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

Below you will find a consensus summary of current evidence-based recommendations related to COVID-19 treatment review by the COVID-19 Therapeutics workgroup. The workgroup will continue to evaluate evidence related to treatments and update recommendations. 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+)
*Inhaled corticosteroids: Not enough data to recommend for or against use specific to COVID-19; Limited data showing potential benefit in select outpatients.		

MONOCLONAL ANTIBODIES: *Currently there are no monoclonal antibody therapies with activity against circulating virus*

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)

Below you will find comments and general recommendations for use at NMH for specific agents as reviewed by the NMH COVID-19 Therapeutics workgroup.

Treatments with evidence to support use in COVID-19	
Medication	**NMH Recommendation**
Tocilizumab (Actemra) FDA approved	**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, GI/bowel perforation, reactivation of latent TB, HBV and HCV.
Baricitinib (Olumiant) EUA	**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)	**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.**
Remdesivir FDA approved	**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	**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)** Exclusion: age <18, pregnancy
Nirmatrelvir/Ritonavir (Paxlovid) EUA	**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)** Exclusion: age <12, weight <40kg, eGFR <30mL/min, nonmodifiable drug-drug interaction, severe hepatic impairment (Child Pugh Class C)
Monoclonal Antibodies (i.e. Sotrovimab, Bebtelovimab, etc.)	**May be considered in high-risk when available and effective against circulating variants. Currently no monoclonal antibodies are authorized.**

The below list are agents that HAVE been reviewed by the NMH COVID-19 therapeutics group and have no evidence to change current practice.

No Evidence to Change Current Practice	
Treatment	**NMH Recommendation**
Vitamin D	**Avoid vitamin D deficiency. Treat vitamin D deficiency as traditionally indicated.**
Inhaled corticosteroids (budesonide/ciclesonide)	**Limited data showing potential benefit in select outpatients.** **Not enough data to recommend for or against use specific to COVID-19**
ACEI/ARB	**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	**Do not change any fever reducing-related treatments, beyond actions based on standard clinical practice.**
Azithromycin	**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>.

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	Anakinra	Fluvoxamine

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.
2/10/2023	39	Simplified table extensively. Added anakinra and removed fluvoxamine from recommended therapies