Immediate Treatment for Early Stage SARS-CoV-2 Infections Recommended To Be Supported Nationally Starting Now

A strategic principle and practical approach to rapid response to novel pandemics

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BOTTOM LINE: Our primary strategic objective must be to prevent ICU overwhelm, which on our current course is imminent in most states. It is an axiom of infectious diseases that treatment in earlier stages is more effective than treating advanced stages. Early COVID-19 treatment is more likely to prevent disease progression to critical status, radically lowering hospitalizations and CFR than inaction. Current clinical drug trials are mostly focused on treating late stages of disease, when immunologic damage is a dominant threat. We believe that trials should focus on earlier stage infection to prevent progression to advanced disease. Given the suggestion of efficacy of hydroxychloroquine (HCQ), and the imperative to treat disease before it progresses to cytokine storm, we believe that the current data are sufficient to recommend FDA provisional approval for early outpatient treatment of COVID-19 with HCQ plus zinc and azithromycin. This triple combination treatment can be modified where needed in patients with prolonged QTc or other contraindications at the physicians' discretion Following this same rationale, we recommend that other clinical trials involving drugs that have already been approved for non-COVID-19 diseases, and for which the safety profile is well understood and reasonably acceptable, should begin clinical trials on patients in early stages of COVID-19 disease, alongside patients with more advanced disease.

OVERVIEW: ICU overload in the U.S. is impending in the very near term unless immediate actions are taken that effectively reduce hospitalization needs. In addition to the critical efforts underway to decrease R0 and increase ICU capacity, advancing early outpatient treatment with known medications may be the fastest and simplest way to decrease hospitalizations and mortality rate. Given that case fatality rate and harm to frontline healthcare workers increases dramatically when hospitals and ICUs reach capacity overload, it is imperative that all reasonable approaches to prevent that risk are employed quickly and at scale. The FDA recently gave emergency authorization for hydroxychloroquine for inpatient treatment of COVID-19.[1] Around the same time France's government authorized broader approval of HCQ for inpatient and outpatient use in infected patients after initial worldwide clinical data suggested potential benefit, especially in earlier stages of infection.[2] We propose the US emergency authorization be extended immediately to include early stage and outpatient treatment at the discretion of the prescribing

[1] https://www.washingtonpost.com/business/2020/03/30/coronavirus-drugs-hydroxychloroquin-chloroquine , https://www.fda.gov/media/136534/download, https://www.fda.gov/media/136538/download

[2] https://francais.medscape.com/voirarticle/3605790

physician, and that this extension also include the registration of those treated individuals into the "loose research protocol" previously proposed.

It's important to note that HCQ, zinc, and azithromycin are very well understood drugs with clear safety profiles; they are widely available, generic, inexpensive, and can be scaled rapidly, including to the developing world, which would be expedited by US leadership in recommendations. Some health authorities have given the typical caution against early treatment until large, peer-reviewed, randomized controlled trials (RCTs) provide conclusive data.[3] We fully support the continued effort to investigate existing and novel pharmaceuticals to determine the best intervention through blinded and controlled trials. Weighing the urgency of this unprecedented situation combined with the effects of inaction, plus the relative safety of the drugs, and the preponderance of data showing effective early treatment significantly decreases the percentage of cases that progress to needing hospitalization, we believe that the proposed recommendation is not only adequately founded but ethically obligate. This suggestion conforms with the widespread precedent to treat infections early to prevent progression and hospitalization even where empirical evidence for treatment would be considered insufficient in formal terms.

According to ClinicalTrials.gov, there are 47 CQ/HCQ & COVID-19 trials with only 1 complete and results not yet published. There are two small RCTs from China available in pre-publication. The assessment in this document considers the preponderance of relevant data, factoring information we gathered from doctors currently conducting informal open label studies, emerging clinical trials, and in vitro mechanistic studies. While additional data from the trials in progress will of course be valuable, and will hopefully give additional actionable insights, the data currently available is sufficient for emergency provisional approval.

TREATMENT:

- HCQ: 6.5-15mg/kg PO in divided loading dose followed by 400-1000mg/day in divided doses for 4-9 days[4]
    - Obtain baseline EKG for QTc, check on day 3 (or remote monitoring of QTc)[5]
    - Check Metabolic Panel for hypokalemia, Magnesium, Liver Function Tests
    - For patients with history of long QT syndrome or renal failure, consult with cardiologist

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[3] https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician

[4] Adapted from unpublished review on pharmacokinetics suggesting HCQ must reach higher levels in lung tissues to reach EC90 than normally achieved with typical dosing protocols, therefore loading dose recommended. These papers also advocate loading dose: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130/, http://www.departement-information-medicale.com/wp-content/uploads/2020/03/InternationalJoAntimicrobialAgents-2020-Covid-19-Chloroquine-Hydroxychloroquine.pdf

[5] https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19

- Zinc: use zinc acetate or gluconate lozenges with minimal excipients and flavorings to provide 18-25mg of ionized zinc taken every 4 hours during days on HCQ[6]
- Azithromycin: 500mg PO on day 1 followed by 250mg for 4 more days

WHEN & WHO TO TREAT: Clinical and in vitro data suggests greatest value is in treating early, similar to other antivirals used for influenza and herpes simplex, and corresponding to nearly universal findings in treating nearly every type of infection. Early clinical reports suggest it's best to treat within 5 days of symptom onset. Waiting until a patient is hospitalized or critically ill is unwarranted and unwise.

- Recommend immediate treatment for moderate to high risk patients with mild symptoms (presumptive diagnosis) or confirmed positive for SARS-CoV-2 (if testing available), especially those with underlying lung or heart conditions, high BMI or elevated HbA1c, shortness of breath, reduced PaO2, or chest pain.
- Strongly consider treatment in low risk patients with moderate to severe symptoms.
- Other than zinc lozenges, HCQ/azithromycin prophylaxis in healthy individuals is not yet indicated. See "Safety and Precautions" for details on prophylactic zinc dosing.

RESEARCH SUMMARY: Conclusive data regarding effective treatment of COVID-19 is not available. Clinical data from small RCTs, observational studies, and case reports in the U.S. and abroad suggest a trend towards faster clinical improvement, less progression to severity, and faster clearing of viral load when treatment with chloroquine (CQ) or HCQ especially when initiated early (note: CQ and HCQ are nearly identical molecules differentiated only by a hydroxyl group). There may be additional benefits of adding zinc and azithromycin to HCQ to reduce viremia and improve R0. One proposed mechanism of action is CQ/HCQ are zinc ionophores and improve delivery of zinc into cells where zinc blocks viral replication.[7] Low zinc status therefore may be a factor that reduces treatment effectiveness. Azithromycin is receiving traction for empiric coverage of superimposed bacterial infections, in vitro antiviral properties, and to treat early pneumonias.[8]

HYDROXYCHLOROQUINE: Originally used in 1955 for malarial prophylaxis and since then for a variety of rheumatic conditions. Prior to discovery of HCQ, CQ was widely used by the U.S. military in WWII for malaria prophylaxis in healthy soldiers, and it was noted their inflammatory rashes and arthritic conditions improved.[9] Chloroquine-primaquine was used by UN forces in the Korean War, and subsequently given to U.S. soldiers in the Vietnam War but with limited efficacy due to growing malarial resistance.[10] However, until at least 2007 the U.S. Navy recommended HCQ prophylaxis in healthy soldiers when deploying to areas where malarial resistance is low;

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[6] https://www.ncbi.nlm.nih.gov/pubmed/19906491
[7] https://www.ncbi.nlm.nih.gov/pubmed/15496046
[8] https://erj.ersjournals.com/content/45/2/428, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4923851/
[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7091063/#CR4
[10] https://academic.oup.com/cid/article/43/1/67/310038

and the Navy and Marine Corps Public Health Center recommends CQ prophylaxis as of 2015.[11] [12] As an immunomodulator, HCQ has been found to reduce IL-6 production which has recently been implicated as one of the cytokines involved in worsening COVID-19 disease progression.[13] In lupus patients, HCQ has been found to control the autoimmune disease "without evidence of fetotoxic or embryotoxic effects."[14] HCQ has most recently received renewed attention for its antiviral effects which we expand upon below. HCQ half-life is 40-50 days with 75% oral bioavailability which varies amongst individuals.[15] It is noted for having a very large volume of distribution which explains part of the rationale for starting with a loading dose.[16] In certain rheumatologic conditions treatment success improved with higher HCQ concentrations.[17] Regarding recommendation for loading dose of 15mg/kg, let it be noted that CQ is widely regarded to be more toxic than HCQ. A recent article from the journal Lancet Infectious Disease in 2018 recommended increasing CQ to 30mg/kg in children under 5 to prevent early recurrence of malaria.[18] Other studies have gone as high as 50mg/kg CQ in children.[19] Doses of 1200mg HCQ per day for 6 weeks have been used to treat rheumatic conditions.[20]. Of relevance to early treatment of SARS-CoV-2 disease is that HCQ is highly concentrated in lung tissue, upwards of 20X of serum levels. Earlier treatment would not only reduce the viral load reaching the lungs, but would also enhance lung concentrations in advance of the progression from upper airway disease to lower airway disease and pneumonitis, requiring ventilation support.

AZITHROMYCIN: One of the most commonly prescribed antibiotics with an estimated 45.7 million prescriptions in the U.S. in 2014.[21] Demonstrated efficacy in reducing treatment failures in exacerbations of COPD: "patients receiving azithromycin also spent 24% fewer days in the hospital and 74% fewer days in the intensive care unit."[22] It is generally well tolerated with approximately 1-5% of patients experiencing mild symptoms such as GI upset, headaches, and dizziness.[23] Another study of 3,995 patients found side effects occurring in up to 12% of people, however, these were mostly mild GI symptoms, frequency was lower than twelve other comparative antibiotics, and ultimately only 0.7% of people stopped treatment early (compared to 2.6% on other antibiotics).[24] It's been well tolerated in preschool children to prevent worsening of

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[11] https://www.med.navy.mil/sites/nepmu2/Documents/entomology/MalariaPocketGuide2007.pdf
[12] https://www.med.navy.mil/sites/nmcphc/Documents/program-and-policy-support/NMCPHC-Malaria-Guide-July2015.pdf
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7091063/#CR4,https://www.hindawi.com/journals/mi/2018/3424136/,https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3674253/,
[14] https://www.nature.com/articles/s41584-020-0372-x?fbclid=IwAR1RSAQL95rRlei2JV0Ufo0qt6yHvWAfeqgH2tnXn6klE0SkHNMF_gTFPuc
[15] https://www.ccjm.org/content/85/6/459.full
[16] https://www.nature.com/articles/s41584-020-0372-x#ref-CR39
[17] https://www.ccjm.org/content/85/6/459.full
[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6105624/pdf/main.pdf
[19] https://academic.oup.com/jid/article/213/8/1315/2459417
[20] https://www.sciencedirect.com/topics/medicine-and-dentistry/hydroxychloroquine-sulfate
[21] https://www.cdc.gov/antibiotic-use/community/pdfs/annual-reportsummary_2014.pdf
[22] https://www.ajmc.com/newsroom/azithromycin-may-reduce-treatment-failure-in-patients-with-acute-exacerbation-of-copd
[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4653965/
[24] https://www.amjmed.com/article/0002-9343(91)90401-I/abstract

lower respiratory tract infections.[25] It has recently been noted for its antiviral and antiinflammatory properties, including the possibility of preventing cytokine storm.[26] It has demonstrated in vitro anti-virality against Zika and Ebola viruses.[27] [28] Given potential additive effects of HCQ with azithromycin for prolonging QTc in predisposed patients, we recommend holding azithromycin in patients with baseline prolonged QTc or risk factors for developing it.

ZINC: There are multiple clinical and in vitro studies demonstrating positive antiviral effects of zinc,[29] including one study demonstrating anti-virality to SARS-CoV-1.[30] While there've been studies with different results leading to confusion on the topic, meta-analysis revealed the preponderance of evidence makes it clear that ionic zinc is safe, well-tolerated, and helpful in preventing a range of viral illnesses, but it must be consumed in specific formulations at sufficient doses to deliver enough ionic zinc to interfere with viral replication.[31] The meta-analysis demonstrated through multiple statistical analyses zinc acetate and zinc gluconate lozenges with minimal excipients and at least 18mg of zinc taken every 2-4 hours is an effective antiviral. According to the paper on SARS-CoV-1, antiviral effects of zinc are enhanced by zinc-ionophores, this combined with data describing chloroquine as a zinc-ionophore explains synergistic effects.[32]

Published and pre-published studies:

- **Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial.** HCQ treatment group shows faster clinical recovery, 80.6% of cases (25/31) improved in pneumonia vs. 54.8% (17/31) in controls (p value not reported), and fewer cases progressing to severe illness (0/31) compared to control (4/31); 2 out of 31 in the HCQ group had mild side effects with 1 rash and 1 headache.[33]
- **Treating COVID-19 with Chloroquine.** Small RCT from China demonstrated better clinical outcomes of CQ vs. Lopinavir/Ritonavir but findings are limited due to weak randomization.[34]
- **Hydroxychloroquine vs. Chloroquine.** HCQ was found to be more potent than CQ in inhibiting SARS-CoV-2 *in vitro*.[35]
- **Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.** "administration of chloroquine before inoculation of SARS-CoV-2

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[25] https://jamanetwork.com/journals/jama/article-abstract/2470445
[26] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4653965/#r1
[27] https://www.pnas.org/content/113/50/14408.full
[28] https://www.longdom.org/open-access/azithromycin-inhibits-the-replication-of-zika-virus-1948-5964-1000173.pdf
[29] https://www.ncbi.nlm.nih.gov/pubmed/15496046, https://www.ncbi.nlm.nih.gov/pubmed/17344507, https://www.ncbi.nlm.nih.gov/pubmed/16982486, https://www.ncbi.nlm.nih.gov/pubmed/23775705, https://www.ncbi.nlm.nih.gov/pubmed/19341987, https://www.ncbi.nlm.nih.gov/pubmed/15189121, https://www.ncbi.nlm.nih.gov/pubmed/18279051
[30] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2973827/pdf/ppat.1001176.pdf
[31] https://www.ncbi.nlm.nih.gov/pubmed/19906491
[32] https://www.ncbi.nlm.nih.gov/pubmed/15496046
[33] https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1.full.pdf
[34] https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjaa014/5814655
[35] https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa237/5801998

onto Vero6-cells, showed greater inhibition of virus replication than simultaneous or later administration."[36]

- **Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro.** HCQ and CQ both found to inhibit entry step and post-entry stages of SARS-CoV-2. Effective HCQ concentration in lung tissue is likely to be achieved to inhibit SARS-CoV-2 infection at a safe dosage.[37]
- **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).** Both CQ and HCQ have good antiviral activity at multiple steps of viral replication. HCQ showed stronger effect sizes.[38]
- **Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study.** Given concerns regarding study design and statistical analysis, after careful consideration we've included this citation for thoroughness but treatment recommendations were not based on results of this study.[39]
- **The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin.** In a retrospective preprint study of 84 relatively sick and high-risk New York inpatients with COVID-19 treated with HCQ/Az, there were 0 episodes of Torsades de Pointes and 0 cardiac deaths. 4 patients died from multiorgan failure, and 11% developed QT prolongation >500ms. 30% of patients QTc increased by >40ms from baseline. Maximal QTc changes seen day 3-4. Acute renal failure but not baseline QTc was a strong predictor of extreme QTc prolongation.[40]
- **No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection.** Study of 11 hospitalized patients with severe COVID-19 found no evidence of significant clinical benefit with combination HCQ and azithromycin when treatment was initiated at a progressed disease state.[41]
- **Combined prophylactic and therapeutic use maximizes hydroxychloroquine anti-SARS-CoV-2 effects in vitro.** Anti-SARS-CoV2 activity of HCQ is maximized when administered before and after the infection of cells in vitro, suggesting that only combined early and sustained therapeutic use of HCQ may be effective in limiting viral replication.[42]
- **The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin.** Retrospective study of 82 inpatients in NY, 30% of patients QTc increased by >40ms from baseline, 11% of patients QTc increased to >500

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[36] https://www.nature.com/articles/s41422-020-0282-0?fbclid=IwAR3c5iy9h65X1cnkrL6i6fJcWwi0ygN1Ltl67SkcgREM4DyxxAcPauRuf5w#citeas

[37] https://www.nature.com/articles/s41421-020-0156-0

[38] https://www.ncbi.nlm.nih.gov/pubmed/32150618

[39] https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf

[40] https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1.full.pdf

[41] https://www.sciencedirect.com/science/article/pii/S0399077X20300858

[42] https://www.biorxiv.org/content/10.1101/2020.03.29.014407v1.full.pdf+html

ms, none developed TdP. Maximal QTc changes seen day 3-4. Acute renal failure but not baseline QTc was a strong predictor of extreme QTc prolongation.[43]

Physicians in our group obtained unpublished data from multiple treating physicians; direct communications confirmed findings from the U.S.-based providers.[44]

- An increasing number of inpatient and outpatient doctors are convinced HCQ/Zn/Az combination works and is safe, including Dr. Alex Lechin in Texas, Dr. William Grace at Lenox Hill Hospital in NYC, former Kansas governor Dr. Jeff Colyer, Dr. Joe Mather in New Orleans, Dr. Vladimir Zelenko in New York State, and Dr. Stephen Smith in New Jersey. These doctors are emphatic that this treatment helped their patients recover faster (with few, if any, side effects), and observed a lower incidence of hospitalizations compared to patients receiving supportive care or no treatment.
- Dr. Zhong Nashan, pulmonologist central to China's COVID-19 efforts shared by video presentation as nonrandomized unpublished study showing 96% improvement in CQ (N=52) group compared to 70% (N=24) for lopinavir/ritonavir and 71% umifenovir (N=21). Only 4% (2/52 patients) CQ group deteriorated to severe, compared to 21% (5/24 patients) in lopinavir/ritonavir and 19% (4/21 patients) in umifenovir groups.
- Dr. Zhong Nashan, shared by video presentation another nonrandomized unpublished CQ trial (N=197). Patients in the CQ group had a shorter time to reach undetectable viral RNA compared to the control group (3 d vs. 9 d, p<.001). Duration of fever was significantly shorter in CQ group vs. control group (p=.003).
- An 82 page Norweigan Report describes large Chinese orders placed for chloroquine, implying use of the drug on a vast scale. Early treatment of infected people in Wuhan City reduced the percentage of severe conditions from 38 to 18%.[45] (Note: This report is presently unverified and is included for thoroughness. Our group of researchers has reached out to the authors to verify their findings.)

SAFETY AND PRECAUTIONS: Physicians unfamiliar with HCQ are understandably concerned about the drug's toxicity despite its long history of use. Much attention is given to QTc prolongation and potential progression to Torsades de Pointes (TdP), though some researchers have concluded that QT interval is "a crude and imperfect predictor of TdP."[46] The concern of HCQ and QTc prolongation is understandably amplified when it's being prescribed with other QTc-prolonging medications such as azithromycin, and while case reports of HCQ-induced TdP can be found in the literature, they are "extremely rare."[47] While we are not aware of any models predicting incidence of TdP from this drug combination, we do have data to suggest overall prevalence of TdP is low. Two European studies point towards TdP being a rare event: a

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[43] https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1.full.pdf
[44] From communications between Dr. Avery Knapp Jr. and treating physicians. Contact him at: avery@knappgroup.com.
[45] https://www.docdroid.net/80glu9f/essential-takeaways-from-chinas-response-to-covid-19-magnus-nordby.pdf
[46] https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.111.080887
[47] https://www.tandfonline.com/doi/full/10.1080/15563650500514558, https://www.hindawi.com/journals/cric/2016/4626279/

prospective German study of all hospitals in Berlin calculated an incidence of 3.2 per million people per year, and a retrospective French study at 10.9 per million people per year.[48] One Belgium study from a tertiary hospital found the inpatient incidence to be 0.16%.[49]

There are approximately 300,000 sudden cardiac deaths (SCD) in the U.S. each year, and while the precise incidence of TdP is unknown it may be associated with 5% of these deaths.[50] Assuming a U.S. population of 300M the absolute risk of SCD is 0.1%. If TdP accounts for a full 20% of these deaths, absolute risk is only 0.02%. We acknowledge this is a population-based statistic and therefore has limited extrapolation to the populations most at risk of COVID-19, however, it demonstrates that TdP is overall rare.

This compared to WHO estimates of 13.8% with severe disease and likelihood of hospitalization, and 6.1% critical requiring ICU,[51] and CDC estimates of 4.9-11.5% requiring ICU.[52] We interpret this to indicate the risk of infection progressing into severity outweighs the risk of TdP, especially when appropriate screening and follow-up measures are taken. The risk of TdP appears to be worsened by hypokalemia and hypomagnesemia, therefore measuring these levels prior to treatment is recommended as is replenishment in all deficient patients. There is evidence that magnesium can treat TdP,[53] and given safety of oral magnesium it may be prescient to supplement patients with magnesium chelates (due to their improved bioavailability) at time of initiating treatment.[54] Patients on potassium-wasting diuretics may benefit from empiric treatment with potassium supplementation assuming no contraindications.

Let it be further known that medications prolonging QTc are commonly prescribed such as citalopram,[55] ondansetron,[56] hydrochlorothiazide,[57] and famotidine.[58] To our knowledge many prescribers provide these medications without dedicated protocols for checking baseline EKGs and screening for hypokalemia and hypomagnesemia. Therefore, collective medical practice and standard of care indicates that risk of QTc prolongation is not reason alone to avoid medication, though concomitant use of multiple QTc prolonging medications certainly deserves clinical diligence and close follow-up. We further recommend holding any non-essential QT-prolonging

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[48] https://academic.oup.com/europace/article/16/1/101/464241
[49] https://www.internationaljournalofcardiology.com/article/S0167-5273(17)30855-0/abstract
[50] https://www.medscape.com/answers/1950863-53315/what-is-the-prevalence-of-torsade-de-pointes
[51] Severe defined as: "dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours"; critical defined as: "respiratory failure, septic shock, and/or multiple organ dysfunction/failure"; https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19), https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30243-7/fulltext
[52] https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm?s_cid=mm6912e2_e&deliveryName=USCDC_921-DM23064#T1_down
[53] https://www.ncbi.nlm.nih.gov/pubmed/16635167
[54] https://www.ncbi.nlm.nih.gov/pubmed/14596323
[55] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871413/
[56] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871413/
[57] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5773415/
[58] https://link.springer.com/article/10.1007/s12012-014-9285-8

medications when initiating HCQ treatment. Given it's statistically unclear the additional value obtained from azithromycin, it's reasonable to treat patients with prolonged QT with only HCQ and zinc, and/or treat higher risk with remote monitoring for QTc changes,[59] inpatient on telemetry, or followup EKG at day 3 per American College of Cardiology recommendations.[60]

Risk of retinopathy with HCQ appears to be time-dependent with an incidence of 2% for <10 years exposure, increasing to 20% with >20 years exposure.[61] Myopathy has been reported to occur at a rate of 1 case in 100 patient-years of treatment and improves with discontinuation of therapy, though it can persist for weeks due to half-life.[62] [63] Apparently no cases of myopathy have been reported in patients taking the medication for fewer than 6 months.[64] Again it bears remembering that the commonly prescribed statin drugs also carry a risk of myopathy. A review on HCQ published by the Cleveland Clinic Journal of Medicine described cardiomyopathy, and specifically neurocardiomyopathy, as "extremely rare."[65] Other studies claim while cardiomyopathy is rare it's perhaps under-recognized, but this is from a small study of patients on the medication for an average of 12.7 years again reflecting that toxicity concerns are mostly associated with long-term use.[66] Prescribers who are new to HCQ should rapidly make themselves familiar with drug-drug interactions; absence of this familiarity is reason to devote time to being educated and empowered rather than avoidant of early treatment. Notable categories to be aware of include diabetic medications (doses may need to be lowered), antiepileptics (HCQ may decrease seizure threshold), digoxin, medications affecting electrolyte balances, and CYP2C8 and CYP3A4 inhibitors.[67] There are reports of fatal toxicity in mice with the combination of CQ or HCQ and metformin.[68] A complete list of drug-drug interactions can be found here: https://www.drugs.com/drug-interactions/hydroxychloroquine-index.html.

For long term prophylactic use of zinc, there are concerns about chronic toxicity and copper deficiency. Potential mineral imbalances arise at greater than 60mg when consumed daily.[69] People choosing zinc prophylaxis for periods of weeks to months may benefit from additional copper (1-4mg per day) and having their copper and zinc levels followed (measured in plasma or serum). The amount recommended for acute treatment with zinc lozenges (18-25mg of ionized zinc taken every 4 hours) is considerably more than the amount recommended for daily prophylaxis. Acute toxicity of zinc is possible and has been reported with large doses (i.e. 570mg of elemental zinc at once). It can include nausea, vomiting, loss of appetite, abdominal cramps,

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[59] https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-provides-urgent-guidance-approach-to-identify-patients-at-risk-of-drug-induced-sudden-cardiac-death-from-use-of-off-label-covid-19-treatments/
[60] https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19
[61] https://www.ccjm.org/content/85/6/459.full
[62] https://www.ccjm.org/content/85/6/459.full
[63] https://jamanetwork.com/journals/jamadermatology/fullarticle/712015
[64] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798076/
[65] https://www.ccjm.org/content/85/6/459.full
[66] https://journals.sagepub.com/doi/abs/10.1177/0961203317734922
[67] http://products.sanofi.ca/en/plaquenil.pdf
[68] https://www.biorxiv.org/content/10.1101/2020.03.31.018556v1
[69] https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

diarrhea, and headaches.[70] Milder GI distress has been reported at doses of 50 to 150 mg/day of supplemental zinc.

RESEARCH QUESTIONS:

- How quickly can a retrospective analysis be performed to compare COVID-19 patients previously started on HCQ vs. age, gender, and co-morbidity matched controls?
- What's the most accurate data on true COVID-19 cases progressing to hospitalization?
- How early are patients being treated with HCQ/Zn/Az in foreign nations?
- Are there quality studies available elucidating the additive benefits (or not) of azithromycin?
- What is the absolute risk of HCQ and/or Az induced QTc prolongation progressing to TdP?

RECOMMENDATIONS BY FOREIGN NATIONS AND ORGANIZATIONS: We realize there may be intentional disinformation/misinformation being spread by foreign governments and organizations. Therefore, we applied a "discount rate" to information coming from China, given tenuous relations with the U.S. However, it bears consideration that information from South Korea (as reported by Korea Biomedical Review, as of yet unconfirmed from reported organizations) and a Belgian task force corroborate their findings leading to a pattern of consistency amongst multiple dispersed sources. Therefore, while the exact protocols and success data are still unclear it appears that a number of other countries have made provisional approvals of HCQ as well. It is our perspective that science be disentangled from politics to the extent possible. Our recommendations are not predicated on these findings, rather they are included for thoroughness of the informational landscape.

- According to Korea Biomedical Review, South Korea's COVID-19 Central Clinical Task Force recommends treatment with chloroquine (CQ) or lopinavir for high-risk patients.[71]
- Belgian Task Force recommends considering starting HCQ in mild to moderate disease at earliest diagnosis/suspicion.[72]
- Guangdong Provincial Department of Science and Technology and the Guangdong Provincial Health and Health Commission reach expert consensus on CQ in treatment of novel coronavirus pneumonia.[73]
- CQ recommended for inclusion in Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China.[74] [75]

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[70] https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

[71] http://m.koreabiomed.com/news/articleView.html?idxno=7428&fbclid=IwAR3AU66b_y8WIEv27aWRiflC1nKq0zf61TpVT2BMsY97JflemntBYU56u6A

[72] https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf

[73] https://www.ncbi.nlm.nih.gov/pubmed/32075365

[74] https://www.acc.org/latest-in-cardiology/articles/2020/03/17/11/22/chinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment

[75] https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article

OBJECTIONS:

- **Why a loading dose?**
    - The volume of distribution is very high (reported at 100L/kg for CQ).[76] A 15mg/kg loading dose is important to rapidly achieving EC90 concentrations in the lungs.
- **Why combination treatment?**
    - There is evidence to suggest ionized zinc in sufficient dosages is synergistic with HCQ. Similarly, in addition to its demonstrated antiviral activity, azithromycin may help prevent and/or treat superimposed bacterial infections and could be preventative/therapeutic for early pneumonias.
- **The FDA approved inpatient treatment, why are you pushing for early treatment?**
    - The preponderance of evidence clearly points towards early treatment being more effective than later treatment. This is consistent with all infections: they are easier to treat earlier. This is the same approach used for influenza, HIV, and essentially ANY viral, bacterial, fungal, or parasitic infection.
- **What about toxic effects of HCQ?**
    - We've done our best to provide you with balanced information on the safety profile and risks of HCQ. We are not going to underplay the tragedy of someone developing a serious side effect from medication, but based on our assessment it appears the risk of worsening COVID-19 disease outweighs the risk of short-term use of the medication especially in patients at higher risk of progression. It is true that hospitalized patients on this cocktail have had cardiac side effects, and it could be that early treatment will carry this risk in a small percentage of patients even though HCQ was used for decades in healthy people as a malarial prophylaxis. However, it is also possible that earlier treatment of the virus will ultimately reduce cardiac complications as myocarditis is a reported complication of severe COVID-19. If you are a provider unfamiliar with the medication, we recommend you speak with pharmacists and rheumatologists in your area who can help guide you to feel more comfortable with prescribing this medication. We encourage you to read the articles we've linked to in our "Safety and Precautions" section and interpret the data for yourself. It may be an important consideration to ask yourself: "If I personally came down with COVID-19, would I be willing to try this treatment?" If the answer is yes, then afford the same care to your patients.
- **What about the studies that show no benefit from HCQ?**
    - Upon closer examination these studies may have either underdosed patients or waited to initiate treatment until the disease was too far progressed to be effective. While HCQ likely decreases IL-6 production (which is implicated in the devastating "cytokine storm"), its antiviral properties appear to only be effective in stopping the early stages of viral entry and replication. For example, a Chinese study on N=30 patients showed HCQ had no additional improvement compared to

[76] https://link.springer.com/article/10.2165%2F00003088-199630040-00002

control arm, but only 400mg daily for 5 days was used vs. 1000mg/day as recommended by the expert Chinese panel.[77]

- **What about the "disagreement" between Trump and Fauci on HCQ?**
    - To our knowledge Fauci did not indicate evidence against HCQ but rather cautioned over-interpretation of preliminary data. Regardless, we are attempting to answer scientific questions, not political ones. We are only interested in quality science and comprehensively understanding clinical experience from those in the trenches making real-time decisions for their patients.
- **What about other treatments?**
    - Our team is turning our attention to researching all reasonable and plausible treatments for COVID-19 that can be supported with scientific data and research. Since getting approval for early treatment is time-sensitive and mission critical, we chose to first focus on the treatments that had the most traction, emerging data, and possibility of scaling rapidly.

CONCLUSION: Base treatment is to start early in patients with risk factors and/or concerning symptoms using HCQ with zinc and azithromycin. In cases where there is concern for QTc prolongation we recommend detection and correction of hypokalemia and/or hypomagnesemia, treating just with HCQ and zinc, and follow-up EKG on day 3. If zinc is unavailable, proceed to treat patients with just HCQ as it's been noted to have meaningful effects on its own. However, given mechanisms of action and some clinical data it appears to increase effectiveness when combined with zinc and azithromycin.

A NEW FUTURE-PROOFING PRINCIPLE AND STRATEGY: We believe that other promising drug therapies with pre-existing FDA approval for other diseases, and with acceptable safety profiles, should undergo clinical trials that include patients with earlier stages of COVID-19 infections. SImilarly, as soon as these drugs are found to have promising results, provisional authorization of earlier treatment may be warranted. We believe that this is an entirely new principle for both accelerated research and emergency authorization in the context of a devastating pandemic. We believe that this principle will apply to additional drugs addressing COVID-19, and will also apply to future pandemic research and application of that research. The evolution of machine learning based strategies to find already approved drugs that can be repurposed for new diseases is emerging as an entirely new business model for drug development, and this paper attempts to outline how this new frontier warrants some new principle-based strategies. The issue with HCQ/Zn/Az is just the first of what will hopefully become MANY future similar opportunities, in the likely event of additional future severe pandemics.

DISCLAIMER: This document is for research and development purposes amongst clinicians, researchers, and decision/policy-makers. It does not constitute medical advice for self-treatment, and in no way replaces clinical judgment by prescribers.

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[77] http://subject.med.wanfangdata.com.cn/UpLoad/Files/202003/43f8625d4dc74e42bbcf24795de1c77c.pdf

If you are a physician and support the extension of the provisional approval as suggested in this document, please click here and add your name. Thank you.

Plain English Context: If ICU capacity is exceeded, case fatality rate jumps dramatically, as does illness and burnout of hospital workers. We are quickly approaching ICU capacity in NY and other hot zone cities. Preventing this should be the primary objective of our current efforts. This can be achieved by decreasing total infections via policies around sheltering in place and PPE use to decrease transmission, which should be advanced nationally. Also by increasing ICU capacity, which is in process and should receive significant national, state, and private sector support. Both of those methods are slow and difficult and not currently sufficient to prevent the impending ICU overload. The additional option is to decrease the percentage of total cases that end up requiring hospitalization through providing early treatment. While preliminary, the current data suggests that when this treatment is given early in the disease cycle there is a significant reduction in the number of cases that progress to severe status requiring hospitalization. In conjunction with existing non pharmaceutical efforts, this is the best route to preventing unnecessary morbidity and mortality and ICU overwhelm currently available.

We would like to see larger controlled trials of early treatment initiated right away, and ongoing research into other treatments that might be even more effective or better for certain populations. Hopefully physicians will continue to have more treatment options available supported by more solid research. As that is happening, and until a fully sanctioned full cure is available, the best of what is currently known, factoring all data available including but not limited to RCTs, should be made available to inform physicians and their discretion should be empowered for reasonable off-label treatments.

It’s generally understood that antivirals only work well when administered early. It's a general practice to treat infections of all types early to prevent progression. The medicines suggested here are very well established with good safety profiles; the drug interactions, contraindications, and mechanisms of action are all well understood. HCQ has been given to healthy US soldiers prophylactically to prevent malaria for decades. Azithromycin is one of the more commonly prescribed antibiotics. Long term safety is much more established for these drugs than it would be for new antivirals. They are generic and simple to produce inexpensively and at scale (including in the developing world).

Even if hesitant to say so publicly for political reasons, most of the doctors we spoke with acknowledged that this treatment is what they would do personally if they came down with Covid.