Beth Israel Lahey Health

COVID-19 Treatment Guideline Version 3.1

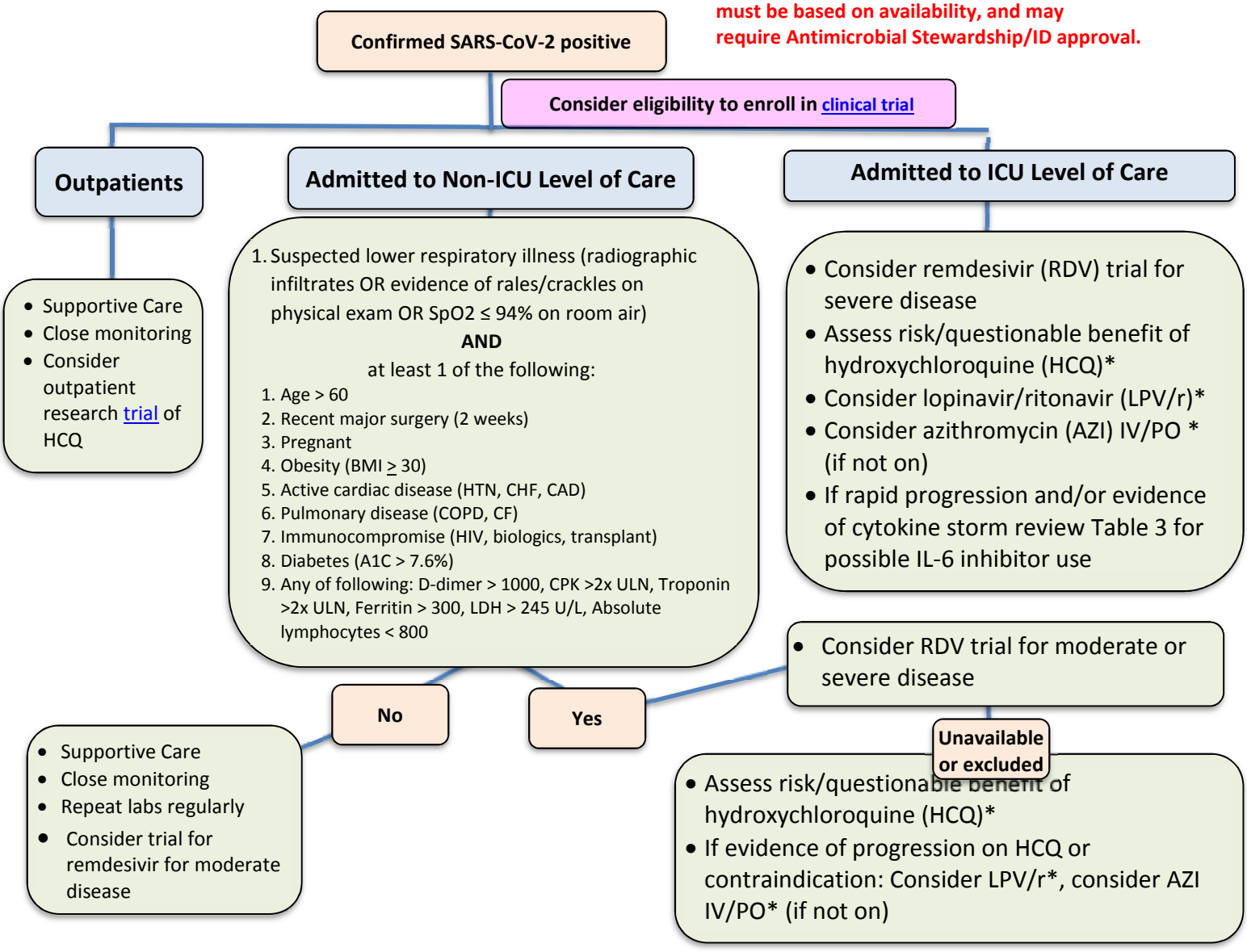
LAST UPDATED: 17 April 2020

- The purpose of these treatment guidelines is to offer guidance to providers when treating a patient with *COVID-19* infection. Guidelines will not cover all potential clinical scenarios and clinical judgment is required for application.
- **No treatment has been proven to be safe and effective** against COVID-19, or is currently endorsed by the FDA, CDC or WHO.[1] Consider the principle, "**Do no harm**."
- **Enrollment of appropriate patients into clinical trials** is the most meaningful way we can improve care of our COVID-19 patients.
- **Please DO NOT engage in empiric, pre-emptive, or prophylactic therapies given the scarcity of supplies and limited understanding of efficacy.**
- All therapies are deemed experimental at this time based on published cases & early trial results, mostly from outside the US. [2-9]
- Supportive care remains the cornerstone of therapy.
- An Infectious Diseases consult is **recommended** for confirmed COVID-19 as clinical guidance/research is rapidly evolving.
- This document does NOT cover recommendations for management of hypoxemia, fluid resuscitation, anticoagulation or the myriad complications in patients with COVID-19. See table 3 for hyperlinks to ICU guidance.

Please note when this document was last updated. Updates will occur in real time as data emerge.

Figure 1: Summary Flow Chart of Treatment

*** Consideration of use of ALL AGENTS must be based on availability, and may require Antimicrobial Stewardship/ID approval.**



Laboratory Testing and Radiology

Note: Given limited drug supplies, specific guidance in this document is intended only for ***COVID-19 confirmed patients****. If the patient has not yet been tested for SARS-CoV-2,* approval for testing may be obtained through the BIDMC HID Pager (33860)

Table 1: Tests for Hospitalized Patients with Confirmed COVID-19

Daily Laboratory Testing

- CBC with diff (trend total lymphocyte count)
- Complete metabolic panel
- Liver function tests (ALT/AST/tbili)

Labs that may be used for risk stratification or trial eligibility (may be repeated if abnormal or with clinical deterioration):

- CPK (creatine kinase)
- Blood type and screen
- D-dimer
- Ferritin
- LDH
- CRP
- Troponin[1]
- Consider IL-6 *if ICU level of care* (send out[2])
- Consider procalcitonin (send out[2])

Viral serologies:[3]

- HBV serologies (sAb, cAb, and sAg)
- HCV antibody, unless positive in past
- HIV 1/2 Ab/Ag

Immunocompromised patients:

If clinically indicated, consider serum beta-d-glucan to evaluate for *Pneumocystis.* Do not routinely induce sputum given risk of aerosolization; yield from non-induced sputum for *Pneumocystis* is low.

Radiology:

- Portable CXR at admission
- CXR PA/lateral in ambulatory patients only if low suspicion for COVID-19 and result would change management or affect PUI status.

Baseline ECG[4]

- If starting QTc prolonging drug particularly HCQ+AZI. If baseline QTc > 500, **DELAY** HCQ+/- AZI, correct reversible causes (e.g., electrolytes, discontinue concomitant QT agents)
- Reassess QTc by **algorithm**, minimally daily

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
- Consider pregnancy test

[1]Elevated troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours and echocardiogram not necessary. Uptrending troponin with hemodynamic compromise or other concerning cardiovascular symptoms /signs should prompt consideration of obtaining an echocardiogram

[2]Sendouts can take 5-7 days for result turnaround time (TAT, refer to individual institution for guidance). Extended TAT will reduce clinical utility.

[3]Viral serologies assist for interpretation of ALT elevations, present in ~25% of presentations.

[4]ECG – also see Table 3.

Non-COVID-19 Therapeutics:

- Symptomatic care:
  - o Antitussive agents
  - o Expectorants
  - o Acetaminophen (avoid NSAIDs if possible)
- Inhaled bronchodilators -- if needed -- via metered dose inhaler rather than nebulization
  - o Nebulization risks aerosolization of the virus
  - o If inhaler shortage, enforce appropriate PPE for nebulizers, following discussion with attending, pharmacist, and respiratory therapy

Empiric treatment for bacterial pneumonia (consider possibility of co-infection with COVID-19):

- Ceftriaxone 1 g [or antipseudomonal beta lactam for ICU or MDR risk factors] + Azithromycin 500 mg x1, then 250 mg daily x 4 days (PO if possible) + Vancomycin if risk factors for MRSA
- De-escalation of antibiotics will be possible for most patients, guided by respiratory cultures and MRSA screen

Unknown or Neutral

- **IL-6 inhibitors (use within clinical trial, if possible):**
  - Tocilizumab - Benefit suggested in uncontrolled study of rapidly progressive disease in ICU patients with cytokine release syndrome, characterized by elevated IL-6 (>40 pg/mL), and supported by D-dimer > 1000 ng/mL, CRP > 100. Consider on individualized basis for selected ICU patients (Table 3).
  - Sarilumab – As above. May be available as part of clinical trial.
- **ACE-Inhibitors (ACEi) / Angiotensin Receptor Blockers (ARBs):**
  - SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. It is unknown if these agents 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. However, for patients receiving ACEi/ARB, if acute kidney injury, hypotension or other contraindication develops, we recommend stopping them at that time.
- **Inhaled steroids:**
  - May theoretically reduce local immunity and promote viral replication, but this consideration must be balanced by potential benefits for management of reactive airways. There is no current evidence that inhaled steroids worsen the course of COVID-19
- **NSAIDs:**
  - NSAID use has been reported preceding clinical deterioration in some patients with severe COVID-19 disease, but the association remains uncertain. Consider avoiding use of NSAIDs while patients are admitted if alternatives such as acetaminophen are available.
- **Statins:**
  - Some theoretical benefit of statins as promoters of innate antiviral immune response, as immunomodulators, and possible cardio protection. However, use must be balanced by concern regarding elevation of CPK and LFTs which could disqualify patients from antiviral clinical trials. *Statins may be continued for patients already receiving these agents.*

Not currently recommended

- **Systemic steroids** - given potential harm and enhanced viral replication. Steroids may be considered if indicated for another reason, e.g., COPD. A randomized controlled trial is testing the safety/efficacy of steroids for COVID-19 (NCT04273321). Until results are available, broad use of steroids, especially in milder forms of the disease, is discouraged.
- **Ribavirin, Interferon Beta-1b:**
  - *Ribavirin* – In crude and multivariable analyses, ribavirin and IFN was associated with higher 90-day mortality compared with no treatment; with no difference in these groups noted after accounting for time-varying confounders. Given this and the significant toxicities related to ribavirin (with or without IFN), we do not recommend use at this time.
  - *Interferon* - Insufficient evidence to support the use of interferons, alone or in combination with other agents, at this time. The pathophysiology of respiratory failure caused by COVID-19 appears to involve an aberrant immune response, which may be exacerbated by interferon administration.

- **Zinc, Ascorbic Acid**
  - **Zinc:** a hypothesis of enhancement of chloroquine activity given ionophore like synergy sparked interest but there is no evidence for this synergy with hydroxychloroquine. Chloroquine does increase the uptake of zinc into cancer cells to induce apoptosis and zinc has been widely studied for symptom reduction for the common cold (see Cochrane review). As of this date no study has specifically evaluated its role in COVID -19 with no recommendations in local, national or international guidelines.
    Ascorbic acid: basic science modeling and research as an immune booster, immunomodulatory agent in the sepsis cascade lends to postulation of a benefit to reduce infection-induced oxidative stress. There are ongoing randomized trials of the role of vitamin C in COVID-19. Chick embryo modeling displayed decreased infectivity to a coronavirus in the 1970s. In ARDS, high dose vitamin C was associated with reduced mortality, with no benefit on surrogate markers due to survivor bias. There are no recommendations in local, national or international guidelines.

Detailed Assessment and Treatment Approach

Step 1: Identify Risk Factors

Table 2: Risk Factors for Severe COVID-19 Disease

Demographic and Comorbidities	Labs
-Age > 60 -Pregnant -Obesity (BMI ≥ 30) -Pre-existing pulmonary disease -Chronic kidney disease -Diabetes with A1c > 7.6% -History of hypertension -History of cardiovascular disease -Use of biologics -History of transplant or other immunosuppression All patients with HIV (regardless of CD4 count) Surgery during COVID-19 incubation period (2 weeks)	-D-dimer > 1000 ng/mL -CPK > twice upper limit of normal -CRP > 100 -LDH > 245 U/L -Elevated troponin (>2x ULN) -Absolute lymphocyte count < 800 -Ferritin > 300 ug/L

Step 2: Treat Based on Severity

Table 3: Suggested Treatments Based on Clinical Severity

Clinical Situation	Recommendation	Notes / Considerations
All hospitalized patients (regardless of severity)	Supportive care Evaluate eligibility for remdesivir (RDV) study (site specific) enrollment for moderate disease: 200 mg iv once, then 100 mg daily	Close monitoring for progression **RDV moderate COVID-19 inclusion:** Fever ≥ 99.0 °F oral or ≥ 100.0 °F rectal, normal oxygen saturation, **SpO2 > 94%** on room air at screening, CXR with pulmonary infiltrates **RDV moderate COVID-19 exclusion:** Evidence of multiorgan failure, on pressors, creatinine clearance < 50, transaminases > 5X ULN, concomitant use of other antivirals

Clinical Situation	Recommendation	Notes / Considerations
Patients requiring floor-level admission with suspected lower respiratory disease (radiographic infiltrates by imaging OR evidence of rales/crackles on physical exam **OR** SpO2 ≤ 94% on room air **AND** At least one additional risk factor (see Table 2)	Evaluate eligibility for remdesivir study (site specific) enrollment for either moderate disease OR severe disease: both trials use 200 mg iv once, then 100 mg daily *RDV moderate inclusion and exclusion as above* **AND (while awaiting RDV evaluation)**	**RDV severe COVID-19 inclusion:** Fever ≥ 99.0 °F oral, or ≥ 100.0 °F rectal, **SpO2 < 94%** on room air at screening, CXR with pulmonary infiltrates **RDV severe COVID-19 exclusion:** Evidence of multiorgan failure, on pressors, creatinine clearance < 50, transaminases > 5X ULN, concomitant use of other antivirals
	Assess risk/questionable benefit of hydroxychloroquine (HCQ)* 400 mg BID x2 doses day 1, followed by 400 mg daily while hospitalized on days 2-5. Note chloroquine has activity but limited supply so hydroxychloroquine preferred	Check ECG prior to HCQ initiation given risk of QT prolongation. Risk is increased in patients on other QT-prolonging agents, including azithromycin. Do not initiate if QT > 500 msec. Follow **algorithm** for approach to prolonged baseline Qtc or development of QTc prolongation. Caution in patients with COVID myocardial injury. Avoid in myasthenia gravis, porphyria, retinal pathology, epilepsy. Pregnancy is not a contra-indication. Assess for drug-drug interactions before starting. Main HCQ side effect is gastrointestinal intolerance. Monitor liver function tests.
	If HCQ contraindicated/not available or evidence for progression on HCQ: With AST/ID approval, can consider starting/adding: lopinavir/ritonavir (LPV/r or Kaletra) 400/100 mg BID for 10 days.	Protease inhibitors require review for drug-drug interactions. Ensure that the patient is not HIV positive prior to therapy. Get baseline LFTs and monitor during therapy.
	If HCQ contraindicated/not available or evidence for progression on HCQ: Can consider starting/adding azithromycin (if not already receiving): 500 mg x1, then 250 mg daily x 4 day	Azithromycin combined with HCQ can further prolong/exacerbate QT elevations. Use PO therapy unless unable.

Clinical Situation	Recommendation	Notes / Considerations
Patients requiring ICU-level admission Special Considerations for the approach to • **Sedation/Analgesia/Paralysis** • **Anticoagulation**	Manage as above. Consider remdesivir trial (site specific) for severe disease, 200 mg IV once, then 100 mg daily *Evaluate eligibility for other clinical trials, including Sarilumab study (clinical trials)* Consider IL-6 inhibitor in rapidly progressive severe disease with mechanical ventilation, hypotension (MAP <65) requiring vasopressors, ARDS type pulmonary infiltrates and P/F ratio <300 and two or more of the following: O D-dimer > 1000 ng/mL, CRP > 100 Rapidly worsening gas exchange (w/in 24h) O Ferritin > 300 µg/L with doubling within 24 hours O Ferritin > 600 µg/L at presentation and LDH > 250 U/L O Serum IL-6 ≥ 3x upper limit of normal if available	*RDV severe inclusion and exclusion as above* *ECG, LFTs, and drug-drug interactions as above* For RDV compassionate use for pregnant intubated patients, apply through portal here: https://rdvcu.gilead.com Send IL-6 level prior to initiating tocilizumab. Avoid if transaminases >5x ULN, ANC < 500, platelets < 50, AST/ALT elevations, infectious complications (TB/Hepatitis), hypersensitivity; consider risk for perforation in patients with IBD or history of diverticulitis

Table 4: Special Populations/characteristics

	Recommendation	Notes
Solid organ and BMT recipients	Guided by transplant and transplant ID teams – please call/consult Request bronchoscopy only if significant decompensation, versus lung biopsy as may be lower risk for aerosolization and exposure to staff Reduction of immunosuppressants needs to be considered with guidance by transplant and transplant ID teams.	Screen for drug-drug interactions with anti-viral agents, if they are being used
If IgG <400	Consider IVIG at standard dose of 1 gm/kg daily x 2 doses	
Pregnancy	Pregnancy may increase risk based on data from SARS, MERS; COVID-19 data remain extremely limited. Management guided by Maternal-Fetal Medicine / ID teams.	
Acute Kidney Injury	Consider Nephrology consult for possible intervention	Niacinamide Protocol
Myocarditis/Cardiomyopathy	Consider Cardiology consult for management and possible intervention	

Table 5: Additional Drug Information			
Agent/dosing	**Target / Mechanism**	**Dosing**	**Monitoring**
Hydroxychloroquine (Plaquenil)	Multiple; alters membrane pH preventing viral fusion, inhibits binding to ACE2, blocks viral protein transport to nucleus.	400 mg PO BID x 2 doses, then 400 mg PO daily for 5days*	ECG baseline: Follow EP algorithm for approach to prolonged QTc at baseline or during therapy. • If baseline QTc > 500, **DELAY** HCQ+/- AZI, correct reversible causes (e.g., electrolytes, discontinue concomitant QT agents) • Reassess QTc by algorithm, minimally daily Use caution in acute or chronic kidney disease, monitor LFTs; many drug-drug interactions
Lopinavir/ritonavir (LPV/r or Kaletra)	3CLpro (viral protease) inhibitor	400/100 mg PO BID x 10days (liquid permitted if intubated ONLY)	LFTs, drug-drug interactions (LPV/r) potent cytochrome P450 enzyme inhibitor
Azithromycin	Macrolide antimicrobial, immunomodulating properties	500 mg x1, then 250 mg daily x 4 days	QT prolongation, caution with HCQ
Remdesivir	RNA-dependent RNA polymerase inhibitor	200 mg IV x1, then 100 mg IV daily, up to 10 days	ALT elevations, hypersensitivity
Tocilizumab (Actemra)	Monoclonal antibody to IL6 receptor / treats cytokine release syndrome	400 mg IV once	Avoid if transaminases >5x ULN, ANC < 500, platelets < 50 AST/ALT elevations, infectious complications (TB/Hepatitis), risk for perforation in IBD, hypersensitivity

*Some experts recommend a dose reduction of 50% for GFR < 10 mL/minute, hemodialysis, or peritoneal dialysis; no dose reduction is recommended if GFR > 10 mL/minute

Liverpool COVID-19 Drug Interactions

UCSF Protease inhibitor drug interactions

Post-exposure Prophylaxis for Healthcare Workers

- There are currently no data for post-exposure prophylaxis for people with a known COVID-19 exposure. Follow current Infection Control guidance around quarantine. Healthcare workers should follow instructions from Occupational Health.
- Healthcare workers and close household contacts of COVID-19 patients may be eligible to enroll in a clinical trial for post-exposure prophylaxis if within 3 days of exposure; email directly: covid19@umn.edu

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Annotated References Link