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 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. The Infectious Disease Society of America (IDSA) has provided guidance that medications should not be given outside of clinical trials. 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. Supportive care remains the mainstay of treatment for patients with COVID-19.

Please call the ID or COVID team with questions about inpatient management of specific patients.

For outpatients with COVID-19, we do not recommend therapy outside of a clinical trial. If patients have risk factors for progression to lower tract disease (e.g. Age>60, cardiopulmonary disease, renal disease, DM, immunosuppression), shared decision making regarding use of off-label medications with the patient could be considered, with discussion of risks and benefits.

Post exposure prophylaxis (PEP) of COVID-19 is not currently recommended. For household contacts or health care workers with COVID-19 exposure, there is an ongoing randomized clinical trial of hydroxychloroquine PEP at UW Medicine (NCT04328961). https://depts.washington.edu/covid19pep/ Contact: covid19pep@uw.edu
SUMMARY of UW Medicine guidelines

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

There are no FDA-approved or clinically proven therapies for treatment of SARS-CoV-2. **When available, clinical trials are preferred.** For inpatient, use ordersets called “Confirmed COVID-19 Protocol Orders” and/or “Hydroxychloroquine for COVID”

<table>
<thead>
<tr>
<th>Patient population with COVID-19</th>
<th>Risk Factors*</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>No</td>
<td>No therapy recommended at this time</td>
</tr>
<tr>
<td>Outpatient</td>
<td>Yes</td>
<td>Shared decision making with patient; Consider hydroxychloroquine</td>
</tr>
<tr>
<td>Upper or Lower Respiratory Tract infection without O2 requirement</td>
<td>No</td>
<td>Symptomatic Treatment HMC Only: Contact ORCHID study team; <a href="mailto:orchidstudy@uw.edu">orchidstudy@uw.edu</a></td>
</tr>
<tr>
<td>Upper or Lower Respiratory Tract infection without O2 requirement</td>
<td>Yes</td>
<td>HMC Only: Contact ORCHID study team <a href="mailto:orchidstudy@uw.edu">orchidstudy@uw.edu</a> Consider Hydroxychloroquine 400mg po BID x 1 day, then 200mg po BID x 4 days <strong>Total Duration: 5 day</strong> Get baseline EKG</td>
</tr>
<tr>
<td>LRTI with O2 requirement</td>
<td>--</td>
<td>HMC only: Contact study team; <a href="mailto:orchidstudy@uw.edu">orchidstudy@uw.edu</a> Start Hydroxychloroquine: 400mg po BID x1day, then 200mg po BID x 4 days <strong>Total Duration: 5 day</strong> Get baseline EKG Monitor for signs of worsening LRTI, cardiac dysfunction and cytokine store Consult ID for additional treatment options</td>
</tr>
<tr>
<td>LRTI with mechanical ventilation</td>
<td>--</td>
<td>Contact Study Team <a href="https://depts.washington.edu/covid19pep/covid19pep@uw.edu">https://depts.washington.edu/covid19pep/covid19pep@uw.edu</a></td>
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*Risk factors: Age>60, cardiopulmonary disease, renal disease, DM, immunosuppression, pregnancy; See complete guidelines for information about management of pregnant individuals.

**Cardiac monitoring for ACUTE CARE:**

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<th>Routine Monitoring:</th>
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*highly-sensitive troponin I results will be reported to cardiology

**Monitoring Routine Labs and Inflammatory Response** (*Labs can be discontinued after 10 days as per clinical judgement*)

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*Imaging* CXR and CT scan as clinically indicated. Not necessary for diagnosis or staging of COVID-19.
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.

*Inclusion/exclusion criteria: ≥18 years, currently hospitalized, symptoms of acute respiratory infection, and Lab confirmed SARS-CoV-2 infection within 10 days or high clinical suspicion. Exclusion: pts who are prisoners, who are pregnant/breastfeeding; seizure disorder, diagnosis of long QT syndrome, Qtc >500 w/in 72 hrs of enrollment, known allergy, receipt of the following medications in 12 hours prior to enrollment: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol or receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment.

Email: orchidstudy@uw.edu

**Information for compassionate use (https://rdvcu.gilead.com). No longer accepting new individuals, with exception of pregnant women and children <18 years of age with confirmed COVID-19 and severe manifestations of disease. We may have expanded access program: For UWMC, contact Paul Pottinger, MD (abx@uw.edu) For HMC, contact Shireesha Dhanireddy (sdhanir@uw.edu); For NWH, contact Maggie Green (mlgreen@uw.edu)

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 >20 mg oral prednisone daily, detectable HIV VL or CD4 count<200 cells/mm3, HCW/first responder with known/probable aerosol exposure, pregnant individuals* See Pregnancy considerations

* Pregnancy considerations: OB/MFM consult required for hospitalized confirmed pregnant or lactating COVID-19 patients; informed shared decision-making requires counseling regarding balancing maternal and fetal risk/benefit. Pregnancy as a COVID-19 risk factor: While limited currently available data do not indicate pregnant individuals are more susceptible to COVID-19 infection or that pregnant individuals with COVID-19 have more severe illness, consider hydroxychloroquine given reassuring safety-profile and additional maternal/fetal risks if maternal critical illness develops.

Imaging: CT requires OB/MFM to discuss risk/benefits with patient prior to CT scan. Labs: During pregnancy lab values may be harder to interpret (e.g. D-dimer and fibrinogen typically elevated; Hgb/Hct, Cr, ferritin typically lower. “Normal” values for non-pregnant individuals (e.g. HCT 40, Cr of 1.0) can be considered elevated and may represent laboratory evidence of preeclampsia. It is critical to work with OB/MFM consult team to interpret laboratory values in pregnancy to prevent missing abnormal laboratory values that may appear “normal” to clinicians who typically work with non-pregnant adults.

Consider enrolling patient in: PRIORITY (Pregnancy CoRonavIrus Outcomes RegisTRY), a nationwide registry for pregnant and postpartum individuals with suspected COVID-19 or confirmed diagnosis https://priority.ucsf.edu/
Recommended Laboratory Monitoring for Patients with Laboratory Confirmed COVID-19

A COVID-19 orderset is active within ORCA “Confirmed COVID-19 Protocol Orders”. This orderset was created with a multidisciplinary team of hospitalists, cardiologists, pulmonologists, infectious disease and laboratory medicine physicians, and administration. The orderset reflects a balance between minimizing PPE and unnecessary work up and cost and learning about this emerging infection so we can best care for our patients.

**Cardiac Monitoring**

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* highly-sensitive troponin I results will be reported to Cardiology

**EKG/Telemetry: To minimize HCW exposure and PPE usage, EKGs will be done by COVID+ patient bedside nurse during the normal course of patient care. Standard protocol will be followed to decontaminate EKG equipment following their use in COVID+ patients (i.e., same protocol used in patients positive for MRSA or C. difficile).

Indications for Telemetry: Use Institutional Standard indications for Telemetry, Elevation in biomarkers of cardiac injury (TNI >0.03), ICU Status

**Monitoring Routine Labs and Inflammatory Response**

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**Imaging**

CXR and CT scan as clinically indicated. Not necessary for diagnosis or staging of COVID-19.
## Potential antiviral therapies

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<th>Adult dose</th>
<th>Notes</th>
<th>Main toxicities</th>
</tr>
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<tbody>
<tr>
<td>Hydroxychloroquine available in 200 mg tablets(^2)</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</td>
</tr>
<tr>
<td></td>
<td><strong>Total Duration: 5 days</strong></td>
<td>Metabolized by CYP2C8, CYP3A4 and lesser extent CYP2D6</td>
<td>Dizziness, headache, loss of appetite, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>No dosing adjustment for renal or hepatic impairment or obesity</td>
<td>~20-30% excreted unchanged in urine.</td>
<td>LFT abnormalities</td>
</tr>
<tr>
<td></td>
<td>Pharmacy can compound suspension if requested</td>
<td>Anuric patient steady state levels are ~30% higher than patients w/ normal renal function</td>
<td>QTc prolonging effects; monitor QTc – see monitoring guidance below</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>We do not recommend co-administration with azithromycin (see text below)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If hydroxychloroquine is unavailable, Chloroquine phosphate 500 mg PO q12h for 10 days (equivalent to 300mg chloroquine base)</td>
</tr>
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</table>
Additional Information

Clinical Trial and Compassionate Use Agents

REMDESIVIR


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)\(^3\-5\). It has been shown to inhibit SARS-CoV-2 *in vitro*. (Wang et al, 2020)\(^6\).

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.\(^7\)

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

Pregnancy: All the Remdesivir trials listed above exclude pregnant and breastfeeding individuals including NCT04280705 (UWMedicine). Pregnanat women were included in the Ebola Virus Disease trial which included Remdesivir\(^8\). 6.1% (17/277) of women enrolled were pregnant at the time of EVD diagnosis: of whom 6/77 (7.8%) were randomized to Remdesivir. In the severe adverse event (SAE) supplemental material there were no maternal, pregnancy or neonatal related SAE noted in the Remdesevir group.

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. Per Gilead website as of 3/22/2020, they unable to accept new individual compassionate use requests, UNLESS the requests are for pregnant women and children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

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, use of other experimental antiviral agents for COVID-19. Pregnancy not currently an exclusion criteria.

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.\(^9\)

Evidence Summary: Hydroxychloroquine has been shown to inhibit replication of SARS-CoV2 in vitro (Wang et al, 2020)\(^6\). 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.\(^10\) In a recently posted 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)\(^11\). Hydroxychloroquine has been granted an Emergency Use Activation through the FDA. The EUA allows unapproved medical products in an emergency to treat conditions when there are no adequate, approved, and available alternatives (FDA.gov).

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

The ORCHID trial (NCT04332991) is recruiting hospitalized patients at Harborview Medical Center.

*Inclusion/exclusion criteria: ≥18 years, currently hospitalized, symptoms of acute respiratory infection, and Lab confirmed SARS-CoV-2 infection within 10 days or with high clinical suspicion for COVID-19 (cough less 10 days, bilateral pulmonary infiltrates on chest imaging or new hypoxemia as SpO2 < 94% on room air, and no alternative explanation for symptoms of acute respiratory infection. Exclusion: pts who are prisoners, who are pregnant/breastfeeding or have a seizure disorder, diagnosis of long QT syndrome, Qtc >500 w/in 72 hrs of enrollment, known allergy, receipt of the following medications in 12 hours prior to enrollment: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol or receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment.

Email: orchidstudy@uw.edu

While there are no current trials available for treatment at UWMedicine, the COVID-19 PEP Study is evaluating its use for post-exposure prophylaxis (NCT04328961) https://depts.washington.edu/covid19pep/

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

Pregnancy: To the best of our knowledge, all listed clinical trials above exclude pregnant and breastfeeding individuals. Hydroxychloroquine is used routinely in pregnancy for indications other than COVID-19; a recent meta-analysis of 800 women taking hydroxychloroquine in pregnancy found no increase in pregnancy complications or congenital malformations, but noted a significant increase in spontaneous abortions that may be attributed to underlying autoimmune disease.\(^12\) Small amounts transferred in breastmilk. Pregnant and

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breastfeeding individuals are eligible for the hydroxychloroquine PEP trials at UWMedicine (PI Barnabas, Bershteyn (NCT04328961), https://depts.washington.edu/covid19pep/), current University of Minnesota trial (PI Boulware, [NCT04308668](https://depts.washington.edu/covid19pep/), and in development ACTG outpatient hydroxychloroquine/azithromycin study.

**Administration**

- 400 mg twice daily X 1 day, followed by 200 mg given twice daily for 4 days, **then discontinue**. The optimal dose and duration is not known, this dosing regimen is based on modeling of in vitro data.¹³
- **Rationale for use**: We prefer clinical trials, but 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. See text below regarding the use of hydroxychloroquine with azithromycin.

**Cardiac monitoring guidance**

**EKG/Telemetry:**

- To minimize HCW exposure and PPE usage, EKGs will be done by COVID+ patient bedside nurse during the normal course of patient care.
  - Standard protocol will be followed to decontaminate EKG equipment following their use in COVID+ patients (i.e., same protocol used in patients positive for MRSA or C. difficile).
- Patients on Hydroxychloroquine:
  - Follow updated EP recommendations for **serial EKG monitoring**
- **Indications for Telemetry:**
  - Use Institutional Standard indications for Telemetry
  - Elevation in biomarkers of cardiac injury (TNI >0.03)
  - ICU Status
General Principles

- Given the growing evidence of myocarditis and arrhythmias with COVID, HCQ should be used with caution in this group of patients. HCQ is a known QT prolonging drug.
- Discontinue all other QT prolonging agents*
- What is optimal? - QTc increase is <50 msec from baseline AND absolute QTc <500 msec (550msec if QRS >120 msec)
- What is NOT optimal? - QTc increase is >50 msec from baseline OR absolute QTc > 500 msec (550msec if QRS >120 msec) → Consider CARDIOLOGY CONSULT

EKG/Tele monitoring recommendations

- EKG#1/QTc#1 – at Baseline
- EKG#2/QTc#2 – 2-4 hrs after 2nd dose of HCQ
- If on Tele - QTc should be checked daily and documented in the chart
- If not on Tele and QTc#2 is <500 msec (or increase <50 msec) – Get pre discharge EKG
  OR if QTc#2 is >500 msec (550 if QRS>120) (or increase ≥50 msec) – Get Daily EKG for QT check
- If the patient is on a QT prolonging drug* that is considered critical for their medical/psychiatric care - then either: 1) HCQ should not be used or, 2) Discussion with Cardiology about the risk and benefits of the drug
- If patient’s QTc increases beyond 50 msec after the second dose, reduce dose as per protocol, but monitor subsequent QTCs closely on telemetry (while making sure that Telemetry QTc matches with EKG QTcs +/-20msec)
- Any questions - please Consult Cardiology email EPCovid@medicine.washington.edu
- A complete list of QT-prolonging drugs is available on https://crediblemeds.org/

The combination of AZITHROMYCIN and HYDROXYCHLOROQUINE has not been rigorously studied; it is unknown if it provides additional benefit. The combination may cause significant cardiac toxicity.

Evidence Summary:

In a small study (n = 36 patients) in France, hospitalized patients were given hydroxychloroquine (HCQ, n=20) for confirmed COVID-19 infection compared to controls (n=16)14. Providers gave azithromycin in addition to the hydroxychloroquine based on clinical judgement to prevent bacterial super infection with daily EKG. Primary endpoint was virologic clearance on day 6. At Day 6, 70% of HCQ-treated patients compared to 12.5% of control patients were virologically cured (p=0.001). At Day 6, 100% of patients (n=6) treated with combination of HCQ and azithromycin were virologically cured compared with 57% of HCQ-treated patients and 12.5% of control patients (p<0.001). These preliminary results suggest a synergistic effect of combination of HCQ and azithromycin but virologic cure is only a surrogate marker, the true clinical benefit is not yet established, and the potential additive risk of QTc prolongation should be carefully considered.

In another observational study published by the same investigators in France, 80 patients with confirmed COVID-19 infections received the combination of hydroxychloroquine 200mg TID x10 days and azithromycin 500mg x1, then 250mg qdaily x 4d. The median age was 53 years old with 41% with URI symptoms and 44% with LRI symptoms, the time between onset of symptoms to hospitalization was about 5 days11. Baseline EKG were performed, and if QTc>500msec, medication was either not started or discontinued. The primary outcomes were clinical course requiring oxygen therapy or transfer to ICU, contagiousness as assessed by PCR or viral culture, and hospital length of stay. Approximately 15% of patients require oxygen therapy and 4% of patients were transferred to the ICU, and about 81% of patients were either discharged home or transferred to step down units with an average length of stay of 5 days. Viral load tested by PCR (CT >34) were negative in 93% of patients at Day 8, and viral culture were negative in 98% of patients at Day 5. The authors concluded that clearing viral carriage may decrease risk of transmission. The limitation of the study is the lack of a control group, and lack of follow up EKG monitoring after initiation of therapy. The clinical benefits of combination hydroxychloroquine/azithromycin remain unclear. This combination is NOT recommended.
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 in individuals receiving chronic therapy with tocilizumab, primarily in individuals being treated with concomitant immunosuppressants, such as methotrexate or corticosteroids.

Evidence summary: Tocilizumab has not been rigorously studied for COVID-19. 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 of tocilizumab in China and Italy and a trial in the U.S. is forthcoming. In an open-label study in 21 patients in China with documented COVID-19 and severe oxygenation impairment, including RR≥30 breaths/min, SpO2≤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)\textsuperscript{15}. Of note all patients were also treated with an antiviral (lopinavir) and methylprednisolone.

Ongoing Clinical Trials:
ChiCTR2000029765, NCT04317092, NCT04310228, NCT04306705, NCT04331795, NCT04320615, NCT04335071, NCT04331808, NCT0433914, NCT04331795, NCT04332094

No clinical trials available at UW Medicine at this time.

Adverse events
• LFT abnormalities

Administration:
• Tocilizumab 400mg x 1

Rationale for use: A profound inflammatory response resulting in ARDS, circulatory collapse, and multiorgan failure appears to be an important component of the critical illness associated with COVID-19. A proportion of critically ill patients will exhibit shock and cardiac dysfunction, presumably due to cytokine storm resulting from the host response to viral infection. IL-6 levels have been found to elevated in patients with severe COVID-19\textsuperscript{16}. The prognosis for critically ill patients with COVID-19 is poor, with mortality ranging from 50-67% in reported case series\textsuperscript{17-19}. There is institutional experience with the use of tocilizumab for CRS after CAR-T therapy, which is mediated by IL-6.

Pregnancy: To the best of our knowledge, all listed clinical trials above exclude pregnant and breastfeeding individuals. Tocilizumab crosses the placenta and into breast milk, but at lower levels than maternal serum in limited case reports\textsuperscript{20}. In two analyses of manufacturer sponsored safety databases including 288 and 61 pregnancies, rates of spontaneous abortion and congenital anomalies for patients on this medication appear to be similar to that found in the general population\textsuperscript{21,22}. Although limited data, breastfeeding on this medication has not been associated with neonatal immunosuppression.

Recommendations:
Treatment: Until more data are available, the routine use of tocilizumab in patients with severe or life-threatening COVID-19 is not recommended. While there may be a theoretical benefit of tocilizumab in hospitalized patients to preempt critical illness, empiric use must be weighed against the availability of the drug which is needed for patients with approved indications, as well as the risk of potential harm including blunting of the antiviral response. However, the use of tocilizumab may be considered, in a shared decision making context
with ID and Pulmonary/Critical Care, in patients with severe disease exhibiting clinical deterioration despite use of empiric antiviral treatment and supportive care, in the following scenario:

- Serum IL-6 > 5x upper limit of normal (normal range = 0-6)
- Persistent fever with temperature ≥38°C AND/OR:
  - Hypoxemic respiratory failure requiring noninvasive or invasive mechanical ventilation
  - Hemodynamic instability requiring vasopressors or inotropic support.

CONTRAINDICATIONS:

- Active Tuberculosis
- Sepsis by other pathogens (definitive)
- Transaminases 10 times above reference values (relative)
- Neutropenia (<1000 cell/mm3) (relative)
- Thrombocytopenia (<50,000 /mm3) (relative)

If tocilizumab is not available, other IL-6 blockers (i.e. siltuximab, sarilumab) may be considered.

CONVALESCENT PLASMA
Passive immunotherapy is under development locally and nationally as a therapy for COVID-19. A recent very small case series indicates safety and clinical improvement\(^\text{23}\). Convalescent plasma infusion (CPI) generated at UW Medicine/Bloodworks Northwest is expected to be available soon and prior to pooled immune globulin products. CPI has been studied in 80 persons for SARS-CoV-1 during the previous outbreak\(^\text{24}\) and was generally safe, as well as for MERS, influenza, and viral hemorrhagic fevers. CPI is considered FDA approved (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds), reducing regulatory burden. Experience from SARS-CoV-1 indicated that early treatment was associated with a higher proportion of patients with good outcomes. In general, IgA deficiency, history of transfusion reactions, or overt volume overload will be contraindications. Recommendations for use will be forthcoming in future iterations of treatment guidelines.
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 empiric courses of 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) 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).

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. 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-β-2a, IFN-β-2b or IFN-β-1) with 205 who received neither. 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-β might have inhibitory effects against SARS-CoV. Additionally, a randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in
death or ventilator-free days. 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.

**IVERMECTIN**

Ivermectin has demonstrated in vitro activity inhibiting the replication of SARS-CoV2, but there are no published clinical data in the treatment of patients with CoVID-19. It should be reserved for other FDA approved indications.

**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, although lower mortality and shorter hospitalization was seen among critical cases and pulse steroids did appear to result in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids. 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. One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death; short courses of low-moderate dose steroids has also been recommended in critically ill patients. 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.

**Pregnancy (non-COVID-19 indications):** Note that administration of corticosteroids is often considered in pregnancy to accelerate fetal lung maturity when a preterm birth is imminent. The decision to administer corticosteroids to a pregnant individual with COVID-19 should be made in consultation with MFM. Late preterm steroids are not recommended. Steroids prior to 34 weeks should be considered with caution given the potential for adverse maternal health effects.

**NON-STERIOdal 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.

**Pregnancy (non-COVID-19 indications):** Note that administration of NSAIDS (primarily indomethacin) are often considered in pregnancy to decrease preterm birth, or postpartum for pain management. NSAIDS should be avoided in pregnancy and postpartum for COVID-19+ women.

Low-dose aspirin is frequently used in pregnancy for pre-eclampsia prophylaxis. MFM consultation is advised regarding low-dose aspirin use for COVID-19+ pregnant women.
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).

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References


