UNIVERSITY HOSPITAL
Newark, New Jersey

Last Updated: Wed, 03/25/20 10am

# TREATMENT PROTOCOL FOR COVID-19 (SARS-COV-2) FOR UNIVERSITY HOSPITAL, NEWARK, NJ (MARCH 25, 2020 10AM)

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: Arun Mattappallil, PharmD (mattapar@uhnj.edu) and Tilly Varughese, MD (varughti@njms.rutgers.edu)

This document was developed in attempt to evaluate the literature and formulate the best treatment plan based on current data. As this is a living document, the treatment recommendations will be constantly reviewed and updated as appropriate.

**Table 1: Laboratories for Diagnosis, Prognosis/Risk Stratification and/or Safety of Agents for suspected COVID-19**

| | |
|---|---|
| Recommended initial labs:<br>• CBC with diff<br>• Complete metabolic panel (CMP)<br>• ABG/VBG (if hypoxic, ABG preferred)<br>• LDH<br>• Troponin<br>• Ferritin/C-reactive protein (CRP)/D-dimer<br>• Creatine kinase (CPK)<br>• Procalcitonin<br>• If clinically indicated: Routine blood cultures, Urine legionella ag, Urine streptococcus ag, MRSA nasal PCR swab<br>• IL-6 levels (if in ICU) | Infectious Workup for those who have high risk for progression of disease (in anticipation for IL-6 antagonist :<br>• HIV ½ Ag/Ab<br>• HBV serologies (sAb, sAg, total cAb)<br>• HCV Ab<br>• Quantiferon Gold<br>• RPR |
| Recommended daily labs:<br>• CBC w/ diff<br>• CMP | Radiology:<br>• Portable CXR<br>• Avoid CT chest for evaluation |
| For risk stratification (q2-3 days):<br>• D-dimer<br>• Ferritin<br>• CRP<br>• LDH<br>• Procalcitonin<br>• Baseline ECG | COVID Testing<br>• F/u Respan test results<br>• SARS-CoV-2 test to be followed<br>o Currently, sent to NJ DOH – will be updated with in-house testing options in the next week |
| Clinical Pearls:<br>• Leukocytosis or leukopenia can be seen<br>o Lymphopenia (ANC < 1) seen most frequently<br>• LDH, CRP and D-dimer can be high-predicator of Severity of disease<br>• Procalcitonin usually normal, but can be elevated in more severe disease, even in the absence of bacterial superinfection | Clinical Pearls cont:<br>• Can have mildly elevated transaminases<br>• Co-infection rate w/ viruses may be as high as 20% in recent Stanford study<br>• CXR – common findings patchy consolidations and peripheral distribution<br>• Nodules/lymphadenopathy/cystic changes/effusion less common, <10% |

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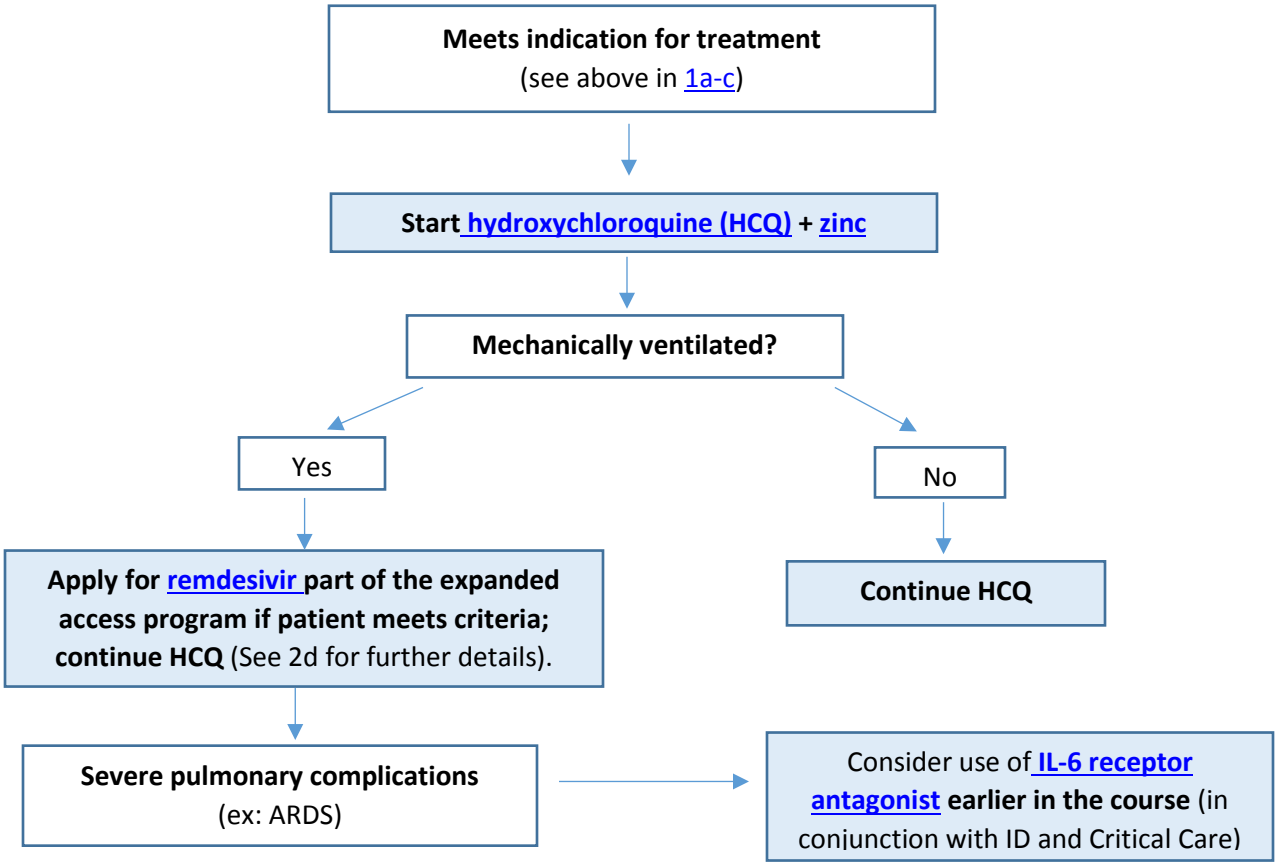
In an inpatient with **positive SARS-CoV-2 PCR test** or **highly suspected person under investigation (PUI)** for COVID-19 (contact with a confirmed case or high-risk travel history or consistent clinical presentation), we recommend the following:

1. Treatment Indications – consider treatment for any **ONE** of the following groups:
    a. Requiring ICU-level of care
    b. Requiring any supplemental oxygen (if not on oxygen at baseline)
    c. Clinical judgment for those with risk factors for progression to severe disease (between age 55-80 years, immunocompromised, significant co-morbid conditions) – Due to drug shortages, this would need to be done on a case to case basis and after a discussion with infectious diseases.




CLICK HERE TO VIEW REGIMENS/DRUGS THAT ARE NOT RECOMMENDED AT THIS TIME FOR TREATMENT

2. Treatment recommendations for qualifying groups per treatment indications as above:
    a. Need **ID approval** to initiate any COVID-19-specific treatment (supportive care as usual by primary team)
    b. Treat with **hydroxychloroquine (HCQ) + zinc**
        i. 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
        ii. Hydroxychloroquine Dose: 400 mg BID x 1 day, then 200 mg BID for at least 4 more days (extend duration depending on clinical response and with conjunction ID consult) – see rationale below for expected drug exposure with this regimen
        iii. No dose adjustment needed in renal impairment
        iv. Zinc sulfate Dose: 220 mg PO BID
            1. Tablets can be crushed for in cases of swallowing difficulties.
            2. No dose adjustment needed in renal impairment

c. Consider treating for community acquired pneumonia in patients coming from the home setting or healthcare acquired pneumonia for patients from skilled nursing facilities or several recent hospitalizations
    i. For community acquired pneumonia, would use:
        1. **Ceftriaxone 1 gm q24 hours IV + doxycycline 100 mg q12 hours**
        2. Alternative : Levofloxacin 500-750 mg q24 hours (renally dose in CrCl <30)
        3. Avoid initiating azithromycin due to drug shortages at this time
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. Will likely need to **discontinue** hydroxychloroquine (or alternative) prior to start of remdesivir (follow Gilead's compassionate use protocol for remdesivir for definitive instructions)
e. Alternative options if unable to use hydroxychloroquine or remdesivir : darunavir + cobsistat
    i. Dosing: 600mg BID of Darunavir + Cobicistat 150mg BID
f. 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) – consider **adjunctive use of IL-6 receptor antagonist**, in consult with critical care team:
    i. **Tocilizumab** (Actemra)
        1. Dose: <30 kg: 12 mg/kg | ≥30 kg: 8 mg/kg | **maximum dose**: 400 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)
        3. Prior to administration, send HIV Ag/Ab, HBV serologies, HCV serology, Quantiferon and RPR
        4. Send IL-6 plasma level (Labcorp send out)
            a. Send out test, won't likely influence real-time decision-making but potentially useful for further understanding of pathogenesis of severe COVID-19
    ii. **Siltuximab** (Sylvant)
        1. **Alternative to Tocilizumab as an IL-6 anatogonist**
        2. Dose : 11 mg/kg x 1 dose
        3. No additional re-dosing is required
        4. Prior to administration, send HIV Ag/Ab, HBV serologies, HCV serology, Quantiferon and RPR
        5. Send IL-6 plasma level (Labcorp)
    **iii. Sarilumab (Kevzara)**
        1. Available through clinical trials at this time
**g. Convalescent Plasma COVID-19 –** use of convalescent plasma collected from recovered COVID-19 patients
    **i.** FDA approved for Emergency INDs on 3/24/20 but it is unclear at this time where and when there will be a repository of plasma to utilize. Updates forthcoming in future documents.

**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

- **Zinc**
  - Zinc (Zn2+) Inhibits SARS-CoV and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture
  - Chloroquine Is a Zinc Ionophore
    - Zinc enhanced chloroquine intracellular uptake

- **Remdesivir** – experimental antiviral drug in phase 3 clinical trials for COVID-19 ; only available for compassionate use in children and pregnant women as of 3/24/20. Has expanded access at this time for clinical trials – in process of investigating this as an option
  - 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 UH, 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

- **Darunavir/cobicistat** – HIV protease inhibitor/booster combination now in clinical trials for efficacy.
  - 3CL is the main protease of the novel coronavirus responsible for their intracellular duplication.
  - Based on virtual screening, there are several approved clinical drugs with high affinity with 3CL active site – Darunavir/cobicistat is a 3CL inhibitor
  - Suggest that 3CL inhibitors may be potential candidates for further activity detection and molecular modification (Wang et al, pre-print)
  - Cobicistat had higher predicated scores than Lopinavir docking, but darunavir, though found to be a candidate, has a lower predicted binding power than Lopinavir

- **Tocilizumab** – IL-6 receptor antagonist currently used for treatment of cytokine release syndrome in CAR T-cell therapy patients
  - 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)- $\alpha$ , 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]

- **Convalescent Plasma**
  - Option for treatment when there are sufficient numbers of people who have recovered and can donate high titer neutralizing immunoglobulin containing plasma.
  - In general, passive immunity is better at the onset of disease or as prophylaxis. Example seen in study where passive antibody therapy for pneumococcal pneumonia was most effective when administered shortly after the onset of symptoms and there was no benefit if antibody administration was delayed past the third day of disease. [Casadevall et al]
  - Studies have looked at using passive immunity for other coronaviruses, including SARS-CoV and MERS
    - 3 patients with SARS in Taiwan were treated with 500 mL of convalescent plasma resulting in a reduction in plasma virus titer and each survived [Yeh et al]
    - 3 patients with MERS in South Korea were treated with convalescent plasma, but only two of the recipients had neutralizing antibody in their plasma and only one of the 2 had a titer high enough in order to produce meaningful serological response after the infusion. [Ko et al] This study highlights the challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody

**REGIMENS/DRUGS THAT ARE *NOT* RECOMMENDED AT THIS TIME FOR TREATMENT**

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)

**Summary of available information**

| Agent | Available Data | Limitation | Recommendation |
|---|---|---|---|
| Chloroquine | Use in China for COVID-19 associated pneumonia | Full results yet to be published | Not recommended at this time due to safety profile, and alternative option (HCQ) |
| Lopinavir/ritonavir | Use in international case reports for COVID-19 associated pneumonia | Variable data suggest benefit regarding morbidity/mortality | Not preferred given lack of clear evidence on outcomes and ideal dosing regime |
| Ascorbic acid (Vitamin C) | Anecdotal use from local hospitals | No published data in COVID-19 cases | Not recommended given lack of clear evidence on outcomes and ideal dosing regime |
| Ribavirin | Anecdotal use from MERS-CoV infections | No published data in COVID-19 cases | Not preferred given lack of clear evidence on outcomes, ideal dosing regime and safety profile |
| Corticosteroids | None | | NOT recommended by CDC, unless indicated for other evidence-based reasons |
| ACE-I/ARBs | Theoretical | Need for use in patients with conditions requiring treatment with ACE-I/ARBs | Not recommended given lack of clear evidence |

**Summary of available information (Continuation)**

| Agent | Available Data | Limitation | Recommendation |
|---|---|---|---|
| Azithromycin | In conjunction w/ hydroxychloroquine | Only 1 study, poor study design | Not recommended given lack of clear evidence, risk of QT prolongation |
| Statins | Suggestion that it may have an immunomodulatory effect, in one study against MERS | Conflicting data about benefit in ARDS, may cause increased AKI or LFT abnormalities (in SAIL study) | If patient on it, would continue, otherwise would not initiate therapy |

- **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.
    - Not recommended at this time due to safety profile

- **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?
    - 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].
    - No benefit observed in use in severe patients in RCT from China [Cao]. Further studies need to be looked at using Lopinavir-ritonavir in early course of the disease as opposed to late in the course of disease as there may have been a suggestion of benefit.

- **Ascorbic acid (Vitamin C)**
    - Ascorbic acid did appear to improve mortality in the multi-center CITRIS-ALI trial.
        - However, interpretation of this trial remains hopelessly contentious due to nearly unsolvable issues with survival-ship bias.
    - Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of coronavirus (Atherton 1978).
    - Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12). This dose seems to be safe.
    - However, there is no high-quality evidence to support ascorbic acid in viral pneumonia.

- **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]

- **Azithromycin** – macrolide antibiotic currently used for several infections, usually for atypical organisms and as part of community acquired pneumonia therapy
    - Recent study suggested addition of azithromycin to hydroxychloroquine can decrease carriage of virus compared to hydroxychloroquine alone (Gautret et al)
        - Several study design flaws: Not designed to look at this as an end point, only 6 patients received the combination of HCQ and azithromycin and at baseline, those who received the combination already had lower viral loads compared to those who received HCQ alone. Study also excluded 5 patients who went to the MICU and died or left the study after they entered the study and they were not included in the analysis.
    - Dose: 500 mg x 1 dose, then 250 mg PO/IV q24 hours for additional 4 days
    - Drug-drug interactions between Azithromycin and Hydroxychloroquine – can prolong QTc interval
    - Not routinely recommended at this time to be initiated for the treatment of SARS CoV 2
    - Discuss benefits and risks of therapy in conjunction with ID

- **Statins -** no good evidence for its use at this time
    - One study suggested a theoretical benefit in MERS patients (Yuan)
        - Premise based on downstream of TLR-MYD88 pathways, activation of NF-KB is the hallmark of coronavirus infections and inhibition of NF-KB reduced lung infection and significantly increased mouse survival
        - Multicenter RCT looking at high dose Rosuvastatin use for Sepsis associated ARDS did not show significant benefit for ARDS and showed higher rates of hepatotoxicity and renal failure (ARDS Clinical Trials Network, NEJM) However, a meta-analysis examining this did not show increased risk for renal failure and hepatotoxicity, but also did not show much benefit
    - Would continue statin therapy if patient already on it, but would not initiate this otherwise during the admission.

- **NSAIDS** – 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 – see above for full theory [Fang et al)
    - Increased ACE 2 increased/upregulation can in turn possibly facilitate infection with COVID 19, but no specific recommendations at this time

**Special Populations: Post- liver transplant Patients**

- Guidelines will be forthcoming for this specific population
- Will need immunosuppression decreased in conjunction with the transplant hepatologists

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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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