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Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review

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Author, Article and Disclosure Information

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Eligible for CME Point-of-Care

Annals Author Insight Video - Adrian V. Hernandez, MD, PhD

In this video, Adrian V. Hernandez, MD, PhD, offers additional insight into the article, "Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review." (Duration 3:19)

Abstract

Background:

Hydroxychloroquine and chloroquine have antiviral effects in vitro against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

Purpose:

To summarize evidence about the benefits and harms of hydroxychloroquine or chloroquine for the treatment or prophylaxis of coronavirus disease 2019 (COVID-19).

Data Sources:

PubMed (via MEDLINE), EMBASE (via Ovid), Scopus, Web of Science, Cochrane Library, bioRxiv, Preprints, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry from 1 December 2019 until 8 May 2020.

Study Selection:

Studies in any language reporting efficacy or safety outcomes from hydroxychloroquine or chloroquine use in any setting in adults or children with suspected COVID-19 or at risk for SARS-CoV-2 infection.

Data Extraction:

Independent, dually performed data extraction and quality assessments.

Data Synthesis:

Four randomized controlled trials, 10 cohort studies, and 9 case series assessed treatment effects of the medications, but no studies evaluated prophylaxis. Evidence was conflicting and insufficient regarding the effect of hydroxychloroquine on such outcomes as all-cause mortality, progression to severe disease, clinical symptoms, and upper respiratory virologic clearance with antigen testing. Several studies found that patients receiving hydroxychloroquine developed a QTc interval of 500 ms or greater, but the proportion of patients with this finding varied among the studies. Two studies assessed the efficacy of chloroquine; 1 trial, which compared higher-dose (600 mg twice daily for 10 days) with lower-dose (450 mg twice daily on day 1 and once daily for 4 days) therapy, was stopped owing to concern that the higher dose therapy increased lethality and QTc interval prolongation. An observational study that compared adults with COVID-19 receiving chloroquine phosphate 500 mg once or twice daily with patients not receiving chloroquine found minor fever resolution and virologic clearance benefits with chloroquine.

Limitation:

There were few controlled studies, and control for confounding was inadequate in observational studies.

Conclusion:

Evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19 is very weak and conflicting.

Primary Funding Source:

Agency for Healthcare Research and Quality.

Chloroquine and hydroxychloroquine were among the first drugs considered for treatment of coronavirus disease 2019 (COVID-19) (1). Both have demonstrated in vitro antiviral efficacy against coronaviruses, including SARS-CoV-2 (1–5). Both have known immunomodulating effects in autoimmune diseases that in theory could attenuate the cytokine storm phenomenon (5, 6). In this living systematic review, we evaluate evidence regarding the potential benefits and harms of using these medicines for treatment or prophylaxis of COVID-19. We conducted this review to help inform Practice Points of the American College of Physicians' (ACP's) Scientific Medical Policy Committee (7).

Methods

Jointly with the ACP's Scientific Medical Policy Committee, we formulated several key questions. We then developed a protocol (Supplement) and followed standard methods for conducting and reporting systematic reviews (8, 9) and guidance for living reviews (10, 11). For this report, we focus on the following questions:

1. Is hydroxychloroquine or chloroquine effective at treating, in any setting, children or adults with COVID-19 infections?

2. Is hydroxychloroquine or chloroquine effective at preventing SARS-CoV-2 infections or COVID-19 in children or adults?

3. What are the potential harms and adverse events associated with use of hydroxychloroquine or chloroquine for treatment or prevention of COVID-19 infection?

Data Sources and Searches

Two investigators (V.P. and A.V.H.) developed the search strategy, which was revised and approved by the other investigators. We searched the following databases from 1 December 2019 to 8 May 2020: PubMed (via MEDLINE), EMBASE (via OVID), Scopus, Web of Science, the Cochrane Library, bioRxiv (www.biorxiv.org), Preprints (www.preprints.org), ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/), and the Chinese Clinical Trials Registry (www.chictr.org.cn) without language restrictions. The Supplement shows the PubMed search strategy.

Study Selection

Studies in any language reporting benefit or harm outcomes from use of hydroxychloroquine or chloroquine in children or adults with suspected COVID-19 or at risk for SARS-CoV-2 infection were included. Three investigators (A.V.H., V.P., Y.M.R.) independently screened each record's title and abstract for potential inclusion. Three investigators (V.P., J.J.B., Y.M.R.) then read the full text of the records whose abstracts had been selected by at least 1 investigator. Discrepancies were resolved through discussion or by a fourth investigator (A.V.H.).

Data Extraction and Risk of Bias Assessment

Two investigators (V.P., J.J.B.) independently abstracted the following details: study characteristics, including setting; intervention or exposure characteristics, including medication dose and duration; patient characteristics, including severity of disease; and outcomes, including mortality, respiratory failure, hospitalization in an intensive care unit, progression to severe disease, alleviation of symptoms, change in pulmonary lesions on computed tomography (CT), virologic clearance, and side effects and adverse events. Discrepancies were resolved through discussion or by a third investigator (A.V.H.).

Two investigators (V.P., Y.M.R.) independently assessed risk of bias by using the ROBINS-I (Risk Of Bias In Non-Randomized Studies—of Interventions) tool (12) for cohort studies and the Cochrane Risk of Bias 2.0 tool (13) for trials; disagreements were resolved by discussion with a third investigator (A.V.H.).

Data Synthesis and Analysis

We synthesized evidence qualitatively, noting study design variability and multiple methodological limitations and heterogeneity in populations, comparisons, and analytic methods. We assessed the overall strength of evidence by question and per outcome by using criteria that involved assessment of study limitations, precision of summary effects, consistency of effects across studies, directness of study results (for example, different populations) and reporting bias (14).

Living Review

We plan monthly surveillance of PubMed (via MEDLINE), EMBASE (via Ovid), Scopus, and Web of Science through November 2020 for new evidence related to the potential benefits and harms of treatment. We will use the selection, data extraction, and quality and evidence assessments methods described in this report, except that case series will be excluded from updates, given their limited value. New evidence that does not substantively change review conclusions will be briefly summarized on a monthly basis; a major update will be performed if new evidence changes the nature or strength of the conclusions.

Role of the Funding Source

This study is based on research conducted by the University of Connecticut under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, Maryland (contract HHSA290-2015-00012I, task order 1). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

A representative from AHRQ served as a Contracting Officer's Representative and provided technical assistance. The AHRQ provided comments on draft versions of the protocol, but did not directly participate in study design, analysis, interpretation of data, preparation or approval of the manuscript, or the decision to submit the manuscript for publication.

Results

A total of 23 studies (4 randomized controlled trials [RCTs] [15–19]), 10 cohort studies (20–29), and 9 case series (30–38]), reported in 24 publications, met inclusion criteria (Figure). Study characteristics are described in Supplement Table 1. One study (39) was excluded because it was determined to be an RCT comparing chloroquine with lopinavir–ritonavir.

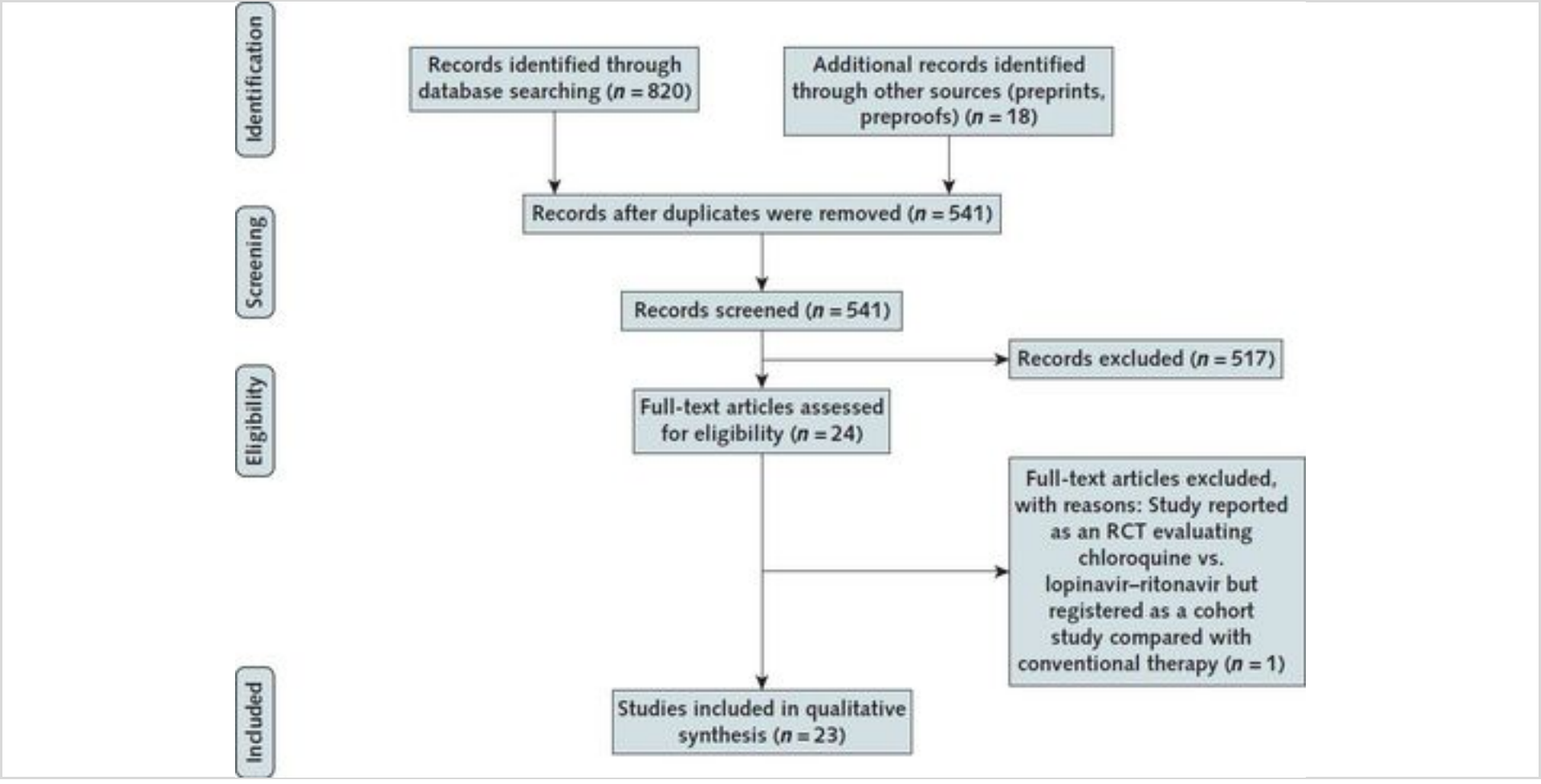

Figure. Evidence search and selection.

RCT = randomized controlled trial.

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Evidence Regarding Potential Treatment Effects

Hydroxychloroquine

Efficacy outcomes for all studies are presented in Supplement Table 2, and Table 1 shows hydroxychloroquine efficacy results for controlled studies only. Risk of bias assessments are included in Supplement Table 3 for cohorts and Supplement Table 4) for RCTs (15–29).

Table 1. Effect of Hydroxychloroquine Reported in Controlled Studies

Table 1. Effect of Hydroxychloroquine Reported in Controlled Studies

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Hydroxychloroquine Versus Control (95% CI)	Strength of Evidence
All-cause mortality				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	0/15 vs. 0/15; absolute RD, 0% (NA)	
Barbosa et al, 2020 (21)	Cohort	Critical	4/31 vs. 1/32; absolute RD, 9.8% (−3.5% to 23.3%)	
Mahévas et al, 2020 (22)	Cohort	Moderate	3/84 vs. 4/97; absolute RD, −0.6% (−6.2% to 5.1%)	
Magagnoli et al, 2020 (23)	Cohort	Serious	27/97 vs. 18/158; absolute RD, 16.4% (6.2% to 26.6%)*	
Yu et al, 2020 (24)	Cohort	No information	9/48 vs. 238/520; absolute RD, −27% (−38.9% to −15.2%)*	
Mallat et al, 2020 (26)	Cohort	Serious	0/23 vs. 0/11 (0%); absolute RD, 0% (NA)	
Membrillo de Novales et al, 2020 (27)	Cohort	Critical	27/123 vs. 21/43; absolute RD, −26.9% (−43.5% to −10.3%)*	
Geleris et al, 2020 (29)	Cohort	Moderate	157/811 vs. 75/565; absolute RD, 6.1% (2.2% to 10%)*	
Composite of intubation or death				**Insufficient**
Geleris et al, 2020 (29)	Cohort	Moderate	262/811 vs. 84/565; absolute RD, 17.4% (13.1% to 21.8%)*	
Composite of ICU admission within 7 days or death				**Insufficient**
Mahévas et al, 2020 (22)	Cohort	Moderate	16/84 vs. 21/97; absolute RD, −2.6% (−14.3% to 9.1%)	
Need for mechanical ventilation				**Insufficient**
Magagnoli et al, 2020 (23)	Cohort	Serious	12/90 vs. 25/177; absolute RD, −0.8% (−9.5% to 7.9%)	
Mallat et al, 2020 (26)	Cohort	Serious	0/23 vs. 0/11; absolute RD, 0% (NA)	
Geleris et al, 2020 (29)	Cohort	Moderate	154/811 vs. 26/565; absolute RD, 14.4% (11.2% to 17.6%)*	
Severe disease progression				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	1/15 vs. 0/15; absolute RD, 6.7% (−6.0% to 19.3%)	
Chen et al, 2020 (16)	RCT	Some concerns	0/31 vs. 4/31; absolute RD, −12.9% (−24.7% to −1.1%)*	
Barbosa et al, 2020 (21)	Cohort	Critical	Respiratory support level: 0.63 points (±0.79) vs. 0.16 points (±0.64); MD, 0.47 (0.11 to 0.83)*	
Mahévas et al, 2020 (22)	Cohort	Moderate	ARDS: 24/84 vs. 23/95; absolute RD, 4.4% (−8.6% to 17.3%)	
Mallat et al, 2020 (26)	Cohort	Serious	High-flow oxygen therapy: 0/23 vs. 0/11; absolute RD, 0% (NA)	
Symptom resolution				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	Fever: 1 vs. 1 day; MD, 0 days (NA)	
Chen et al, 2020 (16)	RCT	Some concerns	Fever: 2.2 d (±0.4) vs. 3.2 d (±1.3); MD, −1 d (−1.5 to −0.5)* Cough: 2.0 d (±0.2) vs. 3.1 d (±1.5); MD, −1.1 d (−1.6 to −0.6)*	
Tang et al, 2020 (19)	RCT	High	Composite symptom resolution: 32/64 vs. 24/55; absolute RD, 6.4% (−11.6% to 24.3%)	
Progression of pulmonary lesions on CT				**Low**
Chen et al, 2020 (15)	RCT	Some concerns	5/15 vs. 7/15; absolute RD, −13.3% (−48.1% to 21.4%)	
Chen et al, 2020 (16)	RCT	Some concerns	2/31 vs. 9/31; absolute RD, −22.6% (−40.8% to −4.4%)*	
Improvement in pulmonary lesions on CT				**Insufficient**
Chen et al, 2020 (16)	RCT	Some concerns	25/31 vs. 17/31; absolute RD, 25.8% (3.4% to 48.2%)*	
Upper respiratory virologic clearance				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	Day 7: 13/15 vs. 14/15; absolute RD, −6.7% (−28% to 14.7%) Day 14: 15/15 vs. 15/15; absolute RD, 0% (NA)	
Tang et al, 2020 (19)	RCT	High	Day 23: 53/75 vs. 56/75; absolute RD, −4% (−18.3% to 10.3%)	
Gautret et al, 2020 (20)	Cohort	Critical	Day 6: 14/20 vs. 2/16; absolute RD, 57.6% (31.8% to 83.3%)*	
Mallat et al, 2020 (26)	Cohort	Serious	Day 14: 11/23 vs. 10/11; absolute RD, −43.1% (−69.6% to −16.5%)*	

ARDS = acute respiratory distress syndrome; CT = computed tomography; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; absolute RD = risk difference.
* Statistically significant.

We found 3 RCTs (all from China) (15, 16, 19), 8 cohort studies (3 from the United States, 3 from Europe, 1 from China, and 1 from the Middle East) (20–24, 26, 27, 29), and 3 case series (all from Europe) (30, 31, 33), all of which assessed hospitalized patients with mostly mild to moderate disease. Overall, 3034 patients (range, 30 to 1376) were assessed in controlled studies (15, 16, 19–24, 26, 27, 29) and 1152 patients (range, 11 to 1061) were assessed in case series (30, 31, 33). Across controlled studies and case series, the mean or median ages (44 to 69 years and 44 to 59 years, respectively), percentage of male participants (42% to 100% and 46% to 64%), and duration of follow-up (5 to 41 days and 10 to 14 days) varied considerably. Five of the controlled studies utilized a loading dose of 800 to 1200 mg (19, 21, 26, 27, 29), standard or maintenance doses ranged from 200 to 800 mg daily (15, 16, 19–24, 26, 27, 29), and the duration of hydroxychloroquine therapy was predominantly 10 days or less (range, 5 days [15, 16] to 2 to 3 weeks [19]). In 2 of the case series (30, 31), hydroxychloroquine 600 mg was given daily for 10 days, whereas 1 case series did not specify dose or duration (33). Results from our bias assessments ranged from no information or some concerns of bias to critical risk of bias (Table 1 and Supplement Tables 3 and 4).

All-Cause Mortality. One RCT with some concerns of risk of bias (15) reported no deaths in

either group. Cohort studies evaluating hydroxychloroquine versus control found effects ranging from large decreases in mortality (no information and critical risk of bias) (24, 27), no changes in mortality (22, 26) (serious and moderate risk of bias), and moderate to large increases in mortality (21, 23, 29) (serious, moderate and critical risk of bias).

One cohort study (29) found a large increase in the composite outcome of intubation or death, whereas another (22) found no effect on the transfer to the intensive care unit (ICU) within 7 days or death with hydroxychloroquine versus control.

Deaths ranged from 5 of 1061 patients (0.5%) to 1 of 11 patients (9.1%) in case series (30, 31, 33) (Supplement Table 2).

Need for Mechanical Ventilation or Composite of Progression to Severe Disease. One cohort study of moderate risk of bias (29) found an increase in the need for mechanical ventilation with hydroxychloroquine versus control, but 2 other cohort studies with serious of risk of bias (23, 26) did not (Table 1).

Whereas 1 RCT (16) found that fewer patients who received hydroxychloroquine than control patients progressed to severe disease, no such benefit was found in another RCT (15), and both had some concerns of risk of bias. A cohort study with critical risk of bias (21) found a moderate increase in the respiratory support needed when hydroxychloroquine was used versus control, whereas others (22, 26) with serious or moderate risk of bias found no changes between groups in acute respiratory distress syndrome or need for high-flow oxygen therapy (Table 1).

In case series, ICU transfers varied considerably from 3 of 80 patients (3.8%) to 2 of 11 patients (18.2%) (30, 31) (Supplement Table 2).

Symptom Resolution. One RCT (16) with some concerns of risk of bias found a 1.0- and 1.1-day reduction in fever and cough, but 2 others (15, 19) with some concerns or high risk of bias found no difference in fever or a composite of temperature 36.6 °C or less, Spo_2 more than 94% on room air, and disappearance of respiratory symptoms with hydroxychloroquine versus control.

Pulmonary Radiologic Assessment. Two RCTs (15, 16) with some concerns of risk of bias found less progression of pulmonary lesions on CT with hydroxychloroquine therapy, but the risk differences varied from –13.3% to –22.6% between studies (Table 1). One study (15) compared day 0 with day 3 CT scans, and the other (16) compared day 0 with day 6 CT scans. One of these RCTs (16) also found better pulmonary lesion improvements on CT with hydroxychloroquine versus control, with a risk difference of 25.8% on day 6, and the investigators reported that 61.3% of hydroxychloroquine recipients had more than 50% pneumonia resorption but did not specify the extent of improvement in the control group.

Upper Respiratory Virologic Clearance. The 2 RCTs with some concerns or high risk of bias (15, 19) found no differences in virologic clearance between hydroxychloroquine and control. The cohort study with critical risk of bias (20) found large increases in virologic clearance for hydroxychloroquine versus control on day 6, whereas another study with serious risk of bias (26) found large decreases in virologic clearance on day 14.

In case series, virologic clearance in patients on hydroxychloroquine varied considerably, from 2 of 10 (20%) to 1017 of 1061 (96%) of patients (31, 33) (Supplement Table 2).

Strength of Evidence. The strength of evidence for all efficacy end points comparing hydroxychloroquine versus control was insufficient, except for progression of pulmonary lesions, for which it was low.

Chloroquine

An RCT (17, 18) from Brazil (81 patients) with high risk of bias directly compared high-dose (total dose, 12 g) with low-dose (total dose, 2.7 g) therapy, and the cohort study (28) from China (373 patients) with critical risk of bias compared chloroquine in either a higher (500 mg twice daily) or lower dose (500 mg once daily) with control for 10 days (Table 2).

Table 2. Effect of Chloroquine Reported in Controlled Studies*

Table 2. Effect of Chloroquine Reported in Controlled Studies*

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Chloroquine Versus Control (95% CI)	Strength of Evidence
All-cause mortality				**Insufficient**
Borba et al, 2020 (17, 18)	RCT	High	16/41 vs. 6/40; absolute RD, 24% (5.4% to 42.6%)†	
Huang et al, 2020 (28)	Cohort	Critical	0/197 vs. 0/176; absolute RD, 0% (NA)	
ICU admission				**Insufficient**
Borba et al, 2020 (17, 18)	RCT	High	1/2 vs. 1/11; absolute RD, 40.9% (-30.4% to 112.3%)	
Huang et al, 2020 (28)	Cohort	Critical	0/197 vs. 0/176; absolute RD, 0% (NA)	
Need for mechanical ventilation				**Insufficient**
Borba et al, 2020 (17, 18)	RCT	High	4/20 vs. 2/19; absolute RD, 9.5% (-12.8% to 31.8%)	
Need for oxygen support				**Insufficient**
Borba et al, 2020 (17, 18)	RCT	High	3/15 vs. 1/13; absolute RD, 12.3% (-12.6% to 37.2%)	
Symptom resolution				**Insufficient**
Huang et al, 2020 (28)	Cohort	Critical	Time to normal body temperature (GM): 1.2 vs. 1.9 d; MD, -0.7 d (95% CI NR)	
Upper respiratory virologic clearance				**Insufficient**
Borba et al, 2020 (17, 18)	RCT	High	Day 4: 0/14 vs. 1/12; absolute RD, -8.3% (-24% to 7.3%)	
Huang et al, 2020 (28)	Cohort	Critical	Day 10: 180/197 vs. 101/176; absolute RD, 34% (25.7% to 42.3%)† Day 14: 189/197 vs. 140/176; absolute RD, 16.4% (9.8% to 23%)†	

GM = geometric mean; ICU = intensive care unit; MD = mean difference; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RD = risk difference.
* Borba et al compared high-dose versus low-dose chloroquine; Huang et al compared chloroquine versus non-chloroquine control.
† Statistically significant.

The RCT (17, 18) only included 62 of 81 patients (77%) with confirmed COVID-19. They found a concerning increase in death, ICU admission, and need for mechanical ventilation, with no effect on virologic clearance, with high-dose versus low-dose chloroquine. The trial was stopped early, without statistically significant findings. A cohort study (28) found a slight reduction in time to body temperature normalization and a modest increase in virologic

clearance at day 14 with chloroquine therapy versus control.

The strength of evidence for all end points was deemed insufficient.

Evidence Regarding Benefit or Harms of Prophylaxis

We found no studies that directly addressed these questions.

Evidence Regarding Potential Harms and Adverse Effects of Treatment

The extracted data for all studies evaluating adverse events are included in Supplement Table 5), and the data from controlled studies only are presented in Table 3.

Table 3. Reported Harms and Adverse Events for Hydroxychloroquine and Chloroquine in Controlled Studies

Table 3. Reported Harms and Adverse Events for Hydroxychloroquine and Chloroquine in Controlled Studies

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Hydroxychloroquine/Chloroquine Versus Control, or High- Versus Low-Dose Chloroquine (95% CI)	Strength of Evidence
Severe adverse events				**Insufficient**
Chen et al, 2020 (16)	RCT	Some concerns	0/31 vs. 0/31; absolute RD, 0% (NA)	
Huang et al, 2020 (28)*	Cohort	Critical	0/197 vs. 0/176; absolute RD, 0% (NA)	
Adverse events				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	4/15 vs. 3/15; absolute RD, 6.7% (−23.5% to 36.8%)	
Chen et al, 2020 (16)	RCT	Some concerns	2/31 vs. 0/31; absolute RD, 6.5% (−2.2% to 15.1%)	
Tang et al, 2020 (19)	RCT	High	21/70 vs. 7/80; absolute RD, 21.3% (8.9% to 33.6%)†	
Huang et al, 2020 (28)*	Cohort	Critical	53/197 vs. 57/176; absolute RD, −5.5% (−14.8% to 3.8%)	
Diarrhea				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	2/15 vs. 0/15(0%); absolute RD, 13.3% (−3.9% to 30.5%)	
Tang et al, 2020 (19)	RCT	High	7/70 vs. 0/80; absolute RD, 10% (3% to 17%)†	
Huang et al, 2020 (28)*	Cohort	Critical	6/197 vs. 11/176; absolute RD, −3.2% (−7.5% to 1.1%)	
Abnormal liver function				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	1/15 vs. 1/15; absolute RD, 0% (−1.7.9% to 17.9%)	
Rash				**Insufficient**
Chen et al, 2020 (16)	RCT	Some concerns	1/31 vs. 0/31; absolute RD, 3.1% (−2.9% to 9.2%)	
Huang et al, 2020 (28)*	Cohort	Critical	1/197 vs. 0/176; absolute RD, 0.5% (−0.5% to 1.5%)	
Headache				**Insufficient**
Chen et al, 2020 (16)	RCT	Some concerns	1/31 vs. 0/31; absolute RD, 3.1% (−2.9% to 9.2%)	
Huang et al, 2020 (28)*	Cohort	Critical	3/197 vs. 3/176; absolute RD, 0.2% (−2.7% to 2.4%)	
QTc prolongation				**Insufficient**
Mah'evas et al, 2020 (22)	Cohort	Moderate	7/84 vs. 0/97; absolute RD, 8.3% (2.4% to 14.2%)†	
Severe QTc prolongation (>500 ms)				**Insufficient**
Borba et al, 2020 (17, 18)‡	RCT	High	7/37 vs. 4/36; absolute RD, 7.8% (−8.5% to 24.1%)	
Mah'evas et al, 2020 (22)	Cohort	Moderate	1/84 vs. 0/97; absolute RD, 1.2% (−1.1% to 3.5%)	
Ventricular tachycardia				**Insufficient**
Borba et al, 2020 (17, 18)‡	RCT	High	2/37 vs. 0/36; absolute RD, 5.4% (−1.9% to 12.7%)	
Anemia				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	0/15 vs. 1/15; absolute RD, −6.7% (−19.3% to 6%)	
Borba et al, 2020 (17, 18)‡	RCT	High	Decrease in hemoglobin level >3 g/dL or ≥30% from baseline: 7/24 vs. 4/18; absolute RD, 6.9% (−19.5% to 33.4%)	
Elevated serum creatinine level				**Insufficient**
Chen et al, 2020 (15)	RCT	Some concerns	0/15 vs. 1/15; absolute RD, −6.7% (−19.3% to 6%)	
Borba et al, 2020 (17, 18)‡	RCT	High	Serum creatinine level ≥30% from baseline: 7/14 vs. 6/19; absolute RD, 18.4% (−15.1% to 51.9%)	

RCT = randomized controlled trial; RD = risk difference.
* Huang et al compared chloroquine versus nonchloroquine control.
† Statistically significant.
‡ Borba et al compared high-dose versus low-dose chloroquine.

Only 1 RCT (16) assessed for the composite end point of severe adverse events, but no events were found in either group. A RCT (19) with high risk of bias found a large increase in adverse events between the hydroxychloroquine and control arms, but 2 others with some concerns of risk of bias (15, 16) only had modest increases in adverse events. Diarrhea was a component of "adverse events," and 2 RCTs (15, 19) found modest increases in diarrhea with hydroxychloroquine versus control. One cohort study with critical risk of bias (28) found no increase in either adverse events or diarrhea with chloroquine versus control.

Hydroxychloroquine was not found to increase the occurrence of abnormal liver function test results (15), increased serum creatinine level (15), rash (16), headache (16), or anemia (15) versus control. Chloroquine was not associated with increases in rash (28) or headache (28) versus control, but those receiving higher-dose chloroquine therapy (17, 18) experienced a slight increase in anemia and a large increase in serum creatinine level compared with those receiving a lower dose.

QTc Interval Prolongation or Arrhythmias. One cohort study assessing hydroxychloroquine (22) and another assessing chloroquine (17, 18) versus control found increases in QTc interval prolongation to 500 ms or greater. Hydroxychloroquine increased the QTc interval more than 60 ms from baseline, whereas chloroquine increased the number of patients experiencing ventricular tachycardia versus control (Table 3).

Another cohort study (25) assessed the effect of hydroxychloroquine with and without azithromycin on the QTc interval in 90 patients (mean age, 60 years; 51% male). Slightly more patients receiving hydroxychloroquine plus azithromycin had a QTc interval of 500 ms or greater (11 of 53 [20.8%] vs. 7 of 37 [18.9%]; mean difference, 1.8% [95% CI, –14.9% to 18.5%]), but more patients had a QTc interval increase of 60 ms or more from baseline (7 of 53 [13.2 %] vs. 3 of 37 [8.1%]; mean difference, 5.1% (CI, –7.6% to 17.8%]) versus hydroxytoluene alone. One patient receiving hydroxychloroquine and azithromycin had a QTc interval of 499 ms but still developed torsade de pointes.

There is insufficient evidence from controlled studies to say that hydroxychloroquine or chloroquine therapy, with or without azithromycin, severely increases QTc intervals or results in torsade de pointes.

Five case series (32, 34–38) (3 from the United States, 1 from Europe, and 1 from the United States and Italy) with sample sizes ranging from 40 to 251 patients assessed the effect of hydroxychloroquine on the QTc interval, although Chorin and colleagues' (36) case series with 251 patients includes 84 patients from their original (32) case series. The ages ranged from 58 to 68 years, and the percentage of men ranged from 57% to 80%. All of the case series assessed the combined use of hydroxychloroquine plus azithromycin. The QTc interval increases greater than 500 ms or 500 ms or greater ranged from 8 of 98 patients (8%) (35) to 7

of 40 patients (17.5%) (34). This is similar to the European case series by van den Broek and associates (38) (95 patients; median age, 65 years; 66% male), in which 22 of 95 (23%) patients receiving chloroquine had a QTc interval greater than 500 ms.

Ongoing RCTs of Hydroxychloroquine and Chloroquine

Supplement Table 6 shows ongoing RCTs evaluating hydroxychloroquine or chloroquine, or both, for the treatment and prevention of COVID-19. As of 8 May 2020, we identified 69 RCTs for treatment (51 of hydroxychloroquine, 5 of chloroquine, and 13 of both drugs), 29 RCTs for prophylaxis (26 of hydroxychloroquine, 1 of chloroquine, and 2 of both drugs), and 5 RCTs for both treatment and prophylaxis. The RCTs are being performed or about to begin in several countries across the world. Primary completion dates range from April 2020 and March 2023.

Discussion

We did not find studies evaluating hydroxychloroquine or chloroquine for prophylaxis against COVID-19. In RCTs and cohort studies, the effects on all-cause mortality, need for mechanical ventilation, progression to severe disease, symptom resolution, and upper respiratory viral clearance with hydroxychloroquine to treat COVID-19 were often conflicting, but mostly no different from conventional therapy. The direction of effect for hydroxychloroquine improving pulmonary CT findings were consistent in the 2 small RCTs that assessed it, although the magnitude of effect was different.

The small sample sizes and low methodological quality of these comparative studies are likely explanations for the variability seen in these results. Although 3 RCTs assessed hydroxychloroquine as a treatment for COVID-19, they lacked placebo controls and neither patients nor clinicians were blinded to treatment assignment. The cohort studies had baseline differences between comparison groups; even when statistically adjusted, some major innate methodological weaknesses remained. Gautret and colleagues' cohort study (20) merits special mention because 6 of the 42 eligible patients without evaluable data on day 6 post-treatment were all in the hydroxychloroquine group. This included 4 patients who were still testing positive for SARS-CoV-2 on polymerase chain reaction assay the day before, which probably skewed the virologic clearance data. In addition, Yu and associates (24) derived their nested cohort from the clinical trial ChiCTR2000029605 (http://www.chictr.org.cn/showprojen.aspx?proj=49051), which assessed traditional Chinese dietary supplements; there were only 48 participants in the hydroxychloroquine group compared with 520 in the control group. The investigators did not state the distribution of the traditional Chinese dietary supplement regimen between groups.

Thirty-five percent of patients assessed for efficacy or safety of hydroxychloroquine in our systematic review were from case series (30–36). Case series have no control group and, thus, no ability to compare the results with and without therapy. As such, the ability to extrapolate the effects from these case series to the clinical environment is very low.

Multiple studies showed that 1% to 18% of patients receiving hydroxychloroquine experienced a severe increase in the QTc interval (22, 32, 34–37). The QTc interval prolongation may be worse when azithromycin is combined with hydroxychloroquine. This association between hydroxychloroquine and QTc interval prolongation is bolstered by indirect evidence from patients without COVID-19, where the product labeling specifically says that QTc interval prolongation and torsade de pointes have been reported. In a 2018 systematic review (40), 86 articles assessing severe adverse events experienced by patients receiving hydroxychloroquine or chloroquine were included. Overall, 85% of the people without COVID-19 reporting adverse events experienced arrhythmias. The American Heart Association, American College of Cardiology, and Heart Rhythm Society (41) have specifically identified concern about QTc interval prolongation and steps to mitigate the risk when hydroxychloroquine is used to treat patients with COVID-19. On 24 April 2020, the U.S. Food and Drug Administration released a warning against use of hydroxychloroquine or chloroquine for COVID-19 outside the hospital setting or a clinical trial due to the risk of heart rhythm problems (42).

There are now 2 studies assessing both the efficacy and safety of chloroquine (17, 18, 28) and 2 case series (37, 38) assessing its QTc interval effects. Borba and coworkers (17, 18) assessed COVID-19 treatment with higher- versus lower-dose chloroquine therapy; the study was stopped early, after a preliminary analysis found lackluster benefits and troubling but nonsignificant increases in all-cause mortality, ICU admission, mechanical ventilation, QTc interval prolongation, and ventricular arrhythmias with higher-dose therapy. Because the trial was stopped at such an early stage, the differences between groups could be caused, in part or in whole, by chance. However, the prescribing information for both chloroquine and hydroxychloroquine state that excessive acute dosing can lead to cardiovascular collapse, shock, and respiratory arrest (43, 44). Huang and associated (28) assessed chloroquine versus nonchloroquine control and found some small improvements in time to fever resolution and virologic clearance, but no effect on all-cause mortality or ICU admission. These potential benefits need to be weighed against the 23% of patients in the van den Broek and colleagues' case series (38) who experienced a QTc interval greater than 500 ms (37).

Recent systematic and rapid reviews and treatment guidelines evaluating the effects of hydroxychloroquine or chloroquine for the treatment of COVID-19 found no differences or inconclusive effects when evaluating a small set of studies (45–49). A recent systematic review (50) did not find comparative studies of chloroquine for the treatment of COVID-19, and another systematic review (51) on prophylaxis of COVID-19 with the use of hydroxychloroquine or chloroquine did not find information from RCTs. We have performed

a more updated systematic review and assessed substantially more studies.

Since the time of our last updated search, we are aware of 1 newly published study with salient information. It is a retrospective cohort study of 1438 patients hospitalized in metropolitan New York that compared with treatment with neither drug, hydroxychloroquine alone, azithromycin alone, or the combination of the 2 (52). The adjusted hazard ratio for in-hospital mortality was 1.08 for treatment with hydroxychloroquine alone, 0.56 for azithromycin alone, and 1.35 for combined hydroxychloroquine and azithromycin, but none of these hazard ratios reached statistical significance. This would not have changed our systematic review's findings. Two other preprint publications included in our review (19, 22) are now published (53, 54), but the additional information provided does not alter our risk of bias assessments.

In conclusion, there is insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19. As such, it is impossible to determine the balance of benefits to harms. There are no assessments of hydroxychloroquine or chloroquine for prophylaxis against COVID-19.

This article was published at Annals.org on 27 May 2020.

Comments

3 Comments

SIGN IN TO SUBMIT A COMMENT

Brian S. Alper, Martin Mayer,Khalid Shahin • Innovations and EBM Development, EBSCO Clinical Decisions • 23 June 2020

Computable Resources to Support Living Systematic Reviews

We thank the authors for their efforts to support living systematic reviews to disseminate knowledge for overcoming COVID-19. Through the COVID-19 Knowledge Accelerator (https://www.gps.health/covid19_knowledge_accelerator.html), we aim to support multiple ways for people identifying, evaluating, and disseminating evidence about COVID-19 to extend and re-use collective efforts.(1) Our curated knowledge that could be used to inform this living systematic review includes a summary of clinical outcomes results extracted from randomized controlled trials of hydroxychloroquine treatment for COVID-19.(2)

From a content perspective, additional information this report provides includes meta-analyses for three outcomes where data from two trials could be combined (albeit only yielding very low certainty evidence and also having the obvious limitations inherent in attempting to meta-analyze such sparse

data regardless of the methods one uses for the meta-analysis) and a finding of moderate certainty of no mortality reduction based on a large randomized trial not yet reported in any published form, but that has a detailed protocol that was made available a priori.(3) From an infrastructure perspective, the citation for this report(2) includes a URL for the human-readable report and a URL for the computable resource. The computable resource provides open access to all the data (evidence variable definitions, statistics, certainty of evidence judgments) in computable code for machine interpretation. Re-use of such data can allow systematic review authors to create and update reviews with much less duplication of effort.

Further development of these systems can provide the earliest possible dissemination pathways for evidence of treatments that could make a meaningful difference for people with COVID-19, such as remdesivir(4) or dexamethasone.(5)

1. Richardson JE, Alper BS, Lehmann HP, Subbian V. It is time for computable evidence synthesis: the COVID-19 Knowledge Accelerator Initiative. J Am Med Inform Assoc 2020 May 22; https://doi.org/10.1093/jamia/ocaa114

2. Alper BS, Mayer M, Shahin K. Hydroxychloroquine Treatment for COVID-19: Clinical Outcomes Results Extracted from Randomized Controlled Trials. COVID-19 Knowledge Accelerator Evidence Reports, entry 23, version 2020-06-16. Created 2020 Jun 10. Revised 2020 Jun 16. Available at: https://gps.health/coka/reports/EvidenceReport/23. Computable resource at: https://gps.health/coka/resources/EvidenceReport/23?version=6

3. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020. Available at https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf (accessed June 6, 2020)

4. Alper BS, Mayer M, Shahin K. Remdesivir Treatment for COVID-19: Clinical Outcomes Results Extracted from Randomized Controlled Trials. COVID-19 Knowledge Accelerator Evidence Reports, entry 24, version 2020-06-16. Created 2020 Jun 10. Revised 2020 Jun 16. Available at: https://gps.health/coka/reports/EvidenceReport/24. Computable resource at: https://gps.health/coka/resources/EvidenceReport/24?version=10

5. Alper BS, Mayer M, Shahin K. Dexamethasone Treatment for COVID-19: Clinical Outcomes Results Extracted from Randomized Controlled Trials. COVID-19 Knowledge Accelerator Evidence Reports, entry 28, version 2020-06-22. Created 2020 Jun 22. Revised 2020 Jun 22. Available at: https://gps.health/coka/reports/EvidenceReport/28. Computable resource at: https://gps.health/coka/resources/EvidenceReport/28?version=4

Disclosures:

The authors are employed by EBSCO Information Services which commercializes evidence-based clinical reference and clinical decision support tools. However the COVID-19 Knowledge Accelerator described in this comment is not a commercial activity, the COVID-19 content is shared openly, and there is no cost to participate in the COVID-19 Knowledge Accelerator.

Charles White, Adrian Hernandez • University of Connecticut • 3 June 2020

Authors' Response to Argen

We thank Dr Argen for the two points in his comment. We agree that the general message being sent to physicians and the public alike through the media is that hydroxychloroquine is a very dangerous drug.(1) It has a long track record of short term use for the malaria and of chronic use for rheumatologic conditions and is generally well tolerated and safe.(2) Rheumatologists have extensive experience using the drug and can be a great resource for their colleagues interested in its use for COVID-19. It is possible that its use in hospitalized COVID-19 patients could enhance or decrease the risks of adverse events versus its outpatient use in rheumatologic conditions and this warrants a specific assessment. In our living systematic review we found the current dataset is insufficient to say whether the adverse events are more or less prevalent than with control therapy.(3) As more evidence comes to light, we will be including it in our ongoing living review so that physicians can have updated information.

1. Lovelace B. FDA issues warnings on chloroquine and hydroxychloroquine after deaths and poisonings reported. CNBC. Apr 24, 2020. Available at https://www.cnbc.com/2020/04/24/fda-issues-warnings-on-chloroquine-and-hydroxychloroquine-after-serious-poisoning-and-death-reported.html. Accessed 6/2/2020.

2. Yazdany J, Kim AHJ. Use of hydroxychloroquine and chloroquine during the COVID-19 pandemic: what every clinician should know. Ann Intern Med 2020; https://doi.org/10.7326/M20-1334.

3. Hernandez AV, Roman YM, Pasupuleti V, et al. Treatment or prophylaxis of COVID-19: a living systematic review. Ann Intern Med 2020; https://doi.org/10.7326/M20-2496.

Ralph J Argen MD FACP • Rheumatologist use of hydroxychloroquine • 2 June 2020

Rheumatologist use of hydroxychloroquine

Hydroxychloroquine has been in use in the treatment of Rheumatological illnesses of all sorts getting back to at least 1960. The dose is used for generally 200 mg two times a day and the results were

usually slow and cumulative. The number of patients using this would be impossible to count but the horrors that have been described are Ridiculous. Strangely enough people using this have never consulted rheumatologist about the drug and made outlandish descriptions. I have viewed the drug for 55 years and everything said about it makes no sense at all. People are evaluating and using it should talk to people who have used it.

PREVIOUS NEXT