Coronavirus Management: Evidence for Treatment and Drug Shortage Updates
Based on publications through 4/13/2020
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Introduction
The coronavirus (SARS-CoV-2) is a novel virus first identified in December 2019 that has dramatically influenced the lives of many throughout the world. This virus has been associated with an infection called COVID-19 which can cause severe pneumonia and death in some patients. There is intense interest in possible treatments, which has led to a number of recent publications and clinical trials in process. The purpose of this newsletter is to clearly summarize the current theorized treatments and assess their level of evidence, discuss the implications of off-label treatment given the current level of evidence, as well as identify best sources of information from appropriate regulatory bodies for clinicians who are navigating frontline work in the face of this epidemic, throughout Oregon and the United States (US). As information is constantly changing, we have created a website that has links to most appropriate sources for government agencies, clinical recommendations, available trials, and evidence as it becomes available: https://pharmacy.oregonstate.edu/drug-policy/newsletter/coronavirus-management.

Drug Therapy
A plethora of medications with anti-inflammatory, immunomodulatory and/or antiviral properties are being studied for the treatment of COVID-19 (Table 1). At this point, no medications have high-quality data supporting their use. The following is a short synopsis of the available published data, potential side effects and current place in therapy for medications being used for COVID-19.

Table 1: Investigational drugs and recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation from current data</th>
<th>Doses (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine sulfate (HCQ) or Chloroquine (CQ)</td>
<td>• Benefit uncertain for inpatient use.5,6 • No evidence for outpatient use or prophylaxis • Prioritize use for FDA labeled indications (e.g., lupus) given shortages.</td>
<td>HCQ 800 mg Day 1 then 400 mg x 3-7 days7 CQ 1000 mg first day then 500 mg x 3-7 days8</td>
</tr>
<tr>
<td>Concomitant Azithromycin with HCQ</td>
<td>• Benefit uncertain for inpatient use. • No evidence for outpatient use or prophylaxis</td>
<td>500 mg day 1, 250 mg Day 2-5</td>
</tr>
</tbody>
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Lopinavir/Ritonavir • Efficacy not established, use not recommended at this time outside of clinical studies9
Remdesivir • Insufficient evidence • Promising in vitro activity • Enroll patients in clinical trials when possible.10-12
Corticosteroids • Use not recommended unless other indication10
NSAIDs • No change for chronic medications • Can consider acetaminophen10
ACEI and ARB • No change in therapy recommended10,13

Hydroxychloroquine/Chloroquine ± Azithromycin
Chloroquine and hydroxychloroquine (HCQ) have been hypothesized to have immunomodulating effects and cause a disruption of PH dependent steps of viral replication, such as fusion and uncoating.14 Some studies have included azithromycin due to its anti-inflammatory and immunomodulatory activity. Overall, there is a lack of high-quality data on the use of these agents in COVID-19.

A randomized, controlled trial of HCQ 200 mg twice daily for 5 days versus standard care in 62 patients was just published, though not peer-reviewed. The study was blinded with equal numbers in both groups, though it is unclear if there was a placebo to maintain blinding. Patients were admitted to the hospital with mild COVID-19 pneumonia. The mean age was 44.7 years (standard deviation 15.3 years), and comorbidities were not reported. Four patients progressed to severe illness, all in the standard care group. Pneumonia, based on change in CAT scan from day 0 to day 6, appears improved, though the outcome of percentage of pneumonia absorption at day 6 is a non-traditional endpoint.

Additionally, a study from China of HCQ is available, though only the abstract is published in English. This study included 30 patients randomized to HCQ 400 mg daily for 5 days or placebo; the presence of blinding is unclear. Endpoints included oropharyngeal viral clearance at day 7, median duration of hospitalization, median time to body temperature normalization, radiological progression, and adverse events. There were no statistically significant differences in any endpoint between the groups.

A published letter describes that over 100 patients enrolled in 15 studies have shown superiority of chloroquine over control
treatment for the outcomes of inhibiting exacerbation of pneumonia, improving radiological findings, viral clearance, and reduction of disease course. The details of these trial designs and data of the results are not yet published. A February 15th, 2020 conference in China used these results to add chloroquine to the People’s Republic of China guidelines for the treatment of COVID-19.

A non-randomized, open-label study from France has been criticized by the medical community for publication due to the very low quality of the research methodology and inability to draw valid conclusions from the results. It evaluated HCQ 200 mg three times day for 10 days in 14 patients and HCQ (same dose) + azithromycin 500 mg on day 1, then 250 mg daily for next 4 days in 6 patients. These 20 patients were compared to 16 control patients, many of which were being treated at other hospitals. An additional 6 patients (6 of 26) receiving HCQ were lost to follow up and were not included in the per protocol analysis. The endpoint was nasopharyngeal viral clearance at day 6. While there was a statistically significant reduction in clearance by day 6 in those receiving HCQ compared to control (70% vs. 12.5%; p=0.001), and this difference was more pronounced when looking only at patients in the HCQ + azithromycin arm compared to HCQ alone (100% vs 57.1%), there are many important drawbacks. This small study was open-label, non-randomized, and had a high rate of attrition. There was no standardization related to the severity of the COVID-19 infection, nor results of clinical indicators related to the treatment. There were significant differences between the HCQ and HCQ + azithromycin group, but the group sizes were extremely small and it is unclear if azithromycin adds any clinical benefit. The extension of this study using the combination did not include a control group to allow comparison. The significant attrition also introduces attrition bias, and of those 6 patient withdrawals, 3 went to the intensive care unit, 1 died, 1 discharged from the hospital on day 3, and 1 had intolerable nausea and vomiting.

HCQ has important side effects, including bone marrow suppression, cardiac and hepatic toxicity, as well as the theoretical risk of hemolytic anemia in patients with G6PD deficiency. The combination with azithromycin further increases the risk of QT prolongation. Patients in this study receiving both drugs were inpatients on daily electrocardiogram (ECG) monitoring and resulting QT measurements were not reported, therefore safety of this combination for outpatient use, particularly in those such as the elderly and those with underlying cardiovascular disease, is unknown. An 80 patient follow-up study of the combination did not report if there was any QTc prolongation when ECG monitoring was performed at baseline and every 2 days.

At this point, the use of HCQ and chloroquine in select inpatients may be reasonable as it may reduce time to viral clearance. Utility of the addition of azithromycin is unclear and requires additional monitoring. Overall quality of data is very low and additional studies are needed to determine if viral clearance reduces disease severity, morbidity, and mortality. Use in outpatients is not yet supported by evidence, and widespread use is not appropriate given risk of shortages of these medications for patients with autoimmune disorders.

Lopinavir/Ritonavir
After case reports and in vitro data suggesting that the HIV protease inhibitors lopinavir/ritonavir have activity against Middle Eastern Respiratory Syndrome (MERS-CoV), researchers in China conducted a randomized, open-label trial with lopinavir 400 mg/ritonavir 100 mg orally twice daily versus standard care for 14 days in hospitalized adults with COVID-19, pneumonia on chest imaging, and impaired oxygenation. Patients were stratified by level of oxygen support at enrollment and followed for 28 days or until hospital discharge or death and analyzed using an intention-to-treat method. The primary endpoint was time to clinical improvement defined as a 2-point improvement on a 7-point ordinal scale. Multiple other clinical, virologic, and safety endpoints were included such as: duration of hospitalization, viral detection over time, and adverse events during treatment. Enrollment was suspended when another investigational agent became available for study. There was no statistical difference in the primary endpoint of time to clinical improvement. The intervention group showed a 15.5% between group difference (45.5% vs 30%; confidence interval 2.2 to 28.8) in the secondary outcome of clinical improvement at day 14, but other clinical, virologic, and safety comparisons were not significant. Notably, 14% of lopinavir/ritonavir patients were unable to complete 14 days of therapy secondary to gastrointestinal side effects, 2 had serious acute gastritis, and 2 developed self-limiting skin ruprations. There were also several protocol violations related to receipt or non-receipt of investigational treatment by randomized group and roughly 1/3 of patients in both groups received glucocorticoids. Use of this combination outside of clinical trials is not yet warranted.

Remdesivir
Remdesivir is an investigational antiviral with significant potential for use in COVID-19 infections based on in vitro data of inhibition of an RNA dependent RNA polymerase and experimental use in Ebola and MERS-CoV infections. There are multiple clinical trials underway for use in COVID-19 infections. The manufacturer was allowing use of this medication outside of the clinical trial setting with a compassionate use protocol. However, due to immense demand, availability has been suspended while transitioning to an expanded access program. Exceptions will only be
There are a number of trials throughout the world and ongoing studies to manage the disease without contraindications, acetaminophen can be used for fever. News reports have stated that non-steroidal anti-inflammatory drugs (NSAID) agents that affect the renin-angiotensin aldosterone system have come with many biases and limitations. Conflicting data indicate that there may be benefit in very severe cases, but these data come with many biases and limitations. Methylprednisolone and dexamethasone are currently being studied in a least one trial each. More information should be available once these have concluded.

Use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have both also come into question due to COVID-19. The binding mechanism of the virus utilizes angiotensin-converting enzyme (ACE) type 2. This has led to speculation of both harm and benefit. Losartan is being studied as a therapy for COVID-19. Until more data are available, no change in therapy is currently recommended for agents that affect the renin-angiotensin aldosterone system, and this recommendation is supported by professional cardiology societies.

News reports have stated that non-steroidal anti-inflammatory medications (NSAID), such as ibuprofen, can worsen COVID-19 outcomes. This is due to an unsubstantiated link to increases of ACE type 2 expression in NSAID users. At this time, the data behind these assertions are anecdotal. The FDA currently makes no recommendations to avoid use, though for those with contraindications, acetaminophen can be used for management of pain or fever as an alternative. Patients taking NSAIDs or aspirin for chronic conditions should continue unless other clinical reasons necessitate a change.

Ongoing studies and data
There are a number of trials throughout the world and the US evaluating therapies for treatment and prophylaxis of COVID-19, including several in the Portland area. Please see our website or clinicaltrials.gov for current updates on available clinical trials in Oregon.

Many additional agents have been purported to have potential use in COVID-19 infection by direct antiviral effect or reduction of inflammatory immune response. Tocilizumab in particular has garnered much interest for patients with high interleukin-6 levels and cytokine release, often seen in severe COVID-19 pneumonia. However, data remain limited as a randomized controlled trial in China is underway and a manufacturer sponsored global trial is being implemented. Agents below are being researched but currently have minimal human data to recommend use outside of a formal clinical trial setting: arbidol, ascorbic acid, avipadil, bevacizumab, bromhexine, camifimycin, cobicistat, darunavir, ecullizumab, favipiravir, fingolimod, interferon, oseltamivir, pirfenidone, ribavirin, sarilumab, tetrudrine, thalidomide, and various traditional Chinese medicines.

Shortages
The development of this pandemic has resulted in widespread shortages of hospital supplies, including drug products. Shortages have been reported for HCQ, which is an essential medication for patients with lupus and other chronic diseases. To avoid further shortages, all prescriptions written for the off-label treatment of COVID-19 should be reviewed for appropriateness and patients should be educated to avoid hoarding and stockpiling of medications. Patients should be encouraged to keep an adequate supply of at least two weeks on hand of chronic medications and advised that pharmacies will remain open during this time. Additionally, many local pharmacies are offering mail or delivery services to avoid interactions during this public health emergency. Early refills and conversion of prescriptions from 1 month to 3 month fills can result in worsening of shortages. Additionally, shortages of products manufactured in places like China may be delayed, though the specific products are not known. Continue to monitor the ASHP or FDA website for information and alternatives as these occur.

Regulatory Guidance for Oregon
On March 25th, 2020, the Oregon Board of Pharmacy instituted a temporary administrative order during the COVID-19 public health emergency (855-007-0085) to restrict use of hydroxychloroquine and chloroquine to chronic therapy for approved indications and proven COVID-19 infections in hospitalized patients.

This order came 2 days after the Oregon Boards of Pharmacy and Medicine issued a joint statement of disapproval for false or inappropriate prescribing in a time of crisis. The reasons prompting the writing of this statement were:
• Creating the risk of adverse effects and additional harm.
• Creating shortages of therapies for patients who have legitimate medical need for the drug’s intended purpose and use.
• Confounding the interpretation of efficacy (particularly when randomized controlled studies are necessary and are currently underway).
• Providing false hope to patients or a false sense of security.

The FDA has issued Emergency Use Authorizations for both medications for certain inpatients as well.4

Conclusions
Providers are encouraged to consult recommended sources for the current recommendation on the most appropriate way to manage COVID-19. At this time there are no data to recommend a therapy for prophylaxis, and outpatient therapy should focus on supportive care and reducing risk of transmission. Additionally, based on the overall uncertainty of risks and benefits, it is best to administer all treatments in the context of a clinical trial if possible.22 Best practices and appropriate prescribing should be adhered to now more than ever to maintain quality patient care and preserve needed resources for those conditions in which there is evidence for use.

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References:


