Protocol for Pharmacologic Management of COVID in **Pediatric Inpatients** and **Outpatients**

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

Inpatient 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	• none
Moderate	No comorbidity, stable • none No comorbidity, worsening disease • CBC, CMP, CRP, ESR, SARS-CoV-2 serology, chest x-ray Comorbidities* • CBC, CMP, CRP, ESR, SARS-CoV-2 serology, chest-x-ray
Severe or Critical	All patients: • 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 and moderate (no oxygen requirement)	No comorbidity, stable • Supportive care • No targeted pharmacotherapy No comorbidity, worsening disease • Consult ID • Consider remdesivir for 3 days if within 7 days of onset of symptoms Comorbidities with high risk of progression • Consult ID • Consider remdesivir for 3 days if within 7 days of onset of symptoms
Severe	All patients: • ID consult recommended • Remdesivir for 5 days • Dexamethasone for 5-10 days • Consider tocilizumab or baricitinib in discussion with ID if evidence of hyperinflammation •
Critical	All patients: • Consult ID • Dexamethasone • Consider Remdesivir (not recommended in critically ill adults as no benefit seen in trials) • Consider tocilizumab or baricitinib

Remedesivir

- 3 days for mild-moderate disease
- 5 days for severe disease

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

Off label dosing for <3.5 kg

- **Consult ID**
- Very limited data available and optimal dose not defined. Dosing below based on 4 reported cases from UK (reference at the end of protocol)
- 2.5 mg/kg for the first dose followed by 1.25 mg/kg for subsequent doses (lyophilized powder)

Contraindications

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

Notes:

The PINETREE study published in NEJM on compared three days of remdesivir to no remdesivir in unvaccinated outpatients at high risk for progression to severe disease (elderly, immunocompromised, diabetes, obesity). There was an 87% lower risk of COVID-related hospitalization or death.

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 for severe infection. 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: **********.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/
IDSA guidelines: **********.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 inhibitors**– rheumatology consultation recommended

Toculizimab

Frequently not available due to high demand. Baricitinib is alternative.

Indications

- Given with dexamethasone for patients with severe or critical COVID-19 and evidence of hyperinflammation (e.g. CRP ≥75 mg/L) in children 2 years of age and older
- Give sarilumab when tocilizumab not available for patients who would qualify for tocilizumab

Dosing:

Tocilizumab

- <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/mm^3
- platelets <50,000/mm^r
- active hepatic disease or hepatic impairment

3. **Janus Kinase inhibitors**

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 toculizumab in combination with dexamethasone in severely ill patients with hyperinflammation
- Give within 96 hours of hospitalization or 24 hours of ICU level care

Dosing

- Children 9 years of age and older: 4 mg enterally once daily for up to 14 days

- Children 2 years to less than 9 years of age: 2 mg enterally once daily for up to 14 days
- May discontinue once patient clinically improving (significant downtrend in inflammatory markers)

Contraindications

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

i. 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

********play.google.com/store/apps/details?id=org.idsociety.guidelines

OUTPATIENTS WITH HIGH RISK OF PROGRESSION TO SEVERE DISEASE

There are several new therapies that are available for the management of outpatients of with mild to moderate COVID-19at high risk for disease progression. Please call Infectious Diseases to discuss.

Previously used monoclonal antibody therapies (bamlanivimab/etesevimab, casirivimab/imdevimab) are not effective against the omicron variant and are not being given in regions where omicron is dominant.

1. Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)
    - Taken orally twice daily for 5 days
    - Available for patients 12 year of age and older and weighing ≥ 40 kg
    - Initiates as soon as possible and start within 5 days of symptom onset
    - Potential for many, complex, drug-drug interactions. Ritonavir, given to boost levels of mirmatrelvir, is a strong inhibitor of CYP3A, and may increase concentrations of medications metabolized through CYP3A. Strong inducers of CYP3A can cause significant reductions in nirmatrelvir and ritonavir concentrations leading to reduced effectiveness.
    - See EUA fact sheet for ritonavir-boosted nirmatrelvir (Paxlovid) for guidance on drug-drug interactions. Review all patient medications (prescription and OTC) before prescribing Paxlovid
    - Available at Walmart and Sam's Club pharmacies

*** Open label treatment trial for children will be available some time in March. Contact Dr. Arnold or Dr. Carrillo-Marquez or see ***********.lebonheur.org/research/clinical-trials/ under infectious diseases**

2. Sotrovimab – monoclonal antibody infusion with activity again omicron variant
    - Single IV infusion of 500 mg
    - Available for patients 12 year of age and weighing ≥ 40 kg
    - Give as soon as possible and within 10 days of symptom onset
    - To obtain an appointment for your patient, call 901-516-9451. Must be ordered by a physician.

3. Remdesivir IV given for three days: discuss with ID. Will probably need admission.
    Children ≥ 40 kg:
    - Loading dose 200 mg x 1 then 100 mg q24h x 2 days

    Children 3.5 kg to 39 kg:
    - Loading dose 5 mg/kg x 1 then 2.5 mg/kg q24h x 2 days
    - Initiate as soon as possible and within 7 days of symptoms onset

4. Molunipiravir 800 mg
    - Taken orally twice daily for 5 days
    - Available for patients **18 years** of age and older
    - Initiate as soon as possible and within 5 days of symptom onset
    - Only used if none of the above options is available as efficacy is lower than the above three therapies (30% reduction in hospitalization versus 85-87%)

- Not recommended for use in pregnant patients due to risk of fetal toxicity from animal studies
- Checklist for prescribers available at **********.fda.gov/media/155118/download

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