



A regular feature of the *American Journal of Critical Care*, Clinical Evidence Review unveils available scientific evidence to answer questions faced in contemporary clinical practice. It is intended to support, refute, or shed light on health care practices where little evidence exists. We welcome letters regarding this feature and encourage the submission of questions for future review.

COVID-19 AND ANTIMALARIAL DRUGS: HARMS OUTWEIGH BENEFITS

By Margo A. Halm, PhD, RN, NEA-BC

Coronavirus disease 2019 (COVID-19) was first associated with a cluster of pneumonia cases during December 2019 in Wuhan, China. After rapid spread of the disease across China and to several countries,¹ the World Health Organization declared a global health emergency on January 30, 2020, followed by a global pandemic on March 11, 2020.

Coronaviruses are a large family of viruses that are widespread among birds and mammals and cause a variety of illnesses. The virus that causes COVID-19 is an enveloped single-strand RNA zoonotic virus associated with a severe respiratory syndrome.² Spread occurs via human-to-human transmission primarily by inhalation of large respiratory droplets associated with coughing, sneezing, singing, or talking (these heavy droplets may travel 6 feet [1.8 m] or more but fall relatively quickly), or tiny aerosolized particles (<5 µm in diameter) that are light and thus can stay suspended in the air for hours, especially in stagnant air. Less commonly, virus particles can be transmitted through contact with infected surfaces (fomites) or feces.^{1,3-6}

Following a short incubation (median 4-5 days),⁴ clinical features most often include fever, fatigue, dry cough, dyspnea, mild pneumonia, myalgia, and anorexia. Less common symptoms include sore throat, dizziness, headache, diarrhea, and other gastrointestinal symptoms.^{1,2,4,7,8} In an early report of more than 70 000 cases in China, most cases were mild (>80%), but severe (14%)

and critical (5%) cases required hospital admission and intensive care. Some patients' condition deteriorated rapidly within 1 week of illness onset.⁴ Severe cases were characterized by dyspnea, respiratory rate greater than 30/min, oxygen saturation less than 93%, and lung infiltrates exceeding 50% within 24 to 48 hours of illness onset; critical cases involved respiratory failure, sepsis, and/or multiple organ dysfunction. Mortality rates were estimated at 2.3% of confirmed cases.⁹ Major risk factors for severe disease and mortality include increasing age and various comorbidities (eg, hypertension, heart disease, prior stroke, diabetes, chronic lung and kidney disease, immunosuppression).^{1,2,4,8,10}

Absent a vaccine and effective treatment, research has been focused on developing COVID-19 diagnostic and antibody tests and on testing therapies such as remdesivir, convalescent plasma, and the antimalarial drugs chloroquine and hydroxychloroquine, which are also used for autoimmune diseases such as lupus erythematosus or rheumatoid arthritis. Given that little evidence is available on therapies for COVID-19, the PICO (patient problem, intervention, comparison, and outcome) question for this evidence synthesis was, Is chloroquine or hydroxychloroquine safe and effective in reducing the severity of COVID-19 symptoms and disease mortality?

Method

The strategy included searching EMBASE. Key words included *COVID-19*, *chloroquine*, *hydroxychloroquine*, *efficacy*, *safety*, *randomized controlled trial (RCT)*, and *critical illness*. The search was limited to RCTs or systematic reviews published in 2020.

Results

Table 1 outlines findings of 5 studies. Of these, 1 was a retrospective cohort study, 2 were systematic reviews, and 2 were randomized controlled trials. An in vitro study included in one of the systematic reviews¹³ demonstrated

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Table 1
Randomized controlled trials on hydroxychloroquine for treatment of coronavirus disease 2019 (COVID-19)

Reference	Design (N, sample)	Main findings	Level of evidence
Rosenberg et al, ¹¹ 2020	Retrospective multicenter cohort (N=7914 patients with COVID-19 admitted to 25 hospitals) Patients treated with: Hydroxychloroquine alone Hydroxychloroquine with azithromycin Azithromycin alone Neither drug	Overall, in-hospital mortality 20.3% No significant difference in abnormal electrocardiographic findings between groups In adjusted analyses: No significant difference in mortality Hydroxychloroquine with azithromycin, 22.5% Hydroxychloroquine alone, 18.9% Azithromycin alone, 10.9% Neither drug, 17.8% Compared with no drug treatment, cardiac arrest was significantly more likely with hydroxychloroquine/azithromycin combination (but not hydroxychloroquine or azithromycin alone)	C
Chen et al, ¹² 2020	Randomized controlled trial (N=62 patients with COVID-19) Control vs experimental (5-day 400 mg hydroxychloroquine)	Hydroxychloroquine group: No progression to severe illness: 0% vs 13% in controls More pneumonia improvement: 81% vs 55% in controls Recovery significantly shortened: Fever remission: 2.2 days vs 3.2 days in controls Cough remission: 2.0 days vs 3.1 days in controls	C
Cortegiani et al, ¹³ 2020	Systematic review (1 in vitro study, 23 ongoing clinical trials, 2 national guidelines, 1 expert consensus, 1 letter, 1 editorial)	Chloroquine highly effective in reducing viral replication (in vitro study); no data yet from ongoing trials Guidelines recommended: Initial chloroquine dose 600 mg followed by 300 mg after 12 hours on day 1, then 300 mg × 2 on days 2-5 (severe infections) or Chloroquine 500 mg × 2 or hydroxychloroquine 200 mg BID × 10 days Expert opinion recommended: Chloroquine 500 mg × 2 BID × 10 days (mild/moderate/severe COVID-19)	C
Tang et al, ¹⁴ 2020	Randomized controlled trial (N=150 admitted patients) Control vs experimental (hydroxychloroquine 1200-mg loading dose x 3 days followed by maintenance dose of 800 mg daily for 2 weeks (mild/moderate COVID) or 3 weeks (severe COVID); doses adjusted with adverse effects)	Probability of negative conversion by day 28 similar between groups (85.4% hydroxychloroquine group vs 81.3% control group) ($P > .05$) Adverse effects in 30% of patients in hydroxychloroquine group (vs 9% in control group) Diarrhea most common 2 patients treated with hydroxychloroquine had serious adverse effects	C
Chowdhury et al, ¹⁵ 2020	Systematic review (n=7 completed trials and 29 registered clinical trials)	Of 7 trials, 5 had favorable outcomes with chloroquine/hydroxychloroquine treatment but 2 had no change Conclusions on efficacy and safety severely limited by poor study designs and various degrees of bias	C

Abbreviation: BID, twice a day.

that chloroquine blocks the virus by increasing pH in endosomes and interfering with glycosylation in the virus' cellular response and subsequently reduces viral replication. In a small randomized controlled trial (N = 62), researchers found that COVID patients treated with hydroxychloroquine had less progression to severe disease, more improvement in pneumonia, and shortened recovery intervals for fever and cough.¹² Other clinical studies in one systematic review reported favorable outcomes of treatment with chloroquine or hydroxychloroquine;

however, conclusions regarding safety and efficacy were severely limited by poor designs and study bias.¹⁵ In another randomized controlled trial¹⁴ and some studies in one systematic review,¹⁵ researchers found no difference in negative conversion between control group patients and those treated with hydroxychloroquine. No significant difference in mortality among COVID patients treated with hydroxychloroquine with azithromycin, either hydroxychloroquine or azithromycin alone, or neither drug was found in the single cohort study.¹¹

Recommendations for Practice

All of the evidence available is *level C* (Table 2). In vitro, chloroquine appears to block the virus' ability to bind to cells and to reduce viral replication; it also seems to suppress aggressive immune responses in some patients.¹³ Clinically, these drugs have been associated with favorable outcomes in a few trials,^{12,15} but data on harms have been mixed. Tang et al¹⁴ reported greater adverse outcomes in patients receiving chloroquine and hydroxychloroquine. Rosenberg and colleagues¹¹ reported an increased risk of cardiac arrest associated with hydroxychloroquine/azithromycin, but no significant mortality differences between treatment arms in a large cohort (N > 7900). Conclusions from these cohort findings are limited because of the study's observational nature.

Because of emerging safety concerns, the Food and Drug Administration (FDA) issued a warning in late April 2020 about use of hydroxychloroquine in off-label and nonresearch situations.¹⁷ Then in late May 2020, a large multinational observational study¹⁸ (N > 96 000) showed that chloroquine and hydroxychloroquine were each associated with an elevated risk of not only cardiotoxic effects including QT prolongation and new ventricular arrhythmias (4%-8% vs 0.3% in controls), but also in-hospital mortality (16%-24% vs 9% in controls). Although researchers reported that study participants' characteristics were accounted for statistically, critics argued that many factors may have contributed to the reported differences in mortality. For example, physicians may have been more likely to prescribe chloroquine and hydroxychloroquine for patients with severe disease and thus those patients who were given the drugs may already have been at greater risk of mortality.¹⁹ This publication was later retracted after researchers could not guarantee the veracity of data included in the analysis.²⁰ But, authors of this retraction contended that prolonged ventricular repolarization that can lead to ventricular arrhythmias has long been substantiated with anti-malarials. These authors further advocated that administering these agents in patients with COVID-19 further elevates the danger of serious cardiac events due to associated disease-related factors that increase the probability of drug-induced pro-arrhythmias (ie, hypokalemia, fever, increased interleukin-6 concentrations, coadministration of other QT-prolonging drugs).

On June 15, 2020, the FDA then revoked its emergency authorization for use of chloroquine and hydroxychloroquine for hospitalized patients when clinical trials were unavailable or participation was not feasible.^{17,21} Additionally, on June 17, 2020,

Table 2
American Association of Critical-Care Nurses evidence-leveling system^a

Level	Description
A	Meta-analysis or meta-synthesis of multiple controlled studies with results that consistently support a specific action, intervention, or treatment (systematic review of a randomized controlled trial)
B	Evidence from well-designed controlled studies, both randomized and nonrandomized, with results that consistently support a specific action, intervention, or treatment
C	Evidence from qualitative reviews, integrative reviews, or systematic reviews of qualitative, descriptive, or correlational studies or randomized controlled trials with inconsistent results
D	Evidence from peer-reviewed professional organizational standards, with clinical studies to support recommendations
E	Theory-based evidence from expert opinion or multiple case reports
M	Manufacturer's recommendation only

^a From Peterson et al,¹⁶ with permission.

the World Health Organization stopped the hydroxychloroquine arm of the international Solidarity trial evaluating treatments for hospitalized COVID patients because of the lack of observed mortality reductions and associated safety concerns.²² The ORCHID trial (Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease) was also halted in mid-June 2020 because no evidence of harm or benefit was observed.²³

Currently, scientists continue studying numerous treatments for COVID-19 in ongoing clinical trials. More than 100 off-label drugs with antiviral or anti-inflammatory properties are being tested to determine their clinical safety and efficacy against COVID-19.^{24,25} Some of these potentially promising treatments include the following:

- Convalescent plasma—Transfusion of plasma from recovered COVID victims to boost patients' immune systems with antibodies that may help them fight the disease more effectively;
- Remdesivir—An intravenous agent with broad antiviral activity whose therapeutic efficacy was first described for Ebola²⁵;
- Dexamethasone—A steroid that may quell the inflammatory cascade of severe disease is showing promising reductions in 28-day mortality; however, results of the RECOVERY trial are pending. Risks and benefits of steroid administration will need to be considered for each individual patient²⁵⁻²⁷;
- Tocilizumab—A monoclonal antibody that blocks the interleukin-6 signaling pathway that may ameliorate the cytokine release syndrome seen in COVID.^{25,28} Researchers in an observational study reported that tocilizumab was associated with a decreased risk of mechanical ventilation and mortality in patients with severe cases of COVID-19.²⁹

Although the verdict is out on the safety and efficacy of various treatments for COVID-19, science strongly suggests the antimalarial agents' chloroquine and hydroxychloroquine cause more harm than benefit in the context of COVID-19.

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None reported.

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