

## 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

- Insufficient data to routinely recommend neutralizing antibodies (**bamlanivimab** or **casirivimab/imdevimab**). These products are reasonable to consider 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\***

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 the 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  
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; 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** ([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
  - **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 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
  
- » **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
  - **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>66</sup>**
  - **Dosing:** 200mg IV once, then 100mg IV daily for a recommended 5 total days of therapy (discontinue earlier if ready for discharge). Although 10 days of therapy was studied, no additional benefit has been determined 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) infiltrates on chest imaging 2) requiring supplemental oxygen 3) SpO2 ≤ 94% on room air.
    - 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.
    - EUA documentation requirements remain in place for children <12 years old and <40kg.
    - Please refer to the institutional guidance document on [Ordering Remdesivir](#) for additional notes, EUA details, and processes. Cost: \$3,744 per 5-day course AWP
  
- » **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</sup> Consider for patients not enrolling into ACTT-4 trial (above)**
- **Dosing:** 4mg PO daily (adjusted for renal function) for up to 14 days until recovered or discharged
  - **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. 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:** JAK and AAK1 inhibitor (anti-inflammatory agent) proposed for use to counter COVID-19 cytokine storm. 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 most improvement in clinical outcomes was seen for patients with severe disease. Cost: \$2,500 per 14-day course AWP
  - **Patient Criteria:**
    - i. Consider as an option with remdesivir for patients on supplemental oxygen >5L/min, high-flow or noninvasive ventilation.
    - ii. Recommended with remdesivir for patients who cannot tolerate corticosteroids. For example: Poorly controlled hyperglycemia; Delirium; Gastrointestinal bleeding
    - iii. In patients with progressive respiratory failure despite standard treatment:
      1. 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 (alphabetical order): Efficacy unproven, risk/benefit may favor use in select patients**

- » **Monoclonal Antibodies Emergency Use Authorization (EUA) - Bamlanivimab<sup>67</sup> or Casirivimab/Imdevimab<sup>68</sup>**
- **Dosing:** Bamlanivimab 700mg IV once or casirivimab/imdevimab 1200mg each, IV once (combined together)
  - **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:
    - i. Age ≥65 years old
    - ii. Body mass index (BMI) ≥35
    - iii. Chronic Kidney Disease
    - iv. Diabetes
    - v. Immunosuppressive disease or treatment
    - vi. Age ≥55 years old AND
      1. Cardiovascular disease, Hypertension or COPD
    - vii. Age 12-17 years old AND
      2. BMI ≥85<sup>th</sup> percentile for age and gender, OR
      3. Sickle cell disease, OR
      4. Congenital or acquired heart disease, OR
      5. Neurodevelopmental disorders, for example, cerebral palsy, OR

6. Medical-related technological dependence, e.g. tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  7. Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control
- **Notes:** Following referral by provider, screening will automatically occur and product is assigned based on availability. Benefit has been shown in preventing subsequent ED visits or hospitalizations. In phase 2 trials that led to these EUAs, the number-needed-to-treat was in the mid-teens for both these agents.

**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.
- » **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.
- » **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</sup>
  - Single *in vitro* study showed inhibition of SARS-CoV-2. However, the 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.
- » **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).
- » **Tocilizumab**<sup>15-16,29-30,48-49,62</sup>
  - IL-6 inhibitor; IV formulation. IDSA guidelines recommend against routine use. Prior *in vitro* work in SARS indicated IL-6-mediated immune hyper-response as a potential cause of poor outcomes. A small, retrospective, pre-print study has suggested that elevated IL-6 levels may predict need for mechanical ventilation in COVID-19. Preliminary clinical experience from China in COVID-19 reported benefit, however neutropenia can be long-lasting so risk of secondary infection is possible

and hasn't been longitudinally evaluated in clinical trials. Outcomes from randomized trials to date are conflicting, perhaps demonstrating improvement in need for mechanical ventilation but not consistently, and do not yet provide clarity on patient selection factors necessary for clear clinical decision-making.

### 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>41,63,65</sup>
  - ASH, CHEST, and the Anticoagulation Forum have released guidance for anticoagulation management. COVID-19 inpatients should receive pharmacologic VTE prophylaxis, preferably with either a low-molecular-weight heparin or fondaparinux to reduce administration frequency. Currently, the role of empiric therapeutically dosed anticoagulation in these patients is unknown, and it is ideal to enroll patients in randomized trials rather than empirically using therapeutic anticoagulation. For patients with recurrent clotting of central access or CRRT/ECMO circuits, an increase in the intensity of anticoagulation or an alternative agent can be considered in a patient-specific fashion. 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>5,6,19,32,37</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, but against using glucocorticoids in COVID-19 patients without hypoxemia requiring supplemental oxygen. Using dexamethasone in patients who are mechanically ventilated or requiring supplemental oxygen, but against using dexamethasone in patients not requiring oxygen supplementation. 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.

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