ASIA PACIFIC CENTER FOR EVIDENCE BASED HEALTHCARE

Should Hydroxychloroquine (HCQ) or Chloroquine (CQ) be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of hydroxychloroquine or chloroquine in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is insufficient evidence to support the routine use of CQ or HCQ for the treatment of

Hydrochloroquine or Chloroquine monotherapy

- At present, there are 2 randomized controlled trials that investigated the efficacy and safety of HCQ compared to standard therapy. Overall risk of bias was moderate.
- Our meta-analysis of these RCTs, which included a total of 92 adults with RT-PCR confirmed COVID-19, showed that treatment with HCQ 400 mg daily for 5 days improved chest CT scan findings compared to standard therapy alone (RR 1.41, 95% CI 1.03, 1.92). There were no significant differences in clinical outcomes (disease progression, symptom improvement).
- Adverse events for HCQ reported in the RCTs (n=6) include diarrhea, fatigue, rash, headache, and transient aspartate aminotransferase elevation. These resolved after drug discontinuation or symptomatic treatment.
- There are currently at least 13 ongoing randomized controlled trials investigating HCQ or CQ alone as treatment for COVID-19 infection.
- Several national (China, Italy, Netherlands, Belgium) guidelines recommend the use of CQ or HCQ as treatment for mild to moderate COVID-19 infection. The US FDA has authorized the emergency use of HCQ and CQ as treatment for COVID-19.
- The Philippine Society for Microbiology and Infectious Diseases (PSMID) has identified HCQ for off-label use as an option for the treatment of hospitalized probable or confirmed COVID-19 cases with moderate to high-risk pneumonia.

Hydrochloroquine and/or Chloroquine in combination with other drugs

- At present, there are no published trials that investigate the efficacy and safety of HCQ or CQ in combination with other drugs.
- Gastrointestinal symptoms (diarrhea, nausea/vomiting) were the most frequent adverse events cited in small cohorts of patients receiving HCQ/Azithromycin combination for COVID-19. One patient developed blurred vision, and another had QTc prolongation on the fourth day. In one cohort (n = 80), one patient died and two needed ICU admission.
- A case series of 84 adult COVID-19 patients with co-morbidities, showed that combination treatment with HCQ/Azithromycin was associated with QTc prolongation in 30% of patients. No arrhythmia-related deaths were reported. The development of acute renal failure was a strong predictor of QTc prolongation (OR: 19.45, 95% CI: 2.06 - 183.38).
- At present, there are at least 6 ongoing randomized controlled trials that investigate HCQ or CQ in combination with other drugs (Favipiravir, Lopinavir/Ritonavir, Azithromycin, Oseltamivir, Darunavir/Cobicistat)

Conflicts of Interest: No relevant conflicts of interest

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Appendix 1. Characteristics of ongoing clinical trials

		Study	Setting/Population	Intervention	Outcomes	Status
1		A multicenter, single-blind, randomized controlled clinical trial for chloroquine phosphate in the treatment of novel coronavirus pneumonia (COVID-19) ChiCTR2000031204	300 adults 18-70 y/o with confirmed COVID and clinical diagnosis of pneumonia China	Oral CQ phospate vs. placebo	Efficacy and safety	Study Period: 01/20/2020 to 04/30/2020
2		A Randomized Controlled Trial for Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (COVID-19) ChiCTR2000030987	150 adults 18-75 y/o, diagnosed with COVID-19 within the last 14 days, and nucleic acid positive w/in 3 days of enrolment China	Favipiravir + CQ phosphate vs. Favipiravir alone vs. placebo	Improvement or recovery of respiratory symptoms Viral nucleic acid shedding	Study Period: 03/05/2020 to 06/25/2020
3		Randomized controlled trial for Chloroquine Phosphate in the Treatment of novel coronavirus pneumonia (COVID-19) ChCTR2000030718	80 adults >18 y/o with confirmed COVID-19 China	CQ phosphate vs No CQ	Time to clinical recovery All-cause mortality Frequency of exacerbation of dyspnea Remission time of non-primary symptoms Time for 2019-nCoV nucleic acid turning negative in throat swabs Duration of oxygen inhalation or noninvasive ventilation Viral load in throat swabs in 1st & 7th day Viral load in anal swabs	Study Period: 02/12/2020 to 05/30/2020

					before discharge or at the end of the study Anti-2019-nCoV 1gG and IgM values in 1st, 7th, 14th day, before discharge and at the end of the study Improved BAP-65 and DECAF scores in 1st, 7th day Blood routine, blood gas analysis, liver and kidney function and blood drug concentration of CQ phosphate in 1st & 7th day Days of mechanical ventilation Time for recovery in images Incidence of progression to critical illness or death Lengh-of-stay in hospital and/or ICU Cost of money Incidence of adverse events	
4		A prospective, open label, randomized, control trial for chloroquine or hydroxychloroquine in patients with mild and common novel coronavirus pulmonary (COVIP-19)	100 adults 18-75 y/o with RT-PCR confirmed COVID or confirmed lung involvement with chest imaging and mild clinical symptoms China	HCQ sulfate 200 mg BID x 14days CQ phosphate 1g x 2 days, then 500 mg x 12 days Usual care	Clinical recovery time Time to 2019-nCoV RT-PCR negativity in upper and lower respiratory trat specimens Clinical Status Time from study entry to discharge Frequency of serious advers drug reactions	Study period: 02/22/2020 to 05/21/2020

		ChCTR2000030054			Dynamic changed of laboratory indexes Dynamic changes of daily vital signs (body temperature, resporiatory rate, blood pressure, heart rate)	
5		A prospective, randomized open label controlled trial for chloroquine and hydroxychloroquine in patients with severe novel coronavirus pneumonia (COVID-19) ChCTR2000029992	100 adults 18-75 y/o, with positive RT-PCR test for novel coronavirus and typical viral pneumonia on lung CT China	CQ phosphate 1g x 2d then 500 mg x 12 days HCQ 200 mg BID x 14 days Routine care	Clinical recovery time Changes in viral load of upper and lower respiratory tract samples vs baseline Day 7, 14, 21, 28 clinical status Time from study entry to discharge Frequency of ADRs Dynamic changed of laboratory indexes Dynamic changes of daily vital signs (body temperature, resporiatory rate, blood pressure, heart rate)	Study period: 02/17/2020 to 05/20/2020
6		Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19) ChCTR2000029988	80 adults 18-70 y/o, severe patients, within 12 days of illness onset China	CQ phosphate vs No CQ	Time to clinical recovery All cause mortality Length of stay in hospital Length of stay in ICU Days of mechanical ventilation Modified BAP-65 and DECAF score Cost of money Incidence of serious adverse events	Study period: 02/13/2020 to 05/31/2020

7		A Single-blind, Randomized, Controlled Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19) ChCTR2000029939	100 adults 18 years and older with confirmed COVID-19 pneumonia China	CQ phosphate + conventional treatment vs conventional treatment alone	Length of hospital stay Progression from mild to severe illness 30-day case-specific mortality 30-day all-cause mortality Relapse within 14 days after discharge C-reactive protein Inflammatory factors Indices of liver function (ALT, TB) Serious adverse events	Study Period: 02/06/2020 to 02/06/2021
8		Hydroxychloroquine treating novel coronavirus pneumonia (COVID-19): a randomized controlled, open-label, multicenter trial ChCTR2000029868	360 adults 18 y/o and older with confirmed COVID-19 pneumonia China	Standard treatment + HCQ 400 mg TID from D1 to D3, then 400 mg BID from D4 to D21 vs Standard treatment alone	Viral nucleic acid test Adverse events	Study Period: 02/06/2020 to 06/30/2020
9		A prospective, open-label, multiple center study for the efficacy of chloroquine phosphate in pateints with novel coronavirus pneumonia (COVID-19) ChCTR2000029609	205 adults >= 18 years, diagnosed with 2019 nCoV pneumonia accdg to national guideline mild to moderate pneumonia: 177 pxs severe pneumonia: 28 pxs China	Mild to Moderate Oral CQ phosphate vs. Oral Lopinavir/ritonavir vs CQ + lopinavir/ritonavir Severe Oral CQ phosphate vs. Oral Lopinavir/ritonavir	Viral nucleic acid negative-tranforming time 28-day all-cause mortality total length of hospitalization ICU admission ratio Length of ICU stay	Study Period: 02/12/2020 to 12/31/2020

10		Efficacy of Chloroquine and Lopinavir/Rionavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter controlled clinical study ChCTR2000029741	112 adults = 18 y/o with confirmed COVI-19 infection based on 5th edition of national guideline China	CQ phosphate vs Lopinavir/Ritonavir	Length of stay Length of severe Oxygenation index during treatment 28-day all-cause mortality Peripheral blood cell count Procalcitonin C-reactive protein Inflammatory factors Lympohocyte subsets and complement Coagulation indicatiors Viral nucleic acid Liver, kidney fucntion, muscle enzymes, myoglobin Adverse events during treatment Chloroquine blood concentration	Study Period: 02/12/2020 to 12/31/2020
11		Therapeutic effect of hydroxychloroquine on novel coronarvirus pneumonia (COVID-19) ChCTR2000029559	300 adults with novel coronavirus pneumonia China	HCQ 100 mg BID vs HQ 200 mg BID vs placebo	Time when nucleic acid of the noval coronavirus turns negative T cell recovery time	Study period: 01/31/2020 to 02/29/2020
12		Anti-Coronavirus Therapies to Prevent Progression of COVID-19, a Randomized Trial PI: Richard Whitlock Open label, parallel group RCT	1500 participants COVID-19 positive Including outpatients Age 18 years and older Ontario, Canada	Azithromycin + chloroquine Chloroquine: ≥ 50 kg: 500 mg twice daily for 7 days; < 50 kg: 500 mg BID on D1-2 then 500 mg OD on D3-7 Azithromycin: 500 mg	Hospital admission or death Invasive mechanical ventilation or mortality	Not yet recruiting Estimated completion date: December 31, 2020

				on day 1 then 250 mg OD x 4 days Comparator: Standard of care		
13		A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID19 AND Lopipinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopipinavir / Ritonavir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID19 Contact: Subsai Kongsaengdao Randomized open label multicenter clinical trial Phase 3	80 participants Ages 16 to 100 years Bangkok, Thailand	Oseltamivir + HCQ (mild COVID-19) Darunavir/ritonavir + oseltamivir Lopinavir/ritonavir + oseltamivir (mild COVID-19) Favipiravir/lopinavir/ritonavir (moderate-severe COVID-19) Darunavir/ritonavir/favipiravir + HCQ (moderate-severe COVID-19) No intervention: Conventional quarantine in mild COVID-19	SARS-CoV-2 eradication time (nasopharyngeal) Secondary outcomes: Number of patients with death Number of patients with recovery Number of days with ventilator Number of patients developing acute respiratory distress syndrome After treatment	Not yet recruiting Estimated completion date: November 30, 2020
14		Treatment of Non-severe Confirmed Cases of COVID-19 and Chemoprophylaxis of	3040 participants Cases: Acute respiratory infection or acute cough alone +	Treating, testing and prophylaxis of SARS-CoV-2	Effectiveness of chemoprophylaxis assessed by incidence of secondary COVID-19	Recruiting Estimated completion

		Their Contacts as Prevention Strategy: a Cluster Randomized Clinical Trial (PEP CoV-2 Study) Contact: Oriol Mitja Open label, cluster randomized trial Phase 3	nCoV positive PCR Age 18 years and older Excludes critically ill patients Barcelona, Spain	Cases: Darunavir/cobicistat + HCQ Darunavir 800mg / cobicistat 150 mg / tab every 24 hours x 7 days + hydroxychloroquine 800 mg on D1 and 400 mg from D2-7 Contacts: HCQ prophylaxis Hydroxychloroquine 800 mg on D1 and 40 mg from D2-4) Comparator: No intervention	cases Secondary outcomes: Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3 Mortality rate of subjects at week 2 Proportion of participants that drop out of study Proportion of participants that show non-compliance with study drug	date: June 15, 2020
15		The Efficacy and Safety of Carrimycin Treatment in Patients With Novel Coronavirus Infectious Disease (COVID-19) : A Multicenter, Randomized, Open-controlled Study PI: Ronghua Jin Open-label parallel assignment randomized trial	520 participants 2019-nCoV pneumonia Age 18 to 75 years SOFA score 1-13 China	Carrimycin Comparator: Lopinavir/ritonavir, or arbidol, or chloroquine phosphate	Fever to normal time Pulmonary inflammation resolution time (by HRCT) Negative conversion rate of 2019-nCoV RNA in throat swabs at end of treatment	Not yet recruiting Estimated completion date: February 28, 2021
16		Efficacy and Safety of Chloroquine Diphosphate for the Treatment of Hospitalized Patients With Severe Acute Respiratory Syndrome Secondary to SARS-CoV2: a Phase IIb,	440 participants Hospitalized due to severe respiratory syndrome with or without a confirmatory diagnosis of SARS-CoV-2	Low Dose Chloroquine Diphosphate (5 days): 450 mg bid (3 tablets of 150 mg, every 12 hours) on D1, 3	Mortality at day 28 Secondary outcomes: Morality at day 7 and 14 Improvement in overall subject's clinical status assessed in standardized	Recruiting Estimated completion date: August 31, 2020

		Double-blind, Randomized Adaptive Clinical Trial Contact: Marcus Lacerda 4-blind, randomized trial Phase 2	Age 18 to 100 years Amazonas, Brazil	tablets of 150 mg once daily from D2 to D5 Comparator: High Dose Chloroquine Diphosphate (10 days): 600 mg bid (4 tablets of 150 mg, every 12 hours) for 10 days	clinical questionnaires on days 14 and 28 Improvement in daily clinical status assessed in standardized clinical questionnaires during hospitalization Duration of supplemental oxygen Duration of mechanical ventilation Duration of hospital stay Prevalence of serious adverse events Change in serum creatinine level, serum troponin-I level, serum AST level, serum CK-MB level Change in detectable viral load in respiratory tract swabs Viral concentration in blood samples Absolute number of causes leading to participant death	
17		Norwegian Coronavirus Disease 2019 Study: An Open Labeled Randomized Controlled Pragmatic Trial to Evaluate the Antiviral Effect of Chloroquine in Adult Patients With SARS-CoV-2 Infection PI: Olav Dalgard	202 participants SARS-CoV-2 positive nasopharyngeal swab Moderately severe disease (NEWS score ≤ 6) Ages 18 years and older Oslo, Norway	Hydroxychloroquine sulfate 400 mg (310 mg base) BID x 7 days Comparator: Standard of care	Rate of decline in SARS-CoV-2 viral load Secondary outcomes: Change in National Early Warning Score (NEWS) Admission to intensive care unit Duration of hospital admission Mortality at 30 and 90 days	Not yet recruiting Estimated completion date: April 1, 2021 (primary), March 3, 2025 (study)

		Two-arm, open label, pragmatic randomized controlled trial Phase 4			Clinical status (death, invasive MV, NIV, supplemental O2)	
18		Evaluation of the Safety and Clinical Efficacy of Hydroxychloroquine Associated With Azithromycin in Patients With Pneumonia Caused by Infection by the SARS-CoV2 Virus - Alliance COVID-19 Brasil II - Severely-ill Patients PI: Otávio Berwanger Randomized open label, multicenter clinical trial Phase 3	440 participants Probable or confirmed infection by SARS-CoV2 Ages 18 years and older Brazil (22 study locations)	HCQ + Azithromycin Hydroxychloroquine 400mg BID + Azithromycin 500 mg OD x 10 days Comparator: HCQ Hydroxychloroquine 400mg BID x 10 days	Clinical status (ordinal scale of 7 points) Secondary outcomes: All-cause mortality Number of days free from mechanical ventilation Duration of mechanical ventilation Duration of hospitalization Other secondary infections Time from treatment start to death	Not yet recruiting Estimated completion date: August 30, 2020
19		A trial evaluating treatments for suspected coronavirus infection in people aged 50 years and above with pre-existing conditions and those aged 65 years and above Contact: Christopher Butler Pragmatic open label individually randomised platform RCT in community care Phase III	3000 participants Possible COVID-19 (continuous cough and/or high temperature within 7 days), either aged 65+, or aged 50+ with comorbidities United Kingdom	Hydroxychloroquine sulphate 200mg BID x 7 days Comparator: Usual care	Need for hospital admission or death Secondary outcomes: Duration of severe symptoms Time taken to full recovery of illness Contacts with the health services Consumption of antibiotics Hospital assessment without admission Oxygen administration Intensive Care Unit admission Mechanical ventilation	Recruiting Estimated completion date: March 24, 2021