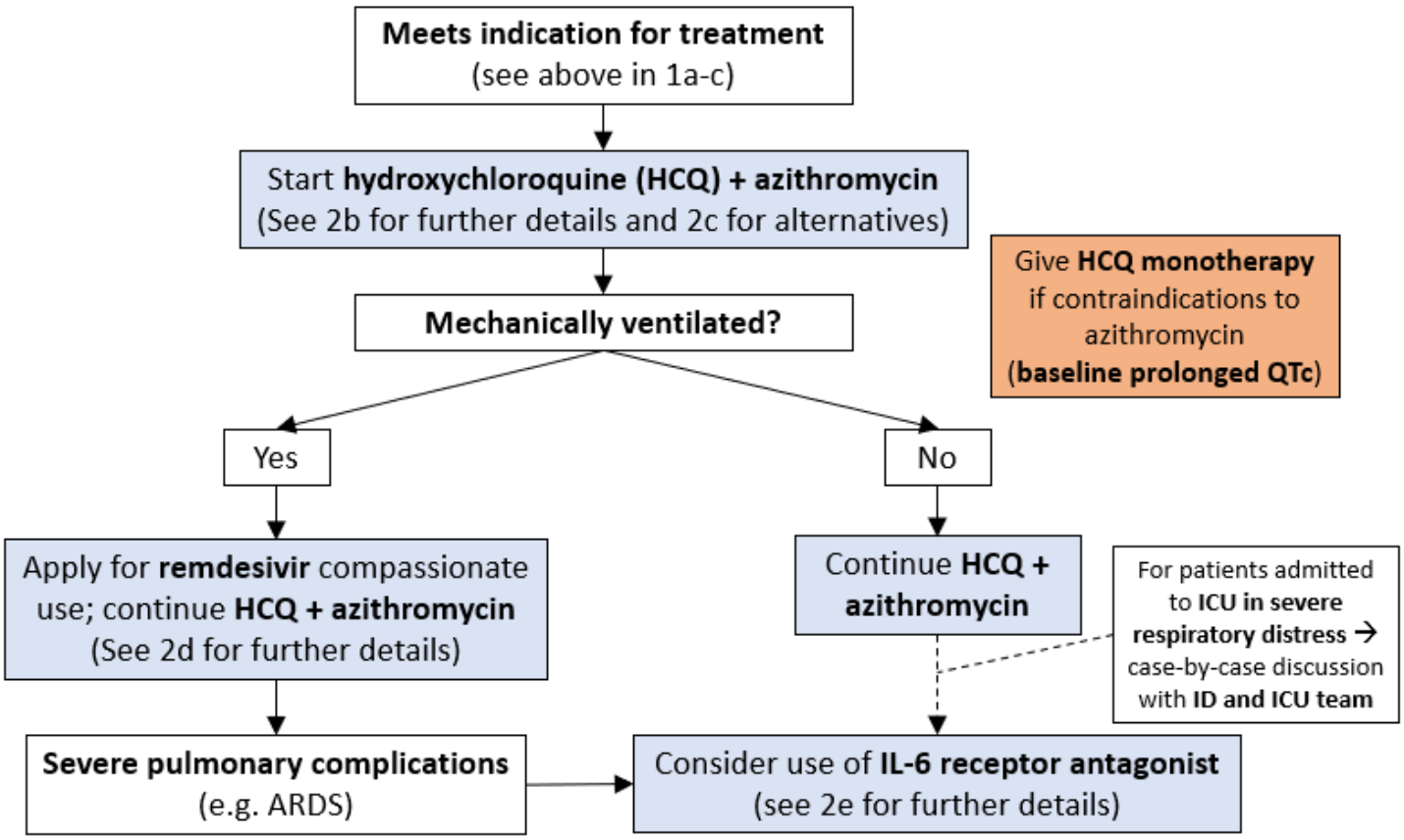
Treatment Protocol for COVID-19 (SARS-CoV-2) for RWJBarnabas Health (March 19, 2020 530pm)

Use of experimental drugs via clinical trials or compassionate use are rapidly evolving. **New drafts will be published as more information becomes available – always note date/time of version**. For protocol updates, contact: Nav Narayanan, PharmD, MPH (navan12@pharmacy.rutgers.edu) or Steve Smoke (steven.smoke@rwjbh.org)

In an inpatient with **positive SARS-CoV-2 PCR test** or **highly suspected person under investigation** for COVID-19 (contact with a confirmed case or high-risk travel history or consistent clinical presentation), we recommend the following:

1. Treatment Indications – consider treatment for any **ONE** following groups:
    a. Requiring ICU-level of care
    b. Requiring any supplemental oxygen (if not on oxygen at baseline)
    c. Lower respiratory tract disease with risk factors for progression to severe disease:
        i. Older age (> 60 years)
        ii. Immunocompromised
        iii. Significant chronic comorbidities (including but not limited to diabetes, pulmonary disease [e.g. COPD], cirrhosis, CKD, cardiovascular disease, hypertension, and any other medical conditions based on clinical judgement by ID attending physician)



2. Treatment recommendations for qualifying groups per treatment indications as above:
    a. **ID approval** to initiate any COVID-19-specific treatment (supportive care as usual by primary team):
        i. Hydroxychloroquine may be restricted to Infectious Disease providers at your site
            1. In general, aim to stay with 5-day regimen as listed below unless severely/critically ill
            2. Consider discontinuation if SARS-CoV-2 PCR is negative and low suspicion for COVID-19
        ii. Tocilizumab requires ID approval via ID attending MD on the COVID-19 multidisciplinary team
    b. Treat with **hydroxychloroquine (HCQ) PLUS azithromycin**
        i. Give HCQ MONOTHERAPY if baseline prolonged QTc – do NOT give **azithromycin** in combination
        ii. Use as primary treatment if not a candidate for remdesivir compassionate use (see 2d below) or in the interim pending receipt of remdesivir for compassionate use

iii. HCQ dose: 400 mg BID x 1 day, then 200 mg BID for 4 more days = 5-day regimen (may extend duration depending on clinical response) – see rationale below for expected drug exposure
    1. May consider 400 mg QD for maintenance dose instead of 200 mg BID to limit entry into patient room (i.e. reduced exposure if unable to batch with other reasons for BID entry)
    2. All patients on the ventilator should receiving HCQ suspension – see compounding instructions below at section 2f; order built in EHR (order item: hydroxychloroquine suspension 25 mg/mL)
    3. No dose adjustment needed in renal impairment
    4. Most toxicity associated with long-term use but for short-term use, still consider:
        a. QTc prolongation – mainly if on other concomitant QTc prolonging medications
        b. It is NOT recommended to routinely check for G6PD deficiency in all patients
iv. Azithromycin dose: 500 mg QD x 1 day, then 250 mg QD for 4 more days = 5-day regimen (may extend duration depending on clinical response)
    1. All patients on the ventilator should receive azithromycin suspension
    2. Toxicity of main concern is additive cardiotoxicity – QTc prolongation
v. All patients need a baseline EKG prior to initiation given additive QTc prolongation risk
vi. Monitor electrolytes (optimize potassium and magnesium) and repeat EKG as needed

c. Alternative antiviral treatment options: **chloroquine** 500 mg PO BID for 10 days
d. **Remdesivir** via **compassionate use** through Gilead (apply via: http://rdvcu.gilead.com/)
    i. Inclusion: hospitalization | confirmed SARS-CoV-2 by PCR | invasive mechanical ventilation
    ii. Exclusion: multiorgan failure | requiring pressors | ALT >5x ULN | CrCl <30 or any dialysis
    iii. May need to **discontinue** hydroxychloroquine (or alternative) prior to start of remdesivir (follow Gilead's compassionate use protocol for remdesivir for definitive instructions)
e. In addition to antiviral treatment, for patients requiring ICU-level of care for COVID-19-related severe pulmonary complications (e.g. ARDS or continued deterioration on mechanical ventilation or before need for intubation) – consider **adjunctive use of IL-6 receptor antagonist**, in consult with ICU team:
    i. **Tocilizumab** (Actemra)
        1. Dose: <30 kg: 12 mg/kg | ≥30 kg: 8 mg/kg | **maximum dose**: 800 mg per dose IV
        2. If clinical improvement does not occur after the first dose, up to 2 additional doses may be administered (with at least an 8 hour interval between consecutive doses)
            a. Number of additional doses is highly dependent on current drug supply
        3. Send IL-6 plasma level (https://www.mayocliniclabs.com/test-catalog/Overview/63020)
            a. Send out test, won't likely influence real-time decision-making but potentially useful for further understanding of pathogenesis of severe COVID-19
        4. Additional lab tests for inflammatory markers may be sent by ICU team
            a. This may include but not limited to CRP, ferritin, ESR, fibrinogen, D-dimer, LDH
        5. Warning related to tuberculosis reactivation – send T-SPOT test to assess for LTBI
            a. Do not hold therapy pending results – can treat LTBI later as needed
f. **Extemporaneous compounding for HCQ** (25 mg HCQ/mL) for pharmacy to make and dispense
    i. Remove coating with alcohol swab
    ii. Crush fifteen 200 mg tablets in mortar to fine powder
    iii. Add 15 mL of Ora-Plus, mix to uniform paste
    iv. Mix while adding additional 45 mL of vehicle
    v. Mix while adding sterile water (SW) for irrigation to almost 120 mL
    vi. Transfer to bottle, rinse mortar with SW and QS to make 120 mL
    vii. Stable up to 30 days stored in the dark at room temperature or refrigerated
    viii. References: Allen, et al. AJHP 1998;55:1915-20. Pesko LJ, Am Druggist 1993;207-57.
g. **COVID-19 drug interactions** (University of Liverpool – reliable resource for HIV and HCV drugs)
    i. http://www.covid19-druginteractions.org/

Rationale and Commentary for Therapeutic Options

- **Hydroxychloroquine (HCQ)** – has the same mechanism as chloroquine and more tolerable safety profile

- HCQ was found to be more potent than chloroquine in vitro [Yao X et al]
- Based on PBPK models, predicts lung tissue concentrations, the optimal dosing for SARS-CoV-2 is 400 mg BID (loading dose) for 1 day then 200 mg BID for 4 more days → 3x time the potency of chloroquine 500 mg BID for 5 days [Yao X et al]
- Both HCQ and chloroquine decrease viral replication in a dose-dependent manner [Yao X et al]
- Despite a 5 day treatment regimen, drug concentrations in the lungs were still above the target concentration on day 10
- Both HCQ and chloroquine have immunomodulatory effects [Yao X et al] → HCQ is a potential ideal drug as it can inhibit virus via antiviral effects and mediate the cytokine storm via immunomodulatory effects
- There is a small ongoing clinical trial in China for HCQ in COVID-19

- **Azithromycin** – in a small French study, the combination of hydroxychloroquine plus azithromycin (n=6) had a higher rate of "virologic cure" vs. hydroxychloroquine alone vs. control. [Gautret P et al] Very limited data but promising with minimal risk of adding azithromycin unless patients has baseline prolonged QTc interval.
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- **Chloroquine** – based on news briefing from China, there is indication that chloroquine has demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China [Gao et al]. Full results yet to be published.
  - Thus far, results from > 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in 1) inhibiting the exacerbation of pneumonia, 2) improving lung imaging findings, 3) promoting a virus-negative conversion, and 4) shortening the disease course [Gao et al]
  - Chloroquine is recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China. [Gao et al]
  - In the early in vitro studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM [Wang et al]

- **Remdesivir** – experimental antiviral drug in phase 3 clinical trials for COVID-19 as well as available for compassionate use for COVID-19
  - Broad-spectrum antiviral with in vitro activity against (not full list) Ebola virus, Marburg virus, Nipah virus, Hendra virus, RSV, and human and zoonotic coronaviruses [Ko et al, Martinez]
  - Although when tested for Ebola, outcomes were not favorable, the clinical safety profile in humans appear reasonable [Ko et al]
  - Remdesivir appears to have a high genetic barrier for viral resistance with decreased fitness and pathogenicity in the remdesivir-resistant mutants [Ko et al, Martinez]
  - At RWJ-NB, we are NOT (currently) a study site for either of the two Gilead-sponsored RCTs
  - Only access is via compassionate use at this time – see above protocol for further details

- **Tocilizumab** – IL-6 receptor antagonist currently used for treatment of cytokine release syndrome in CAR T-cell therapy patients at RWJ-NB. It has been used in China in a case series of 21 patients with positive outcomes – most patients were severely ill (based on respiratory function measures) but not mechanically ventilated [Xu X et al]. It has been used in other countries (e.g. Italy) and recommended in the Chinese national treatment guidelines. This is currently in phase 3 clinical trial in China [ChiCTR2000029765].
  - Dysregulation of immune response, especially T lymphocytes, might be highly involved in the pathological process of COVID-19 [Qin C et al]
  - Severe cases tend to have lower lymphocytes counts, higher leukocytes counts and neutrophil-lymphocyte-ratio (NLR), as well as lower % of monocytes, eosinophils, and basophils. Most of severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. The number of T cells decreased, and more hampered in severe cases [Qin C et al]
  - Most patients in [Qin C et al] to have lymphopenia, higher infection-related biomarkers (i.e. procalcitonin, erythrocyte sedimentation rate, serum ferritin, and C-reactive protein) and several elevated inflammatory cytokines (i.e. tumor necrosis factor (TNF)- α , interleukin (IL)-2R and IL-6),

and there were numerous differences in blood cell counts and infection related biomarkers between severe group and non-severe group [Qin C et al]
    - Inflammatory cytokines were also elevated in severe cases than the non-severe ones, including interleukin (IL)-2R, IL-6 (25.2 vs 13.3 pg/mL; P < 0.001), IL-8, IL-10, and TNF-α. [Qin C et al]
    - Although there is no direct evidence for the involvement of pro-inflammatory cytokines and chemokines in lung pathology during COVID-19, the change of laboratory parameters, including elevated serum cytokine, chemokine levels, and increased NLR in infected patients were correlated with the severity of the disease and adverse outcome, suggesting a possible role for hyper-inflammatory responses in COVID-19 pathogenesis. [Qin C et al]
    - Novel information about dysregulated immune response in COVID-19 patients: SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes, induce a cytokine storm in the body, and generate a series of immune responses to damage the corresponding organs. [Qin C et al]
    - Non-survivors were observed to have significantly higher IL-6 levels versus survivors consistent with the pathophysiology of severe COVID-19 (i.e. cytokine storm and immune dysregulation) [Young et al]

- **Lopinavir/ritonavir** can be given if in place of hydroxychloroquine or chloroquine if these agents are unavailable but why not a "preferred" option in this protocol?
    - The current data and evidence for any recommendation in this protocol is limited to none – there is no "preferred" options given the novelty of this virus and disease (i.e. no proven therapeutics exist)
    - Some data indicate in vitro and in vivo activity against SARS-CoV and MERS-CoV but it is questionable if this translates to activity and effectiveness versus SARS-CoV-2 [Martinez]
    - Clinical benefit of LPV/r was equivocal and "decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs also appeared similar between those treated and not treated with lopinavir-ritonavir." [Young et al]
    - In the Lancet study from Wuhan examining predictors of mortality, "we did not observe shortening of viral shedding duration after lopinavir/ritonavir treatment in the current study." [Zhou et al]
    - This is consistent with anecdotal communication from IDSA IDea Exchange where Doug Richman stated in vitro susceptibility of COVID-19 is >100 fold less than is wild type HIV to lopinavir and PI-resistant mutants of HIV are even more susceptible than COVID-19 – essentially noting the relatively poor potency of lopinavir against COVID-19. Additionally, activity against MERS-CoV is debatable [Martinez].
    - KEY UPDATE: RCT from China published in NEJM March 18, 2020 evaluated LPV/r (plus SOC) vs. SOC only (oxygen, ventilation, antibiotics, pressors, RRT, ECMO) in hospitalized adults with severe COVID-19 (an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg). There was NO DIFFERENCE in the primary endpoint, time to clinical improvement or secondary endpoints, mortality at 28 days and detectable viral RNA at various time points. In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir‑ritonavir treatment beyond standard care.

- **Ribavirin** – data conflicting on patients with MERS-CoV infections that were treated with a combination of ribavirin and IFN (either α2a or β1). Significant toxicity – limits potential as antiviral agent [Martinez].
    - Known data is use in combination with interferon with mixed results at best for MERS-CoV infections – the combination, even if desirable, is relatively toxic and therefore unfavorable

- **Corticosteroids** – have no effect on mortality and may result in delayed viral clearance [Huang et al]. NOT recommended by CDC, unless indicated for other evidence-based reasons (e.g. COPD exacerbation or septic shock) per those guidelines [CDC].

- **ACE inhibitors/ARBs** – there is a working HYPOTHESIS (no clinical or experimental data at this time) that patients on these drugs maybe at increased risk for developing severe disease [Fang et al]
    - SARS-CoV-2 binds to ACE2, expressed by epithelial cells of lung, intestine, kidney and blood vessels
    - Expression of ACE2 is increased/upregulated in patients with DM and hypertension, who are treated with ACE inhibitors or ARBs. ACE2 is also increased by TZDs and ibuprofen.
    - Increased expression of ACE2, in theory, would facilitate infection with COVID-19

- In theory, patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection – no evidence CCBs increase ACE2 expression so [Fang et al] raise CCBs can be potential alternative. This is not validated by any data.
- The Council on Hypertension of the European Society of Cardiology strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection. [de Simone]
- HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19: "The continued highest standard of care for cardiovascular disease patients diagnosed with COVID-19 is top priority, but there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACE-I or ARB medications. We urge urgent, additional research that can guide us to optimal care for the millions of people worldwide with cardiovascular disease and who may contract COVID-19. These recommendations will be adjusted as needed to correspond with the latest research."

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(almost all references are advance access online publication only at this time – Google the title to find published paper)

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