Treatment of PEDIATRIC patients with COVID-19 at MultiCare Health System

Current as of July 15, 2020

This guideline will be continually updated as more evidence becomes available.

A Pediatric Infectious Disease consultation and Pharmacy consultation are required for all pediatric patients with COVID-19 for whom treatment is being considered.

Clinical Symptoms: Range from uncomplicated asymptomatic infection to URI, to pneumonia, to ARDS and shock. (Table 1)

Supportive care: Appropriate treatment of concomitant pneumonia, respiratory failure, ARDS, sepsis, septic shock. Antithrombotic therapy should be risk stratified: 1) Hospitalized patients without DIC should be placed on VTE prophylaxis. 2) Hospitalized patients with suspected or confirmed DIC should be started VTE prophylaxis if no overt bleeding and Peds Hematology-Oncology should be consulted to discuss ongoing screening and prophylaxis after discharge.

Pharmacologic Treatment: The only FDA-approved treatment for COVID-19 currently is remdesivir, which was approved for emergency use in May 2020.[1] This agent has been granted emergency use authorization for treatment of adults and children hospitalized with suspected or laboratory confirmed severe disease with COVID-19. Severe disease is defined as patients with low blood oxygen levels or need for oxygen or ventilator support. -. All other recommendations below are based on in vitro data, non-robust trials, and/or expert opinion. As children generally have asymptomatic or mild symptoms and given the fact that there are no robust data, medications listed below should only be considered for inpatient pediatric patients with confirmed, severe infection, or those at high risk for poor outcomes with symptom complex consistent with COVID pneumonia pending confirmation.

Limited evidence supporting routine use of corticosteroids: Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm.[18,19] Recently, however, more evidence has been emerging that dexamethasone is efficacious in the management of COVID although these studies did not include children.[24-29] Accordingly, the Infectious Disease Society of America updated its guidelines on 6/25/2020 to include the use of glucocorticoids in hospitalized patients with hypoxemia requiring supplemental oxygen.[30] Corticosteroids are also warranted for other medical indications (i.e., ARDS, asthma exacerbation). If steroids are utilized as an inpatient, continue anti-COVID-19 therapy.

Recommend against routine use of azithromycin: Preliminary data evaluating the combination of hydroxychloroquine and azithromycin for treatment of COVID-19 were recently published.[6] The authors of this study conclude that combination therapy led to greater viral load reduction compared to monotherapy with hydroxychloroquine. However, more patients receiving hydroxychloroquine monotherapy had higher baseline viral burden (estimated by cycle threshold values). When limiting the analysis to those with comparable baseline cycle threshold values, combination therapy with hydroxychloroquine and azithromycin led to a similar proportion of negative testing by day 6 compared to hydroxychloroquine monotherapy. Furthermore, the study does not report the clinical outcomes of these patients, and it is unknown if reductions in viral load correlate with improvements in clinical outcomes. Thus, based on this limited (only 6 patients in combination group) and weak evidence, we recommend against the routine use of azithromycin for the treatment of COVID-19 at this time.

Pediatric Outpatients

Pharmacotherapeutic treatment of pediatrics in the outpatient setting is not recommended at this time. Acetaminophen preferred over NSAIDS for fever and pain control (See table). For asthmatics with exacerbation, steroids should NOT be withheld.

Treatment:

- Supportive care
- Physical activity should be encouraged as tolerated to reduce the risks of DVT/PE

Remain in self-isolation until ALL of the following have been met:

- At least 10 days since symptoms first started (or from date of positive test if patient has been asymptomatic for the duration)
- At least 72 hours have passed since last fever without the use of fever-reducing medications
- Improvement in respiratory symptoms

Direct families to information on home isolation at
https://www.doh.wa.gov/Portals/1/Documents/1600/coronavirus/COVIDcasepositive.pdf

Pediatric Inpatients: Consult Peds ID if COVID suspected primary diagnosis

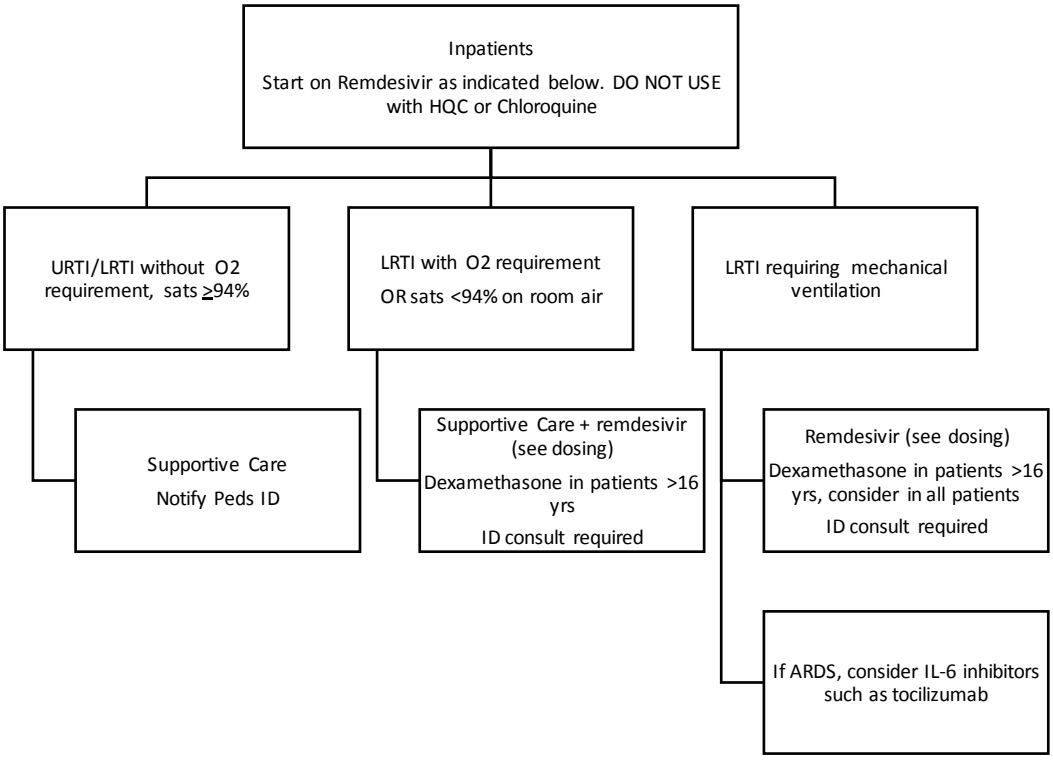

Table 1: Clinical spectrum of COVID-19

Uncomplicated illness	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise. The elderly and immunosuppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis or shortness of breath.
Mild pneumonia	Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40 and no signs of severe pneumonia.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air (adapted from [1]). Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 <90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40.[2] The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome[7-9]	**Onset:** new or worsening respiratory symptoms within one week of known clinical insult. **Chest imaging (radiograph, CT scan, or lung ultrasound):** bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. **Origin of oedema:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. **Oxygenation (adults):** • Mild ARDS: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH_2O,[7] or non-ventilated[8]) • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O,[7] or non-ventilated[8]) • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥5 cmH_2O,[7] or non-ventilated[8]) • When PaO_2 is not available, SpO_2/FiO_2 ≤315 suggests ARDS (including in non-ventilated patients) **Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2):** • Bilevel NIV or CPAP ≥5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis[10,11]	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction*. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock[10,12]	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. Children (based on [12]): any hypotension (SBP <5th centile or >2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO_2; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO_2, oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO_2/FiO_2 x Barometric pressure/760.

* The SOFA score ranges from 0 to 24 and includes points related to 6 organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2), coagulation (low platelets), liver (high bilirubin), cardiovascular (hypotension), central nervous system (low level of consciousness defined by Glasgow Coma Scale), and renal (low urine output or high creatinine). Sepsis is defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score[13] of ≥2 points. Assume the baseline score is zero if data are not available

Table 2 POTENTIAL RISK FACTORS FOR SEVERE COVID, PEDIATRICS		
Epidemiological	**Vital Signs**	**Labs**
Age—unknown, possibly premature and < 1 year may be risk	Respiratory distress	D-dimer > 1000 ng/mL
Chronic lung disease including moderate-severe asthma, CF		CPK > 2 x ULN
Chronic kidney disease		Elevated CRP
Diabetes mellitus		
Sickle cell disease		
History of hypertension		Elevated troponin
History of cardiovascular disease		Admission absolute lymphocyte count < 0.8
Use of biologics for immune suppression		Ferritin > 300 ug/L
History of transplant or other immunosuppression		
All patients with HIV (regardless of CD4 count)		

Table 3: Potential Treatment Options – Peds ID Consult Required			
Drug	**Dose**[a]	**Side Effects**	**Notes**
Remdesivir[8, 10]	≥3.5 to <40 kg: 5mg/kg IV on day 1, followed by 2.5mg/kg IV daily for 5-10 days ≥40 kg: 200 mg IV on day 1, followed by 100 mg IV for 5-10 days Use 10 day course for patients who do not have rapid clinical response or are ventilated	• Transient elevations in LFT's • Reversible AKI (animal studies)	Full adverse effect profile unknown Drug interaction profile unknown • May decrease efficacy of hormonal contraception. Contraindications: Hypersensitivity Renal impairment with eGFR <30ml/minute Use only the lyophilized powder in pediatric patients <40kg
Dexamethasone[26]	0.15 mg/kg/day (max 6 mg/dose) IV or PO for 10 days or until discharge	• Hypertension, hyperglycemia	May consider an alternative corticosteroid if warranted.
Tocilizumab[11]	<30 kg: 12 mg/kg IV once ≥30 kg: 8 mg/kg (max 800 mg) IV once May repeat if febrile continued clinical	• Can cause long-lasting neutropenia with potential increased risk for secondary infection • Can be harmful to newborns-	Drug may be difficult to obtain Therapy with interleukin-6 inhibitors, like tocilizumab, may improve oxygenation and time to symptom resolution in patients at high risk of cytokine storm.

	decompensation 8- 12 hours after first dose *Doses should be rounded to nearest available full vial (80 mg, 200 mg, 400 mg vials)	mothers treated with tocilizumab should refrain from breastfeeding • Serious adverse events: 1. Gastrointestinal perforation 2. Anemia 3. Hepatitis • 4. Infusion reaction	Consider adding to antiviral therapy for COVID-19 positive patients who meet the below: Inclusions 1. Positive COVID-19 2. Diagnosis codes U07.1 (Covid Virus Identified) and R65.11 (Cytokine Release Syndrome) are present on the chart 3. Completion of patient financial screening and Genentech Foundation Enrollment Form submitted (see attached workflow pdf) 4. All of the below: a. Abnormal chest imaging consistent with COVID-19 b. Persistent fever with temperature >/=38C c. Rapidly worsening gas exchange requiring > 6L/min (if not vented) OR Pa02/FIO2<200 (if vented) d. Absence of systemic bacterial or fungal co-infection 5. Lab parameters (at least one): a. Ferritin > 300 ug/L with

			doubling within 24 hrs b. Ferritin > 600 ug/L at presentation AND LDH >250 U/L c. Elevated D-dimer (>1 mg/L) Exclusions 6. AST/ALT > 5x ULN 7. ANC < 500 8. Plt <50K 9. Sepsis or infection from non-COVID pathogens 10. Anti-rejection immunosuppressive therapy
Azithromycin[6] ***NOT recommended as treatment for COVID at this time***	<50 kg: 10 mg/kg x 1 dose, followed by 5 mg/kg daily x 4 doses ≥50 kg: 500 mg x 1 dose, followed by 250 mg daily x 4 doses	• QT_c-prolongation (monitor while on HC therapy) • Nausea/vomiting	Routine use of azithromycin is not recommended for COVID pneumonia. However, it may be used as part of antibiotic regimen **if bacterial pneumonia suspected.**

Table 4: Agents NOT Recommended	
Darunavir/cobicistat[12]	• No in vitro or clinical data yet exists to support use, though a clinical trial has been registered in China.
Immune globulin (IVIG)	• Not routinely used for patients who do not meet diagnostic criteria for Multisystem Inflammatory Syndrome in Children (MIS-C) • There is little rationale for use since available IVIG products are unlikely to contain specific antibodies to SARS-CoV-2, given lack of widespread immunity. IVIG has been suggested to have anti-inflammatory or immunomodulatory effects; however, given the lack of conclusive clinical data for treatment of novel coronaviruses and national shortage of IVIG products, routine use of IVIG is not recommended at this time. • If patient meets diagnostic criteria for MIS-C, refer to the MIS-C guidelines regarding use of IVIG

Interferons[13,14]	• Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Their adverse effect profiles are also generally unfavorable.
Nitazoxanide[14,15]	• Some in vitro studies have demonstrated potency against SARS-CoV-2, though clinical use against other coronaviruses has not demonstrated benefit. Poorly tolerated formulation; safety profile is relatively benign.
Oseltamivir	• Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected. • If influenza is unknown or positive, oseltamivir should be started. Stop if flu A/B PCR negative AND low suspicion.
Ribavirin (oral)[16,17]	• Typically used in combination with an interferon, ribavirin has been studied for patients with other coronaviruses, with mixed results. Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day).
Lopinavir-ritonavir[20]	• Recent study showing lack of benefit in severe cases. • Side effects can be moderate/severe are often treatment limiting • In vitro studies suggesting activity, but clinical reports inconclusive to negative. • Limited supply, many drug interactions
Chloroquine[7-9, 23]	• While early small trials may have showed activity of the drug against SARS-CoV-2, recent data indicates a high number of cardiac complications that have resulted in deaths.
Hydroxychloroquine[24]	• Limited evidence of effectiveness of hydroxychloroquine in treatment of Covid-19 patients, and a recent study showed an association of increased overall mortality was identified in patients treated with hydroxychloroquine alone, highlighting importance of waiting for results of prospective, randomized, controlled studies before widespread use.

[a] Dosing for pediatric patients is derived from recommendations for other indications, extrapolated from adult data, or is being utilized at other pediatric institutions. There are no published clinical studies for the treatment of COVID-19 in pediatric patients.

Table 5: Miscellaneous Agents	
Non-Steroidal Anti-inflammatory Drugs (NSAIDs) [i.e., ibuprofen][21]	• No reliable evidence suggests that use of NSAIDs exacerbates COVID-19 symptoms. However, there are reports of NSAID use preceding clinical deterioration in some patients with severe COVID-19 disease. There is also theoretical concern that NSAID use could increase viral uptake due to its effect on the renin-angiotensin system. Data is limited. APAP is preferred first line, however NSAIDS could be considered if needed as second line • Continue standard of care
Angiotensin/RAS Blocking Agents (ACEi/ARBs)[22]	• Based on multiple cardiology and nephrology societies' review, it is not recommended to routinely discontinue ACEi/ARB therapy to decrease risk for more severe COVID-19 disease.

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