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. The Infectious Disease Society of America (IDSA) has provided guidance that medications should not be given outside of clinical trials[1]. When available, clinical trials are preferred.

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.

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 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**". If hydxoxychloroquine is prescribed, use "Hydroxychloroquine for COVID"

Patient population with COVID-19	Treatment
Outpatient	Hydroxychloroquine is not recommended.* Consider clinical trial enrollment. Contact Study Team. 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 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 LRTI with mechanical ventilation	Hydroxychloroquine is no longer recommended*. Recommend clinical trial HMC Only: Contact ORCHID study team; orchidstudy@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)** 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/ covid19pep@uw.edu

*Recent clinical studies have not demonstrated virologic or clinical benefits, see evidence summary for details.

Cardiac monitoring for ACUTE CARE:	ICU:
Telemetry: **--Standard indications** and **-- +TNI*** *(if >0.03, trend q8h till decrease)* • **12-lead ECG:** --On Admission and --For **hydroxychloroquine** (HCQ) per EP HCQ	• **Telemetry**, continue till discharge • **12-lead ECG** : --On Admission/Transfer (and per EP protocol for HCQ) • Daily ScVO2 (if pt has central) • Consider POCUS

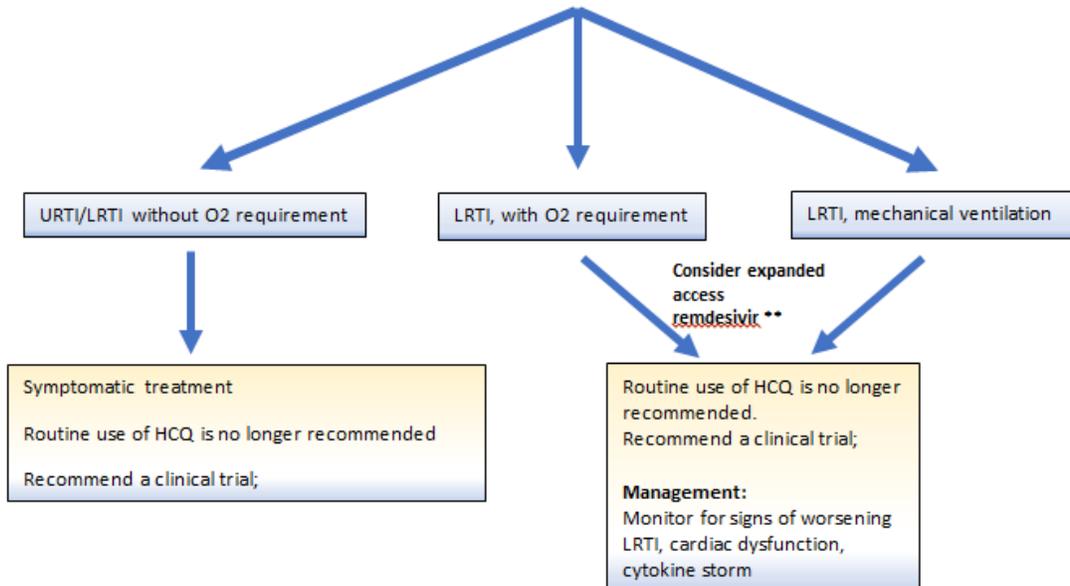*highly-sensitive troponin I results will be reported to cardiology

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

ACUTE CARE:	ICU:
Baseline, q3d, with Clinical Deterioration and Prior to Discharge*: • CMP, CBC with diff • Ferritin, CRP • Fibrinogen Level, PT w/INR and PTT • LDH • IL-6 (Baseline only)	**Baseline, DAILY and Prior to Discharge**: • CMP, CBC with diff • Ferritin, CRP • Fibrinogen Level, PT w/INR and PTT • LDH • IL-6 (Baseline and with clinical deterioration)

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

Algorithm for inpatient management of patients with COVID-19 at UW Medicine

Evaluate for clinical trial eligibility
HMC only: HCQ vs placebo
ORCHID (NCT04332991)*

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│ URTI/LRTI without│  │ LRTI, with O2    │  │ LRTI, mechanical     │
│ O2 requirement   │  │ requirement      │  │ ventilation          │
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Consider expanded access remdesivir **

Symptomatic treatment

Routine use of HCQ is no longer recommended

Recommend a clinical trial;

Routine use of HCQ is no longer recommended.
Recommend a clinical trial;

Management:
Monitor for signs of worsening LRTI, cardiac dysfunction, cytokine storm

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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)

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

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

* 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

ACUTE CARE	ICU
Baseline, q3d, with Clinical Deterioration and Prior to Discharge*: • CMP, CBC with diff • Ferritin, CRP • Fibrinogen Level, PT w/INR and PTT • LDH • IL-6 (Baseline only)	**Baseline, DAILY and Prior to Discharge**: • CMP, CBC with diff • Ferritin, CRP • Fibrinogen Level, PT w/INR and PTT • LDH • IL-6 (Baseline and with clinical deterioration)

*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

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.

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. Data from randomized clinical trials is pending.

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). Pregnant 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/ 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.

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.[9]

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 chikungnya 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/ The COVID-19 Treatment study is evaluating its use alone or in combination with azithromycin for treatment of outpatients with SARS-CoV-2 infection (NCT04354428) 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 (NCT04354428) https://depts.washington.edu/covid19trx/ and COVID-19 PEP Study (NCT04328961) 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 (HCQ) plus standard of care (SOC) vs SOC alone in 150 hospitalized CoVID-19 patients[13]. HCQ 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 hydroxycholorquine against controls in patients who were hospitalized in 4 French hospitals during March 17th to 31st[14]. 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
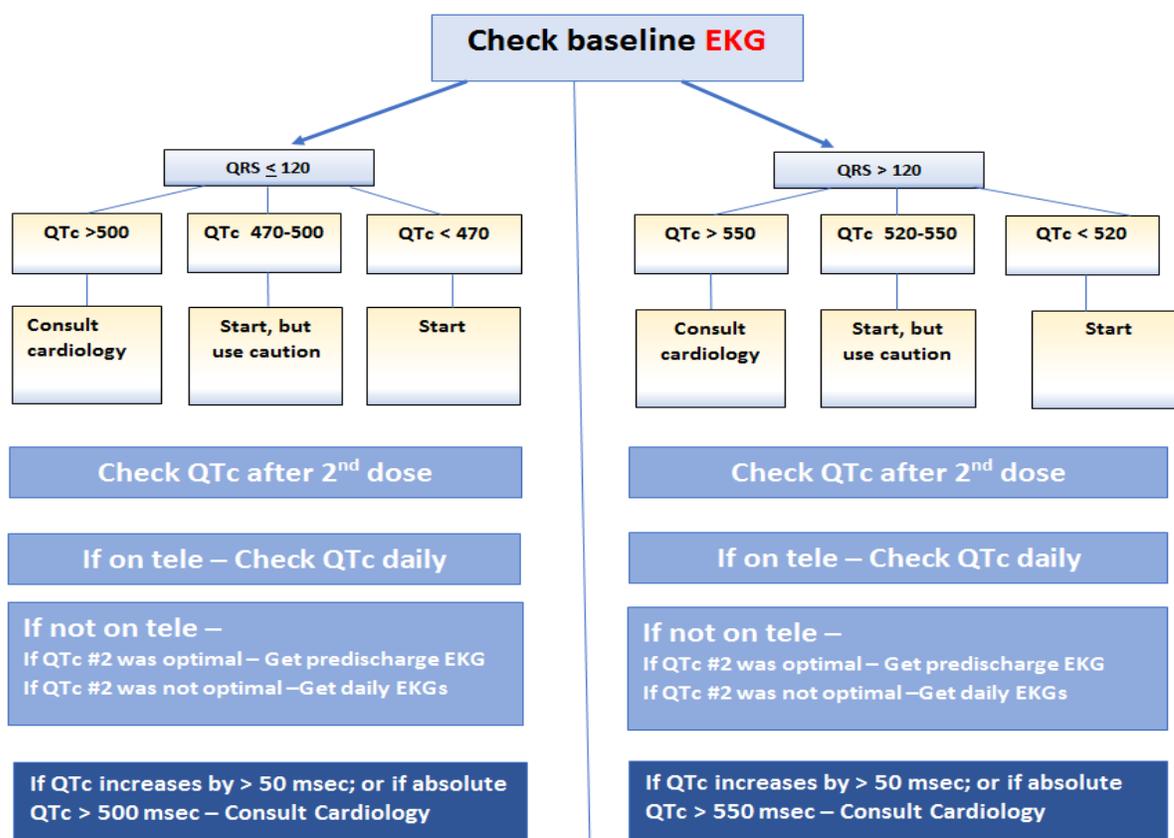
and a trend toward higher mortality[15]. All patients received azithromycin and ceftriaxone, but the safety concern led to early termination of the RCT after enrolling 81 patients from a pre-defined 440 sample size.

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.[16]

Agent	Adult dose	Notes	Main toxicities
Hydroxychloroquine available in 200 mg tablets[17] The estimated half-life is 40 days	400mg PO bid x 1 day, then 200mg PO bid x 4 days **Total Duration: 5 days** No dosing adjustment for renal or hepatic impairment or obesity Pharmacy can compound suspension if requested	Safe in pregnancy Metabolized by CYP2C8, CYP3A4 and lesser extent CYP2D6 ~20-30% excreted unchanged in urine. Anuric patient steady state levels are ~30% higher than patients w/ normal renal function	Most toxicities are associated with long-term use Dizziness, headache, loss of appetite, nausea, vomiting LFT abnormalities QTc prolonging effects; monitor QTc – see monitoring guidance below We do not recommend co-administration with azithromycin (see text below)

Check baseline EKG

QRS ≤ 120

QTc >500	QTc 470-500	QTc < 470
Consult cardiology	Start, but use caution	Start

Check QTc after 2nd dose

If on tele – Check QTc daily

If not on tele –
If QTc #2 was optimal – Get predischarge EKG
If QTc #2 was not optimal –Get daily EKGs

If QTc increases by > 50 msec; or if absolute QTc > 500 msec – Consult Cardiology

QRS > 120

QTc > 550	QTc 520-550	QTc < 520
Consult cardiology	Start, but use caution	Start

Check QTc after 2nd dose

If on tele – Check QTc daily

If not on tele –
If QTc #2 was optimal – Get predischarge EKG
If QTc #2 was not optimal –Get daily EKGs

If QTc increases by > 50 msec; or if absolute QTc > 550 msec – Consult Cardiology

Any evidence of Torsades on Tele – D/c Hydroxychloroquine regardless of QT interval

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 <u>AND</u> absolute QTc <500 msec** (550msec if QRS >120 msec)

- **What is NOT optimal? - QTc increase is >50 msec from baseline <u>OR</u> 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 <u>checked daily</u> and <u>documented</u> 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, 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)[18]. 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[19]. The prognosis for critically ill patients with COVID-19 is poor, with mortality ranging from 50-67% in reported case series[20-22]. 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[23]. 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[24,25]. 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 <u>despite use</u> 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[26]. 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[27,28] and MERS CoV[29,30] infections. 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[18,31,32]. 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[18]. 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[33].

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, and in the protocol under development at UW. Pregnancy and breastfeeding are excluded from NCT04345991, NCT04345679, NCT04347681. Information is not publicly available regarding pregnancy inclusion/exclusion for NCT04345523, NCT04342182, NCT04343755, and NCT04333355. 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[32].

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:

Convalescent plasma is not currently available but this guideline will be updated once ordering process is finalized.

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, double-blinded, 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 use IND (https://www.uscovidplasma.org/#irb), and 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)
    o Requiring mechanical ventilation

- o   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 administration of SARS CoV-2 convalescent plasma, please contact Jason Simmons (jasonds@uw.edu)

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[34].

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.

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)[35]. 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)[36]. 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[37]. 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 ⍰-2a, IFN ⍰-2b or IFN ⍰-1) with 205 who received neither [38]. 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 [37]. Additionally, a randomized controlled trial of IFN-beta-1a for treatment of ARDS did not show improvement in death or ventilator-free days [39]. 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[40]. It should be reserved for other FDA approved indications.

CORTICOSTERIODS

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 [41], although lower mortality and shorter hospitalization was seen among critical cases [42] and pulse steroids did appear to result in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids [43]. 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 [44]. One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU [45]. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death [46] ; short courses of low-moderate dose steroids has also been recommended in critically ill patients[47]. 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[48]. 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[49]. 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

References

1.   Bhrimraj A, Morgan RL, SHirsch Shumaker A, et al. Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020.
2.   de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 2020;13:1922083117.
3.   Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020;24:013056.
4.   Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9.
5.   Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro: Cell Res. Mar;30(3):269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4.; 2020.
6.   Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine 2020.
7.   Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929-36.
8.   Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-303.
9.   Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. International Journal of Antimicrobial Agents 2020;55:105923.
10.   Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res 2020;177:104762.
11.   Gautret P, Lagier JC, Parola P, et al. Clinical and micorbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. 2020.
12.   Kaplan YC, Ozsarfati J, Nickel C, Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. Br J Clin Pharmacol 2016;81:835-48.
13.   Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv 2020:2020.04.10.20060558.
14.   Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv 2020:2020.04.10.20060699.
15.   Borba MGS, Val FdA, Sampaio VS, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2)

infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv 2020:2020.04.07.20056424.

16.   Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;9.

17.   PLAQUENIL®

HYDROXYCHLOROQUINE SULFATE TABLETS, USP Package Insert. 2015. (Accessed 3/19/2020, 2020, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.)

18.   Xu X H, Mingfeng,Li, Tiantian,Sun, Wei,Wang, Dongsheng,Fu, Binqing,Zhou, Yonggang,Zheng, Xiaohu,Yang, Yun,Li, Xiuyong,Zhang, Xiaohua,Pan, Aijun,Wei, Haiming. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. ChinaXiv:20200300026 2020.

19.   Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;13.

20.   Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;24:30079-5.

21.   Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. Jama 2020;19.

22.   Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020;30.

23.   Saito J, Yakuwa N, Kaneko K, et al. Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. Rheumatology (Oxford) 2019;58:1505-7.

24.   Hoeltzenbein M, Beck E, Rajwanshi R, et al. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. Seminars in Arthritis and Rheumatism 2016;46:238-45.

25.   Nakajima K, Watanabe O, Mochizuki M, Nakasone A, Ishizuka N, Murashima A. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. Mod Rheumatol 2016;26:667-71.

26.   Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130:1545-8.

27.   Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44-6.

28.   Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676-8.

29.   Arabi YM, Hajeer AH, Luke T, et al. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis 2016;22:1554-61.

30.   Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23:617-22.

31.   Duan K, Liu B, Li C, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. In. medRxiv - pre-publication (not peer reviewed); 2020.

32.   Zhang B, Liu S, Tan T, et al. Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection. Chest 2020.

33.   Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020;6:2004168117.

34.   Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020.

35.   Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399-406.

36.   Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020.

37.   Stroher U, DiCaro A, Li Y, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon- alpha. J Infect Dis 2004;189:1164-7.

38.   Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis 2019;25.

39.   Ranieri VM, Pettila V, Karvonen MK, et al. Effect of Intravenous Interferon beta-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. Jama 2020;17:22525.

40.   Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research 2020:104787.

41.   Auyeung TW, Lee JS, Lai WK, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51:98-102.

42.   Chen RC, Tang XP, Tan SY, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 2006;129:1441-52.

43.   Ho JC, Ooi GC, Mok TY, et al. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. Am J Respir Crit Care Med 2003;168:1449-56.

44.   Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med 2018;197:757-67.

45.   Zhang G HC, Luo L, Fang F, Chen Y, Li J. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. doi: 101101/2020030220030452 %J medRxiv 2020.

46.   Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;13.

47.   Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia: Lancet. 2020 Feb 29;395(10225):683-684. doi: 10.1016/S0140-6736(20)30361-5. Epub 2020 Feb 12.

48.   Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;3:020-05985.

49.   . (Accessed at https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.)