



## Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance

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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.

[Table 1: Recommended laboratory work-up for hospitalized patients](#)

[Table 2: Risk stratification](#)

[Therapeutic recommendations \(bacterial / viral coinfections, ACEi/ARBs, NSAIDs\)](#)

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### What's New in the July 1, 2020 update:

- Additional information regarding dexamethasone, including more specific guidance regarding pregnant women guided by the Maternal-Fetal Medicine service
- Updates regarding remdesivir, which is no longer available after 10pm.



**Table 1: Work-up for diagnosis, prognosis / risk stratification, and/or safety of therapeutics Suggested for hospitalized patients with confirmed COVID-19<sup>1</sup>**

<p><u>Recommended daily labs (until stable):</u></p> <ul style="list-style-type: none"> <li>• CBC with diff (esp. total lymphocyte count)</li> <li>• Complete metabolic panel<sup>2</sup></li> <li>• CPK (creatine kinase)</li> <li>• Ferritin/CRP (first 2 wks of hospitalization)<sup>3</sup></li> </ul> <p><u>Recommended at baseline then every other day (if in ICU or elevated check daily):</u></p> <ul style="list-style-type: none"> <li>• PT/PTT/fibrinogen</li> <li>• D-dimer</li> </ul> <p>Link to <a href="#">Guidance from MGH Hematology</a></p>	<p><u>For acute kidney injury (i.e. serum creatinine &gt;0.3 above baseline)</u></p> <ul style="list-style-type: none"> <li>• Urinalysis and spot urine protein:creatinine</li> </ul> <p><u>When MAS/sHLH suspected (rising LFTs, falling fibrinogen, hypotension, see <a href="#">Immunomodulation</a>):</u></p> <ul style="list-style-type: none"> <li>• ESR</li> </ul> <p><u>Viral serologies for all patients unless done recently:</u><sup>4</sup></p> <ul style="list-style-type: none"> <li>• HBV serologies (sAb, cAb, and sAg)</li> <li>• HCV antibody, unless positive in past</li> <li>• HIV 1/2 Ab/Ag</li> </ul>
<p><u>For risk stratification:</u></p> <ul style="list-style-type: none"> <li>• LDH (repeat daily if elevated)</li> <li>• Troponin<sup>5</sup> (repeat q2-3d if elevated)</li> <li>• Baseline ECG (<a href="#">QTc monitoring algorithm</a>)</li> </ul> <p>With clinical deterioration, repeat risk stratification labs.</p>	<p><u>If clinically indicated:</u></p> <ul style="list-style-type: none"> <li>• Blood cultures (2 sets) if bacteria suspected</li> <li>• IL-6 if Category 2 or 3 risk factors</li> <li>• β-HCG for women of childbearing age</li> </ul>
<p><u>Radiology:</u></p> <ul style="list-style-type: none"> <li>• Portable CXR at admission</li> <li>• High threshold for PA/lateral, consider only if low suspicion for COVID-19 and result would change management or affect PUI status.</li> <li>• 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; <a href="#">check CORAL tool</a></li> </ul>	<p><u>Following infection control/PPE guidelines:</u></p> <ul style="list-style-type: none"> <li>• SARS-CoV-2 test, if not already performed.</li> <li>• Routine influenza A/B and RSV tests are not currently recommended. Routine expanded respiratory panels may be approved on a case-by-case basis.</li> <li>• If bacterial superinfection highly suspected, routine sputum for gram stain and culture, Legionella urinary antigen. If immunocompromised, see next page.</li> </ul>

<sup>1</sup> 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](#)

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

<sup>3</sup> If beyond 2 weeks hospital stay, inflammatory markers are hard to interpret. Repeat per discretion of primary team.

<sup>4</sup> 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

<sup>5</sup> 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.



**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 steroids 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](#).

**Determine severity and prognosis of patients admitted with COVID-19.** 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), or critical (ICU). These definitions vary in the literature.

**Table 2: Risk Factors for COVID-19 Disease Progression**

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

\*Not yet proven as risk factors for progression, inferred from other infections. Other factors include poverty, racism, recent cancer chemotherapy, recent surgery, pregnancy. For more information about COVID-19 severity, see our [supporting risk factors document](#).



## Medication considerations:

### Anti-infectives

- **Routine empiric antibiotics are not recommended.** MGH has detected low rates of bacterial superinfection in COVID-19 patients, consistent with studies from other centers.<sup>6</sup> Unnecessary antibiotic use increases the risk of multi-drug resistant organisms and *C. difficile*.

<p><b>Does not favor antibiotics:</b>          COVID-19 confirmed / high likelihood          CXR: Peripheral / bilateral infiltrates          Baseline PCT &lt; 0.2          Non-ICU admission</p>	<p><b>Favor empiric antibiotics:</b>          COVID-19 not yet established          CXR: Lobar infiltrate          Baseline PCT ≥ 0.2          ICU admission</p>	<p><b>Recommend:</b>          Sputum GS &amp; culture &amp; Legionella urinary antigen          ceftriaxone 1 gm IV QD + doxycycline 100 mg PO BID          (azithromycin is alternative to doxycycline)          ICU/sepsis: consider MRSA / MDRO coverage</p>
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- If empiric **antibiotics** are given, recommend:
  - Ceftriaxone 1 gm IV daily + either doxycycline 100 mg PO BID 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, duration is 5 days. May discontinue if concern for bacterial pneumonia low (confirmation of 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.<sup>7</sup>

### 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.

<sup>6</sup> [He et al, Infect Control Hosp Epidemiol, 2020; Zhou et al, Infect Control Hosp Epidemiol, 2020; Rawson et al, Clin Infect Dis, 2020](#)

<sup>7</sup> 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, if indicated, 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](#).
- For those who have a guideline indication for a statin and no contraindication (eg. pregnancy), consider starting atorvastatin 40 mg daily. When major drug-drug interactions with atorvastatin are expected, pitavastatin 4 mg daily (or pravastatin 80mg daily if pitavastatin not available) are alternatives. If already on a statin, no need to change to these agents. If elevated CPK  $\geq$  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  $\geq$ 20 weeks gestation who should receive unfractionated heparin.** Please see link for further [guidance from MGH Hematology](#)

### **Other medications:**

- 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.** Nebulization risks aerosolization of virus. If nebulized medications given, use appropriate PPE. For those without pre-existing pulmonary disease, avoid inhaled steroids as they may reduce local immunity and promote viral replication.
- **Systemic steroids.** See discussion under COVID-19 specific management in the next section regarding dexamethasone, which is recommended to patients on oxygen support but avoided for patients with mild or moderate disease (no oxygen support). Steroids 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 steroids, discuss with prescribing physician the management of the underlying condition and whether / how to continue steroids while hospitalized.





### **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. 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.

**Remdesivir (RDV): Remdesivir is recommended for severe disease under an emergency use authorization by the FDA.** RDV is currently available at MGH via the algorithm below. RDV may also be available via compassionate use for pregnant women / children < 18 years of age who do not meet emergency use authorization criteria.

Data regarding remdesivir include an underpowered [trial from China](#) with negative results and a [large randomized control trial](#) showing efficacy in reducing hospital stay and a trend toward mortality benefit.

### **Under the emergency use authorization (EUA) and the Partners Allocation Plan, remdesivir may be used only to treat:**

- Adults, children ( $\geq 3.5$ Kg) and pregnant woman with laboratory confirmed COVID-19, **AND**
- Hospitalized patients with severe COVID-19 defined as one of the following.
  - $SpO_2 \leq 94\%$  on room air
  - Requiring supplemental oxygen
  - Mechanical ventilation
  - Extracorporeal membrane oxygenation (ECMO)

Remdesivir should not be initiated or should be stopped if ALT is  $\geq 5x$  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 mild / moderate COVID-19 with remdesivir is not currently recommended. Critical disease is defined as mechanical ventilation or ECMO.

Remdesivir under the emergency use authorization has been offered to patients eligible per criteria available at this [link](#). To discuss new starts of remdesivir: 1) check eligibility at that link; then 2) please contact Infectious Diseases. See detailed checklist below.

To access RDV via compassionate use for pregnant or pediatric patients who do not meet EUA criteria, use this portal.

Due to safety issues with RDV, need for mixture and preparation in the clinical trials pharmacy, need for different formulations for different patient populations, as well as government requirements for documentation of assent, we are not initiating RDV after 10pm.



**Dexamethasone is recommended for hospitalized patients with severe COVID-19 (requiring supplementary oxygen).** Systemic steroids should be avoided for patients with mild or moderate disease (no oxygen support) unless there is another indication.

A [preliminary 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 0.65,  $p < 0.001$ ) than in those on supplemental oxygen (RR 0.80,  $p = 0.002$ ), with a non-statistically significant trend towards harm in those not on oxygen (RR 1.22,  $p = 0.14$ ). The report is not yet peer-reviewed.

Notes for use at MGH:

- Both PO and IV formulations of dexamethasone 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 recent [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.

Steroid 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.



**Suggested Treatment Algorithm Based on Clinical Severity:**

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

**Table 3:**

<b>Clinical Situation</b>	<b>Recommendation</b>	<b>Notes / Considerations</b>
All hospitalized patients	All patients should receive standard prophylactic anticoagulation with LMWH in the absence of any contraindications <sup>8</sup>	For pregnant patients $\geq 20$ weeks gestation, UFH is preferred to LMWH.
For patients with mild or moderate disease	Supportive care with close monitoring.	See <a href="#">Table 2</a> for list of risk factors
	<b>Dexamethasone:</b> Do not start dexamethasone unless the patient progresses to oxygen requirement (severe disease) or has an alternate indication for corticosteroids	A trend towards harm was seen in the sub-group of patients with the RECOVERY trial who were not on oxygen
	<b>Remdesivir:</b> Remdesivir is not recommended in this patient population at this time.	While a <a href="#">press release</a> has announced that remdesivir has efficacy in moderate disease, the emergency use authorization does not permit use in this population.
	Application for a clinical trial. Please check <a href="#">link</a> for basics of clinical trial inclusion and exclusion criteria.	A Spanish language video regarding clinical trials for patients and families is found at this <a href="#">link</a> .

<sup>8</sup> 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  $< 30$  mL/min), UFH can be used as an alternative. For clarifications, contact Rachel Rosovsky from Hematology, pager [37021](#).





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<p>For patients with severe or critical disease</p>	<p><b><u>Remdesivir</u></b> (RDV) was authorized by the FDA for emergency use, but is in limited supply. Partners allocation plan is at this <a href="#">link</a>.</p> <ol style="list-style-type: none"><li>1. <a href="#">Check eligibility and confirm eligible under Partners / MGB allocation strategy</a></li><li>2. Contact ID to discuss candidacy and availability</li><li>3. If approved by ID, download information sheet for patients and families. Spanish version available.</li><li>4. Obtain assent from the patient or designated proxy and record in chart.</li><li>5. After provider has obtained and documented assent may write order. Dosing of remdesivir is 200 mg IV loading dose following by 100 mg IV daily for a maximum of 5 days; criteria for extension to be determined once a stable supply is established. Remdesivir EUA is an order panel and requires ID approval.</li><li>6. Monitor ALT and eGFR daily, discuss with ID if eGFR &lt; 30 ml/min, discontinue RDV if ALT <math>\geq</math> 5x ULN</li></ol>	<p>RDV remains available via compassionate use for pregnant or pediatric patients via this <a href="#">portal</a>.</p> <p>RDV is also available through the clinical trial ACCT-2, which randomizes patients to RDV + placebo vs. RDV + baricitinib.</p> <p>Key links regarding remdesivir:</p> <ul style="list-style-type: none"><li>• <a href="#">Partners / MGB allocation plan</a></li><li>• <a href="#">Info for providers</a></li><li>• <a href="#">Info for patients/families English</a> or <a href="#">Spanish</a></li><li>• <a href="#">Educational slideset</a></li></ul> <p>Assess for <a href="#">drug-drug interactions</a> before starting.</p> <p>Discontinue remdesivir upon discharge regardless of duration</p>
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	<p><b>Dexamethasone</b> at a dose of 6 mg PO / IV for up to 10 days is recommended for patients with an oxygen requirement and/or requiring mechanical ventilation.</p> <p>Greater benefit was observed for patients requiring mechanical ventilation compared to those receiving oxygen. Refer to critical care guidelines for patients in ICU</p>	<p>Assess for <a href="#">drug-drug interactions</a> before starting.</p> <p>Candidates for steroids / immunomodulation with risk for endemic infections, click <a href="#">here</a>.</p> <p>Discontinue dexamethasone upon discharge regardless of duration, unless previously used as maintenance medications for another indication or continuation required as part of a clinical protocol/trial.</p>
	<p>Application for a clinical trial. Please check <a href="#">link</a> for basics of clinical trial inclusion and exclusion criteria.</p>	<p>A Spanish language video regarding clinical trials for patients and families is found at this <a href="#">link</a>.</p>
<p>For patients with evidence of <a href="#">cytokine release syndrome</a></p>	<p>With ID input, <a href="#">tocilizumab</a> (Actemra) can be considered</p>	<p>Send serum IL-6 level prior to giving first dose of tocilizumab</p>
<p>For patients with evidence of sHLH-like features</p>	<p>With ID input, <a href="#">anakinra</a> (Kineret) can be considered</p>	
<p>For patients with evidence of <a href="#">multisystem inflammatory syndrome</a></p>	<p>Consult infectious diseases, consider rheumatology consult. Steroids, IVIG and/or anakinra can be considered</p>	<p>Current case definition includes persons &lt;21 years of age but may occur at older ages.</p>
<p>Not recommended</p>	<p><a href="#">Hydroxychloroquine (HCQ)</a> should not be initiated outside of a clinical trial. Chloroquine has activity but safety concerns and should not be used.</p> <p><b>Azithromycin</b> and ivermectin are not proven as treatments for</p>	<p>Chloroquine antagonizes remdesivir <i>in vitro</i> against RSV. Chloroquine and HCQ should not be co-administered with remdesivir.</p>



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	<p>COVID-19. Only use azithromycin or ivermectin for other indications.</p> <p>Ribavirin, lopinavir/ritonavir are not recommended</p>	<p>For HCQ or other 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. Consider discharge monitoring for arrhythmia via mobile cardiac telemetry via the EP/Holter service.</p>
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**Table 4: Special Populations**

Special Population	Recommendation	Notes
Pregnancy	<p>Protocols for treating non-pregnant women should be followed, unless there is an intervention specifically precluded by pregnancy.</p> <p>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.</p>	<p>Physiology late in pregnancy and postpartum may potentially place women at risk for more rapid deterioration.</p>
	<p>Steroids: 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.</p>	<p>Dexamethasone has known fetal effects. See <a href="#">steroid</a> section for alternative regimens (hydrocortisone, prednisone or methylprednisolone)</p>
	<p>Remdesivir is available to pregnant women and children through EUA as well as through compassionate use. For compassionate use, apply through portal: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a></p> <p>Nitric oxide therapy may be considered. Clinical guidelines are available at this <a href="#">link</a>.</p>	<p>We are monitoring whether compassionate use remdesivir remains available</p>



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	<p><b>Adjunctive medications:</b></p> <p>For DVT prophylaxis, pregnant women <math>\geq 20</math> weeks gestation should receive unfractionated heparin rather than LMWH.</p> <p>If antibiotics given for concern of bacterial pneumonia, azithromycin is preferred to doxycycline</p> <p>On a case-by-case basis, may discuss statin use with the MFM service.</p>	<p>See <a href="#">MGH hematology guidelines</a></p> <p>Azithromycin has better safety data in pregnancy compared to doxycycline</p> <p>Limited data on IFN, tocilizumab</p>
Patients who are foreign-born from resource-limited countries (at risk for reactivation of tuberculosis or <i>Strongyloides</i> )	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.	For <i>Strongyloides</i> , treat empirically with ivermectin for those receiving steroids and/or immunomodulation.
Patients who are experiencing homelessness, history of incarceration (at risk for tuberculosis reactivation)	If receiving steroids or immunotherapy AND if no prior history of latent or active TB, please send T-Spot and click here for further management advice.	
Patients with underlying lung disease (including asthma or COPD of any severity, ILD, etc. Additional guidance for <a href="#">lung transplantation</a> below)	Please consult Pulmonary for any PUI or COVID+ patient with underlying lung disease and either respiratory symptoms or the need for supplemental oxygen.	For inhaled corticosteroids, please discuss the risk / benefit of discontinuing this medication with Pulmonary. <sup>9</sup>
Patients with myasthenia gravis	Please contact outpatient neurologist or consult inpatient Neurology for any PUI or COVID+ patients with myasthenia gravis	Avoid azithromycin and HCQ in patients with myasthenia gravis; discuss risk / benefit of COVID-19 related medications with Neurology
People living with HIV	<b>Please call/consult Infectious Diseases.</b> HIV with CD4 count	<a href="#">Resource for crushing HIV-medications</a>

<sup>9</sup> 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.





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	<p>&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.</p>	<p><a href="#">medications for intubated patients</a></p> <p><a href="#">Resource for ARV drug-drug interactions</a></p>
<p>If IgG &lt;400</p>	<p>Consider IVIG at dose of 25 grams x1 (unclear benefit)</p>	<p>Note: Titers against SARS-CoV-2 are likely to be low in the population</p>
<p>For patients on biologic medications, disease-modifying anti-rheumatic drugs DMARDs, neurologic disease modifying therapies (DMTs) and other non-transplant immunosuppressive medications</p>	<p><b>Please contact the primary prescribing provider about management of the underlying condition and medications</b></p> <p>Do not abruptly stop prednisone for patients who are on long term prednisone; consider taper.</p>	<p>If the primary prescribing physician is unavailable, please contact the respective inpatient consult team</p> <p>Abrupt cessation may precipitate a flare of underlying conditions</p>
<p>Heart/Liver/Kidney Transplant Recipients</p>	<p><b>Guided by transplant and transplant ID teams – please call/consult</b></p> <p>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 tacro level 3-5 ng/ml, cyclosporine level target 25-50 ng/ml.</p> <p>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</p>	<p>Screen for <a href="#">drug-drug interactions</a> with anti-viral agents, if they are being used</p>



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	<p>Critical illness – in liver and kidney – stop all immunosuppression except for prednisone if they are on it at baseline</p> <p>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.</p> <p>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.</p> <p>Continue low dose prednisone (5 mg) in all patients who were on it before hospitalization.</p> <p>Request bronchoscopy only if significant decompensation, versus lung biopsy as may be lower risk for aerosolization and exposure to staff</p>	
<p>Lung transplant recipients</p>	<p><b>Guided by transplant and transplant ID teams -please call/consult.</b> These are guidelines only, immunosuppression requires case-by-case approach.</p> <p>No change to usual immunosuppression (avoid high levels, tailor to patient)</p> <p>For all those in ICU or with lower respiratory tract disease (most inpatients): pulse</p>	<p>Screen for <a href="#">drug-drug interactions</a> with anti-viral agents, if they are being used</p>



	<p>methylprednisolone 125mg IV q 12 hours</p> <p>Outpatient management: prednisone taper 60mg x 4 days -- 40mg x 4 days – 20mg x 4 days then back to baseline</p>	
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**Postexposure Prophylaxis for Healthcare Workers:**

- There is currently no proven role for post exposure prophylaxis for people with a known COVID-19 exposure. No benefit of hydroxychloroquine was seen in a [double-blinded placebo randomized controlled trial](#). Healthcare workers should follow instructions from Occupational Health.



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

For a more detailed overview of trials at MGH, please refer to the [Apollo Clinical Trials page](#).

<b>Agent</b> (link to package insert)	<b>Classification</b>	<b>Target / Mechanism</b>	<b>Dosing</b>	<b>Key toxicities</b>
<b>Antivirals</b>				
<b>remdesivir</b>	Investigational, emergency use authorization	RNA dependent RNA polymerase inhibitor	200 mg IV x1, then 100 mg IV daily, 5 days for most patients	Nausea, vomiting, ALT elevations
<b>favipiravir</b>	Investigational	RNA dependent RNA polymerase inhibitor	Oral, per study protocol	Elevated uric acid
<a href="#">hydroxychloroquine (Plaquenil)</a>	Off-label, investigational	Multiple actions; prevents binding to ACE2, prevents transport in endosome, and possibly others	400 mg PO BID x 2 doses, then 400 mg daily for a total 5 days	QTc prolongation
Inhaled nitric oxide	Off-label, investigational	Vasodilator, <i>in vitro</i> virucidal properties	Variable	Methemoglobinemia
<b>Immune modulators:</b>				
<a href="#">dexamethasone (Decadron)</a>	Off-label	Corticosteroid	6 mg PO/IV once daily for up to 10 days	Hyperglycemia Avascular necrosis (rare) Reactivation of latent infections
<a href="#">tocilizumab (Actemra)</a>	Off-label, investigational	Monoclonal antibody to IL6 receptor	Dosing for COVID/CRS to be determined	ALT elevations; decline in neutrophils, bowel perforation if history of diverticulitis
<a href="#">sarilumab (Kevzara)</a>	Off-label, investigational	Monoclonal antibody to IL-6 receptor	Dosing for COVID/CRS to be determined	ALT elevations; decline in neutrophils, bowel perforation if history of diverticulitis
<a href="#">ruxolitinib (Jakafi)</a>	Investigational	Janus kinase inhibitor	10 mg BID for 14 days, possible extension to 28 days	Cytopenias, ALT elevations, increased infection risk including herpesvirus reactivation
<a href="#">baricitinib (Olumiant)</a>	Investigational	Janus kinase inhibitor	Per research protocol	Cytopenias, ALT elevations, increased



				infection risk including herpesvirus reactivation
<a href="#">anakinra (Kineret)</a>	Off-label	IL-1 receptor antagonist	Dosing for COVID/CRS to be determined	Injection site reactions, decline in neutrophils
<b>Selected adjunctive medications</b>				
<a href="#">atorvastatin (Lipitor)</a>	Off-label	Cardioprotection; immunomodulatory	40-80 mg PO daily	Avoid if using LPV/r
<a href="#">pravastatin (Pravachol)</a>	Off-label	Cardioprotection; immunomodulatory	80 mg PO daily	
<a href="#">ivermectin (Stromectol)</a>	FDA-approved	Treatment of Strongyloidiasis Not recommended for COVID-19	200 mcg/kg rounded to the nearest 3 mg x 1 (as tablets are 3 mg each), then repeat dose next day	Caution with those from filarial endemic areas (West or Central Africa) Maximum dose is 21 mg

Liverpool COVID-19 Drug Interactions: <http://www.covid19-druginteractions.org/>





## **Immune-Based Therapies**

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

At this time (June 15, 2020), **convalescent plasma/sera/hyperimmune globulin** products are not available for administration at MGH. A clinical trial is planned.

Specific neutralizing antibodies are under investigation, including a trial at MGH (contact site PI: Michael Dougan).

### **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 are limited at this time and the timing and efficacy of such treatments have not been determined.

- **Dexamethasone is recommended for severe COVID-19.**
- 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. While steroids should generally be avoided unless there is another indication, the risk of using other immunomodulatory agents during infection with SARS-CoV-2 has not been established. Also, it is unknown whether data from longer term exposure can be extrapolated to the shorter term use associated with treatments for COVID-19.

Reactivations for 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.

**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.

***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 mcg/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 larval 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](mailto: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 not recommended for COVID-19.**

**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.**



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\*: See risk factors table (Table 2) in this document  
 †: Current list of clinical trials is found at this link.  
 ID strongly recommends referral to clinical trials  
 ‡: Guidance from ID regarding off-label use of immunomodulators or compassionate / emergency use remdesivir is available 8am to 8pm  
 § : Clinical trials may include RDV, may specifically exclude RDV or allow for open label RDV from EUA or compassionate use. If the trial excludes RDV, the patient may or may not decide to de-enroll should they qualify under the EUA  
 ❖ . If not on RDV (eg declined or not qualified earlier in admission), regardless of clinical trial enrollment status, patient may be reconsidered for RDV should they qualify under the EUA.

