UW Medicine Interim Treatment Guidelines for SARS-CoV-2 Infection/COVID-19

There are no FDA-approved or clinically proven therapies for treatment of SARS-CoV-2. Clinical trial data is rapidly emerging from other parts of the world, and these guidelines will be updated frequently. These guidelines reflect what is known about therapies that have in vitro activity against coronaviruses, have been used to treat other coronaviruses, such as SARS or MERS, or may theoretically target of the underlying pathophysiology of severe acute respiratory syndrome due to SARS-CoV-2.

Our best opportunity to understand how to treat COVID-19 is to study stepwise interventions and compare findings to the current best available standard. Although there are interventions available, these are not evidence based and should not be considered effective. The interventions are FDA-approved for other indications and have known toxicity profiles; dosing is based on FDA-approved dosing schedules. When available, clinical trials are preferred. Some medications are in limited supply, and use of these medications for off-label indications will affect patients who need the medications for indicated conditions. Therefore, off-label medications should be reserved for those who are at highest risk for complications as outlined below. Furthermore, patients should recognize that there is a potential RISK of these medications without known benefit. The decision to treat patients should involve shared decision making.

Please call the ID team with questions about management of specific patients.
Algorithm for management of patients with COVID-19 at UW Medicine

Evaluate for clinical trial eligibility

VTEU Remdesivir* (NCT04280705)

Not eligible

- URTI/LRTI without O2 requirement
  - No risk factors
    - Symptomatic treatment
  - Risk factors+
    - Hydroxychloroquine
      - Management: Monitor for signs of cytokine release syndrome
      - Daily Labs: CMP, CBC, LDH, D-dimer, Fibrinogen, PT/PTT, IL-6, CRP, Ferritin

- LRTI, with O2 requirement
  - Hydroxychloroquine
  - Management: CXR, Chest CT as clinically indicated, not necessary for diagnosis or staging
  - Daily Labs: CMP, CBC, LDH, D-dimer, Fibrinogen, PT/PTT, IL-6, CRP, Ferritin

- LRTI, mechanical ventilation
  - Hydroxychloroquine
  - Management: Consider compassionate use remdesivir **

- URTI: Upper respiratory tract infection, defined as sore throat, URI symptoms, with LRTI symptoms. LRTI: Lower respiratory tract infection, defined as cough, shortness, of breath, hypoxemia, or radiographic changes on CXR. VTEU: Vaccine Treatment and Evaluation Unit
- *Inclusion/exclusion criteria≥18 years, non-pregnant. Lab confirmed SARS-CoV-2 infection PCR within 72 hrs of randomization, clinical or radiologic evidence of LRTI. Exclusion: AST/ALT>5x ULN, Stage 4 CKD/dialysis, pregnancy: covidtrial@uw.edu or (206) 598-4942.
- **Information for compassionate use (https://rdvcu.gilead.com). Exclusion: multi-organ failure, pressor requirement, ALT levels > 5 X ULN, continuous veno-venous hemofiltration  CrCl<30 mL/min
- ***Dual therapy not recommended. Lopinavir/ritonavir supply is limited at UW Medicine, ID consult required.
- +Risk factors: Age >60, pulmonary disease, chronic kidney disease, transplant, DM, HTN, CVD, cardiomyopathy, biologic immune modulators (many), other immunosuppressive medications including chronic corticosteroid treatment at the equivalent of 20 mg of oral prednisone or more daily, detectable HIV VL or CD4 count<200 cells/mm3, HCW/first responder with known/probable aerosol exposure
Table 1. Potential antiviral therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adult dose</th>
<th>Notes</th>
<th>Main toxicities</th>
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<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>400mg PO bid x 1 day, then 200mg PO bid x 4 days</td>
<td>Safe in pregnancy</td>
<td>Most toxicities are associated with long-term use; Dizziness, headache, loss of appetite, nausea, vomiting</td>
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<tr>
<td>Pro-drug of chloroquine available in 200 mg tablets¹</td>
<td>No dosing adjustment for renal or hepatic impairment or obesity</td>
<td>Metabolized by CYP2C8, CYP3A4 and lesser extent CYP2D6</td>
<td>LFT abnormalities</td>
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<td></td>
<td>Pharmacy can compound suspension if requested</td>
<td>~20-30% excreted unchanged in urine.</td>
<td>QTc prolonging effects; monitor QTc – see monitoring guidance below</td>
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<td></td>
<td>Chloroquine phosphate 500 mg PO q12h for 10 days, equivalent to 300mg chloroquine base)</td>
<td>Anuric patient steady state levels are ~30% higher than patients w/ normal renal function</td>
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Additional Information

Clinical Trial and Compassionate Use Agents

REMDESIVIR

**Mechanism of Action:** nucleotide analogue, initially developed for treatment of Ebola. Works by inhibiting RNA-dependent RNA polymerase.

**Evidence Summary:** *In-vitro* activity against MERS and SARS, and has shown efficacy in animal models. (Gordon et al, 2020, de Wit et al 2020, Sheahan et al 2017)\(^2\)-\(^4\). It has been shown to inhibit SARS-CoV-2 *in vitro*. (Wang et al, 2020)\(^5\).

Reports of use in patients with SARS-CoV2 in China, no data published yet.

Remdesivir was used in a single patient with COVID-19 infection in Washington State, administration was associated with clinical improvement (Holshue et al, 2020)\(^6\).

**Clinical Trials underway:** NCT04257656, NCT04252664; NCT04280705, NCT04292899, NCT04292730, NCT04302766

NCT04280705 is a randomized placebo-controlled clinical trial being conducted at UWMedicine

Contact: covidtrial@uw.edu or (206) 598-4942

**Compassionate Use:** [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/). The requesting physician and pharmacist must complete all relevant paperwork to qualify a patient for this program.

1. **Key Inclusion criteria:** Hospitalization, confirmed SARS-CoV-2 by PCR, invasive mechanical ventilation
2. **Key Exclusion criteria:** Evidence of multi-organ failure, pressor requirement to maintain blood pressure, ALT levels > 5 X ULN, Cr Clearance < 30 mL/min or dialysis or continuous veno-venous hemofiltration, pregnancy, use of other experimental antiviral agents for COVID-19.

**Toxicities and Drug Metabolism:** Elevated transaminases, reversible kidney injury, hypotension during infusion. AVOID acetaminophen use through day 15.
EMPIRIC THERAPIES

HYDROXYCHLOROQUINE (PLAQUENIL)/CHLOROQUINE

Mechanism of action: Heme polymerase inhibitor; increases the pH of the phagolysosome, which interrupts virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS-CoV (Colson et al, 2020). 7

Evidence Summary: Hydroxychloroquine has been shown to inhibit replication of SARS-CoV2 in vitro (Wang et al, 2020) 5. Chloroquine has been shown to inhibit many viruses in vitro. However, it has not been shown to be an effective antiviral in vivo in limited trials. In an animal model of chikungunya virus infection, chloroquine delayed the immune response, resulting in lack of viral clearance (Reviewed in Touret & deLamballerie, 2020) 8. In a recently published open-label, non-randomized study, of 20 patients with COVID-19 who received hydroxychloroquine 200 mg three times daily 14 (70 %) had clearance of virus from the nasopharynx at day 6, compared to 2 (12.5%) of 16 who did not receive hydroxychloroquine (p= 0.001) (Gautret et al, 2020 in press).

Clinical Trials underway: ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029741, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, ChiCTR2000029542

No clinical trials available for treatment at UWMedicine.

Toxicities and drug metabolism

- Nausea and diarrhea, both mild
- QTc prolongation
- May increase levels of cyclosporine
- Retinopathy with prolonged use (>5 years), not in the acute setting

Administration

- 400 mg twice daily X 1 day, followed by 200 mg given twice daily for 4 days (Yao et al, 2020) 9
- Cardiac monitoring guidance
  - Obtain baseline EKG for Place the patients on telemetry and get baseline EKG (EKG #1)
  - If on telemetry, check QTc and see if that corresponds to EKG QTc -- If yes, please use telemetry for further QTc monitoring. Otherwise Get EKG#2 and daily EKG as noted below
  - Discontinue all other QT prolonging agents
  - Do not start Hydroxychloroquine if baseline QTc > 500 msec (or QTc > 550 msec in wide QRS patients) (or ) discuss with cardiology if benefit vs risk is deemed high
  - Be cautious if Baseline QTc > 470 msec (or QTc>520 msec in wide QRS patients)
  - Check Telemetry Qtc/ Acquire EKG#2 - 2 hours after the 2nd dose of 400 mg Hydroxychloroquine
  - If QTc increases by less <50 msec; and if absolute QTc < 500 msec (<550 in wide QRS) - Can go to lower dose
- If QTc increases by >50 msec; or if absolute QTc > 500 msec (>550 in wide QRS) - Go to lower dose and **recheck EKG daily for 2 days.**
- Any evidence of Torsades on Tele -- D/c Hydroxychloroquine regardless of QT interval.
- **Note - * Wide QRS defined as QRS > 120 msec**

**Rationale for use:** Hydroxychloroquine is an inexpensive and generally safe drug for short term use, with few drug-drug interactions. While it is **unknown** if it is effective to treat COVID-19, there is a favorable risk:benefit and cost ratio. Multiple trials are ongoing, and this recommendation will be updated when further data is available.

### TOCILIZUMAB

**Mechanism of Action:** Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that is FDA-approved for the treatment of rheumatoid arthritis. More recently, it has been used for the treatment of severe/life-threatening cytokine release syndrome after CAR-T cell therapy. An increased risk for developing serious infections is reported, primarily in individuals being treated with concomitant immunosuppressants, such as methotrexate or corticosteroids. There are limited data from uncontrolled studies about the potential benefit of tocilizumab in patients with COVID-19. There are ongoing randomized, controlled clinical trials in China and the U.S. using tocilizumab in this context.

**Evidence summary:** In an open-label study in 21 patients in China with documented COVID-19 and severe oxygenation impairment, including RR≥30 breaths/min, Sp02≤93% on room air, PaO2/FiO2<300mmHg or need for mechanical ventilation, shock, or combined organ failure, tocilizumab reduced oxygen requirement, normalized the CRP, and increased the lymphocyte count to normal; 19 of the 21 patients were discharged (Xu 2020).

**Guidelines to determine when to administer are being determined. Please discuss with ID if tocilizumab is being considered.**

**Ongoing Clinical Trials:** ChiCTR2000029765

No clinical trials available at UW Medicine.

**Adverse events**

- LFT abnormalities
- Local injection site reactions
- Increased risk of serious infections, including tuberculosis and invasive fungal infections as well as other opportunistic pathogens.
- Given that tocilizumab is independently associated with increased risk for active *M. tuberculosis* infections, we recommend screening *M. tuberculosis* should be considered in patients with risk factors for exposure using a blood interferon gamma-release assay (IRGRA) (i.e. Quantiferon-TB Gold).

**Administration:**
- Tocilizumab 400 mg IV x 1
- Check IL-6 and inflammatory markers (IL-6, CRP, Ferritin, LDH, fibrinogen, D-dimer) prior to administration and consider daily monitoring.

**Rationale for use:** Cytokine release syndrome (CRS) appears to be an important component of the critical illness associated with COVID-19. Tocilizumab has not been rigorously studied for COVID-19. Until more data are available, we do not recommend the routine use of tocilizumab in patients with severe or life-threatening COVID-19.

**Recommendations:**
- Until more data are available, the routine use of tocilizumab in patients with severe or life-threatening COVID-19 is not recommended.
- In the interim, we recommend the following testing of all hospitalized patients with COVID-19, starting on the day of admission or diagnosis:
  → Daily for the first 7 days after admission: CBC and CMP, LDH, D-dimer, fibrinogen, PT/PTT, IL-6 (available in-house), CRP, and ferritin
  → After 7 days, testing may be spaced to every other day for patients who are not improving and stopped for patients who are recovering, unless otherwise indicated.

**AGENTS NOT RECOMMENDED:** Several agents have been reported for management of COVID-19. Given a combination of lack of efficacy, potential toxicity, and cost, the following agents are NOT RECOMMENDED for treatment of COVID-19.

**ANTIBIOTICS:**
Hospitalized patients in China were frequently treated with antibiotics, although the true incidence bacterial co-infection has not been fully characterized. We do not recommend routine antibiotics for patients with COVID-19 unless there is another indication for antibiotics.

**LOPINAVIR/RITONAVIR (KALETRA)**
Lopinavir/ritonavir is a fixed-dose combination antiretroviral for treatment of HIV infection. Both drugs are protease inhibitors; ritonavir slows lopinavir metabolism (boosts lopinavir). This medication is hypothesized to inhibit SARS-CoV-2-encoded protease; however, inhibitory lopinavir levels exceed achievable blood levels.

**Evidence Summary:** In vitro activity against SARS-CoV2, retrospective trial in patients with SARS. Improved outcomes when used as initial treatment compared to matched cohort (2.3% death vs 15.6%), no difference in outcomes when used as rescue therapy. (Chan 2003)\(^\text{12}\). In a randomized, open-label study of lopinavir-ritonavir 400-100 mg BID x 14 days vs. placebo for treatment of COVID-19 were enrolled in China (ChiCTR2000029308)\(^\text{13}\). The primary endpoint was time to clinical improvement, secondary endpoints included 28 day mortality and detectable RNA levels during therapy. 199 patients with laboratory documented SARS-CoV-2 infection and evidence of impaired oxygenation (O2 sat≤94% or PaO2:Fio2<300 mm Hg) were enrolled. There was no difference in primary or secondary outcomes. Based on these data, lopinavir-ritonavir is not recommended.
Ribavirin +/- interferon (alpha-2a/b, beta-1)

During the SARS epidemic as well as the MERS-CoV epidemic, ribavirin was often used in clinical practice. However there is no clear evidence of clinical benefit, and toxicities (both early and late) were common. Notably, ribavirin did not inhibit viral growth in one study at concentrations attainable in human serum\(^\text{14}\). The largest clinical study to date on the use of ribavirin plus interferon was a multicenter observational study of MERS-CoV patients, comparing 144 patients who received ribavirin with some form of interferon (IFN $\alpha$-2a, IFN $\alpha$-2b or IFN $\beta$-1) with 205 who received neither\(^\text{15}\). In crude and multivariable analyses, ribavirin and IFN was associated with higher 90-day mortality compared with no treatment; with no difference in these groups noted after accounting for time-varying confounders. Given this and the significant toxicities related to ribavirin (with or without IFN), we do not recommend use at this time.

Interferons

There is no clinical data on monotherapy with any of the interferon formulations for SARS-CoV, MERS-CoV or the current SARS-CoV2 though in vitro data suggest that IFN $\alpha$ might have inhibitory effects against SARS-CoV\(^\text{14}\). Additionally, a randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in death or ventilator-free days\(^\text{16}\). There is insufficient evidence to support the use of interferons, alone or in combination with other agents, at this time. The pathophysiology of respiratory failure caused by COVID-19 appears to involve an aberrant immune response, which may be exacerbated by interferon administration.

Corticosteroids

Data on the use of corticosteroids for novel coronavirus infections are quite variable with mixed results and little clarity on appropriate dosing or timing. In SARS-CoV, any steroid therapy was associated with increased need for ICU admission or mortality\(^\text{17}\), although lower mortality and shorter hospitalization was seen among critical cases\(^\text{18}\) and pulse steroids did appear to result in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids\(^\text{19}\). In MERS-CoV, however, steroid therapy was evaluated both by dose and duration and no effect was seen on mortality; however, increased time to viral clearance was observed\(^\text{20}\). One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU\(^\text{21}\). In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death\(^\text{22}\); short courses of low-moderate dose steroids has also been recommended in critically ill patients\(^\text{23}\). Given these mixed data, and the potential for steroid therapy to worsen disease severity and lead to secondary infections, routine use of steroids is not recommended at this time. Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) could be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

No evidence exists to support its use in mitigating the inflammatory response associated with COVID-19. There have been concerns voiced regarding clinical worsening of COVID-19 in patients taking ibuprofen but these are unsubstantiated at this time. We do not recommend NSAIDS primarily due to lack of evidence for benefit. These drugs can also exacerbate acute kidney injury in the setting of serious illness.
Immune globulin (IVIG)

There is little rationale for this use in COVID-19 since available IVIG products are unlikely to contain specific antibodies to SARS-CoV-2, given lack of widespread immunity. IVIG has been suggested to have anti-inflammatory or immunomodulatory effects; however, given the lack of conclusive clinical data for treatment of novel coronaviruses and national shortage of IVIG products, routine use of IVIG is not recommended at this time.

Angiotensin-receptor blockers and Angiotensin converting enzyme blockers

SARS-CoV-2 uses ACE2 receptor for cell entry in the lungs and thus the course of the infection could be impacted by the use of these antihypertensive agents. Furthermore, ACE2 itself is protective against lung injury, thus reduced levels may exacerbate pulmonary complications. There is no consensus on whether these drugs would exacerbate or ameliorate COVID-19 disease. No clinical data currently exist to guide the initiation or cessation of these agents in patients with SARS-CoV19 infection. The HFSA, ACC and AHA emphasize the lack of experimental or clinical data on these class of drugs in COVID-19 and recommend that patients currently taking these medications for known beneficial indications (HF, HTN, or ischemic heart disease, for example) be advised to continue them. They advise against adding/removing beyond what would be done in standard practice and urge individualized treatment decisions based on patient’s clinical presentation and hemodynamics. Ongoing clinical trials, including of recombinant ACE2, are currently underway (NCT04287686).

These guidelines were drafted by a working group, including Jeannie Chan, Margaret Green, Robert Harrington, Rupali Jain, Christine Johnston, H. Nina Kim, David Koelle, Manoj Menon, Alpana Waghmare

The guidelines were adopted from The America Society of Transplantation and Cellular Therapy Interim Guidelines for COVID-19 Management in Hematopoietic Cell Transplant and Cellular Therapy Patients, V 1.2, March 17, 2020.

References

1. PLAQUENIL®


