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

There are no FDA-approved 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. 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. The standard of care for patients with COVID-19 is evolving. 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. A clinical trial available at UW is COVID-19 Treatment study. https://depts.washington.edu/covid19trx/about/

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** There are no FDA-approved therapies for treatment of SARS-CoV-2. 

**When available, clinical trials are preferred.** For inpatient, use ordersets called “Confirmed COVID-19 Protocol Orders”. If hydroxychloroquine is prescribed, use “Hydroxychloroquine for COVID” orderset.

<table>
<thead>
<tr>
<th>Patient population with COVID-19</th>
<th>Treatment</th>
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</table>
| Outpatient                      | Hydroxychloroquine is not recommended.*  
Consider clinical trial enrollment.  
Contact Study Team. [https://depts.washington.edu/covid19trx/](https://depts.washington.edu/covid19trx/). COVIDTreatment@uw.edu |
| Upper or Lower Respiratory Tract infection without O2 requirement | Hydroxychloroquine is no longer recommended.*  
Recommend clinical trial  
HMC Only: Contact ORCHID study team; orchidstudy@uw.edu  
UWMC/NWH: Contact ACTG study team: actucovidstudies@uw.edu  
If HCQ is started outside of a clinical trial, obtain baseline EKG and share decision-making with the patient.  
HCQ: 400mg po BID x1 day, then 200mg po BID x 4 days **Total Duration: 5d**  
**NOTE: Starting HCQ may disqualify from clinical trial enrollment)** |
| LRTI with O2 requirement         | Hydroxychloroquine is no longer recommended*.  
Recommend clinical trial  
HMC Only: Contact ORCHID study team; orchidstudy@uw.edu  
UWMC/NWH: UWMC/NWH: Contact ACTG study team: actucovidstudies@uw.edu  
UWMC: Consult ID for consideration of Remdesivir  
If HCQ is started outside of a clinical trial, obtain baseline EKG and share decision-making with the patient.  
HCQ: 400mg po BID x1 day, then 200mg po BID x 4 days **Total Duration: 5d**  
**NOTE: Starting HCQ may disqualify from clinical trial enrollment)**  
Monitor for signs of worsening LRTI, cardiac dysfunction and cytokine store  
Consult ID for additional treatment options |
| LRTI with mechanical ventilation | Hydroxychloroquine is no longer recommended*.  
Recommend clinical trial  
HMC Only: Contact ORCHID study team; orchidstudy@uw.edu  
UWMC/NWH: UWMC/NWH: Contact ACTG study team: actucovidstudies@uw.edu  
UWMC: Consult ID for consideration of Remdesivir  
If HCQ is started outside of a clinical trial, obtain baseline EKG and share decision-making with the patient.  
HCQ: 400mg po BID x1 day, then 200mg po BID x 4 days **Total Duration: 5d**  
**NOTE: Starting HCQ may disqualify from clinical trial enrollment)**  
Monitor for signs of worsening LRTI, cardiac dysfunction and cytokine store  
Consult ID for additional treatment options |
| Post-exposure prophylaxis        | Contact Study Team  
[https://depts.washington.edu/covid19pep/](https://depts.washington.edu/covid19pep/) covid19pep@uw.edu |
| Pregnant patients                | Though not a treatment study, consider enrolling in the UW COVID-19 in pregnancy study  
Contact: covidinpregnancy@uw.edu , pager 206-416-0117 |

*Recent clinical studies have not demonstrated virologic or clinical benefits, see evidence summary for details.*
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. Individual providers can choose to alter the laboratory monitoring to optimize care for their patients.

Cardiac Monitoring

<table>
<thead>
<tr>
<th>ACUTE CARE**</th>
<th>ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine Monitoring:</strong></td>
<td><strong>ICU-level Monitoring:</strong></td>
</tr>
<tr>
<td>• Telemetry:</td>
<td>• Telemetry, continue till discharge</td>
</tr>
<tr>
<td>-- Standard indications and</td>
<td>• 12-lead ECG:</td>
</tr>
<tr>
<td>-- ADD - +TNI* (if &gt;0.03, trend q8h till decrease)</td>
<td>-- On Admission/Transfer (and per EP protocol for HCQ)</td>
</tr>
<tr>
<td>• 12-lead ECG:</td>
<td>• Daily ScVO2 (if pt has central line)</td>
</tr>
<tr>
<td>-- On Admission and</td>
<td>• Consider POCUS (point of care ultrasound)</td>
</tr>
<tr>
<td>-- For hydroxychloroquine (HCQ) per EP HCQ protocol</td>
<td></td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>ACUTE CARE</th>
<th>ICU</th>
</tr>
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<tbody>
<tr>
<td><em><em>Baseline, q3d, with Clinical Deterioration and Prior to Discharge</em>:</em>*</td>
<td><strong>Baseline, DAILY and Prior to Discharge:</strong></td>
</tr>
<tr>
<td>• CMP, CBC with diff</td>
<td>• CMP, CBC with diff</td>
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<tr>
<td>• Ferritin, CRP</td>
<td>• Ferritin, CRP</td>
</tr>
<tr>
<td>• Fibrinogen Level, PT w/INR and PTT</td>
<td>• Fibrinogen Level, PT w/INR and PTT</td>
</tr>
<tr>
<td>• LDH</td>
<td>• LDH</td>
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<tr>
<td>• IL-6 (Baseline only)</td>
<td>• IL-6 (Baseline and with clinical deterioration)</td>
</tr>
</tbody>
</table>

* Labs can be discontinued after 10 days as per clinical judgement

Imaging

CXR and CT scan as clinically indicated. Not necessary for diagnosis or staging of COVID-19.
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)\(^2-4\). 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.

A compassionate use study in 53 patients hospitalized with COVID-19 was conducted in several centers around the world, and improvement was seen in the majority (68%) who received remdesivir\(^6\). There was no control group.

Remdesivir was used in a single patient with COVID-19 infection in Washington State, administration was associated with clinical improvement.\(^7\)

Hospitalized patients with COVID-19 lower-tract disease who received remdesivir recovered faster than similar patients who received placebo in an NIH trial of 1063 people. The trial (known as the Adaptive COVID-19 Treatment Trial, or ACTT), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is the first clinical trial launched in the United States to evaluate an experimental treatment for COVID-19\(^8\).

An independent data and safety monitoring board (DSMB) overseeing the trial met on April 27 to review data and shared their interim analysis with the study team. Based upon their review of the data, they noted that remdesivir was better than placebo from the perspective of the primary endpoint, time to recovery. Recovery in this study was defined as being well enough for hospital discharge or returning to normal activity level.

Preliminary results of the first several hundreds of enrolled patients indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (p<0.001). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059).

Based on the above data, the FDA has allowed Remdesivir for Emergency Use. This drug is not FDA approved but will be available on a limited basis\(^9\). At this time, it is unknown when remdesivir will become available at UW Medicine. However, UWMC-ML and UWMC – NWH have access to this medication for a small subset of patients thru an expanded access program.

Clinical Trials underway: NCT04257656, NCT04252664; NCT04280705, NCT04292899, NCT04292730, NCT04302766, NCT04323761

Expanded Access Program: Contact Paul Pottinger (UWMC Montlake) and Maggie Green (UWMC NW) to evaluate eligible patients.

Expanded access criteria:
1. Key Inclusion criteria: Hospitalization, confirmed SARS-CoV-2 by PCR and invasive mechanical ventilation
2. Key Exclusion criteria: Evidence of multi-organ failure, Use of more than 1 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 is not an exclusion criteria.

Compassionate Use: https://rdvcu.gilead.com/ Requests are ONLY for pregnant women and children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

Pregnancy: All the Remdesivir trials listed above exclude pregnant and breastfeeding individuals including NCT04280705 (UWMedicine). Pregnant women were included in the Ebola Virus Disease trial which included Remdesivir\(^\text{10}\) 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 Remdesivir group.

Toxicities and Drug Metabolism: Elevated transaminases, reversible kidney injury, hypotension during infusion.

HYDROXYCHLOROQUINE (PLAQUENIL)/CHLOROQUINE

Routine HCQ use is no longer recommended outside of RCT

- **Rationale for change in recommendation for use**: Recent data from uncontrolled studies in France and China suggest that there is limited utility of hydroxychloroquine. These studies are small and not appropriately powered, but they did raise the concern of potential harm (Qt prolongation) with lack of benefit. These issues will only be resolved in a clinical trial. Given the lack of clear equipoise, and the availability of several clinical trials in our area, we recommend clinical trials over routine use. Please see below for more details of recent studies.

**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.\(^\text{11}\)

**Evidence Summary**: Hydroxychloroquine has been shown to inhibit replication of SARS-CoV2 in vitro (Wang et al, 2020)\(^\text{5}\). 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 chikungnya virus infection, chloroquine delayed the immune response, resulting in lack of viral clearance\(^\text{12}\). 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)\(^\text{13}\). 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 at UW Medicine**: NCT04332991, NCT04358081, NCT04328961, NCT04354428

The ORCHID trial 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

The HAT (Hydroxychloroquine,Azithromycin trial) is a multi-center, Randomized, Double-blinded, Placebo-
controlled Study to Evaluate the Safety and Efficacy of Hydroxychloroquine Monotherapy and in Combination
With Azithromycin in Patients With Moderate and Severe COVID-19 Disease. Eligibility includes Adults > 18 years
old, COVID-19 positive by any respiratory sample within 4 days prior to randomization, hospitalized/being
admitted from ED or clinics with admit status prior to randomization. Excludes patients that are pregnant or
lactating or other eligibility different by study. Study available at UWMC –ML and UWMC -NW
actucovidstudies@uw.edu

The COVID-19 PEP Study is evaluating its use for post-exposure prophylaxis
https://depts.washington.edu/covid19pep/

The COVID-19 Treatment study is evaluating its use alone or in combination with azithromycin for treatment of
outpatients with SARS-CoV-2 infection https://depts.washington.edu/covid19trx/.

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: Pregnancy: 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
breastfeeding individuals are eligible for the COVID-19 Treatment study (hydroxychloroquine alone or in
combination with azithromycin for treatment of outpatients with SARS-CoV-2 infection
(https://depts.washington.edu/covid19trx/) and COVID-19 PEP Study https://depts.washington.edu/covid19pep/

Evidence summary that changed the recommendation:
Open label, randomized trial of 16 government designed CoVID-19 treatment centers in China to assess the
efficacy and safety of hydroxychloroquine (HQC) plus standard of care (SOC) vs SOC alone in 150 hospitalized
CoVID-19 patients16. HQC was administrated as 1,200 mg daily for 3 days followed by 800 mg daily for a total of
2-3 weeks. The primary endpoint was 28-day negative conversion rate of SARS-CoV-2. The secondary endpoints
were negative conversion rate at day 4, 7, 10, 14 or 21, the improvement rate of clinical symptoms within 28-
day, normalization of C-reactive protein and blood lymphocyte count within 28-day. There was no difference in
28-day negative conversion rate between SOC plus HCQ (85%) and SOC group (81%), p=0.34. Negative
conversion rate at day 4, 7, 10, 14 or 21 was also similar between the two groups. No different 28-day symptoms
alleviation rate was observed between the two groups. This was a greater reduction in CRP conferred by the
addition of HCQ (p=0.05) and a trend toward more rapid recovery of lymphopenia though not statistically significant. Adverse events were found in 9% of SOC and 30% of HCQ recipients with two serious adverse events.

Retrospective observational data designed to compare effectiveness of hydroxychloroquine against controls in patients who were hospitalized in 4 French hospitals during March 17th to 31st. The study included 181 patients with SARS-COV2 pneumonia of which 84 patients received HCQ within 48 hours of admission and 97 did not receive the drug. To control for confounding baseline variables, a propensity score model was utilized which included age, gender, comorbidities, BMI, pregnancy, treatment with ACE-I or ARB, time since symptom onset and severity of disease at presentation. The primary endpoint was the transfer to ICU within 7 days of admission and/or death (any cause.) In the weighted analysis, 20.2% patients in the HCQ group were transferred to the ICU or died within 7 days vs 22.1% in the no-HCQ group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47–1.80). In the HCQ group, 2.8% of the patients died within 7 days vs 4.6% in the no-HCQ group (3 vs 4 events, RR 0.61, 95% CI 0.13–2.89), and 27.4% and 24.1%, respectively, developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65–2.00). There were no significant differences between groups in terms of transfer to ICU or death within 7 days, all-cause mortality or development of ARDS. Of the 84 pt that received hydroxychloroquine at admission, 7 experiences Qt prolongation and 1 developed AV block.

Another double blinded randomized phase 2 trial from Brazil evaluating chloroquine as adjunctive therapy for hospitalized CoVID-19 patients was terminated early due to the high rate (25%) of QTc prolongation >500msec and a trend toward higher mortality. All patients received azithromycin and ceftriaxone, but the safety concern led to early termination of the RCT after enrolling 81 patients from a pre-defined 440 sample size.

Taken together, these preliminary data suggest that HCQ given to hospitalized patients with COVID-19 does not result in virologic clearance of SARS-CoV-2 and clinical outcomes were not significantly different compared to standard of care. Given concerns for potential toxicity, and the lack of proven clinical benefits at this point, routine HCQ is no longer recommended outside of RCT.

Dosing and Administration: If HCQ is used for treatment of SARS-CoV-2, the following dosages are recommended:

- 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 unknown, this dosing regimen is based on modeling of in vitro data.
Anuric patient steady state levels are ~30% higher than patients w/ normal renal function

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/
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). 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. The prognosis for critically ill patients with COVID-19 is poor, with mortality ranging from 50-67% in reported case series. 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. 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. Although limited data, breastfeeding on this medication has not been associated with neonatal immunosuppression.

Recommendations:
Treatment: Until more data are available, the 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.

**SARS CoV-2 Convalescent Plasma**

**Mechanism of Action:**

The most likely mechanism is viral neutralization by providing anti-SARS CoV-2 neutralizing antibodies in the recipient, or increasing the circulating antibody titer/quality. Other possible mechanisms include antibody-dependent phagocytosis or cytotoxic lymphocyte responses. Antibody-independent (e.g. coagulation factors, albumin) or non-specific immunologic effects are also possible.

**Evidence Summary:**

Convalescent plasma has been administered since the late 19th century for a variety of infectious and non-infectious entities, most notably including influenza virus (1918, 2009 H1N1 and 2007 H5N1), SARS CoV-1, and MERS CoV. An exploratory meta-analysis of these studies suggested that convalescent plasma offered recipients with respiratory viral infections a mortality benefit (OR 0.25, 95% CI 0.14-0.45), which was largely seen when plasma was administered early after symptom onset (<10-14 days) and prior to seroconversion. However, these studies largely lacked control groups and had high risk of bias. Experience with convalescent plasma in SARS CoV-2 infection is limited to uncontrolled case series. Shen et al. reported on 5 mechanically-ventilated COVID-19 patients who received convalescent plasma long after symptom onset (10-22 days), all of which subsequently improved clinically. Duan et al. similarly showed improvement in 10 patients (all received plasma, no controls), most of which had moderate-to-high anti-SARS CoV-2 titers prior to receipt of plasma raising the possibility that allogeneic factors independent of neutralizing antibody are involved.

**Ongoing Clinical Trials:**

Expanded access (Mayo clinic): NCT04338360

Randomized trials: NCT04345523, NCT04345991, NCT04342182, NCT04348656
Other: NCT04347681, NCT04345679, NCT04343755, NCT04333355. Only one of these is a single-site, double-blind, randomized clinical trial based in the US.

UW Medicine: Protocol for RCT as early intervention being developed.

Pregnancy: Pregnant and breastfeeding people are allowed under the expanded access program (Mayo clinic), NCT04348656. In a small case series of four critically ill patients in China who received convalescent plasma and recovered from COVID-19, one of the patients was pregnant.\(^3\)

Adverse events and cautions:
- Risk of transfusion reactions including TRALI and blood-borne pathogen infection.
- Contraindicated in IgA deficiency or in patients with a history of transfusion reaction; caution in volume overload.
- Theoretical risk of worsening clinical course due to antibody-dependent enhancement, which has been described for MERS-CoV(8), or possibly through non-specific immune activation should be considered.

Administration:
1 unit IV once

**Recommendations:**
In the absence of high-quality supportive data, routine use of convalescent plasma in COVID-19 patients is not recommended outside the context of a clinical trial. A multi-center, randomized clinical trial protocol is under development that will largely target high-risk individuals with recent-onset symptoms who have not yet progressed to severe infection.

While we anticipate the greatest benefit to individuals with early COVID-19 symptoms, the available case series support the safety and possibly benefit of plasma in severely ill patients, so administration may be considered. Convalescent plasma currently can be accessed through the expanded access IND (Mayo clinic). If pursued, we propose restricting use to the following individuals given the anticipated scarcity of this resource:
- Laboratory-confirmed SARS CoV-2 infection
- Life-threatening disease defined as:
  - Multiple organ dysfunction or failure
  - Septic shock
  - Hypoxemic respiratory failure (one of following)
    - Requiring mechanical ventilation
    - Requiring >6 liters/min nasal cannula (or equivalent of FiO2 ≥ 50%) supplemental O2 to maintain SpO2 >92%, or >2X increase in home O2 requirement.
- Please note that administration of convalescent plasma may make the patient not eligible for enrollment in clinical trials.

For questions regarding ordering of SARS CoV-2 convalescent plasma through the expanded access protocol, please contact the study coordinator (206-797-2704) or transfusion service laboratory (UWMC 598-6240, HMC...
744-3088). This guideline will be updated with contact information regarding the RCT once enrollment for that separate study commences.
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.\(^3\,^5\,^6\)

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 therefore should used in a context of a clinical trial.

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 days\(^11\). 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.

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)\textsuperscript{37}. 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)\textsuperscript{38}. 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\textsuperscript{39}. 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\textsuperscript{40}. 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\textsuperscript{39}. Additionally, a randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in death or ventilator-free days\textsuperscript{41}. 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\textsuperscript{42}. 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\textsuperscript{43}, although lower mortality and shorter hospitalization was seen among critical cases\textsuperscript{44} and pulse steroids did appear to result in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids\textsuperscript{45}. 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\textsuperscript{46}. One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU\textsuperscript{47}. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death\textsuperscript{48}; short courses of low-moderate dose steroids has also been recommended in critically ill patients\textsuperscript{49}. 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 stopping or starting NSAIDS primarily due to lack of evidence for risk or 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).

These guidelines were drafted by a working group, including Fred Buckner, Jeannie Chan, Shireesha Dhanireddy, Margaret Green, Robert Harrington, Josh Hill, Rupali Jain, Christine Johnston, H. Nina Kim, David Koelle, Manoj Menon, Sylvia LaCourse, Guang-Shing Cheng, Alpana Waghmare, Anne Woolfrey, and Mark Wurfel.
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References


18. PLAQUENIL®


