

Protocol for pharmacologic management of COVID in pediatric inpatients

See Protocol for Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

Patient population:

This guidance applies to patients with confirmed COVID-19 infection, that is, those who currently have a positive molecular diagnostic test for SARS-CoV-2, seen in the hospital in the ED, or clinic or who are admitted to an inpatient floor or the intensive care unit. Please note there is currently limited data on management of COVID-19. The following is based on the little literature available, CDC and state recommendations, published guidance from professional societies and current shared practices from other children's hospitals. This protocol will continue to change as more information and treatments become available.

Definitions of disease severity level:

- **Mild** – may include fever, sore throat, cough, headache, nasal congestion, myalgias, GI upset
- **Moderate** – may include fever, dyspnea, and/or chest imaging consisted with COVID-19 pneumonia. No change from baseline respiratory support requirement
- **Severe** - additionally new or increased supplemental O2 or non-invasive ventilatory support
- **Critical** – respiratory failure requiring mechanical ventilation, ARDS, SIRS and/or multiorgan failure

1. Laboratory and diagnostic testing

Patients may undergo laboratory and diagnostic testing if they have severe/critical infection. Patients who have moderate infection may undergo this testing if they have a worsening condition or important comorbidities in order to help predict risk of progression to severe disease.

Disease severity	Recommendations
Mild	<ul style="list-style-type: none"> • none
Moderate	No comorbidity, stable <ul style="list-style-type: none"> • none No comorbidity, worsening disease <ul style="list-style-type: none"> • CBC, CMP, CRP, ESR, SARS-CoV-2 serology, chest x-ray Comorbidities* <ul style="list-style-type: none"> • CBC, CMP, CRP, ESR, SARS-CoV-2 serology, chest-x-ray
Severe or Critical	All patients: <ul style="list-style-type: none"> • CBC, CMP, CRP, ESR, BNP, troponin, procalcitonin, ferritin, PT, PTT, D-dimer, fibrinogen, LDH, urinalysis, triglycerides, SARS-CoV-2 serology, chest x-ray, EKG, echo

* Immunocompromise, obesity, diabetes, chronic lung diseases (including severe asthma), heart failure, hemodynamically significant congenital heart disease, < 1 year of age

2. Pharmacotherapy

There are currently limited options for therapy of COVID-19. Most children present with mild to moderate disease and progression to severe disease is infrequent. Signs and symptoms of severe infection and MIS-C overlap and patients can have positive SARS-CoV-2 molecular test and positive serology. These features can make it difficult to distinguish active infection from MIS-C and patients may require treatment for both conditions simultaneously.

Disease severity	Recommendations
Mild	<ul style="list-style-type: none"> Supportive care
Moderate	<p>No comorbidity, stable</p> <ul style="list-style-type: none"> Supportive care No targeted pharmacotherapy <p>No comorbidity, worsening disease</p> <ul style="list-style-type: none"> Consult ID <p>Comorbidities</p> <ul style="list-style-type: none"> Consult ID
Severe	<p>All patients:</p> <ul style="list-style-type: none"> ID consult recommended Remdesivir Dexamethasone Consider tocilizumab or baricitinib in discussion with rheumatology or ID if evidence of hyperinflammation
Critical	<p>All patients:</p> <ul style="list-style-type: none"> Consult ID Dexamethasone Consider Remdesivir (not recommended in critically ill adults as no benefit seen in trials) Consider tocilizumab

Remdesivir

Dosing

- Adults (≥ 18 years old):
 - Loading dose 200 mg x 1 then 100 mg q24h x 4 days
- Children ≥ 40 kg:
 - May receive either liquid or lyophilized remdesivir product

- Loading dose 200 mg x 1 then 100 mg q24h x 4 days
- Children 3.5 kg to 39 kg:
 - Must receive lyophilized remdesivir product
 - Loading dose 5 mg/kg x 1 then 2.5 mg/kg q24h x 4 days

Contraindications

- Known hypersensitivity to remdesivir
- ALT > 5 X ULN
- Creatinine Cl < 30 mL/min, dialysis or CVVH

Notes:

There is limited clinical trial data on remdesivir in children 12 - <18 years of age from a trial comparing 5 and 10 days of therapy. None of the studies comparing remdesivir to no anti-viral included children. Observational studies in children have included some children receiving remdesivir but the safety and efficacy data are not reported.

Adult guidelines differ in their recommendations regarding remdesivir in patients requiring invasive mechanical ventilation or ECMO. NIH guidelines do not recommend remdesivir for this group of patients unless it was started before respiratory support was escalation while IDSA guidelines state that either dexamethasone or dexamethasone plus remdesivir may be used in these patients.

NIH guidelines: <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/>

IDSA guidelines: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>

Immunomodulators

1. Corticosteroids

a. Dexamethasone

Indications

- Patients with COVID lower respiratory tract infection requiring supplemental oxygen, non-invasive (includes high flow) or invasive ventilation

Dosing

- 0.15mg/kg once daily (Max: 6 mg) IV/PO for 10 days (or until discharge)
- Alternatives methylprednisolone 0.8 mg/kg once daily (Max: 32 mg) or prednisolone 1 mg/kg once daily (Max: 40 mg)

b. Methylprednisolone/prednisolone

Indications

- Asthma exacerbation associated with COVID-19
- Suspected MIS-C/overlap with COVID-19 infection

Dosing

- Methylprednisolone 1-2 mg/kg/day or pulse dose 10-30 mg/kg/day (MIS-C only)

Notes: The RECOVERY trial in COVID-19 (+) adults found a reduction in 28-day mortality in those receiving invasive mechanical ventilation or oxygen in combination with dexamethasone. The benefit was not observed in patients receiving dexamethasone that did not require respiratory support. A meta-analysis of the effect of 7 trials of corticosteroids (dexamethasone, hydrocortisone or

methylprednisolone) on all-cause mortality at 28 days demonstrated benefit (OR 0.66, 95% CI, 0.53-0.82). There have been no published clinical trials of steroids that include children.

2. IL-6 blocking agents (tocilizumab) – rheumatology consultation recommended

Currently not available. Discuss other anti-IL-6 agents or baricitinib.

Indications

- Given with dexamethasone for patients with COVID-19 and evidence of hyperinflammation in children 2 years of age and older:
 - hemodynamic instability despite vasoactive medication support, worsening respiratory failure, or myocardial dysfunction
 - DINR; low ALC, platelets, albumin, Hb (anemia)

Dosing

- <30 kg: IV: 12 mg/kg/dose once; if clinical signs or symptoms worsen or do not improve after initial dose, may repeat dose once ≥ 8 hours after initial dose (FDA 2021).
- ≥ 30 kg: IV: 8 mg/kg/dose once; maximum dose: 800 mg/dose; if clinical signs or symptoms worsen or do not improve after initial dose, may repeat dose once ≥ 8 hours after initial dose (FDA 2021).

Contraindications

- ANC $< 1,000/\text{mm}^3$
- platelets $< 50,000/\text{mm}^3$
- active hepatic disease or hepatic impairment

3. Baricitinib

Indications

NIH and IDSA guidelines differ in their recommendations for baricitinib

- NIH guidelines recommend use of baricitinib only when there is a contraindication to dexamethasone
- IDSA guidelines recommend baricitinib as an alternative to tocilizumab in combination with dexamethasone in severely ill patients with hyperinflammation

Dosing

- Children 9 years of age and older: 4 mg enterally once daily
- Children 2 years to less than 9 years of age: 2 mg enterally once daily

Contraindications

- End-stage renal disease, acute kidney injury, dialysis

4. Anakinra

Indications

- Does not currently have EUA for use in COVID-19
- Limited data available and trials are ongoing

Dosing

- 2-10 mg/kg div q6h-q12h IV or SC

Anticoagulation

- Prophylactic anticoagulation with Enoxaparin:
 - Consider in all post-pubertal patients regardless of degree of mobility
 - Should be started in immobilized post-pubertal patients based on standard VTE prophylaxis
- Therapeutic anticoagulation with Heparin / Enoxaparin:
 - Documented thrombosis or an ejection fraction (EF) <35% in consultation with cardiology.
 - Anticoagulation (therapeutic dosing) should be continued in all cardiac cases until inflammatory markers have resolved and EF demonstrates improvement. Discuss further with Peds Cardiology / Heart failure team.
- Long-term Anticoagulation management / discharge plan:
 - Enoxaparin prophylaxis may be discontinued for asymptomatic patients upon discharge at the discretion of the attending on service
 - For patients requiring long-term Enoxaparin administration – Hematology, Cardiology (if low EF / coronary aneurysm) should follow and Pharmacy (education) should be consulted, and appropriate follow-up required upon discharge.

The following drugs are no longer recommended in management of Covid-19:

- Hydroxychloroquine
- Azithromycin (not indicated without suspicion for concomitant atypical pneumonia)
- Lopinavir-ritonavir (Kaletra)
- Ivermectin
- Convalescent plasma

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