Massachusetts General Hospital (MGH)
COVID-19 Treatment Guidance

This document was prepared (in March-November, 2020) by and for MGH medical professionals (a.k.a. clinicians, care givers) and is being made available publicly for informational purposes only, in the context of a public health emergency related to COVID-19 (a.k.a. the coronavirus) and in connection with the state of emergency declared by the Governor of the Commonwealth of Massachusetts and the President of the United States. It is neither an attempt to substitute for the practice of medicine nor as a substitute for the provision of any medical professional services. Furthermore, the content is not meant to be complete, exhaustive, or a substitute for medical professional advice, diagnosis, or treatment. The information herein should be adapted to each specific patient based on the treating medical professional’s independent professional judgment and consideration of the patient’s needs, the resources available at the location from where the medical professional services are being provided (e.g., healthcare institution, ambulatory clinic, physician’s office, etc.), and any other unique circumstances. This information should not be used to replace, substitute for, or overrule a qualified medical professional’s judgment.

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- This document was developed by members of the Infectious Diseases (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 emergency use, 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, personal protective equipment (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.

What’s New in the November 13, 2020 update:

- The FDA approved remdesivir on October 22, 2020. The emergency use authorization (EUA) supply on hand may still be utilized; however, assent is no longer required for all adults and for children (≥12 years and ≥40 Kg). New MGB Remdesivir Criteria for Use are updated and found at this [link](#).
- MGH prioritizes remdesivir for patients on oxygen; others may be considered on a case-by-case basis.
- Emergency use authorization applications for monoclonal antibody therapies have been filed with the FDA; these are currently not yet available at MGH and do not apply to hospitalized patients. Outpatient trials are available.
- The laboratory guide recommends reduced frequency of prognostic labs and removal of routine use of IL-6 measurements
- Influenza rates remain low; further guidance will be updated as we enter flu season
- New section on when to contact or consult infectious diseases
TABLE OF CONTENTS (including hyperlinks)

What labs should I send for a patient hospitalized with COVID-19?
How to risk stratify a hospitalized patient
Figure: Algorithm

Therapeutic recommendations:
- COVID-19 specific management, including remdesivir and dexamethasone
- Recommendations regarding anti-infectives
- Recommendations regarding ACEi/ARBs, statins, and other medications

Table 3: COVID-19 specific recommendations by severity of illness
Table 4: Special populations
Table 5: Brief overview of agents discussed

Modulating host immunity and risk of reactivating latent infections
When should we consult Infectious Diseases?
Table 1: Work-up for diagnosis, prognosis / risk stratification, and/or safety of therapeutics

**Suggested for hospitalized patients with confirmed COVID-19**

<table>
<thead>
<tr>
<th>Recommended daily labs (until stable):</th>
<th>For acute kidney injury (i.e. serum creatinine &gt;0.3 above baseline):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CBC with diff (esp. total lymphocyte count)</td>
<td>• Urinalysis and spot urine protein:creatinine</td>
</tr>
<tr>
<td>• Complete metabolic panel</td>
<td>When MAS/sHLH suspected (rising LFTs, falling fibrinogen, hypotension, see Immunomodulation):</td>
</tr>
<tr>
<td>• CPK (creatinine kinase)</td>
<td>• ESR, Ferritin</td>
</tr>
</tbody>
</table>
| • CRP (first week of hospitalization) | Viral serologies for all patients unless done recently:
| | • HBV serologies (sAb, cAb, and sAg) |
| | • HCV antibody, unless positive in past |
| | • HIV 1/2 Ab/Ag |

<table>
<thead>
<tr>
<th>Recommended at baseline then every other day (if in ICU or elevated check daily):</th>
<th>If clinically indicated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PT/PTT/fibrinogen</td>
<td>• Blood cultures (2 sets) if bacteremia suspected</td>
</tr>
<tr>
<td>• D-dimer</td>
<td>• β-HCG for women of childbearing age</td>
</tr>
</tbody>
</table>

Link to Guidance from MGH Hematology

For risk stratification:

- LDH (repeat daily if elevated)
- Troponin (see below if elevated)
- Baseline ECG (QTc monitoring algorithm)

With clinical deterioration, repeat risk stratification labs.

Radiology:

- Portable CXR at admission
- High threshold for PA/lateral, consider only if low suspicion for COVID-19 and result would change management or affect PUI status.
- Non-contrast CT is of limited utility in definitively diagnosing COVID-19 and should only be considered if it is likely to change management or PUI status; check CORAL tool

Following infection control/PPE guidelines:

- SARS-CoV-2 test, if not already performed.
- **Routine influenza A/B and RSV tests are not currently recommended.** Routine expanded respiratory panels may be approved on a case-by-case basis.
- If bacterial superinfection highly suspected, routine sputum for Gram stain and culture, Legionella urinary antigen. If immunocompromised, see next page.

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1 The prognostic value of some of these labs is being defined or is not yet proven. For PUI, please refer to [COVID-19 Testing Criteria](#) or Infection Control page for biothreats resolution pathways.

2 For a primer on liver issues related to COVID19 and treatment, please see our [supporting liver document](#).

3 If beyond 1 week of hospital stay, inflammatory markers are hard to interpret. Repeat per discretion of primary team.

4 Viral serologies assist for interpretation of ALT elevations, present in ~25% of presentations. Note: follow-up molecular testing for HIV/HBV/HCV may have longer turnaround times than usual.

5 See note on next page regarding elevated troponins.
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.

Additional diagnostic considerations for candidates for corticosteroids or immunotherapy:
If starting steroids or immunotherapy AND if the patient is foreign-born from a resource-limited country, experiencing homelessness, or has a history of incarceration AND if there is no past history of active TB or latent TB infection (LTBI), send T-Spot. Routine screening for TB is unnecessary for most COVID patients. More explanation is found here, accompanied by a separate flowchart.

Procalcitonin is not recommended for most patients admitted with COVID-19. It may have limited utility in those with intermediate risk for bacterial superinfection. 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. Repeating PCT is less specific late in the course of COVID-19 and generally unnecessary. See FAQ.

Considerations for elevated troponin:
Biomarkers of cardiac injury may be elevated due to of COVID-19, an acute cardiac issue such as an MI or heart failure, or both. Significant degree of troponin elevation and rising values both predict in-hospital mortality. For elevated high-sensitivity troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours; echocardiogram not routinely necessary unless otherwise indicated, e.g. unexplained hypotension or reduced central venous O2 saturation. Markedly elevated troponin (e.g. > 5-10x ULN), up-trending troponin with hemodynamic compromise or other concerning cardiovascular symptoms /signs should prompt consideration of obtaining a point of care ultrasound (POCUS), a transthoracic echocardiogram or cardiology consultation. Note: interpretation of troponin elevation in the setting of renal dysfunction can be challenging.
Determine severity: The severity of COVID-19 is categorized into mild (symptoms but no dyspnea or abnormal imaging), moderate (lower respiratory disease w/ SpO2 >94% on room air), severe (SpO2 ≤ 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%), or critical (ICU, respiratory failure, septic shock, and/or multiple organ dysfunction). Note these definitions vary in the literature; the choice of cutoff of ≤ 94% is based on the ACCT-1 trial.

When classifying the severity of COVID-19 based on SpO2, please note whether the hypoxemia is new (as opposed to at or near baseline) or due to other causes (such as volume overload).

Determine prognosis: The following risk factors may predict COVID-19 disease progression to more severe manifestations. Patients with multiple risk factors may warrant closer monitoring or, on a case-by-case basis for moderate disease, be considered for remdesivir.

<table>
<thead>
<tr>
<th>Epidemiological – Category 1</th>
<th>Vital Signs – Category 2</th>
<th>Labs – Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50</td>
<td>Respiratory rate &gt; 24 breaths/min</td>
<td>D-dimer &gt; 1000 ng/mL</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease</td>
<td>Heart rate &gt; 125 beats/min</td>
<td>CPK &gt; twice upper limit of normal</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>SpO2 ≤ 94% on ambient air</td>
<td>CRP &gt; 100</td>
</tr>
<tr>
<td>Diabetes with A1c &gt; 7.6%</td>
<td>PaO2/FiO2 &lt; 300 mmHg</td>
<td>LDH &gt; 245 U/L</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>Elevated troponin</td>
<td>Absolute lymphocyte count &lt; 0.8</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>Ferritin &gt; 500 ug/L</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td></td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Use of biologics*</td>
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<td></td>
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<tr>
<td>History of transplant or other immunosuppression*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV, CD4 cell count &lt;200 or unknown CD4 count*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not yet proven as risk factors for progression, inferred from other infections. Other factors include poverty, racism, recent cancer chemotherapy, recent surgery, sickle cell disease. For more information about COVID-19 severity, see our supporting risk factors document.
Algorithm based on severity

Confirmed COVID Positive, Admitted as Inpatient

1. Assess severity of illness§
2. Assess prognosis*
3. Do not routinely start antibiotics

Clinical trials team considers candidacy for all admissions†

Asymptomatic, mild or moderate disease

Severe disease
SpO2 ≤ 94% on RA, P/F ratio < 300, RR>30

If eligible‡, ensure PT, eGFR, ALT; remdesivir 200 mg IV x 1, then 100 mg IV daily for 4 days
Dexamethasone 6 mg PO or IV daily for up to 10 days
RDV/DEX can be d/c'd upon discharge
Consider statin if CV indication
Supportive care, close monitoring especially for those with multiple risk factors for progression
Repeat labs at regular intervals
If on RDV, follow daily LFTs and eGFR
If not on RDV, may reconsider via the ID antibiotic approval pager*
Other off-label therapies can be considered with guidance from ID‡

Critical disease (ICU, respiratory failure, septic shock, and/or multiple organ dysfunction)

Refer to MGH ICU COVID management guidance
Follow daily LFTs and eGFR if on remdesivir
Dexamethasone strongly recommended
Decisions about alternative steroids, off-label immunomodulatory or other therapies can be considered on a case-by-case basis by the ICU team, with ID guidance

§: When assessing severity, consider whether hypoxia is a new requirement or due to another cause (such as CHF)
*: See risk factors table on previous page
†: Current list of clinical trials is found at this link. ID strongly recommends referral to clinical trials, which occurs automatically for all admissions
‡: Check RDV criteria on next page. Guidance from ID regarding use of remdesivir (e.g. eGFR<30), off-label use, is available 8am to 8pm via the antibiotic approval pager
❖: If not on RDV (e.g declined or not qualified earlier in admission), regardless of clinical trial enrollment status, patient may be reconsidered for RDV should they qualify

No specific COVID-19 therapy
Supportive care, close monitoring, especially for those with multiple risk factors for progression
Repeat labs at regular intervals
Remdesivir may be considered for select patients with multiple risk factors for progression
If progresses to severe disease, may reassess candidacy for clinical trials and other therapies*

Asymptomatic, mild or moderate disease

Severe disease
SpO2 ≤ 94% on RA, P/F ratio < 300, RR>30

If eligible‡, ensure PT, eGFR, ALT; remdesivir 200 mg IV x 1, then 100 mg IV daily for 4 days
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Repeat labs at regular intervals
Remdesivir may be considered for select patients with multiple risk factors for progression
If progresses to severe disease, may reassess candidacy for clinical trials and other therapies*
COVID-19 Specific Management:
Guidance is available from NIH and IDSA. MGH-specific recommendations are below.

The following algorithm provides guidance based on available information to-date regarding possible and investigational treatments. 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.

Remdesivir (RDV): Remdesivir is FDA-approved for hospitalized adults and children (≥12 years and ≥40 Kg). RDV is currently available at MGH via the algorithm below. RDV is available under Emergency Use Authorization (EUA) for pediatric patients under 12 years old (≥3.5 kg) and pediatric patients under 40 kg.

Data regarding remdesivir include a large randomized control trial showing efficacy in reducing duration of hospital stay and a trend toward mortality benefit and a larger open-label trial suggesting no mortality benefit. Data for moderate disease are available from a large open-label RCT indicating a small benefit in improved clinical status at 11 days for the 5 day group compared to standard of care, but no benefit for the 10 day group.

Under the MGB guidance, remdesivir may be given to:
Patients hospitalized at an acute care facility or awaiting hospitalization in the emergency department with documented positive SARS-CoV-2 PCR AND one of the following criteria:
- SpO2 ≤ 94% on room air, requiring supplemental oxygen, or mechanical ventilation
- OR
- COVID-19 is a primary contributor to current hospitalization
- OR
- Patient is at high risk for clinical deterioration due to severe immunocompromise, recent major surgery, or severe pre-existing cardiopulmonary disease

Remdesivir should not be initiated or should be stopped if ALT is ≥10x ULN. For patients with eGFR < 30 ml/min, remdesivir may be considered on an individual basis considering risk/benefit with input from infectious diseases and nephrology. Treatment of moderate COVID-19 with remdesivir may be considered on a case-by-case basis but should not be done routinely. Definitions of moderate, severe, or critical COVID-19 are found earlier in the document at this link. Patients must have ALT, eGFR and PT assessed prior to infusion.

To discuss new starts of remdesivir: 1) check eligibility above; then 2) please contact Infectious Diseases via the antibiotic approval pager. See detailed checklist below. Remdesivir is a restricted antimicrobial that may be started overnight without approval; approval will be required to continue its use the following day.
Dexamethasone is recommended for hospitalized patients with severe COVID-19 (requiring supplementary oxygen). Systemic corticosteroids should be avoided for patients with mild or moderate disease (no oxygen support) unless there is another indication.

A report from the RECOVERY RCT in the UK indicates survival benefit of low dose dexamethasone for patients with severe or critical COVID-19, but no benefit in those not requiring oxygen support. Specifically, the mortality benefit was greater in a pre-specified subgroup of patients receiving mechanical ventilation (RR 0.64) than in those on supplemental oxygen (RR 0.82), with a non-statistically significant trend towards harm in those not on oxygen (RR 1.19). Notably the group on supplemental oxygen in RECOVERY was heterogeneous, and whether there is equal benefit for those patients on a low-level of oxygen compared to high levels is uncertain.

Notes for use at MGH:

- Given no benefit in those who are off oxygen, whether an oxygen requirement is new from a baseline requirement or due to other causes should be considered in the decision to start dexamethasone. Also, subgroup analysis suggests less benefit if administered ≤7 days after symptom onset.
- Both PO and IV formulations of dexamethasone are currently in stock at MGH. Alternatives to dexamethasone include:
  - Hydrocortisone IV 50mg q8hrs (or q6h for refractory shock co-indication)
  - Methylprednisolone IV 30mg daily
  - Prednisone PO 40mg qd
- Dexamethasone has no mineralocorticoid effect, unlike the above alternatives
- No data are available for the combination of dexamethasone and remdesivir at this time.
- Dexamethasone is a moderate CYP3A4 inducer; review of potential drug-drug interactions is recommended before initiation. Coadministration with remdesivir is allowable.
- Dexamethasone has fetal effects; please refer to pregnancy section for specific guidance.
- Please refer to the MGH critical care guidelines, once updated, for more specific guidance in this population. See FLARE on the RECOVERY trial.
- Contraindications to dexamethasone use include previous hypersensitivity and uncontrolled fungal infection.
- Close monitoring for hyperglycemia is recommended, particularly in a person with diabetes mellitus.
- Duration is 10 days or until discharge, whichever comes first. There are no data supporting use beyond 10 days for COVID-19 treatment even if the patient is not improving.
- With at-risk patients, consider adrenal insufficiency after discontinuation.

Corticosteroid administration is associated with reactivation of latent infections. Please check section for further guidance regarding HBV, Strongyloides, and tuberculosis. Routine prophylaxis for herpesviruses and Pneumocystis is not recommended at this time.
Medication considerations:

Anti-infectives

- **Do not start empiric antibiotics if COVID-19 confirmed or high likelihood**
  - Consider antibiotics only if CXR displays lobar infiltrate and/or ICU admission
  - Sputum GS & Culture & Legionella urinary antigen
  - Ceftriaxone 1 gm IV QD + doxycycline 100 mg PO BID
  - If ICU/sepsis, consider MRSA / MDRO coverage

- **Routine empiric antibiotics are not recommended.** MGH has detected low rates of bacterial superinfection in COVID-19 patients, consistent with studies from other centers. Unnecessary antibiotic use increases risks of multi-drug resistant organisms and *C. difficile*. If empiric antibiotics are given, recommend:
  - Ceftriaxone 1 gm IV daily + either doxycycline 100 mg PO x 5 days or azithromycin 500 mg PO x 1 then 250 mg PO daily for 4 days.
  - For nonpregnant patients, doxycycline is preferred over azithromycin.
  - Azithromycin is preferred for pregnant women and patients unable to be upright for 30m to prevent pill esophagitis related to doxycycline.
  - Azithromycin is not proven as an adjunctive treatment with HCQ for COVID-19 and may increase the likelihood of prolonged QTc and arrhythmias.
  - If antibiotics started, maximum duration is 5 days. May discontinue if concern for bacterial pneumonia low (confirmed COVID-19, classic presentation, PCT<0.2)

- **Regularly reassess need for ongoing antibiotics.** For all patients with suspected bacterial pneumonia on empiric antibiotics, reassess for clinical improvement at 48-72h as well as risk factors for MDROs. For guidance on risk factors for MRSA/MRDO and for antibiotic de-escalation after 48-72h of empiric broad spectrum antibiotics in suspected hospital-acquired or ventilator-associated pneumonia, please check link to algorithm.

- Due to low rates of influenza coinfection at MGH, we do not currently recommend starting oseltamivir on most patients with COVID-19.

Cardiovascular medications

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

- **Continue ACEi/ARBs if already prescribed.** 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.

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7 If a known flu contact or high suspicion for flu, request approval for testing and start oseltamivir 75 mg BID in adult patients with normal renal function. Adjust for renal insufficiency. Stop oseltamivir if testing is negative.
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 new ACEi/ARBs can be started if they have a primary indication such as new persistently reduced ejection fraction.

**Statins:**

- **Continue statins if already prescribed.** Cardiovascular disease is a major risk factor for COVID-19 disease severity. Additionally, statins may help promote antiviral innate immune response. For a brief discussion of statins and COVID-19, see our statin rationale document.
- Several retrospective studies suggest that baseline statin use is associated with better hospital outcomes but randomized controlled trial data regarding new initiation of statins are not available. For those who have a guideline indication for a statin and no contraindication (e.g., pregnancy), consider starting atorvastatin 40 mg daily. When major drug-drug interactions with atorvastatin are expected, pitavastatin 4 mg daily (or pravastatin 80 mg daily if pitavastatin not available) are alternatives. If already on a statin, no need to change to these agents. If elevated CPK >/= 500 U/L or if ALT > 3x upper limit of normal, consider not starting a statin. Monitor CPK daily if on both statin and azithromycin.

**Antithrombotic medications:**

- All patients should be routinely placed on routine standard LMWH prophylaxis, with the exception of pregnant women >=20 weeks gestation who should receive unfractionated heparin. Please see link for further guidance from MGH Hematology

**Other medications:**

- NSAIDs. Concerns were raised that NSAIDs may worsen COVID-19 disease. This has not been proven to-date. See FDA statement on NSAIDs dated 3/19/20. Acetaminophen is the suggested first-line anti-pyretic. If NSAIDs are used, lowest effective dose is suggested.
- **Inhaled medications should be given by metered dose inhaler rather than nebulization.** If nebulized medications are given, patients need to have a recent negative COVID test (within 3 days), given the risk of aerosolizing the virus with nebulizers (see MGB Policy). For those without pre-existing pulmonary disease, avoid inhaled steroids as they may reduce local immunity and promote viral replication.
- **Systemic corticosteroids.** See discussion under COVID-19 specific management in the next section regarding dexamethasone, which is recommended for patients on oxygen support but avoided for patients with mild or moderate disease (no oxygen support). Corticosteroids may be considered if indicated for another reason (e.g., refractory septic shock, multisystem inflammatory syndrome, pregnancy for fetal benefit, or specific to lung transplant guidelines, as delineated below). For those prescribed long-term corticosteroids, discuss with prescribing physician the management of the underlying condition and whether/how to continue corticosteroids while hospitalized.

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8 Links to examples of observational studies regarding statins: Hubei Province, New York, Illinois, California.
Suggested Treatment Algorithm Based on Clinical Severity:

(See figure at end of document for schematic layout of algorithm)

Table 3:

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendation</th>
<th>Notes / Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hospitalized patients</td>
<td>All patients should receive standard prophylactic anticoagulation with LMWH in the absence of any contraindications⁹</td>
<td>For pregnant patients &gt;=20 weeks gestation, UFH is preferred to LMWH.</td>
</tr>
<tr>
<td>For patients with mild or moderate disease</td>
<td>Supportive care with close monitoring.</td>
<td>See Table 2 for list of risk factors.</td>
</tr>
<tr>
<td>Mild disease is defined as mild symptoms (e.g. fever, cough, change in taste or smell, no dyspnea).</td>
<td>Dexamethasone: Do not start dexamethasone unless the patient progresses to oxygen requirement (severe disease) or has an alternate indication for corticosteroids</td>
<td>A trend towards harm was seen in the sub-group of patients with the RECOVERY trial who were not on oxygen</td>
</tr>
<tr>
<td>Moderate disease is defined as clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation</td>
<td>Remdesivir: Remdesivir is not routinely recommended in this patient population at this time; consider on a case-by-case basis in people at high risk of clinical deterioration.</td>
<td>Remdesivir may have efficacy in moderate disease.</td>
</tr>
<tr>
<td></td>
<td>Application for a clinical trial. Please check link for basics of clinical trial inclusion and exclusion criteria.</td>
<td>A Spanish language video regarding clinical trials for patients and families is found at this link.</td>
</tr>
</tbody>
</table>

⁹ Contraindications include active bleeding or platelet count less than 25,000; monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication. If LMWH contraindicated due to renal failure (Creatinine Clearance <30mL/min), UFH can be used as an alternative. For clarifications, contact Rachel Rosovsky from Hematology, pager 37021.
For patients with severe* or critical disease

Severe disease is defined as SpO2 ≤ 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%

*For patients who are hypoxemic (SpO2 ≤ 94% on room air) but are at their baseline or who are hypoxemic due to other causes (such as volume overload), consider whether they should be classified as moderate for the purposes of COVID-19 therapy.

Critical disease is defined as ICU, respiratory failure, septic shock, and/or multiple organ dysfunction. Please also see ICU guidance.

<table>
<thead>
<tr>
<th>Remdesivir (RDV) is FDA approved for COVID-19 as of October 22, 2020 for adults and children ≥ 12 years of age and at least 40 Kg. MGB remdesivir policy is at this <a href="#">link</a>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Check eligibility and confirm eligible under MGB Guidance</td>
</tr>
<tr>
<td>2. Ensure PT, ALT, and eGFR are measured</td>
</tr>
<tr>
<td>3. Contact ID Approval pager 21884 to discuss candidacy and availability</td>
</tr>
<tr>
<td>4. If approved by ID, order via order panel.</td>
</tr>
<tr>
<td>5. Dosing of remdesivir is 200 mg IV loading dose following by 100 mg IV daily for a maximum of 5 days; extension to 10 days may be considered in certain patients, please consult ID to discuss.</td>
</tr>
<tr>
<td>6. Monitor ALT and eGFR daily, discuss with ID if eGFR &lt; 30 ml/min, discontinue RDV if ALT ≥ 10x ULN</td>
</tr>
</tbody>
</table>

RDV may be available through the clinical trial ACCT.

Key links regarding remdesivir:

- [Partners / MGB Remdesivir Guidance](#)
- [Info for providers](#)
- [Info for patients/families](#)
- [Educational slide set](#)

Assess for drug-drug interactions before starting. Discontinue remdesivir upon discharge regardless of duration.

<table>
<thead>
<tr>
<th>Dexamethasone at a dose of 6 mg PO / IV daily for up to 10 days is recommended for patients with an oxygen requirement and/or requiring mechanical ventilation. Greater benefit was observed for patients requiring mechanical ventilation compared to those receiving oxygen and for those with &gt;7 days of symptoms. Refer to Assess for drug-drug interactions before starting. Candidates for corticosteroids / immunomodulation with risk for endemic infections, click here. Discontinue dexamethasone upon discharge regardless of duration, unless previously...</th>
</tr>
</thead>
</table>

Dexamethasone at a dose of 6 mg PO / IV daily for up to 10 days is recommended for patients with an oxygen requirement and/or requiring mechanical ventilation. Greater benefit was observed for patients requiring mechanical ventilation compared to those receiving oxygen and for those with >7 days of symptoms. Refer to Assess for drug-drug interactions before starting. Candidates for corticosteroids / immunomodulation with risk for endemic infections, click here. Discontinue dexamethasone upon discharge regardless of duration, unless previously...
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with evidence of sHLH-like features</td>
<td>With ID input, <strong>anakinra</strong> (Kineret) can be considered</td>
<td>A Spanish language video regarding clinical trials for patients and families is found at this <a href="#">link</a>.</td>
</tr>
<tr>
<td>Patients with evidence of <strong>multisystem inflammatory syndrome</strong></td>
<td>Consult infectious diseases, consider rheumatology consult. Corticosteroids, IVIG and/or anakinra can be considered</td>
<td>Current case definition includes persons &lt;21 years of age but may occur at older ages.</td>
</tr>
<tr>
<td>Not recommended</td>
<td><strong>Hydroxychloroquine (HCQ)</strong> should not be initiated. Chloroquine has safety concerns and should not be used. Azithromycin and ivermectin are not proven as treatments for COVID-19. Only use azithromycin or ivermectin for other indications. Ribavirin, lopinavir/ritonavir, tocilizumab are not recommended</td>
<td>Chloroquine antagonizes remdesivir <em>in vitro</em> against RSV. Chloroquine and HCQ should not be co-administered with remdesivir. For QTc prolonging meds, check ECG prior to initiation given risk of QTc prolongation. Guidance for telemetry is found at this <a href="#">link</a>. Risk is increased in patients on other QTc-prolonging agents.</td>
</tr>
</tbody>
</table>
### Table 4: Special Populations

<table>
<thead>
<tr>
<th>Special Population</th>
<th>Recommendation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Protocols for treating non-pregnant women should be followed, unless there is an intervention specifically precluded by pregnancy. Multidisciplinary evaluation should include obstetric, infectious disease and critical care providers. Obstetricians, working with this team, will consider when in the context of a woman’s health status, fetal well-being and gestational age, delivery should be undertaken.</td>
<td>Physiology late in pregnancy and postpartum may potentially place women at risk for more rapid deterioration.</td>
</tr>
<tr>
<td>Corticosteroids:</td>
<td>After consultation with Maternal-Fetal Medicine, treatment with one of the alternative regimens may be considered. If there is concern for risk of preterm birth, betamethasone 12 mg IM q24 hours is the preferred regimen for that indication.</td>
<td>Dexamethasone has known fetal effects. See <a href="#">corticosteroid</a> section for alternative regimens (hydrocortisone, prednisone or methylprednisolone)</td>
</tr>
<tr>
<td>Remdesivir is available to pregnant persons as for non-pregnant persons. Nitric oxide therapy may be considered. Clinical guidelines are available at this link.</td>
<td>Compassionate use remdesivir is no longer available.</td>
<td></td>
</tr>
</tbody>
</table>
Adjunctive medications:
For DVT prophylaxis, pregnant women >=20 weeks gestation should receive unfractionated heparin rather than LMWH.
If antibiotics given for concern of bacterial pneumonia, azithromycin is preferred to doxycycline
On a case-by-case basis, may discuss statin use with the MFM service.

See [MGH hematology guidelines](#).
Azithromycin has better safety data in pregnancy compared to doxycycline
Limited data on IFN, tocilizumab

<table>
<thead>
<tr>
<th>Patients who are foreign-born from resource-limited countries (at risk for reactivation of tuberculosis or <em>Strongyloides</em>)</th>
<th>If receiving steroids or immunotherapy AND if no prior history of latent or active TB, please send T-Spot. Click <a href="#">here</a> for further management advice.</th>
<th>For <em>Strongyloides</em>, treat empirically with ivermectin for those receiving steroids and/or immunomodulation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who are experiencing homelessness, history of incarceration (at risk for tuberculosis reactivation)</td>
<td>If receiving steroids or immunotherapy AND if no prior history of latent or active TB, please send T-Spot and see below for further management advice.</td>
<td></td>
</tr>
<tr>
<td>Patients with underlying lung disease (including asthma or COPD of any severity, ILD, etc. Additional guidance for lung transplantation below)</td>
<td>Please consult Pulmonary for any PUI or COVID+ patient with underlying lung disease and either respiratory symptoms or the need for supplemental oxygen.</td>
<td>For inhaled corticosteroids, please discuss the risk / benefit of discontinuing this medication with Pulmonary.¹⁰</td>
</tr>
<tr>
<td>Patients with myasthenia gravis</td>
<td>Please contact outpatient neurologist or consult inpatient Neurology for any PUI or COVID+ patients with myasthenia gravis</td>
<td>Avoid azithromycin and HCQ in patients with myasthenia gravis; discuss risk / benefit of COVID-19 related medications with Neurology</td>
</tr>
<tr>
<td>People living with HIV</td>
<td><strong>Please call/consult Infectious Diseases. HIV with CD4 count</strong></td>
<td><a href="#">Resource for crushing HIV-medications</a></td>
</tr>
</tbody>
</table>

¹⁰ Discontinuation of inhaled steroids may precipitate exacerbation of underlying lung disease and there are no data to suggest that inhaled corticosteroids exacerbate COVID-related morbidity or mortality.
<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.

| If IgG <400 | Consider IVIG at dose of 25 grams x1 (unclear benefit) | Note: Titers against SARS-CoV-2 are likely to be low in the population |

For patients on biologic medications, disease-modifying anti-rheumatic drugs DMARDs, neurologic disease modifying therapies (DMTs) and other non-transplant immunosuppressive medications

| **Please contact the primary prescribing provider about management of the underlying condition and medications**
Do not abruptly stop prednisone for patients who are on long term prednisone; consider taper. | If the primary prescribing physician is unavailable, please contact the respective inpatient consult team
Abrupt cessation may precipitate a flare of underlying conditions |

| **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 transplant patients and reduce dose by 50% in heart transplant patients. Kidney patients approximate target tacrol 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 | Screen for drug-drug interactions with anti-viral agents, if they are being used |
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 for mild or moderate COVID-19; for severe COVID-19, consider dexamethasone and/or remdesivir.

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

<table>
<thead>
<tr>
<th>Lung transplant recipients</th>
<th><strong>Guided by transplant and transplant ID teams</strong> -please call/consult. Immunosuppression requires case-by-case approach.</th>
<th>Screen for <strong>drug-drug interactions</strong> with anti-viral agents, if they are being used</th>
</tr>
</thead>
</table>

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Table 5: Brief Overview of Agents Discussed

Note listing below does not indicate endorsement for use. For a more detailed overview of trials at MGH, please refer to the Apollo Clinical Trials page.

<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><strong>Antivirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>remdesivir</td>
<td>FDA-approved for adults and children 12 years of age and older and ≥ 40 Kg</td>
<td>RNA dependent RNA polymerase inhibitor</td>
<td>200 mg IV x1, then 100 mg IV daily, 5 days for most patients</td>
<td>Nausea, vomiting, ALT elevations</td>
</tr>
<tr>
<td>bamlanizimab</td>
<td>Investigational, emergency use authorization (high-risk outpatients)</td>
<td>Anti-spike antibody</td>
<td>700 mg IV over 1 hour</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>favipiravir</td>
<td>Investigational</td>
<td>RNA dependent RNA polymerase inhibitor</td>
<td>Oral, per study protocol</td>
<td>Elevated uric acid</td>
</tr>
<tr>
<td>hydroxychloroquine (Plaquenil)</td>
<td>Off-label, investigational</td>
<td>Multiple actions; prevents binding to ACE2, presents transport in endosome, and possibly others</td>
<td>400 mg PO BID x 2 doses, then 400 mg daily for a total 5 days</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>Off-label, investigational</td>
<td>Vasodilator, <em>in vitro</em> virucidal properties</td>
<td>Variable</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td><strong>Immune modulators:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamethasone (Decadron)</td>
<td>Off-label</td>
<td>Corticosteroid</td>
<td>6 mg PO/IV once daily for up to 10 days</td>
<td>Hyperglycemia, Avascular necrosis (rare) Reactivation of latent infections</td>
</tr>
<tr>
<td>tocilizumab (Actemra)</td>
<td>Off-label, investigational</td>
<td>Monoclonal antibody to IL6 receptor</td>
<td>Dosing for COVID/CRS to be determined</td>
<td>ALT elevations; decline in neutrophils, bowel perforation if history of diverticulitis</td>
</tr>
<tr>
<td>Drug</td>
<td>Label Status</td>
<td>Description</td>
<td>Dosing for COVID/CRS</td>
<td>Side Effects</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>sarilumab (Kevzara)</td>
<td>Off-label, investigational</td>
<td>Monoclonal antibody to IL-6 receptor</td>
<td>Dosing for COVID/CRS to be determined</td>
<td>ALT elevations; decline in neutrophils, bowel perforation if history of diverticulitis</td>
</tr>
<tr>
<td>ruxolitinib (Jakafi)</td>
<td>Investigational</td>
<td>Janus kinase inhibitor</td>
<td>10 mg BID for 14 days, possible extension to 28 days</td>
<td>Cytopenias, ALT elevations, increased infection risk including herpesvirus reactivation</td>
</tr>
<tr>
<td>baricitinib (Olumiant)</td>
<td>Investigational</td>
<td>Janus kinase inhibitor</td>
<td>Per research protocol</td>
<td>Cytopenias, ALT elevations, increased infection risk including herpesvirus reactivation</td>
</tr>
<tr>
<td>anakinra (Kineret)</td>
<td>Off-label</td>
<td>IL-1 receptor antagonist</td>
<td>Dosing for COVID/CRS to be determined</td>
<td>Injection site reactions, decline in neutrophils</td>
</tr>
</tbody>
</table>

**Selected adjunctive medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Label Status</th>
<th>Description</th>
<th>Dosing</th>
<th>Side Effects</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>
<tr>
<td>ivermectin (Stromectol)</td>
<td>FDA-approved</td>
<td>Treatment of Strongyloidiasis Not recommended for COVID-19</td>
<td>200 mcg/kg rounded to the nearest 3 mg x 1 (as tablets are 3 mg each), then repeat dose next day</td>
<td>Caution with those from filarial endemic areas (West or Central Africa) Maximum dose is 21 mg</td>
</tr>
</tbody>
</table>

Immune-Based Therapies

IVIG preparations would not be expected to have sufficient antibody titers against SARS-CoV-2 to offer effective passive immunity. Corticosteroids, IVIG and/or anakinra may be considered for adults who present with multisystem inflammatory syndrome.

The EUA for convalescent plasma is based on possible benefit and specifically states that it is not the standard of care for COVID-19. Given the lack of randomized trial data, at this time (September 17, 2020), convalescent plasma/sera/hyperimmune globulin products are not available for off-label administration at MGH. A clinical trial is available.

Specific neutralizing antibodies are under investigation. For hospitalized patients, trials of monoclonal antibodies were recently stopped by data safety monitoring boards as efficacy was unlikely to be seen. For outpatients, unpublished reports from RCTs of monoclonal antibodies suggest some benefit. Bamlanizimab is authorized for high-risk outpatients.

Modulating Host Immunity (tocilizumab, sarilumab, steroids)

*Background*: Cytokine profiles of serum from patients with severe infection with SARS-CoV-2 overlap with those seen in macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (sHLH). This response is also similar to CAR-T cell based immune side effects. Anti-IL-6 and other interventions have been of benefit for MAS, sHLH, and CAR-T cell toxicity. However, data regarding IL-6, IL-1, or other modulation for COVID-19 have yet to prove efficacy and the timing and efficacy of such treatments have not been determined.

- Dexamethasone is recommended for severe COVID-19.
- A benefit of the Janus kinase inhibitor baricitinib when added to remdesivir is suggested in a press release, but there are not enough data to recommend its use at this time.
- Data are mixed regarding the use of IL-6R blockade with sarilumab or tocilizumab; at this time there is insufficient evidence to warrant off-label use.
- For additional immunomodulatory therapies we strongly prefer that the team refer the patient to a clinical trial, if available. See link for details.
- A multidisciplinary team has convened to provide more clarity regarding off-label use for those who are not participating in clinical trials; please discuss with infectious diseases.
- Decisions regarding off-label use of immunomodulatory agents should be made with agreement of both the primary and recommending teams.
Infections, Steroids & Immunomodulation

Immunomodulation may be associated with increased risk of infections. Corticosteroids as part of the armamentarium of treatments for Covid-19 should be used according to the criteria used in the RECOVERY trial. Subspecialty consultation may be required when utilizing steroids for other indications. It is unknown whether data from longer term exposure from steroids or other immunomodulators can be extrapolated to the shorter term use associated with COVID-19.

Reactivation of viruses such as hepatitis B virus (HBV) or herpesviruses (HSV, CMV, VZV) may occur in patients receiving steroids or immunomodulation. Also, parasites such as Strongyloides and intracellular pathogens such as M. tuberculosis may activate years to decades after leaving countries with higher prevalence of these infections. COVID-19 related Strongyloides hyperinfection has been reported.

Screen for HBV: All patients with COVID-19 should be screened for active HBV with HBsAg regardless of country of origin. Contact ID or hepatology for guidance if receiving steroids/immunomodulatory therapy.

Empirically Treat Strongyloides: We favor empiric treatment in patients who are foreign-born (resource-limited settings) with ivermectin prior to steroids/immunotherapy rather than checking serology due to long turnaround times. Ivermectin is safe and recommended treatment is 1 dose of 200 ucg/kg rounded to nearest 3 mg increment PO x 1 (maximum dose 21 mg), then repeat the same dose a day later.

If a patient is West or Central African, do not give empiric ivermectin due to the potential rare complication of larva migration with certain filarial nematodes. Screen the patient with a microfilarial smear (order as a miscellaneous micro test, 2 large purple top tubes) to exclude concomitant high-titer filarial nematodes. If questions, email Dr. Rocio Hurtado (rhurtado@partners.org).

Note there is a report of in vitro inhibition of SARS-CoV-2 by ivermectin. It would require 50-100x standard dosing to achieve in vivo concentrations necessary to inhibit SARS-CoV-2. ivermectin is therefore not recommended for COVID-19.

Consider Tuberculosis: For patients who are foreign-born from resource-limited countries or for patients who are experiencing homelessness or have a history of incarceration, if there is no history of prior active TB disease or infection, we favor checking a T-spot prior to starting immunotherapy. Proceed with immunomodulation while that result is pending. Thus far, there are scant data but no indication that TB reactivation occurs more frequently during COVID-19 illness. If there are concerns for development of active TB disease during a hospital admission, please contact ID for further guidance.

If a patient at risk is considering or has started steroids or off-label immunomodulatory agent, or the patient is entering into a clinical trial of an immunomodulatory agent, please click here for a flowsheet that has more details and guidance. Apply algorithm even if the patient may be receiving a placebo.
When should I consult Infectious Diseases?

At MGH, Infectious Disease consultation is not necessary for most hospitalized patients with COVID-19.

All infection control issues should be referred to this page, which contains a comprehensive guide to CORAL (resolution of COVID-19 status), FAQs, and Whom to Call. Calls to the ID consult pager will be directly referred to this resource.
https://apollo.massgeneral.org/coronavirus/clinicians/infection-control/

Before paging / consulting, please examine relevant sections of this document before consulting ID. Reasons to contact ID for either advice or consultation for COVID-19 patients include:

- Hospital-associated infections for which ID evaluation would be helpful (e.g. VAP, HAP)
- Uncertainty whether an individual requires RDV (e.g. alternate explanation for hypoxemia)
- Relative contraindication to RDV when indicated (e.g. reduced eGFR)
- Pregnancy
- Concern for Multisystem Inflammatory Syndrome in Adults (MIS-A)
- New HIV infection
- Positive HBSAg and/or TB screening and candidate for dexamethasone / other immunomodulation (please read above section and consult algorithm before contacting)
- Concern for re-infection (documented positive test > 90 days prior to the current presentation with a compatible syndrome)
- Concern that persistent PCR positivity may represent prolonged illness in an immunocompromised patient
- Management of COVID-19 associated pulmonary aspergillus (CAPA)