UCONN HEALTH

UCONN JOHN DEMPSEY HOSPITAL

Treatment Protocol for HOSPITALIZED Patients with COVID-19 Infection

These guidelines are for the treatment of HOSPITALIZED patients with a clinical syndrome consistent with COVID-19

AND

CONFIRMED POSITIVE SARS-CoV-2 infection (via PCR)

Version #3 – Release Date 4/10/2020

[Details on this document history, versions, and revisions to the treatment protocol can be found on the last page]

Version #3 – 4/10/2020

IMPORTANT NOTES ABOUT THIS PROTOCOL AND INPATIENT TREATMENT OF COVID-19 INFECTED PATIENTS:

1. At this time, there are **no FDA-approved treatments for COVID-19 infection**. On Saturday, 3/28/2020, the FDA issued an Emergency Use Authorization (EUA) for "*…emergency use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of 2019 coronavirus disease (COVID-19) when administered by a healthcare provider (HCP) pursuant to a valid prescription. […] FDA is issuing this EUA to facilitate the availability of chloroquine phosphate and hydroxychloroquine sulfate during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.* " The FDA's EUA indicates that "*…hydroxychloroquine sulfate product that is distributed from the SNS [Strategic National Stockpile] to public health authorities for response to the COVID-19 pandemic […] may only be used to treat adult and adolescent patients who weigh 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible*."
2. **ALL** patients should receive general supportive care measures.
3. Treatments recommended in this protocol are recommended based on very limited scientific evidence in the time of a global pandemic.
4. Sound clinical judgement and a detailed consideration of the potential risks of each recommended medication should be performed frequently in the context of the current status of each individual patient with COVID-19 infection.
5. Hydroxychloroquine (HCQ) +/- Azithromycin may be started in patients who have a clinical presentation consistent with COVID-19 infection PRIOR TO confirmation of PCR test results
6. Formal Consultation with Infectious Diseases (ID) is **not required** for COVID-19 patients with **MILD** or **MODERATE** symptoms (i.e. patients **NOT** in the ICU). If desired, primary care teams should order an "**E-Consult**" with the ID Consult Service.
7. Formal Consultation with ID is **REQUIRED** for COVID-19 patients with **SEVERE** symptoms (i.e., in the ICU) and for any patient for which use of **Convalescent Plasma therapy** is being considered. Please see Page 8 for details about use of Convalescent Plasma Therapy at UConn Health.
8. At this point, there are no data to support direct benefits of **CORTICOSTEROIDS** as part of the targeted pharmacotherapeutic treatment of patients with COVID-19 infection. Use of corticosteroids (especially inhaled corticosteroids) is strongly discouraged in COVID-19-positive patients. **HOWEVER**, clinicians should use their clinical judgment and could consider using low-dose corticosteroids as part of initial therapy for a patient who presents with respiratory symptoms that could be due to other non-COVID diseases such as asthma or a COPD exacerbation (which would benefit from corticosteroid treatment). In addition, the recently-released ***Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)*** document recommends the following possible uses of corticosteroids in COVID-19 infected patients:
    - In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids (weak recommendation, low quality evidence),
    - In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence),
    - For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid. A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200mg per day administered either as an infusion or intermittent doses.
9. This protocol was jointly-developed with input from clinicians across multiple departments. We expect it will be updated frequently as new data emerge. Please contact Jeff Aeschlimann (Pharmacy / Infectious Diseases) at aeschlimann@uchc.edu for questions or suggestions about content.

Table 1. Treatment for PCR-Confirmed COVID-19 patients with MILD or MODERATE Symptoms (NOT admitted to the ICU):

Pharmacotherapy	**COVID-19 – Specific Laboratory & Other Monitoring[1]**	**Treatment Considerations**
Hydroxychloroquine 400mg PO Q12h X 1 day, then 200mg PO Q12h X 4 days **AND** ****CONSIDER*** addition of **oral or IV Azithromycin** if risks of additive cardiotoxicity are low (See "*Treatment Considerations*" section in this table and **Page 6** for **Risk Score Calculator** for Drug-Associated QTc risks): Azithromycin 500mg PO or IV x 1 day, then 250mg PO or IV x 4 days *(Oral dosage form is preferred for all patients who can take oral medications)*	**Labs:** Draw at **Baseline ONLY**: • HIV-1/HIV-2 antibody/antigen • G6PD test[2] • ABO blood typing • Interleukin-6 (IL-6) Draw at Baseline and Daily: • AST/ALT, CBC with Differential, CHEM-7 Draw at Baseline and every other day: • CRP, Ferritin, LDH, Procalcitonin, Troponin, D-dimer, Fibrinogen, PT/PTT, Serum Triglycerides **Other Testing/Monitoring:** • Baseline ECG (QTc interval) & continuous telemetry ***while on therapy*** • Obtain QTc daily, calculate and record in daily progress note ○ Refer to **Pages 6-7** for approach to monitoring in setting of limited resources/ quarantines • Continuous O2 monitoring	• Hydroxychloroquine (HCQ) +/- Azithromycin may be started in patients who have a clinical presentation consistent with COVID-19 infection ***PRIOR TO confirmation of PCR test results*** • It is recommended (but not required) to assess G6PD levels in patients who receive HCQ who may be at higher risk of hemolytic anemia.[2] Initiation of HCQ *should not be delayed* while awaiting G6PD test results • Both hydroxychloroquine (HCQ) and azithromycin (AZI) may cause cardiac conduction alterations (QTc interval prolongation)[3] • Carefully assess patients for baseline QTc interval and avoid use of concomitant QTc-prolonging medications whenever possible[3] • Limit duration of therapy to **5 days** for both hydroxychloroquine & azithromycin to avoid drug accumulation and potential additive toxicities • Hydroxychloroquine tablets can be crushed & suspended, if needed. Contact your unit Pharmacist if this becomes necessary. • See detailed information on **Page 9** of the document for considerations for use of medications in **Pregnancy**

Table 1 Notes:

1 – These are in addition to any other daily laboratory tests considered part of "routine supportive care" (i.e., basic metabolic panel, CBC, etc.). There will be a COVID-19 – specific lab ordering bundle set up in EPIC in the near future to assist with ordering these recommended labs.

2 – G6PD testing is suggested (but not required) for patients of Asian, African, or Mediterranean descent. *Do not delay start of therapy* awaiting this test if it is ordered

3 – See detailed discussion of assessment of drug-associated QTc prolongation risks and list of commonly-used medications that may prolong QTc interval on **Pages 6-8** of this document. Patients who have completed **at least 2-3 days** of hydroxychloroquine +/- azithromycin who have **stable non-prolonged QTc intervals** may be discharged without specific QTc monitoring at the discretion of the attending physician

Table 2. Treatment for PCR-Confirmed COVID-19 patients with SEVERE Symptoms (Receiving care in the ICU):

Pharmacotherapy	**COVID-19 – Specific Laboratory & Other Monitoring[1]**	**Treatment Considerations**
Hydroxychloroquine 400mg PO Q12h X 1 day, then 200mg PO Q12h X 4 days **AND** ****CONSIDER*** addition of **oral or IV Azithromycin** if risks of additive cardiotoxicity are low (See "*Treatment Considerations*" section in this table and **Page 6** for **Risk Score Calculator** for Drug-Associated QTc risks): Azithromycin 500mg PO or IV x 1 day, then 250mg PO or IV x 4 days *(Oral dosage form is preferred for all patients who can take oral medications)* **AND** ****CONSIDER*** the addition of tocilizumab.[5] (Refer to **Page 5** for criteria for use): Tocilizumab: 400mg IV once[5] **AND** ****CONSIDER*** enrollment of patient in Convalescent Plasma (Mayo Protocol) study or in a clinical trial (more information on **Page #8**)	**Labs:** Draw at **Baseline ONLY**: • HIV-1/HIV-2 antibody/antigen • G6PD test[2] • ABO blood typing • Interleukin-6 (IL-6) Draw at Baseline and Daily: • AST/ALT, CBC with Differential, CHEM-7 Draw at Baseline and every other day: • CRP, Ferritin, LDH, Procalcitonin, Troponin, D-dimer, Fibrinogen, PT/PTT, Serum Triglycerides **Other Testing/Monitoring:** • Baseline ECG (QTc interval) & continuous telemetry ***while on therapy*** • Obtain QTc daily, calculate and record in daily progress note ○ Refer to **Pages 6-7** for approach to monitoring in setting of limited resources/ quarantines • Continuous O2 monitoring	• Hydroxychloroquine (HCQ) +/- Azithromycin may be started in patients who have a clinical presentation consistent with COVID-19 infection ***PRIOR TO confirmation of PCR test results*** • It is recommended (but not required) to assess G6PD levels in patients who receive hydroxychloroquine (HCQ) who may be at higher risk of hemolytic anemia.[2] Initiation of HCQ should not be delayed while awaiting G6PD test results • Hydroxychloroquine tablets can be crushed & suspended, if needed. Contact your unit Pharmacist if this becomes necessary. • Both HCQ and azithromycin (AZI) may cause cardiac conduction alterations (QTc interval prolongation) • Carefully assess patient for baseline QTc interval, use ***Risk Score Calculator*** on Page 6, and avoid use of concomitant QTc-prolonging medications whenever possible[3,4] • Limit the duration of therapy to 5 days for both HCQ & AZI to avoid drug accumulation and potential additive toxicities • Refer to **Page 5** for criteria for **tociluzimab use.** • See detailed information on **Page 9** of the document for considerations for use of medications in **Pregnancy**

Version #3 – 4/10/2020

Table 2 Notes:

1 – These are in addition to any other daily laboratory tests considered part of "routine supportive care" (i.e., basic metabolic panel, CBC, etc.). There will be a COVID-19 – specific lab ordering bundle set up in EPIC in the near future to assist with ordering these recommended labs.

2 – G6PD testing is suggested (not required) for patients of Asian, African, or Mediterranean descent. Do not delay start of therapy awaiting this test if it is ordered

3 - See detailed discussion of assessment of drug-associated QTc prolongation risks and list of commonly-used medications that may prolong QTc interval on **Pages 6-8** of this document. Patients who have completed **at least 2-3 days** of hydroxychloroquine +/- azithromycin who have **stable non-prolonged QTc intervals** may be discharged without specific QTc monitoring at the discretion of the attending physician

4 - Drug Interaction Considerations: Please follow this link for an updated list of possible drug interactions for hydroxychloroquine, azithromycin, and other possible investigational agents to treat COVID-19: http://covid19-druginteractions.org/

5 – Use of **Tocilizumab** should be considered **ONLY FOR THE FOLLOWING PATIENTS**:

- Severe and/or critically-ill patients previously started on COVID-19 therapy who, despite initiation of maximal supportive care measures and other treatments described in this protocol, deteriorate with evidence of sustained fever, hypoxemia, worsening CT image, ARDS, and/or who may have clinical/laboratory data STRONGLY SUGGESTIVE of excessive inflammatory response/cytokine release syndrome.

- Specific **Laboratory** Criteria may include:
  - Elevations of serum Interleukin-6 (IL-6) to more than 25-30 pg/mL (5-6x the normal range of ≤ 5 pg/mL)
  - Serum ferritin > 2000 ng/mL
  - D-dimer > 1000 ng/mL

- Consider calculating an "**H-Score"** using the following online tool: https://www.mdcalc.com/hscore-reactive-hemophagocytic-syndrome.
  - An H-score of **> 169** correlates well with presence of sHLH / hypercytokinemia (see details below)

    - Although not yet validated for use in COVID-19 infection, the H-Score has been suggested in a recent *Lancet Letter to the Editor* (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext) as a potentially helpful tool to assess for hypercytokinemia (a common finding in Secondary haemophagocytic lymphohistiocytosis (sHLH)
    - In adults, sHLH is most commonly triggered by viral infections. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.
    - An H-score >169 had a sensitivity of 93%, specificity of 86%, and accurate classification of 90% of the patients with sHLH (1,2).

- A second dose of tocilizumab MAY BE considered for administration 8-12 hours after the first dose if no clinical improvement is observed (such as continued fever or increased oxygen requirements). The maximum total dose administered per patient should not exceed 800 milligrams.

- ***Please contact Infectious Diseases and the ICU Pharmacist to assist with: toxicity risk assessment, secondary infection risk assessments, drug procurement, and dosage calculations.***

Version #3 – 4/10/2020

Approach to Use of Hydroxychloroquine +/- Azithromycin and Consideration of Risks for Drug-Associated QTc Prolongation:

- A simple prospectively-validated risk-score tool has been developed that can help clinicians to assess risks of drug-associated QTc prolongation (1,2):

Calculation of Risk Score for Drug-Associated QTc Interval Prolongation:

Risk Factors	Points
Age ≥ 68 years	1
Female sex	1
Loop diuretic use	1
Serum K^+ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 ms	2
Acute Myocardial Infarction	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Acute Heart failure	3
One QTc-prolonging drug	3
Risk Assessment (from Tisdale study)	**Incidence of QTc Prolongation**
Low Risk = < 7 points	15%
Moderate Risk = 7-10 points	37%
High Risk = ≥ 11 points	73%

Commonly-used medications that may prolong the QTc interval (NOT an all-inclusive list; Contact your unit Pharmacist for an extensive assessment of your patient's drug regimen):

- Antiarrhythmics: amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotolol
- Antidepressants: anitryptyline, fluoxetine, sertraline, venlafaxine
- Antimicrobials: azithromycin, clarithromycin, erythromycin, levofloxacin (fluoroquinolones), fluconazole (azole antifungals), pentamidine
- Antipsychotics: chlorpromazine, clozapine, haloperidol, quetiapine, risperidone, ziprasidone
- Miscellaneous: methadone, ranolazine, sumatriptan, zolmetriptan

Suggested Monitoring for Inpatients Receiving Hydroxychloroquine +/- Azithromycin *IN SETTING OF LIMITED RESOURCES / QUARANTINES* (4):

- QT-prolonging medication initiation may be considered in the absence of ECG, telemetry or in-office assessment capability **for patients with Tisdale risk score ≤6**, Additional considerations may include:

  Personal protective equipment (PPE) shortages: To minimize use of PPE, ECGs may be performed to coincide with "clustered" care between 2 and 4 hours after dosing. To further reduce exposure or save PPE resources, QTc monitoring may be performed using surrogates for 12-lead ECG assessment, including QTc monitoring via inpatient telemetry.
  Telemetry shortages: If telemetry resources are limited, their use must be triaged based on clinical importance. Patients already on therapy with QTc values in the clearly acceptable range could be considered for ongoing hydroxychloroquine-azithromycin use without telemetry. Patients initiating therapy with Tisdale risk score ≤6 can similarly be considered for use without monitoring. In this telemetry-triage context, any syncope should be considered due to polymorphic VT and should prompt ECG and reinitiation of telemetry.
  Minimizing exposure/contact: It may be reasonable to forego ECG screening to allow patients to remain in quarantine if no high-risk features exist (history of long QT syndrome, concomitant QT prolonging medications, structural or ischemic heart disease, history of prolonged QTc on any ECG, history of abnormal renal function and/or electrolytes).

Version #3 – 4/10/2020

Suggested Monitoring for Inpatients Receiving Hydroxychloroquine +/- Azithromycin *with NO CONCERNS FOR LIMITED RESOURCES / QUARANTINES* (4):

The goal of QTc screening in this setting is not to identify patients whom are not candidates for therapy, but to identify those who are at increased risk for TdP so aggressive countermeasures may be implemented.

1. **Baseline:**
    a. Discontinue and avoid all other non-critical QT prolonging agents.
    b. Assess a baseline ECG, renal function, hepatic function, serum potassium and serum magnesium.
    c. When possible, have an experienced cardiologist/electrophysiologist measure QTc, and seek pharmacist input in the setting of acute renal or hepatic failure.
2. **Relative contraindications (subject to modification based on potential benefits of therapy)**
    a. History of long QT syndrome, or Baseline QTc >500 msec (or >530-550 msec in patients with QRS greater than >120 msec)
3. **Ongoing monitoring, dose adjustment and drug discontinuation**
    a. Place on telemetry prior to start of therapy.
    b. Monitor and optimize serum potassium daily.
    c. Acquire an ECG 2-3 hours after the second dose of hydroxychloroquine, and daily thereafter.
    d. If QTc increases by >60 msec or absolute QTc >500msec (or >530-550 msec if QRS >120 msec):
        - Discontinue azithromycin (if used) and/or reduce dose of hydroxychloroquine and repeat ECG daily.
    e. If QTc remains increased >60 msec and/or absolute QTc >500 msec (or >530-550 msec if QRS >120 msec):
        - Reevaluate the risk/benefit of ongoing therapy, consider consultation with an electrophysiologist & infectious diseases consult service, and consider discontinuation of hydroxychloroquine.

More Background Data on Hydroxychloroquine +/- Azithromycin and QTc Issues:

- Many factors can contribute to increased risk of QTc prolongation and/or drug-induced TdP: female sex, structural heart disease, congenital long-QT syndromes, electrolyte disturbances, hepatic/renal failure and concomitant QT prolonging medications.
- Data show inhibition of HERG channel-mediated iKr (repolarization) and resultant mild QT prolongation associated with use of chloroquine and hydroxychloroquine. Despite these suggestive findings, several hundred million courses of chloroquine have been used worldwide making it one of the most widely used drugs in history, without reports of arrhythmic death under World Health Organization surveillance (3)
- Azithromycin lacks strong pharmacodynamic evidence of iKr inhibition. Epidemiologic studies have estimated an excess of 47 cardiovascular deaths which are presumed arrhythmic per 1 million completed courses, although recent studies suggest this may be overestimated (3,4)
- There is limited data evaluating the safety of combination therapy, however in vivo studies in animals have shown no synergistic arrhythmic effects of azithromycin with or without chloroquine (5)

Version #3 – 4/10/2020

References for Tociluzimab Guidance:

1. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20. PubMed PMID: 24782338. https://doi.org/10.1002/art.38690
2. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, Corazza F. Performances of the H-Score for Diagnosis of Hemophagocytic Lymphohistiocytosis in Adult and Pediatric Patients. Am J Clin Pathol. 2016 Jun;145(6):862-70. Epub 2016 Jun 12. PubMed PMID: 27298397. https://doi.org/10.1093/ajcp/aqw076

References for Drug-Associated QTc Section:

1. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19. https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. (Accessed 3/31/2020).
2. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013 Jul;6(4):479-87. doi: 10.1161/CIRCOUTCOMES.113.000152. Epub 2013 May 28. Erratum in: Circ Cardiovasc Qual Outcomes. 2013 Nov;6(6):e57. PubMed PMID: 23716032; PubMed Central PMCID: PMC3788679. https://doi.org/10.1161/CIRCOUTCOMES.113.000152
3. "The Cardiotoxicity of Antimalarials." World Health Organization- Malaria Policy Advisory Committee Meeting. 22 Mar, 2017, www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf
4. Ray W, Murray K, Hall K, Arbogast P, Stein M. Azithromycin and the risk of cardiovascular death. New Engl J Med. 2012;366:1881-1890.
5. Fossa A, Wisialowski T, Duncan J, et al. Azithromycin/chloroquine combination does not increase cardiac instability despite an increase in monophasic action potential duration in the anesthetized guinea pig. Am J Trop Med Hyg. 2007;77(5): 929-38.

UConn Health Information & Contacts for Discussion of Enrollment of Patients in Clinical Trials for COVID-19 Treatment and Use of Convalescent Plasma Therapy:

*As of **4/10/2020**, UConn Health John Dempsey Hospital is not an active study site for any clinical studies for medication treatment of COVID-19 infection. This section will be updated frequently with contact information as we become approved for clinical studies.*

Convalescent Plasma Therapy:

- UConn Health is now a registered site for the **Mayo Clinic protocol**; the ID and ICU providers have been enrolled online.
- We also can still apply to the FDA for eINDs for individual patients if needed, but the preference is to go through the Mayo Clinic protocol.
- Links for the protocol, consent, and general information are below:

  Link for detailed protocol (Mayo): https://www.uscovidplasma.org/pdf/20-003312%20COVID-19%20Plasma%20EAP%20Version%202.0.pdf
  Link to consent form: https://www.uscovidplasma.org/pdf/EAP%20CP%20English%20Consent%2020.00331200.pdf
  General information page: https://www.uscovidplasma.org/

Version #3 – 4/10/2020

Considerations for Use of COVID-19 Treatments in Pregnancy:

Hydroxychloroquine: Limited human data, but appears to be safe.

Frequency of congenital anomalies was no higher among pregnant women who were treated with hydroxychloroquine during the first trimester of pregnancy compared with the general population (1,2)

Lopinavir/ritonavir: Human pregnancy experience suggest that the risks of use are low (1,3).

The Antiretroviral Pregnancy Registry (APR) has received prospective reports of over 3,000 exposures to lopinavir-containing regimens, including over 1,000 first trimester exposures, and over 5,000 exposures to ritonavir-containing regimens, including over 2,000 first trimester exposures. No association between lopinavir or ritonavir and increases in birth defects overall have been observed in data collected from the APR. Prevalence of birth defects associated with maternal first trimester lopinavir use was 2.1% and prevalence of birth defects associated with maternal second and third trimester lopinavir use was 3%. Prevalence of birth defects associated with maternal first trimester ritonavir use was 2.2% and prevalence of birth defects associated with maternal second and third trimester ritonavir use was 2.9%. The background rate of birth defects in the United States reference population for pregnant women is 2.7%

Azithromycin: Limited human data, but appears to be safe.

Data regarding the use of azithromycin during pregnancy, including information from published observational studies, case series, and case reports, have not shown an association between the agent and an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Limitations of these studies include the lack of randomization and inability to control for confounders, such as underlying maternal disease and concomitant medications (1,4)

Tocilizumab: Limited human data. Consider risks versus benefits.

There are no adequate and well-controlled studies of tocilizumab use during pregnancy. Monoclonal antibodies, like tocilizumab, are increasingly transported across the placenta as pregnancy progresses, with most occurring during the third trimester of pregnancy. This may affect immune response in the in utero exposed infant. In a retrospective review of 61 pregnancies in women with RA who received tocilizumab, the outcomes were known in 50 of those pregnancies with 36 live births. Of the 36 live births no congenital abnormalities were reported. However, 6 neonatal abnormalities were observed and included 5 cases of low birth weight (ie, less than 2500 g) which was thought to be related to fetal growth restriction and one newborn developed neonatal asphyxia that was reported as postnatal death. In studies of cynomolgus monkeys, administration of IV tocilizumab (doses 1.25 times and higher the maximum recommended human dose) during organogenesis resulted in an increased incidence of abortion and embryofetal death, but no evidence of teratogenicity at any dose. (1,5,6)

Remdesivir: Unknown. Consider risk versus benefits.

Pregnancy Use References:

1.) Micromedex (IBM Micromedex). Accessed 3/24/2020.
2.) Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al: Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Arthritis Rheum 2003; 48(11):3207-3211.
3.) Product Information: KALETRA(R) oral tablets, oral solution, lopinavir ritonavir oral tablets, oral solution. AbbVie Inc (per manufacturer), North Chicago, IL, 2017.
4.) Product Information: ZMAX(R) oral extended-release suspension, azithromycin oral extended-release suspension. Pfizer Inc (per FDA), New York, NY, 2019.
5.) Product Information: ACTEMRA(R) intravenous, subcutaneous injection, tocilizumab intravenous, subcutaneous injection. Genentech (per FDA), South San Francisco, CA, 2018.
6.) Nakajima K , Watanabe O , Mochizuki M , et al: Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. Mod Rheumatol 2016; 26(5):667-671.

Version #3 – 4/10/2020

Document History:

PROTOCOL: Treatment Protocol for HOSPITALIZED Patients with COVID-19 Infection	
CATEGORY: Clinical	**Date Originated:** 03/25/2020
Page 10 of 10	**Last Reviewed:** 04/01/2020
Owner: Dept. of Pharmacy, Div. of Infectious Diseases, Depts. of Critical Care, Pulmonology, Internal Medicine	**Last Revised:** 04/10/2020
Approved by:	**Retired:**
Document Revision History:	

3/25/2020	Production & distribution of Version #1
4/1/2020	-Adjusted recommendations on corticosteroid use -Removed recommendations for use of lopinavir/ritonavir -Adjusted recommendations on ordering G6PD testing related to hydroxychloroquine -Added details about considerations for use of Tocilizumab and recommendation for ordering IL-6 levels in COVID-19 infected patients -Adjusted screening methods and guidelines for use of Tocilizumab -Modified list of labs to order in COVID-19 – positive patients -Added summary of FDA's *Emergency Use Authorization* for use of hydroxychloroquine during the COVID-19 pandemic and FDA information about eIND for Convalescent Plasma use -Added section on *Approach to Use of Hydroxychloroquine +/- Azithromycin and Consideration of Risk for Drug-Associated QTc Prolongation*
4/10/2020	-Adjusted recommendations on labs and other diagnostic tests to order and evaluate (types & frequencies); added ABO blood typing, decreased frequencies of ordering for tests such as IL-6, ferritin, D-dimer, etc. -Added information promoting use of oral azithromycin in patients who can take PO medications -Added recommendation that clinicians can consider starting HCQ +/- AZI in a patient who has a clinical presentation consistent with COVID-19 but who does not yet have PCR confirmation of COVID-19. -Adjusted recommendations for ID consultation for non-ICU and ICU patients, as well as for added requirement for ID consult for patients where consideration may be made for use of convalescent plasma -Added/adjusted wording for QTc monitoring recommendations and added guidance for approach to discharge of patients who have received HCQ +/- AZI