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Massachusetts General Hospital
COVID-19 Treatment Guidance

- 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 patients with COVID-19.
- This document covers potential off-label and/or experimental use of medications and immunosuppression management for transplant patients as well as a suggested laboratory work up. It does NOT cover recommendations for infection control, PPE, management of hypoxemia or other complications in patients with COVID-19.
- This is a living document that will be updated in real time as more data emerge.

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

Suggested for all hospitalized patients with confirmed or suspected COVID-19

Recommended daily labs: • CBC with diff (trend total lymphocyte count) • Complete metabolic panel[1] • CPK (creatine kinase)	Viral serologies:[2] • HBV serologies (sAb, cAb, and sAg) • HCV antibody, unless positive in past • HIV 1/2 Ab/Ag
For risk stratification (may be repeated q2-3 days if abnormal or with clinical deterioration): • D-dimer • Ferritin / CRP / ESR • LDH • Troponin[3] • Baseline ECG[4]	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 See below for criteria
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.	**Following up-to-date infection control guidelines and appropriate PPE**: • SARS-CoV-2 test, if not already performed.[5] • If available, send influenza A/B and RSV test

[1] For a primer on liver issues related to COVID19 and treatment, please seek link.
[2] Viral serologies assist for interpretation of ALT elevations, present in ~25% of presentations. Lopinavir/ritonavir should not be used as the sole agent if HIV positive. Active viral hepatitis increases risk of hepatotoxicity due to lopinavir/ritonavir. Note: follow-up molecular testing for HIV/HBV/HCV may have longer turnaround times than usual
[3] Elevated troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours; echocardiogram not necessary unless otherwise indicated. Up-trending troponin with hemodynamic compromise or other concerning cardiovascular symptoms /signs should prompt consideration of obtaining an echocardiogram..
[4] If starting QTc prolonging drug, can repeat ECG in 24-48 hours to monitor QTc. If baseline QTc > 500, repeat within 24 hours and consider stopping other QTc prolonging drugs.
[5] Approval for SARS-CoV-2 may be obtained through the MGH Biothreats Pager, 26876

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• 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	• If available, send respiratory viral panel on all patients (includes human metapneumovirus and parainfluenza 1-3) • 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:

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

    Ceftriaxone 1 g [or cefepime if MDRO risk factors]
    +
    Azithromycin 500 mg x1, then 250 mg daily x 4 days
    +
    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 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.[6]

Not recommended

- **Systemic steroids should in general be *AVOIDED* for these patients given potential harm.** Steroids may be considered if indicated for another reason (e.g. refractory septic shock, or specific to lung transplant guidelines, as delineated below)
  Note: Consider discontinuation of inhaled steroids as they may reduce local immunity and promote viral replication, unless necessary for acute indications
- **At this time, we do not recommend starting ACEi / ARBs or ribavirin for COVID-19**
- **There are reports of NSAID use preceding clinical deterioration in some patients with severe COVID-19 disease. We recommend frontline providers assess and document recent NSAID use and avoid prescribing NSAIDs while patients are admitted**

Identify High Risk Patients: High risk features may include:

Table 2: Risk Factors for Severe COVID-19 Disease

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 < 90% on ambient air	CRP > 100
Diabetes with A1c > 7.6%		LDH > 245 U/L
History of hypertension		Elevated troponin
History of cardiovascular disease		Admission absolute lymphocyte count < 0.8
Use of biologics		Ferritin > 300 ug/L
History of transplant or other immunosuppression		
All patients with HIV (regardless of CD4 count)		

For more information about COVID19 Risk Factors, click here.

[6] The infectious disease consult service is actively discussing how to meet the needs of frontline clinicians. More information to follow.

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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 or rosuvastatin 20 mg daily When major drug-drug interactions with atorvastatin or rosuvastatin are expected, pitavastatin 2 mg daily (or pravastatin 80mg daily if pitavastatin not available) should be considered [7] Avoid NSAIDs	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 statins if ALT > 3x upper limit of normal For a brief discussion of statins and immunity, click here.
For patients with mild disease with SpO2 >90%, no risk factors	Supportive care	See Table 2 for list of risk factors
For patients with mild disease with SpO2 >90% along with risk factors for severe disease	Supportive care with very close monitoring and consideration of application for clinical trial of remdesivir (see below)	
For patients with moderate or severe disease (patients in ICU or with progressive disease)	Obtain **remdesivir** (RDV) through a clinical trial[8] or through compassionate use.[9] Current dosing of remdesivir is 200 mg IV	For compassionate use, apply through portal here: https://rdvcu.gilead.com/

[7] If already on a statin, no need to change to these agents
[8] Currently open trial: https://clinicaltrials.gov/ct2/show/NCT04280705
[9] As of 3/15/2019, compassionate use is for hospitalized patients with confirmed SARS-CoV-2 by PCR and mechanical ventilation. Exclusions include evidence of multi-organ failure, pressor requirement, ALT>5xULN, CrCl<30/ HD/ CVVH, or use of other investigational agents. Investigational agents do not include off-label approved agents.

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	loading dose following by 100 mg IV daily for up to 10 days.	
For patients with moderate or severe disease (patients with at least one Category 1 and one Category 2/3 feature on floor or any patients in ICU or with progressive disease)	With guidance from Infectious Diseases, can consider adding **hydroxychloroquine** (400 mg BID x2 followed by 400 mg daily while hospitalized, up to 5 days). Note chloroquine has activity but limited supply so hydroxychloroquine preferred With guidance from Infectious Diseases can consider: **lopinavir/ritonavir** (LPV/r or Kaletra) 400/100 mg BID for 10 days for certain moderate and severe presentations (avoid if candidate for RDV trial) If LPV/r not available, consider using **darunavir/cobicistat** (DRV/c or Prezcobix) 800/150 mg daily	Check ECG prior to initiation given risk of QT prolongation. Risk is increased in patients on other QT-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 maintenance medications for another indication.
For certain refractory or progressive patients (who are in ICU)	With ID approval, **interferon beta B1** (Betaseron) can be considered	Note IFN would need to be combined with another antiviral (likely LPV/r). It can be combined with HCQ
For patients with evidence of cytokine release syndrome (see staging criteria below in Table 6)	With ID approval, **tocilizumab** (Actemra) can be considered	Need to send serum IL6 level prior to giving first dose of tocilizumab

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Table 4:

Special Populations	Recommendation	Notes
If IgG <400	Consider IVIG at standard dose of 1 gm/kg daily x 2 doses	
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 need plan in place to draw CNI levels without exposing community.	Screen for drug-drug interactions with anti-viral agents, if they are being used

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	For inpatients on belatacept, do not administer any further belatacept. 28 days after last dose, consider adding low dose CNI. For CNI intolerant, consider increasing daily prednisone dose from 5 mg to 7.5-10 mg daily. Continue low dose prednisone (5 mg) in all patients who were on it before hospitalization. Request bronchoscopy only if significant decompensation, versus lung biopsy as may be lower risk for aerosolization and exposure to staff	
Lung transplant recipients	**Guided by transplant and transplant ID teams -please call/consult.** These are guidelines only, immunosuppression requires case-by-case approach. No change to usual immunosuppression (avoid high levels, tailor to patient) For all those in ICU or with lower respiratory tract respiratory 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	

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Table 5: Brief Overview of Agents

Agent	Classification	Target / Mechanism	Dosing	Key toxicities
atorvastatin (Lipitor)	Off-label	Cardioprotection; immunomodulatory	40-80 mg PO daily	
pravastatin (Pravachol)	Off-label	Cardioprotection; immunomodulatory	80 mg PO daily	
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 200 mg BID for 5 days	QT prolongation
lopinavir/ritonavir (LPV/r or Kaletra)	Off-label	3CLpro (viral protease) inhibitor	400/100 mg BID for up to 10 days	QT prolongation, ALT elevations
interferon beta-B1 (Betaseron)	Off-label	Immunomodulatory; enhancement of innate and adaptive viral immunity	Dosing for progressive COVID to be determined	Depression, injection site reaction, flu like syndrome
tocilizumab (Actemra)	Off-label	Monoclonal antibody to IL6 receptor / treats cytokine release syndrome	Dosing for COVID/CRS to be determined	ALT elevations

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

Postexposure Prophylaxis for Healthcare Workers:

- There is currently no 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 6: Augmenting Host Immunity (tocilizumab, steroids)

Background: Studies indicate advanced stage disease responses to beta-coronaviruses including COVID-19 have a high IL-6 cytokine signature. This response is similar to CAR-T cell based immune side effects where anti-IL-6 interventions have been of benefit.

Step 1. Establish clinical status to COVID-19 (adopted and based on the Penn CRS criteria)

Grade 1 – mild reaction
Grade 2 – moderate reaction, fever, need for IVF (not hypotension), mild oxygen requirement
Grade 3 – severe, liver test dysfunction, kidney injury, IVF for resuscitation, low dose vasopressor, supplemental oxygen (high flow, BiPAP, CPAP)
Grade 4 – life threatening, mechanical ventilation, high dose vasopressors

Step 2. Determine treatment intervention

Grade 1 – *no treatment*
Grade 2 – *send for serum IL-6*
Grade 3 – *send for serum IL-6; consider tocilizumab, if no effect can repeat x 2 more doses Q8H apart; if no response, consider low dose corticosteroids*
Grade 4 – *send for serum IL-6; consider tocilizumab as Grade 3; consider corticosteroids*

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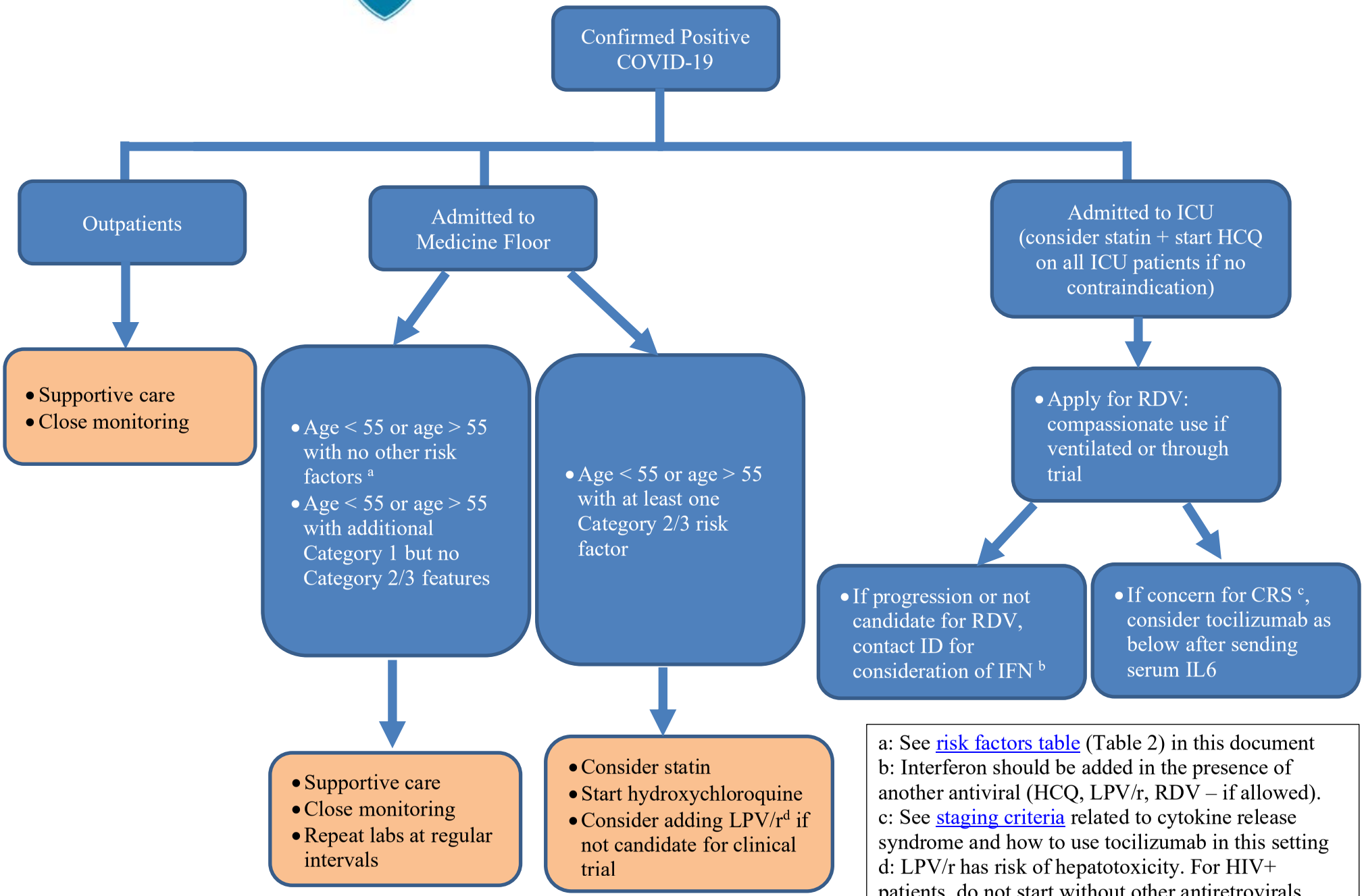

a: See risk factors table (Table 2) in this document
b: Interferon should be added in the presence of another antiviral (HCQ, LPV/r, RDV – if allowed).
c: See staging criteria related to cytokine release syndrome and how to use tocilizumab in this setting
d: LPV/r has risk of hepatotoxicity. For HIV+ patients, do not start without other antiretrovirals