UWTASP
tele-antimicrobial stewardship program

Pharmacotherapy for COVID-19, Part 2: A Practical Discussion

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March 31, 2020

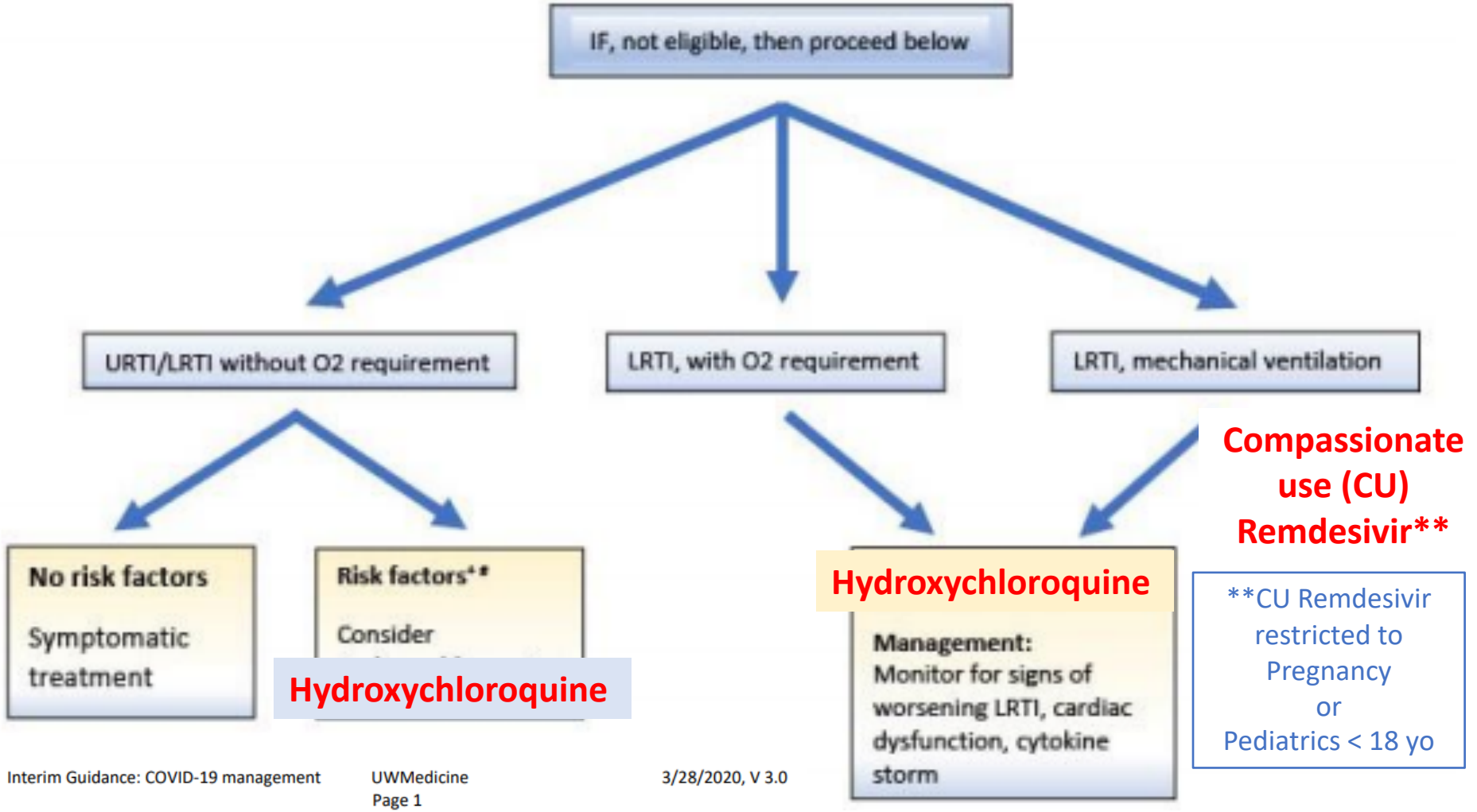
This presentation is intended for educational use only, and does not in any way constitute medical consultation or advice related to any specific patient.

citations

Algorithm for inpatient management of patients with COVID-19 at UW Medicine

Evaluate for clinical trial eligibility

VTEU **Remdesivir** (NCT04280705)



Does your Institution have Access to Remdesivir?

A. Yes, enrolled in the clinical trial
B. Yes, enrolled in compassionate use/expanded use
C. No, denied from clinical trial or other use programs
D. No, have not attempted to enroll/apply
E. Not sure

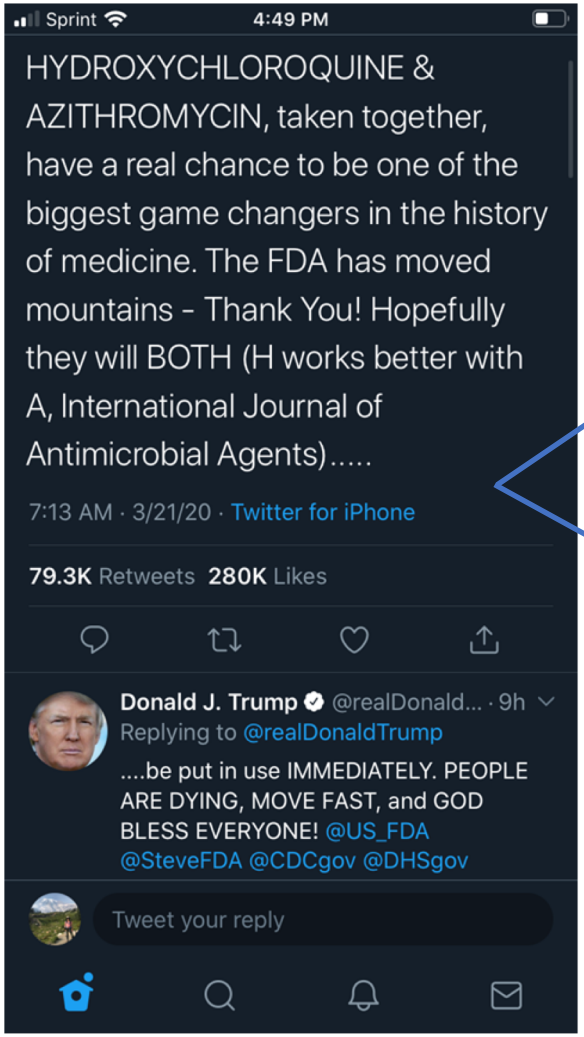
citations

For Outpatients with COVID-19:
We Do Not Recommend Therapy

For outpatients with COVID-19, we do not recommend therapy. If patients have risk factors for progression to lower tract disease (e.g. Age>60, cardiopulmonary disease, renal disease, DM, immunosuppression), shared decision making regarding use of off-label medications with the patient could be considered.

Post exposure prophylaxis (PEP) of COVID-19 is not currently recommended. Several trials of post exposure prophylaxis are currently underway or are planned.

A Message from the Top, 3/21/20



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By Neil Vigdor

March 24, 2020

Man Fatally Poisons Himself While Self-Medicating for Coronavirus, Doctor Says

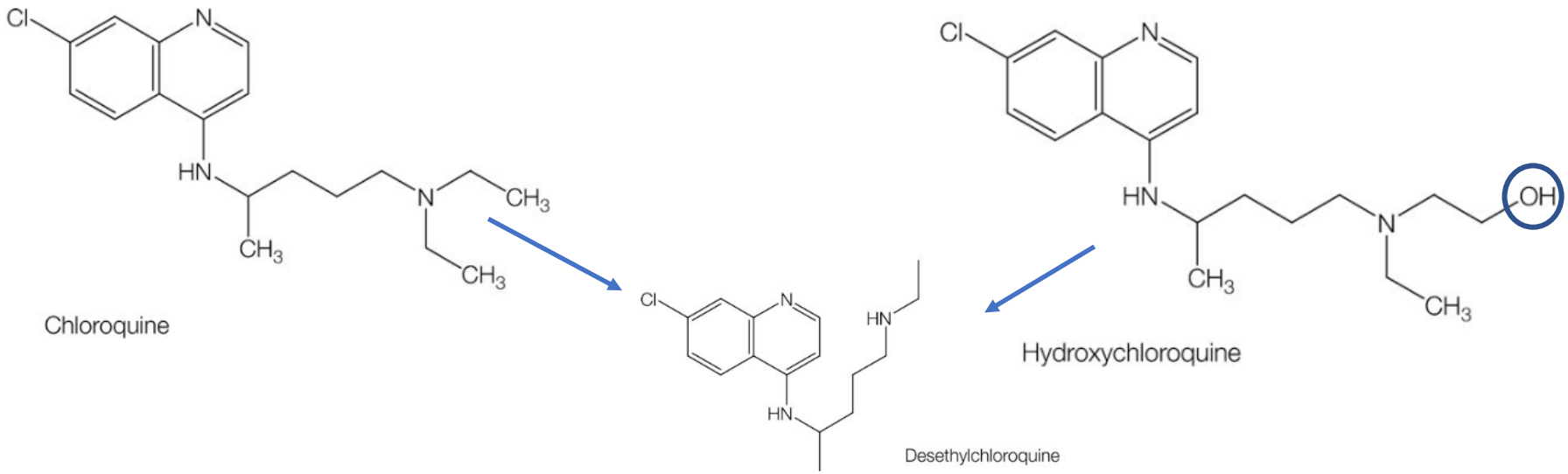
An Arizona man died and
said they treated themsel
remedy for the new coron
has the same active ingredient as an anti-malaria drug.

The drug, known as chloroquine phosphate or chloroquine, has been bandied about by President Trump during White House briefings on the coronavirus pandemic as a potential "game changer" in the treatment of Covid-19.

The couple, who officials at Banner Health, a hospital system based in Phoenix, said were in their 60s and were from Maricopa County, quickly experienced side effects that included nausea and vomiting. They were not tested for the coronavirus.

The man died from cardiac arrest and his wife was initially listed in critical condition, according to hospital officials, who said on Monday that the woman had been upgraded to stable condition and was expected to make a full recovery. Their names were not released.

Chloroquine vs. Hydroxychloroquine



Both possess antiviral activity and are metabolized to the **same active metabolites.** The proportion of metabolite conversion may vary and the relative activity of parent compound vs. metabolite is unknown.

Barber BE, Eisen DP. "Chloroquine" In Kucers' The Use of Antibiotics Sixth Edition.
Lim H et al. Antimicrob Agents Chemother 2009;53(4):1468-1475.
Projean D et al. Drug Metab Dispos 2003;31(6):748-54.

Available Data

- Efficacy
  - Published clinical data for hydroxychloroquine
    N = 36 (20 treated/16 controls) in France
    N = 30 (15 treated / 15 controls) in China Published data of a press release indicated success with chloroquine in 100 patients in China
  - Cell culture (*in vitro)* data
  - Multiple clinical trials evaluating hydroxychloroquine OR chloroquine for COVID19
- Toxicity
  - Chloroquine has been in clinical use since 1946 to treat malaria
  - Hydroxychloroquine was introduced in 1955 to treat malaria and recognized as a treatment for systemic lupus erythematosus (SLE)

Ben-Zvi I et al. Clin Rev Allergy Immunol 2012;42(2):145-53.
Gao J, Tian Z, Yang X. Biosci Trends Feb 19 [Epub ahead of print].
Yao X et al. Clin Infect Dis 2020 Mar 9 [Epub ahead of print].
http://clinicaltrials.gov Accessed 3/17/20

Dosing

- Chloroquine*
  - 500mg PO BID x 10 days

**Dose adjustments for renal failure (ClCr < 10/IHD) and body weight < 60 kg*

- Hydroxychloroquine**
  - 400mg PO BID x 1 day then 200mg PO BID x 5 days (*in vitro* simulation)
  - 200mg PO BID x 7-10 days (Korean clinical trial for mild disease, NCT04307693)
  - 400mg PO BID x 5 days (Chinese clinical trial, NCT04261517)

***No dosing adjustments for renal/hepatic dysfunction, "use with caution"*

Yao X et al. Clin Infect Dis 2020 Mar 9 [Epub ahead of print]. doi: 10.1093/cid/ciaa237
Plaquenil [Hydroxychloroquine] Package Insert. Last revised Aug 26, 2019. http://products.sanofi.ca/en/plaquenil.pdf.
Aralen [Chloroquine] Package Insert. Last Revised 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/006002s044lbl.pdf
http://clinicaltrials.gov Accessed 3/17/20

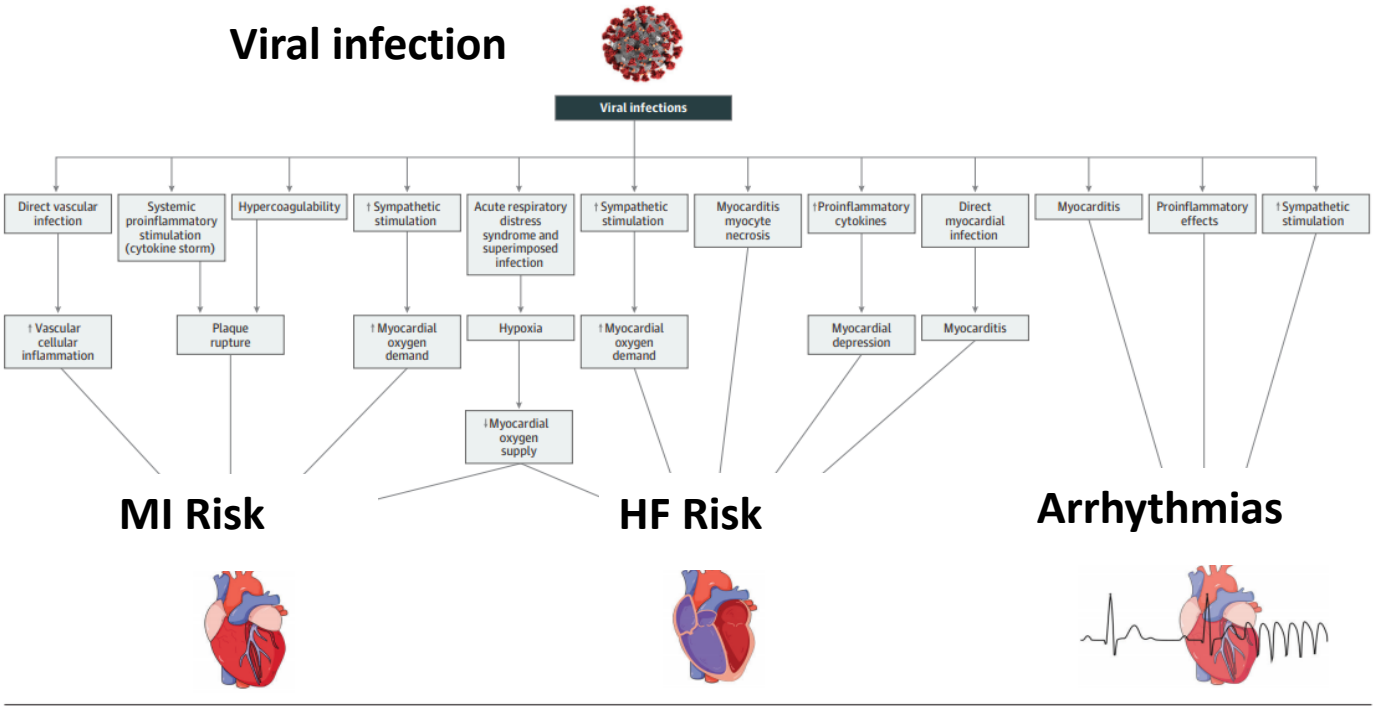
Adverse Drug Reactions

Short-Term	Long-Term
GI Disturbances ECG abnormalities, prolonged QTc Avoid use in QTc > 500ms Hypoglycemia Extrapyramidal reactions	Retinal damage (long-term/high dose) Pregnancy -crosses placenta Used in mothers with SLE Alternate treatment for malaria per CDC Nursing Chloroquine: 0.7% excreted into breastmilk Hydroxychloroquine: 2% excreted in breastmilk

Plaquenil Package Insert. Last revised Aug 26, 2019. http://products.sanofi.ca/en/plaquenil.pdf.
Aralen [Chloroquine] Package Insert. Last Revised 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/006002s044lbl.pdf
CDC Guidelines for Treatment of Malaria in the United States. Last Revised Oct 1, 2019.: https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_120419.pdf.

Potential Mechanisms for Acute Effects of Viral Infections on CV System

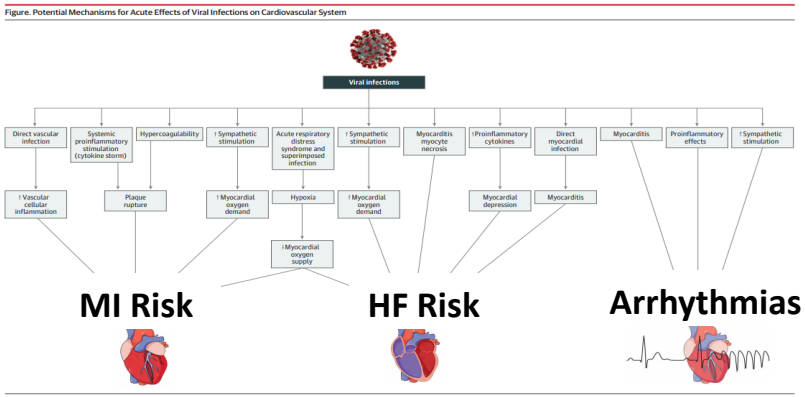
Figure. Potential Mechanisms for Acute Effects of Viral Infections on Cardiovascular System

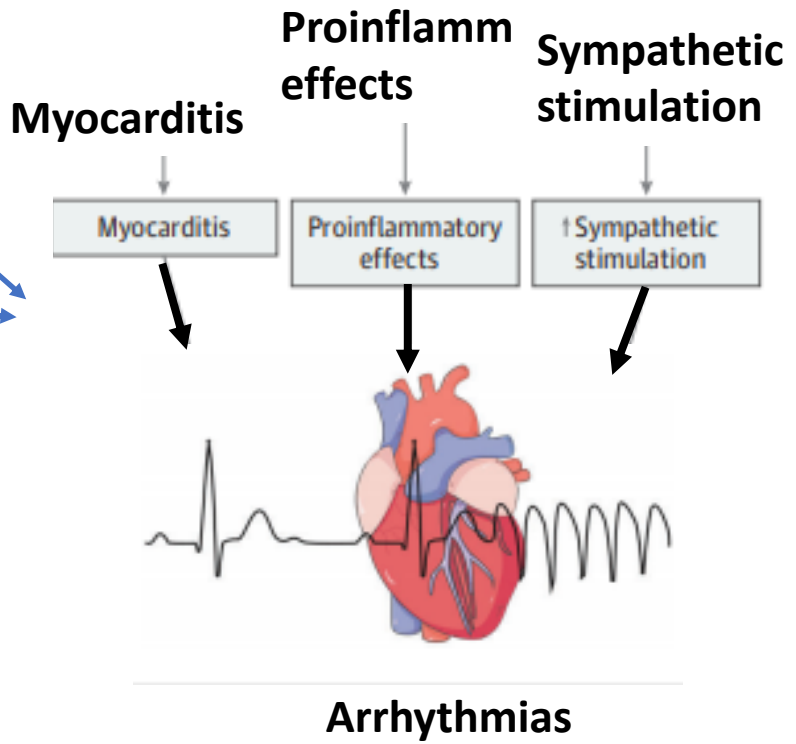


*To date, advanced **age** (>60 years), **male** sex, and presence of **comorbidities** are known to be the major **risk factors for COVID-19 mortality**. **Presence of cardiac injury (defined by elevated troponin levels), myocarditis,** and ARDS **are other strong and independent factors associated with mortality**.*

Madjid M et al. JAMA Cardiology Mar 27, 2020.
https://jamanetwork.com/journals/jamacardiology/fullarticle/2763846

First, Do No Harm





Advanced Age
Baseline cardiovascular disease
Electrolyte abnormalities
Concomitant medications
Hydroxychloroquine

Madjid M et al. JAMA Cardiology Mar 27, 2020.
https://jamanetwork.com/journals/jamacardiology/fullarticle/2763846

Drug-Drug Interactions

Enzyme-Mediated

P450 enzymes convert CQ and HCQ to active metabolites [**CQ, HCQ**]

-Strong 3A4 or 2C8 inhibitors (i.e. azoles): reduction of active metabolite [**CQ, HCQ**]

Additive Toxicities

Additive QT prolongation with other QT-prolonging agents [**CQ, HCQ**]

Increased hemolytic reactions with dapsone [**HCQ**], check G6PD [**CQ,HCQ?**]

Enhanced hypoglycemic effects with anti-diabetic agents [**CQ, HCQ**]

Miscellaneous

Increased concentrations of PO cyclosporin [**CQ**]

Space antacid administration by 4 hours due to decreased bioavailability [**CQ, HCQ**]

Aralen [Chloroquine] Package Insert. Last Revised 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/006002s044lbl.pdf
Plaquenil Package Insert. http://products.sanofi.ca/en/plaquenil.pdf. Last revised Aug 26, 2019.
Projean D et al. Drug Metab Dispos 2003;31(6):748-54.
Lee J et al. Arthritis Rhematol 2016;68(1):184-90
Jallouli et al. Arthritis and Rhematology 2015;67(8):2176-84.
Nampoory et al. Nephron 1992;62:108-9.
Salaffi et al. Scand J Rheumatol 1996;25(1):16-23.

Available Data

citations

BioScience Trends. 2020; 14(1):72-73.

Letter

DOI: 10.5582/bst.2020.01047

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

Jianjun Gao[1,*], Zhenxue Tian[2], Xu Yang[2]

[1] Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, China;
[2] Department of Pharmacy, Qingdao Municipal Hospital, Qingdao, China.

Who were the patients?

What was the control treatment?

How long were they treated?

At what point in their disease course was therapy introduced?

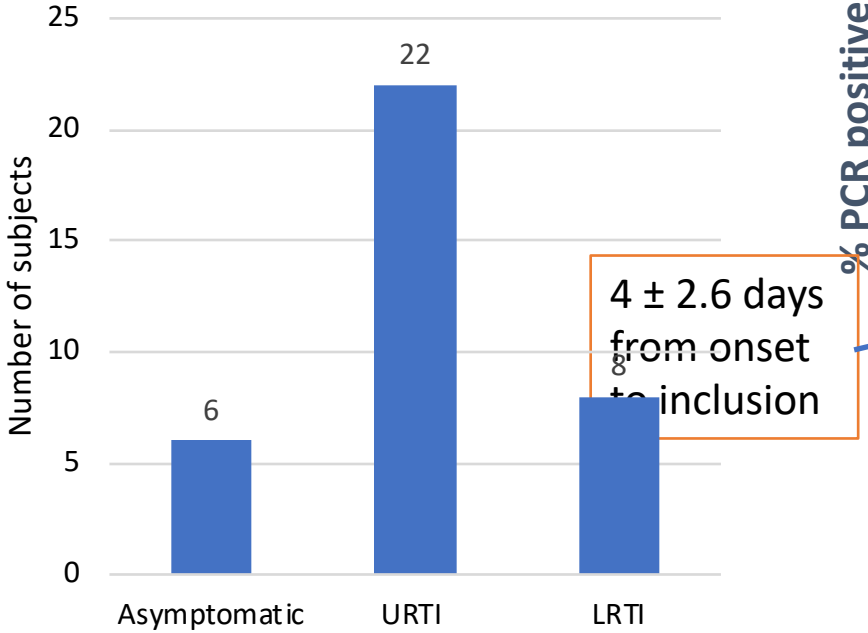
Author Conclusions:

"Results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course…."

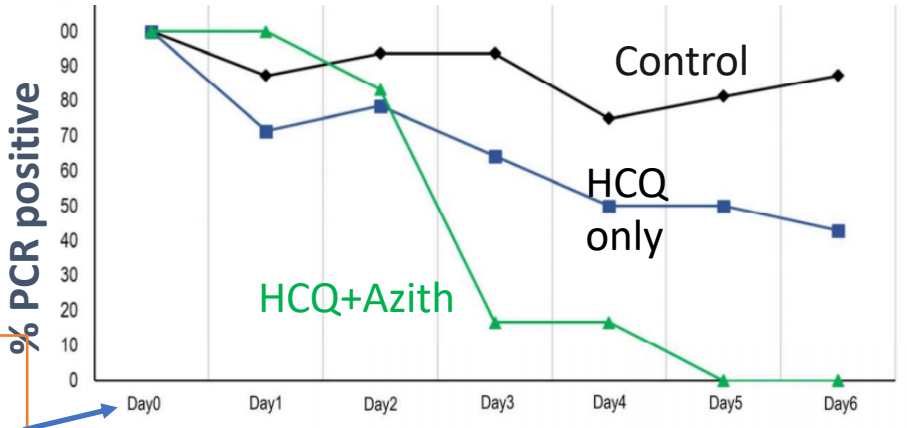
Gao J, Tian Z, Yang X. Biosci Trends Feb 19 [Epub ahead of print] Available at: https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article

H Works better with A
International Journal of Antimicrobial Agents

36 Hospitalized patients 45 ± 22 years old with COVID19



Primary outcome:
Viral suppression 6 days after inclusion



N = 16: Controls
N = 14: HCQ 200 mg PO TID x10 days
N = 6: HCQ + Azithromycin 500 day 1 then 250mg x 4 days

**Exclusion criteria: Allergy, G6PD deficient, prolonged QTc, retinopathy*

International Journal of Antimicrobial Agents – In Press 17 March 2020
DOI : 10.1016/j.ijantimicag.2020.105949

A Pilot Study of HCQ in Patients with COVID-19

On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases and 14 (93.3%) controls.

组别	*n*	男性*	平均年龄	平均病程（d）	发热	基础疾病*		
						高血压	糖尿病	慢性阻塞性肺疾病
试验组	15	9（60.0）	50.5±3.8	6.6±3.9	9（60.0）	5（33.3）	1（6.7）	0（0.0）
对照组	15	12（80.0）	46.7±3.6	5.9±4.1	13（86.7）	3（20.0）	1（6.7）	1（6.7）
t/*U* 值	—	—	0.72	0.45	—	—	—	—
P 值	—	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

组别	*n*	白细胞计数（×10⁹/L）	淋巴细胞计数（×10⁹/L）	ALT（U/L）	eGFR（mL·min⁻¹·1.73m⁻²）	乳酸（mmol/L）	CD4⁺细胞计数(个/μL)	胸部 CT 病灶（两肺/一侧肺）*
试验组	15	5.2(3.9~6.7)	1.11±0.43	18(15~23)	117±29	1.4±0.4	415(275~589)	12/3
对照组	15	4.9(4.5~7.4)	1.18±0.55	24(14~47)	120±29	1.4±0.5	395(272~710)	14/1
t/*U* 值	—	101	0.39	87	0.30	0.19	110	—
P 值	—	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

“—”无相关数据. *Fisher 检验. ALT：丙氨酸转氨酶；eGFR：肾小球滤过率估值.

treatment

control

male

Age

Duration of illness

Fever

HTN

DM

COPD

WBC

Lymph

Lactate

CT Chest (Bilateral/unilateral)

Concurrent antivirals – all patients received interferon alpha; In treatment group 12 (80%) received arbidol; In control group, 10 (66.7%) received arbidol, 2 (13.3%) received lopinavir/ritonavir

Chen J, et al. J Zhejiang Univ (Med Sci) 2020 49(1)
DOI: 10.3785/j.issn.1008-9292.2020.03.03

Translation: Siu Yuan Amy Yeung, PharmD

Treatment (HCQ/CQ) Pearls

- Chloroquine and Hydroxychloroquine have shown promise against SARS-CoV2 in *in vitro* and animal models. This has **not been confirmed** in people
- Short term usage (5-10 days) = much longer exposure due to PK. Doses of 5 days last at least 10 days in circulation due to prolonged half-life
- Would obtain a **baseline EKG** and avoid using if QTc > 500 msec. Stronger cardiac monitoring recommended because of myocardial damage inflicted by SARS-CoV2
- **At this time, known harm outweighs unknown benefits in outpatients**
- The package insert advises against crushing. There is a recipe to make a solution
- **Consider restricting inpatient/outpatient prescriptions to avoid hoarding**

Pesko LJ. Compounding: Hydroxychloroquine. AM Druggist. 1993;207-257.

Summary: First Do No Harm

- **No provider is required to prescribe antiviral agents for COVID-19, at this time there is an absence of convincing data for efficacy and outcomes.**

- What we can do – manage patient symptoms, protect our healthcare workers:
  - Time medication administration to standard times.
  - Convert patients to lower frequency administered agents as much as possible
  - MDIs as much as possible for COVID19 confirmed/PUIs; everyone else can get nebulizer treatment to manage supply

Pesko LJ. Compounding: Hydroxychloroquine. AM Druggist. 1993;207-257.

How Can TASP Best Support you in the Time of COVID-19?