UC San Diego COVID-19 Interim Management Guideline

Purpose
The intent of this guideline is to provide a framework for clinical management of individuals with COVID-19. Infection prevention instructions are outside the scope of this guideline.

Guidelines are intended to assist with clinical decision-making for common situations but cannot replace personalized evaluation and management decisions based on individual patient factors.

The document covers off-label use of medications based on the best evidence currently available.

Given the rapid evolution of the current COVID-19 pandemic, this will be a living document that is likely to change over time.

General principles
During this unprecedented time, remember these principles:

- The practice of evidence-based medicine requires the utilization of rigorous clinical trials. When insufficient evidence is available with which to determine the utility of a therapeutic agent, if a clinical trial is available, in general, patients should be referred to these trials rather than treated off label. Clinical trials that are active or in planning for UC San Diego Patients can be found at this [link].
- Order diagnostic studies only when clinically indicated. Remember that each test may expose additional personnel to potential infection, remove exam rooms from circulation, and utilize additional personal protective equipment (PPE).
- Supply chain issues will impact every piece of clinical care, from lab testing to medications to blood products to personal protective equipment. Practice evidence-based medicine and order only testing and medications that are truly necessary.
- Clean your hands and utilize personal protective equipment as recommended by Infection Prevention and Clinical Epidemiology.

PPE conservation

- Direct contact with the patient in the room should only occur if the provider will perform a direct physical exam or in-room procedure that will provide clinical information to impact patient assessment and clinical care in the next 24-48 hours.
- If deemed necessary, only one team member (the clinical decision maker) should perform the in-person encounter with suspected or confirmed COVID-19 patients. No other team members should enter the room unless needed to assist with a procedure.
- Telephone, E-consultation, and video consultations should be used if direct contact is not essential.
- Bundle care activities to limit the number of entries into the room.
- Limit the number of individuals in the room to essential staff for aerosol-generating procedures.
- The most experienced individuals should preferentially perform necessary procedures.
- Ensure all supplies needed for an exam or procedure are available prior to donning PPE and entering the room.

Approved by P&T Executive Team 4/7/2020. For questions/comments, please contact kclim@health.ucsd.edu. Guidance document to be regularly reviewed and updated.
### Summary Table

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendation</th>
<th>Availability at UC San Diego Health</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remdesivir</strong></td>
<td>Clinical trials currently underway; insufficient data to provide use-recommendations at this time.</td>
<td>A clinical trial is available to UC San Diego Inpatients. Entry &amp; exclusion criteria can be found <a href="#">here</a></td>
</tr>
<tr>
<td><strong>Hydroxychloroquine (HCQ)</strong></td>
<td>Clinical trials of HCQ are being developed for inpatients, outpatients and for post-exposure prophylaxis. There is insufficient data to provide use-recommendations at this time.</td>
<td>Supplies of HCQ are limited at UC San Diego. Currently available for treatment of person with FDA-approved indications (i.e. rheumatoid arthritis, lupus, etc.) Available from the <a href="#">US Strategic National Stockpile</a> for patients who are “hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible” (<a href="#">FDA link</a>). Currently, the mechanism for accessing the Strategic National Stockpile has not been clearly delineated.</td>
</tr>
<tr>
<td><strong>Ritonavir / Lopinavir (Kaletra)</strong></td>
<td>Not recommended for the treatment of patients with SARS-CoV-2 infection</td>
<td>Supplies of Ritonavir/Lopinavir are currently limited but stocked by UC San Diego pharmacy and available for treatment of persons with HIV infection</td>
</tr>
<tr>
<td><strong>Tocilizumab (TOCI)</strong></td>
<td>Clinical trials currently underway. Until more data are available, routine use of tocilizumab in the setting of severe or life-threatening COVID-19 is not recommended.</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with FDA-approved indications (i.e. chimeric antigen receptor (CAR) T-cell induced cytokine reactive syndrome (CRS), etc.) A clinical trial is available to UC San Diego Inpatients. Entry &amp; exclusion criteria can be found <a href="#">here</a></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Interim guidance from WHO recommends that corticosteroids be avoided unless indicated for reasons other than COVID-19. Until more data are available, routine use of corticosteroids in the setting of severe or life-threatening COVID-19 is not recommended outside of a clinical trial setting.</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with various allergic and inflammatory conditions</td>
</tr>
<tr>
<td><strong>ACE Inhibitors and ACE Receptor Blocking Agents</strong></td>
<td>Not contraindicated in the treatment of hypertension in patients with SARS-CoV-2 Infection</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with hypertension</td>
</tr>
<tr>
<td><strong>Antipyretics Including NSAIDs and APAPs</strong></td>
<td>NSAIDs and APAPs are not generally contraindicated in the setting of SARS-CoV-2 infection; acetaminophen should not be used in conjunction with remdesivir</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with fever and inflammatory conditions</td>
</tr>
<tr>
<td><strong>Empiric Antibiotics</strong></td>
<td>Empiric antibiotics should not be used unless bacterial superinfection is clinically suspected or proven</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with suspected or proven bacterial infection</td>
</tr>
<tr>
<td><strong>Zinc sulfate</strong></td>
<td>Zinc sulfate is not recommended for the prevention or treatment of SARS-CoV-2 infection</td>
<td>Currently stocked by UC San Diego pharmacy and available for treatment of persons with FDA-approved indications (i.e. need for nutrition supplementation, in zinc deficiency, etc.)</td>
</tr>
</tbody>
</table>
Medication Mechanisms of Use and Recommendations

Remdesivir

Background and Mechanism:
Remdesivir is an experimental agent that is under investigation for the intravenous treatment of SARS CoV-2 infection. The drug is a nucleotide analog that inhibits the RNA polymerase of all known coronaviruses as well as Ebola virus. The drug blocks viral replication by serving as a chain terminator in the RNA polymerization process. Remdesivir inhibits SARS CoV-2 replication at concentrations of ~0.5 μM (1,2). The drug is beneficial clinically and inhibits viral replication when given prior to or shortly after viral challenge in animal models of the related coronavirus, MERS virus (the Middle Eastern Respiratory Syndrome Virus) (3). Remdesivir was administered to patients in a recent outbreak of Ebola virus infection in the Democratic Republic of the Congo in a three-arm trial in which it was compared to two different monoclonal antibody preparations (4). The drug did not perform as well as the monoclonal antibodies but since there was no placebo group, clinical benefit could not be excluded. The drug was generally well tolerated although reversible hepatocellular enzyme elevations were noted in some trial participants. The drug has been used under compassionate use in a number of cases in the US and elsewhere. In the limited available data, the drug has been well tolerated but no efficacy statements can be made on the basis of these anecdotal experiences. The compassionate use program has been stopped except for pregnant women and children under the age of 19. As of March 27, Gilead is transitioning to an "expanded access" program for Remdesivir. At this time it is unclear if "expanded access" is available to centers enrolled in the NIAID trial.

Availability at UC San Diego:
An NIAID-sponsored placebo-controlled trial is available to UC San Diego inpatients. Entry and exclusion criteria can be found at link. Physicians wishing to refer patients to this clinical trial should contact Dr. Dan Sweeney (dasweeney@ucsd.edu) or Dr. Constance Benson (cbenson@ucsd.edu)

Recommendations:
Clinical trials of Remdesivir are underway. Insufficient information regarding its efficacy in SARS CoV-2 infection is available to recommend its use in the absence of clinical trials data.

References:


Hydroxychloroquine (HCQ)

Background and Mechanism:
Chloroquine and HCQ are alkalinizing lysosomatropic drugs that accumulate in lysosomes (1). Both drugs block viral infection by increasing endosomal pH, which is required for viral particles to fuse with a cell. Chloroquine also interferes with glycosylation of cellular receptors of coronaviruses, including SARS-CoV (2). In vitro data in Vero E6 cells has demonstrated that chloroquine functions at both entry, and at post-entry stages of the SARS-CoV-2 infection, unlike Remdesivir (3). Both drugs also modulate the immune response. HCQ has long been used to treat autoimmune diseases, like rheumatoid arthritis, porphyria cutanea tarda, and lupus (1). Such immune modulation may also help in thwarting ARDS (4).

In Vivo Activity:
In a recent study, 20 patients with SARS-CoV-2 infection were included in a single arm protocol to receive 600mg of HCQ daily. The outcome of the study was viral load from daily nasopharyngeal swabs. All participants were in a hospital setting. Further, azithromycin was added to the HCQ treatment based on clinical status. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day 6 post inclusion was the study end point. The authors showed that HCQ was effective in reducing viral loads (Figure 1). Specifically, HCQ reduced the proportion of persons with SARS-CoV-2 infection with PCR-positive samples by 75% in the 6-day period, and when it was combined with azithromycin, it improved the treatment efficacy to 95% (5).

There are a number of limitations of this study:
1) It was not randomized.
2) A therapeutic effect in the first two days of treatment is unusual, as drug levels are unlikely to have achieved therapeutic levels.
3) The small number of participants
4) The dropout rate in the treatment arm and exclusion from the analysis of death
5) The primary outcome was clearance of SARS-CoV-2 as detected by nasopharyngeal swab, however the current understanding of the natural history of infection is that virus is eventually cleared from the upper respiratory tract, even in severe disease
6) Lower baseline viral load in persons receiving HCQ and azithromycin, compared to the patients receiving HCQ alone

![Figure 1. Clinical Course during HCQ and Azithromycin Treatment](image-url)
Pharmacology:
HCQ has rapid gastrointestinal absorption and elimination by the kidneys. Both are also metabolized by the cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5). HCQ is metabolized to desethylhydroxychloroquine, desethylchloroquine, and bidesethylhydroxychloroquine by the liver and excreted by the kidneys, with desethylhydroxychloroquine being most common (6, 7). HCQ distributes widely into body tissues and given its large volume of distribution, it takes a long time to reach steady-state levels (8,9). The absorption half-life is 3 to 4 hours and the terminal half-life ranges from 40 to 50 days.

Risks:
Retinopathy, anemias, cardiac toxicity, arrhythmias and hypoglycemia events are potentially serious risks with use of HCQ. However, only arrhythmias and G6PD-related hemolysis are real risks with the limited dosing proposed for treatments for COVID-19. Given the low prevalence of G6PD Deficiency in San Diego, only arrhythmias remain as a main risk during the proposed short treatment courses. However, these risks are real in older patients and those taking medications that already prolong the QT interval. Further, as with all serious respiratory illnesses, cardiovascular events remain common, and a number of anecdotal heart attacks and ventricular arrhythmias have been documented. Without rigorous, controlled trials, we will not know the true risk of these events during treatment with HCQ.

Availability at UC San Diego:
Supplies of HCQ are limited at UC San Diego.

Hydroxychloroquine or chloroquine are available from the US Strategic National Stockpile for patients who are “hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible” (FDA link) (10). Currently, the mechanism for accessing the Strategic National Stockpile has not been clearly delineated.

Recommendations:
Clinical trials of HCQ are being developed for UC San Diego inpatients, outpatients and for post-exposure prophylaxis. A randomized placebo-controlled trial is available from the University of Minnesota for those with exposure to or mild symptoms from SARS CoV-2 infection. Details about the study can be found at http://trialcovid.com.

Insufficient information regarding its efficacy in SARS-CoV-2 infection is available to recommend its use in the absence of clinical trials data.

References:


**Lopinavir/ritonavir (Kaletra)**

**Background and Mechanism:**
Lopinavir is an HIV-1 protease inhibitor that is administered orally in conjunction with ritonavir in order to assure adequate systemic exposure of lopinavir on the basis of CYP 3A4 inhibition. There is a vast experience with this combination agent in the treatment of HIV infection. It is generally well tolerated but the ritonavir-driven CYP 3A inhibition leads to significant interactions with a number of other pharmacological agents. At the time of the original SARS outbreak, it was demonstrated to have in vitro activity against SARS-CoV. It was administered to 41 SARS-CoV patients in combination with high dose ribavirin and corticosteroids in an uncontrolled experience during that outbreak. When compared to historical controls who received ribavirin and corticosteroids, a lower fraction of patients experienced adult respiratory distress syndrome or death. It has also been shown to have in vitro activity against the MERS CoV agent and this drug or interferon beta 1-b were each associated with histologic, virologic and clinical improvement. It has been studied in a well-performed randomized, controlled study of patients with SARS-CoV-2 in a 199 patient study that was recently reported in the *New England Journal of Medicine* (2). The drug did not significantly reduce either the time to clinical improvement or 28-day mortality in this trial.

**Availability at UC San Diego:**
The drug is stocked by the UC San Diego pharmacy and is available for the treatment of persons with HIV infection.

**Recommendations:**
Lopinavir/ritonavir is not recommended for the treatment of patients with SARS CoV-2 infection.

**References:**

**Tocilizumab**

**Background and Mechanism:**
An FDA approved recombinant humanized monoclonal antibody against IL-6 receptor used in rheumatoid arthritis. Experience more recently comes from use in the treatment of life-threatening cytokine release syndrome (CRS) after CAR-T cell therapy. There is some increased risk for developing serious infections reported, especially in individuals being treated with immunosuppressants, such as methotrexate or steroids. Limited data about potential benefit exist from uncontrolled studies in patients with COVID-19. There are randomized controlled clinical trials in China and the U.S. using tocilizumab in this context, including an international trial that is sponsored by Genentech: (EudraCT Number: 2020-001110-38) entitled: "Multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia".

**Evidence to on specific use to date:**
In an open-label experience from China (21 patients) with documented COVID-19 and severe O2 impairment, including RR≥30, SpO2≤93% on room air, PaO2/FIO2<300mmHg or need for mechanical ventilation, shock, or combined organ failure Tocilizumab use was associated with reduced O2 requirement, normalization of the CRP level, and increasing the lymphocyte count to normal. Nineteen of the 21 patients were discharged (1). Further guidelines on determining timing of administration are being developed.

**Risks:**
- LFT abnormalities
- Local injection site reactions
- Increased risk of serious infections, including TB, invasive fungal infections; albeit a distinct population in terms of risks in typical CAR-T cell patients, so possibly better able to tolerate therapy from the immunocompromise standpoint.

**Dosing:**
- Tocilizumab 8 mg/kg (max 800 mg) iv. Can repeat again x 1 in 8-12 hours. Can consider 2 additional doses (max 4) with same dosing interval.
- Check IL-6 and inflammatory markers (IL-6, CRP, Ferritin, LDH, fibrinogen, D-dimer) prior to administration and consider daily monitoring.

**Rationale for use:**
Cytokine release syndrome (CRS) (2) is a key component of critical illness associated with COVID-19. However, it has not been rigorously studied in the setting of such viral infection. The role of cytokines and a secondary HLH-analogy syndrome is highlighted as well (3).

**Recommendations:**
Until more data are available, routine use of tocilizumab in the setting of severe or life-threatening COVID-19 is not recommended.

Experimental use is recommended under a randomized clinical trial to be activated the week of 3/30/2020. Physicians wishing to refer patients to this trial should contact Dr. Atul Malhotra (amalhotra@health.ucsd.edu) or Dr. Aaron Carlin (acarlin@health.ucsd.edu). Inclusion and exclusion criteria can be found here.

The UCSD COVID Therapeutics Committee is currently discussing an approach for off-label use in certain patients that will be excluded from the randomized clinical trial, such as those who “have received oral anti-rejection or immunomodulatory drugs within the past 6 months.” Additional information will be available during the week of April 6, 2020.
References:


Corticosteroids

Rationale:
Because COVID-19 has been associated with a hyperinflammatory state characterized by multiorgan failure and cytokine release there is an interest in the use of corticosteroids as an immunomodulatory agent. There is interest in use of corticosteroids specifically to suppress lung inflammation in the setting of ARDS related to COVID-19.

Evidence to date on use of steroids in COVID19:
A retrospective cohort of 201 patients with COVID-19 in China was examined to determine clinical characteristics of patients and outcomes of patients who developed ARDS or died. Methylprednisolone appeared to reduce risk of death in patients with ARDS (1). Steroids have not proven beneficial in prior SARS or MERS epidemics and have been associated with delayed coronavirus RNA clearance (2,3). In influenza, corticosteroid treatment is associated with increased mortality and hospital acquired infections (4). Current clinical evidence is lacking to support use of corticosteroids in treatment of viral pneumonia (5). More data would also be needed to assess any combinations with which corticosteroids could have greater efficacy in the setting of COVID-19 (e.g., interferon plus corticosteroids, as tested in SARS-CoV) than either steroids alone or no steroids in specific groups during the course of illness.

Consensus Statements:
• Interim guidance from WHO recommends that corticosteroids be avoided unless indicated for reasons other than COVID-19 (6).
• Society of Critical Care Medicine recommends against the use of corticosteroids in mechanically ventilated patients with COVID-19 without ARDS. In patients with ARDS, SCCM is recommending use of corticosteroids over not using corticosteroids (7).

Recommendations:
• Until more data are available, routine use of corticosteroids in the setting of severe or life-threatening COVID-19 is not recommended outside of a clinical trial setting.
• Corticosteroid use should be considered in patients with COVID-19 and refractory shock.
• Corticosteroid use should be considered in patients with COVID-19 and chronic steroid use.
• Corticosteroid use should be considered in patients with COVID-19 infection associated with severe ARDS.
• Corticosteroid use should be considered in patients with COVID-19 infection and significant underlying lung disease such as asthma or COPD.

References:


ACE Inhibitors and ACE Receptor Blocking Agents

Patients with underlying cardiovascular disease appear to have an increased risk for adverse outcomes when infected with the SARS-COV2 virus (1,2). Angiotensin converting enzyme 2 (ACE2) receptors, that are present in the lung and other organs have been shown to be the entry point into human cells for SARS-CoV-2 virus (3). Furthermore, in a few experimental studies with animal models, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to upregulate ACE2 expression in the heart (4). As a result, there has been speculation that this potential upregulation of ACE2 receptors by ACE inhibitors or ARBs will increase the risk or severity of COVID-19 infection in patients who are on these drugs (5,6).

At this time, the Heart Failure Society of America, the American College of Cardiology (ACC) and the American Heart Association, do not recommend stopping ACE inhibitors, ARB's or any renin angiotensin aldosterone system (RAAS) antagonists in patients taking these drugs for cardiovascular indications. The rationale includes:

1. Upregulation of ACE2 receptors with ACE or ARB have not been shown in human studies, nor in the setting of COVID-19, and to date there are no clinical data demonstrating beneficial or adverse outcomes of these drugs in COVID-19 patients.
2. Experimental studies have also shown both ACE inhibitors and ARBs reduce severe lung injury in certain viral pneumonias and as a result these agents could potentially be beneficial in COVID-19 infection (7).
3. ACE inhibitors and ARBs have clear beneficial effects in patients with kidney disease, heart failure, hypertension and ischemic heart disease and stopping them has been shown to worsen outcomes.

A more definitive answer about whether ACE inhibitors or ACE receptor blocking agents are beneficial, harmful or neutral in the setting of SARS CoV-2 infection will require a closer evaluation of epidemiological data that examine relationships among these agents and COVID-19 morbidity (8). Ultimately if a patient with cardiovascular disease is diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation (9,10).

References:


Antipyretics: Non-Steroidal Anti-inflammatory Drugs (NSAIDs) vs Acetaminophen (APAP)

Background and Rationale:
Concerns have been raised about the use of non-steroidal anti-inflammatory drugs (NSAIDs) because of the potential that they might blunt the pro-inflammatory immune response and, thus, exacerbate SARS CoV 2 replication. In addition, the potential for aggravating renal injury has been raised (1).

Availability at UC San Diego:
Multiple NSAIDs and other antipyretics including acetaminophen and aspirin are stocked in the UC San Diego pharmacy.

Recommendation:
No clinical evidence presently exists showing a clear connection between worse outcomes and NSAID use in COVID-19 patients. Acetaminophen carries a lower risk and should be used first line as an anti-pyretic agent (limited to 4g daily or less depending on hepatic function) until further evidence emerges. For additional supportive management (e.g., persistent fever despite maximum APAP, insensible volume loss), providers may decide on a case-by-case basis whether isolated doses of NSAIDs may be appropriate. Use of meperidine to treat symptomatic fever or rigors in COVID-19 patients has not been adequately studied.

Note: Patients potentially considered for enrollment in tocilizumab or remdesivir clinical trials are excluded if transaminases exceed 5x upper limit of normal and may need to discontinue antipyretics prior to enrollment; please see corresponding inclusion/exclusion criteria.

Reference:
Empiric Antibiotics

Background and Rationale:
Secondary bacterial infection was documented in 15% of hospitalized patients in one Chinese study (1). Bacterial superinfection is generally not the initial cause of respiratory deterioration in patients with SARS-CoV-2 infection but it can occur in patients after intubation. In critically ill patients with MERS, rates of 18% bacterial and 5% viral co-infections have been documented. COVID-19 does not appear to increase procalcitonin alone, but does appear to increase CRP (2).

Recommendation:
Non-ventilated patients should not be treated with empiric antibiotics without evidence of bacterial infection. Empiric antimicrobials may be considered when the clinical suspicion of bacterial superinfection is high (especially following intubation) while clarifying evidence is gathered (2). Some institutions advise using procalcitonin levels to guide decision making (3).

References:
**Zinc Sulfate**

**Rationale:**
Zn2+ Inhibits SARS-CoV2 RNA polymerase activity *in vitro* (1). Used in combination with zinc ionophores including chloroquine and hydroxychloroquine, *in vitro* viral replication is further disrupted. [2] Zinc sulfate has not been demonstrated to have any beneficial clinical effect alone or in combination with hydroxychloroquine or chloroquine.

**Recommendation:**
The use of Zinc sulfate is not recommended alone or in combination with hydroxychloroquine or chloroquine for the prevention or treatment of persons with or at risk for SARS-CoV-2 infection.

**References:**

UC San Diego Health COVID-19 Therapeutics Committee

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  • Cheryl Wagonhurst (Compliance)

Approved by P&T Executive Team 4/7/2020. For questions/comments, please contact kclim@health.ucsd.edu. Guidance document to be regularly reviewed and updated.
<table>
<thead>
<tr>
<th>Clinical Trial # and Short Title</th>
<th>Investigational Drug</th>
<th>Sponsor</th>
<th>Enrolling ?</th>
<th>N</th>
<th>Co-PIs</th>
<th>Location</th>
<th>Patient Population</th>
<th>Major Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMID 20-0006: Phase 3 Adaptive Trial Comparing Safety and Efficacy of Remdesivir vs. Placebo</td>
<td>Remdesivir</td>
<td>NIH/DMID</td>
<td>Yes</td>
<td>440</td>
<td>Sweeney Benson</td>
<td>UCSD Hillcrest (AVRC support)</td>
<td>Inpatient mod/severe COVID-19</td>
<td>Radiographic infiltrates OR Clinical assessment AND SpO2 &lt; 94% on room air, OR Requiring supplemental O₂, OR Requiring mechanical ventilation</td>
</tr>
<tr>
<td>WA42380: Multicenter RCT to Evaluate Safety and Efficacy of Tocilizumab vs. Placebo</td>
<td>Tocilizumab</td>
<td>Roche Genentech</td>
<td>Pending</td>
<td>330</td>
<td>Malhotra Carlin</td>
<td>UCSD Jacobs</td>
<td>Inpatient COVID-19 Severe</td>
<td>Age ≥18 years Hospitalized with COVID-19 pneumonia confirmed per WHO criteria and chest X-ray or CT scan SpO2 ≤93% or PaO₂/FiO₂ &lt; 300 mmHg</td>
</tr>
<tr>
<td>Internal: RCT of Hydroxychloroquine vs SOC</td>
<td>Hydroxychloroquine</td>
<td>None</td>
<td>Pending</td>
<td>180</td>
<td>Smith Little Horton</td>
<td>UCSD Hillcrest &amp; Jacobs, VAMC</td>
<td>Inpatient Moderate COVID-19</td>
<td>Age ≥18 years Hospitalized with confirmed COVID-19 pneumonia on chest X-ray, dyspnea, fever</td>
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<tr>
<td>Symvivo RCT: Safety, Immunogenicity of bacTRL-Spike Oral Vaccine for Prevention of COVID-19</td>
<td>bacTRL-Spike oral vaccine</td>
<td>Symvivo</td>
<td>No</td>
<td>84</td>
<td>Smith Little</td>
<td>Outpatient AVRC</td>
<td>Outpatient Healthy Volunteers</td>
<td>Age &gt; 18-55yo Healthy adults</td>
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<td>PIRC: Prevalence and Molecular Transmission Dynamics of SARS-CoV-2 in Asymptomatic Adults</td>
<td>No intervention Testing of asymptomatic young adults</td>
<td>NIH/NIAID</td>
<td>No</td>
<td>5,000 per year</td>
<td>Little</td>
<td>Outpatient AVRC Good to Go subsite</td>
<td>Outpatient Asymptomatic</td>
<td>Young adults</td>
</tr>
</tbody>
</table>
5.1 Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
3. Understands and agrees to comply with planned study procedures.
4. Agrees to the collection of oropharyngeal (OP) swabs.
5. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
6. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen collected < 72 hours prior to randomization.

Note – 72 hours is not necessarily time from initial diagnosis. If ≥72 hours since positive PCR, the PCR may be repeated to assess eligibility.

7. Illness of any duration, and at least one of the following:
   • Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
   • Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
   • Requiring supplemental oxygen, OR
   • Requiring mechanical ventilation.

8. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.


5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. ALT/AST > 5 times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR) < 50 or requiring dialysis.
3. Pregnancy or breast feeding.
4. Anticipated transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.
Tocilizumab COVID-19 Inclusion and Exclusion Criteria

Inclusion Criteria
Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative

Age 18 years or greater

Ability to comply with the study protocol, in the investigator’s judgment

Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan

SpO2 < 93% or PaO2/FiO2 < 300 mmHg

For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below: Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 28 days after the final dose of TCZ. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (>12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 28 days after the final dose of TCZ to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.
**Exclusion Criteria**
Patients who meet any of the following criteria will be excluded from study entry:

Known severe allergic reactions to TCZ or other monoclonal antibodies

Active TB infection

Suspected active bacterial, fungal, viral, or other infection (besides COVID-19)

In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments

Have received oral anti-rejection or immunomodulatory drugs (including TCZ) with the past 6 months

Participating in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)

ALT or AST > 10 x ULN detected within 24 hours at screening or at baseline (according to local laboratory reference ranges)

ANC < 1000/µL at screening and baseline (according to local laboratory reference ranges)

Platelet count < 50,000/µL at screening and baseline (according to local laboratory reference ranges)

Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination

Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted after consultation with the Medical Monitor)

Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator’s judgment, precludes the patient’s safe participation in and completion of the study