Coronavirus disease (COVID-19): Treatment - Adult - Inpatient/Emergency Department Consensus Care Model

Population/Problem:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was identified as the pathogen of coronavirus disease 2019 (COVID-19).1 COVID-19 patients present primarily with fever, myalgia or fatigue, and cough.2-4 Loss or impairment of taste and smell (i.e., anosmia, ageusia or dysgeusia) may be early symptoms of the disease as well.5,6 Diarrhea, nausea, and vomiting have been reported too.7 Some patients may develop severe and critical disease, necessitating oxygen supplementation or invasive ventilation following the development of acute respiratory distress syndrome (ARDS).8

There are no approved antiviral medications for the treatment of COVID19. The only recommended therapy for this disease is supportive care. Improved practice guidelines for the treatment of critically ill patients, including mechanical ventilation management and ARDS dramatically improve patient outcomes and should be meticulously provided first. Forty years of pharmaceutical research in the treatment of ARDS has failed to show a benefit from drug therapy; therefore, the recommendations in this guideline are principled in “first do no harm.”

This document summarizes currently identified potential treatment options for patients hospitalized with COVID-19. Due to their periodic and rare epidemiological occurrence, coronavirus infections in humans is relatively unstudied. The treatment recommendations outlined were based on clinical and observational studies in humans (currently, no well controlled trials); however, animal and in vitro data are often the only data available. SARS-CoV1 (2003) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) studies also guided recommendations. The literature supporting these recommendations are changing rapidly. The workgroup is consistently evaluating literature and updating this guideline

This guideline is meant to aid clinicians, including physicians, nurses, pharmacists, and respiratory therapists, apply the rapidly evolving data on COVID-19 therapies to best serve UW Health patients. This guideline is focused on treatments targeting the SARS-CoV2 virus and modulators of the host immune response and also addresses non-antiviral therapies which may impact virus entry, replication, and shedding (for example, angiotensin-II converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], non-steroidal anti-inflammatory drugs [NSAIDs] and other renin–angiotensin–aldosterone system [RAAS] therapies.)
Recommendations

General Principles
1. Due to expected medication supply shortages and no data supporting treatment of clinically stable patients, treatment is recommended for consideration only in symptomatic, hospitalized patients with a COVID-19 positive test. (UW Health Low quality of evidence, S recommendation)

2. To preserve medication supplies and due to lack of studies evaluating combination therapy, monotherapy with the either chloroquine or lopinavir/ritonavir is currently recommended. (UW Health Moderate quality of evidence, S recommendation)

3. Treatment with specific drugs possibly active against SARS-CoV2 should be considered in patients who are symptomatic and hospitalized with a positive COVID-19 test.3,4 (UW Health Moderate quality evidence, S recommendation)
   a. To conserve drug supplies, currently it is not recommended to treat patients for COVID-19 without a positive test result. (UW Health Low quality of evidence, C recommendation)
   b. Consider infectious disease consultation for approval of COVID-19 therapy in patients with rapidly worsening pulmonary function and increasing O2 requirements. (UW Health Low quality of evidence, C recommendation)

4. The duration of antiviral therapy should not exceed 10 days regardless of patient status.3,4 (UW Health Moderate quality of evidence, C recommendation)
   a. For patients who improve and are ready for discharge before 10 days, it is reasonable to discontinue at discharge and patients do not require home antiviral therapy (UW Health low quality of evidence, C recommendation)

5. Evaluation and treatment of community-acquired bacterial pneumonia consistent with UW Health guidelines is recommended.4 (UW Health Moderate quality evidence, S recommendation)

Anti-viral medications
6. **Remdesivir** is an experimental antiviral medication that is more active than lopinavir/ritonavir/interferon-β against MERS-CoV in cell culture.10 Of all potential therapies reviewed to date, remdesivir is the most likely to be active against COVID-19 and would be the preferred treatment drug.11 Patients should be evaluated for inclusion in a clinical trial or expanded access program. (UW Health Low quality of evidence, C recommendation)

7. **Chloroquine or hydroxychloroquine** is recommended for treatment of hospitalized patients with confirmed COVID19 infection.12 (UW Health Moderate quality evidence, S recommendation)
   a. Chloroquine impairs pH-dependent virus uncoating, interferes with cellular receptors glycosylation, and impairs formation of viral replication.
   b. Chloroquine may also have immunomodulating effects that contribute to antiviral properties in-vivo and modulate the cytokine storm that occurs in late-phase, critically ill COVID-19 patients.
   c. A baseline electrocardiogram (EKG) and telemetry is recommended (UW Health High quality of evidence, S recommendation)
      i. Use with caution use in patients with known left ventricular dysfunction. Cardiac toxicity is most serious adverse effect and includes conduction block, cardiomyopathy, and QT prolongation- a precursor of torsades de pointes.
ii. Although long duration of therapy is the main risk factor for cardiomyopathy/cardiac toxicity, total dose, age, pre-existing heart disease, and drug interactions are important moderators.

iii. When possible, other QT prolonging agents should be avoided (i.e. azithromycin for the treatment of CABP)

d. Dosing of chloroquine for COVID-19 is recommended as 1000mg PO daily for 2 days, then 500mg PO daily for 8 days.12,13
e. Dosing of hydroxychloroquine for COVID-19 is recommended as 400mg PO BID for 1 day, then 200mg PO BID for 9 days.
f. The addition of azithromycin to chloroquine or hydroxychloroquine therapy is NOT RECOMMENDED.

8. Chloroquine/Hydroxychloroquine should not be used for patients under investigation, prophylaxis, or ambulatory patients who test positive for COVID-19

9. Lopinavir/ritonavir (Kaletra®) is recommended as an alternative agent for the treatment of COVID-19 in patients who cannot take chloroquine. (UW Health Moderate quality of evidence, C recommendation)

a. A randomized controlled trial of 199 patients with COVID-19 failed to show that treatment with lopinavir/ritonavir reduced time to clinical improvement (primary end-point). Secondary endpoints were mixed: there was a non-statistically significant reduction in 28-day mortality, but higher SARS-CoV-2 viral loads in the lopinavir/ritonavir treated group relative to standard of care alone.14

b. Larger trials are needed to determine if this negative result is due to lack-of-benefit or because the study was not sufficiently powered to detect a (presumably modest) benefit.

c. In-vitro evidence suggests that lopinavir/ritonavir has antiviral activity against human coronavirus but may be less active compared to remdesivir.

Secondary bacterial pneumonia

10. It is recommended to evaluate patients for the presence of secondary bacterial pneumonias in accordance with the UW Health Treatment of Community-Acquired Bacterial Pneumonia (CABP) guideline. (UW Health High quality evidence, S recommendation)

a. Case series from Wuhan and Seattle have reported many patients with secondary bacterial pneumonias.2

b. The DRIP score should be used to evaluate risk of drug-resistant pathogens and determine appropriate antibiotic therapy.

c. Consider avoiding azithromycin and giving preference to doxycycline due to the additive risk of QT prolongation with chloroquine

Host-response modulator therapies

11. Tocilizumab may be considered for the treatment of cytokine storm due to COVID-19. (UW Health Moderate quality evidence, C recommendation)

a. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. Inhibition of IL-6, a major pro-inflammatory cytokine, leads to reduced cytokine and acute phase reactant production.15

b. Reports have shown IL-6 elevation in COVID-19 patients, particularly in non-survivors. Mechanistically, tocilizumab would be expected to benefit COVID-19 patients who develop cytokine storm.

c. Prior to tocilizumab administration, laboratory monitoring with IL-6, ferritin, CRP, ESR, and D-dimer tests is recommended.16
d. The recommended dosing for COVID-19 patients is tocilizumab 400mg IV once. The dose (400mg IV once) may be repeated 12 hours later if the patient has not responded to the first course of therapy.\textsuperscript{15}

12. Systemic corticosteroids should be avoided in clinically stable COVID-19 patients.\textsuperscript{17} (\textit{UW Health Moderate quality evidence, S recommendation}) Corticosteroids, specifically methylprednisone 60mg IV daily, may be considered for the treatment of ARDS in the ICU.\textsuperscript{4} (\textit{UW Health Moderate quality evidence, C recommendation})

a. Corticosteroids have no anti-viral activity but act as immunosuppressants and potent anti-inflammatory agents.

b. Corticosteroid administration should be avoided in patients who have tested posted for influenza. (\textit{UW Health High quality evidence, S recommendation})

c. Corticosteroids may be considered for patients with asthma and/or COPD exacerbation, but benefit should be weighed against the risk of increased viral replication and shedding. (\textit{UW Health Moderate quality evidence, S recommendation})

Supportive Care Therapies

13. ACE inhibitors and ARB therapy: Currently, there is insufficient evidence to recommend stopping or starting ACE inhibitors or ARBs solely for the purposes of COVID-19 treatment.

a. There are opposing arguments in favor of continued use and, conversely, in favor of avoiding ACE inhibitors/ARBs in the context of COVID-19 disease.

b. Given currently published, available data seems incomplete, it suggested to avoid changes in ACE-I or ARB use among COVID-19 patients who were already taking these drugs, unless there is a medical reason to do so (e.g., acute kidney injury, hyperkalemia, hypotension, and others.)

14. ACE-inhibitors or ARBs should not be avoided when there is a standard indication for starting them.\textsuperscript{18} (\textit{UW Health High quality evidence, S recommendation})

15. Ibuprofen and other NSAIDs: It is NOT recommended to discontinue NSAIDs, including ibuprofen, in response to COVID-19 symptoms. (\textit{UW Health Low quality evidence, C recommendation})

a. For relief of fever or pain, it is recommended to use acetaminophen whenever possible. Nonetheless, ibuprofen appears to be safe and effective. (\textit{UW Health Low quality evidence, S recommendation})

16. Ascorbic acid may be considered for patients hospitalized with COVID-19. (\textit{UW Health Moderate quality evidence, C recommendation})

a. Ascorbic acid (AA) can become rapidly depleted during critical illness. Aggressive repletion may promote pulmonary endothelial barrier integrity and function.\textsuperscript{19,20}

b. For patients receiving < 4L O\textsubscript{2} supplemental oxygen, consider ascorbic acid 500-1000mg PO BID. (\textit{UW Health Low quality evidence, C recommendation})

c. For patients requiring \(\geq\) 4L O\textsubscript{2} or mechanical ventilation administer ascorbic acid 3gm IV Q6H.

d. Continue ascorbic acid therapy until O\textsubscript{2} needs < 4L.

Disclaimer

Consensus care models assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Disclosure
It is the policy of UW Health that all workgroup members and other persons who may influence content in this guideline disclose all relevant financial relationships with commercial interests. Any disclosure of a relationship listed is not intended to suggest bias in the information presented but rather to provide the reader with information that may be of importance in their evaluation of the information presented.

Content Expert(s):
Name: Elizabeth Ann Misch, MD- Infectious Diseases
Email Address: eamisch@medicine.wisc.edu

Name: Lucas Schulz, PharmD- Pharmacy (Infectious Disease)
Email Address: L.Schulz2@uwhealth.org

Contact for Changes:
Name: Center for Clinical Knowledge Management (CCKM)
Email Address: cckm@uwhealth.org

Guideline Author(s):
Lucas Schulz, PharmD – Pharmacy

Workgroup Members:
Eric Johannsen, MD – Infectious Diseases
Pierre Kory, MD – Critical Care Medicine
Jeff Fish, PharmD – Pharmacy
Brian Buss, PharmD - Pharmacy

Reviewer(s):
Alex Macbriar, MD – Hospitalist Medicine
Becky Macallister, MD – Hospital Medicine
Michael Pulia, MD – Emergency Medicine
Josh Glazer, MD – Emergency Medicine
Dan Shirley, MD – Infectious Diseases
Jeff Wells, MD – Critical Care Medicine
Hee Soo Jung, MD – Trauma Surgery
Nizar Jarjour, MD – Pulmonology
David Andes, MD – Infectious Diseases
Philip Trapskin, PharmD – Drug Policy
Bart Caponi, MD – Hospital Medicine
Scott Wilson, DO – Hospital Medicine
Aaron Steffenhagen, PharmD – Pharmacy
Lynn Schnapp, MD – Chair, Department of Medicine

Committee Approval(s): (Include the appropriate final approval body)
Nursing Practice Guidelines Committee (MM/DD/YY)
Nursing Practice Council (MM/DD/YY)
Pharmacy & Therapeutics Committee (MM/DD/YY)
Clinical Knowledge Management (CKM) Council (MM/DD/YY)
Plan for review: This guideline will be reviewed as dictated and necessary given public health priorities and as clinical evidence evolves.

Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

<table>
<thead>
<tr>
<th>GRADE Ranking of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE Ratings for Recommendations For or Against Practice</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (S)</td>
<td>Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)</td>
</tr>
<tr>
<td>Conditional (C)</td>
<td>May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)</td>
</tr>
</tbody>
</table>
Collateral Tools & Resources (As Appropriate)

The following collateral tools and resources support staff execution and performance of the evidence-based model recommendations in everyday clinical practice.

Metrics
Describe metrics which could be used to assess compliance with the stated recommendations or to gauge improvement resulting from implementation of the model. Clearly define criteria or operational definitions to assess based on the key recommendations and at a specified interval (e.g., process measures, behavioral measures, clinical or health outcome measures). The data source may also be described (e.g., patient survey, manual chart review, analysis through Clarity). Staff in QSI can also help to identify externally reported measures required of the organization related to a model topic.

Examples:
- % of patients with diabetes and HbA1c < 7%
- % of asthma patients with a completed Asthma Action Plan
- Average number of days that a patient is on an IV antibiotic
- Average amount of time from when patient presents in the ED to when they receive…

Beacon Protocols
Name [#####]

Best Practice Alerts (BPA)
Name [#####]

eConsults
Name [#####]

Order Sets & Smart Sets
Name [#####]

Patient Resources
Name [#####]

Policies
Name [#####]

Procedures
Name [#####]

Protocols
Name [#####]

Reporting Workbench Reports
Name [#####]
References
**Presentation:** Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. The most common symptoms and frequency are fever (99% but 20% low grade <100.4), fatigue (70%), dry cough (59%), anorexia (40%), myalgias (35%), dyspnea (31%), sputum (27%). Less common are headache, sore throat, rhinorrhea, nausea, diarrhea. Loss or impairment of taste and smell (anosmia and ageusia or dysgeusia) may be early symptoms.

**Diagnosis:** Please see the most recent recommendations posted on UConnect for testing of COVID19 suspected patients. The CDC recommends collection of a nasopharyngeal swab specimen to test for SARS-CoV-2. Sputum should only be collected from patients with productive cough; indution of sputum is not indicated. At this point, testing is only being done on NP swabs. SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR). A positive test for SARS-CoV-2 confirms the diagnosis of COVID-19.

**Treatment:** The recommended treatment of COVID19 is supportive care. There are no approved antiviral medications for the treatment of COVID19. Improved practice guidelines for the treatment of critically ill patients, including mechanical ventilation management and ARDS dramatically improve patient outcomes and should be meticulously provided first. Forty years of pharmaceutical research in the treatment of ARDS has failed to show a benefit from drug therapy; therefore, the recommendations in this guideline are principled in “first do no harm.” The UW Health COVID19 Pharmacotherapeutics taskforce has evaluated the available in vitro, animal, and human data for a number of potential therapies. Most data that was reviewed comes from study of SARS-CoV and MERS-CoV infections. SARS and MERS are caused by beta coronaviruses, similar to SARS-CoV2, the virus which causes COVID19 disease. Literature and data in SARS-CoV2 and COVID19 is accumulating daily and this document will be refreshed on a regular basis to keep up with new reports. Please make sure you are using the most recent version available from the UW Health COVID19 response site.

Treatment with specific drugs possibly active against SARS-CoV2 should be considered in patients who are symptomatic and hospitalized with a positive COVID19 test. To conserve drug supplies, at this time, we do not endorse treatment in patients before positive test results. However, consider infectious disease consultation for approval of COVID19 therapy prior to confirmatory test results in patients with rapidly worsening pulmonary function and increasing O2 requirements. The duration of therapy should not exceed 10 days regardless of patient status. For patients who improve and are ready for discharge before 10 days, antiviral therapy may be discontinued at discharge and patients do not require home antiviral therapy. Abbreviated drug monographs are included in the appendices and contain background and references to the available literature used to make our recommendations. Treatment options are listed in Table 1.

It is reasonable in some circumstances to treat COVID-19 patients with antibiotics for concomitant bacterial pneumonia, as co-infection has been reported in 22% of inpatients and 46% of those in ICU (Huang C NEJM 2020). Thus, consider initiation of antibiotic therapy in suspected or confirmed COVID patients who are critically ill, have rapidly increasing oxygen requirements, or have a serum procalcitonin level ≥ 0.25 (UW PCT guideline and Guan NEJM 2020). Clinicians can use the DRIP score as outlined in the Treatment of Community Acquired Bacterial Pneumonia Guideline, available on UConnect, as a decision tool when deciding whether to use narrow or broad antibacterial agents. For example, in patients without a high DRIP score, ceftriaxone and doxycycline are reasonable anti-bacterial agents. Choosing doxycycline in place of azithromycin in patients on chloroquine will minimize the risk of QTc prolongation.
Guidance about the Treatment and Management of Adults Diagnosed with COVID19

azithromycin is selected for atypical coverage or “anti-inflammatory activity,” we recommend obtaining a baseline EKG to ensure the QTc is <500 ms.

Remdesivir is an experimental, antiviral medication that is more active than lopinavir/ritonavir/interferonβ against MERS-CoV in cell culture. Several human clinical studies are underway and recruiting. UW Health is pursuing participation. Of all potential therapies reviewed to date, remdesivir is the most likely to be active and would be the preferred treatment agent. When/if UW becomes a remdesivir trial site, patients should be evaluated for inclusion.

Figure 1. Treatment decision tree for COVID19 + patients.

SARS-CoV-2 is a NEW infection with no RCT proven therapies to date. First line therapy is expert supportive care. Use of the following algorithm is at clinician discretion. Enroll in RCTs when feasible

Outpatient

Symptomatic treatment

Inpatient with O2 requirements

Consider chloroquine

If unable to take chloroquine, consider lopinavir/ritonavir

Inpatient with ventilatory support

Consider Ascorbic acid 500mg PO BID*

Consider Ascorbic acid IV 3gm IV q6hrs

Consider chloroquine

If unable to take chloroquine, consider lopinavir/ritonavir

Monitor for ARDS and cytokine release syndrome**

ARDS: consider systemic corticosteroids

Cytokine release syndrome: consider tocilizumab

* change to ascorbic acid 3gm IV every 6 hours if O2 >4L or CXR abnormalities

** laboratory studies may include: Ferritin, Fibrinogen, CRP, ESR, D-dimer, IL-6 (not available for rapid turnaround at UW right now)

Monotherapy with one antiviral agent (chloroquine or lopinavir/ritonavir) or no therapy is recommended at this time. If considering dual therapy, clinicians must carefully weigh risk and benefit of using combination therapy, both at the patient level and at the public health level. Such considerations include drug-drug interactions (patient level), drug shortages, and extending available resources (public health level).
## Guidance about the Treatment and Management of Adults Diagnosed with COVID19

### Agents with possible anti-viral effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration and contraindications/considerations</th>
<th>Safety and Monitoring</th>
</tr>
</thead>
</table>
| **Chloroquine (CQ)**| Chloroquine phosphate 1000mg PO daily x2 days, then 500 mg PO daily x8 days for a total of 10 days | **contraindications:**  
1. LV dysfunction (EF ≤ 35%)  
2. Left bundle branch block  
3. QTc ≥ 500ms  
   *drug can be crushed or provided as solution*  
   *we do not recommend at this time the addition of azithromycin to chloroquine therapy*  
   *Notes: anti-malarial agent blocks endosome acidification* |
|                     |                                                      | 1. See contraindications in middle column. QT prolongation, a precursor of torsades de pointes, is the most serious effect expected during short term use, though QRS widening and heart block also may occur. See monograph for more details.  
2. A baseline EKG and continuous telemetry are mandatory.  
3. If telemetry monitoring indicates widening of QRS complex or prolongation of QTc after starting CQ, repeat 12-lead EKG to formally assess QTc.  
4. Monitor potassium (goal: ≥ 4.0 meq/L) and magnesium (goal: ≥ 2.0 mg/dL) daily while on chloroquine |
| **Lopinavir/ritonavir** | Lopinavir/ritonavir 400mg/100mg PO every 12 hours for 10 days  
HIV protease inhibitor | Renal dysfunction: generally no adjustment needed  
Crushing and administering tablets via a gastric tube may decrease absorption by ~50%. Decreased absorption is not expected to impact the activity of lopinavir against SARS-CoV.5,6  
1. Ritonavir is a strong CYP3A4 inhibitor.  
2. Contact the clinical pharmacist to assist with management of drug-drug interactions.  
3. Do not initiate in patients on calcineurin inhibitors without consultation with the primary transplant team and transplant pharmacist |

### Agents to consider as adjunctive therapy in patients requiring oxygen support or critical care

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration and contraindications/considerations</th>
<th>Safety and Monitoring</th>
</tr>
</thead>
</table>
| **Ascorbic Acid (AA)** | For patients requiring ≥ 4L O2 or mechanical ventilation: Ascorbic acid 500mg PO BID OR Ascorbic Acid 3gm IV Q6H | Continue IV AA therapy until O2 needs < 4L  
Ascorbic acid (AA) can become rapidly depleted during critical illness. Aggressive repletion may promote pulmonary endothelial barrier integrity and function. |
| **Systemic Corticosteroids (CS)** | ARDS in ICU patients: consider use. Methylprednisone 60mg IV daily | Early COVID19 disease: do not recommend use  
Influenza co-infection: Do not recommend use  
Asthma or COPD exacerbation: use lowest dose possible  
Corticosteroids have no anti-viral activity but act as immunosuppressant and potent anti-inflammatory agents. |
| **Tocilizumab** | Tocilizumab 400mg IV x1. May repeat dose 12 hours later x1 | Limit of 2 doses  
Prior to administration, patients should have ferritin, CRP, ESR, fibrinogen, and D-dimer collected |
### Humanized monoclonal antibody against interleukin-6 receptor

- **Low risk of TB and Hepatitis B reactivation are expected with limited exposure tocilizumab**

### Other Agents

<table>
<thead>
<tr>
<th><strong>ACE inhibitors and ARB</strong></th>
<th>At present, we have no recommendations for or against the use of ACE-I or ARBs when considered solely for the purposes of COVID-19 treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>We do not recommend the discontinuation of NSAIDS, including ibuprofen, in response to COVID-19 symptoms. For relief of fever or pain, we recommend acetaminophen when possible. Nonetheless, ibuprofen appears to be safe and effective. For patients on scheduled ibuprofen and who have received therapy for more than 1 week, continue to use ibuprofen and discuss alternatives with the patient’s primary provider.</td>
</tr>
</tbody>
</table>
**DRUG NAME:** Chloroquine/hydroxychloroquine

**CLINICAL PHARMACOLOGY**
Chloroquine is a cationic amphiphilic drug known to bind to phospholipids and accumulate in lysosomal compartments, impairing their acidification. In COVID-19, this impairs pH-dependent virus uncoating, interferes with cellular receptors glycosylation, and impairs formation of viral replication compartments through effects on autophagy. Chloroquine may also have immunomodulating effects that contribute to its antiviral properties in-vivo.1,2 Hydroxychloroquine has identical properties, but is being reserved for non-COVID purposes (treatment of lupus patients) at our institution at present.

**SUMMARY OF CLINICAL STUDIES**
- *In vitro* data using cell lines shows that chloroquine can inhibit COVID-19 with a 50% inhibitory concentration of 1 uM, implying that therapeutic levels could be achieved in humans.2
- In animal studies, chloroquine improved survival in newborn mice with human coronavirus (HCoV strain OC43) lethal infection. Survival was highest at maternal treatment doses of 15mg/kg (98.6%), 5mg/kg (88%), 1mg/kg (13%).3 The maximum daily dose to the breastfeeding infant was calculated to be 0.7% of the maternal dose.
- Results from more than 100 patients in China suggests that chloroquine phosphate is superior to the control treatment in "inhibiting the exacerbation" of SARS CoV 2 pneumonia.4
- In February 2020, a panel of experts in China endorsed the use of chloroquine in the acute treatment of COVID-19 suggesting increases in clinical success rate, reduction of hospitalization, and improvement in patient outcomes. The Panel from the Italian Society of Infectious and Tropical Diseases recommends the use of chloroquine 500 mg BID or hydroxychloroquine 200 mg BID for 10 days for treatment of COVID-19 in combination with lopinavir/ritonavir or remdesivir depending on severity of illness.8
- If hydroxychloroquine is selected, the dose should be 400mg PO BID x one day followed by 200 mg PO BID x4 days.9

**PHARMACOKINETICS**2,5,7
- Absorption: Oral bioavailability of chloroquine exceeds 75%
- Metabolism: Chloroquine terminal elimination half-life = 1-2 months. Partially metabolized hepatically as a major substrate of CYP2D6 and CYP3A4.
- Excretion: About ~35% is excreted as unchanged drug in the urine. Acidification of urine increases elimination.

**DOSE AND ADMINISTRATION**
- Chloroquine phosphate 1000mg PO x2 days, then 500 mg PO daily x8 days for a total of 10 days
- 500 mg chloroquine phosphate contains 300 mg of chloroquine itself (a.k.a. chloroquine base). May require dose adjustment in renal or hepatic dysfunction.
- We do not recommend the addition of azithromycin due to the risk of addition QT prolongation and concerns about the additional benefits due to confounding clinical trial factors

**SAFETY AND MONITORING**
- Baseline EKG and telemetry are mandatory in use in COVID-19 patients
- **Contraindications:** left bundle branch block, EF ≤35%, QT≥500 ms. Patients who cannot receive chloroquine should be considered for lopinavir/ritonavir
- Chloroquine has been associated with cardiotoxicity. Most notably, it causes QT prolongation in up to 85% of patients. More longer term cardiac toxicity may include conduction blockade, ventricular hypertrophy, hypokinesia, heart failure, pulmonary arterial hypertension, and valvular dysfunction.6 Risk factors for these longer term effects, include total cumulative dose of drug, age, pre-existing heart disease, and drug-drug interactions.
- Other toxicity: **Retinopathy** (4%, early changes may be reversible), tinnitus, bone marrow suppression, **hypoglycemia**, CNS effects (headache, emotional disturbance, insomnia), GI (nausea, diarrhea), dermatologic (alopecia, bleaching of hair, rash, and skin pigmentation changes have been reported.

**REFERENCES**
LOPINAVIR/РИТОНАВИР ДЛЯ ЛЕЧЕНИЯ COVID19 (Сокращенная монография)

**DRUG NAME:** Lopinavir and Ritonavir (Kaletra)

**CLINICAL PHARMACOLOGY**
A number of existing drugs have been screened, using high-throughput assays, for in vitro activity against human coronaviruses, including MERS-CoV. Such screens have identified lopinavir/ритонавир, a drug approved for HIV treatment, as potentially active against beta coronaviruses. Lopinavir is an inhibitor of an HIV protease that cleaves viral protein precursors and allows maturation of viral particles. Ritonavir inhibits the CYP3A metabolism of lopinavir, allowing for increased plasma levels of lopinavir. It is hypothesized that lopinavir may also inhibit the COVID-19 protease (cysteine protease), albeit with less affinity than HIV protease. Additional unidentified host targets may also be a possibility.

**SUMMARY OF CLINICAL STUDIES**
- An RCT of 199 patients with COVID-19 disease failed to show that treatment with lopinavir/ритонавир reduced time to clinical improvement (primary end-point). Secondary endpoints were mixed: there was a non-statistically significant reduction in 28-day mortality, but higher SARS-CoV-2 viral loads in the lopinavir/ритонавир-treated group relative to the group that received standard of care. Larger trials are needed to determine if this negative result is due to true lack of benefit or because the study was insufficiently powered to detect a benefit.
- *In vitro* evidence suggests that lopinavir/ритонавир has antiviral activity against human coronavirus but may be less active compared to remdesivir.
- One study in marmosets (non-human primates) demonstrated improved outcomes in infection due to MERS-CoV, as measured by radiological and pathological findings and lower viral loads.
- Clinical data is limited to case reports and retrospective studies of small cohorts, often confounded by co-administration of other drugs such as ribavirin and interferon. One case report demonstrated a favorable outcome for a single patient with MERS-CoV who received lopinavir/ритонавир monotherapy. A retrospective, matched cohort study (n=75) showed moderate improvement in overall survival and intubation rate when lopinavir/ритонавир was used as early therapy (with ribavirin), but no added benefit when used for as salvage therapy. This study is flawed by reliance on historical controls.

**PHARMACOKINETICS**
- Absorption: the absolute bioavailability of lopinavir co-formulated with ritonavir is not established.
- Metabolism: lopinavir is metabolized by CYP3A4 and may induce its own metabolism. Half-life elimination is 5-6 hours.
- Excretion: lopinavir is excreted through feces 20% as unchanged drug, and minimally excreted in urine (<3% as unchanged drug).

**DOSING AND ADMINISTRATION**
- Lopinavir/ритонавир 400mg/100mg PO every 12 hours for 10 days.
- Generally, no adjustment is made in renal dysfunction.
- Crushing and administering tablets via a gastric tube may decrease absorption by ~50%. Decreased absorption is not expected to impact the activity of lopinavir against SARS-CoV.

**SAFETY AND MONITORING**
- **Dermatologic** (skin rash), **GI upset** (diarrhea, vomiting, nausea, abdominal pain), liver dysfunction (increased liver enzymes), CNS (headache, blurred vision, anxiety, insomnia), hematologic (thrombocytopenia, neutropenia, anemia), asymptomatic bradycardia, and metabolic disorders with longer duration (hypercholesterolemia, hypertriglyceridemia).
- Ritonavir is both a major substrate and strong inhibitor of CYP3A4, and a moderate inducer of CYP2B6.
- In patients on tacrolimus, cyclosporin, or other calcineurin inhibitors (CNI) for transplant immune suppression, levels of CNI should be very carefully monitored to avoid toxicity.

**REFERENCES**
TOCILIZUMAB FOR THE TREATMENT OF CYTOKINE STORM ASSOCIATED WITH COVID19 (ABBREVIATED MONOGRAPH)

DRUG NAME: Tocilizumab (Actemra)

CLINICAL PHARMACOLOGY1-4
Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor. Inhibition of IL-6, a major pro-inflammatory cytokine, leads to reduced cytokine and acute phase reactant production. Reports have shown IL-6 elevation in COVID-19 patients, particularly in non-survivors. Through the mechanism of IL-6 blockade, tocilizumab is postulated to benefit COVID-19 patients who develop cytokine storm.

SUMMARY OF CLINICAL STUDIES5-6

• One case series (N=21, China) has been published investigated the use of tocilizumab in severe or critical COVID-19 patients. Severe illness was defined if any of the following conditions were met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO2 ≤ 93% while breathing room air; (3) PaO2/FiO2 ≤ 300 mmHg. Critical illness was defined if any of the following conditions were met: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) respiratory combined with other organ failure, with ICU admission. The patients in the case series received tocilizumab 400 mg IV once, followed by a second dose if febrile within 12 hours of the first dose. Three patients received a repeat dose. Patients improved clinically, as measured by a reduction in inflammatory markers and oxygen requirements and improvements on lung imaging. Over 90% of patients were discharged (on average 13.5 days after treatment with tocilizumab) and no adverse reactions were observed.
• A randomized, controlled trial (N=93, China) comparing rates of cure, mortality, ventilator utilization, and length of hospitalization in COVID-19 patients following administration of tocilizumab or standard therapy without tocilizumab is ongoing. The study protocol and estimated publication date are not yet available.

PHARMACOKINETICS (Lexicomp)

• Onset: 4 hours to defervescence (in cytokine release syndrome)
• Elimination: Half-life elimination 11-16 days

DOSING AND ADMINISTRATION1, 5, 7

• Tocilizumab 400 mg IV once. Must be given as a 60-minute infusion (do not administer IV push)
• Second dose may be given if there is continued decompensation per clinician judgement. Limit 2 doses.
• Not studied in patients with CrCl <30 mL/minute (no dosage adjustment necessary for CrCl ≥30 mL/minute)
• Not recommended if LFTs >5x ULN (in rheumatoid arthritis and giant cell arteritis)

SAFETY AND MONITORING1

• Prior to administration, measure serum ferritin, CRP, ESR, fibrinogen, and D-dimer
• Common adverse events: Increased cholesterol (20%), LFT elevation (22-36%), infusion-related reaction (4-20%)
• Tocilizumab puts patients at risk for serious infections (e.g. active tuberculosis, invasive fungal, bacterial, viral, protozoal, and other opportunistic infections), hypersensitivity reactions and serious drug-induced liver injuries
• In situations where use is ongoing, a tuberculosis skin test or IGRA, a serum Hepatitis B surface Antigen test, liver function tests (LFTs), serum lipids and a complete blood count are recommended prior to initiation. In the context of using up to 2 doses for treatment of COVID-19 cytokine storm, we deem the risk of reactivation of tuberculosis or Hepatitis B to be low.

REFERENCES

Updated 3/24/2020

**DRUG NAME**: Ascorbic acid

**CLINICAL PHARMACOLOGY**

Ascorbic acid (AA) is a vitamin (i.e. an organic compound required in the diet because it cannot be synthesized by the body) with pleiotropic effects in disease states. AA protects pulmonary endothelial barrier integrity and function, scavenges free-radicals, prevents activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), enhances macrophage activity, T cell function and proliferation, prevents neutrophil apoptosis, increases phagocytosis, and is a critical co-factor for catecholamine production. High concentrations may be found in macrophages, neutrophils, lymphocytes, which support AA’s role in innate and adaptive immune function. Supraphysiologic dosing may potentiate immunologic effects.

**SUMMARY OF CLINICAL STUDIES**

Animal Studies: H3N1 flu was shown to be more lethal in gulo−/− mice mice deficient in the enzyme necessary for AA synthesis compared to wildtype mice. Gulo−knockout mice had worse lung injury in H1N1. Strong dose dependent reduction of mortality and lung injury with IV AA in mice with H1N1 induced pneumonia. Nearly all animal models of bacterial sepsis report protective effects of IV AA in reducing either organ damage, inflammatory markers, or mortality.

Clinical Studies in ARDS/Severe Pneumonia: A multi-center, double-blind RCT in ARDS patients (CITRIS ALI) found lower mortality (29% vs 46%, p<.05) in patients treated with AA as a secondary outcome. A recently published post-hoc analysis of this same study that accounted for early deaths in placebo group, which had not contributed to the severity score in the original analysis, found the primary outcome of SOFA score was significantly reduced in AA-treated patients. In a single-center, propensity matched trial of severe pneumonia in the ICU, the IV AA-treated cohort had lower mortality (17% vs. 39%, p<.04) A prospective RCT conducted in 1989 found that an anti-oxidant regimen which included IV AA led to an ICU mortality of 30% compared to 70% in the control regimen (p<.01).

There is very little data to support a benefit of AA in mild respiratory or viral illness. Long clinical use, however, suggest that AA is not harmful (see Safety and Monitoring, below).

**PHARMACOKINETICS**

- **Bioavailability**: For doses up to 200 mg, nearly 100%; absorption declines with increasing doses with ~33% absorbed with a single 1250mg dose
- **Metabolism**: Oxidized to active metabolite, dehydroascorbic acid (DHA)
- **Excretion**: Eliminated in the urine when high serum concentrations are above the renal threshold
- **Half-life**: 10 hours

**DOSSING AND ADMINISTRATION**

- **Mild respiratory illness**: if O2 requirement is ≤4L, initiate AA 500-1000mg PO BID
- **Lung injury**: O2> 4L or CXR abnormal, start 3 grams IV q6h until either <4L O2 requirement, CXR resolved, or extubated (earliest parameter achieved)

**SAFETY AND MONITORING**

Mylan pharmaceutical insert: no evidence of toxicity in normal adults at doses up to 6 grams a day; case reports of hemolytic anemia in G6PD patients at ‘very high doses’ (40-70 grams); case reports of renal oxalate stones with long-term supplementation (none yet described in short-term use in critical illness); possible pro-oxidative effect in case of iron overload; falsely elevated serum glucose readings in certain glucometers (thus, leading to missed hypoglycemia); decreased cyclosporine levels; blunting of bortezomib efficacy.

Abbreviations: RCT, randomized clinical trial. ARDS, Acute Respiratory Distress Syndrome.

**REFERENCES**