COVID-19 (Acute COVID and MIS-C) Care

The features of acute COVID infection complicated by hyperinflammation and MIS-C may overlap; consider time course and clinical scenario and refer to both MIS-C and acute COVID algorithm as needed (Adapted from Siddiqi, HK, and Mehra, MR. 2020).

- Vaccination
- Acute COVID Diagnosis and Treatment
- MIS-C Diagnosis and Treatment
- Anticoagulation in COVID-19 and MIS-C
- Differential Diagnoses
- Definitions of Organ System Involvement
- Resources

Appendix

Version Changes Approval & Citation Evidence Ratings Bibliography
COVID-19 Pathway v11.0: Vaccination

- COVID-19 vaccination is recommended for all patients and family members. Contraindications include age <6 months, current COVID-19 infection or MIS-C, severe allergy to vaccine component, or receipt of COVID-19 monoclonal antibody product within 90 days.

- Outpatients or family members may schedule now through the Seattle Children's public portal.

- Inpatient care teams may email PatientCOVIDVaccine@seattlechildrens.org with the subject line: Inpatient Vaccination Request.

- Vaccine post-MIS-C: CDC and AAP recommend patients with a history of MIS-C should consider delaying vaccination until after they have recovered from illness (including return to normal cardiac function) and for at least 90 days following their diagnosis of MIS-C. Currently, there are limited data about the safety and efficacy of COVID-19 vaccine in patients with a history of MIS-C. Pediatricians and patients/families should participate in shared decision making in weighing risks and benefits of COVID-19 vaccination for each individual patient.
**COVID-19 Pathway v11.0: Acute COVID**

### Inclusion Criteria
- Suspected COVID-19 acute infection

### Labs

**Tier 1 Labs**
- COVID PCR if no recent positive, CBC/d, CRP, ESR, BMP, ALT, albumin
- Consider UA and RVP
- Testing guidance documents
- Antibody Testing Indications (SCH only)
- Guidance on Who to Test (SCH only)

**Tier 2 Labs**
- BNP, troponin, D-dimer, ferritin, fibrinogen, INR/PT/PTT, specimen storage (red, freeze), COVID IgG, blood culture if indicated

Consider **Sepsis Pathway** labs

### Illness Severity Definitions

**Mild**
- Symptoms of viral illness or upper respiratory tract infection (such as fever, cough, diarrhea, myalgias, minor sore throat, etc.)

**Moderate**
- Signs or symptoms of pneumonia (such as tachypnea, retractions, abnormal chest xray, etc.) AND
- No sustained hypoxia

**Severe**
- Signs or symptoms of pneumonia AND
- New or increased oxygen requirement

**Critical**
- Pneumonia AND one of the following:
  - Requiring positive pressure ventilation OR
  - Signs of sepsis or multi-organ failure

### Asymptomatic, Mild, or Moderate Illness

- No hypoxia

**Treatment for High-Risk Patients with Mild-Moderate COVID-19**
- No labs indicated
- Review admission criteria
- Inpatient or outpatient supportive care and monitoring for increasing severity
- Home Quarantine Handout

### Severe Illness

- New or increased oxygen requirement

**Tier 1 labs**
- EKG, CXR

**Trend labs and add Tier 2 if symptoms worsen to monitor for complications such as hyperinflammation or MIS-C**

### Critical Illness

- Requires positive pressure ventilation, sepsis, or multi-organ failure

**Tier 1 and 2 labs**
- Consider **Sepsis Pathway**
- ED Guidance: Resuscitation for High-Risk COVID Patient
- EKG, CXR, consider ECHO
- Consult Infectious Disease, as needed
- Consult Rheumatology for hyperinflammation
- Imaging for thrombi as indicated by clinical evaluation as D-dimer expected to be elevated in inflammation

**Consider MIS-C if cardiac involvement or labs indicative of severe inflammation and/or multi-organ involvement**

### Inpatient Admit Criteria

- Hypoxia
- Inability to tolerate PO
- Increased work of breathing (grunting, retracting, tachypnea)

**PICU Admit Criteria**
- Concern for respiratory failure, sepsis
- Need for positive pressure ventilation
- Hypotension requiring inotropic support

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**Last Updated: July 2022**
**Next Expected Review: September 2022**
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For questions concerning this pathway, contact: COVID19Pathway@seattlechildrens.org

If you are a patient with questions contact your medical provider. Medical Disclaimer
**COVID-19 Pathway v11.0: Early Treatment for high-risk patients with mild-moderate COVID-19: Antiviral Medications and Monoclonal Antibodies**

**Background:** FDA Emergency Use Authorizations (EUA) allow for the use of monoclonal antibody products and oral antivirals for early treatment of mild-moderate COVID-19 in high-risk patients ≥12 years of age and 40 kg. Efficacy of monoclonal antibodies varies with current circulating SARS-CoV-2 variants. In addition, the FDA has approved IV remdesivir x 3 daily doses for high-risk children of all ages for this indication. Oral antivirals are now readily available at SCH as well as at community pharmacies.

**Guidance statement:** Based on accumulated evidence, we suggest against routine administration of these treatments for COVID-19 in most children or adolescents. Rather, their use should be considered on a case-by-case basis for patients at high risk of progression to severe disease. Oral antiviral therapy (nirmaltrelvir/ritonavir) is preferred option for high-risk patients who are able to receive it (see criteria below).

**Rationale:** There are limited safety or efficacy data for these products in children. Based on our experience both internally and around the globe, children in general have lower risk of progression to severe disease and poor outcomes. In addition, clear risk factor stratification data is limited. Finally, supplies of these products or infusion capacity are often limited.

**Eligibility criteria:**
1. Severe immunocompromise, severe obesity (BMI ≥ 35 or 95%ile), medical complexity WITH respiratory technology dependence OR.
2. MULTIPLE moderate risk factors (diabetes, other immunocompromise, sickle cell disease, obesity (BMI ≥ 25 or 85%ile), other medical complexity, chronic cardiac, respiratory or kidney disease).
3. All currently available products except remdesivir require children to be at least 12 years of age and weigh at least 40 kg.

**Exclusion criteria:**
Hospitalization for COVID-19, supplemental O2 requirements for COVID-19, infection >7 days.
### Procedure for obtaining therapy:

1. **Oral Paxlovid (nirmatrelvir/ritonavir):** for patients ≥12 years AND 40 kg: COVID Therapeutics Committee approval is NOT required for high-risk outpatients who meet eligibility criteria above and are within 5 days from beginning of infection (first symptoms or positive test). Paxlovid can be prescribed at SCH or at community pharmacies. Please refer to SCH formulary and [FDA EUA provider fact sheet](https://www.covid19-druginteractions.org/checker) for prescribing information.
   a. Providers should verify possible drug interactions before prescribing Paxlovid on this site or with a pharmacist: [https://www.covid19-druginteractions.org/checker](https://www.covid19-druginteractions.org/checker).
   b. Paxlovid availability in the community can be checked on this site: [https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/](https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/).

2. **IV remdesivir (3 day course):**
   a. For outpatients: Please submit the Intake form (for SCH only) for approval for remdesivir therapy for outpatients including ED patients who will be discharged. Referring providers will be responsible for arranging with assistance from Infusion Center APP team.
   b. For inpatients (including ED patients who are likely to be admitted): Committee approval is NOT required for high-risk patients who meet eligibility criteria above and have no exclusion criteria. Please follow dosing per Seattle Children’s Hospital formulary.

3. **Monoclonal antibody therapy for patients >12 years AND 40 kg:** COVID Therapeutics Committee approval is required. Please submit Intake form (for SCH only) for patients who meet eligibility criteria. In times of limited availability, monoclonal antibody therapy will be prioritized for those who are incompletely vaccinated or unlikely to respond to vaccination. Referring providers will be responsible for arranging infusion with assistance from Infusion Center APP team.

   SCH Providers who would like their patient considered for Monoclonal Antibody therapy or outpatient IV Remdesivir should submit Intake form (for SCH only).

Community providers can call SCH Infectious Disease on call or email: [COVIDmab@seattlechildrens.org](mailto:COVIDmab@seattlechildrens.org)
Acute COVID Treatment for Patients with Severe or Critical Illness

- Review MIS-C algorithm if indicated
- Consider if clinical trials are applicable
- For patient ≥18, please refer to NIH COVID-19 Treatment Guidelines

### Antiviral Therapy:
- Remdesivir:
  - **Note:** international guidelines do not have consensus on use in adults and benefit is unknown in children
  - Consider for patients with COVID pneumonia age ≥12 at higher risk of poor outcome OR ≥16 regardless of risk factors; AND both of the following
    - with severe illness and increasing need for O₂
    - within first 10 days of illness
  - For patients <12, consider on a case-by-case basis
  - FDA approved for ≥28 days and >3kg
  - Check renal and liver function panels prior to initiation. Refer to formulary for lab monitoring
  - A 5-day course of treatment is recommended for most patients; stop therapy when meeting discharge criteria

### Immunomodulatory:
- Dexamethasone: Consider for patients, especially adolescents, with critical illness or rapidly progressive severe illness
- 0.15 mg/kg/dose (6 mg max) once daily for up to 10 days or until discharge
- Other corticosteroids: Consider for ARDS or in consultation with Rheumatology for hyperinflammation
- Biologic immunomodulatory medications
  - In consultation with Rheumatology for hyperinflammation

### Adjunctive:
- Mechanical thromboprophylaxis with SCDs if possible
- Prophylactic anticoagulation with heparin or enoxaparin if severely or critically ill with risk factors (see anticoagulation page)
- Stress dose hydrocortisone: For patients on chronic glucocorticoids if febrile, requiring O₂, hypotensive, or unexplained vomiting

### Discharge Instructions

**Isolation:**
- Determine length of isolation and need for repeat testing based on severity of illness, first positive PCR or onset of illness, and immunosuppression (patients receiving steroids are considered immunosuppressed by IP) using Infection Prevention Guidance document *(for SCH only).*
- Advise family, PCP, and followup providers of end date of isolation and, if immunosuppressed, that repeat PCR x2 after 20 days of isolation is needed to end healthcare facility-based isolation (it should not be needed to end home isolation).
- Please obtain repeat PCR if result may clear patient from healthcare facility-based isolation (ex: if immunosuppressed and 20 days have passed since first positive PCR).

**Return to sports or exercise:**
- **Children with asymptomatic/mild illness:** PCP evaluation after isolation period.
- **Children with moderate/severe illness (prolonged fever or hospitalized):** PCP evaluation and an ECG after symptom resolution and after isolation.
- **Children with critical illness/MIS-C:** No strenuous exercise for least three to six months and obtain cardiology clearance prior to resuming training or competition (refer prior to discharge).
Stop and Review

For questions concerning this pathway, contact: COVID19Pathway@seattlechildrens.org

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Last Updated: July 2022
Next Expected Review: September 2022

Inclusion Criteria
- Fever AND critically ill
- OR Persistent fever ≥3d AND ill-appearing AND concern for MIS-C
- OR Persistent unexplained fever ≥5 days

MIS-C Case Definitions
- CDC
- WHO

Clinical Features/Evidence of MIS-C
- Most patients have ≥4 organ system involvement; ≥2 required for diagnosis
- Involvement of following systems (percent of patients in case series):
  - Gastrointestinal (92%)
  - Cardiovascular (80%)
  - Hematologic (76%)
  - Muco-cutaneous (74%, 59% had rash)
  - Respiratory (70%)
  - Musculoskeletal (23%)
  - Renal (8%)
  - Neurologic (6%)
- See definitions of organ system involvement
- Recent COVID illness OR exposure (note: not necessary to suspect MIS-C)

Lab Evidence of MIS-C
No lab criteria is diagnostic; most patients have 4 or more markers of inflammation
- Evidence of inflammation, common values:
  - CRP >3 mg/dL, ESR >40 mm/h, ferritin >500 ng/mL, ANC >7700, ALC <1500, platelet <150k, D-dimer >2 ug/mL, fibrinogen >400 mg/dL, albumin <3 g/dL, anemia, ALT >40 U/L, INR >1.1
- Other: AKI, hyponatremia, high LDH, high troponin, BNP >400 pg/mL, prolonged PT or PTT; If ESR low but high ferritin and CRP, consider MAS

Percentages and values adapted from Feldstein et al, NEJM June 2020

Lab Evidence of MIS-C?
Yes
- Obtain Initial Labs
  - If high clinical suspicion, add Additional Labs
  - CXR (if resp sx)
- Obtain Additional Labs
  - EKG, CXR
  - ECHO (early if signs of cardiac dysfunction)
  - Consider Sepsis Pathway
    Caution with boluses; monitor for cardiac dysfunction
- Obtain Initial and Additional Labs, EKG, CXR

No
- Consider alternate diagnoses
- Consider discharge with close follow-up

Complete or Incomplete Kawasaki?

Evidence of MIS-C without alternate diagnosis?

Yes
- Follow Kawasaki Disease Pathway if COVID testing negative or while pending
- Monitor closely for signs of shock

No
- Follow Kawasaki Disease Pathway

Inpatient Admit Criteria
Admit to Special Isolation Unit (SIU)
- Suspected MIS-C (review case definition “clinically severe illness”)

PICU Admit Criteria
- Altered mental status
- Concern for respiratory failure, sepsis
- Need for positive pressure ventilation
- Hypotension or shock

Evidence of MIS-C with recent exposure/infection OR cardiac dysfunction

Patients with MIS-C have significant risk for developing shock

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Stop and Review

Consider differential diagnosis including acute COVID

Initial Labs: CBCd, CRP, ESR, BMP, ALT, albumin, UA, COVID PCR, COVID IgG, RVP

Additional Labs: BNP, troponin, ferritin, D-dimer, coags, fibrinogen, LDH, blood culture if indicated, red top to hold prior to IVIG (freeze), further labs on consultant advice

Stop and Review

Consider differential diagnosis including acute COVID

Initial Labs: CBCd, CRP, ESR, BMP, ALT, albumin, UA, COVID PCR, COVID IgG, RVP

Additional Labs: BNP, troponin, ferritin, D-dimer, coags, fibrinogen, LDH, blood culture if indicated, red top to hold prior to IVIG (freeze), further labs on consultant advice
COVID-19 Pathway v11.0: MIS-C Treatment

**Review case definition:** age <21, >24h fever, lab evidence of inflammation (most patients have 4 or more markers), multi-system involvement, and clinically seriously ill, without alternative diagnosis (review differential diagnosis) plus confirmed recent SARS-CoV-2 or known exposure within 6 weeks. (For age >21 see NIH Guidelines for adults)

- ECHO if not already done; repeat as indicated
- Antibiotics per Sepsis Pathway only if and while bacterial infection suspected
- Consider supportive care only for patients who have mild* illness; monitor for increasing severity until clearly improving
- Consult Infectious Disease, Cardiology, and Rheumatology as needed to support primary team diagnostic or therapeutic decision making

**First-line treatment for all seriously* ill patients with MIS-C:**
- IVIG 2 g/kg (use ideal body weight, max dose 100g) over 12 hours
- Anti-platelet: ASA 3-5 mg/kg (max of 81 mg) due to risk of developing coronary aneurysms, hold ASA if Pt <50 k
- Mechanical thromboprophylaxis with SCDs if possible
- Anticoagulation prophylaxis is usually indicated: see anticoagulation page
- Steroids are indicated for most seriously ill patients with MIS-C; consider short course (3-5 days) for patients who are not critically ill and improve rapidly, or wean over 2-3 weeks
  - Methylprednisolone 1-2 mg/kg/day divided BID (max dose 30mg BID for low/mod dose), PO route when tolerating diet
  - Consider higher dose steroids (methylprednisolone 10mg/kg/day) for patients who are worsening despite treatment, or with moderately or severely depressed cardiac function, in consultation with Heart Failure team and Rheumatology
  - Start H2 blocker for GI ulcer prophylaxis while on both steroids and ASA

**Second-line:** Anakinra if not improving post steroid initiation or if labs suggestive of MAS
- 4 mg/kg/dose q6 hours (or frequency per Rheumatology), max dose 100 mg/dose

Trend CBCd, CRP, LDH, ALT, Albumin, Ferritin, Creatinine, Lytes, D-Dimer, Fibrinogen and BNP (frequency dependent on clinical status and medication weaning; post-discharge labs per consultants)

**Classification of illness severity is not well defined. Consider:**
*Mild: Normal vital signs apart from fever, does not meet inpatient criteria other than poor PO, mild dehydration, or monitoring for worsening.
*Serious: Definitively meets case definition and any of: ill-appearing, evidence of organ dysfunction/injury, require for respiratory or cardiovascular support.

**Discharge Instructions**

**Isolation**
- Determine length of isolation and need for repeat testing based on severity of illness, first positive PCR or onset of illness, and immunosuppression (patients receiving steroids are considered immunosuppressed by IP) using Infection Prevention Guidance document (for SCH only).
- Advise family, PCP, and followup providers of end date of isolation and, if immunosuppressed, that repeat PCR x2 after 20 days of isolation is needed to end healthcare facility-based isolation (it should not be needed to end home isolation).
- Please obtain repeat PCR if result may clear patient from healthcare facility-based isolation (ex: if immunosuppressed and 20 days have passed since first positive PCR).
- Avoid NSAIDs while on aspirin.

**Return to sports or exercise**
- **Children with asymptomatic/mild illness:** PCP evaluation after isolation period.
- **Children with moderate/severe illness (prolonged fever or hospitalized):** PCP evaluation and an ECG after symptom resolution and after isolation.
- **Children with critical illness/MIS-C:** No strenuous exercise for at least three to six months and obtain cardiology clearance prior to resuming training or competition (refer prior to discharge).
Treatment of Mild-Moderate COVID-19 References

FDA EUA for nirmatrelvir/ritonavir (Paxlovid) (28 June 2022): [Paxlovid HCP FS 06282022 (fda.gov)]

FDA EUA for bebtelovimab (17 May 2022): [Bebtelovimab Patient Fact Sheet (fda.gov)]


NIH COVID-19 Treatment Guidelines (8 April 2022): [Nonhospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines (nih.gov)]


NIH Pediatric specific guidance (24 Feb 2022): [Children | COVID-19 Treatment Guidelines (nih.gov)]

Anticoagulation in COVID-19 and MIS-C

Patients with severe or critical acute COVID infection or MIS-C are likely at higher risk for thrombosis and therefore should be considered for anticoagulation; review criteria to determine if they require low dose or therapeutic dosing. Also use mechanical thromboprophylaxis with SCDs if possible.

- Relative contraindications to anticoagulation include active major bleeding, platelet level <50,000, and fibrinogen <100mg/dL.
- Discontinue prophylactic anticoagulation at discharge or earlier if patients are improved and risk factors resolved; consider continuation post-discharge for ongoing severe inflammation with other risk factors.
- Consult Hematology for documented thrombosis or as indicated for recommendations in unusual circumstances.
- Asymptomatic, mild, or moderate COVID is not an indication for anticoagulation, use standard indications.

**Indications for low dose anticoagulation (LMWH goal=0.2-0.4units/mL or UFH goal=0.1-0.3units/mL):**

Hospitalized with MIS-C or severe/critical COVID-19 AND one or more of the following risk factors:
- D-dimer >2.5 mcg/mL
- Age >12 years or post-pubertal
- Obesity (>95th %ile)
- Concomitant estrogen-containing oral contraceptive use
- First degree family history of unprovoked VTE
- History of thrombosis or acquired or inherited thrombophilia
- Central venous catheter
- Any rhythm abnormalities: heart block, etc.
- Inotropic infusion requirement
- Sedated and muscle-relaxed or complete immobility
- Active malignancy, nephrotic syndrome, flare of underlying inflammatory disease state, sickle cell VOC
- Congenital or acquired heart disease with venous stasis or impaired venous return

**Indications for therapeutic anticoagulation (LMWH goal=0.5-1units/mL or UFH goal=0.3-0.6units/mL):**

Hospitalized with MIS-C or severe/critical COVID-19 AND One or more of the following:
- Documented thrombosis (also consult Hematology)
- Moderate to severe ventricular dysfunction per Cardiology
- Coronary aneurysm Z score >10
- **Consider therapeutic anticoagulation for active malignancy, nephrotic syndrome, flare of underlying inflammatory disease state, heart disease with venous stasis or impaired venous return, personal history of thrombosis, or multiple risk factors** – discuss indications with specialist managing underlying condition and/or hematology

Continue therapeutic dosing while indicated and formulate outpatient plan with consultants

Adapted from Goldenberg et al, 2020
Differential Diagnoses

Kawasaki Disease
- More common in younger children, if COVID testing negative, and without shock/cardiac dysfunction
- SARS-CoV-2 antibody can remain positive for months after infection and does not necessarily indicate recent infection

Bacterial Infections/Sepsis
- Obtain cultures and evaluate for source
- Consider meningitis

Staph/Strep Toxin-Mediated or Post-Infectious
- Consider Toxic Shock or Acute Rheumatic Fever
- Obtain cultures and evaluate for source including gynecologic or scarlet fever

Staph Scalded Skin Syndrome (SSSS)
- Increasing erythema and bullae
- Younger children
- Obtain cultures

Tick-Borne Illnesses
- With epidemiologic risk factors
- Rocky Mountain Spotted Fever or Leptospirosis

Viral Infections
- Measles, adenovirus, enterovirus, active COVID infection

Myocarditis
- May overlap with MIS-C or have alternate cause

Drug Hypersensitivity Reactions
- Consider SJS, DRESS, or serum sickness like reaction
- History of recent or semi-recent exposure to drug; consider with arthralgias and diffuse mucositis
Definitions of Organ System Involvement

**Gastrointestinal 92%**
- Nausea/vomiting
- Diarrhea
- Abdominal pain
- Appendicitis
- Pancreatitis
- Hepatitis
- Gallbladder hydrops or edema

**Cardiovascular 80%**
- Hypotension or shock
- Cardiac dysrhythmia or arrhythmia
- Ejection fraction <55%
- Pulmonary edema due to left heart failure
- Coronary artery z score ≥2.5
- Pericarditis or pericardial effusion or valvulitis
- B-type natriuretic peptide (BNP) >400 pg/mL
- Elevated troponin
- Receipt of vasopressor or vasoactive support
- Receipt of cardiopulmonary resuscitation (CPR)

**Hematologic 76%**
- Total white blood cell <4k
- Anemia for age
- Platelet count <150,000 /µL
- Deep vein thrombosis
- Pulmonary embolism
- Hemolysis
- Bleeding or prolonged PT/PTT
- Ischemia of an extremity

**Mucocutaneous 74%**
- Bilateral conjunctival injection
- Oral mucosal changes
- Rash or skin ulcers
- ‘COVID’ toes
- Swollen red cracked lips
- Erythema of palms or soles
- Edema of hands or feet
- Periungual (nails) desquamation

**Respiratory 70% (more frequent in teens)**
- Receipt of mechanical ventilation or any type of supplemental oxygen (or increased support for patients receiving respiratory support at baseline)
- Severe bronchospasm requiring continuous bronchodilators or
- Pulmonary infiltrates on chest radiograph
- Lower respiratory infection
- Pleural effusion
- Pneumothorax or other signs of barotrauma
- Pulmonary hemorrhage
- Chest-tube or drainage required

**Musculoskeletal 23% (more frequent in teens)**
- Arthritis or arthralgia
- Myositis or myalgia

**Renal 8%**
- Acute kidney injury with or without dialysis

**Neurologic 6%**
- Stroke or acute intracranial hemorrhage
- Seizures
- Encephalitis, aseptic meningitis, or demyelinating disorder
- Altered mental status
- Suspected meningitis with negative culture

*Adapted from Feldstein et al, NEJM June 2020*
Resources (All Languages)

Info for parents on child’s illness and home care:
- For parents and guardians: what to do when you or your child gets COVID-19 - King County
- How to care for yourself or others with COVID-19 - King County

Isolation/Quarantine/Testing:
- Isolation vs Quarantine: Isolation and Quarantine for COVID-19: WA Department of Health
- Testing: COVID-19 testing in King County

Financial assistance:
- In King County to stay home from work: Household Assistance Request program – King County
- In other counties in WA: Care Connect Washington: WA Department of Health

WA State Resources:
- List of COVID resources and vaccine locator: WA State Coronavirus Response (COVID-19)

Vaccine information:
- CDC information: Key things to Know About COVID-19 Vaccines
- Vaccine locator above under WA State Resources
Summary of Version Changes

- **Version 1.0 (7/9/2020):** Go live.
- **Version 2.0 (8/13/2020):** Removed CK and triglycerides from Labs. Added consult with Cardiology with Echo and added Indications for therapeutic dosing of anticoagulation to Treatment page.
- **Version 3.0 (9/17/2020):** Added Acute COVID algorithm and treatment pages.
- **Version 4.0 (12/21/2020):** Changes include
  - Updated document to the new CSW algorithm template (incl. a Table of Contents)
  - Added illustration of time course highlighting overlap between viral phase and inflammatory phase
  - Acute COVID Tier 1 labs edited to remove D-dimer, LDH, and ferritin; those were moved to Tier 2 due to concern for overuse, guidance added on getting Tier 2 labs for “worsening” cases
  - Added advice on interpreting D-dimer
  - Monoclonal antibody guidance added
  - Updated anticoagulation information: indications for prophylactic and therapeutic dosing as well as contraindications were edited based on Goldenberg et al, 2020.
  - Inpatient and PICU admit criteria added to MIS-C algorithm
  - Steroid wean over “2-3” weeks changed from “minimum 3 weeks” based on ACR guidelines
  - Discharge isolation guidance box added
  - SIU Policies and Guidance page added
  - Bibliography edited to reflect current references
- **Version 5.0 (5/11/2021):** Updated verbiage to reflect appropriate consultation for Acute COVID treatment, updated policy and job aid links, and added appropriate citations to Monoclonal Antibody Products page and Bibliography.
- **Version 6.0 (7/8/2021):** Changed wording to encourage steroid treatment for critically ill patients with MIS-C and added recommendation for post-discharge sports clearance.
- **Version 7.0 (11/4/2021):** Changes include
  - Added Vaccination tab with information and resources
  - Updated language for Acute COVID Treatment Remdesivir guidance
  - Added NSAID recommendation to MIS-C Treatment Discharge Instructions
  - Updated language and added current FDA EUA references to Monoclonal Antibody Products for Mild-Moderate COVID-19 page
  - Updated the COVID-19 mAb Intake Form
  - Updated Resources page (formerly titled SIU Policies and Guidance) to include Patient and Family Handouts and Website COVID Resources
- **Version 8.0 (12/22/2021):** Changes include
  - Updated language on Monoclonal Antibody Products for Mild-Moderate COVID-19 page
  - Updated references on Monoclonal Antibody Products for Mild-Moderate COVID-19 References page
- **Version 9.0 (1/4/2022):** Changes include
  - Updated language on Monoclonal Antibodies and Antiviral Medications for Mild-Moderate COVID-19 page per new guidelines
  - Updated references on Monoclonal Antibody Products for Mild-Moderate COVID-19 References page
Summary of Version Changes

- **Version 9.1 (1/25/2022):** Updated link to COVID-19 Monoclonal Antibody and Antiviral Intake Form.

- **Version 10.0 (3/15/2022):** Changes include
  - Added information regarding vaccines post-MIS-C
  - Updated MIS-C treatment consultation recommendation
  - Updated MIS-C first line treatment, adding steroids to first line for most seriously ill patients and including greater specificity for steroid use
  - Updated Monoclonal Antibody Products for Mild-Moderate COVID-19 References with current guidance
  - Added information to Differential Diagnoses page under Kawasaki Disease

- **Version 11.0 (7/20/2022):** Changes include
  - Updated Vaccination guidance to reflect current CDC recommendations
  - Updated Acute COVID-19 Treatment to reflect FDA approval of remdesivir
  - Modified consult recommendations for Acute COVID
  - Changed recommendations and procedures on Early Treatment for High-Risk Patients and integrated them into algorithm format (formerly Monoclonal Antibodies and Antiviral Medications for Mild-Moderate COVID-19)
  - Updated references for Early Treatment for High-Risk Patients
  - Updated links to resources
Approval & Citation

Approved by the CSW COVID-19 Pathway team for December 21, 2020, go-live

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Retrieval Website: https://www.seattlechildrens.org/pdf/covid-19-pathway.pdf

Please cite as:
Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

**Certainty of Evidence**
- 🌟🌟🌟🌟 High: The authors have a lot of confidence that the true effect is similar to the estimated effect
- 🌟🌟🌟 Moderate: The authors believe that the true effect is probably close to the estimated effect
- 🌟🌟🌟🌟 Low: The true effect might be markedly different from the estimated effect
- 🌟🌟🌟🌟🌟 Very low: The true effect is probably markedly different from the estimated effect

**Guideline:** Recommendation is from a published guideline that used methodology deemed acceptable by the team

**Expert Opinion:** Based on available evidence that does not meet GRADE criteria (for example, case-control studies)
Literature Search Methods
Both CDC and WHO case definitions were utilized in the development of this pathway. The articles cited are a representation of local and international experts’ and national societies' resources that were being shared widely, some pre-publication and many that were published by the centers that were diagnosing and treating this new syndrome as the pandemic swept across the globe.

A systematic literature review is in process and may inform future versions of this document. Due to the rapidly evolving literature and the need for urgent guidance, a non-systematic review was used to guide the development of the initial version of this algorithm.

Literature Search Results
The search retrieved 1961 records. Once duplicates had been removed, we had a total of 1550 records. We excluded 1173 records based on titles and abstracts. We obtained the full text of the remaining 94 records and excluded 80. We included 14 studies. The flow diagram summarizes the study selection process.

December 2020

Identification
Records identified through database searching (n=1961)

Additional records identified through other sources (n=2)

Screening
Records after duplicates removed (n=1550)

Records screened (n=1550)

Records excluded (n=1456)

Eligibility
Records assessed for eligibility (n=94)

Articles excluded (n=80)

Did not meet quality threshold (n=80)

Included
Studies included in pathway (n=14)

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535
Bibliography

April 2021 Included Study

December 2020 Included Studies


July 2020 Included Studies


Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.