

## 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>. It remains unclear whether multidrug regimens provide any additional benefit in the treatment of COVID-19. Given the paucity of data for monotherapy regimens and the added toxicity of multidrug regimens, it is unlikely that most multidrug combinations will produce a favorable risk/benefit ratio.

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

### Preferential:

- » **Remdesivir + Interferon (ACTT-3) Clinical Trial (NCT04492475)** – E-mail 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  
Interferon beta-1a 44mcg SQ q48h for duration of hospitalization or up to 4 total doses (vs placebo)
  - **Adverse Effects:** Generally mild severity – GI intolerances, LFT abnormalities, infusion-related reactions, influenza-like symptoms, cytopenias
  - **Inclusion Criteria:** Age ≥18; PCR confirmed SARS-CoV-2 infection within past 3 days OR within the past 7 days and progressive COVID-19 disease; one of: 1) infiltrates on chest imaging 2) requiring supplemental oxygen or mechanical ventilation 3)  $S_pO_2 \leq 94\%$  on RA
  - **Exclusion Criteria:** AST or ALT >5x ULN; eGFR<30 or on dialysis; WBC<1.5; platelets<50; on or being prepared for ECMO therapy; pregnancy or breast feeding; anticipated discharge within 3 days; history of chronic liver disease; receipt of >2 doses of remdesivir prior to enrollment; receipt of convalescent plasma or IVIG for COVID-19; receipt of any interferon product in past 2 weeks; receipt of tyrosine kinase inhibitors, TNF inhibitors, interleukin inhibitors, or T- and B-cell monoclonal antibodies in past 2 weeks
- » **Regeneron Monoclonal Antibody Clinical Trial (NCT04426695)** – E-mail 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) 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
- » **Dexamethasone<sup>60-61</sup>**
  - **Dosing:** 6 mg PO or IV once daily
  - **Duration:** Up to 10 days (discontinue prior to discharge)
  - **Adverse Effects:** Hyperglycemia, hypertension, fluid retention, insomnia, increased appetite, skin rash, increased infection risk
  - **Patient Criteria:** Recommended for patients with COVID-19-related ARDS that are requiring mechanical ventilation. Consider in those with acute respiratory failure requiring 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.
  - **Notes:** A large randomized, open-label trial without placebo 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.
- » **Remdesivir Emergency Use Authorization (EUA)** – Consider for patients not enrolling into a clinical trial. Limited allocations available - please discuss clinical appropriateness with COVID ID team
  - **Dosing:** 200mg IV once, then 100mg IV daily for a recommended 5 total days of therapy
  - **Adverse Effects:** Generally mild severity – GI intolerances, LFT abnormalities, infusion-related reactions
  - **Patient Criteria:** Clinical exclusions are less rigid than for the clinical trial, such as inclusion of those with renal dysfunction. Please refer to the institutional [Ordering Remdesivir](#) guidance document for additional details and process.

**Situational (alphabetical order): Efficacy unproven, but risk/benefit may favor use in select patients; do not use outside a clinical trial**

- » **Convalescent Plasma Expanded Access**<sup>51-53</sup> (NCT04338360) – This program run centrally from the Mayo Clinic IRB, through which plasma can be sourced for local administration. NMC site participation has not been coordinated; see [uscovidplasma.org](https://uscovidplasma.org) for additional information. An EUA has been authorized for this product, but further details have not yet been released.
  - **Adverse Effects:** Primarily allergic, hemolytic, and transfusion-related reactions, such as TRALI, volume overload, etc.
  - **Inclusion Criteria:** Age  $\geq 18$ , PCR confirmed SARS-CoV-2 infection, one of: 1) dyspnea 2) RR  $\geq 30$ /min 3)  $S_pO_2 \leq 93\%$  4)  $P_aO_2/F_iO_2 < 300$  5) significant infiltrates on chest imaging 6) respiratory failure 7) septic shock 8) multi-organ dysfunction
  - **Exclusion Criteria:** None

**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.
- » **Baricitinib**<sup>38-39</sup>
  - JAK and AAK1 inhibitor anti-inflammatory agent proposed for use to prevent SARS-CoV-2 viral entry and counter COVID-19 cytokine storm. No data yet to support this use. Was evaluated in addition to standard-of-care in the most recent phase of the NIAID adaptive clinical trial; data are still outstanding. Low rates of opportunistic infections including pneumonias have been described in long-term use for rheumatoid arthritis; risk profile is unknown for short-term treatment of COVID-19.
- » **Darunavir/cobicistat**<sup>10</sup>
  - No *in vitro* or clinical data yet exist to support this use, though a clinical trial has been registered in China.
- » **Hydroxychloroquine**<sup>1-4,11,24-28,33-36,44-46,54-58</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. Being evaluated in addition to standard-of-care in the next phase of the NIAID adaptive clinical trial. Their long-term adverse effect profiles are also 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. Non-peer-reviewed reports are conflicting about whether approved doses 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. Preliminary data from a third large clinical trial also indicated no mortality benefit and this arm of the trial was terminated from further enrollment.
- » **Nitazoxanide**<sup>11-12</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. 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 unquantified. Both tocilizumab and the related IL-6 inhibitor sarilumab are being investigated in clinical trials; preliminary summary statements are conflicting and do not

provide necessary details for clinical decision-making. A recent Phase III RCT of tocilizumab did not meet its endpoints of improved clinical status or decreased mortality at week 4 when compared to placebo.

### 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 well supported. Conversely, these agents should not be initiated solely for treatment of COVID-19 disease.
- » **Anticoagulants**<sup>41,63</sup>
  - ASH has released statements for anticoagulation management. COVID-19 patients 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. A recent observational study of patients receiving systemic anticoagulation found improved survival in a subset of intubated patients, however, this result should be interpreted with caution due to multiple potential biases. This study also found that therapeutic anticoagulation led to no significant increase in hemorrhage. For patients with recurrent clotting of central access or CRRT/ECMO circuits, an increase in the intensity of anticoagulation can be considered in a patient-specific fashion. Development of COVID-19-associated coagulopathy is associated with a poor prognosis and identification and treatment of the underlying cause should continue to be the focus of treatment efforts. Upon discharge, all COVID-19 patients should be educated on signs and symptoms of VTE and thromboprophylaxis should be considered given patient-specific 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>
  - CDC, WHO, and SCCM initially did not recommend steroid therapy for COVID-19 outside of a specific alternative indication, such as sepsis, ARDS, or COPD. Based on recent evidence, IDSA now recommends 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. NIH guidelines recommend 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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