ADULT Treatment Guidance for COVID-19 in the Ambulatory Setting

Updated 12/15/2020

Available Therapy through Emergency Use Authorization (EUA)

(Subject to change as more data becomes available and based on medication availability)

Drug	Mechanism	Rationale for use	Recommendation
Bamlanivimab Casirivimab/ imdevimab	Inhibits viral attachment to human ACE2 receptor	Neutralizing monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing spike protein attachment to ACE2 receptor	▪ **EUA granted for the treatment of non-hospitalized patients with mild-moderate COVID-19 who are at high risk for disease progression.** ▪ Bamlanivimab reduced the need for hospitalization compared with placebo in the BLAZE-1 trial.[1] ▪ Casirivimab/imdevimab reduced the rates of medically attended visits (MAVs) in an ongoing randomized trial[2] ▪ <u>Current YNHH criteria for approval</u>: ▪ Patients must be 12 years of age and older, weigh at least 40 kg, have a documented positive result of a direct SARS CoV-2 viral test within the last 7 days **AND** meet the following criteria listed below: A) Patients <u>≥</u> 75 years of age B) Patient less than 75 years of age AND have one of the following co-morbidities: 1) Chronic Kidney Disease, Stage III or higher or receiving dialysis 2) Congestive Heart Failure NYHA Class III or higher 3) Severe pulmonary disease defined as one of the following: a) COPD with continuous home oxygen b) Pulmonary hypertension or pulmonary fibrosis c) Cystic fibrosis 4) One of the following hematologic/oncologic diagnoses: a) S/P stem cell transplant b) Active chemotherapy for acute leukemia, lymphoma, or myeloma 5) S/P solid organ transplant 6) Immunosuppressive therapy defined as: a) Receiving or have received lymphocyte depleting monoclonal antibody therapy (e.g., rituximab, ofatutumab, ocrelizumab, alemtuzumab, etc.) 7) Parkinson's disease 8) Patient aged 12-17 with one of the following: a) Congenital or acquired heart disease

			b) Neurodevelopmental disorders c) Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19) d) Chronic respiratory disease excluding asthma ▪ Current YNHH exclusion criteria: ▪ Hospitalized due to COVID-19 ▪ Monoclonal antibodies, such as bamlanivimab or casirivimab/imdesivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. **OR** ▪ Patients who require oxygen therapy due to COVID-19 or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity. ▪ Pregnancy and/or lactation is not a contraindication for use, however, recommended risks versus benefits are discussed with patient's OB/GYN and/or pediatrician. ▪ For more information on how to refer patients for monoclonal antibody therapy, refer to Epic tools under "COVID-19 Monoclonal Antibody References" or copy and paste the following link into your browser: https://www.ynhhs.org/patient-care/covid-19/for-employees/for-employees.aspx ▪ Scroll to *Outpatient Clinical Resources* and find *COVID-19 Monoclonal Antibody Therapy Tips and Tricks for Referrals*
Available Therapy through Clinical Trial **Referral for Outpatient Clinical Trials: 1-877-978-8343** **(Subject to change as more data becomes available and based on medication availability)**			
Camostat mesilate	Protease inhibitor	Inhibits human transmembrane surface protease, TMPRSS2, responsible for priming the SARS-CoV-2 spike protein[3]	▪ **Currently under investigation for potential treatment of COVID-19 infection** ▪ Has been shown *in vitro* and in animal models to inhibit SARS-CoV-2 viral replication at clinically achievable blood and respiratory tract concentration[4] ▪ Currently enrolling ambulatory patients for phase II randomized, double-blind, placebo controlled trial ▪ Eligibility criteria: ▪ Adults 18 years of age and older ▪ Positive SARS CoV-2 viral test within the last 3 days ▪ Experiencing mild symptoms (fever/ temperature > 100.4, loss of taste or smell, cough, sore throat, or gastrointestinal complaints such as nausea, vomiting or

			diarrhea, chills, congestion or runny nose, headaches, muscle or body aches, fatigue) **OR** ▪ No symptoms but recent exposure to an individual with a confirmed COVID-19 diagnosis ▪ **Patient Referrals:** ▪ **1-877-978-8343** ▪ **Principle investigator(s)/ Contact information:** ▪ PI: Geoffrey Chupp, MD (geoffrey.chupp@yale.edu) ▪ Lead CRC: Angela Ryan Nuñez (angela.nunez@yale.edu) (203) 393-6591
Apilimod	IL-12/IL-23 inhibitor	Inhibits PIKfyve, an enzyme involved in the endocytosis and fusion of SARS-CoV-2[5]	▪ **Currently under investigation for potential treatment of COVID-19 infection** ▪ *In vitro* data demonstrates potent inhibition of SARS-CoV-2 infection[5] ▪ Currently enrolling patients for phase II randomized, double-blind, placebo controlled trial ▪ Eligibility criteria: ▪ Adults 18 years of age and older ▪ SARS CoV-2 positive by validated test ▪ Mild symptoms characterized by >= 1 of the following: presence of fever (temperature ≥100.4), anosmia (loss of taste or smell), cough, sore throat, or gastrointestinal complaints (e.g. nausea, vomiting, or diarrhea), chills, congestion or runny nose, headaches, muscle or body aches, fatigue, without shortness of breath or dyspnea (RR<20, SpO2 >93% on room air), OR ▪ Asymptomatic patients who have tested positive for COVID-19 within the past 4 days. ▪ **Patient Referrals:** ▪ **1-877-978-8343** ▪ **Principle investigator(s)/Contact Information:** ▪ PI: Charles Dela Cruz, MD, PhD (Charles.delacruz@yale.edu) ▪ Lead CRC: Lindsey Fraczkiewicz (Lindsey.frackiewicz@yale.edu) (203) 747-1845
Medications <u>NOT</u> Recommended for Outpatient Use (Only recommended for the treatment of COVID-19 in HOSPITALIZED patients)			
Dexamethasone	Immune system modulation	Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses	▪ **There is insufficient evidence to support the use of dexamethasone for OUTPATIENTS with COVID-19** ▪ The RECOVERY trial compared the use of oral or IV dexamethasone (6mg once daily) for up to ten days vs. standard of care in **hospitalized patients** with COVID-19[6] ▪ Results demonstrated a benefit with dexamethasone among patients requiring any oxygen supplementation ▪ There are no studies to date, however, that demonstrate benefit in non-hospitalized patients

Anticoagulation	Anti-coagulants	Prevent thrombotic events associated with SARS-CoV-2 infection	▪ **There is insufficient evidence to support the use of anticoagulation for OUTPATIENTS with COVID-19** ▪ **Please see Appendix 1 for more information on the use of anti-coagulants in patients discharged from the hospital following admission for COVID-19**
Medications with NO Proven Clinical Efficacy for the PREVENTION of COVID-19			
Vitamin D2 (ergocalciferol) & Vitamin D3 (cholecalciferol)	Immune system modulation[7]	Lower viral replication[8] Reduce mortality[8] Vitamin D deficiency linked with cytokine storm biomarkers[9-11]	▪ **There is insufficient evidence to recommend vitamin D for prevention of COVID-19** ▪ **Patients who require vitamin D replacement can continue or be initiated as appropriate** ▪ There are no completed trials to date evaluating the use of Vitamin D for COVID-19. There are ongoing clinical trials assessing potential benefit.[12,13] ▪ There is conflicting evidence regarding the benefits of Vitamin D in preventing other respiratory viral infections, such as influenza. In these studies, several studies using lower doses of Vitamin D support its benefit in preventing respiratory tract infections[13,14,15], while another showed opposite effects in pediatric patients[16], and other studies showed mixed results.[17]
Zinc	Supplement	Increased intracellular concentrations of zinc impair replication in a number of RNA viruses like SARS-CoV-2 [18]	▪ **There is no data to support the use of zinc for the prevention of COVID-19** ▪ The NIH COVID-19 Treatment Guidelines recommend against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19 (11 mg daily for men and 8 mg for non-pregnant women) ▪ Retrospective data investigating the benefits of zinc supplementation was flawed as patients who received zinc had higher baseline absolute lymphocyte counts compared with those who did not receive zinc[19]
Vitamin C	Anti-oxidant	Decrease inflammation and vascular injury in patients with COVID-19	▪ **There is insufficient data to recommend the use of vitamin C for the prevention of COVID-19** ▪ Patients who are not critically ill are less likely to experience oxidative stress or severe inflammation, so the role of vitamin C in this setting is unknown ▪ There are no completed clinical trials of vitamin C in patients with COVID-19, and the available observational data are sparse and inconclusive
Famotidine & Cetirizine	Anti-histamines	Potential inhibition of 3CL protease and of histamine-mediated cytokine storm	▪ **There is insufficient evidence to support the use of famotidine or combination histamine blockers to prevent COVID-19** ▪ A retrospective cohort study comparing 84 patients treated with famotidine against 1536 patients not receiving famotidine concluded that famotidine may decrease the composite outcome of death or intubation (HR 0.42; 0.21 to 0.85), however the IDSA guidelines determined this to be very low level evidence given high suspicion of publication bias[20]

			▪ A physician-sponsored cohort study in hospitalized patients found a reduction in the progression of symptoms with the combination of famotidine and cetirizine. However this study is limited by study design and the number of patients not receiving dual antihistamine therapy (12 compared to 110).[21] ▪ No published randomized controlled trial supports the use of famotidine for the prevention or treatment of COVID-19
HMG-CoA reductase inhibitors (statins)	HMG-CoA reductase inhibition	Inhibition of MYD88 pathway related to immunity[22-24] Lower incidence of viral pneumonia[25-27]	▪ **There is insufficient evidence to recommend statins for the prevention of COVID-19** ▪ **Patients who require statins for non-COVID indications should be continued or initiated** ▪ No published peer review studies in medical literature were found to support the usage of statins based solely on COVID positive status. Further studies are necessary to connect its relationship with COVID-19. Current NIH COVID-19 guidance does not recommend to use statins to treat COVID.
Medications with NO Proven Clinical Efficacy for the TREATMENT of COVID-19			
Hydroxychloroquine	Prevents acidification of endosomes interrupting cellular functions and replication	Early *in-vitro* data showed potent SARS-COV-2 inhibition and early clinical data showed possible benefit	▪ **Available data from clinical trials does not demonstrate benefit, and some studies suggest risk. Risks outweigh benefits given theoretic risk for cardiac arrhythmia.** ▪ **Among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.**[28,29]
Azithromycin and other antibiotics	Possible immuno-modulator	In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load	▪ **There is a lack of clinical data to support the use of azithromycin for the treatment of COVID-19** ▪ There is very limited data on use of azithromycin alone or in combination with other agents ▪ Gautret, et al. study is limited by small sample size (only 6 patients received HCQ & azithromycin combination) and those patients had lower viral loads than other included patients[30] ▪ Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation ▪ **Of note, antibiotics in general are not recommended for the treatment of COVID-19**
Ivermectin	Inhibition of SARS CoV-2 viral replication	In vitro data demonstrated potent inhibition of viral inhibition[31]	▪ **There is a lack of clinical data to support the use of ivermectin for the treatment of COVID-19** ▪ Although *in-vitro* data demonstrated potent anti-SARS CoV-2 activity, further validation with *in vivo* models is required

Aspirin	COX- 1/2 inhibition	Prevent thromboembolic events associated with COVID-19	▪ **There is insufficient evidence to support the initiation of aspirin in non-hospitalized patients with COVID-19** ▪ **Patients who take aspirin should CONTINUE TREAMENT for other underlying medical conditions unless they develop significant bleeding or other contraindications**[32] ▪ Sufficiently powered randomized controlled trials are needed to assess the efficacy of aspirin in patients with COVID-19
Vitamin D2 (ergocalciferol) & Vitamin D3 (cholecalciferol)	Immune system modulation[7]	Lower viral replication[8] Reduce mortality[8] Vitamin D deficiency linked with cytokine storm biomarkers[9-11]	▪ **There is insufficient evidence to recommend vitamin D for the treatment of COVID-19** ▪ **Patients who require vitamin D replacement can continue or be initiated as appropriate** ▪ Some recently published retrospective observational studies concluded that patients with COVID-19 had lower levels of vitamin D.[33,34] While these patients may need vitamin D replacement regardless of COVID-19 prevention, further clinical trials are necessary to connect its relationship with COVID-19.
Zinc	Supplement	Increased intracellular concentrations of zinc impair replication in a number of RNA viruses like SARS-CoV-2 [18]	▪ **There is no data to support the use of zinc for the treatment of COVID-19** ▪ Retrospective data investigating the benefits of zinc supplementation was flawed as patients who received zinc had higher baseline absolute lymphocyte counts compared with those who did not receive zinc[19]
Vitamin C	Anti-oxidant	Decrease inflammation and vascular injury in patients with COVID-19	▪ **There is insufficient data to recommend the use of vitamin C for the treatment of COVID-19** ▪ Patients who are not critically ill are less likely to experience oxidative stress or severe inflammation, so the role of vitamin C in this setting is unknown ▪ There are no completed clinical trials of vitamin C in patients with COVID-19, and the available observational data are sparse and inconclusive
Famotidine & Cetirizine	Anti-histamines	Potential inhibition of 3CL protease and of histamine-mediated cytokine storm	▪ **There is insufficient evidence to support the use of famotidine or combination histamine blockers to treat COVID-19** ▪ A retrospective cohort study comparing 84 patients treated with famotidine against 1536 patients not receiving famotidine concluded that famotidine may decrease the composite outcome of death or intubation (HR 0.42; 0.21 to 0.85), however IDSA guidelines determined this to be very low level evidence given high suspicion of publication bias[20] ▪ No published randomized controlled trial supports the use of famotidine for the treatment of COVID-19

Fluvoxamine	SSRI σ-1 receptor agonist	Potential immune modulation via σ-1 receptor (S1R) agonism[35]	▪ **There is insufficient evidence to support the use of fluvoxamine for the treatment of COVID-19** ▪ A randomized trial found a lower likelihood of clinical deterioration in adult outpatients with COVID-19 treated with fluvoxamine compared with placebo[35], however this study had several limitations including small sample size and potential for bias given primary and secondary endpoints were measured using participants' self-reported responses on surveys.
Colchicine	Anti-gout agent	Anti-inflammatory and anti-viral properties[36] Inhibition of PMN cell migration	▪ **There is insufficient evidence to support the use of colchicine for the treatment of COVID-19** ▪ There is an ongoing phase III trial to evaluate the efficacy and safety of colchicine in adult outpatients diagnosed with COVID-19 infection[37], however there is no current published data to support the use of colchicine at this time.
Medications with Previous Safety Concerns in COVID-19			
Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)	COX-1/2 inhibition	Potentially increases ACE2 expression resulting in worsened COVID-19 infection	▪ **Appropriate to use in COVID-19 patients** ▪ **Considerations for NSAID prescribing should always include evaluation of inherent NSAID side effects (i.e. risk of renal dysfunction), regardless of COVID-19 diagnosis** ▪ No published peer reviewed studies support NSAIDs worsening COVID-19 infections. ▪ European Medicines Agency (EMA) and the Food and Drug Administration (FDA) issued statements that there is no scientific evidence connecting NSAID use and worsening COVID-19 symptoms[38,39]
Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors	ACE inhibition and ARB antagonist	Potentially increases ACE2 expression resulting in worsened COVID-19 infection	▪ **RAAS antagonists should be continued for patients currently prescribed such agents for other underlying medical conditions such as heart failure, hypertension, or ischemic heart disease.** ▪ Two recent observational studies found no association between ACEI or ARB use and COVID-19 positivity or infection-related morbidity/mortality[40,41] ▪ Additionally, a retrospective multicenter study of 1128 patients with hypertension and COVID-19 admitted to 9 hospitals in Hubei, China found that ACEI/ARB use may have been associated with lower risk of all-cause mortality[42]

Appendix 1: Recommendations on the management of anticoagulation in patients discharged from the hospital

1. Patients who had initiation of treatment doses during the hospital stay for either presumed or objectively documented venous thrombosis should be discharged on full dose anticoagulation therapy (Direct oral anticoagulant (DOAC), LMWH, warfarin) for a minimum treatment period of three months.
    - We recommend that these patients have follow up with their primary care physician or specialty physician within six weeks of discharge to assess ongoing risk benefit ratio of anticoagulation.

2. Patients who received standard dose VTE prophylaxis in hospital should not ordinarily continue with VTE prophylaxis. If, however, they are being discharged to another medical care facility, standards of care at that facility should prevail.

3. Patients who received escalated dose (intermediate dose) VTE prophylaxis could be considered for extended VTE prophylaxis with rivaroxaban 10 mg daily for 35 days or LMWH if rivaroxaban cannot be used. The following conditions can be used to determine if a patient is eligible to receive extended duration VTE prophylaxis:
    - Patient should have either:
        1. Modified IMPROVE VTE Risk Score is >/= 4
        2. Modified IMPROVE VTE Risk Score is 2 or 3 and a D-dimer is > 2x ULN. (D-dimer measured within 24 hours of discharge should be used for this determination)
    - Patient should **NOT** have any of the following:
        1. Major bleeding during hospital stay or during the three months prior to index hospital stay
        2. Major surgery within the last four weeks
        3. Prolonged PT (INR > 1.5- measured within 24 hours of discharge)
        4. Known bleeding disorder
        5. Current use of anti-platelet therapy
        6. CrCl of < 30 mL/min
        7. Discharge platelet count < 100,000/ul (measured within 24 hours of discharge)
        8. Other contraindications to anticoagulation with a DOAC

Calculating the Modified IMPROVE VTE Risk Score

VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia*	2
Current lower limb paralysis or paresis**	2
History of cancer[¥]	2
ICU/CCU Stay	1
Complete immobilization ≥ 1 day[≠]	1
Age ≥ 60 years	1

*A congenital or acquired condition leading to excess risk of thrombosis (factor V Leiden, lupus anticoagulant, factor C or S deficiency)

**Leg falls to bed by 5 seconds, but has some effort against gravity (taken from the NIH stroke scale)

[¥]Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet criteria)

[≠]Immobilization is being confined to bed or chair with or without bathroom privileges

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