JHMI Clinical Guidance for Available Pharmacologic Therapies for COVID-19

March 22, 2020; Writing Group* of the Johns Hopkins University and Johns Hopkins Hospital COVID-19 Treatment Guidance Working Group

Contents

I. Purpose, Development, and Guiding Principles

Purpose: The purpose of this document is to provide pharmacological treatment guidance for clinicians at Johns Hopkins Hospital (JHH) who are managing the care of patients diagnosed with COVID-19. The guidance provided is based on current knowledge, experience, and expert opinion. The goal is to establish and promulgate a standard approach to the pharmacological treatment of JHH inpatients diagnosed with COVID-19. This guidance is not intended to replace or supersede individualized clinical evaluation and management of patients according to clinicians' best judgment based on unique patient factors.

Development process: Paul Auwaerter, MD, Clinical Director of Johns Hopkins Medicine Division of Infectious Diseases, convened a working group of Johns Hopkins clinical experts in infectious diseases, pulmonary and critical care medicine, clinical pharmacology, and pharmacy to review and weigh the available evidence regarding treatment of COVID-19.

From the larger working group, a smaller writing group[1] was convened to develop draft guidance. The group met by conference call two times to define the scope of the guidance, review the evidence, review draft documents, and establish consensus.

***COVID-19 Treatment Guidance Writing Group Members:** Chair: Paul G. Auwaerter, MBA, MD **Contributing members** (in alphabetical order): Edina Avdic, PharmD., MBA; Robin Avery, MD; Richard Ambinder, MD, PhD; Andrew Cameron, MD, PhD; Larry Chang, MD, MPH; Natasha Chida, MD, MSPH; Franco D'Alessio, MD; Brian Garibaldi, MD; Chris Hoffmann, MD, MPH; Elisa Ignatius, MD, MSc; Kieren Marr, MD; R. Scott Stephens, MD; David Sullivan, MD; Ethel Weld, MD, PhD.

- Consensus guidance: Following teleconferences and review of suggestions, the draft incorporated Writing Group incorporation documents, all members voted for approval.
- Ongoing updates: New information and experience are reviewed daily; guidance will be updated as needed. The Johns Hopkins Health System community should feel free to provide comments to: C19workgroup@jhu.edu.

Guiding Principles

- **Guidance is based on expert opinion:** At the time of this writing, there is minimal available evidence from randomized clinical trials (RCTs) to support recommendations for the use of any specific pharmacologic treatment for patients with COVID-19. Existing data are mostly drawn from *in vitro* and non-randomized studies or are extrapolated from animal models of related coronaviruses. To date, the only published RCT results are from a study of lopinavir/ritonavir that found no evidence of benefit in patients with COVID-19.
  - The committee considered the evidence and potential benefits of the following putative antiviral agents: hydroxychloroquine (HCQ) or chloroquine (CQ), remdesivir,[a] lopinavir/ritonavir, azithromycin, ACE inhibitors/ARBs.
  - The committee will consider evidence and potential benefits of the following putative immune suppressant disease-modifying agents: steroids, tocilizumab, and interferon beta-B1.
- **Agreed upon definition of high-risk patients:** The committee agreed on described or likely risk factors for individuals at high risk of poor outcomes (i.e., need for ICU care, acute respiratory distress syndrome [ARDS] or death), defined in Section II.
- **This guidance applies to the treatment of inpatients only:** This committee does not support the outpatient treatment of patients with COVID-19 using the agents discussed below at this time.
- **Rapid response to emerging evidence and experience:** The committee recognizes the rapid evolution of knowledge and experience and is committed to updating guidance regularly as new evidence or experience is available.
- **Infectious Diseases consultation for specific higher-risk patients is advised:** This committee recommends that prescribing clinicians consult with infectious diseases clinicians for treatment of any solid organ transplant recipient or candidate and any bone marrow transplant recipient or candidate. Consultation with infectious diseases clinicians for evaluation or management for any hospitalized person with suspected (person under investigation [PUI]) or confirmed COVID-19 patient is otherwise up to the judgment and needs of the primary team.

---

[a] For remdesivir, information about the available clinical trial is provided in Section V. Currently, remdesivir appears promising based on *in vitro* and animal model data. Therefore, entry into the remdesivir clinical trial is preferred if a patient agrees and meets the entry criteria.

II. Definition: Patients at Higher-Risk for Poor Outcomes

Patients who are at higher risk for poor outcomes, including acute respiratory distress syndrome (ARDS) and death, are those who meet any 1 of the following criteria:

- Age ≥65 years old
- Any one of the following medical conditions:
  - Cardiovascular disease

  - Diabetes with A1c>7.5%
  - Chronic pulmonary diseases, including asthma
  - End-stage renal disease
  - Advanced liver disease
  - Blood disorders (e.g., sickle cell disease)
  - Neurological or neurodevelopmental disorders
  - Post-solid-organ transplantation, on immunosuppressive therapy
  - Use of biologic agents for immunosuppression
  - Undergoing treatment with chemotherapy or immunotherapies for malignancy
  - Within 1 year post-marrow transplant
  - Undergoing treatment for graft versus host disease
  - HIV infection, with CD4 cell count <200 copies/mm^3
- Any one of the following clinical findings:
  - Oxygen saturation (SaO2) <94% on room air; <90% if known chronic hypoxic conditions or receiving chronic supplemental oxygen
  - Respiratory rate >24 breaths/min
- Laboratory finding: D-dimer >1 µg/mL

Evidence: This definition of patients higher risk for poor outcomes has been established based on an analysis of factors associated with in-hospital death among patients with COVID-19 in China and conditions associated with increased disease severity with seasonal influenza.[1-3] Specifically, older age, decreased oxygen saturation, and D-dimer were associated with COVID-19 mortality in China.[4,5]

Many of the underlying conditions listed were not present in sufficient numbers for evaluation in published studies on COVID-19. The following conditions, known to predispose patients to more severe or prolonged influenza, also have been included: diabetes, heart failure, end-stage kidney disease, advanced HIV, and use of immune-suppressive agents.[1-3] Future studies are likely to refine the risk stratification approach. Whether pregnant patients are at higher risk for severe COVID-19 infection is not known.

III. Use of Antiviral and Immunomodulatory Agents

Available data are limited and there are minimal RCT data on the effectiveness of antiviral or immunomodulatory agents for the treatment of COVID-19. The only reported RCT of available drugs is an open-label study of lopinavir/ritonavir (LPV/RTV) from China, in which treatment with LPV/RTV was not found to improve clinical outcomes among hospitalized patients.[6]

Given the dearth of high-quality evidence, this committee has formulated the guidance in this document based on limited data and expert opinion. Currently, guidance is limited to the use of hydroxychloroquine (HCQ) or chloroquine (CQ).

Remdesivir is an antiviral agent with activity against Ebola virus in humans and other coronaviruses in non-human primates.[7,8] There is an active randomized placebo-controlled clinical trial enrolling at JHH; see Section V for JHH contact information.

IV. Use of HCQ or CQ for Treatment of COVID-19 in Patients at High-Risk for Poor Outcomes

Note: There are currently no definitive data available on the effectiveness or comparative effectiveness of either HCQ or CQ for the treatment of COVID-19.

- Both prescribing clinicians and patients should be aware that drug efficacy for COVID-19 is unclear.
- HCQ is preferred due to better tolerability and lower toxicity.[9] Currently, CQ is in shortage and unavailable for ordering.

This guidance is based on very limited evidence that treatment with HCQ or CQ may result in a more rapid reduction in viral shedding and may be associated with improved clinical outcomes (see evidence discussion below).

If these agents do have clinically significant antiviral activities, then based on experience with other acute viral infections, it is likely that they will be more effective if initiated as soon as possible.[10]

Guidance for the Use of HCQ or CQ for Treatment of COVID-19

Candidates for Treatment

- Clinicians should evaluate all patients admitted for inpatient management of COVID-19 to identify candidates for treatment with HCQ or CQ (if CQ becomes available). Candidates for treatment include patients who meet any 1 of the following criteria:
  - Age ≥65 years old
  - Any one of the following medical conditions:
    - Cardiovascular disease
    - Diabetes with A1c>7.5%
    - Chronic pulmonary diseases, including asthma
    - End-stage renal disease
    - Advanced liver disease
    - Blood disorders (e.g., sickle cell disease)
    - Neurological or neurodevelopmental disorders
    - Post-solid-organ transplantation, on immunosuppressive therapy
    - Use of biologic agents for immunosuppression
    - Undergoing treatment with chemotherapy or immunotherapies for malignancy
    - Within 1 year post-marrow transplant
    - Undergoing treatment for graft versus host disease
    - HIV infection, with CD4 cell count <200 copies/mm^3
  - Any one of the following clinical findings:
    - Oxygen saturation (SaO2) <94% on room air; <90% if known chronic hypoxic conditions or receiving chronic supplemental oxygen
    - Respiratory rate >24 breaths/min
  - Laboratory finding: D-dimer >1 µg/mL
- Any inpatient who, while hospitalized, develops one of the medical conditions or clinical findings listed above.

Guidance for the Use of HCQ or CQ for Treatment of COVID-19

- **Clinicians should NOT prescribe HCQ or CQ treatment for any patient who:**
  - Does not meet at least 1 of the above criteria for being at high-risk of poor outcomes.
  - Is not admitted for inpatient care.
  - Has multiorgan failure. This is due to cardiac concerns with severe COVID-19 and HCQ or CQ.[11]
  - Has QTc >500 ms at baseline, documented cardiomyopathy or myocarditis.[12]
    - If HCQ or CQ treatment is initiated in a patient with elevated QTc at baseline (>450 in men; >470 in women), clinicians should obtain follow-up ECG daily for the first 48 to 72 hours.
    - If QTc increases to >500 ms, clinicians should discontinue HCQ or CQ treatment.
- Clinicians should not delay initiation of HCQ or CQ treatment to obtain either G6PD status or retinal examination.
  - Screening for G6PD deficiency or retinopathy in the context of short-term use of COVID-19 treatment is not recommended.
  - Retinal injury has been associated with long-term HCQ or CQ therapy; the American Academy of Ophthalmology does not recommend retinal screening before short-term use.[13]

HCQ Treatment Duration and Dosing

- For candidates eligible for HCQ treatment, clinicians should prescribe treatment for 5 days, dosed as follows:
  - Day 1 (loading dose): 400 mg by mouth every 12 hours.
  - Days 2 through 5: 400 mg by mouth every 24 hours.
    - Renal or liver impairment: No dosage adjustment necessary.
    - In case of gastrointestinal intolerance, HCQ can be dosed at 200 mg by mouth every 12 hours on days 2 through 5.
    - HCQ tablets can be crushed for administration through a nasogastric (NG) tube.
- **CQ Treatment Duration and Dosing** (note: As of this version date, CQ is unavailable)
  - For eligible candidates, clinicians should prescribe CQ treatment for 7 days, dosed as 500 mg by mouth every 12 hours.
  - Renal or liver impairment: No dosage adjustment necessary.
  - CQ tablets can be crushed for administration through a nasogastric (NG) tube.
- **Combination therapy:** Clinicians should NOT prescribe HCQ and azithromycin combination therapy solely for COVID-19.
  - A small, non-randomized observational study of 36 hospitalized patients with COVID-19 compared 14 patients who were prescribed HCQ alone, 6 patients prescribed HCQ plus azithromycin, and 16 patients prescribed neither agent. HCQ plus azithromycin appeared to lead to faster reduction in viral carriage; however, no pair-wise statistical comparisons were presented, and HCQ failures were removed from analysis.[14] Whether this observation was spurious or has clinical importance is not known. Combination therapy has the known risk of additive QT increase without benefit. Section IV A includes a detailed critique.

A. Review of Limited Evidence Regarding Use of HCQ and CQ

Currently, there are no agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19, and there are no agents with efficacy demonstrated through RCTs. This

document provides guidance for the off-label use of HCQ and CQ (if CQ becomes available) based on results from *in vitro* studies, and use in France[18] and Italy,[14] non-randomized comparative studies, one case report series, and extrapolation from experience treating other diseases.

HCQ and CQ: HCQ and CQ have been found to have *in vitro* activity against SARS-CoV2 and a number of other viruses.[12,15] However, *in vitro* activity of these drugs has not translated into effective activity for any viral infection. Notable studies include failure in animal models for Ebola virus or in humans for influenza and HIV.[12,16,17]

A non-randomized comparison study from France that included 36 patients described a shorter duration of SARS-CoV2 viral shedding among the 20 patients who received HCQ and retention of virus in the 16 patients who did not receive HCQ.[18,19] On day 6 of the study, 70% of the HCQ group compared to 12.5% of the control group had clearance of viral carriage.[18,19] Results of a post-hoc analysis of viral carriage by azithromycin among the 6 patients who received HCQ plus azithromycin are not adequate for guidance on co-administration of azithromycin with HCQ due to the small sample size,[11] lack of statistical significance with a pair-wise comparison, and exclusion of patients who failed therapy (i.e., death or ICU admission). This study has notable limitations: non-randomized design, a small number of patients (36), no clinical outcomes, and no correlation of viral carriage with clinical outcomes.

HCQ & CQ toxicities: The overall risks of HCQ and CQ are likely low, but unknown in treatment of COVID-19.[9] Prolonged QT and potential arrhythmias are the risks of most concern for critically ill patients. This is of most significant concern in patients with cardiomyopathy. In a case series of 21 critically ill COVID-19 patients in Washington State, 33% developed cardiomyopathy.[11] Given the concern for HCQ- or CQ-associated cardiotoxicity in critically ill patients, the risk of use in these patients may outweigh the benefit at later stages of this viral illness.[12]

For patients at higher risk for severe disease but who have not developed cardiac complications, the potential benefit likely outweighs the risk. For patients with mild COVID-19 (i.e., outpatients), the potential risk of treatment with HCQ or CQ outweighs the likely minimal benefit. Similarly, exposing lower-risk hospitalized patients to unproven therapy is not recommended.

Long-term use of HCQ may be associated with retinal toxicities. Short-term use is not associated with retinal damage and may be used in people with pre-existing retinal disease, such as diabetic retinopathy or macular degeneration.

The following common and transient side effects of HCQ have been reported in ≤1% of patients; GI side effects are more common with CQ:[20-23]

- Rash (including pustulosis), pruritus
- Headache, dizziness, tinnitus
- Nausea, vomiting, abdominal pain
- Dry mouth

HCQ and HQ are safe for use in pregnancy [Class B].[24,25]

B. No Evidence to Support Use of HCQ for Pre- or Post-Exposure Prophylaxis

Guidance
• Clinicians should NOT prescribe HCQ for pre-exposure prophylaxis or for post-exposure prophylaxis in individuals with confirmed or suspected exposure to SARS-CoV-2.

There is no experience to support the use of HCQ as pre- or post-exposure prophylaxis. Healthcare workers who have been exposed to SARS-CoV-2 may be eligible for a post-exposure prophylaxis study (covid19@umn.edu; NCT04308668).

V. Use of Remdesivir

Because JHH is a study site for an RCT with remdesivir, clinicians cannot prescribe this medication for compassionate use while the RCT is enrolling.

Guidance for the Use of Remdesivir

- Clinicians should refer patients[a] who meet enrollment criteria for clinical trial[b] screening. Contact Katherine Fenstermacher at 804-695 4720, email: kfenste1@jh.edu.
  - **Inclusion criteria**: For enrollment, patients must be ≥18 years old, with laboratory-confirmed COVID-19 <72 hours prior to randomization (can be a repeat confirmation after an initial diagnosis >72 hours prior) and have least one of the following:
    - Radiographic infiltrates
    - Clinical assessment of rales/crackles and or SpO2 ≤94%
    - Required supplemental oxygen
    - Required mechanical ventilation
  - **Exclusion criteria:**
    - ALT or AST >5 times upper limit of normal
    - Estimated glomerular filtration rate <50 ml/min or required hemodialysis
    - Pregnant or breastfeeding

---

a. Treatment with HCQ, CQ, or any other putative antiviral for COVID-19 will have to be discontinued before trial participation. Patients taking HCQ chronically for a pre-existing condition can continue the agent if enrolled in the RCT.

b. Patients who participate in the RCT cannot be treated for COVID-19 with HCQ or CQ, and they have a 50% chance of receiving a placebo. However, remdesivir is expected to be more effective against SARS-CoV2, so the 50% chance of receiving a more effective treatment makes RCT participation a reasonable choice.

Remdesivir has *in vitro* activity against SARS-CoV2 and other coronaviruses.[26,27] It has been tested in humans for treatment of Ebola virus infection and performed as well as ZMapp but was inferior to human monoclonal antibodies.[7]

In a mouse model, remdesivir was effective when tested as treatment for SARS-CoV1,[19] and it was tested in both a mouse and a primate model for MERS-CoV.[8,28] Compassionate use of remdesivir has also been described for SARS-CoV2.[29]

VI. Use of Other Agents with Speculative Benefit or No Established Benefit Against COVID-19

Do Not Use as a Therapeutic Agent for Treatment of COVID-19 Specifically

- Because there is no evidence of efficacy or effectiveness, clinicians should not use any of the following agents for the treatment of COVID-19 in hospitalized patients.
- **Note:** There is no evidence that any of the following agents are harmful in patients with COVID-19 when used to treat other conditions.
  - ACE/ARB (either initiation or discontinuation of use)
  - Azithromycin
  - Baloxavir
  - Darunavir/ritonavir
  - Favipiravir (not FDA-approved or available in the U.S.)
  - Indomethacin or other NSAIDs
  - Lopinavir/ritonavir
  - Nitazoxanide
  - Oseltamivir
  - Ribavirin
  - Umifenovir (not FDA-approved or available in the United States)

For the agents listed above, either there is no plausible evidence of *in vitro* activity or there is reported *in vitro* activity but no clinical experience.

Angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blocker (ARB): Host cell entry by SAR-CoV2 appears to depend on the ACE2 receptor.[30] ACE-inhibitors block the ACE1 receptor and not the ACE2 receptor, resulting in no clinical benefit. Chronic use of ACE inhibitors and ARBs upregulate ACE2 expression.[31] as do some chronic conditions, such as diabetes. This has led to concerns of a theoretical risk with use of ACE-I or ARBs. At present, there are no clinical data indicating an increased risk of severe disease among individuals receiving either agent, and the time from agent discontinuation to downregulation of ACE2 is likely measured in days.

ACE-I or ARB therapy should be maintained; it should not be discontinued in patients who are diagnosed with COVID-19. Existing clinical recommendations for discontinuation of ACE-I/ARB should be followed. There is no evidence to support the use or discontinuation of these agents for the treatment or the prevention of COVID-19.

Azithromycin: In a small, prospective, case series, the addition of azithromycin to HCQ in 6 patients may have reduced viral carriage, but the results are not adequate to support clinical use of this combination.[19] No efficacy was found in a study of azithromycin against MERS-CoV.[32]

Baloxavir: Baloxavir is licensed for the use against influenza within 48 hours of symptom onset. It is listed as an agent for possible study against SARS-CoV2, although no trial is listed on clinicaltrials.gov.

Darunavir/Ritonavir (DRV/RTV): This combination has weak *in vitro* activity against SARS-CoV2.[33] Given the similar mechanism of action of DRV and lopinavir (LPV; see below), it is unlikely that DRV would provide benefit if LPV does not.

Favipiravir: This agent has been used in China to treat patients with COVID-19.[34,35] An open-label, non-randomized clinical trial comparing favipiravir to LPV/RTV suggested that favipiravir reduced duration of viral shedding and led to more rapid improvement in chest CT findings.[35] An RCT comparing favipiravir to umifenovir reported that the 7-day "clinical recovery rate" was 61% for favipiravir and 52% for umifenovir (p=0.1). A statistically significant reduction in duration of fever was reported for favipiravir.[34] This drug is not approved by the U.S. FDA and is not available in the United States.

LPV/RTV: This combination has weak *in vitro* activity against SARS-CoV2. Although it was widely used in China, an RCT from China reported no clinical benefit among patients hospitalized with COVID-19.[36]

Nitazoxanide: This agent has been tested *in vitro* against MERS-CoV and found to have activity.[37] There is no animal or human data from studies in use against SARS-CoV2.

Non-steroidal anti-inflammatory drugs (NSAIDs): A March 11, 2020 letter hypothesized a potential worsening of COVID-19 with the use of ibuprofen and has caused concern about the potential risk of ibuprofen if used to treat patients with COVID-19.[38] Similar to ACE-I/ARB, ibuprofen has been reported to upregulate ACE2 receptors. However, there currently is no published clinical data to suggest an increased risk in patients with COVID-19. In general, acetaminophen is preferred for treatment of fever in patients with COVID-19, but therapy should be individualized for hospitalized patients, taking into consideration kidney and liver function.

Oseltamivir: Coronaviruses are **not** known to utilize neuraminidase in viral replication; therefore, oseltamivir is *unlikely* to be of any therapeutic value. In one series of 138 hospitalized patients with COVID-19, approximately 90% received oseltamivir, with no reported evidence of benefit.[39]

Umifenovir: This agent was routinely used in China to treat patients with COVID-19.[40] There are no data to support its effectiveness. This drug is not approved by the U.S. FDA and is not available in the United States.

Ribavirin (RBV): RBV was not found to be beneficial against SARS-CoV1.[41] In a study of RBV plus interferon-alpha against MERS-CoV, this combination was not found to reduce mortality.[42]

VII. Use of Immune Modulatory Agents to Treat COVID-19

Guidance

- Clinicians should not prescribe corticosteroids specifically for the treatment of COVID-19.

Corticosteroids: These agents are appropriate for use when indicated for other conditions, but should not be prescribed solely for the treatment of COVID-19.

Interferon beta-B1: (to be developed)

Statins: (to be developed)

Tocilizumab: (to be developed)

REFERENCES

1. Van Kerkhove MD, Cooper MJ, Cost AA, Sanchez JL, Riley S. Risk factors for severe outcomes among members of the United States military hospitalized with pneumonia and influenza, 2000-2012. *Vaccine.* 2015;33(49):6970-6976.
2. Van Kerkhove MD, Vandemaele KA, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med.* 2011;8(7):e1001053.
3. Sheth AN, Althoff KN, Brooks JT. Influenza susceptibility, severity, and shedding in HIV-infected adults: a review of the literature. *Clin Infect Dis.* 2011;52(2):219-227.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020.
5. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.
6. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends.* 2020;14(1):64-68.
7. Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med.* 2019;381(24):2293-2303.
8. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A.* 2020.
9. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. *Inflammopharmacology.* 2015;23(5):231-269.
10. Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. *Clin Infect Dis.* 2005;40(9):1309-1316.
11. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA.* 2020.
12. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. *Drug Saf.* 2018;41(10):919-931.
13. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology.* 2016;123(6):1386-1394.
14. Rosenbaum L. Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. *N Engl J Med.* 2020.
15. 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.
16. Dowall SD, Bosworth A, Watson R, et al. Chloroquine inhibited Ebola virus replication in vitro but failed to protect against infection and disease in the in vivo guinea pig model. *J Gen Virol.* 2015;96(12):3484-3492.

17. Barnard DL, Hubbard VD, Burton J, et al. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and beta-D-N4-hydroxycytidine. *Antivir Chem Chemother.* 2004;15(1):15-22.

18. Wu L, Dai J, Zhao X, Chen Y, Wang G, Li K. Chloroquine enhances replication of influenza A virus A/WSN/33 (H1N1) in dose-, time-, and MOI-dependent manners in human lung epithelial cells A549. *J Med Virol.* 2015;87(7):1096-1103.

19. Gautret P, Lagier J-C, Parola P, et al. Preprint: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. 2020. Accessed 2020 Mar 19.

20. Drent M, Proesmans VLJ, Elfferich MDP, et al. Ranking Self-reported Gastrointestinal Side Effects of Pharmacotherapy in Sarcoidosis. *Lung.* 2020.

21. Liu LJ, Yang YZ, Shi SF, et al. Effects of Hydroxychloroquine on Proteinuria in IgA Nephropathy: A Randomized Controlled Trial. *Am J Kidney Dis.* 2019;74(1):15-22.

22. Lee W, Ruijgrok L, Boxma-de Klerk B, et al. Efficacy of Hydroxychloroquine in Hand Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care Res (Hoboken).* 2018;70(9):1320-1325.

23. Arnaout A, Robertson SJ, Pond GR, et al. A randomized, double-blind, window of opportunity trial evaluating the effects of chloroquine in breast cancer patients. *Breast Cancer Res Treat.* 2019;178(2):327-335.

24. FDA. Plaquenil (hydroxychloroquine sulfate) tablets, USP. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf. Accessed 2020 Mar 21.

25. FDA. Aralen (chloroquine phosphate), USP. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/006002s044lbl.pdf. Accessed 2020 Mar 21.

26. 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(3):269-271.

27. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* 2017;9(396).

28. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020;11(1):222.

29. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med.* 2020;382(10):929-936.

30. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020.

31. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111(20):2605-2610.

32. Arabi YM, Deeb AM, Al-Hameed F, et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. *Int J Infect Dis.* 2019;81:184-190.

33. Wang Q, Zhao Y, Chen X, Hong A. Preprint: Virtual Screening of Approved Clinic Drugs with Main Protease (3CLpro) Reveals Potential Inhibitory Effects on SARS-CoV-2. 2020; https://www.preprints.org/manuscript/202003.0144/v1. Accessed 2020 Mar 21.

34. Chen C, Huang J, Cheng Z, et al. Preprint: Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. 2020; https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v1.full.pdf. Accessed 2020 Mar 22.

35. Cai Q, Yang M, Liu D, et al. Preprint: Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. 2020; https://www.sciencedirect.com/science/article/pii/S2095809920300631. Accessed 2020 Mar 22.

36. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med.* 2020.

37. Cao J, Forrest JC, Zhang X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Res.* 2015;114:1-10.

38. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* 2020.

39. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020.

40. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). 2020; http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. Accessed 2020 Mar 21.

41. Momattin H, Mohammed K, Zumla A, Memish ZA, Al-Tawfiq JA. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy. *Int J Infect Dis.* 2013;17(10):e792-798.

42. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. *Clin Infect Dis.* 2019.