AdventHealth Treatment Algorithm for Hospitalized Adults with COVID-19

Last Update: 01/26/2023

For the management of non-hospitalized patients with COVID-19, refer to the AdventHealth Treatment Algorithm for Non-hospitalized Adults with COVID-19

For management of pediatrics patients (age <12 years or weight<40 kg), refer to AdventHealth Clinical Pediatric Treatment Algorithm

Table of Contents

Therapeutic Options for COVID-19 Treatment, Hospitalized

Severity Scale:

- 0 = Room air
- 1 = Supplemental O2 via NC up to 6L
- 2 = Supplemental O2 in addition to ≥1 of the following:
  - Dyspnea or staccato speech at rest or after minimal activity
  - RR>22 on 6L
  - PaO2<65 mmHg with 6L
  - Worsening infiltrates on imaging (CT preferred)
- 3 = HFNC, CPAP, or NIV
- 4 = Intubated with minimal support PaO2/FiO2, or using PS
- 5 = Intubated, PaO2/FiO2 > 150 mmHg
- 6 = Intubated, PaO2/FiO2 < 150 mmHg
- 7 = Intubated, PaO2/FiO2 < 150 mmHg AND vasopressor support
- 8 = Intubated in prone position or ECMO

All patients should receive supportive care (IV fluids, anti-pyretics, anti-emetics, etc.).

Severity Score	Treatment*^
Hospitalized for Reasons Other Than COVID-19	Refer to AdventHealth Treatment Algorithm for Non-hospitalized Adults with COVID-19. In certain patients with mild-moderate COVID-19 at risk of progressing to severe COVID-19, may utilize one of the following if criteria met: • Nirmatrelvir + ritonavir OR • Remdesivir (based on criteria)
0	Supportive care - if clinically stable, consider discharge for home quarantine Remdesivir (based on criteria)
1	• Remdesivir (based on criteria) • Dexamethasone 6 mg po or IV daily for up to 10 days ○ May use prednisone, methylprednisolone, or hydrocortisone at an equivalent dose if dexamethasone is not available
2	• Remdesivir (based on criteria) • Corticosteroids • Baricitinib, if able to tolerate PO OR Tocilizumab (or sarilumab#) may be considered in cases of progressive hypoxemia (increasing oxygen requirement) with CRP>75 mcg/mL after receiving corticosteroids for at least 24 hours. ○ Tocilizumab or sarilumab is not recommended for use in patients on low-flow oxygen with a stable clinical course.
3	• Corticosteroids • + Baricitinib (or tofacitinib#) if able to tolerate PO OR Tocilizumab (or sarilumab#) • ± Remdesivir (based on criteria)
≥4	• Corticosteroids • + Baricitinib (or tofacitinib) if able to tolerate PO OR Tocilizumab (or sarilumab#)

*Patients can be discharged whenever clinically indicated. Full duration of therapy does not need to be completed if patient is suitable for discharge to home. Isolation should be maintained at home if patient returns home before the period recommended for discontinuation.

^The decision to modify the recommendation for Convalescent Plasma was based on the RECOVERY study results indicating lack of mortality benefit when compared to placebo in hospitalized patients;

however, immunodeficient patients were not included in this study and may still derive a benefit with convalescent plasma for patients requiring low flow or high flow oxygen.

[¥]Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection. Use of baricitinib in combination with tocilizumab is not recommended.

[#]Sarilumab or tofacitinib may be used as alternatives to replace tocilizumab or baricitinib, respectively. Pharmacy will dispense product based on local available inventory.

Laboratory Monitoring

Recommended Laboratory Monitoring for all Hospitalized Patients with COVID-19:

- Daily: CMP, magnesium, CBC with differential
- Procalcitonin (PCT): baseline then every 2 days, as needed
- CRP: baseline then every 3 days
- D-dimer: baseline then every 3 days

COVID-19 Drug Information

Remdesivir

Regulatory Status	FDA approved for adults and pediatric patients (≥12 years older and weighing ≥40 kg) for the treatment of COVID-19 requiring hospitalization
Target Population/ Criteria for Use	SRC Criteria for Use: Based on available scientific evidence, the Scientific Research Committee supports the use of remdesivir • In patients with mild to moderate COVID-19 on room air and at high risk for disease progression OR requiring supplemental oxygen (severity score 0-3) • **For patients who require mechanical ventilation/ECMO, current data has not demonstrated reduction in time to clinical recovery or mortality and should not be routinely used in these patients.** Remdesivir should not be initiated routinely with the following at baseline: • Requiring mechanical ventilation or ECMO • Known hypersensitivity to any ingredient of remdesivir • Expected to expire within 24 hours or in hospice care • Hepatic impairment defined as ALT ≥10x ULN
Dose	200 mg IV x 1 on day 1 followed by 100 mg IV daily
Duration	• Hospitalized with severe COVID-19 (e.g., severity score ≥1): Up to 5 days or until hospital discharge, whichever is first ○ **Use beyond 5 days requires CMO approval* • Hospitalized with mild-moderate COVID-19 (e.g., severity score 0): Up to 3 days of until hospital discharge, whichever is first • If hospitalized for reasons other than COVID-19, the total duration is up to 3 days or until hospital discharge, whichever is first
Renal Impairment	Prescribing information states "Remdesivir is not recommended in patients with eGFR<30 mL/min.", however, expert consensus is that benefits of RDV may outweigh risk for most patients with impaired renal function. (Reference: J Am Soc Nephrol. 2020;31(7):1384-1386. doi:10.1681/ASN.2020050589.)
Hepatic Impairment	RDV should not be initiated in patients with ALT ≥10x ULN
Formulation(s)	IV infusion (30 minutes)
Adverse Effects	• Increased risk of transaminase elevations • Bradycardia - Post-marketing reports have identified bradycardia, including severe and even fatal bradycardia, in patients with COVID-19 receiving remdesivir. The frequency of this potential adverse event is not known at this time. • Hypotension
Monitoring	• HR, LFTs, renal function • Infusion related reaction (nausea, vomiting, diaphoresis, shaking)
Notes	• Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine • Trials have demonstrated improved benefit of giving remdesivir within 2 days of hospitalization • For hospitalized patients with COVID-19 who do not require supplemental oxygen or are on room air, but are at high risk for disease progression,

	have demonstrating clinical benefits with the addition of antiviral therapy in several trials (PINETREE)

For additional details, refer to RDV Prescribing Information

Corticosteroids

In all patients requiring supplemental oxygen:

- Initiate low dose steroids with dexamethasone 6 mg po or IV daily for up to 10 days
- If dexamethasone unavailable, utilize one of the following:
  - Prednisone 40 mg PO daily
  - Methylprednisolone 32 mg PO daily

Dexamethasone

Regulatory Status	Off-label
Target Population/ Criteria for Use	All patients requiring supplemental oxygen (low flow or high flow) or mechanical ventilation
Dose	6 mg IV/PO daily
Duration	Up to 10 days or until hospital discharge (whichever comes first)
Formulation(s)	Oral tablet, oral liquid IV push
Adverse Effects	Minimal with low-dose and short-term use
Monitoring	Blood glucose

Refractory Shock, ARDS, or Cytokine Release Syndrome (CRS)

Early initiation of low dose glucocorticoids have been recommended.

- Methylprednisolone 40 mg IV q8h x 7 days
- Dexamethasone 10 mg IV q12h x 5 days, then 10 mg daily x 5 days

To determine a patient's risk for developing CRS, the following chart may be used as guidance:

		Low Probability of CRS Benefit	**Moderate Probability of CRS Benefit**	**High Probability of CRS Benefit**
Timing	*Initiation*	**Late** (>10 days after decompensation)	**Mid-period** (5-10 days after decompensation)	**Early** (<5 days after decompensation)
	Duration	**Long** (>10 days)	**Moderate** (6-10 days)	**Short** (≤5 days)
Signs and symptoms	*Fever*	<37°C	37-38°C	>38°C
	Cough	No	Yes	-
	ALI	No ALI (P/F >300)	ALI (P/F 200-300)	ARDS (P/F <200)
	O_2	<4L NC	0.4-0.7	>0.7
	Vent	No	Variable	Yes
	CT/CXR	Minimal infiltrates	Patchy infiltrates (25-50%)	Diffuse infiltrates (>50%)
	Shock	No	No	Yes
Inflammatory Markers	*CRP*	<4	4-10	>10
	ESR	<50	50-70	>70
	Ferritin	<250	250-500	>500
	D-dimer	<1	1-3	>3
	Lymphocytes	>1000	750-1000	<750

Baricitinib

<table>
<tr><td>Regulatory Status</td><td>• Adults: FDA approved baricitinib for the treatment of COVID-19 in hospitalized adults and requiring supplemental oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation, or ECMO.
• Pediatrics: FDA Issued EUA for baricitinib to treat hospitalized pediatrics 2 years of age to 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)</td></tr>
<tr><td>Target Population/ Criteria for Use</td><td>Scientific evidence suggests potential benefit of baricitinib + remdesivir only in hospitalized patients requiring oxygen support, including MV

Recommended in addition to corticosteroids rather than receiving no baricitinib in hospitalized patients with severe COVID-19
• In patients unable to receive corticosteroids due to a contraindication, use baricitinib with remdesivir rather than remdesivir alone

Do not initiate therapy in patients with:
• ALC<200 cells/µL
• ANC<1,000 cells/µL
• Hgb<8 g/dL</td></tr>
<tr><td>Dose</td><td>4 mg PO daily</td></tr>
<tr><td>Renal Impairment</td><td><table><tr><th>eGFR</th><th>Dose</th></tr><tr><td>≥60 mL/min/1.73 m^2</td><td>4 mg once daily</td></tr><tr><td>30 to <60 mL/min/1.73 m^2</td><td>2 mg once daily</td></tr><tr><td>15 to <30 mL/min/1.73 m^2</td><td>1 mg once daily</td></tr><tr><td><15 mL/min/1.73 m^2 or dialysis</td><td>Not recommended</td></tr></table></td></tr>
<tr><td>Hepatic Impairment</td><td>Baricitinib has not been studied in patients with severe hepatic impairment. Baricitinib
should only be used in patients with severe hepatic impairment if the potential benefit
outweighs the potential risk.</td></tr>
<tr><td>Duration</td><td>Up to 14 days or until hospital discharge, whichever is first</td></tr>
<tr><td>Formulation(s)</td><td>Oral tablet; May be dispersed in water for administration via G tube or NG tube</td></tr>
<tr><td>Adverse Effects</td><td>• Serious infections
• Thrombosis
• Abnormal laboratory values (neutropenia, lymphopenia, anemia)
• Serious venous thrombosis including pulmonary embolism</td></tr>
<tr><td>Monitoring</td><td>Baseline: eGFR, LFTs, CBC

<table><tr><th>Laboratory Value</th><th>Dose Adjustment</th></tr><tr><td><u>Absolute lymphocyte count (ALC)</u>
≥200 cells/µL
<200 cells/µL</td><td>
Maintain dose
Consider interruption until ALC≥200 cells/µL</td></tr><tr><td><u>Absolute neutrophil count (ANC)</u>
≥500 cells/µL
<500 cells/µL</td><td>
Maintain dose
Consider interruption until ANC≥500 cells/µL</td></tr><tr><td><u>Aminotransferases (ALT or AST)</u></td><td>Interrupt baricitinib until the diagnosis of DILI is excluded</td></tr></table></td></tr>
</table>

	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	
Notes	• Avoid use of live vaccines • Do not use in pregnancy • Do not use in hemodialysis	

For additional information, refer to Baricitinib EUA Fact Sheet for Healthcare Providers.

Tofacitinib **Only to be used as a replacement for baricitinib based on inventory**

Regulatory Status	Off-label • The NIH guidelines, in addition to published literature, suggest tofacitinib may be used as an alternative to replace baricitinib based on available inventory. Currently, there is no FDA EUA for tofacitinib for COVID-19.
Target Population/ Criteria for Use	**Only to be used as a replacement for baricitinib based on inventory** Do not initiate therapy in patients with: • ALC<500 cells/µL • ANC<1,000 cells/µL • Hgb<9 g/dL
Dose	10 mg PO BID • Concomitant use with strong CYP3A4 inhibitor(s) or moderate CYP3A4 inhibitor(s) with strong CYP2C19 inhibitor(s) → reduce to 5 mg PO BID
Renal Impairment	**eGFR** / **Dose** Mild Impairment / No adjustment needed Moderate to Severe Impairment (eGFR <60 mL/min/1.73 m^2 / 5 mg PO BID Hemodialysis / 5 mg PO BID
Hepatic Impairment	Moderate - Reduce dose to 5 mg BID Severe - Avoid use
Duration	Up to 14 days or until hospital discharge, whichever is first
Formulation(s)	Oral tablet
Adverse Effects	• Serious infections • Thrombosis • Abnormal laboratory values (neutropenia, lymphopenia, anemia) • Serious venous thrombosis including pulmonary embolism • Cardiovascular events (acute MI)
Monitoring	Baseline: eGFR, LFTs, CBC **Laboratory Value** / **Dose Adjustment** Absolute lymphocyte count (ALC) <500 cells/µL / Discontinue therapy Absolute neutrophil count (ANC) ≥500 cells/µL to 1000 cells/µL / Reduce dose to 5 mg BID; may resume 10 mg BID if ANC remains >1000 cells/ µL <500 cells/ µL / Discontinue therapy Hemoglobin (Hgb) /

	Hgb decreases >2g/dL or if Hgb drops <8g/dL	Discontinue therapy
Notes	• Avoid use of live vaccines • Do not use in pregnancy • NIOSH Hazardous drug-proper gloving required for handling	

Tocilizumab

Regulatory Status	Adults: FDA approved tocilizumab in combination with corticosteroids for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Pediatrics: FDA issued EUA for tocilizumab in combination with corticosteroids for the treatment of COVID-19 in hospitalized pediatrics 2 years of age to <18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.
Target Population/ Criteria for Use	*Restricted to infectious diseases or critical care providers* For patients unable to tolerate oral baricitinib, tocilizumab may be used in addition to patients requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO, tocilizumab may be considered in cases of progressive hypoxemia while requiring low-flow oxygen with CRP≥75 mcg/mL after receiving corticosteroids for at least 24 hours. • Tocilizumab is not recommended for use in patients on low-flow oxygen with a stable clinical course. Not recommended to initiate in patients with: • ANC <1000/mm^3, Plts <50,000/mm^3, or ALT or AST >10xULN **Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection. Use of baricitinib in combination with tocilizumab is not recommended.**
Dose	8 mg/kg IV based on actual body weight, administered as a single IV dose (max. 800 mg/dose; round to the nearest vial size – 200 mg or 400 mg)
Duration	1-2 doses • If clinical signs/symptoms worsen or do not improve after the first dose, dose may be repeated once at least 8 hours after the initial infusion.
Formulation(s)	IV infusion (Subcutaneous injection is not permitted for COVID-19 indication per FDA approval and EUA)
Adverse Effects	• Serious infections ○ Caution: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including tocilizumab. Some studies have reported no difference in secondary infection rate while other studies have reported a higher prevalence of secondary infection in patients receiving tocilizumab compared with patients who received placebo. • Gastrointestinal perforations • Hepatotoxicity • Neutropenia • Anemia • Hypersensitivity
Monitoring	• LFTs, CBC • Hypersensitivity IL-6 Levels not routinely indicated: An increase in serum IL-6 levels is the expected physiologic response to treatment with tocilizumab. There is no role for

	monitoring of serum IL-6 levels to assess clinical response or to guide decision for a second tocilizumab dose. CRP level serves as a good indicator of the inflammatory status prior to and during tocilizumab treatment.
Notes	• Mortality benefit for tocilizumab has been demonstrated when administered in combination with corticosteroids. • Do not administer if patients have any other concurrent active infection, including localized infection.

For additional details, refer to Tocilizumab EUA Fact Sheet for Healthcare Providers

Sarilumab - **Only to be used as a replacement for baricitinib or tocilizumab based on inventory**

Regulatory Status	Off-label • The NIH guidelines, in addition to published literature, suggest sarilumab may be used as an alternative to replace tocilizumab based on available inventory. Currently, there is no FDA EUA for sarilumab for COVID-19.
Target Population/ Criteria for Use	*Restricted to infectious diseases or critical care providers* **Only to be used as a replacement for tocilizumab based on inventory** Do not initiate therapy in patients with: • ANC <2000 mm^3 • Plts <150,000 mm^3 • ALT or AST >1.5xULN
Dose	400 mg IV in 100 mL NS over 1 hour
Duration	1 dose
Formulation(s)	IV infusion; compound dose for IV infusion using two 200 mg prefilled syringes
Adverse Effects	• Serious infections • Gastrointestinal perforations • Hepatotoxicity • Neutropenia • Anemia • Hypersensitivity
Monitoring	• LFTs, CBC • Hypersensitivity
Notes	• To be given in combination with corticosteroids • Do not administer if patients have any other concurrent active infection, including localized infection.

Nirmatrelvir with ritonavir (Paxlovid)

<table>
<tr><td>Regulatory Status</td><td>• FDA approved EUA for the for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (≥12 years of age and weight ≥40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death</td></tr>
<tr><td>Target population/criteria for use</td><td>• Criteria for use: Nirmatrelvir/ritonavir may be used in patients admitted for reasons other than COVID-19 with mild to moderate disease and at high risk for progression to severe COVID-19 AND unable to tolerate remdesivir</td></tr>
<tr><td>Dose</td><td>• <u>Nirmatrelvir must be co-administered with ritonavir</u>
• Tablets should be swallowed whole and not chewed, broken, or crushed
<table>
<tr><th>eGFR</th><th>Dose</th></tr>
<tr><td>>60 mL/min</td><td>Nirmatrelvir 300 mg + ritonavir 100 mg PO BID</td></tr>
<tr><td><60 to ≥30 mL/min</td><td>Nirmatrelvir 150 mg + ritonavir 100 mg PO BID</td></tr>
<tr><td><30 mL/min</td><td>Not recommended</td></tr>
</table></td></tr>
<tr><td>Duration</td><td>5 days (10 doses total)
• If hospitalized <u>after starting treatment</u>, patients should complete the full 5-day treatment course per the healthcare provider's discretion.</td></tr>
<tr><td>Contraindications</td><td>• History of hypersensitivity to nirmatrelvir or ritonavir
• Co-administration of strong CYP3A4 substrates for which elevated concentrations are associate with serious and/or life-threatening reactions (Examples: amiodarone, dronedarone, flecainide, propafenone, colchicine, lurasidone, clozapine, lovastatin, simvastatin, sildenafil for PAH, oral midazolam)
• Co-administration with potent CYP3A4 inducers where significantly reduced nirmatrelvir or ritonavir concentrations may be associated with loss of virologic response or possible resistance (Examples: carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort)</td></tr>
<tr><td>Drug-drug Interactions and Concomitant Medications</td><td>***Significant interactions*** <u>Paxlovid Drug-Drug Interactions (nih.gov)</u>

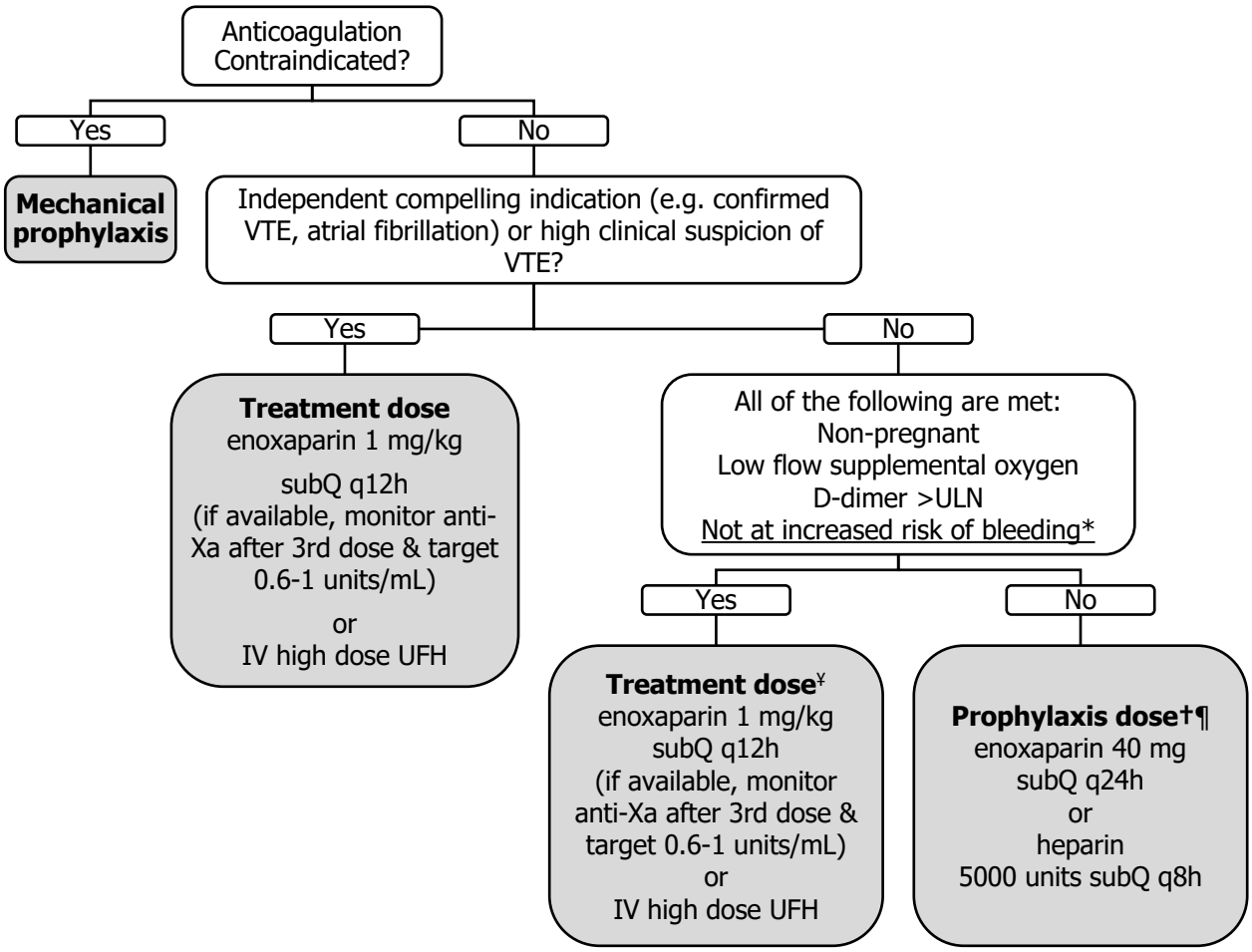
• Clinicians who are not experienced in prescribing ritonavir-boosted drugs should refer to resources such as <u>Fact sheet for ritonavir-boosted nirmatrelvir (Paxlovid)</u> and <u>Liverpool COVID-19 Drug Interactions</u> for additional guidance.
<u>Consultation with an expert (e.g., clinical pharmacist and/or specialist providers) should be considered.</u>
• CYP3A inhibition by ritonavir typically resolves 3-5 days after last dose
• Patients with HIV or hepatitis C virus taking ritonavir- or cobicistat-containing regimens should continue those regimens as indicated
• Patients taking certain concomitant HMG-CoA reductase inhibitors (atorvastatin, ezetimibe, Fluvastatin, pitavastain, pravastatin, rosuvastatin), ACE-inhibitors, or systemic or inhaled corticosteroids, NSAIDs, or acid suppressive therapy should not discontinue these medications unless warranted by their clinical condition</td></tr>
</table>

Renal Impairment	Moderate renal impairment: Dose adjustment Severe renal impairment: Not recommended
Hepatic Impairment	Severe hepatic impairment (Child-Pugh Class C): Not recommended
Monitoring	Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir
Adverse Effects	• Dysgeusia, diarrhea, hypertension, myalgia • Case reports have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment. The frequency, mechanism, and clinical implications are yet to be determined and there is currently no data on administering longer or second courses of nirmatrelvir with ritonavir.
Patient Education	Paxlovid Patient Fact Sheet (English)
Healthcare Provider References	Paxlovid Health Care Provider Fact Sheet
Notes	• May lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection Nirmatrelvir with ritonavir (Paxlovid) [continued] **Pregnancy:** • Adverse events were observed following exposure to nirmatrelvir in some embryo-fetal developmental toxicity studies. A pregnant rabbit study saw reduced fetal body weights; however, this occurred at exposures that were ~10x higher than the human dose. A full description of the data is available in section 8.1 of FACT SHEET FOR HEALTHCARE PROVIDERS: EUA FOR PAXLOVID • ACOG COVID FAQs - COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics | ACOG "Obstetric care clinicians may consider the use of the oral SARS-CoV-2 protease inhibitor for the treatment of non-hospitalized COVID-19 positive pregnant individuals with mild to moderate symptoms, particularly if one or more additional risk factors are present (eg BMI >25, CKD, DM, CV disease). Clinicians should weigh the available data against the individual risks of COVID-19 in pregnancy in each situation…The short-term exposure to these medications must be balanced against the maternal and fetal risks associated with untreated COVID-19 in pregnancy." • The Society for Maternal Fetal Medicine statement - Treatment.pdf "SMFM supports the use of Paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) for treatment of pregnant patients with COVID-19 who meet clinical qualifications. Any therapy that

	would otherwise be given should not be withheld specifically due to pregnancy or lactation.

Anticoagulation

***<u>**EARLY (first 24 hrs of hospital admission)**</u> initiation of prophylactic anticoagulation compared with no anticoagulation among patients admitted to hospital with COVID-19 was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events.
(*BMJ. 2021 Feb 11;372:n311. doi: 10.1136/bmj.n311.*)***



†Heparin preferred in AKI, dialysis, or when unable to reach anti-Xa targets with enoxaparin
¶Patients with BMI≥40, use enoxaparin 40 mg subQ q12h or heparin 7500 subQ q8h
*NIH defines increased bleeding risk based on published clinical trials as:
Platelets <50 x 10^9 g/L, Hgb <8 g/dL, need for dual antiplatelet therapy, known bleeding within the last 30 days requiring an emergency room visit or hospitalization, known history of a bleeding disorder, or an inherited or active acquired bleeding disorder

¥Based on the American Society of Hematology and NIH recommendations, clinicians should carefully assess benefits of higher intensity of anticoagulation against the risk for bleeding on a case-by-case basis. Patients in the clinical trials illustrating benefits with therapeutic anticoagulation utilized primarily LMWH, therefore LMWH is the preferred agent. One study (ACTION Trial) utilized rivaroxaban at therapeutic dose and did not illustrate benefit, therefore we follow NIH recommendations and recommend against using direct oral anticoagulants. Therapeutic anticoagulation should be continued for 14 days or until hospital discharge. If patient progresses to ICU level of care due to COVID-19, NIH guidelines recommend switching from therapeutic to prophylactic-dose anticoagulation unless a VTE is confirmed.

COVID-19 Convalescent Plasma (CCP)

CCP is available only under FDA emergency use authorization (EUA); however, current evidence and guidelines do not recommend the use of CCP in hospitalized patients. While the RECOVERY trial did not demonstrate a mortality benefit with CCP in hospitalized patients when compared to placebo, immunodeficient patients were not included and may still derive a benefit from this therapy. If, based on clinical judgement, a provider wishes to use CCP, patients must meet the EUA criteria for use and ordering physician must attest to the criteria. Per the FDA, this authorization is limited to use of **only** high titer plasma.

Guideline Recommendations for use of CCP in Hospitalized Patients with COVID-19:

- **NIH (Updated August 8, 2022):** There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma (CCP) in patients with COVID-19 who are immunocompromised. Some clinicians would consider the use of CCP in patients who, in their clinical judgment, have severe or progressive COVID-19 and an inadequate response to therapy. In these cases, clinicians should attempt to administer high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a similar SARS-CoV-2 variant as the patient.
- **IDSA (Updated April 7, 2021):** Among hospitalized patients with COVID-19, the panel suggest against the use of CCP.

AdventHealth Transfusion Consent must be obtained from the patient/LAR prior to CCP administration (following routine SOP). Nurse must give patient/LAR CCP fact sheet prior to CCP administration. Note: Availability of CCP is dependent upon collection and distribution of donated plasma from individuals who have recovered from COVID19 and may not be readily available.

Orlando Campus: If patient is being considered for enrollment in COVID-19 clinical trials, be aware that prior or concomitant use of convalescent plasma may exclude patient from participation. Contact clinical trial research coordinator for detailed information about restrictions with each clinical trial. **

Criteria for Use

1. Patients hospitalized with COVID-19, early in the disease course, and those with impaired humoral immunity
   a) FDA defines early course as **prior to** respiratory failure requiring mechanical ventilation
   b) Transfusions administered late in the course of COVID-19, defined as requiring intubation or mechanical ventilation, have not been associated with clinical benefit

Treatment Timing

1. As soon as possible, ideally within 3 days of admission or new oxygen requirement

Administration

1. Treatment with CCP consists of 1 unit of high titer plasma, approximately 200 mL given over 1 hour
2. Premedicate with acetaminophen 650 mg PO and diphenhydramine 50 mg PO 30 minutes prior to start of CCP. May repeat x1 if >12 hours from premedication administration and CCP transfusion not yet complete.

Monoclonal Antibodies - Inpatient

Bebtelovimab
As of 11/30/2022, bebtelovimab is no longer authorized for use in the U.S. due to the rising prevalence of Omicron subvariants, which bebtelovimab is not active against.

Tixagevimab/cilagavimab (Evusheld)
As of 1/26/2023, tixagevimab/cilgavimab (Evusheld) is no longer authorized for use in the U.S. due to the rising prevalence of SARS-CoV-2 subvariants and unlikely to be active.

Limitations of use based on geographic variant predominance

- Due to the predominance of the Omicron variant in the US (>99% of COVID-19 cases as of 1/18/22), **casirivimab/imdevimab and bamlanivimab/etesevimab are not authorized for use in the United States at this time**.
- In addition, as of 3/25/2022, the FDA announced the use of **sotrovimab** is no longer authorized for the treatment of COVID-19 in the US due to increases in the proportion of COVID-19 cases caused by the BA.2 variant.
- As of 11/30/2022, the FDA announced that bebtelovimab is no longer authorized for use in the U.S. as it is not expected to neutralize Omicron subvariants BQ.1 and BQ.1.1
- As of 1/26/2023, tixagevimab/cilgavimab (Evusheld) is no longer authorized for use in the U.S. due to the rising prevalence of SARS-CoV-2 subvariants and unlikely to be active

Refer to **AdventHealth Treatment Algorithm for Non-hospitalized Adults with COVID-19** for additional information about EUA requirements for each monoclonal antibody product.

Therapies NOT Recommended

Disclaimer: The Scientific Research Committee ensures timely review of emerging experimental therapies, therefore, off-label use of therapies with only published *in vitro* data should NOT be implemented until reviewed and sanctioned by this committee. The recommendations below are subject to change based on emerging data or drug shortage information.

The medications listed below have been reviewed, but due to lack of evidence, these medications are not currently recommended for the treatment of COVID-19.

- **ACE I/ARB**
  - The HFSA, ACC and AHA emphasize the lack of experimental or clinical data on these class of drugs in COVID-19 and recommend that patients currently taking these medications for known beneficial indications (HF, HTN, or ischemic heart disease, for example) be advised to continue. They advise against adding/removing beyond what would be done in standard practice and urge individualized treatment decisions based on patient's clinical presentation and hemodynamics.
- **Aviptadil**
  - Synthetic vasoactive intestinal peptide (VIP)
  - Mechanism:
    - Binds to receptors on alveolar type II (ATII) cells in the lung
    - ATII cells bind SARS-CoV-2 via their angiotensin-converting enzyme 2 receptors
  - VIP protects alveolar cells and the surrounding pulmonary epithelium by:
    - 1. Blocking cytokines
    - 2. Preventing apoptosis
    - 3. Upregulating surfactant production
  - Animal models of respiratory distress: potent anti-inflammatory and anti-cytokine activity
  - Clinical data are lacking to establish the potential benefits and risks associated with the use of aviptadil in patients with COVID-19
  - There is insufficient evidence to recommend the use of aviptadil for treatment of critical COVID-19 outside of a clinical trial at this time
  - Phase 2b/3 data
    - Aviptadil vs. placebo in patients treated with RDV or other approved/authorized therapies
    - Primary endpoint = Alive & free of respiratory failure at day 28
      - 2.8-fold increased odds of being alive and free of respiratory failure at day 28 (P=0.03)
      - 4-fold increased odds of surviving to 60 days (P=.006)
    - Patients on ventilators at time of randomization demonstrated 10-fold increased odds of survival (P=.03)
    - AEs = mild to moderate diarrhea, systemic hypotension
  - For more information on the Right to Try program, refer to Aviptadil Right to Try - NRx Pharmaceuticals
- **Azithromycin**
  - Based on current evidence demonstrating lack of benefit in preventing invasive mechanical ventilation or death in hospitalized patients, use of azithromycin for treatment of COVID-19 is not recommended.

- **Bamlanivimab/etesevimab and casirivimab/imdevimab**
  - Due to the predominance of the Omicron variant in the US (>99% of COVID-19 cases as of 1/18/22), casirivimab/imdevimab and bamlanivimab/etesevimab are no longer authorized or recommended for the treatment of COVID-19.
- **Colchicine**
  - Based on the results of a randomized trial in hospitalized patients with COVID-19 (RECOVERY), colchicine demonstrated no benefit with regards to 28-day mortality or any secondary outcomes; use of colchicine in hospitalized patients is not recommended.
- **Hydroxychloroquine or chloroquine**
  - Based on studies demonstrating harm and little clinical benefit, the use of hydroxychloroquine for the treatment of COVID-19 is NOT recommended outside of a clinical trial.
- **Ivermectin**
  - Current evidence for the benefit of ivermectin is weak and the results of two high-quality randomized controlled trials showed no evidence of benefit, thus ivermectin should not be used for the treatment of COVID-19. This recommendation will be periodically re-evaluated if new randomized controlled trials become available.
  - International COVID-19 Guidelines & Statements on the Use of Ivermectin for the Treatment of COVID-19:
    Merck Statement on Ivermectin use in COVID-19
    IDSA Guidelines for Treatment of COVID-19 - Ivermectin
    Statement on Ivermectin | COVID-19 Treatment Guidelines
- **Lopinavir/ritonavir**
  - Use of lopinavir/ritonavir is not recommended because of unfavorable pharmacodynamics and negative clinical trial data.
- **Micronutrients (Vitamin C and Zinc)**
  - Adjunctive use of micronutrients in COVID-19 patients beyond the recommended daily allowances for supplementation is not supported by scientific evidence.
  - If utilization is necessary for the treatment of nutritional deficiencies, a once daily dosing strategy should be employed.
- **NSAIDs**
  - There is no evidence for or against the management of fever with NSAIDs. Acetaminophen is preferred for management of fever, but each clinical scenario should be carefully evaluated.
- **Nebulized respiratory medications**
  - Nebulized respiratory medications should be avoided in non-intubated patients unless otherwise indicated in patients with bronchospasms to prevent the spread of the COVID-19. For COVID-19 negative non-intubated patients, nebulized respiratory medications are preferred over MDIs.
  - If indicated, inhalers (MDIs) with spacers are preferred for non-intubated patients.
  - If indicated, nebulized medications with a closed circuit may be used in intubated patients.
- **Tissue Plasminogen Activator (tPA)**
  - Widespread use of tPA in critically ill COVID-19 patients is not supported by the currently published studies and is not recommended.

References

1. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;24:013056.
2. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro: Cell Res. Mar;30(3):269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4.; 2020.
3. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929-36.
4. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020;368:m1086. doi: https://doi.org/10.1136/bmj.m1086 (Published 17 March 2020)
5. Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. International Journal of Antimicrobial Agents 2020;55:105923.
6. EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19. European Medicines Agency. https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19. Accessed 3/19/2020.
7. Cao R, Wang Y, Wen D et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18; DOI: 10.1056/NEJMoa2001282.
8. Gilead Sciences, Inc. Remdesivir (RDV; GS-5734) for the Treatment of Selected Coronavirus (CoV)Infection: Single Patient Protocol, 25 Feb 2020.
9. Gilead Sciences, Inc. Remdesivir (GS-5734TM) Investigator's Brochure. Ebola Virus Disease, Marburg Virus Disease, Corona Virus Disease. Edition 5. 21 Feb 2020.
10. Holshue ML, DeBolt C, Lindquist S, et.al. Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936.
11. Midgley CM, The COVID-19 Investigation Team. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Prepub ahead of print, 2020. DOI: https://doi.org/10.1101/2020.03.09.20032896doi. Accessed 18 Mar 2020 from https://www.medrxiv.org/content/10.1101/2020.03.09.20032896v1
12. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Medicine. 2020 Mar 20. DOI: 10.1007/s00134-020-06022-5
13. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 [published online ahead of print, 2020 Mar 10]. J Crit Care. 2020;S0883-9441(20)30390-7. doi:10.1016/j.jcrc.2020.03.005
14. Erin K McCreary, PharmD, BCPS, BCIDP, Jason M Pogue, PharmD, BCPS, BCIDP, on behalf of the Society of Infectious Diseases Pharmacists, COVID-19 Treatment: A Review of Early and Emerging Options, Open Forum Infectious Diseases, ofaa105, https://doi.org/10.1093/ofid/ofaa105
15. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents.2020 Mar 17. DOI: 10.1016/j.ijantimicag.2020.105949
16. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet (London, England). 2020;395(10225):683-684.
17. National Health Commission (NHC) of the People's Republic of China. The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection 7th Edition, published March 3rd, 2020. Translated to English. http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm.
18. Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treated adult patients hospitalized with mild/moderate COVID-19 (ELACOI). medRxiv. 2020 March 28. https://www.medrxiv.org/content/10.1101/2020.03.19.20038984v1
19. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf. Accessed March 30, 2020.
20. Wu C, X Chen, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13. doi: 10.1001/jamainternmed.2020.0994. [Epub ahead of print]
21. FDA guidance for use of hydroxychloroquine for COVID-19. Available at https://www.fda.gov/media/136537/download. Accessed 4/13/2020
22. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. Mayo Clinic Proceedings. 2020 Mar 25. https://doi.org/10.1016/j.mayocp.2020.03.024
23. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 infection. IDSA. 2020 Apr 11. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 4/12/2020
24. Iba T, Levy JH, Warkentin TE, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989–1994.
25. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis [published online ahead of print, 2020 Mar 13]. Clin Chim Acta. 2020;506:145–148.
26. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–847.

27. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054–1062.
28. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497–506.
29. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy [published online ahead of print, 2020 Mar 27]. J Thromb Haemost. 2020;10.1111/jth.14817.
30. Lin N, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection – a review of immune changes in patients with viral pneumonia. EmergMicrobes Infect. 2020.
31. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathies in COVID-19. J Thromb Haemost. 2020;10.1111/JTH.14810.
32. Akay O. The double hazard of bleeding and thrombosis in hemostasis from a clinical point of view: A global assessment by Rotational Thromboelasotmetry (ROTEM). Clinical and Applied Thrombosis/Hemostasis 2018; 24(6); 850-8
33. Hincker A et al. Rotational thromboelastometry predicts thromboembolic complications after major non-cardiac surgery. Critical Care 2014; 18: 549-56
34. Thorson C et al. Pre-existing hypercoagulability in patients undergoing potential curative cancer resection. Surgery 2014; 155: 134-44
35. Harahsheh Y et al. Use of viscoelastic tests to predict clinical thromboembolic events: a systematic review and meta-analysis. Eur J Haematol. 2018; 100: 113-23
36. Davies N.A et al. Application of ROTEM to assess hypercoagulability in patients with lung cancer. Thrombosis Research 2015; 135: 1075-80
37. Chelbowski M.C et al. Clinical controversies in anticoagulation monitoring and antithrombin supplementation for ECMO. Critical Care 2020; 24: 19-30
38. Gorton et al. Which TEG variable for monitoring low molecular weight heparin? Anesthesiology 1999; 90: A36
39. Schott U et al. Thromboelastometry versus free-oscillation rheometry and enoxaparin versus tinzaparin: an in-vitro study comparing two viscoelastic haemostatic tests' dose-responses to two low molecular weight heparins at the time of withdrawing epidural catethers from major surgery. BMC Anesthesiology 2015; 15: 170-80
40. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Medicine. 2020 Mar 28. https://doi.org/10.1007/s00134-020-06022-5
41. World Health Organization, Clinical Management of Severe Acute Respiratory Infecting when Novel Coronavirus (nCoV) Infection is Suspected. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratoryinfection-
42. when-novel-coronavirus-(nCoV)-infection-is-suspected. Accessed 4/8/2020
43. Centers for Disease Control and Prevention. Healthcare professionals: frequently asked questions and answers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/fac.html. Accessed April 7, 2020.
44. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduction and Targeted Therapy. 2020 Feb 21. https://doi.org/10.1038/s41392-020-0127-9
45. Zheng C, Want J, Guo H, et al. Risk-adapted treatment strategy for COVID-19 patients. International Journal of Infectious Diseases. 2020 Mar 23. https://doi.org/10.1016/j.ijid.2020.03.047
46. Zhou F, Yu, T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 9. https://doi.org/10.1016/S0140-6736(20)30566-3
47. NCCN Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2020.
48. Grein J, Ohmagari N, Shin D, Diaz G, et al. Compassionate use of remdesivir for patients with severe COVID-19. NEJM. 2020 Apr 23. doi:10.1056/NEJMoa2007016
49. Mahevas M, Tran V, Roumier M, Charbrol A, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medRxiv preprint. https://doi.org/10.1101/2020.04.10.20060699
50. Lane J, Weaver J, Kostka K, Duarte-Salles T, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of wide-spread use for COVID-19: a multi-national, network cohort and self-controlled case series study. medRxiv preprint. https://doi.org/10/1101/2020.04.09.20054551
51. Xue J, Moyer A, Beng P, Wu J, Hannafon B, Ding WQ. Chloroquine is a zinc inophore. Plos One. 2014;9(10): e109180
52. NIH COVID-19 treatment guidelines. NIH. Available at: https://covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/. Accessed 4/22/2020
53. Ji, H. L., Zhao, R., Matalon, S., & Matthay, M. A. (2020). Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility. Physiol Rev, 100(3), 1065-1075. doi:10.1152/physrev.00013.2020
54. Poor, H. D., Ventetuolo, C. E., Tolbert, T., Chun, G., Serrao, G., Zeidman, A, Powell, C. A. (2020). COVID-19 Critical Illness Pathophysiology Driven by Diffuse Pulmonary Thrombi and Pulmonary Endothelial Dysfunction Responsive to Thrombolysis. doi:10.1101/2020.04.17.20057125
55. Wang, J., Hajizadeh, N., Moore, E. E., McIntyre, R. C., Moore, P. K., Veress, L. A., Barrett, C. D. (2020). Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series. J Thromb Haemost. doi:10.1111/jth.14828
56. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed May 13, 2020.
57. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. medRxiv preprint doi: doi.org/10.1101/2020.05.12.20099879

58. Mayo Clinic IRB. Expanded access to convalescent plasma for the treatment of patients with COVID-19. Available at: https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf. Accessed 5/18/2020.
59. Goldman JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. NEJM. 2020 doi: 10.1056/NEJM/Moa2015301
60. University of Oxford. RECOVERY trial: randomized evaluation of COVID-19 therapy. Available at: https://www.recoverytrial.net/. Accessed 6/17/2020.
61. Arshad A, Kilgor P, Chaudhry Z, et al. Treatment with hydroxychloroquine, azithromycin and in combination for patients hospitalized with COVID-19. Int J Infect Dis. June 29, 2020. https://doi.org/10.1016/j.ijid.2020.06.099
62. Davis M, McCreary E, Pogue J. That escalated quickly: remdesivir's place in therapy for COVID-19. Infect Dis Ther. June 9, 2020. https://doi.org/10.1007/s40121-020-00318-1
63. Jorgensen S, Kebriaei R, Dresser LD, et al. Remdesivir: review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. Pharmacotherapy. doi: 10.1002/phar.2429.
64. Remdesivir. COVID-19 Treatment Guidelines. NIH. July 24, 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/
65. Corticosteroids. COVID-19 Treatment Guidelines. NIH. July 30, 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/
66. Olender S, Perez K, Balani B, et al. Remdesivir for severe covid-19 versus cohort receiving standard of care. Clin Infect Dis. July 24, 2020. https://doi.org/10.1093/cid/ciaa1041
67. U.S. Food and Drug Administration. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in admiinistration's fight against pandemic. August 23, 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment
68. Spinner C, Gottlieb RL, Criner GL, et al. Effect of remdesivir vs standard of care on clinical status at 11 days in patients with moderate COVID-19: a randomized controlled trial. JAMA. 2020. Available at: https://jamanetwork.com/journals/jama/fullarticle/2769871
69. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19-Final report. NEJM. 2020 DOI: 10.1056/NEJMoa2007764
70. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19-interim WHO solidarity results. medRxiv. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1
71. Stone JH, Frigault MJ, Serling-Boyd, NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. NEJM. 2020. DOI: 10.1056/NEJMoa2028836
72. Chen P, Nirula A, Heller B, et al; BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849. Epub ahead of print.
73. COVID-19 Treatment Guidelines Panel. The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19 National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua/
74. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 infection. IDSA. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, Accessed 11.19.2020
75. Baricitinib Emergency Use Authorization. Lilly.com. November 24, 2020. Available at: https://www.covid19.lilly.com/baricitinib/hcp?utm_source=Baricitinibemergencyuse.com&utm_medium=redirect&utm_campaign=2020_covid19lilly_redirect
76. Adaptive COVID-19 Treatment Trial 2 (ACTT-2)-Baricitinib. ClinicalTrials.gov. November 24, 2020. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04401579
77. Casirivimab and Imdevimab. Emergency Use Authorization. Available at: Casirivimab and Imdevimab (regeneron.com)
78. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19 [published online ahead of print, 2020 Dec 11]. *N Engl J Med*. 2020;NEJMoa2031994. doi:10.1056/NEJMoa2031994.
79. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results [published online ahead of print, 2020 Dec 2]. *N Engl J Med*. 2020;NEJMoa2023184. doi:10.1056/NEJMoa2023184
80. Tardif, JC, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. medRxiv. 2021. Available at: Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19 | medRxiv
81. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2020.
82. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *Journal of the American College of Cardiology*. 2020;In press.
83. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized Phase II clinical trial (HESACOVID). Thromb Res. 2020;196:359-366.
84. Antithrombotic Therapy in Patients With COVID-19. Available at: https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/. Accessed February 23, 2021.
85. ATTACC, ACTIV-4a & REMAP-CAP multiplatform RCT- Results of Interim Analysis. Available at: https://www.attacc.org/presentations. Accessed February 23, 2021.
86. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021;5(3):872-888.
87. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of vte in patients with coronavirus disease 2019: chest guideline and expert panel report. Chest. 2020;158(3):1143-1163.
88. WHO COVID-19 Clinical management living guidance. January 25, 2021.

89. Billett HH, Reyes-Gil M, Szymanski J, et al. Anticoagulation in covid-19: effect of enoxaparin, heparin, and apixaban on mortality. Thromb Haemost. 2020;120(12):1691-1699.
90. Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. Am J Hematol. Published online January 21, 2021.
91. Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: A retrospective propensity score-weighted analysis. Eur J Haematol. 2021;106(2):165-174.
92. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ*. 2021;372:n311. Published 2021 Feb 11. doi:10.1136/bmj.n311
93. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Gallagher J, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.3.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 8 June 2021.
94. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8 June 2021.
95. Kaka AS, MacDonald R, Greer N, et al. Major Update: Remdesivir for Adults With COVID-19 : A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points [published correction appears in Ann Intern Med. 2021 Mar 16;:]. *Ann Intern Med*. 2021;174(5):663-672. doi:10.7326/M20-8148
96. Marconi V, Ramanan A, de Bono S, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. *medRxiv* 2021.04.30.21255934; doi: https://doi.org/10.1101/2021.04.30.21255934
97. Actemra. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Actemra (tocilizumab). Genentech Inc; 2021.
98. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-1645. doi:10.1016/S0140-6736(21)00676-0
99. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis [published online ahead of print, 2021 Jul 6]. JAMA. 2021;e2111330. doi:10.1001/jama.2021.11330
100. Veklury. Package insert. Gilead Sciences, Inc; 2021.
101. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 June 2021. 11 June 2021. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-7-10-june-2021
102. Touafchia A, Bagheri H, Carrié D, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns [published online ahead of print, 2021 Feb 27]. *Clin Microbiol Infect*. 2021;27(5):791.e5-791.e8. doi:10.1016/j.cmi.2021.02.013
103. Pallotto C, Blanc P, Esperti S, et al. Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19) [published online ahead of print, 2021 May 28]. *J Infect*. 2021;S0163-4453(21)00267-X. doi:10.1016/j.jinf.2021.05.025
104. Gubitosa JC, Kakar P, Gerula C, et al. Marked Sinus Bradycardia Associated With Remdesivir in COVID-19: A Case and Literature Review. *JACC Case Rep*. 2020;2(14):2260-2264. doi:10.1016/j.jaccas.2020.08.025
105. Jacinto JP, Patel M, Goh J, Yamamura K. Remdesivir-induced Symptomatic Bradycardia in the treatment of COVID-19 Disease [published online ahead of print, 2021 May 15]. *HeartRhythm Case Rep*. 2021;10.1016/j.hrcr.2021.05.004. doi:10.1016/j.hrcr.2021.05.004
106. Barkas F, Styla CP, Bechlioulis A, Milionis H, Liberopoulos E. Sinus Bradycardia Associated with Remdesivir Treatment in COVID-19: A Case Report and Literature Review. *J Cardiovasc Dev Dis*. 2021;8(2):18. Published 2021 Feb 12. doi:10.3390/jcdd8020018
107. O'Brien MP, Forleo-Neto BJ, Musser FI, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. NEJM. 2021. DOI: 10.1056/NEJMoa2109682
108. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802. doi:10.1056/NEJMoa2105911
109. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789. doi:10.1056/NEJMoa2103417
110. Lopes RD, de Barros E Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263. doi:10.1016/S0140-6736(21)01203-4
111. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial [published correction appears in JAMA Intern Med. 2021 Dec 28;:]. *JAMA Intern Med*. 2021;181(12):1612-1620. doi:10.1001/jamainternmed.2021.6203
112. COVID-19 and VTE/Anticoagulation: Frequently Asked Questions. Available at: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation. Accessed November 9, 2021.
113. Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. *Am J Hematol*. 2021;96(4):471-479. doi:10.1002/ajh.26102
114. NRx Pharmaceuticals Announces Expansion of ZYESAMI® (aviptadil) US Expanded Access and Right to Try Programs for Patients with COVID-19 Respiratory Failure who have Exhausted All Approved Treatments - NRx Pharmaceuticals

Summary of Revisions

- 03/15/2020
  - General treatment options, dosing, and monitoring
- 03/19/2020
  - Testing guidance for asymptomatic and symptomatic patients
  - Added therapeutic options based on severity using scale and laboratory monitoring for patients with COVID-19
  - Updated dosing for hydroxychloroquine
  - Corticosteroids: use of steroids in patients with severe disease could be considered as part of the supportive care regimen for *patients with ARDS on a case-by-case basis*
  - ACEi/ARB: advised against adding/removing beyond in standard practice
  - NSAIDs: no evidence for against the management of fever with NSAIDs
  - Guidance for use of nebulized respiratory medications
  - Removed chloroquine, ribavirin, atazanavir/ritonavir, atazanavir/cobicistat, darunavir/cobicistat
  - Added Tocilizumab
  - Post-exposure prophylaxis for patients and health care workers
- 03/21/2020
  - Added: Discharge patients should be offered supportive care (anti-pyretics, MDI, etc.)
- 03/25/2020
  - Updated treatment options based on severity score:
    - Severity score 1: removed hydroxychloroquine, lopinavir/ritonavir, darunavir/ritonavir
    - Severity score 2-3: no change
    - Severity score ≥ 4: Remdesivir for eligible patients first, if not: hydroxychloroquine. Removed combination of hydroxychloroquine plus lopinavir/ritonavir or darunavir/ritonavir
  - Lower dose glucocorticoids (equivalent to methylprednisolone 1-2 mg/kg/day for 3-5 days or ≤0.5-1 mg/kg/day methylprednisolone for ≤ 7 days) have been recommended after *careful consideration of risks and benefits.*
  - Azithromycin: insufficient evidence to recommend the use of azithromycin in addition to hydroxychloroquine
  - ECG monitoring at baseline for all hospitalized patients
- 03/31/2020
  - Revised the duration of treatment
    - Severity score: 2-3: changed from 10 days to 5-7 days
    - Severity score ≥ 4: changed from 10-14 days to 7-10 days
  - Corticosteroids: early initiation of lower dose glucocorticoids (equivalent to methylprednisolone 1-2 mg/kg/day for 3-5 days or ≤0.5-1 mg/kg/day methylprednisolone for ≤ 7 days) have been recommended for *patients with refractory shock and/or ARDS*
  - Removed darunavir/ritonavir
  - Added Sarilumab with criteria for use
- 04/15/2020
  - Added: statement regarding use of off-label experimental therapies with only *in vitro* data
  - Added recommendation against use of ivermectin
  - Added anticoagulation pathway
  - Added guidance on cardiac monitoring
  - Added additional steroid guidance and chart with risk factors for CRS
  - Added restriction to ID for lopinavir/ritonavir
  - Revised daily monitoring parameters
- 04/20/2020
  - Added statement regarding use of micronutrients, Zinc and Vitamin C
- 04/27/2020
  - Removed lopinavir/ritonavir from algorithm
  - Added comment regarding use of hydroxychloroquine
  - Updated remdesivir information for compassionate use
- 04/29/2020
  - Updated anticoagulation algorithm, removal of ROTEM
  - Added statement regarding use of tPA
- 05/12/2020
  - Removed hydroxychloroquine from algorithm
- 05/18/2020
  - Added guidance for outpatient anticoagulation
  - Removed cardiac monitoring for patients receiving hydroxychloroquine
  - Removed statement regarding empiric initiation of experimental/investigational therapies for severity score ≥ 4
  - Included information on remdesivir emergency use authorization
  - Included information on convalescent plasma
- 05/26/2020
  - Clarification of outpatient anticoagulation recommendations
- 06/04/2020
  - Updated allocation information on remdesivir
- 06/09/2020

- Updated DOH link to request remdesivir for State of Florida (outside of CFDS)
- 06/18/2020
  - Addition of low-dose dexamethasone recommendation
  - Removal of remdesivir compassionate use information
  - Edited remdesivir allocation information
- 06/30/2020
  - Added warning against use of hydroxychloroquine
  - Modified IL6 antagonist recommendation to include use for severity score ≥ 2
  - Updated remdesivir access process
- 07/03/2020
  - Removal of sarilumab from algorithm
  - Updated tocilizumab recommendation to include use for severity score ≥ 3
- 07/14/2020
  - Modified remdesivir criteria for use
- 08/05/2020
  - Revised remdesivir criteria for use
  - Updated multi-state convalescent plasma inclusion criteria
  - Removal of HERO study details as trial has stopped enrollment
  - Addition of statement regarding insufficient data on use of tocilizumab
- 08/25/2020
  - Updated convalescent plasma criteria based on FDA's EUA announcement
- 09/03/2020
  - Updated verbiage regarding remdesivir criteria for use
- 10/27/2020
  - Updated remdesivir information to reflect changes in regulatory requirements based on FDA approval of remdesivir on 10/22/20
  - Removed tocilizumab and recommended against routine use
- 11/12/2020
  - Added bamlanivimab
- 11/19/2020
  - Added NIH and IDSA recommendations and references for use of bamlanivimab in outpatients
- 11/24/2020
  - Reviewed available data and EUA information on baricitinib
- 12/3/2020
  - Added casirivimab/imdevimab
- 12/22/2020
  - Revised language regarding baricitinib
- 01/07/2021
  - Updated verbiage regarding use of ivermectin
- 01/12/2021
  - Added tocilizumab back into treatment algorithm
- 02/04/2021
  - Included information on colchicine for non-hospitalized patients
- 02/09/2021
  - Modified tocilizumab recommendation to include only patients with severity score ≥3
  - Updated convalescent plasma EUA criteria
- 02/11/2021
  - Updated EUA information on convalescent plasma
  - Added EUA information for bamlanivimab/etesevimab combination
  - Added additional links to ivermectin
- 02/18/2021
  - Updated information on convalescent plasma severity score recommendations based on EUA
- 03/02/2021
  - Updated inpatient and outpatient anticoagulation algorithm
- 03/10/2021
  - Added additional study evaluating ivermectin
  - Updated information and recommendations on MABs
- 03/25/2021
  - Updated criteria for use for remdesivir to include option to use in patients on high flow oxygen
  - Updated information and recommendations on MABs
- 04/20/2021
  - Updated guideline recommendations on MABs
  - Included FDA EUA updates and information on the revoked EUA for bamlanivimab monotherapy
- 05/03/2021
  - Updated tocilizumab criteria to reflect provider restrictions
- 05/25/2021
  - Updated EUA requirements for MABs

- 05/27/2021
  - Updated bamlanivimab-etesevimab information on distribution to the state of Florida
- 06/03/2021
  - Modified recommendation for use of COVID-19 convalescent plasma
- 06/07/2021
  - Updated FDA EUA information for casirivimab/imdevimab: new dosing and route of administration
- 06/15/2021
  - Clarified language regarding scientific basis for avoiding routine use of remdesivir in patients on room air or mechanical ventilation
  - Removed statement about insufficient data for baricitinib and the warning against use of baricitinib with corticosteroids
  - Updated FDA EUA information for new MAB, Sotrovimab
- 06/25/2021
  - Updated information regarding distribution of bamlanivimab-etesevimab in the U.S.
- 07/13/2021
  - Updated tocilizumab to reflect EUA and results of the RECOVERY trial
- 07/29/2021
  - Added bradycardia and hypotension to Adverse Effects for remdesivir
  - Updated baricitinib information to reflect update to EUA
- 08/05/2021
  - Updated EUA criteria for casirivimab-imdevimab for use in post-exposure prophylaxis
  - Added guidance on utility of IL6 levels
- 08/17/2021
  - Updated recommendations on use of colchicine in non-hospitalized patients and addressed inpatient use
  - Updated ivermectin studies-no change to overall recommendation for use
  - Updated baricitinib drug information to warn against initiation for low ALC, ANC, or Hgb
- 08/24/2021
  - Edited information on baricitinib labs for imitation of therapy (ALC <200 cells/µL instead of <500 cells/µL)
- 08/30/2021
  - Edited information to include tofacitinib and sarilumab as alternatives to baricitinib and tocilizumab in cases of supply issue
- 10/04/2021
  - Updated monoclonal antibody information to reflect renewed availability of bamlanivimab/etesevimab and to incorporate post-exposure prophylaxis
- 11/16/2021
  - Edited inpatient anticoagulation algorithm
  - Added chart on preferred outpatient therapies
  - Added information on fluvoxamine
- 12/17/2021
  - Edited EUA information for bamlanivimab/etesevimab for use in individuals of any age
  - Added EUA information for tixagevimab/cilgavimab (Evusheld) for use as pre-exposure prophylaxis in certain adult and pediatric patients
- 01/20/2022
  - Rename as AH Treatment Algorithm for Hospitalized Adults
  - Remove all non-hospitalized or outpatient treatment
  - Remove bamlanivimab/etesevimab and casirivimab/imdevimab from recommended therapies due to predominance of Omicron variant in the US
- 01/25/2022
  - Updated mAb section to state that bamlanivimab/etesevimab and casirivimab/imdevimab no longer authorized for use
- 01/27/2022
  - Removed intermediate anticoagulation for D-dimer≥5
  - Revised criteria for therapeutic anticoagulation in patients on low flow supplemental oxygen
- 3/1/2022
  - Updated therapies not recommended to include avipdatil
  - Editing monoclonal antibody information to include bebtelovimab
- 4/6/2022
  - Removed sotrovimab information based on BA.2 subvariant and updated EUA
  - Edited tixagevimab/cilgavimab dosing to match updated EUA
  - Edited information on ivermectin
- 6/8/2022
  - Edited information on baricitinib to reflect FDA approval for COVID-19 in hospitalized adults
- 9/16/2022
  - Edited tixagevimab/cilgavimab treatment guidelines to match with updated EUA
  - Edited baricitinib treatment guidelines to match with updated IDSA guidelines

- Modified recommendation for use of COVID-19 convalescent plasma
- 12/02/2022
  - Edited information on the use of tixagevimab plus cilgavimab in the setting of increased prevalence of circulating Omicron subvariants
  - Removed bebtelovimab from algorithm as no longer authorized for treatment in the U.S.
- 01/26/2023
  - Edited information on tixagevimab/cilgavimab as it is no longer authorized for treatment in the U.S.
  - Edited information on tocilizumab to incorporate FDA approval for adult patients hospitalized for COVID-19

From: COVID-19 Scientific Research Committee

To: COVID-19 Pandemic Response Team

Dear Committee:

The Scientific Research Committee (SRC) was asked to review literature surrounding therapeutic treatment of COVID-19 in adult patients. As a committee, we believe the documented algorithm is thought to be the most up to date, comprehensive and scientifically current treatment algorithm. The committee supports the adaptation of the algorithm prepared and approved by the Chief Medical Officer approval board.

Sincerely,

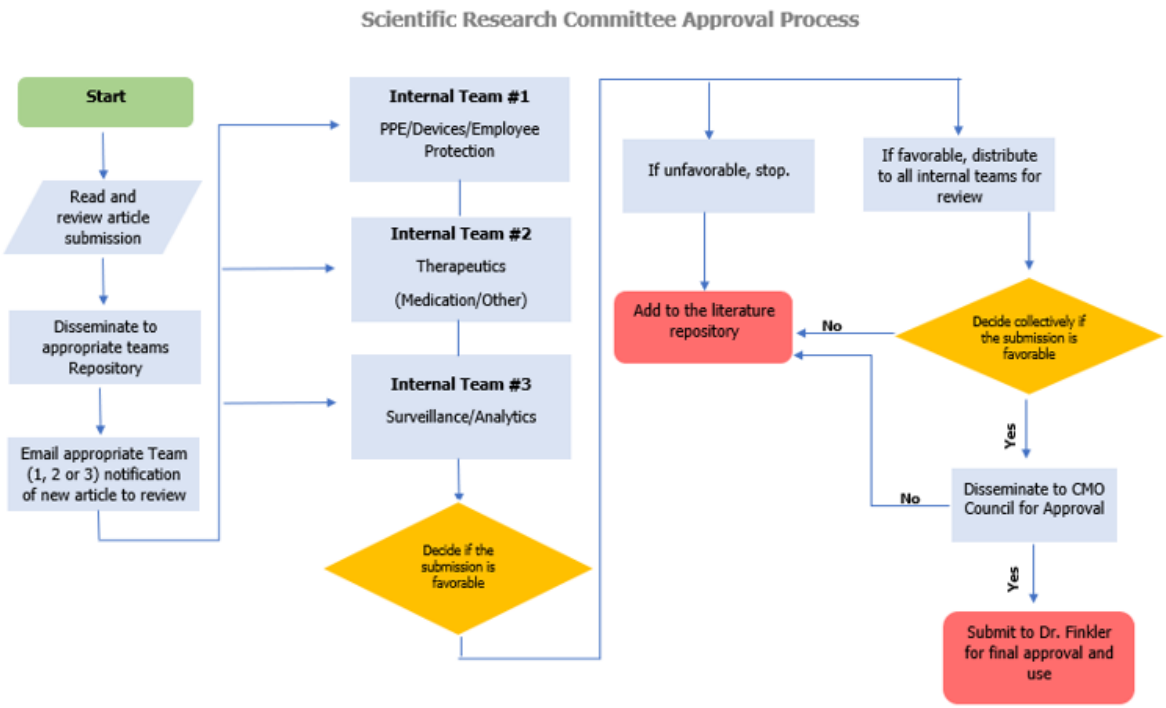
COVID-19 Scientific Committee

Alric Simmonds, MD, Chair
Ariel Watson, OTR/L, CAPM, Project Manager
Nancy Aldrich, MLIS
Atalie Ashley-West, PhD, MPH, CPH
Fortune Alabi, MD
Rohit Bhatheja, MD
Amy Carr, PharmD, BCIDP
Cherie Danielson, BS
Benita David, DBA
Sarah Minor, PharmD, MHA, BCPS
Alberto Monreal, MD
Okorie, Okorie, MD
Amay Parikh, MD
Richard Pratley, MD
Steve Smith, MD
Jason Sniffen, DO
J. Michael Yurso, MD

Chief Medical Officers

Neil Finkler, MD
Miles Bennett, DO
Dennis deLeon, MD
David Goldman, DO
Victor Herrera, MD
Darin Jordan, MD
Michael Keating, MD
Jennifer Keehbauch, MD
Mark Kilman, MD
Steve Knych, MD
Omayra Mansfield, MD
Sanjay Pattani, MD
Jason Porter, MD
Floriano Putigna, DO
Thomas Scoggins, MD
David Sinclair, MD
Alric Simmonds Jr., MD
Joe Smith, MD

Disclaimer: The Scientific Committee was formed under the Medical Management Branch of the COVID-19 Pandemic Response Team. The committee's goal is to create a repository, interrogate research literature as it pertains to the treatment of COVID-19 and provides a rapid approval process. The algorithm below is the decision-making process that governs our decisions.



Dr. Neil Finkler	Chief Clinical Officer, CFD	Dr. Jennifer Keehbaugh	Winter Park
Dr. David Sinclair	Altamonte	Dr. Dennis DeLeon	Kissimmee
Dr. Omayra Mansfield	Apopka	Dr. Joe Smith	DeLand
Dr. Alric Simmonds Jr.	Celebration	Dr. David Goldman	New Smyrna
Dr. Sanjay Pattani	Mission Control	Dr. Darin Jordan	FH Health Care Partners
Dr. Jason Porter	East Orlando	Dr. Mark Kilman	AH Palm Coast
Dr. Victor Herrera	Orlando	Dr. Steven Knych	Fish
Dr. Michael Keating	Children's	Dr. Floriano Putigna	Waterman
Dr. Sasha Grek	Heart of Florida / Lake Wales	Dr. Thomas Scoggins	DeLand
Dr. Miles Bennett	Winter Garden		