

AdventHealth Treatment Algorithm for Hospitalized Adults with COVID-19

Last Update: 02/09/2023

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

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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
 - o RR>22 on 6L
 - o 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	 <u>Corticosteroids</u> + <u>Baricitinib</u> (or tofacitinib) if able to tolerate PO OR <u>Tocilizumab</u> (or <u>sarilumab</u>*)

^{*}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.

⁴Because 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/	SRC Criteria for Use:
Criteria for Use	Based on available scientific evidence, the Scientific Research Committee
Criteria for USE	·
	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 <u>not</u> 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
Burucion	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
Renai Impairment	"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	,
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
	Trypotension
Monitoring	HR, LFTs, renal function
	Infusion related reaction (nausea, vomiting, diaphoresis, shaking)
Notes	Risk of reduced antiviral activity when co-administered with chloroquine or
INUCES	· · · · · · · · · · · · · · · · · · ·
	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,
	on year or are on room any bac are at high his for allocase progression,



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

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/	All patients requiring supplemental oxygen (low flow or high flow) or
Criteria for Use	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
		Late	Mid-period	Early
	Initiation	(>10 days after	(5-10 days after	(<5 days after
Timing		decompensation)	decompensation)	decompensation)
	Duration	Long (>10 days)	Moderate (6-10 days)	Short (≤5 days)
	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)
Signs and	<i>O</i> ₂	<4L NC	0.4-0.7	>0.7
symptoms	Vent	No	Variable	Yes
	CT/CVP	CT/CXR Minimal infiltrates	Patchy infiltrates	Diffuse infiltrates
	CI/CAK		(25-50%)	(>50%)
	Shock	No	No	Yes
	CRP	<4	4-10	>10
	ESR	<50	50-70	>70
Inflammato	Ferritin	<250	250-500	>500
ry Markers	D-dimer	<1	1-3	>3
	Lymphocyt es	>1000	750-1000	<750



Baricitinib

Regulatory Status	 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		
Target Population/	(ECMO) Scientific evidence suggests note	ntial her	nefit of baricitinib + remdesivir only in
Criteria for Use	hospitalized patients requiring ox		<u> </u>
	hospitalized patients with severe • In patients unable to rec	COVID- eive cor	ids rather than receiving no baricitinib in 19 ticosteroids due to a contraindication, ther than remdesivir alone
	Do not initiate therapy in patients	- with:	
	ALC<200 cells/µL	o vvicii.	
	ANC<500 cells/µL		
Dose	4 mg PO daily		
Renal Impairment	eGFR		Dose
	≥60 mL/min/1.73 m ²		4 mg once daily
	30 to <60 mL/min/1.73 m ²		2 mg once daily
	15 to <30 mL/min/1.73 m ²		1 mg once daily
	<15 mL/min/1.73 m ² or dialysis		Not recommended
Hepatic	Baricitinib has not been studied in patients with severe hepatic impairment.		ts with severe hepatic impairment.
Impairment	Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit		
	outweighs the potential risk.		
Duration	Up to 14 days or until hospital dis	scharge,	whichever is first
Formulation(s)			r administration via G tube or NG tube
Adverse Effects	Serious infections		
	Thrombosis	_	
	Abnormal laboratory values (
Manikaniaa	Serious venous thrombosis including pulmonary embolism		
Monitoring	Baseline: eGFR, LFTs, CBC		
	Laboratory Value	Dose	Adjustment
	Absolute lymphocyte count		
	(ALC)	Mainta	ain dose
	≥200 cells/µL	Consid	ler interruption until ALC≥200 cells/µL
	<200 cells/μL		
	Absolute neutrophil count		
	(ANC)		ain dose
	≥500 cells/µL	Consid	der interruption until ANC≥500 cells/µL
	<500 cells/µL	-	
	Aminotransferases (ALT or AST)	Interro	upt baricitinib until the diagnosis of DILI



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

For additional information, refer to <u>Baricitinib EUA Fact Sheet for Healthcare Providers</u>.

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

	_			
Regulatory Status	Off-label	Little of the control		
	The NIH guidelines, in addition to published literature, suggest tofacitinib may be used as an alternative to replace baricitinib based on available			
	inventory.	nace daricitinid dased on available		
	Currently, there is no FDA EUA for to	sfacitinih for COVID-10		
Target Population/	*Only to be used as a replacement for b			
Criteria for Use	Only to be used as a replacement for b	ancicinib basea on inventory		
Criteria for osc	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) with strong CYP2C19 inh			
Renal Impairment	eGFR	Dose		
	Mild Impairment	No adjustment needed		
	Moderate to Severe Impairment	5 mg PO BID		
	(eGFR <60 mL/min/1.73 m ²	5 20 272		
	Hemodialysis	5 mg PO BID		
Hepatic	Moderate - Reduce dose to 5 mg BID			
Impairment		Severe - Avoid use		
Duration	Up to 14 days or until hospital discharge, whichever is first			
Formulation(s) Adverse Effects	Oral tablet Serious infections			
Adverse Effects	Th			
	I nrombosisAbnormal laboratory values (neutrop	penia lymphonenia anemia)		
	 Serious venous thrombosis including 			
	Cardiovascular events (acute MI)	paintonary embolism		
Monitoring	Baseline: eGFR, LFTs, CBC			
J. J. J.	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
	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 colls/ ul	Discontinue therapy		
	<500 cells/ μL Hemoglobin (Hgb)	Discontinue therapy		
	<u>Пентодіовін (Пув)</u>			



	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 re 	equired for handling



Tocilizumab

Regulatory Status	Adults: FDA approved tocilizumab <u>in combination with corticosteroids</u> 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/mm³, Plts <50,000/mm³, 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/	Restricted to infectious diseases or critical care providers		
Criteria for Use			
	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 <u>with corticosteroids</u>		
	Do not administer if patients have any other concurrent active infection,		
	including localized infection.		



Nirmatrelvir with ritonavir (Paxlovid)

MITHIALIEIVII WILLI	<u>itonavir (Paxiovid)</u>				
Regulatory Status	 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 				
Target	Criteria for use: Nirmatrelvir/ritonavir may be used in patients				
population/criteria	admitted for reasons other than COVID-19 with mild to moderate				
for use	disease and at high risk for progression to severe COVID-19 AND				
101 450	unable to tolerate remdesivir				
Dose	Nirmatrelvir must be co-administered with ritonavir				
Dose					
	Tablets should be swallowed whole and not chewed, broken, or crushed				
	eGFR	Dose			
	>60 mL/min	Nirmatrelvir 300 mg + ritonavir 100 mg PO BID			
	<60 to ≥30 mL/min	Nirmatrelvir 150 mg + ritonavir 100 mg PO BID			
	<30 mL/min	Not recommended			
Duration	5 days (10 doses total)				
Duration	, , ,				
	If hospitalized <u>after starting treatment</u> , patients should complete the				
	full 5-day treatment course per the healthcare provider's discretion.				
Contraindications		nsitivity 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)				
Drug-drug	***Significant interact	tions*** Paxlovid Drug-Drug Interactions (nih.gov)			
Interactions and					
Concomitant	Clinicians who are not experienced in prescribing ritonavir-				
Medications	boosted drugs s	hould refer to resources such as Fact sheet for			
	_	nirmatrelvir (Paxlovid) and Liverpool COVID-19			
	<u>Drug Interactions</u> for additional guidance.				
	Consultation with an expert (e.g., clinical pharmacist and/or				
	specialist providers) should be considered.				
	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				
	medications unless warranted by their clinical condition				



Renal Impairment	rmont Modorato ronal impairment: Doco adjustment				
Renai Impairment	Moderate renal impairment: Dose adjustment Severe renal impairment: Not recommended				
Hepatic	Severe hepatic impairment (Child-Pugh Class C): Not recommended				
Impairment	Severe riepade impairment (erina r agri elass e)t riot 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					
Healthcare	Paxlovid Patient Fact Sheet (English) Paxlovid Health Care Provider Fact Sheet				
Provider	Paxiovid Health Care Provider Fact Sheet				
References					
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				
	17101 51121 1 51112 1 1 51113 112 1 110 112 1 101 2 5110 1 2 511 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1				
	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 situationThe 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 -				
	<u>Treatment.pdf</u>				
"SMFM supports the use of Paxlovid (nirmatrelvir [PF-07]					
	tablets and ritonavir tablets) for treatment of pregnant patients				
	with COVID-19 who meet clinical qualifications. Any therapy that				

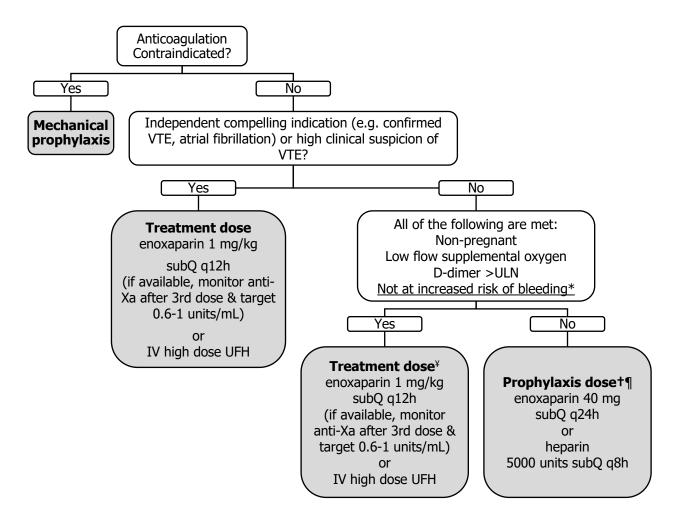


would otherwise be given should not be withheld specifically due to pregnancy or lactation.

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 g12h or heparin 7500 subQ g8h

Platelets $<50 \times 10^9$ 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

^{*}NIH defines increased bleeding risk based on published clinical trials as:



¥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 <u>FDA emergency use authorization (EUA)</u>; 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, <u>bebtelovimab</u> 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, <u>tixagevimab/cilgavimab (Evusheld)</u> 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.

<u>Limitations of use based on geographic variant predominance</u>

- 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, <u>tixagevimab/cilgavimab (Evusheld)</u> 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

<u>Disclaimer:</u> 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 <u>Aviptadil Right to Try NRx Pharmaceuticals</u>

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.
- o 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.





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Summary of Revisions

- 03/15/2020
 - o General treatment options, dosing, and monitoring
- 03/19/2020
 - o 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
 - o ACEi/ARB: advised against adding/removing beyond in standard practice
 - o NSAIDs: no evidence for against the management of fever with NSAIDs
 - o Guidance for use of nebulized respiratory medications
 - o Removed chloroquine, ribavirin, atazanavir/ritonavir, atazanavir/cobicistat, darunavir/cobicistat
 - o Added Tocilizumab
 - o 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 hydroxychloroguine, 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 <u>careful consideration of risks and benefits</u>.
 - o Azithromycin: insufficient evidence to recommend the use of azithromycin in addition to hydroxychloroquine
 - o 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 <u>patients with refractory</u> <u>shock and/or ARDS</u>
 - o Removed darunavir/ritonavir
 - Added Sarilumab with criteria for use
- 04/15/2020
 - o Added: statement regarding use of off-label experimental therapies with only in vitro data
 - o Added recommendation against use of ivermectin
 - Added anticoagulation pathway
 - o Added guidance on cardiac monitoring
 - o Added additional steroid guidance and chart with risk factors for CRS
 - o Added restriction to ID for lopinavir/ritonavir
 - o Revised daily monitoring parameters
- 04/20/2020
 - o 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
 - $\circ \qquad \text{Removed cardiac monitoring for patients receiving hydroxychloroquine} \\$
 - o Removed statement regarding empiric initiation of experimental/investigational therapies for severity score ≥ 4
 - o Included information on remdesivir emergency use authorization
 - Included information on convalescent plasma
- 05/26/2020
 - o 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
 - o Removal of remdesivir compassionate use information
 - Edited remdesivir allocation information
- 06/30/2020
 - o Added warning against use of hydroxychloroquine
 - o Modified IL6 antagonist recommendation to include use for severity score ≥ 2
 - o 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
 - o Modified remdesivir criteria for use
- 08/05/2020
 - Revised remdesivir criteria for use
 - o Updated multi-state convalescent plasma inclusion criteria
 - o 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
 - o Added NIH and IDSA recommendations and references for use of bamlanivimab in outpatients
- 11/24/2020
 - o Reviewed available data and EUA information on baricitinib
- 12/3/2020
 - Added casirivimab/imdevimab
- 12/22/2020
 - Revised language regarding baricitinib
- 01/07/2021
 - $_{\odot}$ Updated verbiage regarding use of ivermectin 01/12/2021
- 01,12,2021
 - Added tocilizumab back into treatment algorithm
- 02/04/2021

 Included information on colchicine for non-hospitalized patients
 - 7/2021
- 02/09/2021
 - Modified tocilizumab recommendation to include only patients with severity score ≥3
 - Updated convalescent plasma EUA criteria
- 02/11/2021
 - o 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
 - o Added additional study evaluating ivermectin
 - Updated information and recommendations on MABs
- 03/25/2021
 - O 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
 - o 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
 - $\circ \qquad \text{Updated EUA requirements for MABs}$



- 05/27/2021
 - o 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
 - o Updated information regarding distribution of bamlanivimab-etesevimab in the U.S.
- 07/13/2021
 - o Updated tocilizumab to reflect EUA and results of the RECOVERY trial
- 07/29/2021
 - o 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
 - o 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
 - o Added chart on preferred outpatient therapies
 - o 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
 - o Rename as AH Treatment Algorithm for <u>Hospitalized</u> Adults
 - o 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
 - $\circ \qquad \text{Removed intermediate anticoagulation for D-dimer}{\geq} 5$
 - Revised criteria for therapeutic anticoagulation in patients on low flow supplemental oxygen
- 3/1/2022
 - o Updated therapies not recommended to include avipdatil
 - Editing monoclonal antibody information to include bebtelovimab
- 4/6/2022
 - o Removed sotrovimab information based on BA.2 subvariant and updated EUA
 - Edited tixagevimab/cilgavimab dosing to match updated EUA
 - O Edited information on ivermectin
- 6/8/2022
 - o Edited information on baricitinib to reflect FDA approval for COVID-19 in hospitalized adults
- 9/16/2022
 - O Edited tixagevimab/cilgavimab treatment guidelines to match with updated EUA
 - O Edited baricitinib treatment guidelines to match with updated IDSA guidelines



- $_{\odot}$ 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.
 - o Edited information on tocilizumab to incorporate FDA approval for adult patients hospitalized for COVID-19
- 02/09/2023
 - O Updated laboratory contraindication for baricitinib to reflect updated package insert



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

Chief Medical Officers

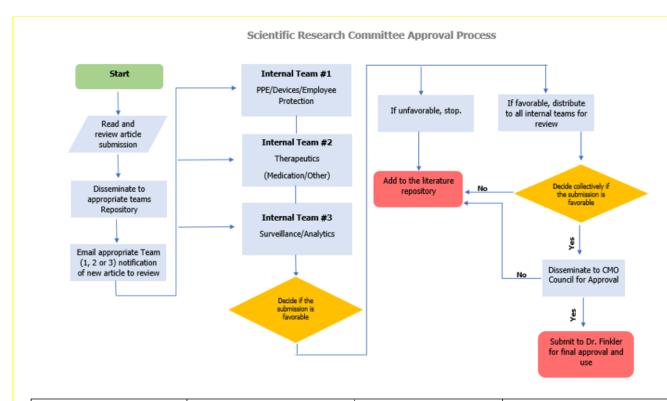
Neil Finkler, MD
Miles Bennett, DO
Dennis deLeon, MD
David Goldman, DO
Victor Herrera, MD
Darin Jordan, MD
Michael Keating, MD
Jennifer Keehbauch, MD
Mark Kilman, MD

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Sarah Minor, PharmD, MHA, BCPS
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Sanjay Pattani, MD
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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		