Remdesivir

- **Considerations for use:**
  - Believed to be initial therapy to consider for COVID-19
  - Discuss indications and contraindications with Gilead representative (see below)
- **Acquisition and Administration:**
  - Not FDA approved. Available only through compassionate use or Clinical Trials with gilead or NIAID (see Remdesivir procurement process below)
  - Dosage: 200 mg IV on day 1 followed by 100 mg IV once daily on days 2-5 or 2-101,2
    - Of note clinical trials are ongoing for 5- or 10-day durations of remdesivir for both moderate and severe COVID-19. In advance of results of these trials the optimal duration of therapy is unknown.1,2
- **Tolerability**
  - May be associated with transient transaminitis but it should be noted that COVID-19 also clinically associated with transaminitis.
  - Drug is co-formulated sulfobutylether β-cyclodextrin (SBECD). There is a theoretical risk of accumulation in renal failure promoting further renal injury but the clinical relevance of this is uncertain.3
  - Appears to be well tolerated from clinical trials in Ebola in which 175 patients received remdesivir 200 mg IV loading dose on day 1 followed by 100 mg IV daily for 9-13 days thereafter. One patient in the remdesivir group had hypotension that resulted in cessation of a loading dose of remdesivir and that was followed rapidly by cardiac arrest. However, even in these cases, the deaths could not readily be distinguished from underlying fulminant Ebola virus disease itself.4 Consult remdesivir package insert with shipment if procured regarding extension of infusion time for tolerability.
- **Drug interactions:**
  - Remdesivir is a prodrug requiring CYP3A4 for activation thus there is potential for reduced conversion in the presence of CYP3A4 inhibitors like lopinavir, ritonavir, darunavir, or cobicistat.5
- **Supportive Data:**
  - Non-FDA approved investigational nucleotide analog from Gilead Sciences6
  - In vitro activity against novel coronavirus7
  - Reports on clinical outcomes of remdesivir are limited, however, it was used in the first confirmed case of 2019 novel coronavirus disease (COVID-19) in the United States. The patient initially presented with mild symptoms but, after the first week of largely supportive care, had progression of disease to pneumonia requiring supplemental oxygenation, which prompted the initiation of remdesivir through compassionate use and the patient’s clinical condition subsequently improved.8
The Adaptive COVID-19 Treatment trial (NCT04280705) is a phase II, randomized, placebo-controlled trial in US of remdesivir for mild/moderate or severe (including mechanical ventilation) COVID-19 being sponsored by NIAID. Notable exclusions: Age < 18 years, pregnancy or breastfeeding, stage 4 CKD or dialysis (i.e. eGFR < 30 ml/min), or ALT/AST > 5 times ULN.

Two planned randomized clinical trials in US of moderate and severe COVID-19 (NCT04292730 and NCT04292899).

\[ \text{Inclusion criteria for both trials are documented SARS-CoV-2, hospitalized with fever, and radiographic pulmonary infiltrates as well as room air SpO2 95% or greater for moderate trial or 94% or less for severe trial.} \]

\[ \text{Key exclusion criteria are: Participation in any other clinical trial of an experimental treatment for COVID-19, Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited < 24 hours prior to study drug dosing, Requiring mechanical ventilation at screening, Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN), Creatinine clearance < 50 mL/min} \]

Two ongoing randomized, placebo-controlled clinical trials in China of mild/moderate and severe COVID-19 (NCT04252664 and NCT04257656). Notable exclusions: Age < 18 years, severe liver disease (e.g. Child Pugh score ≥ C, AST>5 times upper limit), pregnancy or breastfeeding, severe renal impairment (eGFR ≤ 30 ml/min), receipt of any experimental COVID-19 treatment (off-label, compassionate use, or trial related) within the 30 days prior to the time of the screening evaluation.

**Expert Comments:** Remdesivir is currently considered our first line treatment option, when available for treatment of SARS CoV-2. This opinion is based on limited clinical experience among our ID community --- though obviously, clinical trial data are still needed. Access to Remdesivir will likely be limited – see comments below.

**Hydroxychloroquine**

- **Considerations for use:**
  - Use of any off-label drug for COVID-19 may or may not prevent approval of remdesivir. This should be considered before initiating any therapy other than remdesivir. However, in anecdotal experience, this has generally not prevented approval of compassionate use remdesivir.
  - Caution in patients with underlying heart disease.

- **Acquisition and Administration:**
  - Hydroxychloroquine available, no anticipated delay to administration assuming no drug shortage
  - Chloroquine is currently in shortage with sporadic availability. Consult with a pharmacy regarding availability of this agent if anticipating use.

- **Dosing/Administration**
  - Hydroxychloroquine Dosage: 400 mg PO daily x 5 days (based on an ongoing clinical trial [NCT04261517])
- An alternative dosing regimen of 400 mg PO BID on first day followed by 200 mg PO BID thereafter has been proposed but based on an in vitro model not being clinically studied currently.\textsuperscript{14}
- Tablet should not be split or crushed but drug may be prepared into an oral suspension in patients who cannot take whole tablets, discuss with pharmacy.\textsuperscript{5}
- No renal or hepatic dose adjustments in label, use caution in renal/hepatic impairment.\textsuperscript{5}
  - Chloroquine Dosage: Treatment regimen recommended by Chinese New Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7\textsuperscript{th} Edition) is 500 mg PO BID x 7 days.\textsuperscript{12}
    - Bodyweight less than 50kg: 500mg twice daily for day 1 and 2, 500mg once daily for day 3 through 7.\textsuperscript{12}

- Tolerability
  - General:
    - Dizziness, headache, dizziness, loss of appetite, nausea, vomiting, abdominal pain, diarrhea, tinnitus, irritability. Most are mild and remit upon drug discontinuation.\textsuperscript{15}
  - Cardiotoxicity (long term use, possibly also short term use):
    - Causes suppression of SA node, which can lead to arrhythmia.\textsuperscript{15} In a 2018 systematic review of 127 patients of whom 58% received chloroquine and 39% hydroxychloroquine (both drugs in the remainder), conduction disorders most common (85% of patients). Median treatment duration was 7 years but minimum duration was 3 days.\textsuperscript{16}
    - Risk cannot be quantified because of lack of controlled trials but mainly appears to be associated with long term use. That said, minimum duration was 3 days in this study, thus, toxicity with short term use is not impossible and may be a more significant consideration in critically ill patients and those with underlying cardiac conditions.\textsuperscript{16}
    - QTc prolongation is of concern with one reported case of TdP (associated with long term hydroxychloroquine use for SLE).\textsuperscript{17} It is prudent to monitor QTc interval and electrolytes, and if possible avoiding other drugs that prolong QTc.
  - Retinal toxicity (long term use):
    - Chloroquine secreted by lacrimal glands. Accumulation of chloroquine may be associated with retinopathy, macular degeneration. Observed in long term use for rheumatologic conditions.\textsuperscript{15}
    - Unlikely to be observed during shorter courses for COVID-19.
  - Hematologic toxicity (rare)
    - Hemolysis, aplastic anemia, reversible agranulocytosis, thrombocytopenia are rare.\textsuperscript{15}
    - G6PD Deficiency: It has been proposed that patients with G6PD deficiency may be at higher risk of hemolytic anemia with hydroxychloroquine. In a retrospective study of 275 patients on hydroxychloroquine for rheumatologic indications (i.e. long term therapy) and a total of 700 combined months of exposure, 4% (N=11) of patients G6PD deficient and zero reported episodes of
hemolysis among them. There were two episodes of hemolysis but they did not occur on hydroxychloroquine therapy.\textsuperscript{18}

- Other toxicities
  - Other toxicities have been observed with unknown incidence rates. Dystonia, dyskinesia, tongue extension, torticollis, drug-induced psychosis, leukopenia, purple scar, rash, dermatitis, photosensitive dermatitis and even exfoliative dermatitis, psoriasis, whitening of hair, hair loss, neuromuscular pain, mild transient headache have been described.\textsuperscript{15}

\begin{itemize}
\item **Supportive Data:**
\end{itemize}

- Hydroxychloroquine and chloroquine have in vitro activity against novel coronavirus\textsuperscript{7} Antiviral activity may be due to increase in endosomal pH and interference with glycosylation of cellular receptors of SARS-CoV.\textsuperscript{19}
- in vitro data suggested that chloroquine is less potent than hydroxychloroquine against COVID-19.\textsuperscript{14}
- Ongoing phase III placebo-controlled clinical trial in China (NCT04261517) of hydroxychloroquine for pneumonia caused by novel 2019 coronavirus.\textsuperscript{13} Notable exclusions: Age < 18 years, pregnant women, severe heart, lung, kidney, brain, blood disease, retinal disease, hearing loss, or severe neurological or mental illness
- Initial reports from more than 100 patients showed superiority of chloroquine to control treatment in inhibiting exacerbation of pneumonia, promoting negative conversion, and shortening the disease. This is per a news briefing in China.\textsuperscript{19}
- A multicenter collaborative Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia recommended chloroquine phosphate for mild, moderate, and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine.\textsuperscript{15}
- in vitro data has also suggested that immunomodulatory activity of hydroxychloroquine may inhibit cytokine storm late in COVID-19 disease process.\textsuperscript{14}
- **Expert Comments:** Hydroxychloroquine and Chloroquine are FDA approved medications that will be more readily available for widespread use compared to Remdesivir. While we are obviously waiting final results from the trial, the potential to accelerate time to viral clearance may have significant impacts on viral transmission dynamics. Accelerating time to viral clearance will allow healthcare workers to return to work more rapidly after viral resolution. From a purely hypothetical perspective, reduction in time to viral clearance may reduce likelihood of transmission in the hospital setting and may have benefit in other healthcare settings. ID physicians have attempted treatment with Hydroxychloroquine in SARS CoV-2 patients in the US. Obviously, our opinion is based on limited clinical experience among our ID community --- though obviously, clinical trial data are still needed increased testing and treatment of Coronavirus with FDA available agents may be an important tool to reduce spread of disease.
Lopinavir/Ritonavir

- Clinical considerations
  - Use of any off-label drug for COVID-19 may or may not prevent approval of remdesivir. This should be considered before initiating any therapy other than remdesivir. However, in anecdotal experience, this has generally not prevented approval of compassionate use remdesivir.
  - Of note, lopinavir/ritonavir may have a significant drug interaction with remdesivir (see remdesivir section). This should be strongly considered prior to initiating therapy.5
  - Lopinavir is an HIV protease inhibitor that has been reported to have activity against 2019-nCoV. It is unclear whether inhibitors of HIV protease (in the aspartic protease family) can effectively inhibit that of 2019-nCoV (in the cysteine protease family).20

- Acquisition and Administration
  - Lopinavir/ritonavir is currently available
  - Dosage: 400/100 mg PO BID for up to 10 days12
    - If administering via feeding tube, liquid formulation available but may be in shortage. Crushed tablets administered via feeding tube decreased AUC by 45 and 47% for lopinavir and ritonavir, respectively.21 If liquid unavailable and must use crushed tablets via feeding tube, consider doubling dose either 800/200 mg PO BID or 400/100 mg PO 4x daily. The latter may have better GI tolerance.

- Supporting evidence
  - In a study of 5 patients with COVID-19 in Singapore who received lopinavir/ritonavir, clinical benefit was equivocal and progressive disease occurred in 2 patients. Of note this study used a lower dose (200/100 mg twice daily) of lopinavir/ritonavir.22
  - In a study of 4 patients, 2 with mild, 2 with severe COVID-19 in Shanghai who received lopinavir/ritonavir (400/100mg PO BID x 6-15 days) along with other treatments including arbidol and traditional Chinese medicine, 3 improved, 2 of which had negative viral testing at end of data collection. The fourth patient, with severe COVID-19, showed signs of improvement at end of data collection.23
  - Rapid advice guidelines for 2019-nCoV pneumonia from the Zhongnan Hospital of Wuhan Novel Coronavirus Management and Research Team published February 6, 2020 provided a weak recommendation for use of lopinavir/ritonavir based on benefits found in patients with SARS or MERS, especially with earlier administration.24
  - In a retrospective case control study of 75 patients with SARS, addition of lopinavir 400 mg/ritonavir 100 mg orally twice daily for 10-14 days as initial treatment showed association with lower death rate (2.3% vs 15.6%), intubation rate (0% vs 11.0%) compared with 634 matched controls. Excluded pregnancy, liver disease.25
  - In a retrospective case control study of 41 patients with SARS who received LPV/r 400/100 mg orally twice daily x 14 days with ribavirin compared to 111 patients who received ribavirin only, incidence of ADRS or death was significantly lower in LPV/r group (2.4% vs. 28.8%, p<0.001) at day 21.26
  - Expert Comments: In general, we are less enthusiastic about Lopinavir/Ritonavir compared to other options for treatment of SARS CoV2, although the drug has been tried in combination with other agents.
Adjunctive Therapy

- Adjunctive corticosteroids have not shown clinical benefit and delayed viral RNA clearance in other coronavirus disease (SARS and MERS) and may increase risk of side effects (psychosis, diabetes, avascular necrosis) and increased mortality in influenza.27
  - An open labelled, randomized, controlled trial of 48 patients will be conducted in China comparing corticosteroid therapy (methylprednisolone 1-2 mg/kg/day IV for 3 days) to control group (no corticosteroid) in patients with severe COVID-19. Currently only the study protocol is published.28
- Recent revisions to Chinese guidance (“New Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Version 7)”) has proposed the use of tocilizumab for cytokine storm in patients with severe disease (e.g. acute respiratory distress syndrome) and elevated interleukin-6 levels.29 Though other data suggests that hydroxychloroquine may accomplish this goal without associated immunosuppressive risk.14

Other agents with potential activity or being studied against COVID-19

Other agents exist with varying indications and evidence.20 Data on nitazoxanide, ribavirin, inhaled alpha interferon, favipirvir, baloxivir, Darunavir/r and tocilizumab are limited. In one report, tocilizumab may have demonstrated some benefit in 19/20 patients with severe disease. Treatment experience with Tocilizumab may be as high as 272 patients.30 Cedars Sinai Medical center apparently considering Tocilizumab as a possible treatment option. (Personal Communication Cyril Gaultier)

For additional academic contributions, please send comments and questions to jmckinnell@ph.lacounty.gov. Preferred method of adding revisions is to send in word version with track changes with complete references. Please include a copy of the primary academic reference for any treatment additions.
Remdesivir Procurement Process (subject to change)

Remdesivir requires a multiple approval process (approval from Gilead and eIND approval from FDA)

- **Step 1: Request approval from Gilead**
  - ID Physician to fill out form: [https://rdvcu.gilead.com](https://rdvcu.gilead.com)
    - Review inclusion/exclusion criteria on website (subject to change)
    - Some browser incompatibility, may require mobile device to submit
  - Gilead representative will contact physician with approval/rejection and guidance on next steps
- **Step 2: Request emergency investigational new drug (eIND) approval from FDA**
  - Call FDA at 301-796-3400 (5am – 1:30pm, M-F) or 866-300-4374 (after 1:30pm M-F or weekends)
    - For reference: FDA eIND guidance website: [https://www.fda.gov/news-events/expanded-access/expanded-access-how-submit-request-forms#PhysicianEmergency-sbs](https://www.fda.gov/news-events/expanded-access/expanded-access-how-submit-request-forms#PhysicianEmergency-sbs)
- **Step 3: Notify Pharmacy**
- **Step 4: Consent patient to receive remdesivir**
  - Have patient sign local IRB Consent Form and Gilead Consent Form
- **Step 5: Order remdesivir**
References


5. Lexicomp Online.


21. Ovid: Pharmacokinetics of Lopinavir/Ritonavir Crushed Versus Whole Tablets in Children. http://ovidsp.dc2.ovid.com.laneproxy.stanford.edu/sp-4.0.4a/ovidweb.cgi?QS2=434f4e1a73d37e8c6114a63cc85fea09bb115a7a6847814cf6dea392f35e40ecd813ec8872a700c3220bb8907c0bf31d348c476617c42781433390c1bf832d939341a35cf72eae1d28c19d199602e5cd3ae9a2d22de5edf1622afbe8151c894c0f1bdce56adbbb9d92791adea8bf8a7dfaf91f80a6327cfa6af48f2ead7eb2b2f0e0a89fa865c8ba11c75b96210be4c7919ed3756c281ce0c31fa3f12fae89bb1d1e3ebc4fdd1cfc0f0ff6b604b4400ff86a444a21010bb876c246870d8506dfbcb787656df615217e5b925e6cada0edc03055b6b139b0bd63f05af231f0f48c8c5dfe611c624e52197106850ab567ee33bf41b400afed2fa1c1913f01fb94ee3f1f2bd22b2a262de1fe4e4f9819e180e8bc3cd29fc02dcb67379accdb543f0a664d6eef036b465a02dd32861be540799d50ec76b464fb7203951eaf19df13529bb13e828c07b7f66bd36fc55cb44b767f835db1492a143ff9006e0c1b05c7f5497b6aedae816289a375012fe0e96ccc11d14558dfa522c7a2b26a2e5b3c9cf3f20afd322. Accessed March 8, 2020.


30. Reported Interview with Dr. Daniel Lucey (Georgetown University Medical Center), accessed on March 12, 2020. https://sciencespeaksblog.org/2020/03/09/covid-19-on-initial-autopsies-and-lung-transplants/