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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.

MASSACHUSETTS GENERAL HOSPITAL

Table 1: Laboratories for diagnosis, prognosis / risk stratification, and/or safety of agents Suggested for hospitalized patients with confirmed or suspected COVID-19[1]	
Recommended daily labs: • CBC with diff (esp. total lymphocyte count) • Complete metabolic panel[2] • CPK (creatine kinase) • Ferritin/CRP/ESR Recommended every other day (if in ICU or elevated check daily): • PT/PTT/fibrinogen[3] • D-dimer	Viral serologies:[4] • HBV serologies (sAb, cAb, and sAg) • HCV antibody, unless positive in past • HIV 1/2 Ab/Ag
For risk stratification: • LDH (repeat daily if elevated) • Troponin[5] (repeat q2-3d if elevated) • Baseline ECG (guidance for QTc below)[6] With clinical deterioration, repeat risk stratification labs even if baseline was previously normal.	If clinically indicated: • Routine blood cultures (2 sets) • For acute kidney injury (i.e. serum creatinine >0.3 above baseline), send urinalysis and spot urine protein:creatinine • Procalcitonin • IL-6* if Category 2 or 3 risk factors
Radiology: • Portable CXR at admission • High threshold for PA/lateral in ambulatory patients, 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	**Following up-to-date infection control guidelines and appropriate PPE**: • SARS-CoV-2 test, if not already performed.[7] • Routine influenza A/B and RSV tests are no longer recommended based on low current prevalence. • Routine expanded respiratory panels are also not recommended, but may be approved on a case-by-case basis."

[1] The prognostic value of some of these labs is being defined or is not yet proven
[2] For a primer on liver issues related to COVID19 and treatment, please see our supporting liver document.
[3] Guidance from MGH Hematology
[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] 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..
[6] If starting QTc prolonging drug, please see QTc monitoring algorithm.
[7] Please refer to COVID-19 Testing Criteria

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	• As indicated, routine sputum for bacterial gram stain and culture, Legionella/*Strep pneumo* urinary antigen

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:

- Due to low rates of coinfection at MGH, we do not recommend starting oseltamivir on most patients with COVID-19 at this time. If a known flu contact or high suspicion for flu, can start oseltamivir 75 mg BID in adult patients with normal renal function (and request approval for flu A/B PCR and stop oseltamivir if negative)
  - Adjust for pediatric patients and those with renal insufficiency
- Considerations for empiric treatment for bacterial pneumonia if clinically suspected:
  - 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.

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.

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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.

At this time (April 1, 2020), **convalescent plasma/sera/hyperimmune globulin** products are not available for administration at MGH.

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. See FDA statement on NSAIDs dated 3/19/20.

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).
- For those without pre-existing pulmonary disease, avoid inhaled steroids as they may reduce local immunity and promote viral replication.
- **At this time, we do not recommend starting ACEi / ARBs or ribavirin for COVID-19**

Identify High Risk Patients: High risk features may include:

Table 2: Risk Factors for COVID-19 Disease Progression

Epidemiological – Category 1	*Vital Signs – Category 2*	*Labs – Category 3*
Age > 55	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 ≤ 93% 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
Use of biologics*		Ferritin > 500 ug/L
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.

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

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

Table 3:

Clinical Situation	Recommendation	Notes / Considerations
All hospitalized patients	Continue statins if already prescribed. If no contraindication, and for those who have a guideline indication for a statin, consider starting: atorvastatin 40 mg daily[8] When major drug-drug interactions with atorvastatin are expected, pitavastatin 4 mg daily (or pravastatin 80mg daily if pitavastatin not available) are alternatives[9] See statement above regarding NSAIDs. Acetaminophen is the suggested first-line anti-pyretic, unless unsuitable. If NSAIDs are used, lowest effective dose is suggested. All patients should receive standard prophylactic anticoagulation with LMWH in the absence of any contraindications[10]	Note cardiovascular disease is a major risk factor for COVID-19 disease severity. Additionally, statins may help promote antiviral innate immune response. If elevated CPK >/= 500 U/L, consider not starting a statin Avoid initiation of statins if ALT > 3x upper limit of normal For a brief discussion of statins and immunity, see our statin rationale document.
For patients with no Category 2 or 3 risk factors for severe disease	Supportive care with close monitoring and consideration of application for clinical trial of remdesivir (see below)	See Table 2 for list of risk factors

[8] Simvastatin was studied in ARDS https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201750/
[9] If already on a statin, no need to change to these agents
[10] 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 (Creatine Clearance <30mL/min), UFH can be used as an alternative. For clarificaitons, contact Rachel Rosovsky, pager 37021.

MASSACHUSETTS GENERAL HOSPITAL

For patients with moderate or severe disease, i.e. patients with any Category 2/3 feature (regardless of age or other category 1 features)	Application for **remdesivir** (RDV) through a clinical trial or, through compassionate use.[11] Current dosing of remdesivir is 200 mg IV loading dose following by 100 mg IV daily for up to 10 days. Application for **sarilumab** through a clinical trial. Please check FAQ for basics of clinical trial inclusion and exclusion criteria. With guidance from Infectious Diseases, can consider adding **hydroxychloroquine** **(HCQ)** (400 mg PO BID x2 followed by 400 mg daily while hospitalized, up to 5 days).[12] Note chloroquine has activity but limited supply so hydroxychloroquine preferred. **Lopinavir/ritonavir**[13] (LPV/r or Kaletra) is generally not recommended. Avoid if candidate for RDV trial. **Darunavir/cobicistat** (DRV/c or Prezcobix) is generally not recommended.	RDV is only currently available via compassionate use for pregnant or pediatric patients. Expanded use of RDV is not available at MGH due to participation in a clinical trial. Check ECG prior to initiation given risk of QTc prolongation. Risk is increased in patients on other QTc-prolonging agents. Assess for drug-drug interactions (including with calcineurin inhibitors) before starting. For protease inhibitors, main side effect is gastrointestinal intolerance. Monitor liver function tests while on therapy. Discontinue these agents upon discharge regardless of duration, unless previously used as

[11] Please check the portal for exclusion/inclusion criteria to see if remdisivir compassionate use is an option.
[12] HCQ has a long half-life. If the patient is improving, there is no need to complete the 5 day course. See FAQ.
[13] Based on a published report in NEJM 3/19/20, lopinavir/ritonavir's role in COVID-19 is likely very limited

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		maintenance medications for another indication.
For patients with evidence of cytokine release syndrome	With ID input, **tocilizumab** (Actemra) can be considered	Send serum IL-6 level prior to giving first dose of tocilizumab

Table 4: Special Populations

Special Population	Recommendation	Notes
Pregnancy	Do not use statins Remdesivir available through compassionate use for pregnant patients and children only. For compassionate use, apply through portal here: https://rdvcu.gilead.com/ No contraindication to hydroxychloroquine, lopinavir/ritonavir, azithromycin Limited data on IFN, tocilizumab	Remdesivir: Pregnancy an exclusion for clinical trial Manage with MFM / Perinatal ID
For patients with underlying lung disease (including asthma or COPD of any severity, ILD, etc. Additional guidance for lung transplantation 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.[14]
People living with HIV	HIV with CD4 count <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	Avoid LPV/r monotherapy in people with HIV Resource for crushing HIV-medications medications for intubated patients

[14] 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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	higher risk for complications regardless of CD4 cell count.	Resource for ARV drug-drug interactions
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
Heart/Liver/Kidney Transplant Recipients	**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 tacro 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.	Screen for drug-drug interactions with anti-viral agents, if they are being used

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	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 Occupational Health.

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Table 5: Brief Overview of Agents Discussed

Agent (link to package insert)	**Classification**	**Target / Mechanism**	**Dosing**	**Key toxicities**
remdesivir	Investigational	RNA dependent RNA polymerase inhibitor	200 mg IV x1, then 100 mg IV daily, up to 10 days	Nausea, vomiting, ALT elevations
hydroxychloroquine **(Plaquenil)**	Off-label	Multiple actions; prevents binding to ACE2, presents transport in endosome, and possibly others	400 mg BID x 2 doses, then 400 mg daily for a total 5 days	QTc prolongation
lopinavir/ritonavir (LPV/r or Kaletra)	Off-label	3CLpro (viral protease) inhibitor	400/100 mg BID for up to 10 days	QTc prolongation, ALT elevations
tocilizumab (Actemra)	Off-label	Monoclonal antibody to IL6 receptor / treats cytokine release syndrome	Dosing for COVID/CRS to be determined	ALT elevations
sarilumab **(Kevzara)**	Off-label, investigational	Monoclonal antibody to IL-6 receptor	Dosing for COVID/CRS to be determined	ALT elevations
atorvastatin (Lipitor)	Off-label	Cardioprotection; immunomodulatory	40-80 mg PO daily	Avoid if using LPV/r
pravastatin (Pravachol)	Off-label	Cardioprotection; immunomodulatory	80 mg PO daily	

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

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Modulating Host Immunity (tocilizumab, sarilumab, steroids)

Background: Cytokine profiles of serum from patients with severe infection with SARS-CoV-2 infection 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.

- For immunomodulatory therapies we strongly prefer that the team refer the patient to a clinical trial, if available. At MGH, a randomized controlled trial has opened for sarilumab, see FAQ for details.
- 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 a future update.
- Decisions regarding off-label use of immunomodulatory agents should be made with agreement of both the primary and recommending teams.

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a: See risk factors table (Table 2) in this document
b: Current list of clinical trials as of 4/1/20 is contained in the FAQ