

## **University of Iowa Health Care Guidance on Treatment Options for Patients with SARS-CoV-2**

Clinical trial data regarding therapeutics for COVID-19 are rapidly emerging and local and national guidelines addressing treatment options have been published and are frequently updated. UIHC Guidance on Treatment Options for Patients with SARS-CoV-2 will assist UIHC staff when making treatment decisions in patients with SARS-CoV-2 (COVID-19). These guidelines are meant to serve as guidance and are not intended to replace clinical judgement. There is a great deal of uncertainty around this evolving pandemic and information may change rapidly. Additionally, UIHC is unable to guarantee supply of these agents particularly during periods of rising national case counts.

This document has been vetted by UIHC experts in the fields of infectious disease and adult and pediatric hematology and has been reviewed by the Pharmacy & Therapeutics Working Group, as well as Hospital Incident Command System. Information will be updated as new information becomes available and can be subsequently evaluated. COVID-19 is an emerging, rapidly evolving situation. It is important to remember that data becomes available before it is peer reviewed, and that in the current COVID-19 pandemic environment, there are more recalls of “evidence” than we have seen in the past.

Evidence of summary for individual therapeutic agents can be found in Appendices A-H.

### ***Key Points Regarding TREATMENT of Patients with COVID-19:***

- Standard of care for many patients continues to be appropriate isolation and supportive care. Guidelines provided by the [National Institutes of Health \(NIH\)](#) as well as the [Infectious Disease Society of America \(IDSA\)](#) recommend pharmacologic therapies in select patient groups with more severe disease or those at particular risk of progression to severe disease.
- **This document provides a brief overview of therapeutic agents for use in COVID-19; it will be subject to updates and changes as additional information becomes available**
- Inpatient therapies are orderable for providers within Epic; patients should be carefully assessed for eligibility based on clinical status. Therapies for inpatient treatment of mild-moderate infection can be found within the order set “UIHC: Inpatient Therapy for Mild-Moderate COVID”
- Outpatient therapies are orderable for providers within Epic within the order set “UIHC: COVID Outpatient Therapy”

### ***Key Points Regarding Pre-Exposure Prophylaxis***

- There are currently no available therapies authorized or indicated for pre-exposure prophylaxis of COVID-19
- Tixagevimab-cilgavimab (Evusheld®) is no longer authorized by the FDA as of 1/26/2023 because it is unlikely to be active against more than 90% of the SARS-CoV-2 variants currently circulating in the U.S. based on the latest CDC data

### ***Key Points Regarding Post-Exposure Prophylaxis***

- There are currently no available therapies authorized or indicated for post-exposure prophylaxis of COVID-19.

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***Therapeutic Considerations for Adults with COVID-19 Based on Clinical Status***

<b>Clinical Status</b>	<b>Therapeutic Recommendations</b>
Non-hospitalized with mild-moderate COVID-19	Patients should be evaluated for eligibility for antivirals (i.e. nirmatrelvir-ritonavir, remdesivir, and molnupiravir) based on EUA criteria (see Appendix E, F, and I)
Hospitalized for reasons other than COVID-19 with mild-moderate COVID-19	Patients should be evaluated for eligibility for antivirals (i.e. nirmatrelvir-ritonavir, remdesivir, and molnupiravir) based on EUA criteria (see Appendix E, F, and I)
Hospitalized for COVID-19 but without supplemental oxygen requirement	Dexamethasone should <b>not</b> be initiated
Hospitalized for COVID-19 and requires supplemental oxygen	Dexamethasone should be initiated (see Tier 1a table below for additional information)  Remdesivir initiation may be considered (see Appendix A)
Hospitalized for COVID-19 and requires oxygen delivery through a high-flow device or noninvasive ventilation	Dexamethasone should be initiated (or continued)*  Addition of a monoclonal immunomodulator may be considered within 24-48 hours following decompensation (see appendices for additional criteria) <sup>&amp;</sup> : <ul style="list-style-type: none"> <li>• Tocilizumab IV if C-reactive protein (CRP) <math>\geq 7.5</math> mg/dL (see Appendix B) OR</li> <li>• Baricitinib PO if elevated CRP <math>&lt; 7.5</math> mg/dL (see Appendix C)</li> </ul>
Hospitalized for COVID-19 and requires invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	Dexamethasone should be initiated (or continued)*  Addition of a monoclonal immunomodulator may be considered within 24-48 hours following decompensation (see appendices for additional criteria) <sup>&amp;</sup> : <ul style="list-style-type: none"> <li>• Tocilizumab IV if C-reactive protein (CRP) <math>\geq 7.5</math> mg/dL (see Appendix B) OR</li> <li>• Baricitinib PO if elevated CRP <math>&lt; 7.5</math> mg/dL (see Appendix C)</li> </ul>
Hospitalized for COVID-19 and requires vasopressor or inotrope therapy for hypotension and/or reduced cardiac output attributed to COVID-19; no supplemental oxygen requirement	Dexamethasone should be initiated (or continued)*  Addition of a monoclonal immunomodulator may be considered within 24-48 hours following decompensation (see appendices for additional criteria) <sup>&amp;</sup> : <ul style="list-style-type: none"> <li>• Tocilizumab IV if C-reactive protein (CRP) <math>\geq 7.5</math> mg/dL (see Appendix B) OR</li> <li>• Baricitinib PO if elevated CRP <math>&lt; 7.5</math> mg/dL (see Appendix C)</li> </ul>

\*Remdesivir may be initiated and/or continued based on patient-specific risk/benefit assessment

<sup>&</sup>Caution should be exercised when initiating therapy with monoclonal immunomodulator in the setting of ongoing immunosuppression. Tocilizumab and baricitinib should usually not be added on top of previous IL-6 or JAK inhibition.

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**Therapeutic Considerations for Children with COVID-19 Based on Clinical Status<sup>‡</sup>**

- Most data generated to date regarding COVID-19 disease course and treatment has come from studies that exclusively or primarily enrolled adult patients.
- Epidemiologic studies suggest children have a significantly different typical disease course, with substantially fewer pediatric patients manifesting symptoms of severe disease and a significantly lower mortality rate.
- While some FDA approvals and emergency use authorizations have included select pediatric populations, it is important to acknowledge the limitations of our knowledge around applications of these agents in children, particularly since many clinical trials that led to emergency use authorizations did NOT include pediatric patient groups.
- **Consideration for utilization of therapeutic agents for COVID-19 in pediatric patients should involve assessment of potential benefits and risks on a case-by-case basis.** Consultation with pediatric infectious diseases service may be considered to help clarify potential risks and benefits.

Clinical Status	Therapeutic Recommendations
Non-hospitalized with mild-moderate COVID-19	Patients may be evaluated for eligibility for antivirals based on EUA and institutional eligibility criteria (see Appendix E and F) <sup>%</sup>
Hospitalized for reasons other than COVID-19 with mild-moderate COVID-19	Patients may be evaluated for eligibility for antivirals based on EUA and institutional eligibility criteria (see Appendix E and F) <sup>%</sup>
Hospitalized but without supplemental oxygen requirement	Dexamethasone should <b>not</b> be initiated  Remdesivir should <b>not</b> be initiated in most patients but either remdesivir or monoclonal antibody therapy may be considered in patients within 7 days of symptom onset and at high risk of progression to severe disease
Hospitalized and requires supplemental oxygen	Dexamethasone initiation may be considered  Remdesivir initiation may be considered (see Appendix A)
Hospitalized and requires oxygen delivery through a high-flow device or noninvasive ventilation	Dexamethasone should be initiated (or continued) <sup>*</sup>  Addition of a monoclonal immunomodulator may be considered within the first 24-48 hours after escalation in respiratory support (see appendices for additional criteria) <sup>¶&amp;</sup> : <ul style="list-style-type: none"> <li>• Tocilizumab IV if C-reactive protein (CRP) <math>\geq 7.5</math> mg/dL (see Appendix B) OR</li> <li>• Baricitinib PO if elevated CRP <math>&lt; 7.5</math> mg/dL (see Appendix C)</li> </ul>
Hospitalized and requires invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	Dexamethasone should be initiated (or continued) <sup>*</sup>  Addition of a monoclonal immunomodulator may be considered within the first 24-48 hours after escalation in respiratory / cardiac support (see appendices for additional criteria) <sup>¶&amp;</sup> : <ul style="list-style-type: none"> <li>• Tocilizumab IV if C-reactive protein (CRP) <math>\geq 7.5</math> mg/dL (see Appendix B) OR</li> <li>• Baricitinib PO if elevated CRP <math>&lt; 7.5</math> mg/dL (see Appendix C)</li> </ul>

<sup>‡</sup> This table EXCLUDES patients with evidence of post-infectious hyper-inflammatory syndromes (i.e. MIS-C). Consultation with Pediatric Rheumatology service is recommended for all patients with signs and symptoms consistent with MIS-C.

<sup>%</sup> Emergency use authorization has been granted for use of these agents in select patients at least 12 years of age and weighing at least 40 kg.

<sup>\*</sup> Remdesivir may be initiated and/or continued based on patient-specific risk/benefit assessment

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¶ Use should be considered on a case by case basis due to the paucity of pediatric-specific safety and efficacy data for immunomodulator therapy in COVID-19. Consider consultation with pediatric rheumatology or allergy/immunology prior to initiation of therapy.

& Caution should be exercised when initiating therapy with monoclonal immunomodulator in the setting of ongoing immunosuppression. Tocilizumab and baricitinib should usually not be added on top of previous IL-6 or JAK inhibition.

**Tier 1a: medications with evidence of benefit for patients with severe disease**

Medication	Details
Steroids	<ul style="list-style-type: none"> <li>In adult patients, initiation of dexamethasone 6 mg daily for up to 10 days should be considered in hospitalized patients with COVID-19 requiring either invasive or non-invasive oxygen support. Dexamethasone for treatment of COVID-19 should be discontinued at time of discharge unless needed for other reasons.</li> <li>In pediatric patients, steroid use may be considered on a case-by-case basis for patients hospitalized with concern for disease secondary to SARS-CoV-2 infection per the discretion of the treating team with the acknowledgement that there remains a paucity of data in this patient population.</li> </ul>
Tocilizumab	<ul style="list-style-type: none"> <li>A one-time dose of tocilizumab may be considered in select critically ill patients with COVID-19</li> <li>Detailed inclusion and exclusion criteria for use of tocilizumab in patients with COVID-19 are provided in Appendix B. It should notably only be used in combination with dexamethasone therapy.</li> <li>Limited data exists for use in treatment of pediatric patients with COVID-19 and considerations on risk and benefit profile needs to be made on a case-by-case basis. Questions specific to initiation in pediatric patients under the age of 18 may be directed to pediatric infectious diseases consult service.</li> </ul>
Baricitinib	<ul style="list-style-type: none"> <li>Baricitinib may be considered as an alternative to dexamethasone in the setting of a significant contraindication to use of glucocorticoids.</li> <li>Baricitinib may also be considered as an alternative to tocilizumab particularly in the setting of drug shortage. For this indication it should be combined with dexamethasone. Of note, baricitinib should <i>not be combined</i> with tocilizumab. For additional details see Appendix C</li> <li>No data exists for use in treatment of pediatric patients with COVID-19 and considerations on risk and benefit profile needs to be made on a case-by-case basis. Questions specific to initiation in pediatric patients under the age of 18 may be directed to pediatric infectious diseases consult service.</li> </ul>
Remdesivir	<ul style="list-style-type: none"> <li>Initiation of therapy for inpatients with severe disease requires fulfillment of the institutional eligibility criteria (see Appendix A)</li> <li>No demonstrated mortality benefit in patients with severe disease</li> <li>Questions specific to initiation of remdesivir in patients under the age of 18 may be directed to pediatric infectious disease consult service</li> </ul>

**Tier 1b: medications with evidence of benefit for mild-moderate disease**

Medication	Details
Anti-SARS-CoV-2 Monoclonal Antibodies	Availability of anti-SARS-CoV-2 monoclonal antibodies is dependent on susceptibility of known circulating variants. <b>As of 11/30/2022, no monoclonal antibody therapies retain emergency use authorization for treatment of COVID-19.</b>
Nirmatrelvir-Ritonavir	<ul style="list-style-type: none"> <li>Must be administered within 5 days of symptom onset</li> <li>Patient must be screened appropriately for drug-drug interactions</li> <li>Refer to Appendix F for additional information on clinical data, and institutional criteria for use</li> </ul>

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Remdesivir	<ul style="list-style-type: none"> <li>• Must be administered within 7 days of symptom onset for 3 consecutive days</li> <li>• Not able to be routinely administered in outpatient setting at UIHC</li> <li>• Refer to Appendix A for additional information on clinical data and institutional criteria for use</li> </ul>
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**Tier 1c: medications with evidence of benefit for pre-exposure prophylaxis**

Medication	Details
Tixagevimab - Cilgavimab	<ul style="list-style-type: none"> <li>• As of 1/26/2023, no therapy retains emergency use authorization for pre-exposure prophylaxis of COVID-19</li> </ul>

**Tier 2: medications with evidence of less benefit compared to Tier 1 – may be considered in the context of unavailability of alternatives**

Medication	Rationale for Recommendation
Anakinra	<ul style="list-style-type: none"> <li>• Anakinra is authorized for use in hospitalized adult patients requiring supplemental oxygen who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)</li> <li>• NIH COVID Treatment Guidelines state there is not enough evidence to recommend for or against use</li> <li>• See Appendix H for additional information on clinical data</li> </ul>
Convalescent Plasma	<ul style="list-style-type: none"> <li>• Plasma is available through FDA emergency use authorization for patients with immunosuppressive disease or receiving immunosuppressive treatment</li> <li>• Special populations such as patients under the age of 18 years and patients who are pregnant or nursing should be evaluated for risk/benefit on a case-by-case basis as little is known about safety or efficacy.</li> </ul>
Molnupiravir	<ul style="list-style-type: none"> <li>• Molnupiravir is authorized for use in treatment of COVID-19 in the absence of available alternatives</li> <li>• See Appendix I for additional information on clinical data and criteria for use at UIHC</li> </ul>

**Tier 3: not recommended for treatment unless in the context of a clinical trial – theoretical benefit unproven and potentially outweighed by risks (in alphabetical order)**

Medication	Rationale for Recommendation
Azithromycin	Studies to date have suggested no benefit for treatment of COVID-19
Famotidine	There are no conclusive studies demonstrating benefit in COVID-19 and IDSA Guidelines recommend against use outside of the context of a clinical trial.
Fluvoxamine	<p>Selective serotonin reuptake inhibitor (SSRI) that is approved for treatment of OCD and other conditions including depression. It is notably not approved for treatment of any infection.</p> <p>Data from three randomized clinical trials show variable results. While NIH guidelines are equivocal citing lack of compelling data for or against its use, IDSA recommends use only in the context of a clinical trial.</p>

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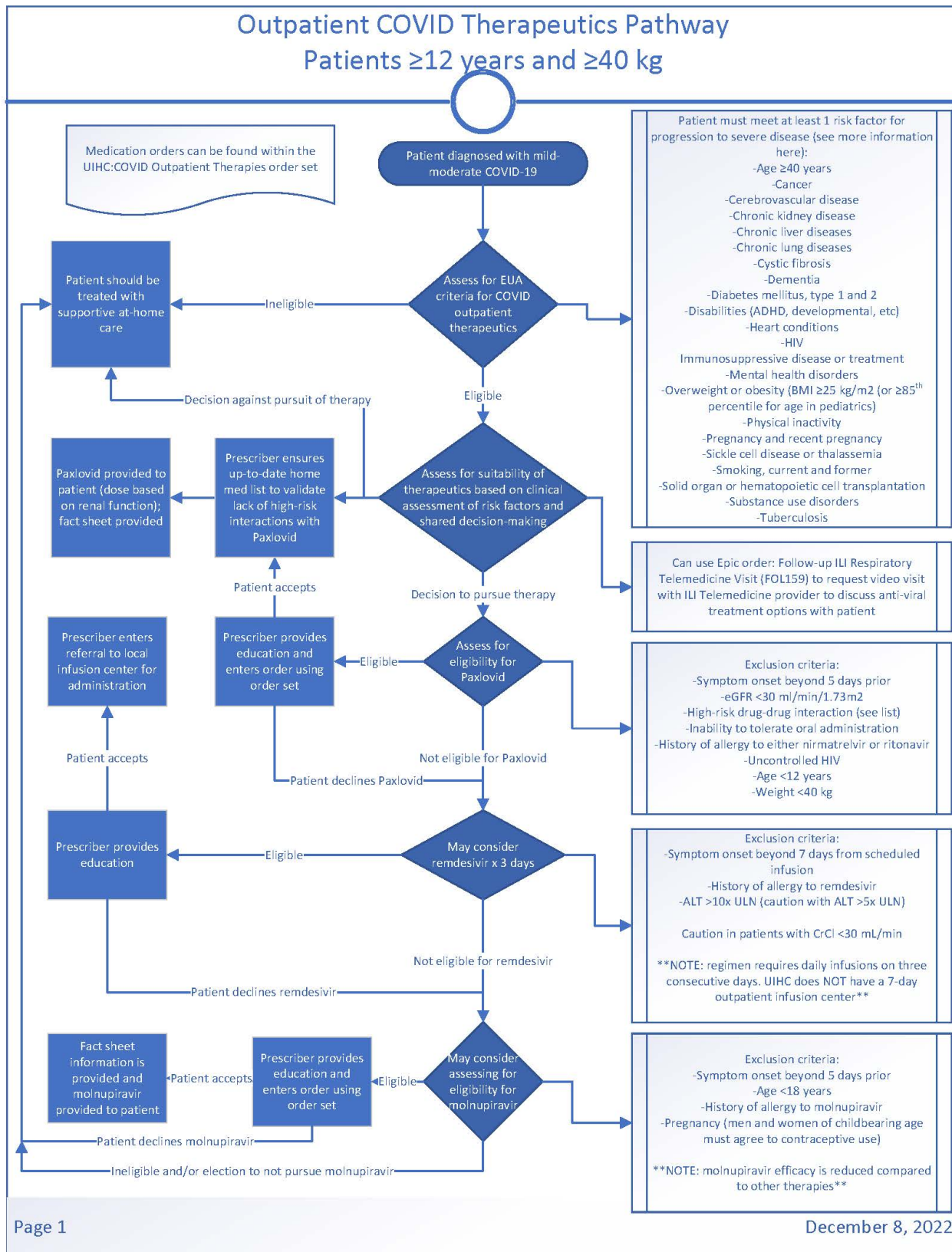
Hydroxychloroquine / Chloroquine	Though both chloroquine and hydroxychloroquine demonstrated potent <i>in vitro</i> inhibition of SARS-CoV-2, trial information available to date suggests no benefit in treatment of COVID-19 disease either as monotherapy or in combination with azithromycin.
Influenza Agents	Coronaviruses do not utilize neuraminidase for replication and no activity is expected.
Ivermectin	Initial reports suggest that drug is unlikely to achieve adequate concentrations in humans for antiviral activity against SARS-CoV-2. Subsequent clinical studies have not demonstrated benefit
Metformin	Two randomized controlled trials have evaluated the use of metformin in non-hospitalized adults with COVID-19 and neither demonstrated a benefit in reducing the risk of hospitalization or death

**Vaccines**

- There are currently three COVID-19 vaccines that have received emergency use authorization for use in the United States. UIHC recommends vaccination against COVID-19 for all eligible patients as outlined by guidance from regulatory agencies including the FDA, CDC, and the Advisory Committee on Immunization Practices (ACIP) and adheres to EUA criteria\*. Please refer to agency websites for most up-to-date information and guidance.
- Suspected or confirmed adverse reactions to any vaccine including COVID-19 should be reported to the Vaccine Adverse Event Reporting System (VAERS)

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## Outpatient COVID Therapeutics Pathway for Patients ≥12 Years and ≥40 kg



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### Appendix A: Remdesivir

**Mechanism of Action:** nucleotide analogue, initially developed for treatment of Ebola. It works by inhibiting RNA-dependent RNA polymerase.

**Evidence Summary:** In-vitro activity against MERS and SARS and has shown efficacy in animal models. It inhibits SARS-CoV-2 in vitro.

Remdesivir for mild-moderate disease: The PINETREE study evaluated the clinical benefit of remdesivir as an early outpatient treatment in a randomized, placebo-controlled trial. Patients with risk factors for disease progression were randomized within 7 days of symptom onset. The primary outcome was the proportion of participants who were hospitalized for  $\geq 24$  hours or who died from any cause by Day 28. Participants were randomized to receive 3 days of remdesivir or placebo. The treatment group observed a significant decrease in hospitalizations and/or death (0.7% compared to 5.3%) resulting in a 4.6% absolute reduction and an 87% relative reduction in hospitalizations and/or death for remdesivir (HR 0.13; 95% CI 0.03-0.59;  $p=0.008$ ).

Remdesivir for severe disease: Clinical trial data out of China and published in The Lancet suggest a lack of robust benefit in patients with severe COVID-19. However, a clinical trial in the United States led by NIH showed a statistically significant reduction in time to clinical improvement in patients with severe COVID-19 treated with remdesivir compared to placebo. Detailed data from this study reveal that the benefit may be limited to a select group of hospitalized patients with disease requiring treatment with only low-flow oxygenation, but is underpowered for subgroup analysis. The study also showed a trend towards improved mortality, though this finding did not reach statistical significance. Additionally, a separate study suggests that shortened courses of 5 days is likely to be non-inferior to 10 days in certain patient populations.

It was approved by FDA on 10/22/2020 for remdesivir for adults and pediatric patients  $\geq 12$  years old and weighing  $\geq 40$  kg

Approval was subsequently expanded in April 2022 by the FDA to include pediatric patients who are older than 28 days, weighing at least 3 kg, and are either hospitalized with COVID-19 or have mild-to-moderate COVID-19 and are considered high risk for progression to severe COVID-19, including hospitalization or death.

### **Dosing for patients with mild-moderate disease**

- Adults: 200 mg IV x1, followed by 100 mg IV daily x 2 days. Patients should not remain hospitalized for sole intent of completing 3-day course. Consideration may be made for extension to 5-day total course if patient is hospitalized and patient progresses to severe disease. Therapy should be permanently discontinued if patient develops adverse effects.
- Pediatrics: dosing is dependent on weight
  - $\geq 40$  kg: 200 mg IV x1, followed by 100 mg IV daily x 2 days. Consideration may be made for extension to 5-day total course if patient is hospitalized and patient progresses to severe disease
  - 3 to 40 kg: 5 mg/kg IV x1, followed by 2.5 mg/kg IV daily x 2 days. Consideration may be made for extension to 5-day total course if patient is hospitalized

### **Dosing for Patients with Severe Disease:**

- Adults: 200mg IV x1, followed by 100mg IV daily x 4 days
- Pediatrics: dosing is dependent on weight
  - $\geq 40$  kg: 200 mg IV x1, followed by 100 mg IV daily x 4 days
  - 3 to 40 kg: 5 mg/kg IV x1, followed by 2.5 mg/kg IV daily x 4 days
- Duration (regardless of age of patient)



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- 5-day total course
- Therapy should be permanently discontinued if patients develop adverse effects or is discharged from the hospital prior to completion of 5-day course
- Therapy may be discontinued or shortened if disease progresses to critical illness at the discretion of the primary treatment team

**Toxicity:** elevated transaminases (reversible upon drug cessation), reversible kidney injury (avoid other nephrotoxic agents if possible, including NSAIDs), hypotension during infusion

**Monitoring/labs:** patients should minimally receive the below monitoring. Please direct questions on monitoring plan to the antimicrobial stewardship team or refer to the package insert or FDA fact sheet for healthcare providers.

- Hepatic enzymes: ALT should be obtained at baseline prior to initiation and at least every other day while on therapy, particularly in those with elevations at baseline or deemed high risk for transaminitis. Therapy should be discontinued if ALT rises above 5-times the upper limit of normal
- Serum creatinine: obtain at baseline prior to initiation and at least every other day while on therapy. Diminished creatinine clearance is not considered an absolute contraindication, but discontinuation may be considered at CrCl below 30 ml/min.

**Drug metabolism:** remdesivir is a prodrug requiring CYP3A4 for activation thus there is potential for reduced conversion in the presence of CYP3A4 inhibitors like lopinavir/ritonavir, cobicistat, etc.

**IV compatibility:** Is compatible with 0.9% NaCl, no other compatibility information is available

**Administration/handling instructions:** per prescription instructions and / or study team guidance. Dose is administered via IV infusion over 30-120 minutes.

**Routes of Access to Remdesivir at UIHC:** UIHC is acquiring the drug commercially at this time. If significant supply constraints occur, UIHC cannot and will not guarantee access to patients even if they appear to meet criteria as described below.

Key inclusion criteria for patients with mild-moderate disease

- Confirmed SARS-CoV-2
- Symptoms consistent with mild-moderate disease
- Risk factor for progression to severe disease (at least 1)
  - Age ≥40 years
  - Cancer
  - Cerebrovascular disease
  - Chronic kidney disease
  - Chronic liver diseases
  - Chronic lung diseases
  - Cystic fibrosis
  - Dementia
  - Diabetes mellitus, type 1 and 2
  - Disabilities (ADHD, developmental, etc)
  - Heart conditions
  - HIV
  - Immunosuppressive disease or treatment
  - Mental health disorders
  - Overweight or obesity (BMI ≥25 kg/m<sup>2</sup> (or ≥85<sup>th</sup> percentile for age in pediatrics)

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- Physical inactivity
- Pregnancy and recent pregnancy
- Sickle cell disease or thalassemia
- Smoking, current and former
- Solid organ or hematopoietic cell transplantation
- Substance use disorders
- Tuberculosis

Key Exclusion Criteria for patients with mild-moderate disease

- ALT >10x ULN (caution with ALT >5x ULN)
- Caution in patients with CrCl <30 ml/min (not absolute contraindication)
- Symptom onset that is definitively greater than 7 days prior to planned initiation of therapy

Key inclusion criteria for inpatients with severe disease:

- Hospitalization
- Confirmed SARS-CoV-2
- SpO<sub>2</sub> ≤94% on room air OR requirement for supplemental oxygen above baseline

Key exclusion criteria for inpatients with severe disease:

- ALT > 10x ULN (caution with ALT >5x ULN)
- Caution in patients with CrCl <30 ml/min (not absolute contraindication)
- Symptom onset that is definitively greater than 10 days prior to planned initiation of therapy
- Mechanical ventilation for ≥5 days at time of initiation of therapy
- VV ECMO for ≥5 days at time of initiation of therapy
- Any duration of VA ECMO

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### **Appendix B: Tocilizumab:**

**Mechanism of Action:** tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody. It is hypothesized that modulating the levels of pro-inflammatory IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness.

**Evidence Summary:** Tocilizumab and other IL-6 inhibitors have been proposed as treatment options since the beginning of the pandemic; however, several early randomized trials showed conflicting results. Notably, many of these trials had relatively low enrollment numbers and evaluated heterogeneous patient populations with varying levels of disease severity and background standard of care. Evidence for use in children with COVID-19 is very limited.

The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) enrolled a narrowly defined population of critically ill patients requiring respiratory and/or cardiac support who were admitted to the ICU and randomized to receive open-label tocilizumab (n=353) or usual care (n=402). It additionally enrolled a small number of patients randomized to an alternative IL-6 inhibitor (sarilumab). Participants were enrolled within 24 hours of ICU admission, and within a median of 1.2 days of hospitalization. Corticosteroids were given to 92.7% and 93.9% of the patients in the tocilizumab and usual care arms respectively. Compared to usual care, tocilizumab use reduced both in-hospital mortality (28% of the tocilizumab recipients vs 36% of the usual care recipients died) and time to hospital discharge (HR 1.41; 95% CI 1.18 – 1.70) and increased the number of organ support-free days (10 days in tocilizumab vs 0 days in usual care).

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial enrolled hospitalized patients with COVID-19 into an open-label, platform trial of several treatment options. A subset of participants with hypoxemia and CRP levels greater than 75 mg/L were offered enrollment in a second randomization (1:1) to tocilizumab versus usual care. Across the tocilizumab arm (n=2022) and the usual care (n=2094) arm, the median duration of hospitalization was 2 days and 82% of the participants were receiving concomitant steroids. At baseline, 45% of the participants were on conventional oxygen, 41% on HFNC or NIV, and 14% on IMV. The study reported that tocilizumab reduced all-cause mortality through 28 days (29% of tocilizumab recipients vs 33% of usual care recipients died by day 28; RR 0.86; 95% CI 0.77-0.96), as well as the median time to being discharged alive.

Tocilizumab received emergency use authorization for treatment of select hospitalized patients with COVID-19 on June 24, 2021. Use of tocilizumab for patients with COVID-19 at UIHC is subject to the following inclusion / exclusion criteria and dosing regimen. In the setting of drug shortage, tocilizumab drug supply may have to be allocated to certain non-COVID patient populations such as those undergoing CAR-T therapy.

**Dosing:** patient should receive a one-time intravenous administration of ~8 mg/kg according to the following dosing regimen (to minimize drug waste based on vial size).

- Total body weight >90 kg = 800 mg
- Total body weight >65 – 90 kg = 600 mg
- Total body weight 40-65 kg = 400 mg
- Total body weight 30-40 kg = 8 mg/kg
- Total body weight <30 kg = 12 mg/kg

**Toxicity:** toxicity is better described in chronic use of tocilizumab and major adverse effects have not been commonly observed in the published trials of treatment of patients with COVID-19. Potential adverse effects include elevated liver enzyme levels, serious secondary bacterial or fungal infections, and/or bowel perforation.

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**Monitoring / Labs:** baseline labs should be obtained to evaluate for inclusion / exclusion criteria: C-reactive protein (CRP), alanine aminotransferase (ALT), absolute neutrophil count (ANC), platelet count

**Drug Metabolism:** typical half-life for IV administration is 10-13 days

**Administration:** administered via IV infusion over 60 minutes. Patient SHOULD be receiving standard dexamethasone course for treatment of COVID-19 in conjunction with tocilizumab. Tocilizumab SHOULD NOT be administered with baricitinib.

**Restriction Criteria for Use in COVID-19:**

Inclusion Criteria (patient must meet ALL of the following):

- Confirmed positive SARS-CoV-2 infection
- New requirement (within the past 24-48 hours) for pulmonary and/or cardiovascular support (includes invasive or noninvasive mechanical ventilation, high-flow nasal canula requiring  $\geq 30$  L/min of O<sub>2</sub> flow, and/or requirement for intravenous vasopressor or inotrope support)
- Evidence of inflammation with C-reactive protein  $\geq 7.5$  mg/dL

Exclusion Criteria (patient must meet NONE of the following):

- Alanine aminotransferase  $> 5x$  ULN
- Absolute neutrophil count  $< 500$  cells/uL
- Platelets  $< 50,000$  cells/uL
- Uncontrolled non-SARS-CoV-2 coinfection
- High risk for gastrointestinal perforation
- Survival predicted to be less than 24 hours
- Alternative explanation for respiratory symptoms
- Concomitant use of IL-6 inhibitor or JAK inhibitor

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### Appendix C: Baricitinib

**Mechanism of Action:** inhibitor of Janus kinase which can interfere with the phosphorylation of signal transducer and activator of transcription proteins that are involved in vital cellular functions. It is theorized to potentially have additional direct antiviral activity through interference with viral endocytosis.

**Evidence Summary:** baricitinib was studied in a multinational, randomized, placebo-controlled trial sponsored by NIH that included 1033 hospitalized patients with COVID-19 and evidence of pneumonia. The trial met its primary endpoint of time to recovery on an ordinal scale with the baricitinib group having a slightly shorter median time to recovery (7 days) vs the placebo group (8 days). The greatest benefit was found in the subgroup of patients that were on high-flow oxygen or noninvasive ventilation at the time of enrollment. There was no statistically significant mortality benefit observed.

Baricitinib was also studied in the multinational, randomized, placebo-controlled trial COV-BARRIER. This trial included 1525 hospitalized patients with COVID-19 who had evidence of pneumonia and an elevation in at least one inflammatory marker who were randomized 1:1 to receive baricitinib 4 mg daily or placebo in addition to local standard of care for up to 14 days (or until hospital discharge). Notably, the standard of care included corticosteroids for 79% of the participants and remdesivir for 19% of the participants. The trial did not meet statistical significance its primary endpoint of proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death by day 28 (27.8% vs 30.5%, OR 0.85 with 95 CI of 0.67 to 1.08). However, benefit was seen in its key secondary outcome of all-cause mortality by day 28 (8.1% vs 13.1%, HR 0.57 with 95% CI of 0.41-0.78).

Baricitinib received emergency use authorization from the FDA on 11/19/2020 for use in hospitalized adults and children aged  $\geq 2$  years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In May 2022, the FDA acted to grant full FDA approval for baricitinib for the indication of treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The EUA continues to apply to pediatric patients 2 years of age to less than 18 years of age.

### **Dosing:**

- Adults and pediatric patients 9 years of age and older: dosing is dependent on renal function
  - eGFR  $\geq 60$ : 4 mg PO daily
  - eGFR 30-60: 2 mg PO daily
  - eGFR 15-30: 1 mg PO daily
  - eGFR  $< 15$ : not recommended
- Pediatric patients between 2 and 8 years of age: dosing is dependent on renal function
  - eGFR  $\geq 60$ : 2 mg PO daily
  - eGFR 30-60: 1 mg PO daily
  - eGFR  $< 30$ : not recommended
- Duration (regardless of age of patient)
  - 14 days total treatment or until hospital discharge, whichever is first

**Toxicity:** baricitinib has been associated with several significant adverse effects including serious infections and thrombosis. Risk versus benefit should be assessed before initiating therapy.

**Monitoring/labs:** patients should minimally receive the below monitoring. Please direct questions on monitoring plan to the antimicrobial stewardship team or refer to the package insert or FDA fact sheet for healthcare providers.

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- Hepatic enzymes: ALT and AST should be obtained at baseline prior to initiation and at least every other day while on therapy, particularly in those with elevations at baseline or deemed high risk for transaminitis. Consideration for discontinuation should be made if liver enzyme elevation ( $\geq 5 \times$  ULN for ALT and  $\geq 10 \times$  ULN for AST) is observed and drug-induced liver injury is suspected.
- Serum creatinine: obtain at baseline prior to initiation and at least every other day while on therapy. Dose adjustments may be required based on renal function.
- Complete blood count: obtain at baseline and at least every other day while on therapy. Consideration for discontinuation should be made at low absolute lymphocyte count (ALC less than 200) and/or absolute neutrophil count (ANC less than 500)

**Drug metabolism:** baricitinib has elements of both hepatic and renal metabolism. There are renal dose adjustments noted above, but no clear guidance in patients with severe hepatic impairment. There are dose adjustments recommended for patients on co-administered OAT3 inhibitors such as probenecid.

**Administration/handling instructions:** baricitinib tablets are given orally once daily with or without food. For patients who are unable to swallow whole tablets, alternative administration may be considered in the form of oral dispersion or administration via gastrostomy tube or nasogastric tube.

**Restriction Criteria for Use in COVID-19:** UIHC can acquire baricitinib through traditional commercial distribution. Use of baricitinib in COVID-19 is limited to the below criteria, which describes two separate indications. It can be utilized as the alternative to dexamethasone in patients with contraindication to glucocorticoids OR as an additive immunomodulator particularly in the setting of drug shortage. For situations outside of this criteria, approval must be granted by the antimicrobial stewardship team (pager #1282) and special order request must be completed.

Indication	<b>Alternative to Dexamethasone in Patient with COVID-19</b>	<b>Additive Immunomodulation in Patient with COVID-19</b>  <b>*Patient should receive concomitant dexamethasone therapy if used for this indication</b>
Inclusion Criteria	<ul style="list-style-type: none"> <li>• Hospitalization</li> <li>• Confirmed SARS-CoV-2 infection</li> <li>• Requirement for supplemental oxygen above baseline</li> <li>• Age <math>\geq 2</math> years</li> <li>• Contraindication to use of glucocorticoids (i.e. dexamethasone)</li> </ul>	<ul style="list-style-type: none"> <li>• Hospitalization</li> <li>• Confirmed positive SARS-CoV-2 infection</li> <li>• New requirement for pulmonary and/or cardiovascular support (includes invasive or noninvasive mechanical ventilation, high-flow nasal canula requiring <math>\geq 30</math> L/min of O2 flow, and/or requirement for intravenous vasopressor or inotrope support). Baricitinib should ideally be initiated within 24-48 hours of escalation in support</li> <li>• Evidence of inflammation with C-reactive protein <math>&gt;0.5</math> mg/dL</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• eGFR <math>&lt;15</math> (<math>&lt;30</math> if less than 9 years of age)</li> <li>• Absolute lymphocyte count less than 200</li> <li>• Absolute neutrophil count less than 500</li> <li>• Known active tuberculosis infection</li> </ul>	<ul style="list-style-type: none"> <li>• eGFR <math>&lt;15</math> (<math>&lt;30</math> if less than 9 years of age)</li> <li>• Absolute lymphocyte count less than 200</li> <li>• Absolute neutrophil count less than 500</li> <li>• Uncontrolled non-SARS-CoV-2 coinfection, including active tuberculosis infection</li> <li>• Survival predicted to be less than 24 hours</li> <li>• Alternative explanation for respiratory symptoms</li> </ul>

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	<ul style="list-style-type: none"><li>• Concomitant use of alternative JAK inhibitor or IL-6 inhibitor</li></ul>	<ul style="list-style-type: none"><li>• Concomitant use of alternative JAK inhibitor or IL-6 inhibitor</li></ul>
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Patients **MUST** receive the EUA fact sheet prior to initiation of therapy in patients receiving it for treatment of COVID-19 if they are under the age of 18.

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**Appendix D: Convalescent Plasma (CCP) (investigational blood product)**

**Mechanism of Action:** Antibody development in plasma of patients recovered from COVID-19 is used for passive transfer to treat individuals currently ill with COVID-19. This plasma is to be given to individuals with COVID-19 to try to help eliminate virus from the system and recover.

**Evidence Summary:** The method of CCP has been used at various times for previous infections. There has been some evidence of benefit with Ebola, polio, measles, and influenza. Small case series with prior SARS and MERS demonstrated safety and faster viral clearance after administration of CCP, particularly when given early in the disease course.

The National Expanded Access Treatment Protocol sponsored by the Mayo Clinic published preliminary data on 35,322 patients who received product through the program. Though this was not a randomized, controlled trial the authors cited potential signals of efficacy. These signals included reduced mortality correlated with both earlier time to transfusions and receipt of transfusion with high antibody levels.

A prospective randomized controlled trial of 228 patients hospitalized with severe COVID-19 in Argentina demonstrated no benefit in terms of clinical status at 30 days after intervention or mortality. The median time from the onset of symptoms to enrollment in the trial was 8 days. However, a study of 160 patients (all at least 75 years old with at least one risk factor for progression to severe disease) treated with high-titer plasma within 72 hours of initial symptom onset demonstrated a reduction in progression to severe disease compared to placebo.

On 8/23/2020, the FDA announced emergency use authorization to permit the use of COVID-19 CCP to treat hospitalized patients with COVID-19. This emergency use authorization has been revised several times based on evolving evidence and availability of other therapies. On 12/28/2021 the EUA was amended to restrict use to high-titer antibody therapy for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting. This is based on pre-print study data demonstrating a reduction in hospitalization rate when compared against placebo in outpatients with mild-moderate disease enrolled within 8 days of symptom onset.

Special populations such as patients under the age of 18 years and patients who are pregnant or nursing should be evaluated for risk/benefit on a case-by-case benefit as little is known about safety or efficacy.

**Dosing:** Standard dose is 1-2 units with each unit transfused over 1-4 hours. Patients at risk for volume overload (impaired cardiac or renal function, positive fluid balance) should receive one unit over 4 hours and a second unit given the next day if desired.

**Toxicity:** similar risks with any plasma infusion, allergic reaction and viral infections

**Monitoring/labs:** type and screen needed on file prior to dispensing of blood product

**Administration/handling instructions:** per order instructions. Each unit may be transfused over 2-4 hours.



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**Appendix E: Monoclonal antibodies targeting SARS-CoV-2 spike protein**

Multiple products are available with similar mechanisms of action and criteria for emergency authorization for use. They will be utilized based on their efficacy against circulating variants. **As of 11/30/2022, there are no currently authorized anti-SARS-CoV-2 monoclonal antibody products with active authorizations for emergency use in the United States due to the shift in circulating variants and diminished activity of previously authorized agents. Alternative therapy options (i.e. nirmatrelvir-ritonavir, remdesivir, and molnupiravir) should be considered for patients with risk factors for progression to severe disease.**

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### Appendix F: Nirmatrelvir-Ritonavir

**Mechanism of Action:** nirmatrelvir is an orally bioavailable protease inhibitor that is active against M<sup>PRO</sup>, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins. It has demonstrated activity against all coronaviruses that are known to infect humans. Nirmatrelvir is packaged with ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.

### Evidence Summary:

The EPIC-HR study was a multinational, randomized trial that compared the use of ritonavir-boosted nirmatrelvir given orally twice daily for 5 days to placebo in nonhospitalized adults with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible participants were randomized within 5 days of symptom onset, were unvaccinated, and had at least 1 risk factor for progression to severe disease.<sup>8</sup> Patients were excluded if they used medications that are highly dependent upon CYP3A4 for clearance or are strong inducers of CYP3A4. The primary composite outcome was COVID-19-related hospitalization or death from any cause through Day 28 among the participants who were randomized within 3 days of symptom onset.

A total of 2,246 participants enrolled in the trial. The mean age was 46 years, 51% of the participants were men, and 72% were white. Forty-seven percent of the participants tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Participants who were randomized within 3 days of symptom onset (n = 1,379) were included in the modified intention-to-treat (MITT) analysis. COVID-19-related hospitalizations and all-cause deaths occurred by Day 28 in 5 of 697 participants (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 participants (6.45%) in the placebo arm. Among the 2,085 participants who were randomized within 5 days of symptom onset (MITT1 analysis), COVID-19-related hospitalizations and all-cause deaths occurred in 8 of 1,039 participants (0.8%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 participants (6.3%) in the placebo arm (88% relative risk reduction; -5.62% estimated absolute reduction; 95% CI, -7.21% to -4.03%; P < 0.0001). There were no deaths in the ritonavir-boosted nirmatrelvir arm and 12 deaths in the placebo arm.

### Dosing:

- eGFR ≥60: 300 mg nirmatrelvir and ritonavir 100 mg twice daily x 5 days
- eGFR ≥30 - <60: 150 mg nirmatrelvir and ritonavir 100 mg twice daily x 5 days
- eGFR <30: not recommended

### Toxicity / Adverse Effects:

Among the 2,224 participants who were included in the EPIC-HR safety analysis set (i.e., those who received at least 1 dose of either ritonavir-boosted nirmatrelvir [Paxlovid] or placebo), the adverse events that occurred more frequently in ritonavir-boosted nirmatrelvir (Paxlovid) recipients than in placebo recipients were dysgeusia (6% vs. <1%) and diarrhea (3% vs. 2%). Fewer ritonavir-boosted nirmatrelvir (Paxlovid) recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

On May 24<sup>th</sup>, 2022, the CDC issued a health advisory on the potential for recurrence of COVID-19 or “COVID-19 rebound” with nirmatrelvir-ritonavir therapy. See [alert](#) for additional information. At this time, it is not recommended to provide additional treatment for COVID-19 in the setting of rebound. Symptoms of recurrence often resolve within a few days without any additional intervention and rarely progress to severe infection. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of nirmatrelvir/ritonavir (Paxlovid).

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**Restriction Criteria at UIHC for initiation of therapy:**

Supply of nirmatrelvir-ritonavir is under allocation through the government and is available at multiple pharmacy locations both within and outside of the UIHC system. Patients will minimally need to fulfill the criteria below.

Inclusion Criteria (patient must meet ALL of the following):

- Confirmed positive SARS-CoV-2 infection
- Symptom onset  $\leq$  5 days
- At least one risk factor for progression to severe disease
  - Age  $\geq$ 40 years
  - Cancer
  - Cerebrovascular disease
  - Chronic kidney disease
  - Chronic liver diseases
  - Chronic lung diseases
  - Cystic fibrosis
  - Dementia
  - Diabetes mellitus, type 1 and 2
  - Disabilities (ADHD, developmental, etc)
  - Heart conditions
  - HIV
  - Immunosuppressive disease or treatment
  - Mental health disorders
  - Overweight or obesity (BMI  $\geq$ 25 kg/m<sup>2</sup> (or  $\geq$ 85<sup>th</sup> percentile for age in pediatrics)
  - Physical inactivity
  - Pregnancy and recent pregnancy
  - Sickle cell disease or thalassemia
  - Smoking, current and former
  - Solid organ or hematopoietic cell transplantation
  - Substance use disorders
  - Tuberculosis

Exclusion Criteria (patient must meet NONE of the following):

- Symptom onset beyond 5 days prior
- History of allergy to nirmatrelvir or ritonavir
- Age < 12 years
- Weight <40 kilograms
- eGFR <30 ml/min/1.73 m<sup>2</sup>
- High risk drug-drug interactions (refer to package insert or alternative resource for guidance)
- Inability to tolerate oral administration
- Uncontrolled HIV
- Hospitalized for COVID-19

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**Appendix G: Tixagevimab-Cilgavimab**

- **As of 01/26/2023, tixagevimab-cilgavimab is no longer authorized for emergency use in the United States due to the shift in circulating variants and diminished activity of the previously authorized agent. There are currently no available therapies authorized or indicated for pre-exposure prophylaxis of COVID-19**

**Appendix H: Anakinra**

**Mechanism of Action:** Anakinra is a recombinant human IL-1 receptor antagonist approved in the US to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease. It is used off-label to treat severe chimeric antigen receptor T cell-mediated cytokine release syndrome and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

**Evidence Summary:** SAVE-MORE was a randomized controlled trial in 594 hospitalized patients with moderate or severe COVID-19 pneumonia and plasma suPAR levels  $\geq 6$  ng/mL. Patients who required noninvasive or invasive mechanical ventilation were excluded from the study. Patients were randomized 2:1 to receive anakinra 100 mg subcutaneously once daily for 10 days or placebo. The primary endpoint was clinical status at Day 28 on the 11-point WHO Clinical Progression Scale. Patient who were randomized to receive anakinra had a lower odds of progression to COVID-19 on the WHO score (OR 0.36; 95% CI, 0.26-0.50;  $p < 0.0001$ ). The secondary endpoints also favored anakinra, including an absolute decrease in WHO scores from baseline at Days 14 and 28. Notably, the suPAR assays utilized in this trial are not commonly available.

REMAP-CAP evaluated anakinra as part of an open-label adaptive platform trial. Patients were eligible for enrollment in the immunomodulation therapy arm within 24 hours of receiving respiratory or cardiovascular support in the ICU with confirmed or suspected COVID-19. Anakinra 300 mg IV was administered as a loading dose, followed by 100 mg IV every 6 hours for up to 14 days. The primary outcome measured was an ordinal scale that included a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support at 21 days. Of the 2274 participants who were randomized to receive an immunomodulator, 365 patients were assigned to receive anakinra and included in the analysis. This was compared against 406 participants who were assigned usual care. The median number of organ support-free days was similar for patients who received anakinra and those who received usual care was similar. 60% of those who were assigned to receive anakinra survived compared to 63% of those assigned to usual care.

**Toxicity:** anakinra has been associated with an increased incidence of serious infections in clinical trials of patients with rheumatoid arthritis although this has not necessarily been observed in studies of patients with COVID-19. Additional possible toxicities include increased transaminitis, leukopenia, and neutropenia.

**Monitoring / Labs:** consider monitoring of liver enzymes (ALT, AST), and cell counts including neutrophils and leukocytes while on therapy

**Appendix I: Molnupiravir**

**Mechanism of Action:** molnupiravir is a prodrug that is rapidly metabolized to NHC in plasma. NHC is distributed into cells where it is phosphorylated to form pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation into viral RNA by the viral polymerase results in accumulation of errors in the viral genome leading to inhibition of replication. NHC introduces viral RNA error through a two-step mechanism: first incorporating into the nascent RNA by substituting for either CTP or UTP, then when copied, base-pairing with either guanosine or adenosine resulting in errors in RNA products.

**Evidence Summary:**

Primary pharmacology studies demonstrated antiviral activity of molnupiravir against SARS-CoV-2 and other RNA viruses in vitro and in vivo. NHC was equally effective in vitro against SARS-CoV-2 variants of concern B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta). In vitro activity was seen against isolated with reduced susceptibility or resistance to remdesivir.

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It was studied in outpatients in the MOVE-Out trial. This was a randomized, double blind, placebo-controlled phase 2/3 trial that enrolled unvaccinated adults ( $\geq 18$  years) at increased risk of severe illness with mild to moderate disease with a positive SARS-CoV-2 test result with symptom duration for  $\leq 5$  days. Increased risk for severe illness from COVID-19 was defined as age  $> 60$  years of age, active cancer, COPD, obesity (BMI  $\geq 30$ ), serious heart conditions (CAD, heart failure, cardiomyopathies), diabetes mellitus. Pregnant women were excluded from the study and participants of childbearing age were required to use contraception. Molnupiravir 800mg Q12h x 5 days or placebo was given. The primary endpoint was hospitalization or death through Day 29. The interim analysis showed the primary endpoint was met in 7.3% (28/385) of molnupiravir group vs. 14.1% (53/377) in the placebo group. In the interim analysis there was no deaths in the molnupiravir group vs. 8 in the placebo group. This represented a NNT of 14.7 and a 50% risk reduction. Enrollment was stopped after the interim analysis based on recommendations of the DMSB. Full data set analysis showed the primary endpoint was met in 6.8% (48/709) of molnupiravir group vs. 9.7% (68/699) in the placebo group. The full analysis had 1 death in the molnupiravir group vs. 9 for placebo. This represented a NNT of 33.3 and a 30% risk reduction.

It was studied in hospitalized patients in a phase 2 trial called the MOVE-IN trial with no plan for a phase 3 trial based on lack of efficacy.

A trial for post-exposure prophylaxis called MOVE-AHEAD is being conducted.

Molnupiravir received emergency use authorization for treatment of select patients with COVID-19 on December 23rd, 2021 for treatment of mild-moderate COVID-19 in adults who are high risk of progressing to severe disease and for whom alternative treatment options are not accessible or not clinically appropriate. Use of molnupiravir for patients with COVID-19 at UIHC is subject to availability and the following inclusion / exclusion criteria and dosing regimen.

### **Dosing:**

- 800mg (4x 200mg) twice daily x 5 days
- No renal or hepatic adjustments required

**Toxicity:** the full toxicity profile is unknown at this time due to limited data with the drug. In animal models bone marrow toxicity was seen especially at  $> 2$  weeks for therapy, but this was not seen in the phase 3 clinical trial when use was limited to 5 days. Molnupiravir may cause embryofetal toxicity and use in pregnancy. It has been associated with bone and cartilage toxicity in animals and currently is not recommended in pediatrics until this is further investigated. There are concerns for potential mutagenicity and enhanced viral evolution.

**Monitoring / Labs:** none. Patients of childbearing age should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after receiving molnupiravir. Men of reproductive potential who are sexually active with individuals of childbearing age should abstain from sex or use a reliable method of contraception for the duration of treatment and for at least 3 months after the last dose.

**Restriction Criteria at UIHC for initiation of therapy:** Supply of molnupiravir is under allocation through the government and is available at multiple pharmacy locations both within and outside of the UIHC system. Patients will minimally need to fulfill the criteria below.

Inclusion Criteria (patient must meet ALL of the following):

- Outpatient with confirmed positive SARS-CoV-2 infection
- Symptom onset  $\leq 5$  days
- At least one risk factor for progression to severe disease

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- Age ≥40 years
  - Cancer
  - Cerebrovascular disease
  - Chronic kidney disease
  - Chronic liver diseases
  - Chronic lung diseases
  - Cystic fibrosis
  - Dementia
  - Diabetes mellitus, type 1 and 2
  - Disabilities (ADHD, developmental, etc)
  - Heart conditions
  - HIV
  - Immunosuppressive disease or treatment
  - Mental health disorders
  - Overweight or obesity (BMI ≥25 kg/m<sup>2</sup> (or ≥85<sup>th</sup> percentile for age in pediatrics)
  - Physical inactivity
  - Pregnancy and recent pregnancy
  - Sickle cell disease or thalassemia
  - Smoking, current and former
  - Solid organ or hematopoietic cell transplantation
  - Substance use disorders
  - Tuberculosis
- Lack of available alternative for treatment of mild-moderate COVID-19 (i.e. nirmatrelvir-ritonavir, monoclonal antibody, remdesivir)

Exclusion Criteria (patient must meet NONE of the following):

- Symptom onset beyond 5 days prior
- History of allergy to molnupiravir
- Inability to tolerate oral administration
- Age < 18 years
- Pregnancy
- Hospitalized for COVID-19

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**Appendix K: COVID-19-Associated Coagulopathy in Adults**

The pathophysiology of COVID-19-associated coagulopathy is complex and multifactorial, involving both cellular and plasmatic elements of the hemostatic system. Risk of VTE is highest within the first week of a positive COVID result and then decreases to baseline for the next 6 to 8 weeks, with some data finding that risk doesn't return to baseline for up to 12 months. Development of coagulopathy has been suggested to be a predictor of mortality in patients with COVID-19.

Pharmacologic venous thromboembolism (VTE) prevention with low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) for patients with COVID is recommended.

**Laboratory Monitoring for COVID-19-Associated Coagulopathy:**

Although some guidelines suggest monitoring of complete blood count (CBC) including platelet count, coagulation studies [prothrombin time (PT) and activated partial thromboplastin time (aPTT)], fibrinogen, and D-dimer, these may be non-specific and may not guide decision-making related to hypercoagulability in the absence of clinical indications and are not necessarily required for monitoring or management of COVID patients. If patient is requiring oxygen support and is not at high risk of bleeding, consider obtaining a d-dimer to assist with decision to use therapeutic-dose enoxaparin (or UFH) for VTE prevention (see "Pharmacologic VTE Prevention in Hospitalized Patients with COVID" section below for more information).

**Diagnosis of VTE:**

Evaluation of VTE may be challenging because symptoms of PE overlap with COVID-19, and imaging studies may not be feasible in all cases. The threshold for evaluation or diagnosis of DVT and PE should be low given the high frequency of these events and the presence of additional VTE risk factors in these patients.

- Deep Vein Thrombosis (DVT): Individuals with suspected DVT should be treated following standard practice.
- Pulmonary Embolism (PE):
  - A normal D-dimer (unusual in critically ill individuals with COVID-19) is sufficient to exclude the diagnosis of PE if the pretest probability for PE is low or moderate but is less helpful in those with a high pretest probability. An increase in D-dimer is not specific for VTE and is not sufficient to make the diagnosis.
  - Consider PE and diagnostic CTA in the case of:
    - Acute worsening of hemodynamic or respiratory status including:
      - Acute worsening of oxygenation
      - Fluctuating blood pressure
      - Tachycardia with imaging findings not consistent with worsening Covid-19 pneumonia
      - Hemoptysis
    - Certain ECG signs [right heart strain, sinus tachycardia, simultaneous T wave inversions in the inferior (II, III, aVF) and right precordial leads (V1-4)]

**Pharmacologic VTE Prevention in Hospitalized Patients with COVID:**

All patients admitted to UIHC for COVID-19 should receive enoxaparin (or UFH) for VTE prevention in the absence of any contraindications. Pharmacologic VTE prevention should continue during hospitalization for the duration COVID symptoms, then follow standard of care for that patient population.

- Patients who are asymptomatic (COVID+ result was an incidental finding): follow standard of care typical for the patient population
- **Non-ICU (non-pregnant) patients**

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- Non-ICU patients admitted for other reasons with mild COVID symptoms (who do NOT have COVID symptoms severe enough which would have otherwise warranted admission): prophylactic dose enoxaparin (alternative: SQ UFH). Refer to the Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients for prophylactic dosing recommendations.
- Non-ICU patients admitted for COVID symptoms:
  - D-dimer above upper limit of normal AND requires oxygen AND does NOT have an increased risk of bleed: **consider therapeutic dose enoxaparin** (1 mg/kg SQ twice daily) for at least 14 days or until hospital discharge, whichever comes first (alternative: continuous infusion UFH at the non-VTE “no thrombus or low thrombus burden” dose)
    - If patient transfers to ICU: switch to prophylactic-dose enoxaparin. Refer to the Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients for prophylactic dosing recommendations.
    - Contraindications for therapeutic anticoagulation for COVID-19 due to an increased bleeding risk are as follows:
      - Bleeding within the last 30 days requiring emergency room visit or hospitalization
      - Inherited or acquired bleeding disorder
      - Dual antiplatelet therapy
      - History of bleeding diatheses (e.g., hemophilia)
      - Intracranial malignancy
      - Recent ischemic stroke
      - History of gastrointestinal bleed within last 3 months
      - Thrombolysis within last 7 days
      - Presence of epidural or spinal catheter
      - Major surgery in the last 14 days
      - Uncontrolled hypertension (> 200/120 mmHg)
      - Platelet count <50 x 10<sup>9</sup>/L
      - Hemoglobin <8 g/dL
    - All other non-ICU patients: prophylactic dose enoxaparin (alternative: SQ UFH). Refer to the Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients for prophylactic dosing recommendations.
- **ICU (non-pregnant) patients:** follow standard practice (typically, prophylactic dose enoxaparin or SQ UFH). Refer to the Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients for medication and prophylactic dosing recommendations.

• **Thromboprophylaxis Recommendations in Pregnant Patients with COVID-19**

COVID+ Pregnant Patient	<p>All pregnant women admitted with confirmed or suspected COVID-19 should be given prophylaxis, unless birth is expected within 12 to 24 hours, there is active bleeding, or patient has a condition that places her at risk for significant bleeding (e.g. placenta previa, placenta accreta spectrum)</p> <p>Preferred: Enoxaparin (dose based on patient weight)            BMI ≤ 40 kg/m<sup>2</sup>: Enoxaparin 40 mg SQ daily            BMI &gt; 40 kg/m<sup>2</sup>: Enoxaparin 40 mg SQ q12h</p> <p>Alternative: UFH (recommended if CrCl &lt; 30 mL/min/1.73 m<sup>2</sup>)            1<sup>st</sup> Trimester: 5000 to 7500 units SQ q12h            2<sup>nd</sup> Trimester: 7500 to 10000 units SQ q12h            3<sup>rd</sup> Trimester: 10000 units SQ q12h</p> <p>The Maternal-Fetal Medicine (High Risk Obstetrics) physician on service/on call may be contacted if there are questions about VTE prophylaxis for pregnant or postpartum women. The Family Medicine OB</p>
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	Service (pager 9024) may be contacted if there are questions about VTE prophylaxis for pregnant or postpartum women who are cared for by their service.
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UFH: unfractionated heparin

- If patients with COVID-19 are admitted and have been receiving therapeutic anticoagulation (with direct acting oral anticoagulant or warfarin) prior to admission due to an appropriate indication (e.g., atrial fibrillation, prosthetic valve, h/o VTE, etc.) or if they require treatment with therapeutic anticoagulation due to an acute DVT/PE, therapeutic anticoagulation during admission should be carried out using therapeutic-dose enoxaparin per standard of care (preferred over UFH in order to minimize blood draws). If enoxaparin is contraindicated in a patient and heparin continuous infusion must be used, see table 2 for recommendations on monitoring.
  - Special considerations and monitoring

**Recommendations for Monitoring Heparin Continuous Infusions in Patients with COVID-19**

Scenario	Yes	No
<b>aPTT prolonged at baseline*</b>	Use anti-Xa (consult Pharmacy for goal range and adjustment parameters)	Use aPTT
<b>Heparin resistance<sup>‡</sup></b>	Use anti-Xa (consult Pharmacy for goal range and adjustment parameters)	Use aPTT

\* Consider reasons other than COVID-19 infection for baseline aPTT prolongation as this laboratory finding could be due to an underlying coagulopathy that increases the risk of anticoagulant-associated bleeding.

<sup>‡</sup>Heparin resistance: >35,000 units of heparin administered per 24 hours

- Extending VTE prophylaxis for patients with COVID-19 after discharge may not be necessary and is not recommended by guidelines, although data from the MICHELLE trial (open-label, multicenter, randomized, controlled) have suggested extending prophylaxis with rivaroxaban 10 mg daily for 35 days post-discharge in certain high-risk patients (Ramacciotti, et al. 2022). An individualized assessment of the patient’s risk of thrombosis and bleeding and shared decision-making is important when deciding whether to use post-discharge thromboprophylaxis. Validated risk assessment models to estimate thrombotic and bleeding risk in COVID-19 patients following hospital discharge are not available. Post-discharge thromboprophylaxis may be reasonable in patients judged to be at high thrombotic risk and low bleeding risk.

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**Appendix L: Pediatric Considerations for Treatment of COVID-19**

- Most data generated to date regarding COVID-19 disease course and treatment has come from studies that exclusively or primarily enrolled adult patients.
- Epidemiologic studies suggest children have a significantly different typical disease course, with substantially fewer pediatric patients manifesting symptoms of severe disease and a significantly lower mortality rate.
- While some FDA approvals and emergency use authorizations have included select pediatric populations, it is important to acknowledge the limitations of our knowledge around applications of these agents in children, particularly since many clinical trials that led to emergency use authorizations did NOT include pediatric patient groups.
- **Consideration for utilization of therapeutic agents for COVID-19 in pediatric patients should involve assessment of potential benefits and risks on a case-by-case basis.** Consultation with pediatric infectious diseases service may be considered to help clarify potential risks and benefits.
- Below is a summary of key pediatric-specific considerations for therapeutic agents that have received either emergency use authorization or full FDA approval for treatment of COVID-19 (plus corticosteroids and tocilizumab).
- **For additional information on any of these agents see separate appendices or table at the top of the document that includes considerations for treatment of COVID-19 in children based on clinical status.**

<b>Agent</b>	<b>Comments</b>	<b>Adult Dosing</b>	<b>Pediatric Dosing<sup>#</sup></b>
Steroids	<ul style="list-style-type: none"> <li>• Dexamethasone remains the steroid with the most robust evidence in COVID-19</li> <li>• Limited pediatric enrollment in the RECOVERY trial in the UK but overall showed mortality benefit in patients requiring supplemental oxygen</li> </ul>	Dexamethasone 6 mg IV/PO daily for up to 10 days or discharge from hospital, whichever occurs first	Patients under 40 kg: Dexamethasone 0.15 mg/kg IV/PO daily for up to 10 days or discharge from hospital, whichever occurs first
Tocilizumab – refer to appendix B	<ul style="list-style-type: none"> <li>• Tocilizumab has exhibited clinical benefit in two trials of <b>adult</b> patients with COVID-19 (REMAP-CAP and RECOVERY) but use in children remains extremely limited</li> <li>• Decision for use of tocilizumab in critically ill pediatric patients with COVID-19 may be made on a case-by-case basis through coordination of a multi-disciplinary team</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;90 kg = 800 mg</li> <li>• &gt;65 – 90 kg = 600 mg</li> <li>• 40-65 kg = 400 mg</li> <li>• &lt;40 kg = 8 mg/kg</li> </ul>	See adult dosing section
Baricitinib – refer to appendix C	<ul style="list-style-type: none"> <li>• Received EUA down to 2 years of age but <b>there is no clinical data in pediatric patients for COVID-19</b></li> </ul>	4 mg PO once daily for up to 14 days or until discharge	Patients 2-8 years of age: 2 mg PO once daily for up to 14 days or until discharge
Monoclonal antibodies – refer to Appendix E	<ul style="list-style-type: none"> <li>• As of 11/30/2022, there are no currently authorized anti-SARS-CoV-2 monoclonal antibody products with active authorizations for emergency</li> </ul>		

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	use in the United States due to the shift in circulating variants and diminished activity of previously authorized agents		
Remdesivir – refer to Appendix A	<ul style="list-style-type: none"> <li>• Only FDA-approved treatment option for COVID-19</li> <li>• Shown to reduce time to clinical improvement in select adult patients but no trial has shown mortality benefit or clinical benefit in children</li> <li>• Use in any patient requires fulfillment of restriction criteria</li> </ul>	200 mg IV loading dose followed by 100 mg daily x 2-4 days	Patients under 40 kg: 5 mg/kg loading dose followed by 2.5 mg/kg daily x 2-4 days
Convalescent Plasma – refer to Appendix D	<ul style="list-style-type: none"> <li>• Available through EUA for immunocompromised patients within 8 days of symptom onset</li> <li>• Limited dosing information particularly for pediatric patients</li> </ul>	Typically 1-2 units	No data
Nirmatrelvir-ritonavir – refer to Appendix F	<ul style="list-style-type: none"> <li>• Received EUA for outpatients down to age 12 years weighing at least 40 kg with mild-moderate COVID-19 who are high risk for severe disease / hospitalization</li> <li>• Limited clinical data available for pediatric patients</li> </ul>	See dosing based on renal function in Appendix F	See dosing based on renal function in Appendix F
Tixagevimab-Cilgavimab –	<ul style="list-style-type: none"> <li>• <b>As of 01/26/2023, tixagevimab-cilgavimab is no longer authorized for emergency use in the United States due to the shift in circulating variants and diminished activity.</b></li> </ul>		

#Default maximum dose in the adult dose

**Appendix L: COVID-19-Associated Coagulopathy in Pediatrics**

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**Consult Pediatric Hematology for hospitalized pediatric patients with symptoms of COVID-19 and a positive COVID-19 test.**

Despite the growing number of reported cases there remains a knowledge gap regarding the infectious, epidemiologic and clinical features associated with COVID-19 illness in children. Signs and symptoms of COVID-19 in children can range from asymptomatic to acute upper respiratory tract infection as well as gastrointestinal symptoms, respiratory failure, shock, coagulation dysfunction and renal injury in severe cases. The pathophysiology of COVID-19-associated coagulopathy in pediatrics it not yet well understood; hence, these patients require additional laboratory monitoring as recommended in Table 1.

**Table 1: Lab Monitoring for hospitalized pediatric patients with symptoms of COVID-19 and a positive COVID-19 test:**

Admission at UIHC	Non-ICU	Covid-19 Decompensation or in ICU
CBC with differential D-dimer PT PTT Fibrinogen Extra blue top (sodium citrate) tube	If patient is already having labs drawn, then draw these 2 labs daily with the other labs: CBC with differential D-dimer  If patient has clinical deterioration, then adjust labs to include these DAILY: CBC with differential D-dimer Fibrinogen Extra blue top (sodium citrate) tube	Daily: CBC with differential D-dimer PT PTT Fibrinogen Extra blue top (sodium citrate) tube

Pediatric patients **12 years of age or older** who are hospitalized with symptoms of COVID-19 and have a positive COVID-19 test should receive standard prophylactic anticoagulation with enoxaparin (see Table 2 for recommendations) in the absence of any known contraindications to anticoagulation (i.e., actively bleeding or platelet count < 25,000/mm<sup>3</sup>). If patient has a contraindication, the physician must determine risk vs. benefit to determine what is best for the patient.

Pediatric patients **younger than 12 years of age** a who are hospitalized with symptoms of COVID-19 and have a positive COVID-19 test should be evaluated for risk of thrombosis and provided thromboprophylaxis per standard of care, which typically does not include chemoprophylaxis.

**Table 2: Thromboprophylaxis Recommendations for Pediatric Patients who are hospitalized with symptoms of COVID-19 and have a Positive COVID-19 test:**

Patient Age	
<b>12 years and older</b>	Enoxaparin 0.5 mg/kg SQ q12hr (maximum dose 60 mg SQ q12hr) Monitor anti-Xa levels as recommended in the <a href="#">University of Iowa Stead Family Children’s Hospital Anticoagulation Medication Guidelines</a>  If CrCl < 30 mL/min/1.73m <sup>2</sup> : Enoxaparin* 0.25 mg/kg SQ q12hr
<b>Less than 12 years</b>	Evaluate for risk of thrombosis and provide thromboprophylaxis per standard of care, if applicable.