Massachusetts General Hospital
COVID-19 Treatment Guidance

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- This document was developed by members of the ID division at MGH in conjunction with pharmacy, radiology, and other medicine divisions to provide guidance to frontline clinicians caring for adult patients with COVID-19.
- This document covers potential off-label and/or experimental use of medications and immunosuppression management for transplant patients as well as a suggested laboratory work up. It does NOT cover recommendations for infection control, PPE, management of hypoxemia or other complications in patients with COVID-19.
- This is a living document that will be updated in real time as more data emerge.

### Table 1: Laboratories for diagnosis, prognosis / risk stratification, and/or safety of agents

| Suggested for hospitalized patients with confirmed or suspected COVID-19 |
|---|---|
| **Recommended daily labs:** | **Viral serologies:**\(^2\) |
| • CBC with diff (trend total lymphocyte count) | • HBV serologies (sAb, cAb, and sAg) |
| • Complete metabolic panel\(^1\) | • HCV antibody, unless positive in past |
| • CPK (creatine kinase) | • HIV 1/2 Ab/Ag |

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\(^1\) For a primer on liver issues related to COVID19 and treatment, please see our supporting liver document.

\(^2\) Viral serologies assist for interpretation of ALT elevations, present in ~25% of presentations. Lopinavir/ritonavir should not be used as the sole agent if HIV positive. Active viral hepatitis increases risk of hepatotoxicity due to lopinavir/ritonavir. Note: follow-up molecular testing for HIV/HBV/HCV may have longer turnaround times than usual.
Suggested for immunocompromised patients:

If clinically indicated, consider sending *Pneumocystis* DFA from sputum (no induced sputum given risk of aerosolization). If unable to send sputum, consider sending serum beta-d-glucan.

If clinically indicated, consider sending fungal/AFB sputum cultures.

**Therapeutically:**

- If flu unknown or positive, start oseltamivir 75 mg BID in all adult patients with normal renal function (may stop if flu A/B PCR negative and low suspicion)
  - Adjust for pediatric patients and those with renal insufficiency
- Considerations for empiric treatment for bacterial pneumonia:
  - Other centers have reportedly not, to date, seen a lot of bacterial superinfection in COVID-19 patients; we should monitor for this on a case-by-case basis.

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3 Elevated troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours; echocardiogram not necessary unless otherwise indicated. Up-trending troponin with hemodynamic compromise or other concerning cardiovascular symptoms/signs should prompt consideration of obtaining an echocardiogram.

4 If starting QTc prolonging drug, can repeat ECG in 24-48 hours to monitor QTc. If baseline QTc > 500, repeat within 24 hours and consider stopping other QTc prolonging drugs. Continue monitoring every 1-2 days if on two or more QTc prolonging drugs.
Ceftriaxone 1 g [or cefepime if MDRO risk factors]  
  + Azithromycin 500 mg x1, then 250 mg daily x 4 days (note QT prolongation risk)  
  + Vancomycin if risk factors for MRSA  
    ▪ All for 5 days, or longer guided by clinical status and microbiology  
  ▪ Note that from studies to date, procalcitonin remains low in the first 7-10 days of COVID-19 infection and can rise later on, even without bacterial superinfection.  
  ▪ **Inhaled medications should be given by metered dose inhaler rather than nebulization.**  
    Nebulization risks aerosolization of SARS-CoV-2. If nebulized medications given, use appropriate PPE.

**ACE-Inhibitors (ACEi) / Angiotensin Receptor Blockers (ARBs):**

▪ Note there is interest in the potential role of ACE-inhibitors (ACEi) / angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. There are theories these may either help or worsen COVID-19 disease.  
▪ Currently there are no data to support either starting or stopping ACEi/ARBs on any patients with COVID-19. We do not currently routinely recommend stopping these agents for patients with COVID-19. However, if acute kidney injury, hypotension or other contraindication develops, we recommend stopping them at that time. After a person is recovering from their viral syndrome, their home medications can be restarted, and, if indicated, new ACEi/ARBs can be started if they have a primary indication such as new persistently reduced ejection fraction.

**COVID-19 Suggested Management:**

There are no proven or approved treatments for COVID-19. The following algorithm provides guidance based on available information to-date regarding possible and investigational treatments. Caution is advised as there are either no data or limited data for efficacy for COVID-19. As appropriate, these recommendations will be updated frequently to include new or emerging data. For clarifications or approval of certain agents, please consult Infectious Diseases.  

**Not recommended**

▪ **Systemic steroids should in general be AVOIDED for these patients given potential harm.**  
  Steroids may be considered if indicated for another reason (e.g. refractory septic shock, or specific to lung transplant guidelines, as delineated below).  
  **Note:** Consider discontinuation of inhaled steroids as they may reduce local immunity and promote viral replication, unless necessary for acute indications  
▪ **At this time, we do not recommend starting ACEi / ARBs or ribavirin for COVID-19**

Concern has been raised that NSAIDs may worsen COVID-19 disease. This has not been proven clinically to-date, so we cannot make a recommendation for or against their use at this time.

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6 The infectious disease consult service is actively discussing how to meet the needs of frontline clinicians. More information to follow.
Identify High Risk Patients: High risk features may include:

<table>
<thead>
<tr>
<th>Table 2: Risk Factors for Severe COVID-19 Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological – Category 1</strong></td>
</tr>
<tr>
<td>Age &gt; 55</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Diabetes with A1c &gt; 7.6%</td>
</tr>
<tr>
<td>History of hypertension</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
</tr>
<tr>
<td>Use of biologics*</td>
</tr>
<tr>
<td>History of transplant or other immunosuppression*</td>
</tr>
<tr>
<td>HIV, CD4 cell count &lt;200 or unknown CD4 count*</td>
</tr>
</tbody>
</table>

*Not yet proven as risk factors for progression, inferred from other infections.

For more information about COVID19 Risk Factors, please see our supporting risk factors document.

Suggested Treatment Algorithm Based on Clinical Severity:
(See figure at end of document for schematic layout of algorithm)

<table>
<thead>
<tr>
<th>Table 3:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Situation</strong></td>
</tr>
<tr>
<td>All hospitalized patients</td>
</tr>
</tbody>
</table>

\(7\) Simvastatin was studied in ARDS [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201750/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201750/)

\(8\) If already on a statin, no need to change to these agents
<table>
<thead>
<tr>
<th>For patients with no Category 2 or 3 risk factors for severe disease</th>
<th>Supportive care with close monitoring and consideration of application for clinical trial of remdesivir (see below)</th>
<th>See Table 2 for list of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with moderate or severe disease, i.e. patients with any Category 2/3 feature (regardless of age or other category 1 features)</td>
<td>Application for <strong>remdesivir</strong> (RDV) through a clinical trial(^9) or, if available, through compassionate use.(^{10}) Current dosing of remdesivir is 200 mg IV loading dose following by 100 mg IV daily for up to 10 days.</td>
<td><strong>RDV</strong> is only currently available via compassionate use for pregnant or pediatric patients</td>
</tr>
<tr>
<td>With guidance from Infectious Diseases, can consider adding <strong>hydroxychloroquine (HCQ)</strong> (400 mg PO BID x2 followed by 400 mg daily while hospitalized, up to 5 days). Note chloroquine has activity but limited supply so hydroxychloroquine preferred</td>
<td><strong>Lopinavir/ritonavir</strong>(^{11}) (LPV/r or Kaletra) is generally not recommended. Avoid if candidate for RDV trial.</td>
<td>Check ECG prior to initiation given risk of QTc prolongation. Risk is increased in patients on other QTc-prolonging agents.</td>
</tr>
<tr>
<td><strong>Darunavir/cobicistat</strong> (DRV/c or Prezco) is generally not recommended.</td>
<td>Assess for <strong>drug-drug interactions</strong> (including with calcineurin inhibitors) before starting.</td>
<td>For protease inhibitors, main side effect is gastrointestinal intolerance. Monitor liver function tests while on therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue these agents upon discharge regardless of duration, unless previously used as maintenance medications for another indication.</td>
</tr>
</tbody>
</table>

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\(^{9}\) Currently open remdesivir trial: [https://clinicaltrials.gov/ct2/show/NCT04280705](https://clinicaltrials.gov/ct2/show/NCT04280705)

\(^{10}\) Please check the portal for exclusion/inclusion criteria to see if remdesivir compassionate use is an option.

\(^{11}\) Based on a published report in NEJM 3/19/20, lopinavir/ritonavir’s role in COVID-19 is likely very limited
For certain refractory or progressive patients (who are in ICU) With ID input, interferon beta B1 (Betaseron) can be considered but is generally not recommended. Note IFN would typically be combined with either LPV/r or HCQ for patients with COVID-19

For patients with evidence of cytokine release syndrome (see staging criteria below in Table 6) With ID input, tocilizumab (Actemra) can be considered Need to send serum IL-6 level prior to giving first dose of tocilizumab

Table 4:

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Recommendation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Do not use statins. Remdesivir available through compassionate use for pregnant patients and children only. For compassionate use, apply through portal here: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a> No contraindication to hydroxychloroquine, lopinavir/ritonavir, azithromycin Limited data on IFN, tocilizumab</td>
<td>Remdesivir: Pregnancy an exclusion for clinical trial Manage with MFM / Perinatal ID</td>
</tr>
<tr>
<td>People living with HIV</td>
<td>HIV with CD4 count &lt;200 is a risk factor for complications of other respiratory infections. Additional caution in this group is warranted. Because people with HIV may also have other conditions (lung disease, smoking) or vulnerabilities, they may be at higher risk for complications regardless of CD4 cell count.</td>
<td>Avoid LPV/r monotherapy in people with HIV</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="https://rdvcu.gilead.com/">Resource for crushing HIV-medications medications for intubated patients</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="https://rdvcu.gilead.com/">Resource for ARV drug-drug interactions</a></td>
</tr>
<tr>
<td>If IgG &lt;400</td>
<td>Consider IVIG at dose of 25 grams x1 (unclear benefit)</td>
<td>Note: Titers against SARS-CoV-2 are likely to be low in the population</td>
</tr>
<tr>
<td>Heart/Liver/Kidney Transplant Recipients</td>
<td>Guided by transplant and transplant ID teams – please call/consult Consider decreasing tacrolimus/cyclosporine by 50%, stop mycophenolate (CellCept/Myfortic) and Azathioprine in kidney/liver</td>
<td>Screen for drug-drug interactions with anti-viral agents, if they are being used</td>
</tr>
</tbody>
</table>
transplant patients and reduce dose by 50% in heart transplant patients. 
Kidney patients approximate target tacrolimus level 3-5 ng/ml, cyclosporine level target 25-50 ng/ml.

In the setting of ground glass opacities can consider switching mTor to CNI (tacrolimus) given possibility of pneumonitis w/ mTor; discuss with heart transplant before making switch

Critical illness – in liver and kidney – stop all immunosuppression except for prednisone if they are on it at baseline

For outpatients on belatacept, consider switching to tacrolimus or cyclosporine starting 28 days after last dose, to avoid clinic visit. Levels will need to be checked and thus institute plan to draw them without exposing community.

For inpatients on belatacept, do not administer any further belatacept. 28 days after last dose, consider adding low dose CNI. For CNI intolerant, consider increasing daily prednisone dose from 5 mg to 7.5-10 mg daily.

Continue low dose prednisone (5 mg) in all patients who were on it before hospitalization.

Request bronchoscopy only if significant decompensation, versus lung biopsy as may be lower risk for aerosolization and exposure to staff.

| Lung transplant recipients | Guided by transplant and transplant ID teams - please call/consult. These are guidelines only, immunosuppression requires case-by-case approach. |
No change to usual immunosuppression (avoid high levels, tailor to patient)

For all those in ICU or with lower respiratory tract disease (most inpatients): pulse methylprednisolone 125mg IV q 12 hours

Outpatient management: prednisone taper 60mg x 4 days → 40mg x 4 days → 20mg x 4 days then back to baseline

**Postexposure Prophylaxis for Healthcare Workers:**

- There is currently no proven role for post exposure prophylaxis for people with a known COVID-19 exposure. They should follow self-quarantine for 14-days and monitor for symptoms. Healthcare workers should follow instructions from [Institution's Occupational Health Department].

**Table 5: Brief Overview of Agents Discussed**

<table>
<thead>
<tr>
<th>Agent (link to package insert)</th>
<th>Classification</th>
<th>Target / Mechanism</th>
<th>Dosing</th>
<th>Key toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>remdesivir</td>
<td>Investigational</td>
<td>RNA dependent RNA polymerase inhibitor</td>
<td>200 mg IV x1, then 100 mg IV daily, up to 10 days</td>
<td>Nausea, vomiting, ALT elevations</td>
</tr>
<tr>
<td>hydroxychloroquine (Plaquenil)</td>
<td>Off-label</td>
<td>Multiple actions; prevents binding to ACE2, presents transport in endosome, and possibly others</td>
<td>400 mg BID x 2 doses, then 400 mg daily for a total 5 days</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>lopinavir/ritonavir (LPV/r or Kaletra)</td>
<td>Off-label</td>
<td>3CLpro (viral protease) inhibitor</td>
<td>400/100 mg BID for up to 10 days</td>
<td>QTc prolongation, ALT elevations</td>
</tr>
<tr>
<td>interferon beta-B1 (Betaseron)</td>
<td>Off-label</td>
<td>Immunomodulatory; enhancement of innate and adaptive viral immunity</td>
<td>Dosing for progressive COVID to be determined</td>
<td>Depression, injection site reaction, flu-like syndrome</td>
</tr>
<tr>
<td>tocilizumab (Actemra)</td>
<td>Off-label</td>
<td>Monoclonal antibody to IL6 receptor / treats</td>
<td>Dosing for COVID/CRS</td>
<td>ALT elevations</td>
</tr>
</tbody>
</table>
**Table 6: Modulating Host Immunity (tocilizumab, steroids)**

**Background:** Studies indicate advanced stage disease responses to beta-coronaviruses including COVID-19 have a high IL-6 cytokine signature. This response is similar to CAR-T cell based immune side effects where anti-IL-6 interventions have been of benefit. However, data regarding IL-6 modulation are limited at this time and the timing and efficacy of such treatments have not been determined.

- For immunomodulatory therapies we strongly prefer that the team refer the patient to a clinical trial, if available.
- A multidisciplinary team has convened to provide more clarity regarding off-label use for those who are not participating in clinical trials; further guidance will be provided in the next update.
- Decisions regarding off-label use of immunomodulatory agents should be made with agreement of both the primary and recommending teams.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Status</th>
<th>Cardioprotection; immunomodulatory</th>
<th>Dose</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin (Lipitor)</td>
<td>Off-label</td>
<td>Cardioprotection; immunomodulatory</td>
<td>40-80 mg PO daily</td>
<td>Avoid if using LPV/r</td>
</tr>
<tr>
<td>pravastatin (Pravachol)</td>
<td>Off-label</td>
<td>Cardioprotection; immunomodulatory</td>
<td>80 mg PO daily</td>
<td></td>
</tr>
</tbody>
</table>


*NOTE: Multiple departments across MGH are working towards clinical trials of off-label and investigational agents. This table and document will be updated once available.*
Confirmed COVID Positive

Medicine Ward

Consider eligibility for clinical trials

Any category 2 or 3 risk factors\(^a\) for severe disease?

- Supportive care
- Close monitoring
- Repeat labs at regular intervals

- With guidance from ID, start hydroxychloroquine
- Consider statin if CV indication
- Other off-label therapies can be considered with guidance from ID
- Repeat labs at regular intervals

Intensive Care Unit (ICU)

Consider eligibility for clinical trials

1. Refer to [MGH ICU COVID management guidance](#)
2. With guidance from ID, consider hydroxychloroquine
3. Decisions about steroids, immunomodulatory or other therapies can be considered on a case by case basis by the ICU team

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a: See [risk factors table](#) (Table 2) in this document

COVID-19 has been reported to cause increased liver biochemistries in 15-53% of patients [1,2]. The profile of the liver biochemistry abnormalities is most commonly an elevation of the aminotransferases (AST and ALT), with occasional alkaline phosphatase and total bilirubin elevations [1-3]. There has been only one reported case of severe liver injury in the context of COVID-19 infection with the ALT reaching 7590 U/L and AST 1445 U/L, but no details about concomitant diagnoses or medications were reported [4]. Liver injury appears to be more common in severe cases of COVID-19.

![Figure from citation 2.](image1)

| Figure adapted from citation 3. |

We know that the SARS virus from China in 2002 was found in parenchymal and vascular endothelium of the liver. That SARS virus used angiotensin-converting enzyme 2 (ACE2) as the receptor for cell entry, which is found abundantly in the liver [1]. Studies into the mechanism of COVID-19 related liver injury is limited, but may also use ACE2 receptors for cell entry [1]. Postmortem analysis of a COVID-19 patient revealed moderate microvascular steatosis and mild lobular and portal activity. Whether those changes can be attributed to COVID-19 infection or are the result of some other cause such as drug-induced liver injury remains unclear [5].

According to NIH Liver Tox and their supporting references, atorvastatin (as an example) is associated with mild and transient ALT and/or AST elevations in 1-3% of patients. Transaminase elevations above 3 times the upper limit of normal occur in 0.7% of cases, though higher (2.3%) with higher atorvastatin doses of 80 mg daily. Most elevations self-resolved without dose modification. Atorvastatin leads to severe hepatic injury in 1:3000-1:5000 cases. The presentation of atorvastatin hepatotoxicity can be cholestatic (most common), hepatocellular,
or mixed. Atorvastatin can also very rarely induce autoimmune hepatitis. The injury typically arises within 6 months of initiation or dose escalation.

The risk of statin related DILI is no higher in patients with baseline abnormal liver biochemical abnormalities than those without. A study compared 342 patients with baseline LFT abnormalities and 1437 patients without LFT abnormalities who were started on a statin. It showed no difference between the groups in the development of severe LFT elevation, which occurred in 0.6% of cases [6]. The group with abnormal LFTs was more likely to have mild-moderate elevations in LFTs with statin initiation, at a rate of 4.7%. Severe elevation was defined here as TB > 3 mg/dL or ALT or AST 10 times the upper limit of normal or the patient’s baseline value. HBV and HCV patients were excluded from the abnormal LFT group.

We propose the following liver safety monitoring strategy for initiation of statin therapy for COVID-19: do not initiate statin therapy in patients with AST and ALT already 3 times the upper limit of normal (i.e. ALT > 165 U/L, AST 120 U/L) or ALP and TB 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL) unless approved by hepatology consultation. Monitor LFTs daily while on statin therapy for COVID and discontinue therapy if AST and ALT exceed 5 times the upper limit of normal (i.e. ALT > 275 U/L, AST 200 U/L) or ALP and TB exceed 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL). The statin therapy should be held until LFTs have returned to under these values.

2. Proposed hepatic monitoring for patients being initiated on Remdesivir:

We propose the following liver safety monitoring strategy for initiation of Remdesivir for COVID-19 therapy: do not initiate Remdesivir therapy in patients with AST and ALT already 5 times the upper limit of normal (i.e. ALT > 275 U/L, AST 200 U/L) or ALP and TB 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL). Monitor LFTs daily while on Remdesivir therapy for COVID and discontinue therapy if LFTs exceed the above values. Remdesivir therapy should be held until LFTs have returned to under these values and re-initiation can be considered on a case by case basis.

3. Evaluation of abnormal LFTs in a person presenting with suspected or confirmed COVID-19.

- COVID-19 is associated with elevated LFTs in 15-53% of patients
- LFT pattern is often mild AST and ALT elevations
- Severe liver injury appears to be rare
- HBV/HCV viral load (PCR) testing should be AVOIDED unless there is an identifiable risk factor or needed for a COVID-treatment protocol
- Ultrasound should be AVOIDED unless there is concern for biliary obstruction, cholangitis, or venous thrombosis
- Consider medications as a cause of LFT elevations
- Monitor the LFT trend daily and consult hepatology for LFTs over 5 times the upper limit of normal or rapid rise

References:


<table>
<thead>
<tr>
<th>Epidemiological</th>
<th>Vital Signs</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 (^a)</td>
<td>Respiratory rate &gt; 24 breaths/min (^j)</td>
<td>D-dimer &gt; 1000 ng/mL (^m)</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease (^b)</td>
<td>Heart rate &gt; 125 beats/min (^k)</td>
<td>CPK &gt; twice upper limit of normal (^n)</td>
</tr>
<tr>
<td>Chronic kidney disease (^c)</td>
<td>SpO2 &lt; 90% on ambient air (^l)</td>
<td>CRP &gt; 100 (^o)</td>
</tr>
<tr>
<td>Diabetes with A1c &gt; 7.6% (^d)</td>
<td></td>
<td>Admission absolute lymphocyte count &lt; 0.8 (^p)</td>
</tr>
<tr>
<td>History of hypertension (^e)</td>
<td></td>
<td>LDH &gt; 245 U/L (^q)</td>
</tr>
<tr>
<td>History of cardiovascular disease (^f)</td>
<td></td>
<td>Elevated troponin (^r)</td>
</tr>
<tr>
<td>Use of biologics (^g)</td>
<td></td>
<td>Ferritin &gt; 300 ug/L (^s)</td>
</tr>
<tr>
<td>History of transplant or other immunosuppression (^h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled HIV (viremic or CD4 &lt;200) (^i)</td>
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</tbody>
</table>

Note abnormalities on chest radiographs are common in both severe and non-severe cases for hospitalized patients with COVID-19. Patients without severe disease may be more likely to have normal radiographs.(1-3)

a: Most studies to date have identified age as one of the main risk factors for severe disease.(1, 3-5)
b: Pre-existing pulmonary disease is a risk factor for severe disease with increased mortality (3, 5)
c: Chronic kidney disease is reported in more patients with severe disease(3)
d: Diabetes is a risk factor for severe disease according to multiple studies (3-5)
e: Baseline hypertension seems to be one of the major risk factors predicting worse disease (3-5)
f: Pre-existing cardiovascular disease is thought to be a major risk factor for worse disease severity (3, 4, 6)
g: Predicted worse disease severity, existing data are limited
h: Predicted worse disease severity, existing data are limited
i: Possible worse disease outcome, existing data are limited
j: Expected based on physiology and available data (3)
k: Expected based on physiology and available data (3)
l: Expected based on physiology
m: Multiple studies have shown that elevated D-dimer compared to normal is either associated with ICU versus non-ICU or non-surviving versus surviving outcomes.(2, 3)
n: CPK may be elevated in patients with severe disease (3)
o: CRP is commonly elevated above normal for hospitalized patients with COVID-19. (1) Available data suggests it is often higher in patients with worse outcomes (> 100 versus around 50-75 for patients with less severe outcomes). (6)
p: Multiple studies have shown a low absolute lymphocyte count on admission can be associated with worse outcomes. (1, 3, 4) Patients may with worse outcomes may also have an elevated total white blood cell count driven by neutrophilia on admission.
q: Elevated LDH is more likely to be seen in patients with severe presentations according to multiple studies (3, 4)
r: Elevated troponin is a marker of severe disease (3)
s: Ferritin > 300 ug/L may be a marker of severe disease (3)
References:

Rationale for Consideration of Statins for COVID-19 Patients

There is no clinical evidence to date that statins are benefit for patients with COVID-19. However, there are at least 4 reasons we might consider them for these patients. First one of the greatest risk factors for severe COVID-19 disease is underlying cardiovascular disease (and another is diabetes), so many of these patients likely already have a primary indication for them. Second, there have been described a number of cardiovascular complications of COVID-19 infection and statins might be beneficial in preventing these. Third, there is the theoretical role that statins may play in protecting innate immune responses to viral respiratory infections (including to SARS-CoV) through inhibiting the MYD88 pathway. And fourth, there is some epidemiological evidence that statins may lead to fewer severe viral pneumonias. Importantly statins are safe and widely prescribed and so the likelihood of harm is felt to be very low with these agents with which we have extensive experience.

A. Risk Factors for Severe COVID-19 Presentations:

Diabetes and pre-existing cardiovascular disease are two of the major risk factors for severe COVID-19 disease. This has been shown in multiple studies to date. In a series of 138 hospitalized patients cardiovascular disease was found in 25% of patients in ICU compared with 10.8% non-ICU (p=0.04) and diabetes in 22.2% of ICU patients and 5.9% of non-ICU patients (p=0.009). (1) In another study of 191 hospitalized patients 31% of non-survivors had diabetes compared with 14% of survivors (p=0.0051) and 24% of non-survivors had coronary heart disease, compared with 1% of survivors (p<0.0001). (2) In a series of 1099 patients, 16.2% of severe patients had diabetes compared with 5.7% of non-severe patients and 5.8% of severe patients had coronary heart disease compared with 1.8% of non-severe patients. (3) In a summary report of 72,314 cases of COVID-19 from China, the authors noted the overall case fatality rate (CFR) was 2.3%. However, they noted the CFR was elevated to 10-15% for those with pre-existing cardiovascular disease and 7.3% for those with pre-existing diabetes. (4) Another analysis also reportedly markedly elevated risk of death for patients with COVID-19 with underlying cardiovascular disease. (5)

Unfortunately, there is not currently available data about the epidemiology of these patients and how many were on statins at the time of infection. Hopefully this will be published soon.

B. Cardiovascular Complications of COVID-19:

From many of the same studies discussed above, we know that elevated troponins and myocardial injury are more frequently seen in patients with severe presentations compared to non-severe presentations. (1, 2) Furthermore patients with pre-existing cardiovascular disease seemed more likely to have cardiac complications of COVID-19. The mechanisms for this are not yet worked out. We know that ACE2 receptors are present in the myocardium and there may
be a direct viral myocarditis in some patients. (6) Furthermore some patients present to care with cardiovascular complaints including palpitations and chest tightness or pain. From follow up studies of patients who survived SARS, we know that there can be long term changes in lipid profiles.

C. **Statin and Innate Immunity:**

There is an additional theoretic role that statins might play in helping protect the innate immune response to COVID-19. It was noted that SARS-CoV infection led to the MYD88 gene being highly induced. (7) Downstream effects of this include activation of the NF-κB pathway (and a reduction in type 1 interferon) and marked inflammation, a hallmark of SARS-like infections. (8) When NF-κB inflammation is attenuated, SARS-infected transgenic mice are more likely to survive. (8) Of note MYD88/- mice are more prone to infection from SARS-like coronaviruses. (9) It seems a balance of this pathway is important to maintain.

Statins are known inhibitors of the MYD88 pathway. (7) Importantly they do not significantly alter the level of MYD88 under normal conditions but rather maintain normal levels during hypoxia and under stress (such as after treatment with hydrogen peroxide). (7) The ability of statins to maintain MYD88 levels at normal levels, may be protective for patients with COVID-19.

D. **Statin and Viral Pneumonia:**

While no clinical data yet exists for a protective role for statins for COVID-19 infection, there are some data that are suggestive that they may be associated with less severe viral pneumonia (perhaps for similar reasons described in point C). A large matched cohort study found a reduced risk of COPD death and influenza death for patients on moderate dose statins.
compared to not.(10) Another found a statistically significant but small protective effect against influenza mortality among statin users. Another study showed a similar protective effect of statins on influenza related mortality.(11) An analysis of hospitalized patients with pandemic H1N1 influenza did not find a statistically significant association between pre-admission statin use and severity of outcome after adjustment for age and sex but they noted “point estimates are compatible with a small but clinically significant protective effect of statin use.”(12)

E. Safety of Statins:
There is extensive clinical experience with statins, and they are accepted as quite safe medications in general. The overall safety of statins in patients with COVID-19 disease has not yet been established.

COVID-19 has been reported to cause increased liver biochemistries in 15-53% of patients.(13, 14) The profile of the liver biochemistry abnormalities is most commonly an elevation of the aminotransferases (AST and ALT), with occasional alkaline phosphatase and total bilirubin elevations.(3, 13, 14) There has been only one reported case of severe liver injury in the context of COVID-19 infection with the ALT reaching 7590 U/L and AST 1445 U/L, but no details about concomitant diagnoses or medications were reported.(15) Liver injury appears to be more common in severe cases of COVID-19.

![Liver-function related index](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=1099)</th>
<th>Disease Severity</th>
<th>Presence of Composite Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nonsevere (N=936)</td>
<td>Severe (N=173)</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;40 U/liter</td>
<td>168/757 (22.2)</td>
<td>112/615 (18.2)</td>
<td>56/142 (39.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;40 U/liter</td>
<td>158/741 (21.3)</td>
<td>120/606 (19.8)</td>
<td>38/135 (28.1)</td>
</tr>
<tr>
<td>Total bilirubin &gt;17.1 µmol/liter</td>
<td>76/722 (10.5)</td>
<td>59/594 (9.8)</td>
<td>17/128 (13.3)</td>
</tr>
</tbody>
</table>

(3)
We know that the SARS virus from China in 2002 was found in parenchymal and vascular endothelium of the liver. That SARS virus used angiotensin-converting enzyme 2 (ACE2) as the receptor for cell entry, which is found abundantly in the liver. (13) Studies into the mechanism of COVID-19 related liver injury is limited, but may also use ACE2 receptors for cell entry. (13) Postmortem analysis of a COVID-19 patient revealed moderate microvascular steatosis and mild lobular and portal activity. Whether those changes can be attributed to COVID-19 infection or are the result of some other cause such as drug-induced liver injury remains unclear. (16)

According to NIH Liver Tox and their supporting references, atorvastatin (as an example) is associated with mild and transient ALT and/or AST elevations in 1-3% of patients. Transaminase elevations above 3 times the upper limit of normal occur in 0.7% of cases, though higher (2.3%) with higher atorvastatin doses of 80 mg daily. Most elevations self-resolved without dose modification. Atorvastatin leads to severe hepatic injury in 1:3000-1:5000 cases. The presentation of atorvastatin hepatotoxicity can be cholestatic (most common), hepatocellular, or mixed. Atorvastatin can also very rarely induce autoimmune hepatitis. The injury typically arises within 6 months of initiation or dose escalation.

The risk of statin related DILI is no higher in patients with baseline abnormal liver biochemical abnormalities than those without. A study compared 342 patients with baseline LFT abnormalities and 1437 patients without LFT abnormalities who were started on a statin. It showed no difference between the groups in the development of severe LFT elevation, which occurred in 0.6% of cases. (17) The group with abnormal LFTs was more likely to have mild-moderate elevations in LFTs with statin initiation, at a rate of 4.7%. Severe elevation was defined here as TB > 3 mg/dL or ALT or AST 10 times the upper limit of normal or the patient’s baseline value. HBV and HCV patients were excluded from the abnormal LFT group.

We propose the following liver safety monitoring strategy for initiation of statin therapy for COVID-19: do not initiate statin therapy in patients with AST and ALT already 3 times the upper limit of normal (i.e. ALT > 165 U/L, AST 120 U/L) or ALP and TB 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL) unless approved by hepatology consultation. Monitor LFTs daily while on statin therapy for COVID and discontinue therapy if AST and ALT exceed 5 times the upper limit of normal (i.e. ALT > 275 U/L, AST 200 U/L) or ALP and TB exceed 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL). The statin therapy should be held until LFTs have returned to under these values.

### F. Recommendation:

We recommend continuing previous statins in house even with new LFT abnormalities which are more likely due to other causes. If there is a clear pre-existing primary indication, consider starting for cardioprotection given the CV complications late in severe COVID-19.

For patients naïve to statins without CV indications, a trial of starting statins is in planning stages.
G. Dosing:
If not on interacting meds, then atorvastatin 40 mg daily
If on interacting meds, pravastatin 80 mg daily or pitavastatin 4 mg daily

H. Availability:
We do not expect shortages of these medications
References:


