

New Mexico Medical Advisory Team (MAT) Assessment

MAT Workgroup Name: MAT Clinical Care

Date: April 24, 2020

Question or request:

1. Are there any updates based on recent studies or stories in the public media that would modify the previous recommendation dated 4/9?
2. Should New Mexico obtain hydroxychloroquine sulfate for treatment of COVID-19 under the newly issued FDA emergency use authorization (EUA)?
3. Should the request for 50,000 tablets of hydroxychloroquine sulfate be updated?

Recommendation/s in bullet form:

- The MAT Clinical Care Workgroup has revised the guidelines following release of NIH treatment guidelines on April 21 (<https://covid19treatmentguidelines.nih.gov>) and additional guidance from the FDA.¹ The NIH guidelines conclude that there is insufficient clinical data to recommend either for or against using hydroxychloroquine (HCQ) for treatment of COVID-19. The NIH guidelines also recommend that clinicians should monitor for adverse effects, especially prolonged QTc interval when HCQ is used.²
- The MAT Clinical Care Workgroup also notes that individual providers may consider treatment of inpatients using the emergency use access (EUA) approval guidelines provided by the FDA, with the understanding that clinical data regarding hydroxychloroquine (HCQ) in the treatment of COVID-19 is based on studies that are low quality and are largely not peer-reviewed and includes data suggesting: 1) no clinical benefit (most studies), 2) clinical benefit, and 3) increased risk of death.
- The MAT agrees with NIH COVID-19 treatment guidelines which **do not recommend** the use of any agents for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) outside the setting of a clinical trial.
- The MAT recommends securing 50,000 Tablets (200 mg) of HCQ for use under the **crisis standards of care**. We recommend seeking a source other than the FDA stockpile due to reporting requirements.
- Some protocols also discuss using HCQ with azithromycin. MAT does NOT recommend the addition of azithromycin due to lack of adequate supporting evidence and potential side effects. No action is needed by the State of New Mexico to secure azithromycin.
- These recommendations are based on current and evolving scientific evidence and should not supersede clinical judgment. Each individual clinician should assess the risks of individual agents prior to use and the risks versus benefits should be decided on a case-by-case basis as part of the discussion between patient and provider.

Assessment:

Although there are no FDA-approved medications indicated for the treatment of COVID-19, treatment of inpatients with COVID-19 with HCQ may be considered under FDA emergency use guidelines.

- Two recent meta-analyses showed that hydroxychloroquine had little or no benefit in treating other viral diseases and no benefit in treating COVID-19 patients.^{3,4} However, the available data regarding treatment of COVID-19 is very limited. The Clinical Care Workgroup Therapeutics Subcommittee feels that additional information from robust and rigorous clinical trials is needed and a meta-analysis should not substitute for more robust data from a randomized controlled trial (RCT).
- The Infectious Diseases Society of America (IDSA) has released guidelines that recommend that use of HCQ/chloroquine among COVID-19 inpatients be used in the context of a clinical trial (www.idsociety.org/COVID19guidelines), but IDSA does not state that it should **only** be used in clinical trials for this indication.

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- HCQ can be prescribed off label at the physician's discretion; physicians are not required to participate in a clinical trial to prescribe this medication.
- Under the emergency use access approval by FDA, the suggested dose for HCQ sulfate to treat adults and adolescents who weight 50kg or more and are hospitalized with COVID-19 is 800mg of HCQ on the first day of treatment followed by 400mg daily for 4 to 7 days of total treatment based on clinical evaluation. While Randomized Controlled Trial (RCT) study data is not yet available, this group recommends continuing to pursue IRB-approved clinical trials and procurement of HCQ. We will continue to monitor the scientific literature and update recommendations as appropriate.
- The State of New Mexico should work with industry to secure 50,000 tablets of HCQ that can be used to treat patients with moderate to severe COVID-19 disease. If industry supply is not available, then medication should be obtained through the Strategic National Stockpile. However, there are significant stipulations and reporting requirements for use of HCQ obtained through the Strategic National Stockpile which may not be feasible for smaller health systems.

EVIDENCE:

Use of Hydroxychloroquine (HCQ) for COVID-19:

HCQ has been shown, in preliminary data from one small randomized trial in China, to shorten the time to clinical recovery, whereas another randomized trial in China and a retrospective French study designed to emulate a RCT showed no clinical benefit.^{5, 6, 7} In a manuscript released on April 21, Magagnoli *et al.* reported the results of a large retrospective study in US veterans hospitalized with COVID-19.⁸ They found no evidence that HCQ with or without azithromycin reduced the risk of mechanical ventilation, and the risk of death was significantly increased in patients treated with HCQ alone. No peer-reviewed results from RCTs are available at this time, but several RCTs are in progress (<http://clinicaltrials.nih.gov>).

Silva *et al.* recently reported preliminary safety results a study comparing two doses of chloroquine diphosphate in patients hospitalized with COVID-19. In this study, subjects treated with 600 mg twice daily for 10 days had more QTc prolongation >500 ms (25%) and a trend toward increased risk of ventricular tachycardia 2/28 vs 0/28 ($p=0.51$), respectively, when compared to subjects receiving 450 mg twice on day one followed by 450 mg daily for 4 days. In 14 subjects with paired samples, respiratory samples at day 4 were negative in only one subject.⁹

If the pharmaceutical industry is not able to supply the HCQ, the State of New Mexico should request this medication through the Strategic National Stockpile. However, drugs obtained through the Strategic National Stockpile have tighter controls and will require administering facilities to report on the use of the medications; this can be an onerous process for those acute care facilities who are not accustomed to participating in clinical trials.¹⁰

Validity of HCQ for Treatment of COVID-19 Patients

In-vitro evidence has demonstrated that HCQ is more potent against SARS-COV-2 than chloroquine at inhibiting the virus, so HCQ is preferred.^{11, 12} As a result of this in vitro data, some academic medical centers have included use of HCQ to treat COVID-19 inpatients as an option in treatment guidelines developed prior to release of the NIH guidelines.^{13, 14, 15, 16} Justification for inclusion in these guidelines was based on in vitro activity of HCQ rather than on results of clinical trials, and they caution about the potential for adverse effects. Vanderbilt treatment guidelines specifically caution about HIV and Chikungunya trials suggesting that HCQ may worsen outcomes by increasing viral load.¹⁶ Additionally, a recent study from France found no benefit of HCQ use among patient hospitalized for document SARS-COV-2 positive hypoxic pneumonia,⁷ and Magagnoli recently reported increased risk of death in inpatients in US VA hospitals treated with HCQ alone.⁸ All of the trials conducted to date have limited data with small

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sample sizes and are largely non peer-reviewed. Thus, additional information from RCTs is needed to assess the risk versus benefit of HCQ treatment for COVID-19 patients.

Dosing: The preferred dosing is 800mg by mouth on Day 1) followed by 200mg every 12 hours (400mg daily) for days 2 to 7 for a 5 to 8-day total duration.¹⁷

Side Effects: HCQ is not without risk and may exacerbate cardiovascular and hepatic comorbidities and cause renal and hepatic injury. However, HCQ has been prescribed to lupus and rheumatologic arthritis patients long-term and has shown significant clinical benefit.

Hydroxychloroquine/Azithromycin Combination: HCQ and azithromycin combined have been shown to significantly increase the risk of cardiovascular mortality, chest pain/angina and heart failure compared to HCQ and are therefore not being recommended at this time.¹⁸

Red flags and concerns:

- Ideally HCQ would be obtained from industry and NOT from the FDA stockpile, as the reporting requirements will make a statewide distribution and the required tracking of complication difficult.
- Please see attached Presbyterian Healthcare Services COVID-19 (SARS-CoV-2) Summary of Adult Antimicrobial Pharmacotherapy Considerations.

Although HCQ has a variety of side effects including cardiovascular problems (QT prolongation), bone marrow suppression, neuropathy and many drug-drug interactions, these side effects are infrequent and many patients use HCQ chronically for autoimmune diseases.¹³ Despite the potential side effects and higher risk profile for those with COVID-19. We will continue to monitor the scientific literature regarding therapeutic studies and approaches and will update these recommendations as additional information is made available.

Contributors: There was moderate consensus on these recommendations among the following contributors.

- Cristina Beato, MD (UNM)
- Jon Femling, MD, PhD (UNM)
- Richard Larson, MD, PhD (UNM)
- Ebany Martinez-Finley, PhD, MBA (Presbyterian)
- Greg Mertz, MD (UNM)
- Justin Schmetterer, PharmD (Presbyterian)
- Renee Mercier, PharmD (UNM)
- Nestor Sosa, MD (UNM)
- Norbert Topf, MD (Presbyterian)

Resources/Reference:

¹ NIH COVID-19 Treatment Guidelines: <https://covid19treatmentguidelines.nih.gov>

² FDA Drug Safety Communication - FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>

³ Wang, J., Yu, L., and Li, K., (2020) Benefits and Risks of Chloroquine and Hydroxychloroquine in The Treatment of Viral Diseases: A Meta-Analysis of Placebo Randomized Controlled Trials. medRxiv Available from: <https://doi.org/10.1101/2020.04.13.20064295> [Accessed April 20, 2020]

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⁴ Shamshirian A, Hessami A, Hydari K, *et al.* Hydroxychloroquine versus COVID-19: a rapid systemic review and meta-analysis. **doi:** <https://doi.org/10.1101/2020.04.14.20065276>

⁵ Tang, W., Cao, Z., Han, M., Wang, Z., *et al.* (2020) Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial medRxiv Available from: <https://doi.org/10.1101/2020.04.10.20060558> [Accessed April 20, 2020]

⁶ Chen J, Lui D, Liu L, *et al.* A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19) *J of Zhejiang U.* 2020; DOI : 10.3785/j.issn.1008-9292.2020.03.03. [Accessed March 25, 2020]

⁷ Mahevas, M., *et al.* (2020) No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. Available from: <https://doi.org/10.1101/2020.04.10.20060699> [Accessed April 20, 2020]

⁸ Magagnoli J, Narendran S, Pereira F, *et al.* Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. <https://doi.org/10.1101/2020.04.16.20065920>

⁹ Silva MG, Ameida FF, soursa V, *et al.* Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, Phase IIb clinical trial (CloroCovid-19 Study). **doi:** <https://doi.org/10.1101/2020.04.07.20056424>

¹⁰ U.S. Food and Drug Administration, “Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease” Available from: <https://www.fda.gov/media/136534/download>. [Accessed March 28, 2020]

¹¹ Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A., & Einav, S. (2020). A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *Journal of critical care.* Available from: <https://www.sciencedirect.com/science/article/pii/S0883944120303907>. [Accessed April 7, 2020]

¹² Wang M, Cao R, Zhang L *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020; 30:269-271. (PubMed 32020029) (DOI 10.1038/s41422-020-0282-0)

¹³ Harvard University, Treatments for COVID-19 Available from: <https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19>. [Accessed April 6, 2020]

¹⁴ Massachusetts General Hospital COVID-19 Treatment Guidelines Available from: <https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/mass-general-COVID-19-treatment-guidance.pdf> [Accessed April 7, 2020]

¹⁵ Yale University, COVID-19 Treatment Algorithm Updated April 3, 2020. Available from: https://medicine.yale.edu/intmed/COVID-19%20TREATMENT%20ADULT%20Algorithm%204.3.20_382832_5_v2.pdf [Accessed April 7, 2020]

¹⁶ Vanderbilt University Faculty in Infectious Diseases, Emergency Medicine, Pulmonary/Critical Care, Hospital/General Medicine, Cardiology & Radiology, “Clinical Recommendations for Treatment of COVID-19 Adult Patients” March 22, 2020. Available from:

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<https://www.vumc.org/coronavirus/sites/default/files/COVID%20Documents/Weekly%20COVID-19%20Clinical%20Guidelines%20Update%20Summary%20-%203.22.2020-%20FINAL.pdf>. [Accessed April 6, 2020]

¹⁷ Sophie Perinel, Manon Launay, Élisabeth Botelho-Nevers, Éric Diconne, Aurore Louf-Durier, Raphaël Lachand, Martin Murgier, Dominique Page, Régine Vermesch, Guillaume Thierry, Xavier Delavenne, Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients, *Clinical Infectious Diseases*, , ciaa394, <https://doi.org/10.1093/cid/ciaa394>

¹⁸ Lambert, Christophe (2020) Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. Available from: <https://data.ohdsi.org/Covid19EstimationHydroxychloroquine/>. [Accessed April 7, 2020]