

## COVID-19 Antiviral and Pharmacotherapy Information

***Supportive therapy is the cornerstone of treatment.*** Recent IDSA and NIH guidelines reinforce this general approach to pharmacological treatment, with data for only a few specific therapies in certain circumstances<sup>32,40</sup>. The treatment framework below is adapted from the NIH, which is routinely updated at [www.covid19treatmentguidelines.nih.gov/therapeutic-management/](http://www.covid19treatmentguidelines.nih.gov/therapeutic-management/).

### Patient Profile

### Recommendation

Not hospitalized, mild to moderate COVID-19

- Neutralizing antibodies (**bamlanivimab/etesevimab or casirivimab/imdevimab**) are recommended for outpatients that meet high-risk criteria for progressive COVID-19 disease under FDA Emergency Use Authorization (EUA).
- Should **NOT** use **Dexamethasone, Remdesivir, or Baricitinib**

Hospitalized, but does Not require Supplemental Oxygen

- **Remdesivir** for patients at high-risk of COVID-19 progression (see drug sections below)
- Should NOT use **Dexamethasone** or **Baricitinib**

Hospitalized and Requires Supplemental Oxygen

- **Recommend clinical trial enrollment**
- Otherwise, use one of the following options:
- **SUPPLEMENTAL OXYGEN ≤5L/min:**
  - **Remdesivir**
- **SUPPLEMENTAL OXYGEN >5L/min:**
  - **Baricitinib plus Remdesivir\*** OR
  - **Dexamethasone plus Remdesivir\***

Hospitalized and Progressive Respiratory Failure Requiring High Level Oxygen Delivery / Non-invasive Mechanical Ventilation

- **Recommend clinical trial enrollment**
- **Dexamethasone plus Remdesivir\*** OR
- **Baricitinib plus Remdesivir\***
- See text for additional details on anti-inflammatory combination therapy

Hospitalized and Requires Invasive Mechanical Ventilation or ECMO

- Use one of the following options:
- **Dexamethasone plus Remdesivir** OR
- **Dexamethasone** alone
- See text for additional details on anti-inflammatory combination therapy

\*see below for patient criteria and risk of adverse effects to guide choice

Therapies below have been tiered based on the available data, current availability, toxicity profile, and practical considerations specific to Nebraska Medicine. Updates are expected during this fluid situation.

## Preferential:

- » **ACTT-4: NIH Adaptive Clinical Trial of Remdesivir + either Dexamethasone or Baricitinib (NCT04640168)** – E-mail Dr. Andre Kalil ([akalil@unmc.edu](mailto:akalil@unmc.edu)) and LuAnn Larson ([llarson@unmc.edu](mailto:llarson@unmc.edu)) for evaluation
  - **Dosing:** Remdesivir 200mg IV once, then 100mg IV daily for duration of hospitalization or up to 10 total days PLUS Dexamethasone 6mg IV daily for up to 10 days vs. baricitinib 4mg PO daily for up to 14 days while hospitalized
  - **Adverse Effects:** Generally mild severity – GI intolerances, LFT abnormalities, infusion-related reactions, cytopenias
  - **Inclusion Criteria:** Age ≥18; Hospitalized with symptoms of COVID-19 on supplemental oxygen; Laboratory confirmed SARS-CoV-2 within ≤14 days;
  - **Exclusion Criteria:** On mechanical ventilation, on or being prepared for ECMO therapy; AST or ALT >5x ULN; eGFR<20 or on dialysis; neutropenia (ANC <700/mL), lymphopenia (ALC<200/mL); platelets<50/mL; pregnancy or breast feeding; anticipated discharge within 3 days; history of chronic liver disease; receipt of ≥5 doses of remdesivir or >1 dose of dexamethasone 6mg equivalent or more prior to enrollment; receipt of small molecule tyrosine kinase inhibitors, monoclonal antibodies or other agents targeting cytokines (TNF inhibitors, anti-IL-1 or IL-6 [tocilizumab]), convalescent plasma or IVIG for COVID-19; active or latent Tb, treated less than 4 weeks with appropriate therapy - if known (no screening required).
  
- » **MK-4482 (molupiravir) Phase 2/3 Randomized Clinical Trial for Outpatients or Inpatients with COVID-19 (NCT4575597 & NCT04575584)**: E-mail Dr. Diana Florescu ([dflorescu@unmc.edu](mailto:dflorescu@unmc.edu)) and Mason McCain ([mason.mccain@unmc.edu](mailto:mason.mccain@unmc.edu)) for evaluation
  - **Mechanism:** Antiviral that inhibits replication of SARS-CoV-2; different mechanism than remdesivir
  - **Dosing:** 200mg, 400mg, or 800mg PO every 12 hours x 5 days vs. placebo
  - **Adverse Effects:** Unknown
  - **Inclusion Criteria:** Age ≥18; PCR or antigen confirmed SARS-CoV-2 infection within past 10 days; onset of COVID-19 symptoms ≤10 days and at least one symptom remains present at randomization; negative pregnancy test within 24 hours for women of child-bearing age; willing and able to use contraception or abstinence (for 7 months in women, 90 days in men)
  - **Exclusion Criteria:** Critical Covid-19 with any of the following: Respiratory failure defined as mechanical ventilation or high-flow oxygen (>20L/min with fraction of delivered oxygen ≥0.5), non-invasive positive pressure ventilation, shock (<90 DBP or <60 SBP), multi-organ dysfunction; eGFR<30 mL/min or on dialysis; Immunosuppressed as defined by: HIV viral load > 50/mL or CD4 <200 cell/mL, chemotherapy required with 6 weeks before randomization, ANC <500/mL, HSCT; active hepatitis B or C infection (defined as HBsAg-positive or detectable HCV RNA), platelet count <100,000/mL or received platelet transfusion within 5 days prior to randomization; history of acute pancreatitis within 3 months of randomization or any chronic pancreatitis; baseline heart rate <50 bpm, expected survival ≤2 days; pregnancy or breast feeding; receiving ECMO therapy
  - **Notes:** Patients that have received monoclonal antibodies are still eligible for enrollment
  
- » **Regeneron Monoclonal Antibody Clinical Trial (NCT04426695)** – E-mail Dr. Diana Florescu ([dflorescu@unmc.edu](mailto:dflorescu@unmc.edu)) and Mason McCain ([mason.mccain@unmc.edu](mailto:mason.mccain@unmc.edu)) for evaluation
  - **Dosing:** Low-dose (1200mg) or high-dose (4000mg) combination monoclonal antibody preparation IV once (vs placebo)
  - **Adverse Effects:** Infusion-related reactions and hypersensitivity
  - **Inclusion Criteria:** Age ≥18; PCR or antigen confirmed SARS-CoV-2 infection within past 3 days; onset of COVID-19 symptoms ≤10 days; hospitalized ≤3 days, not on mechanical ventilation
  - **Exclusion Criteria:** Expected survival ≤2 days; pregnancy or breast feeding; receiving ECMO therapy; new-onset stroke or seizure; receiving any form of dialysis due to COVID-19; requiring vasopressors for circulatory shock; receipt of convalescent plasma or IVIG in past 5 months
  
- » **Remdesivir<sup>39,66,79</sup>**
  - **Dosing:** 200mg IV once, then 100mg IV daily for a recommended 5 total days of therapy (discontinue earlier if ready for discharge). 10 days of therapy was studied, although no additional benefit has been identified from a longer course.
  - **Adverse Effects:** Generally mild severity – GI intolerances, LFT abnormalities, infusion-related reactions
  - **Patient Criteria:** Age ≥18; PCR confirmed SARS-CoV-2 infection with symptoms starting ≤10 days ago or progressive COVID-19 disease; and one of: 1) requiring supplemental oxygen 2) SpO2 ≤ 94% on room air 3) infiltrates on chest imaging.
    - Examples of patients with high-risk criteria that may benefit from early treatment before requiring oxygen include, but are not limited to: age ≥65, BMI ≥35, immunosuppression, or other chronic health conditions.
    - For children <12 years old and <40kg, EUA documentation requirements remain in place.
    - Please refer to the institutional guidance document on [Ordering Remdesivir](#) for additional notes and processes. Cost: \$3,744 per 5-day course AWP.

**Preferential (continued):**

- » **Dexamethasone**<sup>60-61</sup>
  - Dosing: 6mg PO or IV once daily for up to 10 days (discontinue prior to discharge or when recovered)
  - Adverse Effects: Hyperglycemia, gastrointestinal bleeding, secondary infections, delirium, hypertension, fluid retention, insomnia, increased appetite
  - Patient Criteria: Recommended for patients with COVID-19-related ARDS that are requiring mechanical ventilation. Consider in those with acute respiratory failure requiring increasing supplemental oxygen, *specifically* >5L/min or  $F_iO_2 > 40\%$ . Only those patients with acute hypoxemic respiratory failure due to COVID-19 (not due to chronic comorbidities) are expected to benefit. Has not been studied with remdesivir, but they are regularly used together. The ongoing ACTT-4 study is comparing this combination to baricitinib with remdesivir. Enrollment in the clinical trial is recommended when possible.
  - Notes: A large randomized, [open-label trial](#) demonstrated that dexamethasone provided significant reductions in mortality, hospital discharge within 28 days, and progression to invasive mechanical ventilation or death. Subgroup analysis by level of respiratory support revealed that benefit was seen in patients receiving invasive mechanical ventilation or supplemental oxygen, but not in patients who were not receiving supplemental oxygen or respiratory support. More information on steroids generally can be found below within the Drug Class Guidance section. Cost: \$12/course AWP
  
- » **Baricitinib Emergency Use Authorization (EUA)**<sup>38-39,76</sup> Consider for patients not enrolling into ACTT-4 trial (above)
  - Mechanism: JAK and AAK1 inhibitor (anti-inflammatory agent) proposed for use to counter COVID-19 cytokine storm.
  - Dosing: 4mg PO daily (adjusted for renal function) for up to 14 days until recovered or discharged (2mg/d if 2-8 years old)
  - Adverse Effects: Long-term use for rheumatoid arthritis showed low rates of opportunistic infections including pneumonias and VTEs; short-term treatment of COVID-19 was very well-tolerated in ACTT-2 trial.
  - EUA Criteria: Hospitalized patients requiring remdesivir and respiratory support. VTE prophylaxis recommended. Use SmartPhrase in note before ordering: “.baricitinibEmergencyUse”.
    - Contraindications: eGFR <20 mL/min or on dialysis; neutropenia (ANC <700/mL); lymphopenia (ALC<200/mL); active or latent Tb, treated less than 4 weeks with appropriate therapy - if known (no screening required).
  - Notes: Evaluated in combination with remdesivir in the NIH adaptive clinical trial ACTT-2. Compared to remdesivir alone, the combination resulted in a statistically significant reduction in median time to recovery of one-day overall and eight-days in the subset of patients on high-flow oxygen or non-invasive ventilation. Similar to dexamethasone, the largest improvement in clinical outcomes was seen in patients with severe disease. Cost: \$2,500 per 14-day course AWP
  - Patient Criteria:
    - Consider as an option with remdesivir for patients on supplemental oxygen >5L/min, high-flow, or noninvasive ventilation. However, press release results of the COV-BARRIER study indicates equivocal benefit in this population.
    - Recommended with remdesivir for patients who cannot tolerate corticosteroids (for example, in patients with poorly controlled hyperglycemia, delirium, or gastrointestinal bleeding).
    - In patients with progressive respiratory failure despite standard treatment. Baricitinib and dexamethasone together are not routinely recommended, but may be considered on an individual basis for patients with severe ARDS who are likely to have an intense inflammatory dysregulation (e.g.  $PaO_2/FiO_2 < 100$ ) where a clinician feels the potential unknown benefit outweighs the risk of increased immunosuppression.

**Situational: Efficacy unproven, and/or risk to benefit may favor use in select patients only**

- » **Monoclonal Antibodies Emergency Use Authorization (EUA) – Bamlanivimab/Etesevimab**<sup>67,77</sup> or Casirivimab/Imdevimab<sup>68,78</sup>
  - Dosing: Bamlanivimab/etesevimab 700mg/1400mg or casirivimab/imdevimab 1200mg each, IV once
    - Bamlanivimab alone is no longer recommended for treatment of COVID-19 due to circulation of resistant variants
  - Adverse Effects: Infusion-related reactions and mild hypersensitivity
  - EUA Patient Criteria: Outpatients with mild, symptomatic COVID-19, not requiring supplemental oxygen for COVID-19 (or an increase from baseline in those already on supplemental oxygen). Must meet at least one of the following criteria:
    - Age ≥65 years old
    - Body mass index (BMI) ≥35
    - Chronic Kidney Disease
    - Diabetes
    - Immunosuppressive disease or treatment
    - Age ≥55 years old AND
      - Cardiovascular disease, Hypertension, or COPD
    - Age 12-17 years old AND

- BMI  $\geq 85^{\text{th}}$  percentile for age and gender, OR
  - Sickle cell disease, OR
  - Congenital or acquired heart disease, OR
  - Neurodevelopmental disorders, for example, cerebral palsy, OR
  - Medical-related technological dependence, e.g. tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control
  - **Notes:** All outpatients testing positive for SARS-CoV-2 at Nebraska Medicine will automatically be screened for eligibility criteria above and contacted if eligible. For Nebraska Medicine patients with external positive PCR tests, processes are in place to accept those results for eligibility screening - e-mail: [PharmacyOutreachTeam@univnebrmedcntr.mail.onmicrosoft.com](mailto:PharmacyOutreachTeam@univnebrmedcntr.mail.onmicrosoft.com) or page Antimicrobial Stewardship with questions: (402) 888-0349.
    - Benefit has been shown in preventing subsequent ED visits or hospitalization in populations at high-risk of progression. In phase 2-3 trials, the number-needed-to-treat was in the mid-teens for both these agents.
- » **Convalescent Plasma Emergency Use Authorization (EUA)**<sup>51-53,80</sup> – Plasma must be ordered through the blood bank for inpatient administration (on-call transfusion pager: 402-888-0364).
- **Dosing:** 1-2 units of high-titer plasma (200-400mL) IV once
  - **Adverse Effects:** Primarily allergic, hemolytic, and transfusion-related reactions, such as TRALI, volume overload, etc. Studies thus far have shown very low rates of these events in COVID-19 patients.
  - **Patient Criteria:** Evidence to date suggests optimal use is for patients administered therapy as early in the disease process as possible, or for those with impaired humoral immunity. However, results from the RECOVERY randomized trial did not demonstrate an impact on mortality, disease progression, or time to discharge in hospitalized patients. Patients are not eligible for therapy under the EUA once respiratory failure with need for invasive ventilatory support is present. EUA patient education, documentation, and adverse event reporting requirements must be adhered to.
- » **Tocilizumab**<sup>15-16,29-30,48-49,62,73-75</sup>
- **Mechanism:** IL-6 inhibitor for cytokine release syndrome (CRS) in oncology patients receiving CAR-T cell therapy
  - **Dosing:** 8mg/kg IV once (max 800mg)
  - **Adverse Effects:** Neutropenia can be long lasting so risk of secondary infection is possible and has not been longitudinally evaluated in clinical trials. In one report, superinfections were identified in 54% of tocilizumab-treated patients compared to 24% of untreated COVID patients. In long-term use for RA, intestinal perforation has been reported.
  - **Patient Criteria:** Patients with progressive respiratory decline on high-flow oxygen (30L/min), non-invasive ventilation, or recent mechanical ventilation despite anti-inflammatory therapy with dexamethasone or baricitinib can be considered for therapy after weighing the potential benefit with risk of long-term immunosuppression. The goal of treatment is prevention of progression to mechanical ventilation and death. Those with a suspected or proven bacterial infection should not receive this therapy.
    - Receipt of tocilizumab will exclude patients from the ACTT-4 study
  - **Notes:** Prior *in vitro* work in SARS indicated IL-6-mediated immune hyper-response as a potential cause of poor outcomes. A small, retrospective study suggested that elevated IL-6 levels may predict need for mechanical ventilation in COVID-19, although this lab value is not routinely available at hospitals to guide patient care. Cost of single dose: \$5,000 AWP
    - Early clinical experience from treating COVID-19 in China and the US reported anecdotal benefit with tocilizumab; however, outcomes from randomized trials are conflicting, perhaps demonstrating improvement in need for mechanical ventilation but not consistently. They do not provide clarity on patient selection factors necessary for clear clinical decision-making overall but patients who are most severely have benefited to a greater extent. Over time, an increasing amount of patients have also been treated with corticosteroids, such as dexamethasone, which have previously shown benefit to patients with respiratory failure from COVID-19. The latest 3 large trials are below.
      - **COVACTA** was an industry-sponsored, randomized, placebo-controlled trial that failed to show a difference in clinical outcomes compared to placebo during Apr-May 2020, before glucocorticoids became standard care.
        - Of 438 patients evaluated, 38% were mechanically ventilated, 14% were on high-flow oxygen, 30% were on supplemental low-flow oxygen, and 31% did not require oxygen at baseline
        - Median CRP was 157 mcg/mL (15.7 mg/dL) in the tocilizumab group
        - Mortality rates in each arm were 19.7% vs. 19.4%
        - Glucocorticoids were used in 19.4% and 28.5% of patients
      - **REMAP-CAP** is an international open-label, adaptive platform trial. Tocilizumab (or sarilumab, another IL-6 inhibitor) were compared to standard of care, primarily from June-Nov 2020 when steroids became standard of care

- At baseline, the 353 patients assigned tocilizumab were more critically ill in than previous trials
  - 29% of patients were on high-flow oxygen ( $\geq 30\text{L}/\text{min}$  with  $40\% \text{ FiO}_2$ ), 42% on non-invasive ventilation, 29% received invasive mechanical ventilation, and 18% were on vasopressors
- For patients assigned tocilizumab, median CRP was  $15\text{mg}/\text{dL}$  (IQR 8.9-22.1)
- The primary endpoint was the number of days patients were free of organ support at hospital day 21
- Patients in the tocilizumab group had 10 fewer days of organ support (median 10 vs 0 days for placebo)
- Mortality with tocilizumab was 28% vs 36% with placebo. The adjusted odds ratio for in-hospital survival was 1.64 (1.14-2.35) in favor of tocilizumab.
- Benefit of IL-6 antagonists was greater in those receiving glucocorticoids
- ~80% received corticosteroids and 33% received remdesivir
- [RECOVERY](#) is an adaptive, randomized, open-label platform trial of hospitalized patients in the UK. For the tocilizumab portion of the study, patients were included with CRP  $>7.5 \text{ mg}/\text{dL}$  and  $\text{O}_2\text{sat} <92\%$ .
  - Median CRP was  $14.3\text{mg}/\text{dL}$  (IQR 10.7-20.4) for the 2022 patients allocated tocilizumab
  - 14% were on mechanical ventilation, 41% received non-invasive respiratory support, and 45% were receiving no respiratory support other than oxygen
  - The primary endpoint was 28-day mortality, which was lower in the tocilizumab group: 29% to 33%
  - 82% of patients were on corticosteroids, which appeared to have a significant impact on the survival benefit of patients receiving tocilizumab. No patients received remdesivir.
  - Although this is by far the largest study on the drug, it has not been published in a peer-reviewed journal, and its open-label nature without a placebo control opens it up to a high risk of bias.

**Not Recommended (alphabetical order): Risk/benefit ratio does not favor use**

- » **Azithromycin**<sup>24,26,36</sup>
  - No activity for SARS-CoV-2. Studies of combination therapy with hydroxychloroquine do not suggest added benefit with azithromycin combination therapy, particularly given study limitations and concern for excess toxicity and antibiotic overuse.
- » **Budesonide**<sup>37,84-85</sup>
  - Observational data suggested lower rates of poor COVID-19 outcomes among patients with asthma and COPD, which led to the hypothesis that inhaled corticosteroid use may be responsible for this finding. A single open-label preliminary trial in early outpatient COVID-19 suggests possible benefit in progression of disease or hospitalization. Preliminary data from a larger extension of this trial are consistent with the initial results. Additional randomized trials are needed to confirm these findings.
- » **Colchicine**<sup>81-82</sup>
  - ColCORONA outpatient trial demonstrated minimal benefit of colchicine in mitigating COVID-19 progression, with the number-needed-to-treat much larger than the number-needed-to-harm. RECOVERY randomized trial arm with colchicine has been closed due to lack of evidence for efficacy in hospitalized patients also receiving concomitant dexamethasone. Toxicity can occur at standard doses, particularly in the presence of existing hepatic/renal disease or interacting medications.
- » **Darunavir/cobicistat**<sup>10-11</sup>
  - Available data have not demonstrated efficacy in the treatment of COVID-19 of any severity, although the medication does appear to be well tolerated for the short durations utilized.
- » **Fluvoxamine**<sup>86-88</sup>
  - An SSRI antidepressant with potent affinity for the  $\sigma$ -1 receptor, which regulates cytokine production and inflammatory response. One preliminary randomized controlled trial and one larger open-label prospective cohort both demonstrated efficacy in reduction of need for hospitalization and time to symptom resolution in early outpatient COVID-19. A large nationwide randomized controlled trial is enrolling investigating this therapy for early, mild COVID-19.
- » **Hydroxychloroquine**<sup>1-4,24-28,33-36,44-46,54-58</sup>
  - There were multiple uncontrolled or non-peer-reviewed early clinical reports describing use, with one research group responsible for most of the positive clinical reports. However, there are now multiple clinical trials within various clinical severity and geographic contexts that have demonstrated no benefit in the treatment of COVID-19 disease.



- » **Interferons**<sup>8-9</sup>
  - Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Evaluated in addition to remdesivir as standard-of-care in the third installment of the NIAID adaptive clinical trial, ACTT-3. Results are pending. Their long-term adverse effect profiles are generally unfavorable, but unclear for short-term treatment of COVID-19.
- » **Ivermectin**<sup>31,42-44,83</sup>
  - Single *in vitro* study showed inhibition of SARS-CoV-2, however, concentrations used appear to have been far in excess of those achieved in humans with standard doses. It is highly unlikely that any dose which has thus far been studied in humans may achieve adequate lung concentrations to inhibit SARS-CoV-2. Only one appropriately powered, well-designed randomized clinical trial has been completed, and it did not demonstrate any impact on time to resolution of symptoms.
- » **Lopinavir/ritonavir**<sup>13-14,18,44,47,59</sup>
  - Multiple *in vitro* studies suggesting activity, however, two clinical trials did not demonstrate benefit in either hospitalized or mild/moderate disease patients, or demonstrate an antiviral effect. A third very large clinical trial (RECOVERY) has also now concluded there to be no mortality or other clinical benefit in hospitalized patients.
- » **Nitazoxanide**<sup>12</sup>
  - Some *in vitro* studies have demonstrated potency against SARS-CoV-2, though clinical use against other coronaviruses has not demonstrated benefit. Poorly tolerated formulation; safety profile is relatively benign.
- » **Oseltamivir**
  - Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected.
- » **Ribavirin (oral)**<sup>7-9</sup>
  - Typically used in combination with an interferon, ribavirin has been studied for patients with other coronaviruses, with mixed results. Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day).
- » **Zinc**<sup>89</sup>
  - Varied formulations and dosages of elemental zinc have historically suggested limited efficacy in shortening symptoms due to common cold coronaviruses. There have been a number of small, uncontrolled, or non-peer-reviewed early clinical reports describing use. However, when tested in a small randomized clinical trial for outpatient COVID-19, zinc with or without concomitant high-dose vitamin C did not limit symptom duration, and the trial was terminated for futility.

### Drug Class Guidance (alphabetical order)

- » **Angiotensin/RAS Blocking Agents (ACEi/ARBs)**<sup>17,40,50</sup>
  - Do not discontinue these therapies for COVID-19 disease. Multiple recent retrospective studies now support the earlier conclusions of professional societies in cardiology and nephrology that suggestions to discontinue ACEi/ARB therapy to decrease risk for more severe COVID-19 disease appear not to be well supported. Conversely, these agents should not be initiated solely for treatment of COVID-19 disease.
- » **Anticoagulants**<sup>40,41,63,65,69-71</sup>
  - Published guidelines from all relevant associations recommend that COVID-19 inpatients receive pharmacologic VTE prophylaxis. Either a low-molecular-weight heparin or fondaparinux can be used to reduce administration frequency, though heparin may be preferred in ICU patients due to its shorter half-life. Currently, the role of empiric therapeutically dosed anticoagulation is unknown, and it is ideal to enroll patients in randomized trials rather than empirically using therapeutic anticoagulation.
  - Interim results from REMAP-CAP, ACTIV-4, & ATTACC demonstrate safety and a decrease in need for ventilation or other organ supportive interventions with therapeutic anticoagulation in moderately ill patients. Mortality benefits are being evaluated in this population as well, and peer-reviewed data is anticipated soon which should help inform decision making for these patients. These trials also demonstrated no reduction in need for organ support and noted safety concerns in ICU patients receiving therapeutic anticoagulation, and enrollment was halted in this arm. For patients with recurrent clotting of central access or CRRT/ECMO circuits, anticoagulation should be considered per standard institutional protocols for those

without COVID-19.

- Identification and treatment of the underlying cause(s) of COVID-19 associated coagulopathy should continue to be the focus of treatment efforts. Upon discharge, all COVID-19 patients should be educated on signs and symptoms of VTE. Extended thromboprophylaxis beyond discharge should not be routine, however, can be considered on a case-by-case basis if patient-specific risk factors dictate (i.e. low bleeding risk and ongoing VTE risk factors).

» **Ibuprofen/NSAIDs**<sup>22-23,32,40</sup>

- Do not discontinue these therapies for COVID-19 disease. Acetaminophen and NSAIDs are both reasonable options for fever reduction in COVID-19 and may be selected in a patient-specific manner. Although there has been theoretical concern raised for NSAIDs worsening outcomes, no data currently exist to support this. WHO has revised their early statements and issued a clarification consistent with the above recommendation. NIH guidelines similarly recommend that patients taking NSAIDs continue this therapy and that antipyretics be selected in a patient-specific manner without regard for COVID-19 status.

» **Inhaled Pulmonary Vasodilators**<sup>19-21,40,64</sup>

- Limited *in vitro* evidence suggests nitric oxide may inhibit coronaviruses, and clinical experience has shown that inhaled nitric oxide can reduce mean pulmonary artery pressure and improve oxygenation in patients with non-COVID-19 ARDS. Despite this, SCCM guidelines recommend against use of nitric oxide given an unfavorable risk/benefit ratio for ARDS. NIH guidelines recommend inhaled pulmonary vasodilators only in mechanically ventilated COVID-19 patients with hypoxemia refractory to optimized therapy. If rapid improvement in oxygenation is not seen, therapy should be tapered off. Nitric oxide and others in its class (e.g., iloprost) are being investigated in clinical trials, and agents in this group are still recommended in the presence of clinical factors where they would routinely be considered for critical care.

» **Steroids**<sup>5,6,19,32</sup>

- Initially CDC, WHO, and SCCM did not recommend steroid therapy for COVID-19 outside of a specific alternative indication, such as sepsis, ARDS, or COPD. Based on recent evidence, NIH and IDSA now recommend the use of glucocorticoids (e.g., dexamethasone) in patients with severe COVID-19 disease requiring supplemental oxygen or mechanical ventilation, but against using them in COVID-19 patients without hypoxemia requiring supplemental oxygen. SCCM recommends using glucocorticoids in mechanically ventilated COVID-19 patients with ARDS, but against their use in the absence of ARDS. Steroids are likely to be beneficial in selected patient populations; more specific information regarding dexamethasone use can be found in its standalone section above.

## References

- 1) Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia *Chinese Journal of Tuberculosis and Respiratory Diseases* 43, no. 0. <https://www.ncbi.nlm.nih.gov/pubmed/32075365>.
- 2) Yao X, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020 Mar 9. <https://www.ncbi.nlm.nih.gov/pubmed/32150618>.
- 3) Cortegiana, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*. 2020 Mar 10. <https://www.sciencedirect.com/science/article/pii/S0883944120303907>.
- 4) Hydroxychloroquine clinical trials (NCT04261517, NCT04315896, NCT04318015, NCT04308668, NCT04307693). <https://clinicaltrials.gov/>
- 5) WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Accessed 2020 Aug 27. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
- 6) CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Accessed 2020 Mar 12. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>.
- 7) Gross AE, Bryson ML. Oral Ribavirin for the Treatment of Noninfluenza Respiratory Viral Infections: A Systematic Review. *Ann Pharmacother*. 2015 Oct;49(10):1125-35. <https://www.ncbi.nlm.nih.gov/pubmed/26228937>.
- 8) Arabi YM, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. *Clin Infect Dis*. 2019 Jun 25. <https://www.ncbi.nlm.nih.gov/pubmed/31925415>.
- 9) Mo Y, Fisher D. A review of treatment modalities for Middle East Respiratory Syndrome. *J Antimicrob Chemother*. 2016 Dec;71(12):3340-3350. <https://www.ncbi.nlm.nih.gov/pubmed/27585965>.

- 10) Chen J, et al. Antiviral activity and safety of darunavir/cobicistat for treatment of COVID-19. *Open Forum Inf Dis*. 2020 Jun 21. <https://academic.oup.com/ofid/article/7/7/ofaa241/5860459>.
- 11) Nicolini LA, et al. Reply to: "Antiviral activity and safety of darunavir/cobicistat for treatment of COVID-19". *Open Forum Inf Dis*. 2020 July 29. <https://academic.oup.com/ofid/article/7/8/ofaa321/5877884>.
- 12) Gamino-Arroyo AE, et al. Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness. *Clin Infect Dis*. 2019 Dec 69;11:1903-11. <https://academic.oup.com/cid/article/69/11/1903/5308603>.
- 13) Yao TT, et al. A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option. *J Med Virol*. 2020 Feb 27. <https://www.ncbi.nlm.nih.gov/pubmed/32104907>.
- 14) Young BE, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. 2020 Mar 3. <https://jamanetwork.com/journals/jama/fullarticle/2762688>.
- 15) Li Y, et al. Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. *Microbes Infect*. 2013 Feb;15(2):88-95. <https://www.ncbi.nlm.nih.gov/pubmed/23123977>
- 16) Xiaoling X, et al. Effective treatment of Severe COVID-19 Patients with Tocilizumab. *Proc Natl Acad Sci USA*. 2020 May 19 <https://pubmed.ncbi.nlm.nih.gov/32350134/>
- 17) Vaduganathan M, et al. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19. *NEJM*. 2020 Mar 30. <https://www.nejm.org/doi/full/10.1056/NEJMsr2005760>.
- 18) Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *NEJM*. 2020 Mar 18. <https://www.nejm.org/doi/full/10.1056/NEJMoa2001282>.
- 19) Alhazzani W, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Accessed 2020 Aug 27. <https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19> and <https://sccm.org/getattachment/SurvivingSepsisCampaign/Guidelines/COVID-19/SSC-COVID-19-Guidelines-Microlearning-Therapy.pdf?lang=en-US>
- 20) Nitric oxide clinical trials (NCT04290871 and NCT04290858). <https://www.clinicaltrials.gov/ct2/show/NCT04290871>; <https://www.clinicaltrials.gov/ct2/show/NCT04290858>.
- 21) Akerstrom S, et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol*. 2005 Feb;79:1966-9. <https://www.ncbi.nlm.nih.gov/pubmed/15650225>.
- 22) Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020. <https://www.ncbi.nlm.nih.gov/pubmed/32171062>.
- 23) WHO Twitter clarification on ibuprofen. <https://twitter.com/WHO/status/1240409217997189128>.
- 24) Gautret P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Ag*. In press. 2020 Mar 20. <https://www.sciencedirect.com/science/article/pii/S0924857920300996>.
- 25) Chen J, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)*. 2020 Mar 6. <http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03>.
- 26) Furtado RHM, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomized clinical trial. *Lancet*. 2020 Oct;396:959-67. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31862-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31862-6/fulltext).
- 27) Chen Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1>
- 28) Molina JM, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine et Maladies Infectieuses*. 2020 Mar 30. <https://www.sciencedirect.com/science/article/pii/S0399077X20300858>.
- 29) Salvarani C, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2020 Oct 20. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772186>.
- 30) Herold T, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. 2020; 146(1): 128-36. [https://www.jacionline.org/article/S0091-6749\(20\)30685-0/fulltext](https://www.jacionline.org/article/S0091-6749(20)30685-0/fulltext).
- 31) Caly L, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Research*. 2020 Apr 3. <https://www.sciencedirect.com/science/article/pii/S0166354220302011>.
- 32) Bhimraj A, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Accessed 2021 Apr 9. <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>.
- 33) Tang W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1>.
- 34) Mahevas M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1>.



- 35) Borba MG, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *JAMA Network Open* 2020. 3(4): e208857. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499>.
- 36) Lane JC, et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. *Lancet Rheum*. 2020 Aug 21. [https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30276-9/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30276-9/fulltext).
- 37) Rogliani P, et al. Reduced risk of COVID-19 hospitalization in asthmatic and COPD patients: a benefit of inhaled corticosteroids? *Exp Rev Res Med* 2021; 15(4): 561-8. <https://www.tandfonline.com/doi/full/10.1080/17476348.2021.1850275>.
- 38) Stebbing J, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Inf Dis* 2020. 20(4): 400-2. [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30132-8/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30132-8/fulltext).
- 39) Kalil AC, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Eng J Med*. 2020 Dec 11. <https://www.nejm.org/doi/10.1056/NEJMoa2031994>
- 40) NIH. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Accessed 2021 Apr 9. <https://covid19treatmentguidelines.nih.gov/>.
- 41) American Society of Hematology, COVID-19 Resources. COVID-19 and VTE/Anticoagulation: <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>. COVID-19 and Coagulopathy: <https://www.hematology.org/covid-19/covid-19-and-coagulopathy>.
- 42) Chaccour C, et al. Ivermectin and novel coronavirus disease (COVID-19): keeping rigor in times of urgency. *Am J Trop Med Hygiene*. 2020 Apr 16. <https://www.ajtmh.org/content/journals/10.4269/ajtmh.20-0271>.
- 43) Schmith V, et al. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. *Clin Pharmacol Ther*. 2020 May 7. <https://pubmed.ncbi.nlm.nih.gov/32378737/>.
- 44) Arshad U, et al. Prioritisation of potential anti-SARS-CoV-2 drug repurposing opportunities based on plasma and target site concentrations derived from their established human pharmacokinetics. *Clin Pharmacol Ther*. 2020 May 21. <https://pubmed.ncbi.nlm.nih.gov/32438446/>.
- 45) Magagnoli J, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2>.
- 46) FDA Drug Safety Communication. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020 Apr 24. <https://www.fda.gov/media/137250/download>.
- 47) Li Y, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med* 2020; 1: 105-13. <https://www.cell.com/action/showPdf?pii=S2666-6340%2820%2930001-5>.
- 48) Hermine O, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2020 Oct 20. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772187>.
- 49) Salama C, et al. Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia. *NEJM*. 2021; 384: 20-30. <https://www.nejm.org/doi/full/10.1056/NEJMoa2030340>.
- 50) Jarcho JA, et al. Inhibitors of the renin-angiotensin-aldosterone system and COVID-19. *NEJM*. 2020 May 1. <https://www.nejm.org/doi/full/10.1056/NEJMe2012924>.
- 51) Joyner MJ, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020 Jun 11. <https://www.jci.org/articles/view/140200>.
- 52) Salazar E, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol*. 2020 Aug 10. [https://aip.amipathol.org/article/S0002-9440\(20\)30370-9/fulltext](https://aip.amipathol.org/article/S0002-9440(20)30370-9/fulltext).
- 53) Joyner MJ, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1>.
- 54) Boulware DR, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. *NEJM*. 2020; 383: 517-25. <https://www.nejm.org/doi/full/10.1056/NEJMoa2016638>.
- 55) Skipper CP, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. *Ann Int Med*. 2020 July 16. <https://www.acpjournals.org/doi/10.7326/M20-4207>.
- 56) Mitja O, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. *Clin Infect Dis*. 2020 July 16. <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1009/5872589>.
- 57) Cavalcanti AB, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *NEJM*. 2020 July 23. <https://www.nejm.org/doi/full/10.1056/NEJMoa2019014>.
- 58) Recovery Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *NEJM*. 2020 Oct 8. <https://www.nejm.org/doi/full/10.1056/NEJMoa2022926>.
- 59) Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. *Lancet*. 2020 Oct 5. [https://www.thelancet.com/journals/lanct/article/PIIS0140-6736\(20\)32013-4/](https://www.thelancet.com/journals/lanct/article/PIIS0140-6736(20)32013-4/).
- 60) The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19: Final report. *N Engl J Med*. 2021 Feb 25. <https://www.nejm.org/doi/10.1056/NEJMoa2021436>
- 61) Villar J, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomized controlled trial. *Lancet Resp Med* 2020; 8: 267-76. <https://pubmed.ncbi.nlm.nih.gov/32043986>.

- 62) Rosas IO, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. NEJM. 2021 Feb 25. <https://www.nejm.org/doi/full/10.1056/NEJMoa2028700>
- 63) Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019 CHEST guideline and expert panel report. CHEST 2020; 158(3): 1143-63. [https://journal.chestnet.org/article/S0012-3692\(20\)31625-1/pdf](https://journal.chestnet.org/article/S0012-3692(20)31625-1/pdf).
- 64) Wu R, et al. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep 2020; 6: 56-70. <https://pubmed.ncbi.nlm.nih.gov/32395418/>.
- 65) Barnes GD, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020; 50: 72-81. <https://link.springer.com/article/10.1007/s11239-020-02138-z>.
- 66) Beigel JH, et al. Remdesivir for the treatment of COVID-19 – final report. NEJM 2020; 383:1813-26. <https://www.nejm.org/doi/full/10.1056/NEJMoa2007764>.
- 67) Chen P, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. NEJM 2020; 384: 229-237. <https://www.nejm.org/doi/full/10.1056/NEJMoa2029849>
- 68) Casirivimab and imdevimab. FDA Emergency Use Authorization. Fact Sheet for Healthcare Providers. Accessed Dec 15, 2020. <https://www.fda.gov/media/143902/download>
- 69) NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patient <https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients>. Accessed Dec 31, 2020
- 70) NIH ACTIV initiation launches adaptive clinic trials of blood-clotting treatment for COVID-19. <https://www.nih.gov/news-events/news-releases/nih-activ-initiative-launches-adaptive-clinical-trials-blood-clotting-treatments-covid-19>. Accessed 27 Jan 2021
- 71) Full-dose blood thinners decreased need for life support and improved outcome in hospitalized COVID-19 patients. <https://www.nhlbi.nih.gov/news/2021/full-dose-blood-thinners-decreased-need-life-support-and-improved-outcome-hospitalized>. Accessed 27 Jan 2021.
- 72) Kimmig LM, et al. IL-6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. Frontiers in Medicine. 2020 Oct 28 <https://www.frontiersin.org/articles/10.3389/fmed.2020.583897/full>
- 73) Somers EC, et al. Tocilizumab for Treatment of Mechanically Ventilated Patients with COVID-19. Clin Infect Dis. 2020 July 11 <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa954/5870306>
- 74) REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. NEJM. 2021 Feb 25 <https://www.nejm.org/doi/full/10.1056/NEJMoa2100433>
- 75) RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): Preliminary results of a randomized, controlled, open-label, platform trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.supplementary-material>
- 76) Baricitinib COV-BARRIER phase 3 clinical trial; Eli Lilly, press release. <https://investor.lilly.com/node/44871/pdf>. 8 Apr 2021.
- 77) Extension of BLAZE-1 phase 3 trial for bamlanivimab/etesevimab; Eli Lilly, press release. <https://investor.lilly.com/node/44756/pdf>. 10 March 2021.
- 78) REGEN-COV phase 3 trial in high-risk outpatients; Regeneron, press release. <https://investor.regeneron.com/node/24986/pdf>. 2021 March 2.
- 79) Garibaldi, et al. Comparison of time to clinical improvement with vs without remdesivir treatment in hospitalized patients with COVID-19. JAMA Netw Open. 2021 Mar 24. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2777863>.
- 80) RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2021.03.09.21252736v1>.
- 81) Tardif J, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1>.
- 82) RECOVERY Collaborative Group. RECOVERY trial closes recruitment to colchicine treatment for patients hospitalized with COVID-19, press release. <https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19>. 2021 Mar 5.
- 83) Lopez-Medina E, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19. JAMA. 2021 Mar 4. <https://jamanetwork.com/journals/jama/fullarticle/2777389>.
- 84) Ramakrishnan S, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial. Lancet Resp Med. 2021 Apr 9. [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00160-0/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00160-0/fulltext).
- 85) PRINCIPLE Collaborative Group. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analysis from the PRINCIPLE trial. [Pre-print – not peer reviewed]. <https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1>.
- 86) Lenze EJ, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020; 324(22): 2292-2300. <https://jamanetwork.com/journals/jama/fullarticle/2773108>.
- 87) Seftel D, et al. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum Inf Dis. 2021 Feb 1. <https://academic.oup.com/ofid/article/8/2/ofab050/6124100>.
- 88) STOP COVID 2 clinical trial. [NCT04668950](https://clinicaltrials.gov/ct2/show/study/NCT04668950) or <https://stopcovidtrial.wustl.edu/>.
- 89) Thomas S, et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open. 2021 Feb 12. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776305>.

**Prepared and Reviewed by:**

**Bryan Alexander, PharmD**

**Scott Bergman, PharmD**

**Trevor Van Schooneveld, MD**

**Mark Rupp, MD**

**Emilie Langenhan, PharmD**

**Erica Stohs, MD**

**Andrew Watkins, PharmD**

**Kelly Cawcutt, MD**

**Angela Hewlett, MD**

**Jasmine Marcelin, MD**

**Logan Olson, PharmD**

**Richard Hankins, MD**

**Andre Kalil, MD**