Treatment Recommendations for COVID-19

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In December 2019, a novel coronavirus (2019-nCoV or SARS-CoV-2) was first identified as a cause of respiratory illness (coronavirus disease 2019, COVID-19) among patients in Wuhan, Hubei Province, China. Since that time, the spread of this virus has become a global health concern.

Currently, there are no medications licensed specifically for use against COVID-19, though several agents are undergoing evaluation in pre-clinical and clinical studies. In the absence of targeted therapies, several FDA-approved agents have been proposed as potential options to repurpose for use against COVID-19. The rationale for use of these agents is based mostly on data extrapolated from other viruses, including related coronaviruses such as those associated with Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS).

The recommendations below are meant to inform clinicians until further guidance becomes available from organizations such as the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). Because the data surrounding COVID-19 treatment is rapidly evolving, these recommendations are subject to change.

For additional up-to-date information, the CDC and WHO websites can be accessed via the links below:
CDC: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html
WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance

Recommended Therapies

Because there are currently no medication therapies directed specifically at COVID-19, the following measures represent the mainstay of treatment for most patients:

- Supportive care
  - Conservative fluids, electrolyte repletion, advanced organ support (if indicated)
- Appropriate infection prevention and control measures to prevent transmission
  - Hand hygiene, appropriate isolation, etc.

Some additional therapies have demonstrated safety and may potentially be efficacious against COVID-19. However, these agents should be used with caution and reserved for critically ill patients or those deemed to be at higher risk for COVID-19 complications (Table 1). Use of these agents (Table 2) for the treatment of COVID-19 is restricted to ASP approval (via **pager #10307**) or ID consult **24 hours per day, 7 days per week.** Refer to Appendix C for additional details.

Table 1: Highly Suspected or Confirmed COVID-19 Adjunctive Treatment Recommendations Based on Treatment Setting and Illness Severity

Treatment Setting	Adjunctive Treatment Recommendations Regardless of Age, Comorbidities, or Immunocompromised Status
Outpatient Setting	Supportive Care
Inpatient Setting*	**Mild Disease** – Without pneumonia and requiring <4L of new O2
	Supportive Care
	Moderate Disease – Pneumonia requiring hospitalization, not meeting criteria for severe disease OR no evidence of pneumonia, but requiring ≥4L of new O2
	Consider Treatment**
	Severe Disease – Requiring mechanical ventilation OR impending respiratory failure requiring intubation (RR>30 breaths/min; O2 saturation ≤93% on room air; PaO2/FiO2 ratio ≤300mmHg)
	Treatment Indicated

*Treatment requires approval 24/7 – see Appendix C
**Strongly consider treatment if duration of illness ≥ 7 days

Table 2: Adjunctive Therapies to Consider in Patients Meeting Criteria for Treatment of COVID-19

Medication	Dose	Indication for Use	Other Information
If Patient Is Intubated			
Remdesivir	**200 mg IV x1 day, then 100 mg IV daily x5-10 days** No adjustment for renal impairment/ECMO	• Non-FDA-approved agent soon to be available via expanded access program only • **First line agent for severe, confirmed COVID-19 in pregnant patients only until further notice**	• See Appendix A for inclusion/ exclusion criteria and application to obtain product
Hydroxychloroquine* (Plaquenil®) suspension	**400 mg BID x1 day, then 200 mg PO BID x5 days**** No adjustment for renal impairment	• First line agent for patients not meeting criteria for remdesivir or while awaiting remdesivir	• May cause QTc prolongation – See Appendix B
Lopinavir/ritonavir (Kaletra®) PO solution	**400/100 mg (5 mL) PO BID x5-10 days** No adjustment for renal impairment/CRRT ECMO: 600/150 mg (7.5 mL) PO BID	• Second line agent for patients not meeting criteria for remdesivir or while awaiting remdesivir • Alternative to hydroxychloroquine in patients with contraindication (e.g., significant QTc prolongation at baseline or on therapy)	• Contains potent CYP3A4 inhibitor – screen for drug interactions • Rapid HIV test should be ordered if status unknown; do not delay initiation of therapy while result is pending • Low risk of QTc prolongation with short term therapy
If Patient Is NOT Intubated			
Hydroxychloroquine* (Plaquenil®) tablets	**400 mg BID x1 day, then 200 mg PO BID x5 days**** No adjustment for renal impairment	• First line agent	• Tablets cannot be crushed – use hydroxychloroquine suspension for tube administration • May cause QTc prolongation – See Appendix B
Lopinavir/ritonavir (Kaletra®) PO tablets	**400/100 mg (2 tabs) PO BID x5-10 days** No adjustment for renal impairment	• Second line agent in patients with contraindication to hydroxychloroquine (e.g., significant QTc prolongation at baseline or on therapy)	• Tablets cannot be crushed – use PO solution for tube administration • Contains potent CYP3A4 inhibitor – screen for drug interactions • Rapid HIV test should be ordered if status unknown; do not delay initiation of therapy while result is pending • Low risk of QTc prolongation with short term therapy

*****If inadequate hydroxychloroquine supply, may substitute chloroquine 500 mg PO BID x5-10 days. See Appendix B.
******May extend hydroxychloroquine course up to 10 days based on clinical response.

Therapies That May Be Considered in Select Situations: Other agents have limited data and/or are currently under investigation for use in the treatment of COVID-19 (Table 3). While not routinely recommended, these agents may be considered on a case-by-case basis in consultation with Infectious Diseases.

Table 3: Other Adjunctive Therapies

Medication	Dose	Other Information
Tocilizumab (Actemra®)	**4 mg/kg (max 400 mg) IV recommended** OR 8 mg/kg (max 800 mg) IV based on clinical judgment 2nd dose may be repeated 8-12 hours later based on clinical response. Not to exceed 2 doses.	*Proposed Therapeutic Effect:* • Recombinant humanized monoclonal IL-6 antibody, approved for certain rheumatological diseases and Chimeric Antigen Receptor (CAR) T cell-induced cytokine release syndrome. • The role of IL-6 in COVID-19 induced cytokine release and acute respiratory distress syndrome is unclear. Other adaptive/innate immune cells and cytokine factors may be implicated. • No specific IL-6 cut-off has been established to predict illness severity. In an open-label study of 21 patients with severe/critical disease, mean IL-6 levels were 132.38 ± 278.54 pg/ml. Tocilizumab reduced body temperatures and supplemental oxygen requirements, as well as improved CT findings in most patients. In another report, IL-6 levels averaged 25.2 pg/ml in severe cases compared to 13.3 pg/ml in non-severe cases. *OSUWMC Clinical Use:* • Due to the lack of data from controlled studies, **routine use of tocilizumab is not recommended**. Randomized controlled trials are presently underway and results may help determine role in therapy for COVID-19 infection. • Following discussion with the Critical Care faculty attending and Infectious Diseases attending, tocilizumab may be considered on a case-by-case basis if there is evidence of worsening oxygenation after trialing first line therapies (as described in Table 2). • Prior to administration, IL-6, CRP, D-dimer, fibrinogen, and ferritin should be obtained and trended daily. If these tests are ordered over the weekend, the provider should contact the flow cytometry manager to ensure the IL-6 test is performed if therapy is immediately necessary. *Therapy-Related Considerations:* • Black box warning for severe infection; long half-life with potential for ongoing immunosuppression • Hepatotoxicity has been described. Consider avoiding therapy in patients with ALT or AST greater than 5x the upper limit of normal. • Expensive with limited supply on hand
PO Ribavirin (in combination with lopinavir/ ritonavir)	**2000 mg PO load, then 10 mg/kg PO q8h x5-10 days** CrCl 20-50 mL/min: 2000 mg PO load, then 200 mg PO q8h x5-10 days CrCl <20/HD: 2000 mg PO load, then 200 mg PO q12h x5-10 days	• Some data from other coronaviruses suggesting synergy when given with lopinavir/ritonavir • Higher doses have been used against SARS and MERS, but may lead to excessive risk of toxicity • Significant adverse reactions reported, including bone marrow suppression and hemolytic anemia • Contraindicated in pregnancy

*Consultation with Infectious Diseases prior to initiation not required, but may consider pulmonary consult

Therapies Not Currently Recommended

Due to lack of efficacy data and/or evidence of potential harm, the therapies below are not recommended for the specific treatment of COVID-19 at this time, unless otherwise indicated. Of note, Vitamin C, Vitamin D, zinc, nor any medications listed in Tables 2-4 have been shown to prevent COVID-19.

Table 4: Therapies Not Currently Recommended

Medication	Comments
Azithromycin	Insufficient data to support use. Open label study (n=80) suggested benefit when given in combination with hydroxychloroquine, but many patients were asymptomatic or had upper respiratory symptoms only, and only 15% were febrile or required oxygen. Previous study in MERS showed no benefit on mortality or viral clearance.
Baloxavir marboxil	No evidence to support use and potential for adverse effects, including severe and sometimes fatal hypersensitivity reactions
Corticosteroids	Corticosteroids are NOT recommended for treatment of COVID-19 pneumonia. The CDC recommends avoiding corticosteroids unless for other clinical indications (e.g. COPD exacerbation, septic shock) due to potential for prolonged COVID-19 viral replication.
Cyclosporine	No evidence to support use and immunosuppressive effects may cause undue harm
Interferon	No definitive evidence of benefit against SARS-CoV-2 and other coronaviruses and significant potential for adverse effects.
Ivermectin	In vitro activity against SARS-CoV-2 and other viruses, but no clinical outcomes data specific to COVID-19 to suggest safety or efficacy. Based on in vitro findings, significantly higher doses than usually given would be required to achieve adequate serum concentrations.
IVIG	No evidence to support use
Nitazoxanide	In vitro activity against SARS-CoV-2 and other coronaviruses but no clinical outcomes data specific to COVID-19. Failed to demonstrate benefit when added to standard care in randomized controlled trial of patients hospitalized with respiratory viral illness including small number with other coronaviruses.
Oseltamivir	No in vitro activity against coronaviruses. Should only be used if influenza is suspected or confirmed.
Other antiretrovirals (e.g. abacavir, boosted darunavir, tenofovir)	Ongoing clinical trials with darunavir/cobicistat but no in vitro or clinical outcomes data. Other agents such as abacavir, tenofovir, and nelfinavir have been proposed, but not enough data to support use at this time.

Other Medication Considerations

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

Conflicting hypotheses have emerged surrounding the role of ACEIs and ARBs in the pathogenesis of COVID-19. However, there is currently no data in humans to suggest either benefit or harm of these agents toward the risk and severity of infection. Until such data becomes available, **the decision to initiate, withhold, or discontinue an ACEI or ARB should be independent of considerations surrounding COVID-19.**

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Questions have also arisen regarding the use of NSAIDs to treat patients with COVID-19 due to the potential of these medications to exacerbate the disease. Currently, these concerns are based on theoretical and anecdotal reports rather than clinical outcomes data specific to COVID-19. However, NSAIDs are linked to a number of other adverse effects, which may be worse among the patient populations at an increased risk of poor outcomes from COVID-19 (e.g., elderly, those with comorbidities such as cardiovascular disease including heart failure and coronary artery disease). COVID-19 has also been associated with increased risk of acute cardiac injury, which provides further justification to avoid NSAIDs in higher risk patient populations. **Therefore, acetaminophen is preferred over NSAIDs as a first line antipyretic and analgesic among inpatients and outpatients with COVID-19.**

Appendix A. Remdesivir Compassionate Use How-To

Remdesivir is a non-FDA approved agent manufactured by Gilead Sciences.
OSUWMC is not enrolled in remdesivir clinical trials, therefore, the mode of acquisition is via compassionate use which is only available for pregnant patients at this time. Gilead is working toward providing remdesivir to other patients via an expanded access program in the near future.

Inclusion/exclusion criteria for remdesivir compassionate use as set forth by Gilead at this time are as follows (subject to change):

Inclusion Criteria:

- Hospitalization
- Confirmed SARS-CoV-2 by PCR
- Mechanical ventilation
- Pregnancy

Exclusion Criteria:

- Evidence of multi-organ failure
- Pressor requirements to maintain blood pressure
- ALT levels > 5 X ULN
- CrCl < 30 mL/min or dialysis or continuous veno-venous hemofiltration
- Remdesivir cannot be used in conjunction with other experimental antiviral agents for COVID-19

If a patient warrants treatment according to Table 1 above and meets inclusion/exclusion criteria for use, the treating physician should submit a compassionate use request on behalf of the patient to Gilead at https://rdvcu.gilead.com/
Once the request is submitted, Gilead will be in communication with the provider to approve or decline use or to request additional information.
For shipment of remdesivir use the following information when completing the form:

Pharmacy/Hospital Name: The Ohio State University Medical Center
Pharmacist/pharmacy Contact Name: Investigational Drug Service
Address: Investigational Drug Service
460 W. 10th Ave, Room C150N
Columbus, OH 43210
E-mail: pharmacy.ids@osumc.edu
Phone: 614-293-4560
Cell Phone: 614-293-3312 (central pharmacy)

For after-hours assistance with drug receipt, see service coverage for IDS on-call or page 614-730-4615.

For more information regarding the compassionate use process in general, please refer to the OSUWMC Expanded Use ("Compassionate Use") of Investigational Products guideline.

Appendix B. Cardiac Monitoring for Chloroquine (CQ)/Hydroxychloroquine (HCQ)

1. Place patients on telemetry and obtain baseline 12 lead ECG
2. Discontinue all QT-prolonging medication if possible. Consult medical specialty associated with medication for concerns with discontinuation risk or for alternatives. Consult pharmacy for assistance if needed for profile review to identify QT-prolonging medications.
3. Please correct electrolyte abnormalities, specifically potassium (> 4mmol/L) and magnesium (> 2mg/dL). We recommend that as you are starting to replete electrolytes, the drug therapy should not be delayed
4. Recognize that the likelihood for a malignant ventricular arrhythmia or a worrisome prolongation of the QTc is quite low (< 2%)
5. Regardless of the pre-drug / baseline QTc, give first dose
6. Obtain 6-lead telemetry or 12-lead ECG 2 hours after first dose
    a. If pre-drug QRS duration is < 120ms, can proceed with the second dose if the QTc < 520msec
    b. If pre-drug QRS duration is > 120ms, with native (meaning not paced) conduction, can proceed to give second dose if the QTc is < 570msec
    c. For paced QRS complex, QTc monitoring is not indicated, and thus would hold the medication and obtain an EP consult **only** if the patient experiences a ventricular arrhythmia
7. For concerns regarding ventricular arrhythmias or excessive QT prolongation, EP consult can be obtained to review the ECG
    a. Activation of a consult is completed using the usual protocol through IHIS
    b. For these consults, the primary team **must** upload each of the concerning telemetry strips and/or 12-lead ECG to the *Media tab* of the patient's IHIS chart
    c. The EP staff will complete a remote e-consult by reviewing the uploaded images in the *Media tab* of IHIS. The consult will provide an interpretation of the rhythm and QTc but cannot discern the risks/benefits of continued medical therapy
    d. EP staff will not be evaluating the patient with a face-to-face visit
    e. Overnight consultation will be reviewed the subsequent day and the e-consult will be completed in a timely manner
8. If any evidence of torsade de pointes on telemetry, discontinue CQ/HCQ and request EP consultation
9. Telemetry should be continued while the patient is receiving CQ/HCQ
10. Unless there is worrisome arrhythmia, the ECG needs to be obtained only at baseline and after the first dose of the medication

Appendix C. COVID-19 Medication Approval Process

	Day Response (0800-1700)	Night Response (1701-0759)
Patient Scenario	**Who To Contact**	**Who To Contact**
No ID consult or ID consult pending, COVID test pending	On-Call ID Fellow	On-Call ID Fellow
No ID consult or ID consult pending, COVID test positive	COVID Medication Approval Pager	COVID Medication Approval Pager
ID actively following, review of ID note does not indicate need for therapy and COVID testing results **did not** return after ID note provided in chart	ID Service Fellow	On-Call ID Fellow
ID actively following or suspect COVID note left, COVID positive result **did** return after ID note provided in chart	ID Service Fellow	COVID Medication Approval Pager
ID actively following or suspect COVID note left, medication recommended but approval code not provided in note or order	ID Service Fellow	On-Call ID Fellow

Notes:

- Active/pending ID consults can be seen under the Referrals tab→IP Consult to Infectious Disease
- Remdesivir requests will be processed 0800-1700 each day
- Requests for emergent tocilizumab **must** be routed to the ID service fellow/on-call ID fellow (requires a conversation with the intensivist and ID attending)
- Discussion of the benefits vs risks of corticosteroids should be routed to the ID service fellow/on-call ID fellow

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