University of Iowa Health Care

Guidance on Treatment Options for Patients with SARS-CoV-2

PROTOCOL TEMPORARILY CREATED PURSUANT TO AUTHORITY OF HOSPITAL INCIDENT COMMANDER ACTIVATED IN RESPONSE TO COVID-19. EFFECTIVE UNTIL FURTHER NOTICE.

Date Created Per HICS: 3/20 **Date Amended Per HICS:** 3/24

We have developed this document in response to the current global pandemic. This situation is rapidly evolving, and we will update this document as often as possible. We urge you to be mindful of the date on the document and to check that against current knowledge and evolving clinical standards. Please call the infectious disease team with questions about management of specific patients.

Key Points Regarding PROPHYLAXIS:

- There are notably no therapeutic regimens that have evidence to support their use for post-exposure prophylaxis. A study is being conducted at the University of Minnesota to further clarify the utility of hydroxychloroquine for this indication. Questions regarding the study may be submitted to faq.covid19@gmail.com. Eligibility to participate may be found at https://is.gd/covid19pep
- Given the baseline needs of patients with current clinical conditions requiring these medications we **recommend against any prescribing for pre- and post-exposure prophylaxis**

Key Points Regarding TREATMENT:

- Standard of care continues to be appropriate isolation and support of organ systems based on the most recent guidance from US Centers for Disease Control (CDC) and World Health Organization (WHO)
- There are numerous antiviral therapies being proposed as options for treatment of SARS-CoV-2; however, data is lacking at this time to identify any medication therapy that can be considered the gold standard. **This document provides a brief overview of therapeutic agents as assessed by the UIHC Antimicrobial Stewardship Team; it will be subject to updates and changes as additional information becomes available**
- In the case of lab-confirmed SARS-CoV-2, remdesivir is considered the agent with the highest potential for therapeutic benefit. At this time, it is only available through enrollment in clinical trial (subject to randomization) or compassionate use (if patients do NOT meet criteria for any onsite clinical trials).

Tier 1: Preferred – most promising efficacy / safety data

Medication	Details
Remdesivir	• Nucleotide prodrug with *in vitro* activity against a variety of RNA viruses including coronaviruses. *In vivo* clinical trials are still ongoing with data eagerly anticipated • Currently available only through clinical trial and / or compassionate use access from Gilead Pharmaceuticals • Only available through compassionate use at UIHC currently. See appendix A for full criteria; patient must be intubated. Immediately Page x1282 (24/7) if patient meets criteria • Clinical trial anticipated to start at UIHC week of 3/23/20 (updates will be given at that time for criteria and screening)

Tier 2: Equivocal - less promising efficacy data and/or increased toxicity profile

Medication	Details
Hydroxychloroquine / chloroquine	• Both chloroquine and hydroxychloroquine have been noted to have potent *in vitro* inhibition of SARS-CoV-2; however, robust clinical trials have not confirmed *in vivo* success. Only hydroxychloroquine is readily available at this time

	• Use of this therapy may be considered in hospitalized patients of any severity that do NOT qualify for remdesivir though the benefits must be weighed against the potential risks (see appendix B)
	• **Hydroxychloroquine at UIHC is restricted to the below criteria. Notably hydroxychloroquine is not allowed for prophylaxis given supply constraints.**
	  ○ **Inpatient: approval through rheumatology or ID, continuation of home therapy, AND/OR confirmed COVID-19**
	  ○ **Outpatient: new prescriptions by rheumatology or ID, continuation of prior therapy, AND/OR TREATMENT of confirmed COVID-19 (limited to a 5-day supply)**
	• Standard preferred dosing regimen in adults: 400 mg PO twice daily x 2 doses; then 200 mg twice daily x 8 doses
	• The addition of azithromycin to either of these agents is not recommended at this time given the lack of compelling data to support its impact on clinical outcomes

Tier 3: Not Recommended – theoretical benefit unlikely and potentially outweighed by risks (in alphabetical order)

Medication	**Rationale for Recommendation**
Azithromycin	One piece of literature has proposed addition of azithromycin to hydroxychloroquine decreased time to viral clearance. No clinical outcomes were assessed and only 6 patients received azithromycin. There is not enough evidence currently to recommend this combination
Darunavir / cobicistat	There is no laboratory or clinical data to demonstrate potency against SARS-CoV-2
Interferon	Interferons have been studied (often in combination with ribavirin) in other coronaviruses including SARS-CoV-1 and MERS without clinical success. Side effects are likely to outweigh the clinical benefit
Influenza Agents	Coronaviruses do not utilize neuraminidase for replication and no activity is expected
Lopinavir / ritonavir	Though there have been *in vitro* studies suggesting some level of activity against coronaviruses, RCT of 200 patients showed no benefit over placebo and an open label trial compared to a Japanese antiviral drug showed no association for better outcomes with lopinavir/ritonavir
Ribavirin	Ribavirin has been studied (often in combination with interferon) in other coronaviruses including SARS-CoV-1 and MERS without clinical success. Side effects such as anemia are likely to outweigh the potential benefit

Supportive Agents (in alphabetical order)

Medication	**Details**
Acetaminophen / NSAIDs (non-steroidal anti-inflammatory drugs)	There is no conclusive evidence to suggest that NSAIDs such as ibuprofen increase the severity of COVID-19 disease and they are NOT contraindicated; however, acetaminophen may be considered the preferred fever-reducer / pain reliever in patients with viral illness based on more benign side effect profile overall
ACE-inhibitors / ARBs	Theoretical concern has been described over the risk of ACE-inhibitors and ARBs increasing therapeutic targets for SARS-CoV-2. At this time, professional societies in cardiology and nephrology are **advising not to add or remove any RAAS-related treatments beyond actions based on standard clinical practice.**
Interleukin inhibitors (including anakinra, sarilumab, tocilizumab)	There is not evidence to routinely recommend for patients with COVID-19. Additional guidance will be provided soon regarding criteria for use of these agents in this patient population.
Intravenous Immunoglobulin (IVIG)	Routine use not recommended by Society of Critical Care Medicine (SCCM); however, it may be considered in the context of cytokine storm (additional criteria forthcoming)

Steroids	**May be considered if patient is intubated with ARDS if potential benefit outweighs risk per (SCCM) recommendation:** • Mechanically ventilated without ARDS-suggest against the routine use of corticosteroids • Mechanically ventilated with ARDS: suggest using systemic corticosteroids over not using **CDC and WHO do not recommend steroid therapy for SARS-CoV-2 outside of a specific alternative indication, such as sepsis.** Systematic reviews in other coronavirus and respiratory viral infections have demonstrated no survival benefit and possible harm. Early reports from China have suggested possible benefit from methylprednisolone.

Appendix A: Remdesivir (investigational drug)

Only available currently by compassionate use: If patient meets criteria page x1282 (24/7) immediately to begin the request process. Takes average of 72 hours from request to drug administration, if approved by the company.

Key Inclusion criteria*:

- Hospitalization
- Confirmed SARS-CoV-2 by PCR
- Invasive (ie intubated or tracheostomy) Mechanical Ventilation

Key Exclusion criteria*:

Evidence of Multi-organ failure

- Pressor requirement to maintain blood pressure (ok if patient has been on, but is currently off)
- ALT levels > 5 X ULN
- Cr Clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration

*These criteria is subject to change without notice

Mechanism of Action: nucleotide analogue, initially developed for treatment of Ebola. It works by inhibiting RNA-dependent RNA polymerase.

Evidence Summary: In-vitro activity against MERS and SARS and has shown efficacy in animal models. It was been shown to inhibit SARS-CoV-2 in vitro

Reports of use in patients with SARS-CoV2 in China, publication pending

Remdesivir was used in a single patient with COVID-19 in Washington State, administration was associated with clinical improvement

Dosing:

- Adults: 200mg IV x1, followed by 100mg daily x 9 more days

Toxicity: elevated transaminases (reversible upon drug cessation), reversible kidney injury (avoid other nephrotoxic agents if possible, including NSAIDS), hypotension during infusion

Monitoring/labs: CBC with differential, BMP, hepatic panel. More specific labs will be updated and directed based on study protocol.

Drug metabolism: Remdesivir is a prodrug requiring CYP3A4 for activation thus there is potential for reduced conversion in the presence of CYP3A4 inhibitors like lopinavir/ritonavir, cobicistat, etc.

IV compatibility: Is compatible with 0.9% NaCl, no other compatibility information is available

Administration/handling instructions: If not in a dedicated line, flush line prior to administration. Administer 250ml bag over 30 minutes, after infusion flush the line with at least 30ml NS to ensure all the remdesivir solution has been administered. Should be treated with hazardous (non-chemotherapy) precautions.

Clinical Trials: NCT04257656, NCT04252664, NCT04280705, NCT04292899, NCT04292730, NCT043028766

- University of Iowa will be a study site for NCT04292730 and NCT04292899
- Study activation date TBD (anticipating activation during weeks of March 23rd)

Appendix B: Hydroxychloroquine

Mechanism of Action: Heme polymerase inhibitor; increases the pH of the phagolysosome, which interrupts virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS- CoV

Evidence Summary: Hydroxychloroquine has been shown to inhibit replication of SARS-CoV2 in vitro. Chloroquine has been shown to inhibit many viruses *in vitro*. However, it has not been shown to be an effective antiviral *in vivo* in limited trials. In an animal model of chikungnya virus infection, chloroquine delayed the immune response, resulting in lack of viral clearance . A small, open-label, non-randomized study conducted in France showed reduced time to viral clearance in the oropharynx compared to patients that did not receive hydroxychloroquine.

Dosing:

- Adults: 400 mg PO twice daily x 2 doses; then 200 mg twice daily x 8 doses
- No adjustments in hepatic or renal dysfunction

Toxicities:

- QTc prolongation
- dizziness, headache, nausea, vomiting, appetite loss
- LFT abnormalities
- Retinopathy with prolonged use (>5 years), not in the acute setting
- Anemia (potentially higher rate in G6PD-deficiency, but not necessarily an indication to withhold therapy)

Clinical trials underway: NCT04308668 (Minnesota), NCT04307693, NCT04261517, NCT04315896

It is being investigated in clinical trials in China and Korea for treatment. It is being evaluated at the University of Minnesota for post-exposure prophylaxis.

Note on supply chain issues: given the national attention that has been put on the potential benefit of chloroquine and hydroxychloroquine for the treatment of COVID-19, the United States is facing significant supply chain issues related to both medications. UIHC currently has a small supply of hydroxychloroquine and guidance for its use in this document attempts to maximize the potential (unproven) benefit for patients at highest risk of negative clinical outcomes. **At this time, patients with COVID-19 that do not fall into the inpatient / outpatient criteria listed below may still receive a 5-day supply of drug at the discretion of their provider; however, hydroxychloroquine is NOT available for any patient that does not have confirmed COVID-19.**

Guidance Regarding Inpatients:

- Inclusion criteria: hydroxychloroquine may be considered in any hospitalized patients that do NOT qualify for remdesivir (either through clinical trial or compassionate use)
- Contraindications: allergy to hydroxychloroquine, prolonged QTc (consider 500 milliseconds as maximum acceptable measurement and use with caution above 470 milliseconds), uncorrected electrolyte abnormalities (i.e. potassium <3.5 mEq/L, calcium < 8.5 mg/dL, magnesium <1.5 mg/dL)
- Recommended monitoring:

- Recommend obtaining baseline EKG in the setting of any of the following conditions: concomitant use of one or more prolonging QTc agents (aside from hydroxychloroquine), known history of prolonged QTc, bradycardia, heart failure, chronic kidney disease
- Recommend baseline electrolytes including potassium and magnesium and repletion as needed

Guidance Regarding Outpatients:

- Inclusion criteria: hydroxychloroquine may be considered in the following patient populations in the outpatient setting include adult patients that meet the following criteria that put that at increased risk for severe disease:
  - Confirmed SARS-CoV-2 by PCR; AND
  - Age > 60 years; AND
  - One of the following criteria:
    - Pulmonary disease (including COPD and asthma)
    - Chronic kidney disease
    - Diabetes mellitus
    - Cardiovascular disease (including cardiomyopathy and coronary artery disease)
    - Immunosuppression (including use of biologic immunomodulators, chronic steroids at a dose equivalent of 20 mg of oral prednisone daily or higher, patients with HIV)
- It is acknowledged that there may be other patient populations (such as patients with history of organ transplantation or oncologic diagnoses) that may be considered high risk for severe disease regardless of age. Hydroxychloroquine may still be prescribed for up to a 5-day course for any patient positive for COVID-19 at the discretion of the prescriber at this time.
- Contraindications: allergy to hydroxychloroquine, patient already receiving hydroxychloroquine for alternative indication, prolonged QTc (consider 470 milliseconds as a maximum acceptable measurement), uncorrected electrolyte abnormalities (i.e. potassium <3.5 mEq/L, calcium < 8.5 mg/dL, magnesium <1.5 mg/dL)
- Recommended monitoring:
  - Recommend obtaining baseline EKG in the setting of any of the following conditions: concomitant use of one or more prolonging QTc agents (aside from hydroxychloroquine), known history of prolonged QTc, bradycardia, heart failure, chronic kidney disease
  - Recommend collecting electrolyte labs (including potassium and magnesium) prior to initiation of hydroxychloroquine if any of the following are present: vomiting, diarrhea, other clinical indication of dehydration, new diuretic use (started in the last 1-2 weeks), chronic kidney disease, heart failure. Provide repletion as needed prior to starting therapy.

Appendix C: Chloroquine (not currently in ready supply within US)

Mechanism of Action: Heme polymerase inhibitor; increases the pH of the phagolysosome, which interrupts virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS- CoV

Evidence summary: see hydroxychloroquine

Dosing:

- Adults: 500mg Q12h x 5 days

Toxicities:

- Cardiac: Hypotension, QTc prolongation, Torsades de pointes, AV block, and ventricular fibrillation/tachycardia, Cardiomyopathy
- Hypoglycemia (severe)
- Hematologic: Hemolytic anemia, aplastic anemia, agranulocytosis
- Dermatologic: Erythema multiforme
- Neurologic: Extrapyramidal symptoms and seizure, anxiety, agitation, psychosis
- Myopathy
- Increased LFTs

Monitoring/labs: Obtain baseline EKG for patients receiving concomitant Qtc prolonging drugs, CBC, BMP, LFTs

Note on supply chain issues: given the national attention that has been put on the potential benefit of chloroquine and hydroxychloroquine for the treatment of COVID-19, the United States is facing significant supply chain issues related to both medications. UIHC currently has NO reliable supply of chloroquine.

Appendix D: References

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