Hydroxychloroquine and chloroquine the real importance for the new pandemic COVID 19

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Hydroxychloroquine sulfate

Brand names: include Reuquinol®, (Apsen) Plaquenil®, Hydroquin®, Axemal® (in India), Dolquine®, Quensyl®, Quinoric®

AHFS Class: Antimalarial HCQ is in the antimalarial and 4-aminoquinoline families of medication. *Observation:* Acronym definition. AHFS, American Hospital Formulary Service.

Rationale

In vitro activity against various viruses, including coronaviruses 5, 8. 12-14 In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed 8, 12 Has immunomodulatory activity that theoretically could contribute to an antiinflammatory response in patients with viral infections 3, 8, 13, 15, 16 Known pharmacokinetics and toxicity profile Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects; 13, 14 may have more favorable doserelated toxicity profile than chloroquine, 13-16 but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs 13, 20. Hydroxychloroquine was approved for medical use in the United States in 1955. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. In 2017, it was the 128th most commonly prescribed medication in the United States, with more than five million prescriptions.

Pharmacokinetics

Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption, large distribution volume, and elimination by the kidneys. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5) metabolize hydroxychloroquine to N-desethylhydroxychloroquine.

Mechanism of action

Hydroxychloroquine increases [34] lysosomal pH in antigen-presenting cells. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells (PDCs).[35] Toll-like receptor 9 (TLR 9), which recognizes DNA-containing immune complexes, leads to the production of interferon and

causes the dendritic cells to mature and present antigen to T cells. Hydroxychloroquine, by decreasing TLR signaling, reduces the activation of dendritic cells and the inflammatory process.[medical citation needed] In 2003, a novel mechanism was described wherein hydroxychloroquine inhibits stimulation of the toll-like receptor (TLR) 9 family receptors. TLRs are cellular receptors for microbial products that induce inflammatory responses through activation of the innate immune system.[36] As with other quinoline antimalarial drugs, the antimalarial mechanism of action of quinine has not been fully resolved. The most accepted model is based on hydrochloroquinine and involves the inhibition of hemozoin biocrystallization, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing death.[37]

In vitro activity against various viruses, including coronaviruses. (**Yao X, Ye F, Zhang M 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). Clin Infect Dis. 2020; In Press. (PubMed 32150618) (DOI 10.1093/cid/ciaa237**) (**Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; :105932. Editorial. (PubMed 32145363) (DOI 10.1016/j. ijantimicag.2020.105932**) (**Liu J, Cao R, Xu M et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:1-4. (PubMed 32194981. DOI 10.1038/s41421-020- 0156-0**))(**Barber BE. Chloroquine and Hydroxychloroquine. In: Grayson ML, ed. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs. 7th ed. Boca Raton, FL: CRC Press; 2018: 3030-48**.)(**Rolain MJ, Colson, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30:297-308. (PubMed 17629679) (DOI 10.1016/j.ijantimicag.2007.05.015**)

In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed (**Yao X, Ye F, Zhang M 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). Clin Infect Dis. 2020; In Press. (PubMed 32150618) (DOI 10.1093/cid/ciaa237**)(**Liu J, Cao R, Xu M et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:1-4. (PubMed 32194981) (DOI 10.1038/s41421-020- 0156-0**).

Trials or Clinical Experience

Only limited clinical trial data available to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19 Clinical experience in treating pts with COVID-19 accumulating; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 7, 18 Hydroxychloroquine small pilot study conducted in China: 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; 18 both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV. 30 Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up). 18 Hydroxychloroquine randomized, parallelgroup study in adults in China (ChiCTR2000029559): 31 pts with COVID19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 5 days) and standard treatment (O2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids) and 31 other pts received standard treatment alone (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group). 31 Note: This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, 32 data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported. 31 Hydroxychloroquine with azithromycin open-label, nonrandomized study in

France (Gautret et al): Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6.7 Note: This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented. Hydroxychloroquine with azithromycin open-label, uncontrolled study in France (Molina et al): 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O2. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. 33 Note: In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit. Hydroxychloroquine with azithromycin uncontrolled, retrospective, observational study in France (Gautret et al): 80 adults with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O2 saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O2; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1

days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. 34 Note: Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease. Hydroxychloroquine (with or without azithromycin) in a retrospective analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers (Magagnoli et al): Data for 368 males (median age >65 years) treated with hydroxychloroquine in addition to standard supportive management were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in those treated with hydroxychloroquine, 22.1% (25/113) in those treated with hydroxychloroquine and azithromycin, and 11.4% (18/158) in those not treated with hydroxychloroquine; rate of ventilation was 13.3, 6.9, and 14.1%, respectively. Use of hydroxychloroquine alone (but not use of hydroxychloroquine and azithromycin) was associated with increased overall mortality compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation. 40 Note: The pt population included only elderly males 59- 75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures. Efficacy measures: Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. 7, 18 RTPCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; 19, 21 however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined. 22, 23 Multiple clinical trials to evaluate hydroxychloroquine for treatment of COVID19 are registered at clinicaltrials.gov (some listed below): 10 NCT04329923 NCT04332991 NCT04334967 NCT04335552 NCT04341727 NCT04345692 NCT04350450 NCT04351620 NCT04353037 NCT04362332 Multiple clinical trials to evaluate hydroxychloroquine for prevention of COVID19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed below): 10 NCT04303507 NCT04318015 NCT04318444 NCT04328961 NCT04330144

Optimal dosage and duration of treatment

Optimal dosage is not known 20, 26 Various dosages recommended or being investigated for treatment of COVID-19 Oral hydroxychloroquine sulfate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation 26 Oral hydroxychloroquine sulfate: 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 8, 20 Oral hydroxychloroquine sulfate: 400 mg once or twice daily for 5-10 days 10, 18 Oral hydroxychloroquine sulfate: 600 mg twice daily on day 1, then 400 mg daily on days 2-5 20 Oral hydroxychloroquine sulfate: 100-200 mg twice daily for 5-14 days 4 Oral hydroxychloroquine sulfate: 200 mg 3 times daily for 10 days 7, 34

Final comments

Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established 10, 24, 39 Additional data needed to determine whether in vitro activity against SARSCoV-2 corresponds with clinical efficacy for treatment or prevention of COVID19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. Additional data needed regarding toxicity profile when used in patients with COVID-19 Hydroxychloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. 11 NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against use of hydroxychloroquine for the treatment of COVID-19. 35 IDSA recommends that hydroxychloroquine be used for the treatment of COVID-19 in the context of a clinical trial. 38 NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial. 35 IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial. 38 NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection outside of clinical trials. 35 Because hydroxychloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; 36, 39 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects 35, 36, 39 FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia,

ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. 39 Emergency use authorization (EUA) for hydroxychloroquine: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. 24, 26 To request the drug, healthcare providers should contact local or state health departments; 26 distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. 29 To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch). 24, 26 FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks. 24 Consult the EUA, 24 EUA fact sheet for healthcare providers, 26 and EUA fact sheet for patients and parent/ caregivers 28 for additional information.

Chloroquine Phosphate
AHFS Class: Antimalarial
Rationale: In vitro activity against various viruses, including coronaviruses 1-3, 13, 14 In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; some evidence it may block infection in Vero E6 cells exposed to SARS-CoV-2 1, 4, 12 Active in vitro against SARSCoV-1 and MERS-CoV 2, 3, 5, 9. Has immunomodulatory activity that theoretically could contribute to an antiinflammatory response in patients with viral infections 1-3, 13, 15-16 Known pharmacokinet
Trials or Clinical Experience
Only limited clinical trial data available to date to evaluate use of chloroquine for treatment or prevention of COVID-19 Clinical experience in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 4-6 Double-blind randomized phase 2b study in Brazil (Borba et al) to evaluate two different chloroquine dosages as adjunctive therapy in hospitalized adults with severe COVID-19 (NCT04323527): The first 81 enrolled pts were randomized 1:1 to receive high-dose chloroquine (600 mg

twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. By day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QTc >500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data were insufficient to evaluate efficacy. Study continuing using only the lower dosage. 37 Multiple clinical trials to evaluate chloroquine for the treatment of COVID-19 are registered at clinicaltrials.gov (some listed): 10 NCT04323527 NCT04328493 NCT04331600 NCT04333628 NCT04353336 NCT04360759 NCT04362332

Optimal dosage and duration of treatment

Not known 20, 25 Consider: 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base 17 Various dosages recommended or being investigated for treatment of COVID-19 Oral chloroquine phosphate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation 25 Oral chloroquine phosphate: 500 mg twice daily for 7 days (adults 18- 65 years weighing >50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing

Comments

Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established 10, 24, 39 Additional data needed to determine whether in vitro activity against SARSCoV-2 corresponds with clinical efficacy for treatment or prevention of COVID19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. 11 NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of chloroquine for the treatment of COVID-19.35 IDSA recommends that chloroquine be used for the treatment of COVID-19 in the context of a clinical trial. 38 NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including chloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection outside of clinical trials. 35 Because chloroquine is associated with QT prolongation, caution is advised in pts at risk for QT

prolongation or receiving other drugs associated with arrhythmias; 36, 39 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 35, 36, 39 FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. 39

Emergency use authorization (EUA) for chloroquine: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. 24, 25 To request the drug, healthcare providers should contact local or state health departments; 25 distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. 29 To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch). 24, 25 FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks. 24 Consult the EUA, 24 EUA fact sheet for healthcare providers, 25 and EUA fact sheet for patients and parent/caregivers 27 for additional information

References for Chloroquine and Hydroxychloroquine

1. 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)
2. Keyaerts E, Vijgen L, Maes P et al. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004; 323:264-8. (PubMed 15351731) (DOI 10.1016/j. bbrc.2004.08.085)
3. Devaux CA, Rolain JM, Colson P et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. Int J Antimicrob Agents. 2020; :105938. (PubMed 32171740) (DOI 10.1016/j. ijantimicag.2020.105938)
4. Cortegiani A, Ingoglia G, Ippolito M et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020; (PubMed 32173110) (DOI 10.1016/ j.jcrc.2020.03.005)
5. Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; :105932. Editorial. (PubMed 32145363) (DOI 10.1016/j. ijantimicag.2020.105932)
6. 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; 14:72-73. (PubMed 32074550) (DOI 10.5582/bst.2020.01047)

7. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agnts. 2020; In Press. (DOI 10.1016/jantimicag.2020.105949)
8. Yao X, Ye F, Zhang M 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). Clin Infect Dis. 2020; In Press. (PubMed 32150618) (DOI 10.1093/cid/ciaa237)
9. Vincent MJ, Bergeron E, Benjannet S et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2:69. (PubMed 16115318) (DOI 10.1186/1743-422X-2-69)
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 26. Available at https://www.clinicaltrials.gov/.
11. National Health Commission (NHC) & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (http:// busan. china-consulate.org/chn/zt/4/P020200310548447287942.pdf)
12. Liu J, Cao R, Xu M et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:1-4. (PubMed 32194981) (DOI 10.1038/s41421-020- 0156-0)
13. Barber BE. Chloroquine and Hydroxychloroquine. In: Grayson ML, ed. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs. 7th ed. Boca Raton, FL: CRC Press; 2018: 3030-48.
14. Rolain MJ, Colson, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30:297-308. (PubMed 17629679) (DOI 10.1016/j.ijantimicag. 2007.05.015)
15. Sahraei Z, Shabani M, Shokouhi S et al. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. Int J Antimicrob Agents. 2020; :105945. (PubMed 32194152) (DOI 10.1016/j.ijantimicag.2020.105945)
16. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020; In Press. (PubMed 32196083) (DOI 10.1093/jac/ dkaa114)
17. Rising Pharmaceuticals. Chloroquine phosphate tablets prescribing information. Saddle Brook, NJ; 2018 Feb 3.
18. Chen J, Liu D, Li L et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ. 2020; Mar. (DOI 10.3785/j.issn. 1008- 9292.2020.03.03)
19. CDC 2019-Novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. For emergency use only. Instructions for use. Catalog # 2019-nCoVEUA-01 (https://www.fda.gov/media/134922/ download)
20. US Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Information for Clinicians on Therapeutic Options for COVID-19 Patients. From CDC website. Accessed 2020 Mar 26. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html).
21. CDC. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). From CDC website (https://www.cdc.gov/ coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html). (Accessed March 26, 2020).
22. Pan Y, Zhang D, Yang P et al. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020. pii: S1473-3099(20)30113-4. (PMID: 32105638) (DOI: 10.1016/S1473-3099(20)30113-4) Updated 5-15-20. The current version of this document can be found on the ASHP COVID-19 Resource Center. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License

23. Zhang W, Du RH, Li B et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020. 9:386-389. PMID (32065057) (DOI: 10.1080/22221751.2020.1729071)
24. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 Coronavirus disease. 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136534/download)
25. US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136535/download)
26. US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136537/download)
27. US Food and Drug Administration. Fact sheet for patients and parent/caregivers emergency use authorization (EUA) of chloroquine phosphate for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136536/download)
28. US Food and Drug Administration. Fact sheet for patients and parent/caregivers emergency use authorization (EUA) of hydroxychloroquine sulfate for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. From FDA website. (https://www.fda.gov/media/136538/download)
29. US Department of Health and Human Services (HHS). HHS accepts donations of medicine to strategic national stockpile as possible treatments for COVID-19 patients. March 29, 2020. From HHS website. (https://www.fda.gov/media/136537/download)
30. Song Y, Zhang M, Yin L, et al. COVID-19 treatment: Close to a cure ? – a rapid review of pharmacotherapies for the novel coronavirus. 2020. 2020030378. Doi: 10.20944/ preprints202003.0378.v1.
31. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Preprint. https://www.medrxiv.org/ content/ 10.1101/2020.03.22.20040758v2.full.pdf.
32. Chinese Clinical Trial Registry. ChiCTR2000029559. Accessed 2020 Apr 4. Available at http://www.chictr.org/cn.
33. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020; Mar 30. Epub. PMID: 32240719 DOI: 10.1016/j.medmal.2020.03.006.
34. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020; Apr 11. Epub. PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663.
35. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website. Accessed 2020 Apr 21. Available at https://www.covid19treatmentguidelines.nih.gov/.
36. Giudicessi JR, Noseworthy PA, Friedman PA et al. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID19. Mayo Clin Proc. Preprint (not peer reviewed). DOI: 10.1016/j.mayocp.2020.03.024.
37. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized

clinical trial. JAMA Netw Open. 2020; 3:e208857. Epub. PMID: 32330277 DOI: 10.1001/jamanetworkopen.2020.8857.

38. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Accessed 2020 Apr 22. Available at https:// www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
39. US Food and Drug Administration. 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. April 24, 2020. Available at https://www.fda.gov/media/137250/download.
40. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Preprint (not peer reviewed). (https:// www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf