratory: ARDS, pulmonary embolism

Renal: acute kidney injury or failure

LABORATORY EVIDENCE OF INFLAMMATION

Elevated CRP and/or ESR
Elevated d-dimer
Elevated ferritin
Elevated IL-6
Elevated neutrophils and/or reduced lymphocytes

	Respiratory	Inflammatory	Infection	Cardiac	Thrombosis
Clinical criteria	Any respiratory symptoms	Fever or any other symptoms Abnormal CXR		1. Fever for 3+ days with one or more of the following: - Abdominal pain, vomiting, diarrhea - Conjunctivitis, mucositis, lymphadenopathy - Rash - Hand and/or feet swelling OR 2. Hypotension, tachycardia/arrhythmia, progressive hypoxia	
Initial assessment	CXR, SpO2	CBC/d, CRP, ESR, CMP, DIC panel if febrile	COVID-19 PCR, CBC/diff, BCx if febrile	Troponin, pro-BNP, EKG Consider telemetry	CBC/d, retic, CMP, DIC panel, FVIII, AT3, ferritin, LDH
Ongoing assessment (routine)	SpO2 Q8h Daily RA pulse ox if on O2 Coagulation evaluation if abnormal CXR, hypoxemia, or respiratory symptoms	CBC/d, AST, ALT, CRP daily Consider triglycerides, ferritin, and fibrinogen, if cytopenia or transaminitis	Consider repeat PCR if high suspicion and initial negative COVID IgG	Trend troponin and pro-BNP if initial abnormal Echocardiogram if abnormal troponin and/or pro-BNP	CBC/d and DIC panel daily
Consultants	PICU if requiring >2L/min Pulmonary if any respiratory symptoms Consider evaluation for PTE	Rheum if KD-like features and/or TSS, >1 cytopenia or transaminitis	Peds ID for all cases	Cardiology if elevated troponin and/or pro-BNP or abnormal EKG Signs of shock Cardiomegaly, pleural edema/effusion on CXR Considering Kawasaki disease	Hematology if initial d-dimer >2,500 ng/mL or uptrending d-dimer or if considering therapeutic anticoagulation
Treatment of complications	LFNC and HFNC Proning Intubation Consider therapeutic anticoagulation	Consider IVIG, anakinra, infliximab tocilizumab, and/or steroids	Remdesivir if hypoxemia due to COVID-19. May also consider convalescent plasma.	Steroids, aspirin IVIG, ionotropic support, afterload reduction, antiarrhythmics	See Table Ppx Therapeutic
Ongoing assessment (intensive)	If intubated, monitor OI Consider therapeutic anticoagulation Consider CT	Daily CBC/d, AST, ALT, CRP Consider triglycerides, ferritin, and fibrinogen, if cytopenia or transaminitis	Daily CBC/d, CRP; cultures if concern for new worsening		

Table 3: Therapeutic Considerations for COVID-19

Agent	Dosing and Regimen	Considerations	Adverse Effects and Interactions	Indicated for Acute COVID-19?	Indicated for MIS-C?
Remdesivir Available via: Emergency Use Authorization (EUA) OR Single-patient emergency IND	<40 kg: 5 mg/kg IV x1, followed by 2.5 mg/kg IV daily ≥40 kg: 200mg IV x1, followed by 100mg IV daily Course: 5 days	Requires ASP approval; Peds ID requests. Criteria (abbreviated): SpO2 <94% on RA. eGFR > 30. ALT < 5x ULN. Hospitalized <10 days; intubated <5 days. Not pregnant.	Nausea, vomiting, elevation of hepatic transaminases. Daily LFTs **required**. ALT must be <5x ULN to start therapy; therapy must be discontinued if ALT rises >5x ULN.	YES	NO
Convalescent plasma	Single dose of 1 or 2 units of plasma (200-500 mL) from a single COVID-19 recoveree.	**Experimental** therapy only. Requires eIND from FDA for patients <18 years. Patient/family **consent required**.	Adverse effects appear comparable to standard FFP transfusions.	YES	NO
Dexamethasone	<40 kg: 0.15 mg/kg PO/IV daily >40 kg: 6 mg PO/IV daily Alternatives: prednisolone 1 mg/kg daily (40 mg max), methylpred 0.8 mg/kg daily (32 mg max)	Proven benefit for *adults* requiring oxygen or greater respiratory support. Other corticosteroids would likely have similar effect.	Hypertension +/- PRES, bradycardia, delirium	YES	NO
Methylprednisolone **Prednisolone** **Prednisone**	Severe: 30 mg/kg daily x 3 days Moderate: 10 mg/kg daily x 3 days Mild: 1-2 mg/kg day Consider starting with IV MP then transition to oral and taper	Consider administering in the morning	Hypertension +/- PRES, bradycardia, delirium	NO	YES
IVIG	1-2 gm/kg/dose x1 (maximum 70-100 gm/dose)	Pre-medication is not required prior to IVIG administration Consider in patients with cytokine storm or concerns for KD/MIS-C	Increased risk for clot or thrombosis if other risk factors present; aseptic meningitis; hemolytic anemia	YES	YES
Anakinra	1-2 mg/kg/day SC; May consider increasing up to a maximum of 10 mg/kg/day Use may be limited by pharmacy availability	IL-1 receptor antagonist **Criteria:** Confirmed COVID-19; SpO2 <94% on RA or <96% on 3L or PaO2/FiO2 <300; abnormal chest imaging; CRP>100 mg/L OR MIS-C high suspicion/meets criteria	Generally well-tolerated with favorable profile. Administered in sepsis trials without untoward effects. Short half-life. Use with caution in renal insufficiency	YES	YES
Tocilizumab	8-12 mg/kg/dose IV x1; May consider additional dosing if no improvement Use may be limited by pharmacy availability	IL-6 receptor monoclonal antibody **Criteria:** Same as criteria for anakinra above.	Elevated transaminases, thrombocytopenia, neutropenia, hypersensitivity reaction, GI perforation. Use with caution/avoid with cytopenia or transaminitis.	YES	YES
Infliximab	5-10 mg/kg/dose IV x1 Use may be limited by pharmacy availability	TNF inhibitor Consider in patients with classic KD presentation and treatment-resistant	TB reactivation, hypersensitivity reaction	NO	YES

Figure 1: Pediatric COVID-19 Anticoagulation Management

Patients admitted to Pediatric ICU for COVID-19 should be considered for thromboprophylaxis, unless bleeding contraindications are present.

Consider pediatric hematology consultation for patients admitted to regular floor if very high initial D-Dimer (> 2,500 ng/mL) [i.e. 10x upper limit of normal] with UNC assay) or uptrending D-Dimer.

Thoroughly consider and factor into the decision-making a patient's bleeding and VTE risk factors.

INITIAL LABS: CBC/D, retic, CMP, DIC panel, FVIII, AT3, ferritin, LDH **DAILY LABS: CBC/D, DIC panel (consider less frequent if stable)**

Group A – Therapeutic Anticoagulation

- Confirmed DVT/PE or other established reason for therapeutic anticoagulation
- High suspicion of DVT/PE, but objective documentation cannot be obtained. Strongly consider of O2 requirement is >5 L HFNC.
- Renal failure patient on dialysis with repetitive clotting of dialysis tubing
- MISC-C: Coronary artery aneurysm (CAA) with z-score>10.0 or moderate to severe LV dysfunction (EF<35%)

Treat with Enoxaparin (target anti-Xa level 0.6-1; monitor renal function)
or
UFH (Heparin Pediatric Nomogram: Thrombosis Panel, target hep correlation or anti-Xa: 0.3-0.7 U/ml). Consider heparin for first 48 hours if clinically unstable

UNC Medical Center: Heparin Guideline

*** MIS-C: Dual therapy with therapeutic enoxaparin + aspirin 3-5 mg/kg/day; max 81 mg/day for MIS-C with CAA with z-score ≥10.0

Group B – Prophylaxis Anticoagulation

- Admission to the Pediatric ICU with no evidence or suspicion for VTE without a diagnosis of MIS-C

Prophylaxis with Enoxaparin (monitor renal function)
or
UFH (Heparin Pediatric Nomogram: Sub-Therapeutic Panel)

*Order via Peds VTE PPX order set

UNC Health: VTE Prophylaxis Guideline

Group C – Antiplatelet Therapy

- MIS-C and KD-like features and/or thrombocytosis (platelet count ≥ 450K)
- CAAs and a max z-score of 2.5-10

Low dose aspirin (3-5 mg/kg/day; max 81 mg/day). Avoid if platelet count ≤ 80K

After Hospital Discharge

- Patients admitted to UNC for non-COVID reasons (but found to be infected with the SARS-CoV-2 virus): Consider anticoagulation for up to 30 days, particularly if they were in the ICU, have prior history of VTE, are obese, or have a D-Dimer before discharge of >10x normal or uptrending.
- Any patient with COVID-19 discharged from the hospital should be educated about the 4 main symptoms of DVT (swelling, pain, redness, warmth), PE (SOB, CP, tachycardia, cough/hemoptysis), CSVT (worsening headache, nausea/vomiting, changes in vision, or focal neuro deficits). www.clotconnect.org
- Anticoagulation of choice: enoxaparin if < 15 yo or apixaban if ≥ 15 yo AND weight of ≥ 50 kg.
- Patients on anticoagulation should have a pediatric hematology consultation AND follow up within 2 weeks of discharge.
- Patients on aspirin therapy for MIS-C or KD should have a pediatric cardiology consultation AND follow up within 2 weeks of discharge.

Table 4. **Post-discharge follow-up recommendations.** These are guidelines only. Follow-up plans must be individualized for each patient.

	Acute COVID-19	MIS-C
Acute COVID-19 service	Contact PCP at discharge	Contact PCP at discharge
Primary care physician	Consider check-in 3-5 days after discharge. Phone or virtual generally OK.	Consider check-in 3-5 days after discharge. Ensure adequate follow-ups. Monitor for recrudescence (e.g., fever, rash). In selected cases, labs may be needed prior to subspecialist follow-up.
Pulmonology	-1-month symptom check (virtual OK) -2-month in-person: PFTs and 6-minute walk test	2 months after discharge with PFTs
Hematology	If discharged on anticoagulation, virtual follow-up within 2 weeks.	If discharged on anticoagulation, virtual follow-up within 2 weeks
Rheumatology	If discharged on immunomodulator (e.g., prednisone, anakinra), follow-up within 2 weeks. Virtual OK.	Within 2 weeks with labs, in-person preferred
Cardiology	As needed only	If cardiac involvement, at 2 weeks and 4 weeks, in-person, with echocardiogram.
Infectious Diseases	As needed only	As needed only

Special Precautions during follow-up:
Patients recovering from COVID-19 disease should be considered contagious until 10 days have passed since symptom onset *and* at least 3 days have passed since resolution of symptoms, including improvement in respiratory symptoms and resolution of fever without fever-reducing agents. Patients with MIS-C are likely to NOT be contagious at the time of discharge, regardless of PCR status, especially if they test positive for SARS-CoV-2 antibodies. However, family members are *highly likely* to have been infected. For in-person visits, only one family member should attend with the child, and that family member should be screened for symptoms and history of COVID-19 prior to the visit.

When in doubt, use full precautions.

Appendix 1. Risk factors for more severe COVID-19 disease. Additional conditions of similar severity that are not listed here may also be considered risk factors.

Immunocompromised Status
Hematopoietic stem cell transplant recipient
Solid organ transplant recipient
Receiving anticancer chemotherapy
Primary immunodeficiency
HIV infection
Chronic steroid therapy
Other immunosuppressive medications (e.g., TNF blockade)

Hematologic Disease
Sickle-cell disease

Symptomatic cardiac disease
Major congenital heart defects
Cardiomyopathy

Significant pulmonary disease
Severe chronic lung disease with lung function <50% or ≥2 hospitalizations in the past year
Oxygen while awake and/or asleep
Tracheostomy
Pulmonary hypertension
Asthma requiring chronic oral steroids
OSA

Metabolic or endocrine disease
Diabetes mellitus requiring insulin
Morbid obesity (BMI >99th percentile or >40)
Metabolic disorders significantly affecting multiple organ systems

Medically complex
Technology dependence associated with developmental delay and/or genetic abnormalities