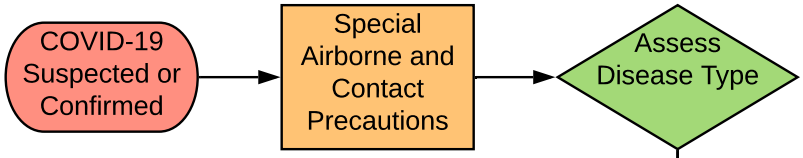
UNC Children's COVID-19 Guidelines
Page 1: Overall Management Algorithm

Contact: Zach Willis, MD, zwillis@med.unc.edu
Version Date: 8/17/2021



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.

	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, D-dimer (or DIC panel) -COVID-19 PCR AND IgG -CXR, EKG -Echocardiogram ASAP	-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 to PICU** if sepsis or requiring HFNC or greater support	Admit ALL patients with suspected MIS-C. Refer to Pediatric ED MIS-C pathway for more details. -**Admit to PICU** if shock, concern for heart failure, or requiring HFNC or greater support	As indicated based on presenting condition
Consults	<u>Required</u> -Pulmonary (in-person) -Infectious Diseases (in-person) -Hematology (virtual OK) <u>As needed</u> -Cardiology, Rheumatology -Others as indicated	<u>Required</u> -Rheumatology (in-person) -Infectious Diseases (in-person) <u>If cardiac involvement</u> -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 <u>Labs (daily, space as appropriate)</u> -CBC/diff, CMP, CRP -BNP, troponin (if initial abnormal) -DIC panel, anticoagulation labs as indicated	-Monitors, cont pulse ox -Telemetry if cardiac involvement -Echocardiogram <u>Labs (daily, space as appropriate)</u> -CBC/diff, CMP, CRP -BNP, troponin (if initial abnormal) -F/u EKG, echo as indicated	As appropriate for underlying condition
Treatment Considerations	Anticoagulation (most, see page 5) No O2 requirement: *consider remdesivir* if considered high-risk. +O2 requirement: remdesivir +/- dexamethasone. Page 2 for details. If **high-risk**, **not on O2, and >=12** years old, may *consider* monoclonal antibody therapy (see page 2)	<u>Commonly used</u> -IVIG -Methylprednisolone -Aspirin Selection and dosing per Rheumatology	Treatment not indicated unless determined to be symptomatic. For **high-risk** patients age 12 and older, may consider monoclonal antibody therapy. See UNC Health definitions of "high-risk."

UNC Children's COVID-19 Guidelines
Page 2: Treatments used for Acute COVID-19

Agent	Dosing and Regimen	Considerations	Adverse Effects and Interactions	Recommendation
Frequently Used in Hospitalized Pediatric Patients with Acute COVID-19				
Remdesivir FDA approved for patients ≥12 years and ≥40 kg. Other patients: available under EUA.	<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 or ID approval. May be ordered by primary team. 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 (monitor closely) Under EUA: Daily LFTs **required**. ALT must be <5x ULN to start therapy; therapy must be discontinued if ALT rises >5x ULN.	**Recommended** in patients admitted for COVID-19 and requiring supplemental oxygen or greater support. **Consider** in patients considered at high risk to progress to requiring respiratory support.
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	**Consider** if requiring low-flow oxygen, especially if consistent or escalating requirement. **Recommended** if requiring HFNC or greater respiratory support.
Heparin OR **Low molecular-weight heparin**	See Page 5 for anticoagulation recommendations.			**Used in most cases of COVID-19.** See page 5 for detailed recommendations.
Rarely used in Pediatric Patients with Acute COVID-19				
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. Requires informed consent.	Adverse effects appear comparable to standard FFP transfusions.	**Not recommended.** Recent data has not supported a therapeutic benefit.
Tocilizumab	8 mg/kg/dose x1, max 800 mg Monoclonal antibody against IL-6	In adult patients, recommended if receiving HFNC or greater support, or if worsening and high CRP (>75).	Avoid if: already immune suppressed, neutropenic, platelets <50K, ALT >5x ULN, concern for pre-existing chronic infection such as TB or *Strongyloides*	**Consider only in critical COVID-19**. Not generally recommended. Used in addition to other therapies (steroids, remdesivir, etc.).
Baricitinib Available under EUA for acute COVID-19 down to age 2	≥9 years: 4 mg PO daily <9 years: 2 mg PO daily Can be dispersed in water and taken PO or via NG or GT	JAK inhibitor used as anti-inflammatory.	Thrombosis is more common; patients must be on thromboprophylaxis unless contraindicated.	**Not generally recommended.** May be considered as alternative to tocilizumab when toci unavailable or contraindicated. **Do not co-administer with tocilizumab.**
Used ONLY for Outpatients (or inpatients admitted for another reason)				
Casirivimab/ Imdevimab Or **Bamlanivimab/ Etesivimab**	Cas/Imd: 600/600 mg IV x1 BAM/ETS: 700/1400 mg IV x1 As of this writing, **Casirivimab/Imdevimab** is the only preferred product due to efficacy against newer variants.	Monoclonal antibodies against the spike protein. 1-2-hour infusion with at least 1 hour observation. No benefit in patients hospitalized for COVID-19.	Infusion reactions (fever, chills, hypotension) may occur. Anaphylaxis may rarely occur.	**Rarely recommended inpatient.** Occasionally may be used in patients *admitted for another reason* and found to have COVID-19 and meeting criteria for treatment.

UNC Children's COVID-19 Guidelines
Page 3: Treatments used for COVID-19 MIS-C

Agent	Dosing and Regimen	Considerations	Adverse Effects and Interactions	Recommendation
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	**Used very often in MIS-C**. May be used alone without IVIG. Use in addition to IVIG with organ-threatening disease or shock and/or refractory to IVIG. Dose is based on severity of illness.
IVIG	1-2 gm/kg/dose x1 (maximum 70-100 gm/dose) May consider additional dose if no improvement or rebound after 1st dose	Pre-medication is not required prior to IVIG administration Can be divided over 2 days if needed	Increased risk for clot or thrombosis if other risk factors present; aseptic meningitis; hemolytic anemia	**Used in most cases of MIS-C**.
Aspirin	3-5 mg/kg/day, max dose 81 mg	Anti-platelet and anti-inflammatory	Slightly increased risk of bleeding. Avoid if baseline PLT<100K	**Use in almost all MIS-C cases.**
Anakinra	1-2 mg/kg/day SC; May consider increasing up to a maximum of 10 mg/kg/day	IL-1 receptor antagonist Use may be limited by pharmacy availability	Generally well-tolerated with favorable profile. Administered in sepsis trials without untoward effects. Short half-life. Use with caution in renal insufficiency	**Considered in severe cases only**.
Tocilizumab	8-12 mg/kg/dose IV x1; May consider additional dose if no improvement	IL-6 receptor monoclonal antibody Use may be limited by pharmacy availability	Elevated transaminases, thrombocytopenia, neutropenia, hypersensitivity reaction, GI perforation. Use with caution/avoid with cytopenia or transaminitis.	**May consider for severe cases or treatment resistance to IVIG +/- steroids**
Infliximab	5-10 mg/kg/dose IV x1	TNF inhibitor Use may be limited by pharmacy availability	TB reactivation, hypersensitivity reaction	**Consider in patients with KD features or treatment resistance to IVIG +/- steroids**

UNC Children's COVID-19 Guidelines
Page 4: Evaluation of Suspected 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. Obtain echocardiogram as soon as possible
7. If considering initiation of immunosuppressive therapy (see Page 3), consult pediatric rheumatology

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

UNC Children's COVID-19 Guidelines
Page 5: Anticoagulation Management in Pediatric COVID-19

START
Patient admitted with acute COVID-19 OR MIS-C

→

Initial Labs
CBC/diff, retic, CMP, DIC panel, FVIII, AT3, ferritin, LDH

→

Determine Thrombosis Risk Group

Group A: Therapeutic Anticoagulation

Any of the following:

- Confirmed DVT/PE or other indication for therapeutic anticoagulation
- High suspicion of DVT/PE but not documented. Strongly consider if O2 requirement if >5L HFNC
- Hemodialysis with repetitive clotting of dialysis tubing
- MIS-C with coronary artery aneurysm and Z-score >=10
- MIS-C with documented VTE *or* ejection fraction (EF) < 35%

High-risk Acute COVID-19

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

High-risk 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

Daily Labs
CBC/diff, DIC Panel (consider less frequent if stable)

Group B: Prophylactic Anticoagulation

- Hospitalized and D-dimer >5x ULN with or without non-COVID-19 VTE risk factors
- Hospitalized with D-dimer <5x ULN *with* ≥3 non-COVID-19 VTE risk factors (see Table 1 below)
- **Consider** Pediatric Hematology consult if initial D-dimer >10x ULN (>2,500 ng/mL) or rising

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 (PLT > 450K)
- Coronary artery aneurysms with z-score 2.5-10

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

Table 1. Risk Factors for Hospital-Associated VTE in Children

- Central venous catheter
- Mechanical ventilation
- Prolonged length of stay (eg, anticipated >3 days)
- Complete immobility (eg, Braden Q Mobility Score = 1)
- Obesity (BMI > 95th percentile)
- Active malignancy, nephrotic syndrome, CF exacerbation, sickle cell disease vaso-occlusive crisis, or flare of underlying inflammatory disease (eg, lupus, JIA, IBD)
- Congenital or acquired heart disease with venous stasis or impaired venous return
- Previous history of VTE
- First-degree family history of VTE before age 40 or unprovoked VTE
- Known thrombophilia (eg Protein S, Protein C, or anti-thrombin deficiency; Factor V Leiden; factor II G0210A; persistent antiphospholipid antibodies
- Pubertal, post-pubertal, or age > 12 years
- Estrogen-containing oral contraceptive pill
- Status-post splenectomy for underlying hemoglobinopathy

Table 2. Management After Hospital Discharge

- Continued anticoagulant thromboprophylaxis post-discharge from hospital can be *considered* in patients with COVID-19 or MIS-C who have markedly elevated D-dimer levels at discharge and superimposed clinical risk factors for VTE with a planned duration of the sooner of clinical risk factor resolution or 30d post discharge
- Patients with MIS-C and documented thrombosis or an Ef <35% should receive therapeutic anticoagulation with enoxaparin until at least two weeks after discharge from the hospital
  - Indications for longer outpatient therapeutic enoxaparin dosing include: CAA with z-score >10 (indefinite treatment), documented thrombosis (treatment ≥ 3mos pending thrombus resolution), or ongoing moderate to severe left ventricular dysfunction
- 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.

UNC Children's COVID-19 Guidelines
Page 6: 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.

UNC Children's COVID-19 Guidelines
Appendix: Risk Factors for Severe Disease

In many cases, data are limited. For all these patient groups, families should be advised to take particular care to avoid infection, and patients with these conditions who test positive require careful follow-up. Additional conditions of similar severity that are not listed here may also be considered risk factors.

Putative Risk Factors	Comments
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)	Strikingly, immunocompromised status has not been a common risk factor for severe acute infection. Immunocompromised patients may be at greater risk of prolonged illness/shedding.
Hematologic Disease Sickle-cell disease	Limited data, but patients likely at increased risk for severe pneumonia.
Symptomatic cardiac disease Major congenital heart defects Cardiomyopathy	Limited data. Caution and careful follow-up are advised
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 daily controller Obstructive sleep apnea	Baseline compromised pulmonary function likely increases the risk of requiring hospitalization and risk of severe disease. **Many hospitalized patients have had baseline OSA or poorly controlled asthma.**
Metabolic or endocrine disease Diabetes mellitus requiring insulin Obesity (BMI >95th percentile or >30) Metabolic disorders significantly affecting multiple organ systems	These are clear risk factors in adults. Most adolescents with severe COVID-19 in our hospital have been obese.
Medically complex Technology dependence associated with developmental delay and/or genetic abnormalities	These patients have diminished tolerance for an acute infection.