North Memorial Health System Treatment Guidelines and Evidence for SARS-CoV-2 (COVID-19)

Below you will find a frequently updated summary of current evidence related to COVID-19 and clinical study options. The COVID-19 Therapeutics workgroup will continue to evaluate evidence related to treatments and update recommendations. Besides remdesivir, all antiviral or immunomodulatory therapies listed below are off-label for use in SARS-CoV-2. IDSA COVID-19 Treatment Guidelines and NIH COVID-19 Treatment Guidelines are available online and utilized in our review of recommendations.

Inpatient Group	NMH Treatment options for COVID POSITIVE
Hospitalized not requiring supplemental O2	• Supportive care
Hospitalized requiring supplemental O2 (low flow) or O2 needs above baseline	• Dexamethasone 6mg daily for 10 days (or until hospital discharge) if not already on steroids. Oral route preferred ○ If already on an alternative steroid at less than 35mg methylprednisolone equivalents daily, consider increasing that steroid dose. ○ Evidence suggests that methylprednisolone is a reasonable alternative, with higher doses resulting in beneficial outcomes in some patients. • *Remdesivir no longer routinely recommended. ID consult required (consider in patients already on steroids or who are not eligible for steroids within 10 days of COVID-19 positive result)* • *Convalescent plasma no longer routinely recommended. ID consult required (consider in severe immunocompromise).*
Hospitalized requiring High-Flow O2 (ex. BiPAP, CPAP) or mechanical ventilation	• Dexamethasone 6mg daily for 10 days (or until hospital discharge) if not already on steroids for ARDS, septic shock, or stress dose steroids (higher dose indicated). Oral route preferred ○ If already on an alternative steroid at less than 35mg methylprednisolone equivalents daily, consider increasing that steroid dose. ○ Evidence suggests that methylprednisolone is a reasonable alternative, with higher doses resulting in beneficial outcomes in some patients. • Consider tocilizumab 400mg IV x1 for weight ≤ 60 kg; 8mg/kg IV x1 (up to 800mg) for weight > 60 kg (see criteria for use in tocilizumab section below) • Consider baricitinib *when tocilizumab is unavailable or CRP <7.5 mg/dL (does not qualify for tocilizumab)* ○ 4mg daily for 14 days or until hospital discharge (see criteria for use in baricitinib section below) ○ Dose adjustments required for age under 10 and eGFR <60 mL/min/1.73 m^2 • *Convalescent plasma no longer routinely recommended. ID consult required (consider in severe immunocompromise).*

Outpatient Group		NMH Treatment recommendations for COVID POSITIVE and post exposure prophylaxis
Post-Exposure Prophylaxis • Confirmed exposure in the last 4 days at time of referral • Not fully vaccinated or unlikely to mount adequate immune response		*As of 4/2022 no monoclonal antibodies with activity are currently authorized for post-exposure prophylaxis*
COVID-19 positive Within 5 days of symptom onset	MASSBP Score ≥ 1	Oral antiviral: Paxlovid (age 12+) **(preferred option)** OR Molnupiravir (age 18+) or Monoclonal antibody (age 18+) if unable to use Paxlovid
	MASSBP Score 0 +	*Can consider* Fluvoxamine 100mg BID x10 days with one or more high-risk criteria (below)
COVID-19 positive between 5-7 days of symptom onset	MASSBP Score ≥ 1	Monoclonal antibody (age 18+) if available
	MASSBP Score 0 +	*Can consider* Fluvoxamine 100mg BID x10 days with one of more high-risk criteria (below)
*Inhaled corticosteroids: Not enough data to recommend for or against use specific to COVID-19; Limited data showing potential benefit in select outpatients.		

MONOCLONAL ANTIBODY CRITERIA & REFERRAL PROCESS

• Refer to MNRAP for monoclonal antibody treatment • https://www.health.state.mn.us/diseases/coronavirus/mnrap.html	• *as of 3/2022 with high Omicron variant prevalence – bebtelovimab remains active. Supply is limited & may be reserved for treatment in pregnancy, high-risk children, and higher MASSBP scores who are ineligible for Paxlovid*

MASSBP score is calculated as follows:

- Age ≥65 years (2 points)
- BMI ≥35 kg/m^2 (2 points)
- Diabetes mellitus (2 points)
- Chronic kidney disease (3 points)
- Cardiovascular disease in a patient ≥55 years (2 points)
- Chronic respiratory disease in a patient ≥55 years (3 points)
- Hypertension in patient ≥55 years (1 point)
- Immunocompromised status (4 points)
- Pregnancy (4 points)
- Member of BIPOC community (Black/African American, Hispanic/Latino, Asian, Native Hawaiian or Pacific Islander, or American Indian or Alaskan Native) (2 points)

FLUVOXAMINE CRITERIA consider if all inclusion criteria are met AND one or more high risk criteria and unable to give

Treatment Inclusion

- Positive PCR & within 7 days of symptom onset
- Unvaccinated for COVID-19*
- Age 18+
- Not pregnant
- No concurrent use of a SSRI, uncontrolled psychiatric disorder, or suicidal ideation
- One or more high risk criteria (see right)

Adverse Effects:

- *Common (>10%): headache, insomnia, nausea, diarrhea (higher incidence when compared to fluoxetine or sertraline)*
- *Rare but serious: Stevens-Johnson syndrome (rate similar to all other SSRIs)*

** no data in vaccinated individuals. May consider in populations thought to not fully respond to the vaccine*

High risk criteria

- Age >/= 50 years
- BMI >30
- Diabetes
- hypertension requiring treatment with at least one oral medication
- cardiovascular disease (including congenital)
- symptomatic lung disease or treatment for such (emphysema, fibrosing diseases)
- symptomatic asthma requiring chronic use of medications to treat
- smoking
- prior transplant
- stage IV CKD or on dialysis
- immunosuppression or use of corticosteroids (equivalent to 10mg prednisone per day) or other immunosuppressive therapy
- history of cancer in last 6 months or undergoing current cancer treatment

Below you will find comments and general recommendations for use at NMH for specific agents as reviewed by the NMH COVID-19 Therapeutics workgroup. For more extensive review of literature on each agent, please see ASHP Assessment of Evidence for COVID-19 Related Treatments, which is a frequently updated resource.

Treatments with evidence to support use in COVID-19		
Medication	**Evidence**	**NMH Recommendation**
Tocilizumab (Actemra) **EUA approved on 6/24/2021 for the treatment of COVID-19. The Fact sheet for patients, parents and caregivers must be provided prior to administration of tocilizumab.** Fact sheet for health care providers	Thought to inhibit cytokine storm response to COVID-19 by and reducing pro-inflammatory cytokine IL-6. COVACTA RTC. Roche phase III trial evaluating tocilizumab in hospitalized patients with severe COVID-19 associated pneumonia. Did not meet its primary endpoint of improved clinical status or its secondary endpoint of reduced patient mortality. The first global, randomized, double-blind, placebo-controlled phase III trial investigating tocilizumab. [1] In July 2020, update released on phase III trial using Sarilumab (an IL-6 inhibitor similar to Tocilizumab) in COVID-19 patients requiring mechanical ventilation showing it did not meet its primary endpoint or key secondary endpoints compared to placebo and the US-based trial was being stopped. [2] BACC Bay October 2020. A double-blind, placebo controlled, multisite RCT showed that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 and evidence of hyperinflammatory state. 161 patients received tocilizumab and 81 patients received placebo. Primary outcome: intubation or death was not shown to be statistically significant between the two groups, there was a trend for disease worsening in the tocilizumab group though also not statistically significant. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P=0.69). [3] CORIMUNO-TOCI October 2020. A multicenter, open label RCT in 130 hospitalized patients in France with moderate to severe COVID-19 PNA requiring at least 3L/min of O2 support. 63 patients received tocilizumab compared with 67 randomized to usual care. Primary outcome (1) >5 on WHO CPS scale: 12 vs 19 patients, no statistically significant difference (2) survival with no need for noninvasive (including HFNC) or mechanical ventilation on day 14: 24% vs 36%, HR 0.58; 95% CI [-28 to 4]. No difference in MV or death at day 14 or overall survival at 28 days. [4] RTZ-TCZ-COVID-19 October 2020. A prospective, open-label, RTC in 126 hospitalized patients in Italy with COVID-19 PNA, PaO2/FiO2 ratio 200-300 mmHg, fever, and elevated. CRP. Primary outcome was entry into ICU with invasive mechanical ventilation, death from all causes, or clinical aggravation. Trial was prematurely ended after an interim analysis for futility. 17 patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86; P = .87). Two patients in the experimental group and 1 in the control group died before 30 days. 6 patients in the experimental and 5 in the control group were intubated. [5] EMPACTA December 2020. A randomized, double-blind, placebo-controlled trial in 377 adults hospitalized with COVID-19 PNA with SPO2 <95% on RA not requiring mechanical ventilation. 249 received 8mg/kg tocilizumab, 128 received placebo. Primary outcome of mechanical ventilation or death by 28 days was shown to be reduced in the tocilizumab group. 12% vs 19.3%, HR 0.59 [0.33-0.97; p=0.04]. There was no difference seen in time to hospital discharge, time to clinical improvement or mortality at 28 days. This trial adds to the building information on tocilizumab. [6] REMAP-CAP immune modulation therapy domain. *Preprint preliminary report 1/9/2021.* 865 adults with COVID-19 withing 24 hours of initiating organ support (respiratory of cardiovascular) randomized to receive either tocilizumab (8mg/kg, 800mg max, n=353), sarilumab (400mg, n-48), or SOC (n=402). Primary outcome of respiratory and cardiovascular organ support free days up to day 21 was found to be improved with IL-6 use. Tocilizumab vs SOC OR 1.64 [1.25-2.14]. Hospital survival for tocilizumab compared to SOC OR 1.64 [1.14-2.35]. Steroid use was 88%.	**Consider for use in severe COVID-19** **INCLUSION CRITERIA:** 1. CRP ≥ 7.5 mg/dL (day of evaluation) 2. Within 48h of new HFNC, CPAP, or BiPAP. May consider use in mechanically ventilated patients if hospitalized within the past 48hrs. 3. COVID-19 positive with symptom onset ≤ 7 days. Reduction in mortality was more likely with symptom onset ≤ 7 days. Clinical judgement should be used in patients with rapid decline in respiratory symptoms and symptom onset between 7-10 days. 4. On steroids for treatment of COVID-19 pneumonia with disease progression despite steroid use. **EXCUSION CRITERIA:** 1. Hospitalized or symptom onset > 10 days 2. Active (non-COVID) infection – viral, bacterial, TB, or fungal 3. ALT/AST > 5x ULN 4. Platelets < 50K/UL 5. Imminent death **CONDITIONAL EXCUSION CRITERIA:** 1. Immunocompromised patient – consult ID Potential risks: prolonged immunosuppression leading to secondary bacterial infections,

	Vegia et al 1/21/2021. Hospitalized COVID patients receiving O2 or mechanical ventilation (<24h) AND abnormal levels of at least 2 inflammation markers were randomized to either toci (N=65, 8mg/kg 800mg max) vs SOC (n=64). Trial was stopped early at interim analysis due to increased deaths at 15 days in the tocilizumab group 11(17%) vs 2(3%) OR 6.42 [1.59-43.2]. Steroid use was 71%. [7] RECOVERY, tocilizumab therapy domain. May 2021. 4116 adults hospitalized with severe COVID-19 requiring respiratory support and evidence of inflammation were randomized to either toci (N=2022, 400mg, 600mg or 800mg based on weight) versus standard of care (n=2094). Primary outcome of 28-day mortality was found to be decreased 596 (29%) vs 694 (33%) RR 0.86 [0.77-0.96] with tocilizumab use. Steroids use was 82%. [8] PROSPERO July 2021 meta-analysis (WHO REACT) reviewed a total of 10,930 patients participating in 27 trials in which evaluated IL-6 antagonist administration to no IL-6 antagonist. Primary outcome measure was all-cause mortality at 28 days and demonstrated a reduction in mortality in those randomized to IL-6 antagonists (1407/6649) vs usual care or placebo (1158/4481) OR 0.65 [0.79-0.95] [9]	GI/bowel perforation, reactivation of latent TB, HBV and HCV.
Baricitinib (Olumiant) **EUA approved on 11/19/2020 (updated 7/28/2021) for the treatment of COVID-19. The Fact sheet for patients, parents and caregivers must be provided prior to administration of tocilizumab.** Fact sheet for health care providers	EUA approved on 11/19/20 based on ACTT-2 results (study published on 12/11/2020) [10]. ACTT-2 is a randomized, double-blind, placebo-controlled trial that compared baricitinib + remdesivir (BAR+RDV) to placebo + remdesivir (PLA +RDV) in hospitalized patients. The median time to recovery for the treatment arm was 7 days vs 8 days in placebo group [hazard ration 1.15 (95% CI 1.00, 1.31); p=0.047]. The proportion of patients who died by day 29 was 4.7% (24/515) for treatment arm compared to 7.1% (37/518) for placebo which was not statistically significant. Concomitant corticosteroid use for treatment of COVID-19 was not permitted in this study which is current standard of care. ACTT-4 was designed to examine remdesivir + baricitinib vs. remdesivir + corticosteroids for COVID-19 treatment but was stopped for futility on 4/13/21 with just more than 1,000 participants since neither treatment regimen is likely significantly better than the other. EUA updated on 7/28/21 based on COV-BARRIER results (released as a pre-print in May 2021). [11] This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial that compared baricitinib or placebo daily for up to 14 days or discharge from the hospital (whichever was first). Local standard of care was used which could include corticosteroids and/or antivirals (other concomitant immunosuppressants or high-dose steroids were excluded). 764 patients randomized to baricitinib arm and 76 to placebo. Primary composite endpoint of participants who progressed to high-flow oxygen or non-invasive ventilation, invasive ventilation or ECMO, or death by day 28 did not meet statistical significance. Secondary endpoint of all-cause mortality by day 28 was 13.1% vs 8.1% (p=0.0018) in favor of baricitinib. The benefit was most pronounced in patients at baseline ordinal scale 6 (high-flow oxygen/non-invasive ventilation). RECOVERY, baricitinib therapy domain, March 2022. 4148 patients randomized to baricitinib 4mg daily x10d compared to 4008 given usual care. Primary outcome measure was all cause mortality at 28 days was found to be decreased 513 (12%) vs 546 (14%) RR 0.87 [0.77-0.98; p=0.026]. When this was restricted to positive COVID19 test RR 0.9 [0.79-1.02]. No difference seen in rates of infection, thrombotic events, or bleeding. A higher rate of cardiac arrhythmia was seen in the baricitinib arm (3.1% vs 2.3%, p=0.017). [12] NIH guidelines released an updated to their guidance on 5.27.21 stating recommendation to use either baricitinib or tocilizumab in combination with dexamethasone for treatment of hospitalized COVID-19 on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation. NIH guidelines recommend against the use of baricitinib in combination with tocilizumab due to increased risk of infection.	**Consider for use in severe COVID-19 when tocilizumab is unavailable or CRP <7.5 mg/dL (does not qualify for tocilizumab)** **INCLUSION CRITERIA:** 1. Elevated CRP, D-dimer, LDH, or ferritin (> ULN, day of evaluation) 2. Within 48h of new HFNC, CPAP, or BiPAP 3. COVID-19 positive with symptom onset ≤ 10 days. 4. On steroids for treatment of COVID-19 pneumonia disease progression despite steroid use. **EXCUSION CRITERIA:** 1. Hospitalized or symptom onset > 10 days 2. Active (non-COVID) infection – viral, bacterial, TB, or fungal. If developed infection after administration, hold baricitinib. 3. ALT/AST > 5x ULN 4. eGFR <30 mL/min 5. On a strong OAT3 inhibitor & unable to hold (probenecid), on another JAK inhibitor or DMARD, received tocilizumab or monoclonal antibody for COVID-19 6. Recent (within 12 weeks), recurrent (>1), or active VTE 7. Imminent death **CONDITIONAL EXCUSION CRITERIA:**

		1. Immunocompromised patient – consult ID Potential risks include: VTE (DVT/PE) and prolonged immunosuppression leading to secondary bacterial infections, reactivation of latent TB, HBV, and HCV.
Corticosteroids (systemic)	Initial data on steroid use to treat COVID was mixed with a potential for prolonging viral replication as observed in MERS-CoV patients. [13] As more data has become available with COVID-19, this theoretical potential harm has not been demonstrated. [14] [15] [16]. Corticosteroids are now considered standard of care for patients receiving oxygen support. • Results from The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was published in NEJM July 2020. 2104 patients were randomized to receive dexamethasone 6 mg once per day (either PO or IV) for ten days and were compared with 4321 patients randomized to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14). [17] • CoDEX RTC was published in JAMA 9/2/2020. ICU patients with moderate-severe COVID. 151 patients received dexamethasone (20mg IV daily x5 days followed by 10mg daily x5 days) vs 148 receiving standard of care. Primary outcome was ventilator free days: 6.6 days vs 4.0 days; 2.26 [0.2-4.38; P=0.04] [18] • CAPE COVID RTC published in JAMA 9/2/2020 and REMAP-CAP corticosteroid domain both evaluated hydrocortisone versus standard of care/placebo and found no difference in the primary outcome – however notably both were stopped early due to publication of the Recovery Trial. [19] [20] • WHO REACT workgroup meta-analysis of 7 studies utilizing corticosteroids for COVID-19. 222 deaths among 678 patients randomized to steroids and 425 deaths among 1025 randomized to standard of care. OR 0.66; P<0.001. Dexamethasone specific OR 0.64 [0.5-0.82], hydrocortisone OR 0.69 [0.43-1.12], methylprednisolone OR 0.91 [0.29-2.87]. [21] • The METCOVID trail published May 2021, evaluated patients hospitalized with COVID randomized to either methylprednisolone 0.5mg/kg BID (n=194) versus placebo (n=199) and showed no difference in the primary outcome of mortality. [22] Further evidence on methylprednisolone suggests that a higher dose may be beneficial. A small trail published April 2021 compared high dose methylprednisolone at 2mg/kg/day (n=44) versus dexamethasone 6mg/day (n=42), showing lower mortality in the methylprednisolone group. [23]	**Add dexamethasone 6mg daily for 10 days (or until hospital discharge) in any COVID-19 positive patients requiring supplemental O2 (moderate or severe disease).** **Oral route preferred** *Dexamethasone 6mg daily is ~equivalent to methylprednisolone 32mg daily **Evidence suggests that methylprednisolone is a reasonable alternative, with higher doses resulting in beneficial outcomes in some patients.**
Fluvoxamine	A small (n=152) placebo-controlled, randomized trial showed promising data. Fluvoxamine (50mg on day 1, 100mg BID on day 2&3, then 100mg TID to complete a 15-day course) versus placebo in patients with confirmed COVID-19 in the ambulatory setting. Primary outcome of clinical deterioration (shortness of breath or hospitalization AND O2 sat less than 92% or need for supplemental O2) found to be reduced in the fluvoxamine group by 8.7% (p=0.009). There were significant trial limitations including 20% loss to follow up, exclusion of a 62% of patients screened, small sample size and validation of symptoms. [24] TOGETHER randomized platform clinical trial released interim results via preprint on 8/23/21 and was published on 10/27/21 reviewing fluvoxamine 100mg BID x10 days vs. placebo in adult unvaccinated outpatients within 7 days of positive test and at least one high risk criterion (~750 per arm). Primary outcome was a compositive of emergency room observation for >6 hours or hospitalization from COVID-19 up to 28 days post randomization at 11 centers in Brazil. The primary outcome was statistically significant in favor of fluvoxamine in the intention to treat analysis (79 (11%) vs. 119 (16%) with a RR of 0.68 and a 95% BCI (0.52-0.88). Secondary outcomes did not show statistical significance for viral clearance at day 7 (p=0.090) or hospitalization for COVID (p=0.10) but did show statistical significance in favor of fluvoxamine for emergency setting visit for at least 6h (p=0.0001), time to the emergency visit for at least 6h (0.002), and in death per protocol (0.022). Adherence was statistically significant in favor of placebo (p=0.0003) [25]	**Consider for select outpatients:** • Positive PCR and within 7 days of symptom onset • Unvaccinated for COVID-19 • Age 18+ • Not pregnant • No concurrent use of a SSRI, uncontrolled psychiatric disorder, or suicidal ideation • One or more high risk criteria (see treatment table above)

Remdesivir FDA Approved 10.22.20	Remdesivir is a broad spectrum antiviral with efficacy against coronaviruses, including SARS-CoV-2 in-vitro, and in animals. [26] [27] Initial case reports and cohort data suggested remdesivir had the potential to be a safe and effective treatment option [28] [29] These initial reports lacked a comparator group making it difficult to assess outcomes and safety data The initial randomized, double-blind, placebo-controlled trial out of 10 hospitals in Hubei, China, published on 4/29/20 in Lancet was insufficiently powered to detect differences in clinical outcome and enrollment was terminated early. 237 adult patients with lab-confirmed SARS-CoV-2 with severe manifestations were randomly assigned 2:1 to IV remdesivir x10 days or placebo. Primary endpoint of time to clinical improvement at 28 days or discharged alive from the hospital (whichever was earlier) did not show a statistically significant difference between groups but was numerically shorter in the remdesivir group. [30] A 5 versus 10-day remdesivir duration randomized, open-label, phase 3 trial was published in NJEM on 5/27/2020. 397 patients with PNA and O2 sat <94% not requiring mechanical ventilation at time of enrollment, were randomized to receive remdesivir for either 5 or 10 days. Clinical status on day 14 showed no significant difference in efficacy between the two groups. The 10-day group included a significantly higher percentage of patients in the most severe disease category, and only 44% of patients in the 10-day treatment group completed the full course of therapy due to improvement and discharge. These results cannot be extrapolated to critically ill patients or those receiving mechanical ventilation. [31] The ACTT-1 Phase 3, randomized, placebo-controlled trial, sponsored by NIAID, preliminary report was published on 5/22/2020 in NEJM and updated to the final report on 10/9/2020 (541 randomized to remdesivir and 521 to placebo). Patients that received remdesivir had a faster recovery time: 10 days vs 15 days (Rate ratio for recovery: 1.29; 95% CI, 1.12-1.49; P<0.001). Highest benefit seen in subgroup of patients receiving supplemental oxygen only. Recovery rate ratio statistically significant benefit only in those with symptom duration <10 days. Mortality was not statistically significant, but largest difference again seen in ordinal group 5 (hospitalized with supplemental oxygen). [32] [33] A randomized open-label trial of hospitalized patients with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air O2 sat >94%) comparing standard of care vs. 5 days and 10 days of remdesivir was published in JAMA on 8/21/2020. Patients randomized to 5 days of remdesivir had a statistically significant difference in clinical status evaluated on an ordinal scale compared to standard care at day 11, but this was not seen with the 10-day remdesivir duration and is of uncertain clinical importance. Mortality was low (1-2%) and not statistically different among the 3 groups. [34] WHO SOLIDARITY data released in pre-print on 10/15/20. The study is a large, simple, multi-country, open-label randomized trial in hospitalized patients looking at in-hospital mortality of COVID-19 treatments. Adaptive trial with results released on the first 4 agents (remdesivir, HCQ, lopinavir, and interferon-beta). Participants were randomized in equal proportions between control and whichever other study drugs were locally available (up to 5 options). HCQ and Lopinavir discontinued for futility on 6/8 and 7/4 respectively and interferon is ceasing on 10/16. 11,266 patients were included in the intention to treat analysis, 2750 allocated to Remdesivir. No study drug had any definite effect of mortality (primary outcome) either overall or in any subgroup defined by age or ventilation at entry (or other entry characteristics, geographic region, or corticosteroid use --supplement). No study drug appreciably reduced secondary outcomes of initiation of ventilation (295 in remdesivir group vs 284 in control group) and time to discharge (69% hospitalized at day 7 in remdesivir arm vs 59% in control arm). [35] PINETREE trial randomized 562 mild-moderate outpatients with COVID-19 and at least 1 risk factor for progression to severe disease to either 3 days of IV RDV (279) or placebo (283). Primary efficacy outcome of composite of hospitalization related to COVID19 (>24h acute care) or death from any cause by day 28 showed a 87% relative risk reduction favoring RDV (0.7% (2) vs 5.3% (15); [0.03-0.59]; p=0.008). [36]	**Remdesivir is no longer recommended for routine use. ID consult required.** Consider ID consult for remdesivir: • Patients already on steroids prior to admission or not eligible for steroids AND • Documented positive PCR within 10 days AND • Requiring supplemental O2 or O2 needs above baseline (not yet progressed to high flow O2, CPAP, BiBPAP, or mechanical ventilation). Remdesivir precautions: • Infusion-related reaction • ALT elevations (discontinue if greater than 10 times upper limit of normal; discontinue if signs of liver inflammation) • GFR ≤ 30 ml/min **Known associated risks:** GI: Nausea, vomiting, constipation Hepatic: elevated LFTs Other: headache, phlebitis, pain in extremity, hypotension, infusion reaction, bradycardia, decreased PTT

Molnupiravir (Lagevrio) EUA approved on 12/23/21 for outpatient treatment for those at risk of progression to severe disease (HCP Fact Sheet)	MOVe-OUT trial final results available in the EUA dated 12.23.21. MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying molnupiravir vs. placebo for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible patients were 18 years of age and older and had one of more pre-defined risk factors for disease progression (age >60, diabetes, BMI ≥30, CKD, serious heart conditions, COPD, or active cancer). 1,433 subjects were randomized 1:1 to molnupiravir or placebo BID for 5 days. Primary endpoint was the percentage of subjects who were hospitalized or died through day 29 due to any cause which showed a 30% risk reduction (6.8% (n=48) vs. 9.7% (n=68); p=0.0024)). The risk reduction was much more pronounced in the pre-interim analysis population than the post-interim analysis group.	**Recommended for use in outpatients aged 18 and up within 5 days of symptom onset who are at high risk of progression to severe disease (MASSBP score ≥1; priority to scores ≥4)** Exclusion: age <18, pregnancy
Nirmatrelvir/Ritonavir (Paxlovid) EUA approved on 12/22/21 for outpatient treatment for those at risk of progression to severe disease (HCP Fact Sheet)	EPIC-HR final results available in the EUA dated 12.22.21 and published in NEJM [37]. EPIC-HR is a phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a lab confirmed SARS-CoV-2 infection in adults aged 18 or older with at least 1 risk factor for progression to severe disease (diabetes, BMI >25, chronic lung disease, CKD, current smoker, immunosuppressive disease or treatment, cardiovascular disease, hypertension, sickle cell disease, age >60, etc.). Subjects randomized 1:1 to Paxlovid or placebo Q12hours for 5 days (n=2,246). The study excluded individuals with a history of prior COVID-19 infection or vaccination. Efficacy endpoint presented in the EUA was the proportion of subjects with COVID-19 related hospitalization or death from any cause through day 28 when treated within 5 days of symptom onset, which showed an 89% reduction (0.8% (n=8) vs 6.3% (n=66); p <0.0001). Additional studies in standard-risk population ongoing.	**Recommended for use in outpatients aged 12 and up within 5 days of symptom onset who are at high risk of progression to severe disease (MASSBP score ≥1; priority to scores ≥4)** Exclusion: age <12, weight <40kg, eGFR <30mL/min, nonmodifiable drug-drug interaction, severe hepatic impairment (Child Pugh Class C)
Bebtelovimab EUA approved on 2/11/22 for outpatient treatment in high-risk subgroups	EUA based on in vitro data that showed activity against circulating Omicron subvariants and clinical efficacy from a small, Phase 2 clinical trial in individuals with mild to moderate Covid-19 at low risk of disease progression. With limited data, bebtelovimab is only recommended if preferred outpatient therapies are unavailable or not clinically appropriate.	**Recommended for use in outpatients aged 12 and up within 7 days of symptom onset at high risk of progression to severe disease when alternate therapies are not accessible or clinically appropriate.**
Casirivimab + Imdevimab EUA approved on 11/21/20 for outpatient treatment in high-risk subgroups EUA expanded on 7/30/21 for post-exposure prophylaxis in select subgroups	Regeneron halted its own study of REGN-COV2 (casirivimab + imdevimab) in patients requiring high-flow oxygen or mechanical ventilation on 10/30/20, citing both a lack of efficacy and a potential safety concern as recommended by their independent data monitoring committee. Continued enrollment in hospitalized patient requiring no or low-flow oxygen is ongoing as the risk/benefit profile remains acceptable in that cohort. EUA approval based on phase 1/2/3 Trial R10933-10987-COV-2067 (partial data published) data in 799 adult outpatients who had completed at least 28d of study duration. The study is a randomized, double-blinded, placebo-controlled clinical trial in adults with mild to moderate COVID19. Treatment was initiated within 3 days of obtaining positive SARS-CoV-2 viral infection determination and subjects randomized in a 1:1:1 manner to single infusions of 2400mg, 8000mg, or placebo. The pre-specified primary endpoint was the time weighted average (TWA) change from baseline in viral load as measured by RT-qPCR showed a 0.68 log10 copies/mL greater reduction with REGN-COV2 compared to placebo (combined dose groups; p<0.0001). There was a 1.08 log greater reduction with REGN-COV2 treatment by day 5, which corresponds to REGN-COV2 patients having, on average, a greater than 10-fold reduction in viral load, compared to placebo. In the overall patient group with detectable virus at baseline, the average daily reduction in viral load through day 7 was a 0.36 log10 copies/mL greater reduction with REGN-COV2 compared to placebo (combined dose groups; p=0.0003). The predefined secondary endpoint was medically attended visits (hospitalizations, ER visits, UC visits, or physician office/telemedicine) for COVID-19. Lower proportion of treatment arm 2.8% vs 6.5% with placebo had these visits within 28 days (p value of 0.024 noted in the press release, not EUA). The EUA provided additional breakdown of this as a post hoc analysis looking at hospitalizations or ER visits within 28 days in patients that had lab confirmed PCR via NP swab prior to randomization showing 2% vs 4% (n=10 v 4	****not currently recommended due to circulating variants for which there is not activity**

	(2400mg dose)). Absolute risk reduction was greater in subjects at high risk for progression (~34% of patients of the post hoc) showing 3% v 9% (n=7 v 2 (2400mg dose)). Published interim analysis of first 275 patients enrolled during phase 1-2 of the trial that the EUA was based on. 1:1:1 randomization in non-hospitalized adults (18+ as described above) with positive result no more than 72h before randomization and symptom onset no more than 7 days before randomization. Of the initial 275 patients, 269 received treatment. 90 assigned to received high dose REGN-COV2 (84 completed trial), 92 assigned to low dose (80 completed trial), and 93 to receive placebo (88 completed). Viral efficacy endpoint was the time-weighted average change form baseline in viral load through day 7 as measured by RT-qPCR in patients in the modified full analysis set who were serum antibody-positive at baseline showed difference from placebo of -0.52 log10 copies/mL (CI, -1.04 to 0.00) for low dose, -0.60 log10 copies/mL (CI, -1.12 to -0.08) for high-dose group, and -0.56 log10 copies/mL (CI, -1.02 to -0.11) in the combined REGN-COV2 group. In the overall trial population, the differences were -0.25 (CI, -0.60 to 0.10), -0.56 (CI, -0.91 to -0.21) and -0.41 (CI, -0.71 to -0.10) respectively. Clinical endpoint was percentage of patients with 1 or more MAVs. In the full analysis set 6 of 93 patients (6%) in the placebo group and 6 of 182 patients (3%) in the combined REGN-COV2 group had a MAV, a relative difference of ~49% (CI, -16 to 9). In the serum antibody-negative subgroup, 5 of 33 (15%) in the placebo group and 5 of 80 (6%) in the combined REGN-COV2 group had a MAV, a relative difference of 59% (CI, -29 to 11). [38] In June, 2021 cohort 1 from phase 3 was published with patients randomized to either REGN-COV2 2400mg or 1200mg, with concurrent placebo groups serving as control. Primary endpoint showed that REGN-COV2 2400mg and 1200mg similarly reduced Covid-19-related hospitalization or all-cause death by 71.5% (1.3% vs 4.6% placebo; 95% CI: 51.7%, 82.9%; p<0.0001) and 70.4% (1.0% vs 3.2% placebo; 95% CI: 31.6%, 87.1%; p<0.0024), respectively. [39] RECOVERY Collaborative Group released a pre-print reviewing casirivimab + imdevimab 8gm IV compared 1:1:1 with SOC and SOC + convalescent plasma (until 1/15/21) in hospitalized patients. Between 9/18/20 and 5/22/21, 4839 were randomized to REGEN-COV and 4946 to SOC alone. Primary outcomes of death within 28 days was not statistically significant when including all participants (20% REGEN-COV vs 21% SOC; CI .86-1.03). In seronegative subgroup (1633 in REGEN-COV and 1520 in SOC), primary outcome was 24% vs 30% (CI 0.70-0.91)). [40] EUA expansion to post-exposure prophylaxis occurred on 7/30/21 and was supported by published data from the efficacy analysis of data from the Phase 3 COV-2069 trial which is a randomized, double-blind, placebo-controlled clinical trial studying REGEN-COV for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2. Subjects were randomized 1:1 to 1.2gm of REGEN-COV or placebo given SQ within 96 hours of index cases' positive test. Primary analysis population included subject's PCR negative and seronegative at baseline (753 randomized to REGEN-COV and 752 to placebo). Primary efficacy endpoint was proportion of subjects who developed PCR confirmed COVID-9 through day 29. In the primary analysis population, there was an 81% risk reduction in development of symptomatic COVID-19 with REGEN-COV treatment vs. placebo (11/753 (1%) and 59/752 (8%); p<0.0001). [41]	
Bamlanivimab EUA approved on 11/9/2020 for <u>outpatient treatment</u> in high-risk subgroups has been revoked Bamlanivimab+Etesevimab EUA approved on 2/9/2021 for <u>outpatient treatment</u> in high-risk subgroups—	BLAZE-1, a phase 2 study of bamlanivimab (LY-CoV555) in adult outpatients with COVID-19, published interim results on 10/28/2020 in NEJM [42]. Final results were published in JAMA on 1/21/21 which added a study arm of bamlanivimab + etesevimab in combination [43]. Primary outcome was change from baseline in the SARS-CoV-2 viral load at day 11 (+/-4 days) after positive results on testing. Nine secondary outcomes were evaluated including 3 on viral load, 5 on symptoms, and 1 clinical outcome (COVID19 related hospitalization, ED visit, or death at day 29). 577 patients underwent randomization to 5 groups (156 to placebo and ~100 to each monotherapy dose groups of 700mg, 2800mg, and 7000mg and ~100 to combination 2800mg bamlanivimab + 2800mg etesevimab). By day 11 majority of patients had a substantial trend toward viral clearance including the placebo group (primary outcome). Of the subgroups, the combination bamlanivimab/etesevimab had a difference from placebo that was shown statistically significant (CI -1.00 to -0.14 p=0.01), the other doses were non-significant (interim analysis had shown significance for 2800mg bamlanivimab monotherapy which was no longer significant on final analysis). At day 29, when compared to placebo only 1 treatment arm (bamlanivimab + etesevimab) showed statistical difference compared to placebo for composite secondary clinical endpoint of hospitalization/ED visit/death (-4.9%; 95% CI, -8.9% to -0.8%; p=0.049). Post hoc-analyses of patients aged 65 years or older or with BMI 35 or greater compared to placebo showed -13.5% (95% CI, -	****not currently recommended due to circulating variants for which there is not activity**

distribution halted on 6/25/21; resumed 9/2021	22.7% to -4.2%; p=0.04), but only around 30 patients in treatment group with 0 events, 7 events/52 patients in placebo arm.. Of note, only 1 patient in the trial was admitted to an ICU (placebo arm). BLAZE-1, phase 3 was published 7/14/21 in NEJM. 1035 ambulatory patients with mild or moderate COVID-19 at high risk for progression to severe disease were randomized 1:1 to either 2800mg bamlanivimab and 2800mg etesevimab or placebo within 3 days after lab diagnosis of SARS-CoV-2 infection. Primary outcome was the overall clinical status of the patients, defined as hospitalization (acute care ≥24 hours) or death from any cause by day 29. A total of 2.1% (11 of 518) in the treatment group met primary outcome compared to 7% (36 of 517) in the placebo arm (CI -7.4 to -2.3; p<0.001). Rates of serious adverse events were 1.4% vs 1% and all adverse events were 13.3% vs 11.6%. [44] ACTIV-3 was published on 12/22/20 [45]. This preliminary report of the first TICO trial found hospitalized patients with COVID19 who received a single infusion of the neutralizing monoclonal antibody (7000mg dose) did not have better clinical outcomes at day 5 than placebo group (95% of patients were also receiving remdesivir). With this, LY-CoV555 met prespecified criteria for futility and enrollment was stopped. Day 5 outcomes used for early futility assessment closely associated with primary outcome of the time until a sustained recovery which was no better in LY-CoV555 group than in the placebo group. The authors conclude with these findings that there is a low likelihood that LY-CoV555 improves outcomes among hospitalized patients with COVID19. Two retrospective studies were published comparing outcomes of bamlanivimab monotherapy infused patients with matched controls of eligible patients not infused. Bariola, et al released a preprint on 3/30/21 (published 5/27/21 in OFID) with 232 patients in the infusion arm and 1160 propensity matched patients not receiving bamlanivimab. Primary outcome of hospitalization or all-cause mortality within 28 days of study eligibility was 6.9% infused vs 15.5% not infused (p=0.00001). [46] Kumar, et al published on 4/12/21 in CID included 218 patients in their treatment arm and 185 in the comparison group. Primary outcome was hospitalization within 30 days from initial positive which was 16 events (7.3%) for bamlanivimab vs. 37 (20%) for no bamlanivimab (p<0.001). [47]	
Sotrovimab EUA approved on 5/26/21 for <u>outpatient treatment</u> in high-risk subgroups	EUA approved based on interim analysis of Phase 1/2/3 COMET-ICE trial of 583 randomized subjects. COMET-ICE is a, randomized, double-blind, placebo-controlled trial studying sotrovimab in mild-moderate COVID-19 (not hospitalized). Eligible patients were 18 years of age and older with at least one comorbidity (diabetes, obesity, CKD, CHF, COPD, moderate-severe asthma, or age 55+ regardless of comorbidities). Symptomatic patients included with lab confirmed COVID-19 and onset within 5 days of enrollment. Interim efficacy results showed 1% (n=3) vs. 7% (n=21) for progression of COVID-19 at day 29 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) for a relative risk reduction of 85% (CI 44-96; p=0.002). [48] Final results available via preprint reviewed 1351 patients screened from 8/2020 through 3/2021. Final results for the primary outcome were similar to the interim showing 79% relative risk reduction (1% (6/528) vs. 6% (30/529) for hospitalization or death. [49]	****not currently recommended due to circulating variants for which there is not activity**

Below you will find comments and general recommendations for agents with no evidence to change current practice

No Evidence to Change Current Practice		
Treatment	**Evidence**	**NMH Recommendation**
Vitamin D	Avoiding low vitamin D status is important for many health reasons, and possibly also because of the potentially, but NOT proven lower risk of infection and death from COVID-19, as more studies are needed From a consensus of experts from the UK on vitamin D and SARS-CoV-2: We recommend appropriate vitamin D RCTs to evaluate the effects of vitamin D supplementation on COVID-19 infections. Until there is more robust scientific evidence for vitamin D, we strongly caution against the use of high vitamin D supplementation (greater than the upper limit of 4000 IU/day (100 µg/day)). Rather, we strongly endorse avoidance of vitamin D deficiency. [50]	**Avoid vitamin D deficiency. Treat vitamin D deficiency as traditionally indicated.**
Inhaled corticosteroids (budesonide/ciclesonide)	An observational cohort evaluation with asthma or COPD compared the outcome of COVID-19 related death between those managing their disease with an inhaled corticosteroid (ICS) versus those prescribed alternative respiratory medications. Patients with COPD on an ICS (n=105,249) vs LABA-LAMA (n=43,308) were found to have an increased risk of COVID-19 death. HR 1.39 [1.1-1.76]. Patients with asthma on high dose ICS (n=101,077) vs SABA only (n=108,441) were found to have an increased risk of death. HR 1.55 [1.1-2.18]. No difference seen in those on low/medium ICS vs SABA only. [51] A randomized, open label trial out of the UK randomized adults within 7 days of onset of mild symptoms suggestive of COVID-19 to either inhaled budesonide 800 mcg twice daily (n=70) or usual care (n=69). Primary outcome of COVID-19 related urgent care/ED assessment (could be a phone call) or hospitalizations was shown to be reduced (occurred in 1% of treatment population versus 14% in usual care group). Self-reported time to symptom resolution was 7 days vs 8 days. No statistically significant difference was seen in symptom resolution at day 14, median time to symptom resolution, or proportion of days with low O2 stats. [52] A multicenter open-label randomized controlled trial in the UK (interim analysis; preprint) randomized high risk adults with suspected COVID-19 in the community to receive either inhaled budesonide 800mcg twice daily (n=751) or usual care (n=1028) for 14 days. High risk was defined as either people ≥ 65 years old or ≥ 50 years old with comorbidities. Time to first self-reported recovery was different between groups (11 days in budesonide treatment arm versus 14 days in usual care arm), and the change in hospitalizations or death related to COVID-19 was not statistically significant. [53] A phase 3, multicenter, double-blind, randomized placebo-controlled trial at 10 US centers that enrolled ages ≥12 years of age from 6/11/20 to 11/3/20 with mild-moderate non-hospitalized SARS-CoV2. Primary outcome of time to alleviation of all COVID-19 related symptoms by day 30 (for a continuous 24h) did not show a statistically significant difference. The secondary endpoint of subsequent ED or hospital admission related to COVID-19 by day 30 was showed to be statistically significant in favor of ciclesonide (n=2 (1%) vs. 11 (5.4%); OR 0.18; CI 0.04-0.85; p=0.03). [54]	**Limited data showing potential benefit in select outpatients.** **Not enough data to recommend for or against use specific to COVID-19**
ACEI/ARB	ACE2 receptors are the entry point into human cells for SAQRS-CoV-2. [55] The interface between ACE2 and the viral spike protein SARS-S has been elucidated and the efficiency of ACE2 usage is a key determinant of SARS-CoV transmissibility. [55] It has been speculated, and a variety of mechanisms proposed, to both suggest a beneficial use of ARBs to reduce COVID transmission and severity AND to put patients at a higher risk of severe COVID-19 transmission/severity of infection. [56] [57] [58] [59] [60] [61] [62] Animal studies suggests that ACEI/ARBs may be protective against serious lung complications. [59] [61] A retrospective, multicenter study in China of 1128 COVID-19 positive, hospitalized patients with HTN compared patients who received ACE/ARB during hospitalization to those who did not. All-cause 28-day mortality rate was lower in the ACEI/ARB group (3.7% vs 9.8%; P=0.01). [63] Joint statement by the HFSA/ACC/AHA surrounding the use of RAAS antagonists in COVID-19 concludes "be advised not to add or remove any RASS-related treatments, beyond actions based on standard clinical practice." [64] Position statement from the European Society of Cardiology recommends that "patients should continue treatment with their usual anti-hypertensive therapy. There is no clinical or scientific evidence to suggest that treatment with ACEI or ARBs should be discontinued because of COVID-19." [65] RTC published in JAMA 1/19/2021 of hospitalized patients with COVID taking an ACEI or ARB PTA randomized patients to either continue (n=325) or discontinue (n=334) therapy for 30 days. Showed no difference in mortality, or COVID-9 progression. [66]	**Do not add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.** STOPPING ACE/ARB is not advised unless indicated based on BP, STARTING ACE/ARB continues to be recommended for appropriate indications

Ibuprofen and other NSAIDs	A physician from southern France noted that 4 young patients without underlying health conditions with COVID-19 went on to develop serious symptoms after using NSAIDs in the early stage of their symptoms. Theorized to be due to the anti-inflammatory effects which could "dampen" the immune system. [67] WHO does not recommend the need to avoid ibuprofen. Per a statement made by the European Medicines Agency (EMA) on 3/18/20, there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19.	**Do not change any fever reducing-related treatments, beyond actions based on standard clinical practice.**
Azithromycin	NIH COVID-19 Treatment Guidelines Panel, and the IDSA recommends against the use of the combined HCQ and azithromycin (or CQ) regimen for treatment of COVID-19, except in the context of a clinical trial. Preliminary data was published on 12/14/20 of the azithromycin treatment arm in the RECOVERY study (randomized, controlled, open-label, adaptive platform trial in the UK). Between 4/7 and 11/27 2582 patients randomly allocated to received azithromycin (500mg IV or PO daily for 10 days or discharge) and 5182 to usual care alone. No statistically significant differences were seen in the primary outcome of 28-day mortality (19% died in both groups; RR 1; CI 0.9-1.12). There was also no difference seen in duration of hospitalization (12 v 13days), proportion of patients discharged from hospital alive within 28 days (60% v 59%), or in composite endpoint of progressing to invasive mechanical ventilation or death (21% v 22%). Final results will be published after follow-up completes for remaining patients for the primary endpoint after 12/25/20. [68]	**Do not use azithromycin for COVID-19 treatment. Azithromycin may be used for associated bacterial pneumonia if indicated.**

The below list are agents that HAVE been reviewed by the NMH COVID-19 therapeutics group and are <u>not recommended</u>. For more extensive review of literature on each agent, please see ASHP Assessment of Evidence for COVID-19 Related Treatments, which is a frequently updated resource.

Agents NOT Recommended for use				
B-complex/vitamin B	Chloroquine (CQ)	Colchicine	Convalescent Plasma	Darunavir/cobicistat
Hydroxychloroquine	Inhaled Nitric Oxide	Interferons	Ivermectin	IV vitamin C (+/- thiamine)
Lopinavir-Ritonavir	Nitazoxanide	Omega-3 Fatty Acids	Oseltamivir or other influenza agents, Acyclovir, Ganciclovir, Cidofovir	Quercetin
Thalidomide	Tofacitinib	Zinc		

Table of Revisions

Date	Version	Description of Changes(s)
3/16/2020	2	Creation, initial version posted on intranet
3/18/2020	3	Added information and recommendation on ACE/ARB and ibuprofen
3/19/2020	4	Updated evidence on lopinavir-ritonavir
3/20/2020	5	Added darunavir/cobicistat. Added treatment option table. Updated recommendations for remdesivir and HCQ. Updated HCQ evidence
3/31/2020	6	Updated patient group definitions on treatment option table. Added information on currently enrolling studies at UMN on HCQ. Added recommendations for zinc, azithromycin, and IV vitamin C. Updated hydroxychloroquine and tocilizumab evidence.
4/7/2020	7	Combined tables to create a new table for non-human, in vitro, and no evidence therapeutics. Added ivermectin, nitazoxanide, and inhaled nitric oxide. Updates made to HCQ and tocilizumab. Modified potential treatment option table with stronger consideration for avoiding HCQ in at risk patients
4/16/2020	8	Updated UMN HCQ PrEP study to enrolling. Updates made to HCQ precautions, CQ, and remdesivir. Added link to new IDSA treatment guidelines. Removed recommendations to use HCQ. Added information regarding current clinical trials and convalescent plasma.
4/23/2020	9	Updated corticosteroid evidence and recommendation, updated ACEI/ARB evidence
4/30/2020	10	Updated remdesivir and HCQ evidence. Updated enrollment statement for remdesivir EAP.
5/21/2020	11	Updated initial treatment table. Updated Remdesivir with EUA information
6/2/2020	12	Added literature for remdesivir, hydroxychloroquine, and chloroquine. Updated azithromycin. Summarized sections as able.
6/3/2020	13	Added literature for hydroxychloroquine and convalescent plasma. Removed UMN HCQ PEP and PrEP studies since no longer enrolling.
6/16/2020	14	Added losartan study information, and vitamin D. Noted EUA removal for HCQ and CQ & moved to DO NOT recommend. Added initial treatment option table and added literature for corticosteroids
6/30/2020	15	Added link for NIH treatment guidelines. Updated lopinavir-ritonavir evidence, updated convalescent plasma safety data, and added baricitinib.

8/11/2020	16	Updated treatment table to reflect provider review of remdesivir and removed tocilizumab. Updated evidence for tocilizumab and removed retracted study from HCQ evidence along with shortening HCQ section with link to ASHP table for detailed review of studies.
8/28/2020	17	Updated information regarding convalescent plasma EUA
9/2/2020	18	Remdesivir evidence updated
9/23/2020	19	Baricitinib evidence updated
10/27/2020	20	Updated treatment recommendations. Updated data around remdesivir, steroids, steroids, ivermectin, quercetin, omega-3 fatty acids, interferon, vitamin B. Split document
11/25/2020	21	Baricitinib & fluvoxamine evidence updated
12/9/2020	22	Convalescent Plasma recommendations updated, and evidence added. Added bamlanivimab, imdevimab, and casirivimab. Updated Tocilizumab evidence
12/17/2020	23	Baricitinib and Azithromycin evidence updated
1/6/2021	24	Updated evidence around bamlanivimab, imdevimab/casirivimab, and tocilizumab
1/25/2021	25	Updated ivermectin, ACE/ARB, tocilizumab
2/10/2021	26	Updated mono- and polyclonal antibodies. Added colchicine. Removed losartan study (enrollment complete), Gilead compassionate use information (no longer available).
3/16/2021	27	Updated tocilizumab evidence with criteria for use and treatment table. Added inhaled budesonide information
3/26/2021	28	Updated remdesivir. No longer recommended for routine use. ID consult required.
4/15/2021	30	Updated polyclonal antibodies, inhaled corticosteroids, and baricitinib
6/7/2021	31	Updated convalescent plasma, colchicine, and baricitinib. Added sotrovimab.
6/25/2021	32	Added tocilizumab Emergency use authorization information with links to fact sheets
8/3/2021	33	Updated polyclonal antibodies and ivermectin
8/25/2021	34	Updated treatment table, baricitinib, steroids
9/14/2021	35	Added outpatient treatment table, updated monoclonal antibody sections and moved to recommended agent section. Updated fluvoxamine and added tofacitinib
11/15/2021	36	Added fluvoxamine to outpatient table, updated fluvoxamine section and move to recommended agent section
1/12/2022	37	Updated mAbs due to circulating variants for which there is limited activity. Updated inhaled steroids and remdesivir sections. Shortened the not recommended section. Added molnupiravir and nirmatrelvir/ritonavir. Updated outpatient treatment recommendation table.
4/6/2022	38	Updated mAbs due to circulation variants with limited activity. Updated baricitinib, remdesivir, and Paxlovid sections. Added bebtelovimab. Updated outpatient treatment section.

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