



PROVISIONAL GUIDANCE: COVID-19 TREATMENT OPTIONS

Most recent version: <http://intranet.bhssf.org/en/departments-and-directories/ebcc/pages/coronavirus.aspx>

There are no FDA-approved antiviral medications clinically proven to treat SARS-CoV-2. New data are emerging daily as the pandemic progresses and research is completed. This guidance document reflects recommendations from local experts regarding therapies that have *in vitro* activity against coronaviruses or have been used to treat similar infectious diseases. This is not meant to replace sound clinical judgement. Risks versus benefits for each unique patient case should be carefully considered.

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TREATMENT RECOMMENDATIONS: BRIEF SUMMARY

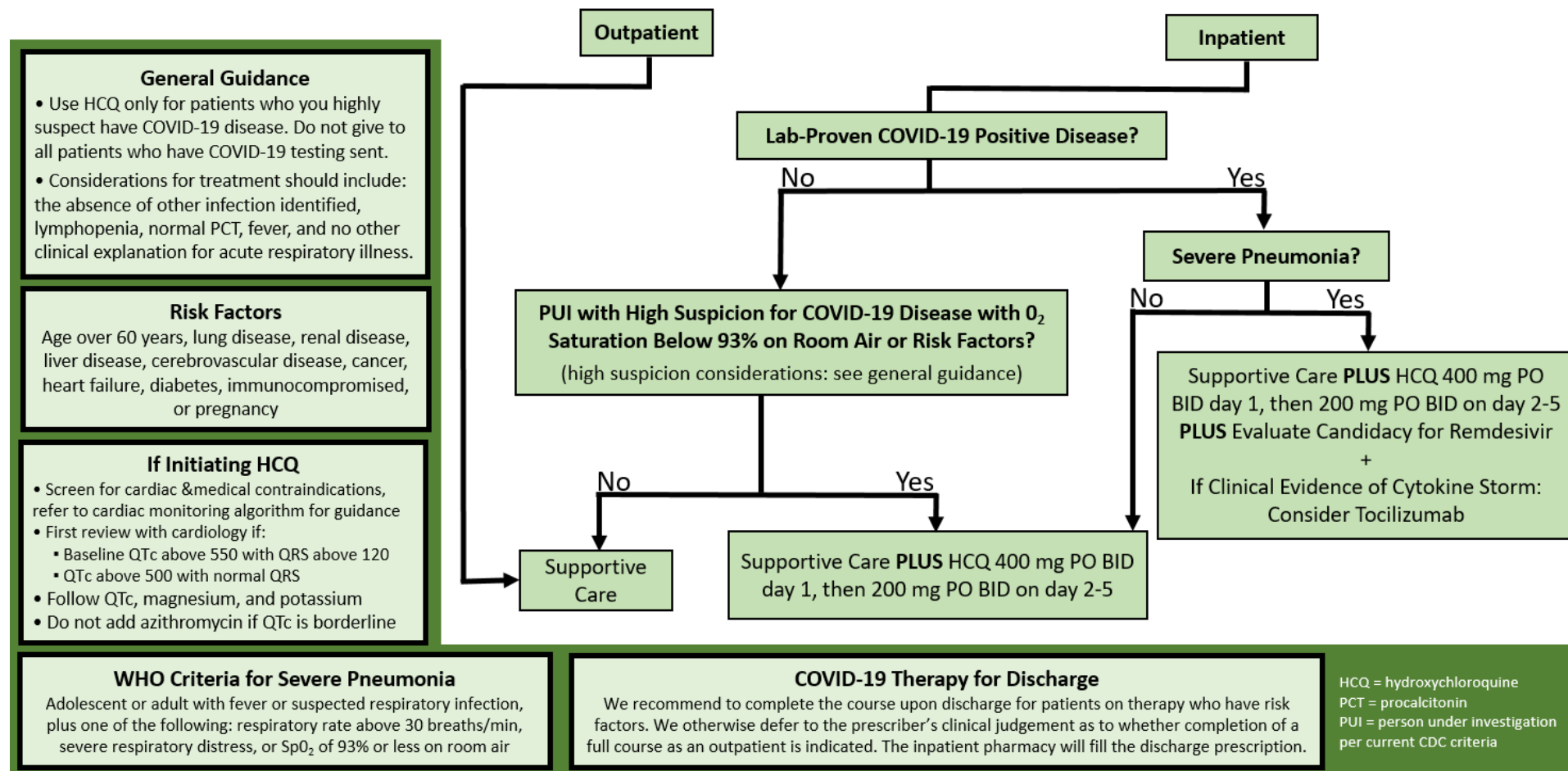
At this time we are recommending to consider the following for adults and pediatric patients:

1. Hydroxychloroquine for any inpatients with proven COVID-19 disease of any severity
2. Hydroxychloroquine for inpatients with suspected COVID-19 disease that is severe
3. Adjunctive, combination, or experimental therapies for inpatients with COVID-19 disease that is severe

COVID-19 KEY POINTS

- Infection control should be kept aware of any suspected or confirmed COVID-19 patients, as per institutional protocols
- Patients with suspected or proven COVID-19 infection should be counseled on quarantine and infection prevention practices
- Proper droplet and contact precautions should be practiced when managing proven or suspected COVID-19 patients
- Not all patients (especially those with mild disease) will require hospitalization. Clinical judgement should be used in deciding which patients can be safely discharged home versus admitted to the hospital. Some factors that are associated with more severe diseases include hypoxemia, older age, elevated SOFA score, D-dimer above 1, lymphopenia, elevated ESR, and underlying cardiovascular disease.
- Patients with mild symptoms not admitted to the hospital but suspected or confirmed with COVID-19 should be instructed to seek medical assistance or go to the hospital if their condition worsens. Risk factors include:
 - Older age
 - Underlying medical condition (e.g., lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, diabetes, immunocompromising conditions, or pregnancy)
- Supportive care is the corner-stone of COVID-19 therapy
 - Consider limiting IV fluids (which can exacerbate ARDS) unless otherwise indicated
 - Acetaminophen is recommended over NSAIDs (e.g., ibuprofen)
 - Preliminary data suggest that NSAIDs may be associated with a more severe outcome. Try to avoid use of these agents in cases of suspected or confirmed COVID-19 infection, unless medically necessary.
- Nebulizer treatments can potentially aerosolize the virus and increase the risk of exposing others
 - Metered dose inhalers (MDIs) are difficult to procure and should not be ordered unless medically indicated
- High flow oxygen nebulizer treatments and non-invasive positive pressure ventilation (CPAP/BiPAP) are highly discouraged in patients with suspected or confirmed COVID19 as they create aerosolized particles
- Corticosteroids should be avoided due to potential for prolonging viral replication, unless indicated for other reasons
- Concomitant infection with influenza or bacterial pneumonia with COVID-19 is unlikely, anti-influenza and antibacterial drugs should not be initiated or continued unless clinically indicated

COVID-19 Provisional Guidance Algorithm for Treatment



- Case management will assist in identifying patients eligible for discharge
- Inpatient pharmacists will ensure a quantity no greater than what is required to finish the 5-day course is dispensed and will not provide refills
- The inpatient pharmacy will appropriately log and label hydroxychloroquine prescriptions for discharge
- This guidance will be updated as the situation evolves, we monitor the literature, and our supplies are monitored
- Routine addition of azithromycin to the recommended regimens is not recommended
- Lopinavir/ritonavir use is not recommended as monotherapy and should be reserved for severe cases

Inpatient Adult <u>SUSPECTED</u> COVID-19 Infection	
Strongly consider infectious diseases and/or pulmonary consultation	
<u>Severity of Illness*</u>	<u>Recommendations</u>
Mild Illness	Supportive care
Pneumonia (non-severe)	
Severe Pneumonia	Supportive Care PLUS <u>First Choice:</u> Hydroxychloroquine sulfate 400 mg oral BID x 2 doses, then 200 mg oral BID x 4 days OR <u>Second Choice:</u> Chloroquine 500 mg oral BID x 10 days
Inpatient Adult <u>LAB-CONFIRMED</u> COVID-19 Infection	
Strongly consider infectious diseases and/or pulmonary consultation	
<u>Severity of Illness*</u>	<u>Recommendation</u>
Mild Illness	Supportive Care PLUS <u>First Choice:</u> Hydroxychloroquine sulfate 400 mg oral BID x 2 doses, then 200 mg oral BID x 4 days OR <u>Second Choice:</u> Chloroquine 500 mg oral BID x 10 days
Pneumonia (non-severe)	
Severe Pneumonia	Supportive Care PLUS Consider remdesivir through Gilead compassionate use pathway <u>Key inclusion criteria for remdesivir (expecting change soon)</u> <input type="checkbox"/> Must be age less than 18 years or pregnant <input type="checkbox"/> Hospitalization <input type="checkbox"/> Lab-confirmed COVID-19 pneumonia <input type="checkbox"/> Mechanical ventilation <u>Key exclusion criteria for remdesivir</u> <input type="checkbox"/> Evidence of multi-organ failure <input type="checkbox"/> Pressor requirement to maintain blood pressure <input type="checkbox"/> ALT > 5x upper limit of normal <input type="checkbox"/> CrCl below 30 mL/min or ECMO If ineligible for remdesivir OR while waiting for remdesivir, START: <u>First Choice:</u> Hydroxychloroquine sulfate 400 mg oral BID x 2 doses, then 200 mg oral BID x 4 days OR <u>Second Choice:</u> Chloroquine 500 mg oral BID x 10 days <u>Note:</u> Once remdesivir is initiated, other experimental anti-SARS-CoV-2 therapies must be discontinued For patients unresponsive and experiencing severe COVID-19 with clinical evidence of cytokine storm: consider tocilizumab (criteria for use provided below)

*Refer to WHO guidance for more detailed information on severity of illness categorization (page 4 of this document)

- We do not recommend routine addition of azithromycin or lopinavir/ritonavir to the recommended regimens
- We recommend EKG at baseline before starting hydroxychloroquine or chloroquine

THERE ARE NO SYSTEM-WIDE DRUG RESTRICTIONS. ENTITY-SPECIFIC RESTRICTIONS MAY APPLY.
Disclosure to the patient and/or caregiver regarding the use of off-label medications is recommended with chart documentation.

Inpatient Pediatric <u>SUSPECTED</u> COVID-19 Infection	
Strongly consider infectious diseases and/or pulmonary consultation	
<u>Severity of Illness*</u>	<u>Recommendations</u>
Mild Illness	Supportive care
Pneumonia (non-severe)	
Severe Pneumonia	Supportive Care PLUS Hydroxychloroquine sulfate 6.5 mg/kg (max dose 400 mg) oral BID x2 doses, then 3.25 mg/kg (max dose 200 mg) oral BID x4 days
Inpatient Pediatric <u>LAB-CONFIRMED</u> COVID-19 Infection	
Strongly consider infectious diseases and/or pulmonary consultation	
<u>Severity of Illness*</u>	<u>Recommendation</u>
Mild Illness	Supportive Care PLUS Hydroxychloroquine sulfate 6.5 mg/kg (max dose 400 mg) oral BID x 2 doses, then 3.25 mg/kg (max dose 200 mg) oral BID x 4 days
Pneumonia (non-severe)	
Severe Pneumonia	Supportive Care PLUS Consider remdesivir (through Gilead compassionate use pathway) <u>Key inclusion criteria for remdesivir (expecting changes soon)</u> <ul style="list-style-type: none"> <input type="checkbox"/> Must be age less than 18 years or pregnant <input type="checkbox"/> Hospitalization <input type="checkbox"/> Lab-confirmed COVID-19 pneumonia <input type="checkbox"/> Mechanical ventilation <u>Key exclusion criteria for remdesivir</u> <ul style="list-style-type: none"> <input type="checkbox"/> Evidence of multi-organ failure <input type="checkbox"/> Pressor requirement to maintain blood pressure <input type="checkbox"/> ALT > 5x upper limit of normal <input type="checkbox"/> CrCl below 30 mL/min or ECMO If ineligible for remdesivir OR while waiting for remdesivir, START: Hydroxychloroquine sulfate 6.5 mg/kg/dose (max dose 400 mg) oral BID x 2 doses, then 3.25 mg/kg/dose (max dose 200 mg) oral BID x 4 days <u>Note:</u> Once remdesivir is initiated, other experimental anti-SARS-CoV-2 therapies must be discontinued For patients unresponsive and experiencing severe COVID-19 with clinical evidence of cytokine storm: consider tocilizumab (criteria for use provided below)

*Refer to WHO guidance for more detailed information on severity of illness categorization (page 4 of this document)

- We do not recommend routine addition of azithromycin or lopinavir/ritonavir to the recommended regimens
- We recommend EKG at baseline before starting hydroxychloroquine or chloroquine

WHO Classification of Clinical Syndromes Associated with COVID-19

Table 2. Clinical syndromes associated with COVID-19

Mild illness	<p>Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea and vomiting (3, 11-13).</p> <p>The elderly and immunosuppressed may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, such as e.g. dyspnea, fever, GI-symptoms or fatigue, may overlap with COVID-19 symptoms.</p>
Pneumonia	<p>Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen.</p> <p>Child with non-severe pneumonia who has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40, and no signs of severe pneumonia.</p>
Severe pneumonia	<p>Adolescent or adult: fever or suspected respiratory infection, plus one of: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2 \leq 93\%$ on room air (adapted from 14).</p> <p>Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or $SpO_2 < 90\%$; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (15). Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 (16). While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.</p>
Acute respiratory distress syndrome (17-19)	<p>Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms.</p> <p>Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.</p> <p>Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present.</p> <p>Oxygenation impairment in adults (17, 19):</p> <ul style="list-style-type: none"> Mild ARDS: $200 \text{ mmHg} < PaO_2/FiO_2^a \leq 300 \text{ mmHg}$ (with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) Moderate ARDS: $100 \text{ mmHg} < PaO_2/FiO_2 \leq 200 \text{ mmHg}$ (with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) Severe ARDS: $PaO_2/FiO_2 \leq 100 \text{ mmHg}$ (with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients). <p>Oxygenation impairment in children: note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2. Use PaO_2-based metric when available. If PaO_2 not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate OSI or SpO_2/FiO_2 ratio:</p> <ul style="list-style-type: none"> Bilevel (NIV or CPAP) $\geq 5 \text{ cmH}_2\text{O}$ via full face mask: $PaO_2/FiO_2 \leq 300 \text{ mmHg}$ or $SpO_2/FiO_2 \leq 264$ Mild ARDS (invasively ventilated): $4 \leq OI < 8$ or $5 \leq OSI < 7.5$ Moderate ARDS (invasively ventilated): $8 \leq OI < 16$ or $7.5 \leq OSI < 12.3$ Severe ARDS (invasively ventilated): $OI \geq 16$ or $OSI \geq 12.3$.

Source: [World Health Organization. Clinical management of severe respiratory infection \(SARI\) when COVID-19 disease is suspected: Interim guidance V 1.2 \[accessed 18 March 2020\]](#)

THERE ARE NO SYSTEM-WIDE DRUG RESTRICTIONS. ENTITY-SPECIFIC RESTRICTIONS MAY APPLY.

Disclosure to the patient and/or caregiver regarding the use of off-label medications is recommended with chart documentation.

Hydroxychloroquine sulfate (Plaquenil®)

Rationale for use: Hydroxychloroquine and chloroquine have the same mechanism of action. They have been found to be active against SARS-CoV-2 *in vitro*. Reports out of China have indicated chloroquine is an effective therapeutic option for COVID-19, but human data are generally lacking. One study found hydroxychloroquine is more potent *in vitro* as compared to chloroquine versus SARS-CoV-2. The Italian Government, Chinese Government, an expert consensus publication, and numerous American Institutions are now recommending hydroxychloroquine and/or chloroquine for treating COVID-19 infection.

NOTE: A small non-randomized clinical trial incidentally found that addition of azithromycin to hydroxychloroquine resulted in PCR-negativity more rapidly than hydroxychloroquine alone. The clinical significance of this finding is unknown. These data do not warrant the routine addition of azithromycin to hydroxychloroquine for treatment of COVID-19 disease.

Proposed mechanism of action: alters the pH of the cell membrane thus inhibiting fusion of the virus, interferes with the glycosylation of cellular receptors of the SARS-CoV-2 virus, and impairs the acidification of endosomes resulting in less viral trafficking within cells

Hydroxychloroquine (Plaquenil®)

- All doses expressed as hydroxychloroquine sulfate. Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine
- Adult dosing:
 - BHSF-recommended (reference #3):
 - 400 mg oral BID x 2 doses followed by 200 mg oral BID x 4 days
- Pediatric dosing:
 - Extrapolated from Lexi-comp by BHSF:
 - Hydroxychloroquine 6.5 mg/kg (max dose 400 mg) oral BID x2 doses, then 3.25 mg/kg (max dose 200 mg) oral BID x 4 days
- Tablets can be crushed for oral administration or crushed and made into an oral solution
 - <https://www.nationwidechildrens.org/specialties/pharmacy-services/compounding-formulas>
 - Administer with milk or food
- Obtain EKG at baseline, can prolong QTc
 - Use with caution in patients with a history of cardiac disease, ventricular arrhythmias, hypokalemia, hypomagnesemia
 - Use with caution if patients are on other QTc-prolonging medications
- Associated with fetal ocular toxicity, discuss the risk:benefit ratio prior to use in pregnant or breastfeeding women
- Use with caution in patients with:
 - Diabetes (may cause hypoglycemia)
 - Myocardial dysfunction (potential to cause cardiomyopathy)
 - Renal or hepatic impairment
 - Gastrointestinal disorders
 - Porphyria
 - Psoriasis
- Consider G6PD deficiency testing, use with caution in patients with G6PD deficiency
- Can cause neuromuscular weakness
- Adverse effects are generally associated with long-term use and high doses
- **Contraindicated** in retinal or visual field changes of any etiology

Chloroquine

Chloroquine

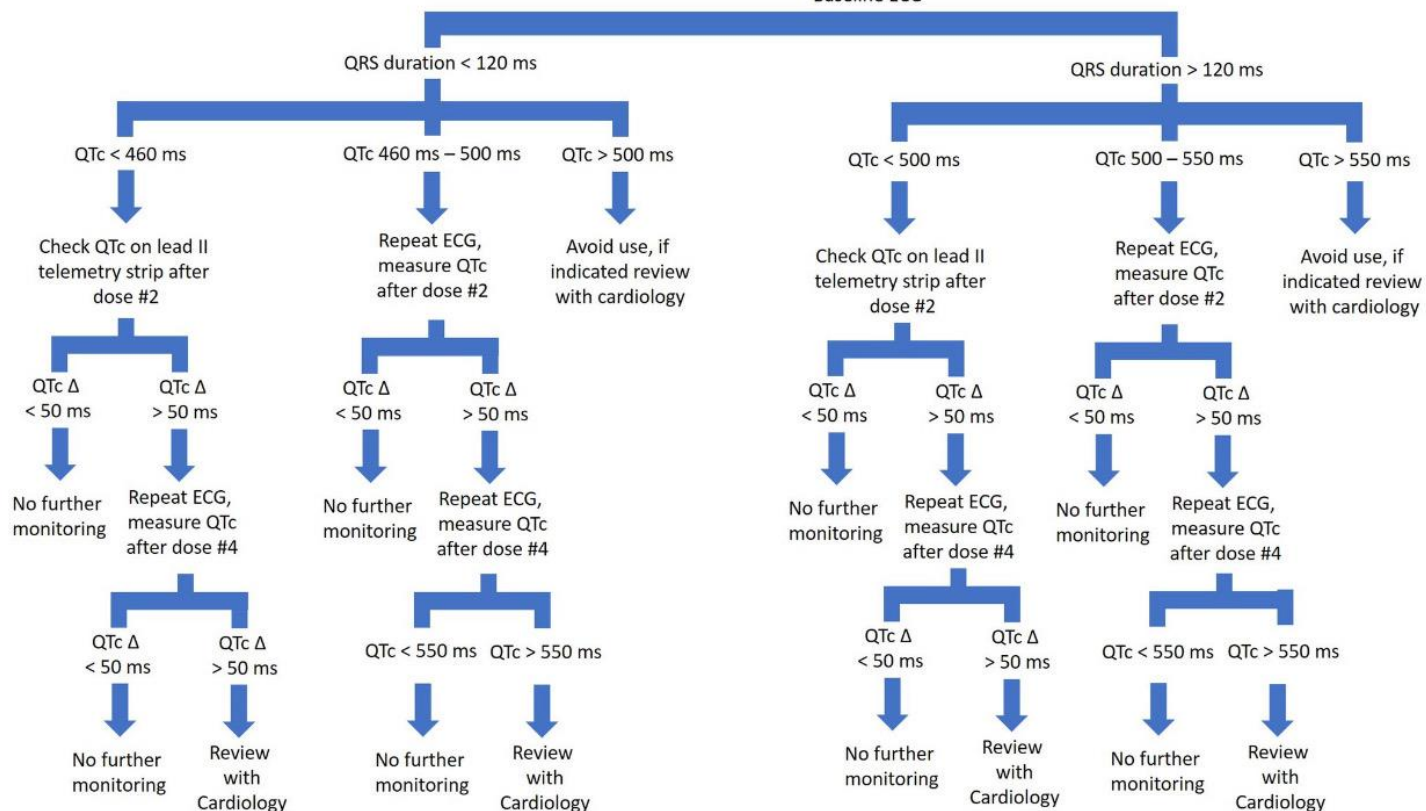
- Information listed for hydroxychloroquine also applies to chloroquine (except dosing)
- Adult dose: 500 mg oral PO BID x 10 days
- Tablets can be crushed for oral administration or crushed and made into an oral solution
 - <https://www.nationwidechildrens.org/specialties/pharmacy-services/compounding-formulas>
- Chloroquine is generally not tolerated as well as hydroxychloroquine, warnings listed above also apply to chloroquine
- Can cause extrapyramidal effects
- Use with caution in patients with seizure disorders
- Separate from antacids by at least 4 hours, may reduce chloroquine concentrations

COVID19 patient initiating
Chloroquine, hydroxychloroquine

- ↓
- Discontinue QT prolonging medications
 - Replete K > 4.0, Mg > 2.0

↓

Baseline ECG



Note: Credit to Dr. Pascual and Dr. Viles Gonzalez via University of Washington

Lopinavir/ritonavir (Kaletra®, LPV/r)

Rationale for use: LPV/r has been studied as monotherapy and as part of combination therapy for COVID-19 disease. Data from *in vitro* studies shows it does have activity versus SARS-CoV-19. Human data indicate LPV/r is not effective as monotherapy. LPV/r may be clinically useful for COVID-19 management when used in combination therapy.

NOTE: The Society of Critical Care Medicine recommends against routine use of lopinavir/ ritonavir (weak recommendation, low quality of evidence)

Proposed mechanism of action: Lopinavir inhibits viral protease activity and prevents the cleavage of the viral precursors into individual functional proteins resulting in the formation of immature, noninfectious particles. Ritonavir is also a protease inhibitor, but it is used in this combination as a “booster”, because it increases lopinavir concentrations by inhibiting CYP-3A4 enzymes.

****Has no role for monotherapy when treating COVID-19****

- **Adult dose:** 400-100 mg oral BID x 14 days
- **Pediatric dose:**
 - 14 days to 6 months of age:
 - 16 mg/kg oral BID based upon LPV component x 14 days
 - 6 months to 18 years:
 - 15-25 kg: 200-50 mg oral BID x 14 days
 - 26-35 kg: 300-75 mg oral BID x 14 days
 - Above 35 kg: use adult dosing
- Oral solution may be intolerable due to high alcohol content
 - Can administer with sweet foods, tangy foods, chocolate syrup, or peanut butter to improve palatability
- Administer oral solution with food
- Oral tablet may be crushed for oral administration, but is expected to reduce exposure by approximately 50%
- Ritonavir is a CYP3A4 inhibitor, beware drug-drug interactions (it increases concentrations of some drugs)
 - Resource for managing drug-drug interactions: <http://www.covid19-druginteractions.org/>
- Drugs metabolized by the liver may interact with lopinavir and ritonavir
- Consider HIV testing at baseline
- Adverse effects are more likely with prolonged therapy
- Beware potential adverse effects of: diarrhea, increased ALT, altered cardiac conduction (QTc prolongation), skin rash, nausea, vomiting, hyperglycemia

Remdesivir (GS-5734, RDV)

Rationale for use: Initially studied for Ebola virus, remdesivir was also found to have *in vitro* activity versus a wide array of viruses, including SARS-CoV-2. It is currently being investigated as a therapeutic option in the management of patients with COVID-19 disease.

Proposed mechanism of action: Nucleotide analogue prodrug that is intracellularly metabolized into an analogue of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses.

** Investigational drug available for compassionate use application only**

- Remdesivir cannot be used simultaneously with other experimental antiviral agents for COVID-19
- The treating physician must initiate a request for compassionate use remdesivir
 - Initiating remdesivir requests does not have to be done by an infectious diseases physician
 - We recommend infectious diseases consult should be involved in remdesivir patients
- If considering remdesivir therapy, please make pharmacy services aware so they can assist
- **Adult dose:**
 - Day 1: 200 mg IV once over 30 to 60 minutes
 - Days 2-10: 100 mg IV once daily over 30 to 60 minutes
- **Pediatric dose:**
 - Body weight < 40 kg:
 - Day 1: 5 mg/kg IV once over 30 to 60 minutes
 - Days 2-10: 2.5 mg/kg IV daily over 30 to 60 minutes
 - Body weight > 40 kg: follow adult dosing
- **Key inclusion criteria**
 - At this time patients must be less than 18 years of age or pregnant to qualify, this inclusion criteria is expected to change in the near future
 - Hospitalization
 - Confirmed SARS-CoV-2 by PCR
 - Invasive Mechanical ventilation
- **Key exclusion criteria**
 - Evidence of multi-organ failure
 - Pressor requirement to maintain blood pressure
 - ALT levels > 5 X upper limit of normal
 - Creatinine clearance < 30 mL/min or dialysis or continuous veno-venous hemofiltration
- Helpful information to gather when initiating a request for compassionate use remdesivir:
 - Prescriber name, address, email, and phone number associated with the treatment center
 - Professional designation (e.g., MD) or qualifications of requester including medical license number
 - Institution/ hospital name, address, email, and phone number
 - Shipping information (including pharmacy hours)
 - Patient case information, including previous or current treatments and clinical status
- Gilead webpage listing inclusion/exclusion criteria: <https://rdvcu.gilead.com/>
- For information about compassionate use: compassionateaccess@gilead.com

Tocilizumab (Actemra®)

Rationale for use: Cytokine release syndrome (CRS) may be an important component of the critical illness associated with COVID-19. This agent does not possess antiviral activity and therefore should only be utilized as adjunctive therapy in the setting of suspected cytokine release syndrome. Chinese guideline, "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan" (Provisional 7th Edition) recommends for patients with extensive and bilateral lung disease and severely ill patients with elevated IL-6 levels. The Italian COVID-19 treatment recommend it be considered for use in patients with ARDS after 24 hours.

NOTE: The Society of Critical Care Medicine cites ongoing clinical trials of tocilizumab for COVID-19 and does not provide a recommendation on safety or efficacy.

Proposed mechanism of action: IL-6 receptor antagonist leading to a reduction in cytokine and acute phase reactant production

Tocilizumab does not have antiviral activity

- Should be reserved for patients that have failed alternative therapies, have severe COVID-19 disease, and clinical evidence of cytokine storm.
- **Inclusion criteria (must meet all):**
 - Approved by infectious diseases physician
 - Hospitalized patient who is intubated
 - Lab-confirmed SARS-CoV-2
 - Bilateral lung disease
 - Extensive lung disease
 - Severe COVID-19 illness per WHO criteria
 - Clinical evidence of cytokine storm
 - Elevated IL-6 – may be a send out test, does not necessarily preclude use
 - Other markers (persistent high fever, elevated D-dimer, elevated C-reactive protein, elevated ferritin, low fibrinogen)
- **Exclusion criteria (must not meet any):**
 - Current invasive bacterial, viral (non-COVID-19), or fungal infection
 - AST/ALT above 5x upper limit of normal (soft exclusion, depends on underlying cause)
 - Platelets below 50,000
 - Long-term oral anti-rejection or immunomodulatory drugs
 - Recent history of GI perforation
 - History of hypersensitivity to tocilizumab or any excipients
- Considerations for Massachusetts General Hospital guidance should be given (see next page below)
- **Adult dose:** infuse over 60 minutes
 - Option #1 (BHSF-recommended):
 - 400 mg IV x 1 dose followed by an additional 400 mg IV dose if fever persists after 12 hours
 - Option #2:
 - 30 to 100 kg: 400 mg IV x 1 dose
 - > 100 kg: 600 mg IV x 1 dose
- **Pediatric dose:** infuse over 60 minutes
 - Less than 30 kg: 12 mg/kg IV x 1 dose (round to nearest 50 mg)
 - 30 kg or more: 8 mg/kg IV x 1 dose (maximum 400 mg per dose), if fever persists after 12 hours
- Has a half-life of up to 13 days in adults
 - The long half-life may predispose patients to infection at a later time
- **FDA- approved indications:**
 - Cytokine release syndrome due to chimeric antigen receptor-T cell therapy
 - Giant cell arteritis
 - Rheumatoid arthritis
- IL-6, C-reactive protein, D-dimer, and LDH levels should be used to diagnose cytokine release syndrome and monitor therapy
- Assess for Hepatitis B with surface antigen and core antibody. Test results do not preclude treatment.
 - If either antigen or antibody are positive, obtain a viral load (HBV DNA)
 - If detectable viral load, consider starting antiviral therapy
- The H-score may be a useful tool for evaluating patients for cytokine storm
- Use caution in patients with a history of GI perforation, diverticulitis, or elevated LFTs
- All patients receiving tocilizumab should be ruled out for latent TB prior to administration per package insert. Does not preclude treatment.
- Very expensive (single adult dose is thousands of dollars) and product is available in limited supply from wholesaler

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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 – <i>no treatment</i>
Grade 2 – <i>send for serum IL-6</i>
Grade 3 – <i>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</i>
Grade 4 – <i>send for serum IL-6; consider tocilizumab as Grade 3; consider corticosteroids</i>

- Note: Follow BHSF tocilizumab dosing guidance as described in BHSF document (previous page)

REFERENCES

1. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. [accessed 19 March 2020]
2. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). [accessed 19 March 2020]
3. Yao X, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*. 2020; Caa237.
4. Chinese government's New Coronavirus Pneumonia Diagnosis and Treatment Plan (Version 7). Translated into English. Accessed 19 March 2020.
5. Jie Z, et al. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus. *CMA*. 2020. 12; 43(3): 185.88.
6. McHenry AR, et al. Stability of extemporaneously prepared hydroxychloroquine sulfate 25-mg/mL suspension in plastic bottles and syringes. *IJPC*. 2017; 21(3): 241-54.
7. Wang, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*. 2020;30:269-71.
8. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020 Feb 19 [Epub ahead of print]; doi:10.5582/bst.2020.01047.
9. Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J of Antimicrob Agents* (2020); <https://doi.org/10.1016/j.ijantimicag.2020.105932>
10. Chu CM et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59: 252–56
11. Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *NEJM*. Published March 18 2020. [Accessed 19 March 2020]
12. Best, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Deficiency Syndrome*. 2011;58:385-91.
13. Alhazzani W, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease (COVID-19). Accessed 20 March 2020.
14. Mehta P. COVID-19: consider cytokine storm syndromes and immunosuppression. *The LANCET*. Published March 16, 2020.
15. Xu X, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *ChinaXIV*. ePub. Accessed 16 March 2020.
16. Massachusetts General Hospital COVID-19 Treatment Guideline. Version 1.0. Accessed 20 March 2020.
17. Gautret P, et al. Hydroxychloroquine and azithromycin as a treatment for COVID-19: results of an open-label non-randomized clinical trial. *IJAA*. Published online March 20, 2020.
18. McCreary EK, Pogue JM. COVID-19 Treatment: A review of early and emerging options. *Open Forum Infectious Diseases*. 2020; ePub ahead of print.
19. Zhou D, et al. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *JAC*. 2020. ePub ahead of print.

The COVID-19 pandemic is rapidly evolving. New data is coming out every day. We will continue to take guidance from our clinicians, review documents released by professional organizations, and monitor the literature. We are aware there are other potential therapies under investigation for COVID-19. This document will be updated periodically.

Contact: TimothyGA@BaptistHealth.net