COVID-19 Antiviral and Pharmacotherapy Information

Supportive therapy is the cornerstone of treatment. No antiviral therapy option can currently be recommended in addition to supportive care, nor should any be considered comparatively superior for SARS-CoV-2 given the available data. Recent IDSA and NIH guidelines reinforce this general approach to pharmacological treatment\textsuperscript{32,40}. It is also currently unclear whether multidrug regimens provide any additional benefit in the treatment of COVID-19. Given the current lack of data over monotherapy regimens and the added toxicity of multidrug regimens, it is very unlikely that multidrug combinations will produce a favorable risk/benefit ratio.

Antiviral therapy should only be considered in patients with confirmed infection. 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 (clinical trial enrollment):

Remdesivir Clinical Trial (NCT04280705) – The remdesivir phase of the NIAID adaptive trial has completed enrollment. This trial will be unavailable for enrollment for a few weeks while data are analyzed for the next phase is prepared with baricitinib.

- **Dosing**: 200mg IV once, then 100mg IV daily for duration of hospitalization or up to 10 total days
- **Adverse Effects**: Generally mild severity - GI intolerances, LFT abnormalities, infusion-related reactions
- **Inclusion Criteria**: Age ≥18, PCR confirmed SARS-CoV-2 infection within past 3 days, one of: 1) infiltrates on chest imaging 2) requiring supplemental oxygen or mechanical ventilation 3) respiratory physical exam findings and $S_2O_2 ≤ 94\%$ on RA
- **Exclusion Criteria**: AST or ALT >5x ULN, eGFR<50 or on dialysis, pregnancy or breast feeding, anticipated discharge within 3 days

Remdesivir Expanded Access (NCT04323761) – This is an IRB-approved medication expanded access program. The UNMC Clinical Research Center (llarson@unmc.edu) can be contacted for the latest status.

- **Dosing**: 200mg IV once, then 100mg IV daily for up to 10 total days
- **Adverse Effects**: Generally moderate severity – GI intolerances, LFT abnormalities, infusion-related reactions
- **Inclusion Criteria**: Age ≥18, PCR confirmed SARS-CoV-2 infection or known contact of a confirmed case with PCR pending, requiring mechanical ventilation
- **Exclusion Criteria**: AST or ALT >5x ULN, eGFR<30 or on dialysis, pregnancy, multi-organ failure, requiring vasopressor support

Convalescent Plasma Expanded Access (NCT04338360) – This program is being 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 for additional information.

- **Adverse Effects**: Primarily allergic, hemolytic, and transfusion-related reactions, such as TRALI, volume overload, etc.
- **Inclusion Criteria**: Age ≥18, PCR confirmed SARS-CoV-2 infection, one of: 1) dyspnea 2) RR ≥ 30/min 3) $S_2O_2 ≤ 93\%$ 4) $P_{a}O_2/F_{O_2} < 300$ 5) significant infiltrates on chest imaging 6) respiratory failure 7) septic shock 8) multi-organ dysfunction
- **Exclusion Criteria**: None

Hydroxychloroquine\textsuperscript{1,4,11,24-28,33-36,44-46}

- **Dosing**: 400mg PO BID x2 doses, then 200mg PO BID. Preferentially give with food.
- **Duration**: 5-10 days. Up to 20 total days of therapy have been reported in manuscripts.
- **Adverse Effects**: Generally moderate severity - GI intolerances, cytopenias, QT prolongation, headaches, dizziness
- **Notes**: An in vitro inhibitor of SARS-CoV-2; a non-peer-reviewed report proposed that approved doses achieve adequate lung concentrations to inhibit SARS-CoV-2, but not necessarily serum concentrations. There are multiple inconclusive, uncontrolled, or non-peer-reviewed early clinical reports describing use and the bulk of clinical reports to date have released negative results; one research group is responsible for most of the positive clinical reports. Being investigated for all stages of disease severity; use is most appropriate only within a registered clinical trial. Use with caution in pediatrics. Impact of immunosuppressive effects is unknown. Has been studied in combination with azithromycin, without additive benefit but potential for additive cardiac toxicities, as recently highlighted in an FDA warning. Use for COVID-19 may exacerbate current shortages for patients with autoimmune indications where this drug has a well-accepted place in therapy.
» **Lopinavir/ritonavir**\(^{13-14,18,44,47}\)
- **Dosing:** 400/100mg (2 tabs) PO BID
- **Duration:** 5-10 days. Up to 14 total days of therapy have been reported, but many patients have adverse effects requiring early termination.
- **Adverse Effects:** Occur in most patients and can be moderate/severe – GI intolerances, hepatitis, and LFT abnormalities
- **Notes:** Multiple *in vitro* studies suggesting activity. A non-peer-reviewed report proposed that approved doses achieve adequate lung concentrations to inhibit SARS-CoV-2, but not necessarily serum concentrations. Early clinical reports are inconclusive. One underpowered randomized trial with LPV/r initiated late in the disease course in moderately-ill hospitalized patients did not demonstrate benefit. Another underpowered randomized study in mild/moderate disease also showed no benefit, and neither of these studies demonstrated an antiviral effect with LPV/r. Use is most appropriate only within a registered clinical trial; further clinical trials are ongoing, particularly in early disease. Many clinically significant drug-drug interactions. Adverse effects are common.

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

- **Angiotensin/RAS Blocking Agents (ACEi/ARBs)**\(^{17}\)
  - Do not discontinue these therapies for COVID-19 disease. Multiple professional societies in cardiology and nephrology have reviewed the current data and conclude that the evidence suggesting discontinuation of ACEi/ARB therapy to decrease risk for more severe COVID-19 is not well supported at this time.

- **Anticoagulation**\(^{41}\)
  - 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 therapeutic anticoagulation in these patients is unknown. 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.

- **Azithromycin**\(^{24,26,36}\)
  - No activity for SARS-CoV-2. Studies of combination therapy with hydroxychloroquine do not convincingly suggest added benefit with azithromycin combination therapy, given study limitations and concern for excess toxicity and antibiotic overuse.

- **Baricitinib**\(^{38-39}\)
  - 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; will be evaluated in addition to standard-of-care in the next phase of the NIAID adaptive clinical trial. 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**\(^{10}\)
  - No *in vitro* or clinical data yet exist to support this use, though a clinical trial has been registered in China.

- **Ibuprofen/NSAIDs**\(^{22-23}\)
  - 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.

- **Inhaled Pulmonary Vasodilators**\(^{19-21}\)
  - Limited *in vitro* evidence nitric oxide may inhibit coronaviruses. However, SCCM guidelines recommend against use of nitric oxide given an unfavorable risk/benefit ratio for ARDS; this agent is being investigated in clinical trials. Other agents in this group are only recommended in the presence of clinical factors where they would routinely be considered for critical care.

- **Interferons**\(^{8-9}\)
  - Typically used in combination with ribavirin, interferons have been studied for patients with other coronaviruses, with mixed results. Their adverse effect profiles are also generally unfavorable.

- **Ivermectin**\(^{31,42-44}\)
  - 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.

- **Nitazoxanide**\(^{15-12}\)
  - 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.
Osdematamivir
- Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected.

Ribavirin (oral)7-9
- 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).

Steroids5,6,19,37
- CDC, WHO, and SCCM do not recommend steroid therapy for COVID-19 outside of a specific alternative indication, such as sepsis, ARDS, or COPD. Preliminary clinical experience reporting benefit for low-dose therapy in some patients; this is being investigated in multiple clinical trials. Systematic reviews in other coronavirus and respiratory viral infections have demonstrated no survival benefit and possible harm.

Tocilizumab15-16,29-30,48-49
- 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.

References


23) WHO Twitter clarification on ibuprofen. [https://twitter.com/WHO/status/1240409217997189128].


37) Steroid clinical trials (NCT04244591, NCT04325061, and NCT04323592): [https://clinicaltrials.gov/].


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