

Infectious Disease Division Guidance on Pharmacotherapeutics for COVID-19 Patients

Last updated 5/24/20

New information about management of COVID-19 is published daily. This guidance will be updated frequently as new clinical trials start at Stanford and as clinical trial data become available from other centers.

INTRODUCTION

The mainstay of treatment for COVID-19 is supportive therapy. Although there are still no FDA-approved therapies for COVID-19, on May 1, 2020, after positive preliminary results were released from two randomized-controlled trials sponsored by NIAID (NCT04280705) and Gilead (NCT04292899), the FDA issued an emergency use authorization for the RNA polymerase inhibitor remdesivir (RDV)¹. The assessment of the FDA was *“it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19”*¹.

Our recommendation, in line with that of the FDA and NIH², is that remdesivir is indicated in the treatment of hospitalized patients with severe disease due to COVID-19 (defined as SpO₂ ≤ 94% on ambient air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation). In line with NIH recommendations, we recommend against use of remdesivir for the treatment of mild or moderate COVID-19 outside of a clinical trial.

Several other products are available which we do not affirmatively recommend, except in the context of a clinical trial. These therapies include convalescent plasma, chloroquine, hydroxychloroquine, interleukin-1 inhibitors, and interleukin-6 inhibitors. We recommend against use (except in a clinical trial) of high-dose chloroquine (600 mg twice daily), hydroxychloroquine plus azithromycin, HIV protease inhibitors such as lopinavir/ritonavir, IVIG, interferons, and Janus kinase inhibitors.

Currently at Stanford we are enrolling inpatients in clinical trials of remdesivir, remdesivir+baricitinib, outpatients in a trial of interferon lambda and patients discharged from the ED in a trial of convalescent plasma.

We also have convalescent plasma available on a compassionate use basis for patients with severe disease who are ineligible for a clinical trial.

Remdesivir Access at SHC

SIMPLE / Gilead Trial – study pager 15013

We will continue to be able to enroll patients with moderate and severe COVID-19 in the Gilead (SIMPLE) remdesivir trial through May 29, 2020. The trial now includes patients who would have been eligible for the moderate and severe (SIMPLE 1 and 2) trials. It is no longer randomized and each patient will receive remdesivir. For the Gilead trial, inclusion criteria include: age ≥ 18 , SARS-CoV2 infection confirmed by RT-PCR, SpO₂ $\leq 94\%$ on RA or requiring supplemental O₂. Exclusion criteria are: Pregnancy, AST/ALT $\geq 5x$ ULN, CrCl <50 mg/ml and multi-system organ failure.

ACTT-2 / NIAID Trial – study pager 27402

As of 5/19/20, the NIAID trial (ACTT-2) comparing remdesivir plus baricitinib with remdesivir alone is recruiting. Baricitinib³ is an orally administered, selective inhibitor of Janus kinase 1 (JAK1) and JAK2 and also has other immunomodulatory effects.

Inclusion criteria	Age ≥ 18 SARS-CoV2 infection confirmed by RT-PCR At least ONE of the following: radiologic infiltrates on CXR or chest CT, SpO ₂ $\leq 94\%$ on RA or requiring supplemental O ₂ , or mechanical ventilation or ECMO.
Exclusion criteria	Participating in another clinical trial for COVID-19 Pregnancy AST/ALT $\geq 5x$ ULN CrCl <30 mg/ml or on dialysis Neutropenia within 2 weeks of enrollment Use of probenecid that cannot be discontinued Current active tuberculosis or latent TB treated for less than 4 weeks Other suspected serious infection (besides COVID-19) Recent live or live-attenuated vaccine in the preceding 4 weeks History of DVT or PE in the last 12 weeks or history of recurrent (>1 PE or DVT) VTE

Emergency Use Access

Remdesivir was granted emergency use access (EUA) by the FDA on May 1, 2020 and is available on a limited supply allocated by Santa Clara County Department of Public Health. If available, remdesivir may be used at SHC under EUA provided the patient meets the following criteria:

1. Treatment of suspected or laboratory confirmed COVID-19 with severe disease defined as patients with an oxygen saturation (SpO₂) $\leq 94\%$ on room air or requiring supplemental oxygen or requiring invasive mechanical ventilation or requiring ECMO, AND

2. Patient is not eligible to receive remdesivir through a clinical trial or compassionate use, AND
3. Infectious diseases service is consulted, AND
4. Use has been approved by Dr. Aruna Subramanian

Pregnant women: At the time of writing, compassionate use is the primary mechanism to access remdesivir in pregnancy. Pregnancy is an exclusion criteria for all clinical trials. Compassionate use remdesivir access is facilitated through consulting the infectious disease consult service. Pregnancy is not an exclusion criteria for convalescent plasma use. The ID consult service can be reached at: General ID 24308 | ICU ID 27190 | BMT ID 17000 | SOT ID 17008.

Please note that starting patients on hydroxychloroquine or other investigational agents targeting COVID-19 will delay their entry into the remdesivir clinical trial by 24h after cessation of HCQ.

If the patient is on a clinical trial, orders for the study drug will be placed by the investigational pharmacy (650-736-1990). Except in an emergency, please do not stop the study drug without first discussing with the study team (pager 15013 for Gilead trial or pager 27402 for NIAID trial).

Remdesivir	
Dosing	200 mg IV x1 then 100 mg IV daily x 9 days
Dose adjustment in renal dysfunction	Hold if CrCl decreases by $\geq 50\%$ from baseline
Known side effects	Transient elevation of AST/ALT, and serum Cr. Nausea

Baricitinib	
Dosing	4 mg PO (or crushed via NGT) daily for the duration of the hospitalization up to 14-days
Dose adjustment in renal dysfunction	Patients with eGFR < 60 will be given 2 mg po daily
Side effects	Black box warning: VTE, malignancy, serious infections, including tuberculosis reactivation and herpes zoster Laboratory changes may include: decreased hemoglobin and neutrophils, and increased platelets, ALT, Cr

Other Clinical Trials Enrolling at SHC

Hydroxychloroquine (ORCHID trial) – note as of 5/24/20, this trial was not yet active

Background. This antimalarial and anti-inflammatory drug has activity *in vitro* against SARS-CoV-2⁴. Early anecdotal data showed possible benefit, but it was not effective for COVID19 in one small (n=30), poor quality, clinical trial⁵. Furthermore, a phase IIb randomized clinical trial of 81 patients with COVID-19 was stopped early based on an unplanned interim analysis recommended by an independent data safety and monitoring board. This study found that relative to lower dose HCQ (450 mg po BID x 2 doses followed by 450 mg daily x 4 days), higher dose HCQ (600 mg po BID x 10 days) was associated with QT prolongation and an increased risk of death (OR 3.6; 95% CI, 1.2-10.6)⁶. The limited sample size did not allow the study to show any benefit overall regarding treatment efficacy. However, larger observational studies have shown no benefit.^{7,8} More recently a larger RCT from China comparing HCQ with placebo showed no benefit in mild to moderate disease⁹.

Stanford is participating in a multicenter RCT (NCT04332991) which was designed to compare HCQ with placebo. Study coordinators can be reached at pager 26432 or 25524. Patients who are enrolled in the RDV trial above can be subsequently enrolled in the HCQ trial.

Exclusion criteria for the HCQ trial include:

Being a prisoner	Allergy to HCQ or related medications
Pregnancy	Use in the last 5 days of: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol
Breast feeding	Receipt of HCQ or CQ in the last 10d
Seizure disorder	Inability to receive enteral medications
Porphyria cutanea tarda	
QTc >500 ms	

G6PD deficiency testing is NOT needed before starting this agent. Using hydroxychloroquine will cause a delay of 24h of entry into the remdesivir clinical trial

Expanded Access Program for Convalescent Plasma (EACP)

Convalescent plasma refers to plasma from donors who have recovered from documented SARS-CoV2 infection and have antibody titers at a level (>1:80) that are felt to be potentially therapeutic. Data for this intervention is currently limited to case series,^{10,11} although a multicenter RCT is underway. An

observational study of ~5000 patients showed favorable safety data (Preprint: <https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1>). Stanford is participating in an expanded access (compassionate use) program for convalescent plasma for severely ill inpatients with COVID-19. This involves one-time administration of 1-2 units of ABO matched convalescent plasma.

To be included, patients must be:

- At least 18 years old
- Have laboratory confirmed SARS-CoV-2 infection
- Be able to provide informed consent in person or via healthcare proxy
- Have severe or life-threatening COVID-19 disease

Severe disease is defined as having ANY of the following: dyspnea, RR>30, RA O2 saturation <93%, paO₂/FIO₂ <300, infiltrates involving >50% of the lungs

Life-threatening disease is defined as respiratory failure, septic shock, or multisystem organ failure

To access EACP, page 15125; a physician will review the case and determine eligibility. If the patient is eligible, a member of the study team will meet with the patient to complete the informed consent process and instructions will be given to the primary team on how to order the convalescent plasma in EPIC.

Other potential therapies for COVID-19

For patients ineligible for remdesivir or other drugs as part of a clinical trial, we do not recommend unproven experimental therapies, although they may be considered on a case by case basis.

Nitazoxanide – this anti-parasitic agent has *in vitro* activity against SARS CoV-2¹². It is being investigated for the management of influenza and other acute respiratory infections at a dose of 600 mg extended release PO BID¹³ (note, this extended release formulation is not available in US) as well as for enteric viruses (e.g. norovirus and sapovirus) at 500 mg PO BID. FDA approved dosing for diarrhea caused by *Cryptosporidium* is 500 mg PO BID x 3 days.

Biologics / immunomodulators – We recommend that use of biologics (for example, tocilizumab, sarilumab, anakinra) in COVID-19 outside of a clinical trial be restricted by pharmacy. Consultation with a committee comprising pulmonary critical care and infectious diseases should be obtained prior to ordering these agents. Teams should contact Anne Liu (anneliu@stanford.edu) or Angela Rogers
Shanthi Kappagoda, MD, David Epstein, MD, Dora Ho, MD, PhD, Jenny Aronson, MD, David Ha, PharmD, Upi Singh, MD, Stan Deresinski, MD

(ajrogers@stanford.edu) to discuss the patient if biologics are being considered. Please see [here](#) for additional guidance from Stanford Healthcare about use of immunomodulators in COVID-19.

Chloroquine – this antimalarial agent has activity *in vitro* against SARS-CoV-2¹² but significantly more side effects than hydroxychloroquine including QTc prolongation, arrhythmias, nausea and tinnitus. There are no good quality RCT data showing efficacy¹⁴, but multiple clinical trials are ongoing in China. Given the lack of evidence and side-effects, the ID division recommends against this at this time.

Azithromycin – In a small (n=36), poorly designed (non-randomized, with controls (n=16) including patients who declined to participate and patients at a non-participating hospital) single arm study¹⁵ looking at the effects of HCQ 200 mg TID (n=20) on viral eradication for COVID-19 in outpatients, 6 patients who received HCQ were also prescribed azithromycin. The investigators found viral eradication was numerically superior in this subgroup (6/6, 100%) compared to those who received hydroxychloroquine alone (8/14, 57%). However, there are numerous flaws in this study which may invalidate these findings¹³. Given the lack of evidence and risk of side effects (including QT prolongation and diarrhea), the ID division recommends against this at this time.

Lopinavir/ritonavir – this HIV protease inhibitor was studied two small randomized clinical trials (n=30 and n=44)^{16,17} and showed no benefit. Given the lack of evidence and side-effects (diarrhea and drug-drug interactions), the ID division recommends against this at this time.

Ribavirin + Interferon beta 1b – A multicenter, open-label, randomised, phase 2 trial in adults with COVID-19 compared 14-days of combination therapy of lopinavir 400 mg and ritonavir 100 mg BID plus ribavirin 400 mg BID, plus three doses of 8 million international units of interferon beta-1b on alternate days (n=86) with 14 days of lopinavir 400 mg and ritonavir 100 mg BID (n=41)¹⁸. The primary endpoint was the time to negative nasopharyngeal (NP) swab for SARS-CoV2. The combination therapy group had a significantly shorter median time to negative NP swab (7 days versus 12 days) and also shorter median hospital stay (9 days versus 14.5 days). Mortality was no different in the two groups (no patients died during the study).

Investigations of many other agents are ongoing and this guidance will be updated frequently.

Additional Information

Updated NIH guidelines on the treatment of COVID-19 can be found at

<https://covid19treatmentguidelines.nih.gov/>.

An easily navigable detailed database of preclinical and clinical therapeutic trials for SARS-CoV2 is

available at <https://covdb.stanford.edu/page/covid-review/>

A list of ongoing clinical trials worldwide is available here <http://med.stanford.edu/id/covid19.html>.

Information on drug-drug interactions with emerging potential therapies for COVID-19 are available at

<http://www.covid19-druginteractions.org/>

Please see the ID COVID-19 therapeutics website for curated literature on novel therapeutics for COVID-19 at <http://med.stanford.edu/id/covid19.html>.

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