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

**Key Points Regarding Pre-Exposure Prophylaxis**
- There is one monoclonal antibody formulation tixagevimab-cilgavimab (Evusheld®) authorized by the FDA for use in pre-exposure prophylaxis against COVID-19. It is limited to use in patients with immunocompromised status that cannot mount adequate response to vaccination OR patients that have contraindications to vaccination due to history of severe reaction.
- Supply of tixagevimab-cilgavimab is extremely limited and eligibility for this agent is determined by institutional prioritization criteria for use and patients will be offered therapy in a tiered fashion as drug becomes available

**Key Points Regarding Post-Exposure Prophylaxis**
- Multiple monoclonal antibody formulations have authorizations for use in post-exposure prophylaxis in select patient populations; however, UIHC cannot offer therapy for this indication at this time due to limitations secondary to high circulation of the Omicron variant.

**Therapeutic Considerations for Adults with COVID-19 Based on Clinical Status**
**University of Iowa Health Care**  
**Guidance on Treatment Options for Patients with SARS-CoV-2**  
**PROTOCOL TEMPORARILY CREATED PURSUANT TO AUTHORITY OF HOSPITAL INCIDENT COMMANDER ACTIVATED IN RESPONSE TO COVID-19. EFFECTIVE UNTIL FURTHER NOTICE.**  
*Date Created Per HICS: 3/20/2020*  
*Date Amended: 3/10/2022*

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hospitalized with mild-moderate COVID-19</td>
<td>Patients should be evaluated for eligibility for anti-SARS-CoV-2 monoclonal antibody products and antivirals (i.e. nirmatrelvir-ritonavir and molnupiravir) based on EUA and institutional eligibility criteria (see Appendix E)</td>
</tr>
</tbody>
</table>
| Hospitalized but without supplemental oxygen requirement | Dexamethasone should **not** be initiated  
Remdesivir may be considered in patients that are at high risk for disease progression and within 7 days of symptom onset (see Appendix A) |
| Hospitalized and requires supplemental oxygen | Dexamethasone should be initiated (see Tier 1 table below for additional information)  
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)*  
Addition of a monoclonal immunomodulator may be considered within 24-48 hours following decompensation (see appendices for additional criteria)§:  
- Tocilizumab IV if C-reactive protein (CRP) ≥7.5 mg/dL (see Appendix B) OR  
- Baricitinib PO if elevated CRP <7.5 mg/dL (see Appendix C) |
| Hospitalized 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)§:  
- Tocilizumab IV if C-reactive protein (CRP) ≥7.5 mg/dL (see Appendix B) OR  
- Baricitinib PO if elevated CRP <7.5 mg/dL (see Appendix C) |
| Hospitalized 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)§:  
- Tocilizumab IV if C-reactive protein (CRP) ≥7.5 mg/dL (see Appendix B) OR  
- Baricitinib PO if elevated CRP <7.5 mg/dL (see Appendix C) |

*Remdesivir may be initiated and/or continued based on patient-specific risk/benefit assessment  
§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.  
**Therapeutic Considerations for Children with COVID-19 Based on Clinical Status***
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

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hospitalized with mild-moderate COVID-19</td>
<td>Patients may be evaluated for eligibility for anti-SARS-CoV-2 monoclonal antibody products and/or antivirals based on EUA and institutional eligibility criteria (see Appendix E)%</td>
</tr>
<tr>
<td>Hospitalized but without supplemental oxygen requirement</td>
<td>Dexamethasone should <strong>not</strong> be initiated</td>
</tr>
<tr>
<td></td>
<td>Remdesivir should <strong>not</strong> be initiated in most patients but may be considered in patients within 7 days of symptom onset and at high risk of progression to severe disease</td>
</tr>
<tr>
<td>Hospitalized and requires supplemental oxygen</td>
<td>Dexamethasone initiation may be considered</td>
</tr>
<tr>
<td></td>
<td>Remdesivir initiation may be considered (see Appendix A)</td>
</tr>
<tr>
<td>Hospitalized and requires oxygen delivery through a high-flow device or noninvasive ventilation</td>
<td><strong>Dexamethasone should be initiated (or continued)</strong>*</td>
</tr>
<tr>
<td></td>
<td>Addition of a monoclonal immunomodulator may be considered within the first 24-48 hours after escalation in respiratory support (see appendices for additional criteria)¶&amp;:</td>
</tr>
<tr>
<td></td>
<td>• Tocilizumab IV if C-reactive protein (CRP) ≥7.5 mg/dL (see Appendix B) OR</td>
</tr>
<tr>
<td></td>
<td>• Baricitinib PO if elevated CRP &lt;7.5 mg/dL (see Appendix C)</td>
</tr>
<tr>
<td>Hospitalized and requires invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)</td>
<td><strong>Dexamethasone should be initiated (or continued)</strong>*</td>
</tr>
<tr>
<td></td>
<td>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)¶&amp;:</td>
</tr>
<tr>
<td></td>
<td>• Tocilizumab IV if C-reactive protein (CRP) ≥7.5 mg/dL (see Appendix B) OR</td>
</tr>
<tr>
<td></td>
<td>• Baricitinib PO if elevated CRP &lt;7.5 mg/dL (see Appendix C)</td>
</tr>
</tbody>
</table>

* 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.

% 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.

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
</table>
| Steroids                | • 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.  
• 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. |
| Tocilizumab             | • A one-time dose of tocilizumab may be considered in select critically ill patients with COVID-19  
• 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.  
• 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. |
| Baricitinib             | • Baricitinib may be considered as an alternative to dexamethasone in the setting of a significant contraindication to use of glucocorticoids.  
• 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 not be combined with tocilizumab. For additional details see Appendix C  
• 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. |
| Remdesivir              | • Initiation of therapy for inpatients with severe disease requires fulfillment of the institutional eligibility criteria (see Appendix A)  
• No demonstrated mortality benefit in patients with severe disease  
• Questions specific to initiation of remdesivir in patients under the age of 18 may be directed to pediatric infectious disease consult service |

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-SARS-CoV-2 Monoclonal Antibodies</td>
<td>• Emergency use authorizations from the FDA have been granted to multiple products for treatment of patients with mild to moderate COVID-19 not requiring oxygen (above baseline) and deemed to be high risk for progression to severe disease and/or</td>
</tr>
</tbody>
</table>


hospitalization. These have been modified or revoked based on circulating viral variants. Certain products also have data supporting use for post-exposure prophylaxis but use for this indication is dependent on local availability. See Appendix E for additional details.
  
  - Sotrovimab – authorized for treatment and expected to have activity against Omicron
  - Bebtelovimab – authorized for treatment and expected to have activity against Omicron and known subvariants.
  - Bamlanivimab – no longer authorized due to risk of inferior activity against certain variants
  - Bamlanivimab plus etesivimab – available for both treatment and post-exposure prophylaxis in select patients. Notably authorized in patients of all ages. Not considered active against Omicron variant
  - Casirivimab plus imdevimab – available for both treatment and post-exposure prophylaxis in select patients. Not considered active against Omicron variant

Nirmatrelvir-Ritonavir

- Patients enrolled in ILI monitoring program will be assessed for eligibility by outpatient pharmacy team
- Must be administered within 5 days of symptom onset
- Patient must be screened appropriately for drug-drug interactions
- Refer to Appendix F for additional information on clinical data, and institutional criteria for use

Remdesivir

- See Appendix A for institutional criteria for use in mild-moderate infection

**Tier 1c: medications with evidence of benefit for pre-exposure prophylaxis**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
</table>
| Tixagevimab - Cilgavimab | • Emergency use authorization was granted in December 2021 for pre-exposure prophylaxis of COVID-19 in patients who have moderate-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate response to COVID-19 vaccination OR in who vaccination is not recommended due to history of severe adverse reaction  
  • Eligibility for this agent is determined by institutional prioritization criteria for use and patients will be offered therapy in a tiered fashion as drug becomes available (see Appendix G) |

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Rationale for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convalescent Plasma</td>
<td>Plasma is available through FDA emergency use authorization for patients with immunosuppressive disease or receiving immunosuppressive treatment</td>
</tr>
</tbody>
</table>
University of Iowa Health Care
Guidance on Treatment Options for Patients with SARS-CoV-2

PROTOCOL TEMPORARILY CREATED PURSUANT TO AUTHORITY OF HOSPITAL INCIDENT COMMANDER ACTIVATED IN RESPONSE TO COVID-19. EFFECTIVE UNTIL FURTHER NOTICE.

Date Created Per HICS: 3/20/2020
Date Amended: 3/10/2022

- 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.

Molnupiravir
- Molnupiravir is authorized for use in treatment of COVID-19 in the absence of available alternatives
- See Appendix H for additional information on clinical data and criteria for use at UIHC

**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)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Rationale for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Studies to date have suggested no benefit for treatment of COVID-19</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Hydroxychloroquine / Chloroquine</td>
<td>Though both chloroquine and hydroxychloroquine demonstrated potent in vitro 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.</td>
</tr>
<tr>
<td>Influenza Agents</td>
<td>Coronaviruses do not utilize neuraminidase for replication and no activity is expected.</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>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</td>
</tr>
</tbody>
</table>

**Supportive Agents (in alphabetical order)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen / NSAIDs (non-steroidal anti-inflammatory drugs)</td>
<td>There is no conclusive evidence to suggest that NSAIDs such as ibuprofen increase the severity of COVID-19 disease; however, acetaminophen may be considered the preferred fever-reducer / pain reliever in patients with viral illness based on more benign overall side effect profile</td>
</tr>
<tr>
<td>ACE-inhibitors / ARBs</td>
<td>Professional societies in cardiology and nephrology are advising not to add or remove any RAAS-related treatments beyond actions based on standard clinical practice. Clinical trials have substantiated this approach.</td>
</tr>
<tr>
<td>Intravenous Immunoglobulin (IVIG)</td>
<td>Routine use not recommended by Society of Critical Care Medicine (SCCM); however, it may be considered in the context of cytokine storm (additional criteria forthcoming) or clinical trial.</td>
</tr>
<tr>
<td>Steroids</td>
<td>See Tier 1 above</td>
</tr>
<tr>
<td>Venous Thromboembolism Prophylaxis &amp; COVID-19-Associated Coagulopathy</td>
<td>Adults: Thromboprophylaxis should be provided to all patients with COVID-19. See Appendix G for more information about prophylaxis in adult patients. Pediatrics: Consult Pediatric Hematology. See Appendix H for more information. Pediatrics 12 years of age and older: thromboprophylaxis should be provided to all patients in this age group with COVID-19</td>
</tr>
</tbody>
</table>
Pediatrics less than 12 years of age: standard of care thromboprophylaxis for any hospitalized pediatric patient, which typically does not include chemoprophylaxis. For critically ill patients in this age group, strongly consider prophylactic anticoagulation.

### Vaccines

- There are currently three COVID-19 vaccines that have received emergency use authorization for use in the United States (see table below). 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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**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 ≥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 ≥12 years old and weighing ≥40 kg.

Remdesivir for pediatric patients <12 years of age weighing at least 3.5 kg or patients weighing 3.5 kg to <40 kg is available through FDA emergency use authorization.

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
  - ≥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
  - 3.5 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
  - ≥40 kg: 200 mg IV x1, followed by 100 mg IV daily x 4 days
  - 3.5 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)
  - 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 ≥65 years
  - BMI ≥30 kg/m² or BMI ≥85th percentile for their age range and gender based on CDC growth chart
  - Pregnancy
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease or immunosuppressive treatment
  - Cardiovascular disease (including congenital heart disease) or hypertension
  - Chronic lung diseases (including chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
  - Sickle cell disease
  - Neurodevelopmental disorders or other conditions that confer medical complexity
  - Medical-related technological dependence (including tracheostomy, gastrostomy)

**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
• SpO₂ ≤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

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 (appendix H).

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.

**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 ≥30 L/min of O2 flow, and/or requirement for intravenous vasopressor or inotrope support)
- Evidence of inflammation with C-reactive protein ≥ 7.5 mg/dL

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

- Alanine aminotransferase > 5x ULN
- Absolute neutrophil count <500 cells/μL
- Platelets <50,000 cells/μL
- 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

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 ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Dosing:

- Adults and pediatric patients 9 years of age and older: dosing is dependent on renal function
  - eGFR ≥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 ≥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.

- 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 transaminisitis. Consideration for discontinuation should be made if liver enzyme elevation (≥5 × ULN for ALT and ≥10 × 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.
University of Iowa Health Care
Guidance on Treatment Options for Patients with SARS-CoV-2

PROTOCOL TEMPORARILY CREATED PURSUANT TO AUTHORITY OF HOSPITAL INCIDENT COMMANDER ACTIVATED IN RESPONSE TO COVID-19. EFFECTIVE UNTIL FURTHER NOTICE.

Date Created Per HICS: 3/20/2020
Date Amended: 3/10/2022

- 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 due to indications for other disease states; however, it remains a non-formulary inpatient drug. 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.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Alternative to Dexamethasone in Patient with COVID-19</th>
<th>Additive Immunomodulation in Patient with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>Confirmed SARS-CoV-2 infection</td>
<td>Confirmed positive SARS-CoV-2 infection</td>
<td></td>
</tr>
<tr>
<td>Requirement for supplemental oxygen above baseline</td>
<td>New requirement for pulmonary and/or cardiovascular support (includes invasive or noninvasive mechanical ventilation, high-flow nasal canula requiring ≥30 L/min of O2 flow, and/or requirement for intravenous vasopressor or inotrope support).</td>
<td></td>
</tr>
<tr>
<td>Age ≥2 years</td>
<td>Evidence of inflammation with C-reactive protein &gt;0.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Contraindication to use of glucocorticoids (i.e. dexamethasone)</td>
<td>Baricitinib should ideally be initiated within 24-48 hours of escalation in support</td>
<td></td>
</tr>
</tbody>
</table>

| **Exclusion Criteria** |                      |                                                   |
| eGFR <15 (<30 if less than 9 years of age) | eGFR <15 (<30 if less than 9 years of age) |                                                   |
| Absolute lymphocyte count less than 200 | Absolute lymphocyte count less than 200 |                                                   |
| Absolute neutrophil count less than 500 | Absolute neutrophil count less than 500 |                                                   |
| Known active tuberculosis infection | Uncontrolled non-SARS-CoV-2 coinfection, including active tuberculosis infection |                                                   |
| Concomitant use of alternative JAK inhibitor or IL-6 inhibitor | Survival predicted to be less than 24 hours |                                                   |
| | Alternative explanation for respiratory symptoms |                                                   |
| | Concomitant use of alternative JAK inhibitor or IL-6 inhibitor |                                                   |

*Patient should receive concomitant dexamethasone therapy if used for this indication
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.

**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. UIHC is making these treatments available to qualifying patients meeting the criteria for use outlined in the emergency use authorizations (see table below). Currently only one product is being offered to patients as the others are inactive to the dominant variant, Omicron.

1. Sotrovimab
   a. **Mechanism of action:** monoclonal antibody that targets an epitope in the receptor binding domain of SARS-CoV-2 Spike protein
b. Evidence summary: sotrovimab was studied in the Phase 1/2/3 COMET-ICE trial which is a randomized, double-blind, placebo-controlled trial that included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized to receive sotrovimab 500 mg IV (n=291) or placebo (n=292). The primary endpoint was the proportion of participants who were hospitalized (for ≥24 hours) or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm (p=0.002), resulting in a 6% absolute reduction and an 85% relative reduction compared to placebo.

c. The FDA granted emergency use authorization for sotrovimab for use in patients with mild to moderate COVID-19 disease not on supplemental oxygen (above baseline) and deemed to be high risk for progression (see table below for FDA criteria for use).

d. Pending drug availability, outpatients meeting the EUA criteria will be contacted and offered the opportunity to receive a one-time infusion after careful discussion of the potential risks and benefits.

e. Dosing: 500 mg sotrovimab as a single intravenous (IV) infusion over 15-30 minutes

f. Toxicity / adverse effects: most frequently reported adverse events were nausea and diarrhea. Hypersensitivity and infusion-related reactions are possible and have been reported in small numbers in the ongoing, blinded trials. There remains limited clinical trial data available so serious and unexpected adverse effects MAY occur that have not been previously reported.

2. Bebtelovimab

a. Mechanism of action: recombinant neutralizing monoclonal antibody to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. It binds to the spike protein and blocks protein attachment to the human ACE2 receptor.

b. Evidence summary: bebtelovimab has been included in several arms of the BLAZE-4 trials. It was shown to improve symptoms in patients with mild-moderate COVID-19 and showed a reduction in SARS-CoV-2 viral load on day 5 relative to placebo. The placebo-controlled phase 2 data are limited by enrollment of only subjects without risk factors for progression to severe COVID-19 and the trial was not powered to determine differences in clinical outcomes of death or hospitalization. Bebtelovimab was emergently authorized based on the totality of the available evidence including safety data, limited clinical efficacy data, and in vitro activity against SARS-CoV-2 variants.

c. The FDA granted emergency use authorization for bebtelovimab for use in patients with mild to moderate COVID-19 disease not on supplemental oxygen (above baseline) and deemed to be high risk for progression (see table below for FDA criteria for use) and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

d. Pending drug availability, outpatients meeting the EUA criteria will be contacted and offered the opportunity to receive a one-time infusion after careful discussion of the potential risks and benefits.

e. Dosing: 175 mg bebtelovimab as a single intravenous injection over at least 30 seconds

f. Toxicity / adverse effects: most frequently reported adverse events were nausea and vomiting. Hypersensitivity and infusion-related reactions are possible and have been reported in small numbers in the ongoing, blinded trials. There remains limited clinical trial data available so serious and unexpected adverse effects MAY occur that have not been previously reported.

UIHC Criteria for Use of Sotrovimab and Bebtelovimab for Treatment of Mild-Moderate COVID-19*:
<table>
<thead>
<tr>
<th>UIHC Institutional Criteria for Use</th>
<th>FDA Criteria for Use per Emergency Use Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult patients 18 years and older</strong></td>
<td><strong>Patient with mild(^8) to moderate(^6) COVID-19</strong></td>
</tr>
<tr>
<td>Monoclonal antibody therapy for adult patients (18 years and above) may be offered if they meet FDA criteria for use</td>
<td><strong>Positive results of COVID-19 test</strong></td>
</tr>
<tr>
<td>The column to the right outlines the conditions specified in the EUA. Non-hospitalized adult patients with positive COVID tests at UIHC will be proactively evaluated for eligibility based on these specified criteria and offered therapy if appropriate.</td>
<td><strong>Within 7 days of symptom onset at time of infusion</strong></td>
</tr>
<tr>
<td>Additional information on medical conditions and factors associated with increased risk for progression to severe disease can be found at the CDC website: <a href="https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html">https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html</a></td>
<td><strong>High risk for progression to severe disease and/or hospitalization as defined by one or more of the following:</strong></td>
</tr>
<tr>
<td></td>
<td>o Age ≥65 years</td>
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<tr>
<td></td>
<td>o BMI ≥30 kg/m(^2)</td>
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<td></td>
<td>o Pregnancy</td>
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<td></td>
<td>o Chronic kidney disease</td>
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<td>o Diabetes</td>
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<tr>
<td></td>
<td>o Immunosuppressive disease or immunosuppressive treatment</td>
</tr>
<tr>
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<td>o Cardiovascular disease (including congenital heart disease) or hypertension</td>
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<tr>
<td></td>
<td>o Chronic lung diseases (including chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)</td>
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<tr>
<td></td>
<td>o Sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>o Neurodevelopmental disorders or other conditions that confer medical complexity</td>
</tr>
<tr>
<td></td>
<td>o Medical-related technological dependence (including tracheostomy, gastrostomy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric patients 12 to 17 years of age</th>
<th><strong>Patient with mild(^8) to moderate(^6) COVID-19</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibody therapy for pediatric patients aged 12-17 years of age may be offered if they meet FDA criteria for use</td>
<td><strong>Positive results of COVID-19 test</strong></td>
</tr>
<tr>
<td>The column to the right outlines the conditions specified in the EUA. Non-hospitalized patients with positive COVID tests at UIHC will be proactively evaluated for eligibility based on these specified criteria and offered therapy if appropriate.</td>
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<td>Additional information on medical conditions and factors associated with increased risk for progression to severe disease can be found at the CDC website: <a href="https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html#higher-risk">https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html#higher-risk</a></td>
<td><strong>High risk for progression to severe disease and/or hospitalization as defined by one or more of the following:</strong></td>
</tr>
<tr>
<td></td>
<td>o BMI ≥85(^{th}) percentile for their age and gender based on CDC growth charts</td>
</tr>
<tr>
<td></td>
<td>o Pregnancy</td>
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<td></td>
<td>o Chronic kidney disease</td>
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</tr>
<tr>
<td></td>
<td>o Neurodevelopmental disorders or other conditions that confer medical complexity</td>
</tr>
</tbody>
</table>
Pediatric patients under 12 years of age | Medical-related technological dependence (including tracheostomy, gastrostomy)
---|---
Monoclonal antibody therapy for pediatric patients below age 12 is unavailable. The only formulation authorized for this age group (bamlanivimab-etesivimab) has limited activity against Omicron variant.

*At times of limited supply qualifying criteria may change and be more restrictive. Refer to the COVID-19 Antibody Therapy process tab on the Loop for more information.

**Mild**: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

**Moderate**: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO₂) ≥94% on room air at sea level

Setting of Administration for Monoclonal Antibody Therapy:

- **Outpatients**: administered at Iowa River Landing within a dedicated COVID-19 infusion suite. Referrals for treatment can be made by addressing an Epic message to the inbasket ‘P RX COVID ANTIBODY THERAPY’ or for post-exposure prophylaxis through the “Pharmacy Referral for Monoclonal Antibody Prophylaxis” order with the relevant patient information.
  - Adult patients (18 years of age and older) – patients with positive SARS-CoV-2 tests are proactively reviewed by specialty pharmacy staff. Patients meeting criteria are contacted to discuss therapy and outline the potential risks and benefits of therapy as outlined by the emergency use authorization materials. If patient is agreeable, they are scheduled for infusion.
  - Pediatric patients (12 years of age to 17 years of age) – patients with positive SARS-CoV-2 tests are proactively reviewed by specialty pharmacy staff. Patients meeting criteria are contacted to discuss therapy and outline the potential risks and benefits of therapy as outlined by the emergency use authorization materials. If patient is agreeable, they are scheduled for infusion. Patients may also be referred to the infusion center by their pediatric provider using the Epic message inbasket ‘P RX COVID ANTIBODY THERAPY’. Questions specific to initiation in pediatric patients under the age of 18 years may be directed to the pediatric infectious disease consult service.

- **Inpatients**: not available at this time. Contact antimicrobial stewardship pager (1282) if you have any questions including potential for alternatives in select patients.
Appendix F: Nirmatrelvir-Ritonavir

**Mechanism of Action:** Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M\(^{\text{PRO}}\), 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. 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%).

**Restriction Criteria at UIHC for initiation of therapy:**
Supply of nirmatrelvir-ritonavir is under allocation through the government and supply is expected to be well below the number of eligible patients for the foreseeable future. Patients will minimally need to fulfill the criteria below. Patients who meet criteria are being prioritized for medication administration depending on their risk factors and published recommendations and will be systematically contacted to provide education and scheduling according to their prioritization status. There is no available inpatient supply of nirmatrelvir-ritonavir. Continuation of therapy initiated in the outpatient setting is at the discretion of provider but reliant on patient-supplied medication.

**Inclusion Criteria (patient must meet ALL of the following):**
- Outpatient with confirmed positive SARS-CoV-2 infection
- Symptom onset ≤ 5 days
- At least one risk factor for progression to severe disease
  - Age ≥65 years
  - BMI ≥30 kg/m² or BMI ≥85th percentile for their age range and gender based on
  - Pregnancy
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease or immunosuppressive treatment
  - Cardiovascular disease (including congenital heart disease) or hypertension
Chronic lung diseases (including chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)

- Sickle cell disease
- Neurodevelopmental disorders or other conditions that confer medical complexity

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 m²
- High risk drug-drug interactions (refer to package insert or alternative resource for guidance)
- Inability to tolerate oral administration
- Uncontrolled HIV

Appendix G: Tixagevimab-Cilgavimab

**Mechanism of Action:** combination of monoclonal antibodies (tixagevimab and cilgavimab) the bind to non-overlapping regions of the receptor binding domain of the SARS-CoV-2 spike protein. A modification in the Fc region gives these anti-SARS-CoV-2 monoclonal antibodies prolonged half-lives that result in protection for up to 6 months.

**Evidence Summary:**

Tixagevimab-cilgavimab is being studied in an ongoing, double-blind, Phase 3 randomized controlled trial that evaluated the use of this combination therapy for adult patients who have not received a COVID-19 vaccine and who were at increased risk of severe SARS-CoV-2 infection or who had an increased risk of acquiring SARS-CoV-2 infection due to their occupation or living situation. The study excluded those with history of confirmed SARS-CoV-2 infection or who were antibody positive at screening.

Participants were given either tixagevimab 150 mg plus cilgavimab 150 mg as 2 consecutive IM injections (n = 3,441) or 2 placebo IM injections (n = 1,731). The primary endpoint was symptomatic SARS-CoV-2 infection and a positive SARS-CoV-2 RT-PCR result during the 183 days of follow-up.
On December 8th, 2021 the FDA issued an Emergency Use Authorization for the anti-SARS-CoV-2 monoclonal antibody combination of tixagevimab plus cilgavimab to be used as pre-exposure prophylaxis (PrEP) in certain individuals who, if infected, are at high risk of progressing to severe COVID-19. This was subsequently updated to double the dose in the setting of the Omicron variant.

**Dosing:** 300 mg tixagevimab and 300 mg cilgavimab administered as 2 consecutive intramuscular injections

**Toxicity / Adverse Effects:**

Thirty-five percent of the 3,461 tixagevimab plus cilgavimab recipients and 34% of the 1,736 placebo recipients experienced adverse events. Serious adverse events were reported in 1% of participants in both arms, with 1 participant from the tixagevimab plus cilgavimab arm reporting an anaphylactic reaction that resolved with epinephrine therapy. Most adverse events were mild (73%) or moderate (24%), with similar incidences for mild and moderate adverse events between the arms. Serious cardiac adverse events occurred in 0.6% of participants in the tixagevimab plus cilgavimab arm and 0.2% of participants in the placebo arm. All participants who experienced a cardiac event had cardiac risk factors and/or a history of cardiac disease at baseline. There was no clear temporal pattern between these cardiac events and administration of the mAbs.

**Restriction Criteria for UIHC:**

Supply of tixagevimab plus cilgavimab is under allocation through the government and supply is expected to be well below the number of eligible patients for the foreseeable future. Patients will minimally need to fulfill the emergency use authorization criteria:

- Moderately-severely immunocompromised that may have an inadequate immune response to COVID-19 vaccination OR not able to be fully vaccinated with any available COVID-19 vaccine due to documented history of severe adverse reactions to a COVID-19 vaccine of any of it components
- Aged ≥12 years
- Weight ≥40 kilograms

Patients who meet authorization criteria are being prioritized for medication administration depending on their risk factors and published recommendations and will be systematically contacted to provide education and scheduling according to their prioritization status.
Appendix H: 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.

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 (≥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 ≤5 days. Increased risk for severe illness from COVID-19 was defined as age >60 years of age, active cancer, COPD, obesity (BMI ≥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 of 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 supply is expected to be below the number of eligible patients. Patients will minimally need to fulfill the criteria below. Patients who meet criteria are being prioritized for medication administration depending on their risk factors and published recommendations and will be systematically contacted to provide education and scheduling according to their prioritization status. There is no available inpatient supply of molnupiravir. Continuation of therapy initiated in the outpatient setting is at the discretion of provider but reliant on patient-supplied medication.

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

- Outpatient with confirmed positive SARS-CoV-2 infection
- Symptom onset ≤ 5 days
- At least one risk factor for progression to severe disease
Guidance on Treatment Options for Patients with SARS-CoV-2

PROTOCOL TEMPORARILY CREATED PURSUANT TO AUTHORITY OF HOSPITAL INCIDENT COMMANDER ACTIVATED IN RESPONSE TO COVID-19. EFFECTIVE UNTIL FURTHER NOTICE.

Date Created Per HICS: 3/20/2020

Date Amended: 3/10/2022

- Age ≥65 years
- BMI ≥30 kg/m² or BMI ≥85th percentile for their age range and gender based on
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (including chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders or other conditions that confer medical complexity
- Medical-related technological dependence (including tracheostomy, gastrostomy)

- 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

Appendix I: References for COVID-19 Therapeutic Treatment Options


Appendix J: COVID-19-Associated Coagulopathy in Adults

The pathophysiology of COVID-19-associated coagulopathy appears to be complex and multifactorial, involving both cellular and plasmatic elements of the hemostatic system. Development of coagulopathy has been suggested to be a predictor of mortality in patients with COVID-19. Treatment with low-molecular weight heparin (LMWH) in prophylactic doses was associated with better outcomes in severe cases of COVID-19 meeting ISTH criteria for DIC in a retrospective analysis.

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

<table>
<thead>
<tr>
<th>Presentation at UIHC</th>
<th>Non-ICU</th>
<th>COVID-19 Decompensation or in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Daily:</td>
<td>CBC with differential</td>
</tr>
<tr>
<td>D-dimer</td>
<td>CBC with differential</td>
<td>D-dimer</td>
</tr>
<tr>
<td>PT</td>
<td>D-dimer</td>
<td>PT</td>
</tr>
<tr>
<td>PTT</td>
<td>Every other day monitoring:</td>
<td>PTT</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fibrinogen</td>
<td>Fibrinogen</td>
</tr>
</tbody>
</table>

**Management:**

All patients admitted to UIHC for COVID-19 should receive standard prophylactic anticoagulation with enoxaparin in the absence of any contraindications, refer to the [Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients](#) for medication and dosing recommendations and also, Table 1 for recommendations in pregnant patients. Extending VTE prophylaxis for patients with COVID-19 is not necessary and should follow standard practice (a multidisciplinary discussion should occur at or near the time of discharge to determine if a patient has ongoing risk factors, may benefit form extended post-hospital VTE prophylaxis). Whether or not COVID-19-infected patients have a unique increased risk of VTE compared to other critical infections or processes is not currently known. At this time, we do not suggest intermediate or therapeutic doses of anticoagulation or thrombolytics for thromboprophylaxis. However, patients may be evaluated to participate in a clinical trial comparing standard prophylactic dose vs. intermediate-dose enoxaparin (see below for more information).

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.

Imaging:

Concern for DVT:
- For patients with suspected DVT and elevated D-dimer, obtain lower extremity venous studies to evaluate asymmetric limb pain or edema. If DVT is present, start therapeutic dose anticoagulation (enoxaparin preferred).
- If D-dimer is normal, but provider feels strongly that a lower extremity venous studies should be done, contact the vascular staff on call.
- If patient has a known PE, do not order lower extremity venous studies, patient should already be receiving therapeutic dose anticoagulation (enoxaparin preferred).
- If patient is already receiving therapeutic dose anticoagulation, lower extremity venous studies will not be performed.
- No “follow-up DVT” lower extremity venous studies will be performed without discussion with vascular staff on call.
- If patient is unable to get lower extremity venous studies due to concern of staff exposure to Covid-19, and clinical suspicion for DVT is high, consult Hematology attending.

Concern for Pulmonary Embolism (PE):
- 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)]
- Diagnostic evaluation:
  - Preferred: CTA
  - Alternative: ECHO may be useful if patient is unstable, CTA is unavailable, or when there are contraindications for CTA
- Comments:
  - Elevated D-dimer is a hallmark of Covid-19 disease and higher levels have been associated with worse outcomes in Covid-19 disease. Therefore, elevated, marked increase, or rising D-dimer may not be useful in calculating pre-test probabilities scores in PE, as we these values cannot differentiate between worsening Covid-19 disease and developing PE.
  - Lower extremity venous studies should not be considered a routine part of an evaluation for suspected PE in patients with Covid-19.

Treatment:
Refer to the Guidelines for Venous Thromboembolism (VTE) Prophylaxis in (non-pregnant) Hospitalized Adult Patients for medication and dosing recommendations, Table 1 for recommendations in pregnant patients, and Table 2 for special considerations and monitoring.

Table 1: Thromboprophylaxis Recommendations in Preganant Patients with COVID-19

<table>
<thead>
<tr>
<th>Pregnant Patient</th>
<th>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</th>
</tr>
</thead>
</table>
patient has a condition that places her at risk for significant bleeding (e.g. placenta previa, placenta accreta spectrum)

<table>
<thead>
<tr>
<th>Preferred: Enoxaparin (dose based on patient weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI $\leq$ 40 kg/m$^2$: Enoxaparin 40 mg SQ daily</td>
</tr>
<tr>
<td>BMI $&gt; 40$ kg/m$^2$: Enoxaparin 40 mg SQ q12h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative: UFH (recommended if CrCl &lt; 30 mL/min/1.73 m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{st}$ Trimester: 5000 to 7500 units SQ q12h</td>
</tr>
<tr>
<td>2$^{nd}$ Trimester: 7500 to 10000 units SQ q12h</td>
</tr>
<tr>
<td>3$^{rd}$ Trimester: 10000 units SQ q12h</td>
</tr>
</tbody>
</table>

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 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.

UFH: unfractionated heparin
Table 2: Recommendations for Monitoring Heparin Continuous Infusions in Patients with COVID-19

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT prolonged at baseline*</td>
<td>Use anti-Xa (consult Pharmacy for goal range and adjustment parameters)</td>
<td>Use aPTT</td>
</tr>
<tr>
<td>Heparin resistance¥</td>
<td>Use anti-Xa (consult Pharmacy for goal range and adjustment parameters)</td>
<td>Use aPTT</td>
</tr>
</tbody>
</table>

* 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.

¥ Heparin resistance: >35,000 units of heparin administered per 24 hours

References for COVID-19 Associated Coagulopathy:


Anticoagulation Forum Webinar: Thrombosis in the Hospitalized COVID Positive Patient - April 16, 2020


Appendix K: 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.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
<th>Adult Dosing</th>
<th>Pediatric Dosing#</th>
</tr>
</thead>
</table>
| Steroids                     | • Dexamethasone remains the steroid with the most robust evidence in COVID-19  
• Limited pediatric enrollment in the RECOVERY trial in the UK but overall showed mortality benefit in patients requiring supplemental oxygen                                                                                                                                                                   | 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 | • Tocilizumab has exhibited clinical benefit in two trials of adult patients with COVID-19 (REMAP-CAP and RECOVERY) but use in children remains extremely limited  
• 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                                                                                                                                                   | • >90 kg = 800 mg  
• >65 – 90 kg = 600 mg  
• 40-65 kg = 400 mg  
• <40 kg = 8 mg/kg                                                                                                                                                                                                                                           | See adult dosing section                                                                                                           |
| Baricitinib – refer to appendix C | • Received EUA down to 2 years of age but there is no clinical data in pediatric patients for COVID-19                                                                                                                                                                                                                               | 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 | • Casirivimab plus imdevimab, sotrovimab, and bebtelovimab have received EUA for outpatients down to age 12 years with mild-moderate COVID-19 who are high risk for severe disease / hospitalization. Bamlanivimab plus Sotrovimab 500 mg IV once for treatment. Bebtelovimab 175 mg IV once for treatment. | No data for children under 12 years of age                                                                                 |                                                                                  |
etesevimab has authorization for any age range.
  - Questions specific to initiation in pediatric patients under the age of 18 years may be directed to the pediatric infectious disease consult service.

| Remdesivir – refer to Appendix A | • Only FDA-approved treatment option for COVID-19  
• Shown to reduce time to clinical improvement in select adult patients but no trial has shown mortality benefit or clinical benefit in children  
• Use in any patient requires fulfillment of restriction criteria | 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 | • Available through EUA for immunocompromised patients within 8 days of symptom onset  
• Limited dosing information particularly for pediatric patients | Typically 1-2 units | No data |
| Nirmatrelvir-ritonavir – refer to Appendix F | • 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  
• Limited clinical data available for pediatric patients  
• Outpatients are being prioritized based on risk for progression to severe disease given lack of available supply | See dosing based on renal function in Appendix F | See dosing based on renal function in Appendix F |
| Tixagevimab-Cilgavimab – refer to Appendix G | • Received EUA to be used as pre-exposure prophylaxis (PrEP) in certain individuals who, if infected, are at high risk of progressing to severe COVID-19.  
• Outpatients are being prioritized based on risk for progression to severe disease given lack of available supply | 300 mg tixagevimab and 300 mg cilgavimab administered as 2 consecutive intramuscular injections | For patients at least 12 years of age and 40 kg – see adult dosing section. No availability for patients <12 years of <40 kg |

#Default maximum dose in the adult dose
Appendix L: COVID-19-Associated Coagulopathy in Pediatrics

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:

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

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/mm³). 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:

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 years and older</td>
<td>Enoxaparin 0.5 mg/kg SQ q12hr (maximum dose 60 mg SQ q12hr) Monitor anti-Xa levels as recommended in the University of Iowa Stead Family Children’s Hospital Anticoagulation Medication Guidelines If CrCl &lt; 30 mL/min/1.73m²: Enoxaparin* 0.25 mg/kg SQ q12hr</td>
</tr>
<tr>
<td>Less than 12 years</td>
<td>Evaluate for risk of thrombosis and provide thromboprophylaxis per standard of care, if applicable.</td>
</tr>
</tbody>
</table>