Medical & Public Health Considerations of Chloroquine & Hydroxychloroquine Use during the COVID-19 Pandemic

MODERATOR

- Dr. Paul Wax, FACMT
  - Executive Director, ACMT
  - Professor of Emergency Medicine, University of Texas at Southwestern, Dallas, Texas, USA

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Telehealth Visits to Support Medical Toxicology Practice in the Time of COVID-19

Given the extraordinary time of the COVID-19 Pandemic, physicians and other health care providers are rapidly switching to a virtual delivery of patient care (where appropriate) through telehealth. Suddenly in a matter of days, regulations regarding the delivery of telehealth have quickly evolved, and 1000s of physicians have rapidly set up shop remotely to deliver such care. In fact, some medical facilities are insisting that certain consultants only employ telehealth, if able, so as not to be a burden to the front-line physicians who have no choice but to continue to provide patient care at the bedside.

This webinar will explore ways where medical toxicologists who have a bedside service may be able to start to utilize conventional and non-conventional ways of providing medical toxicology consultations through telehealth.

Dr. Timothy Wiegand, Associate Professor of Emergency Medicine at University of Rochester, will lead a discussion about Medical Toxicology and Telehealth, and how medical toxicologists should be exploring opportunities to continue to provide medical toxicology consultations through telehealth mechanisms.

Event address for attendees: CLICK HERE

Date and time: Thursday, March 26, 2020

2:00 pm Eastern Daylight Time (New York)
1:00 pm Central Daylight Time (Chicago)
12:00 pm Mountain Daylight Time (Denver)
11:00 am Pacific Daylight Time (San Francisco)

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PRESENTER

- Ziad Kazzi, MD, FAAEM, FACEP, FACMT, FAACT
  - Associate Professor of Emergency Medicine, Emory University, Atlanta, Georgia, USA
  - Board Member, American College of Medical Toxicology
  - President, Middle East and North Africa Clinical Toxicology Association

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PANELISTS

- Dr. Michelle Ruha, FACMT
  - President, ACMT
  - Professor of Emergency Medicine, University of Arizona College of Medicine Phoenix, Arizona, USA

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PANELISTS

- Dr. Bruno Megarbane
  - Board Member, MENATOX
  - Past President, EAPCCT
  - Professor of Critical Care Medicine
  - Head, Department of Medical and Toxicological Critical Care at Lariboisière Hospital, Paris, France

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DISCLOSURE

- No conflicts of interest to disclose

OBJECTIVES

- Summarize the current anecdotal evidence related to the use of chloroquine or hydroxychloroquine in COVID-19 infections
- Describe the adverse effects related to the therapeutic use of chloroquine or hydroxychloroquine
- Describe the clinical manifestations and management of acute chloroquine or hydroxychloroquine overdose

JOHNS HOPKINS UNIVERSITY & MEDICINE | Coronavirus Resource Center

Map Information Map FAQ

Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hop…

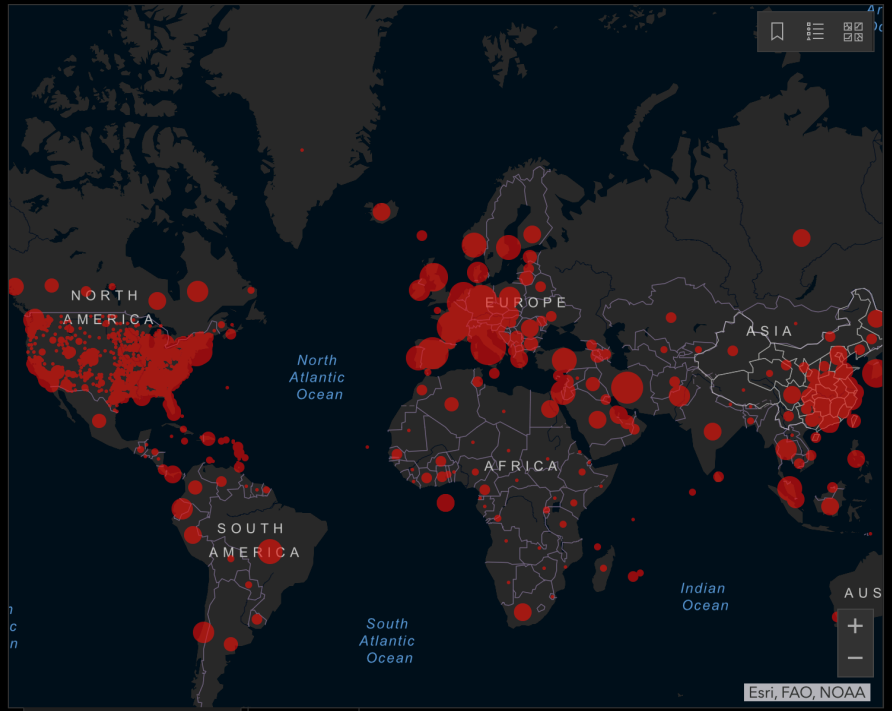
Total Confirmed
422,915

Confirmed Cases by Country/Region/Sovereignty

- 81,591 China
- 69,176 Italy
- 55,148 US
- 42,058 Spain
- 32,991 Germany
- 24,811 Iran
- 22,633 France
- 9,877 Switzerland
- 9,137 Korea, South
- 8,164 United Kingdom
- 5,585 Netherlands
- 5,283 Austria
- 4,269 Belgium
- 2,866 Norway

Admin1

Last Updated at (M/D/YYYY)
3/24/2020, 8:38:34 PM



Cumulative Confirmed Cases | Active Cases

170 countries/regions

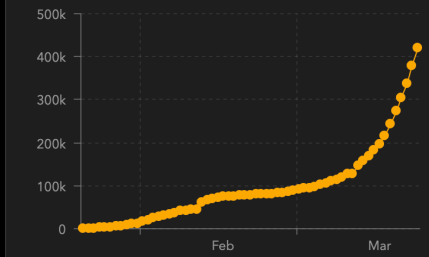
Lancet Inf Dis Article: Here. Mobile Version: Here. Visualization: JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports. Read more in this blog.

Total Deaths
18,915

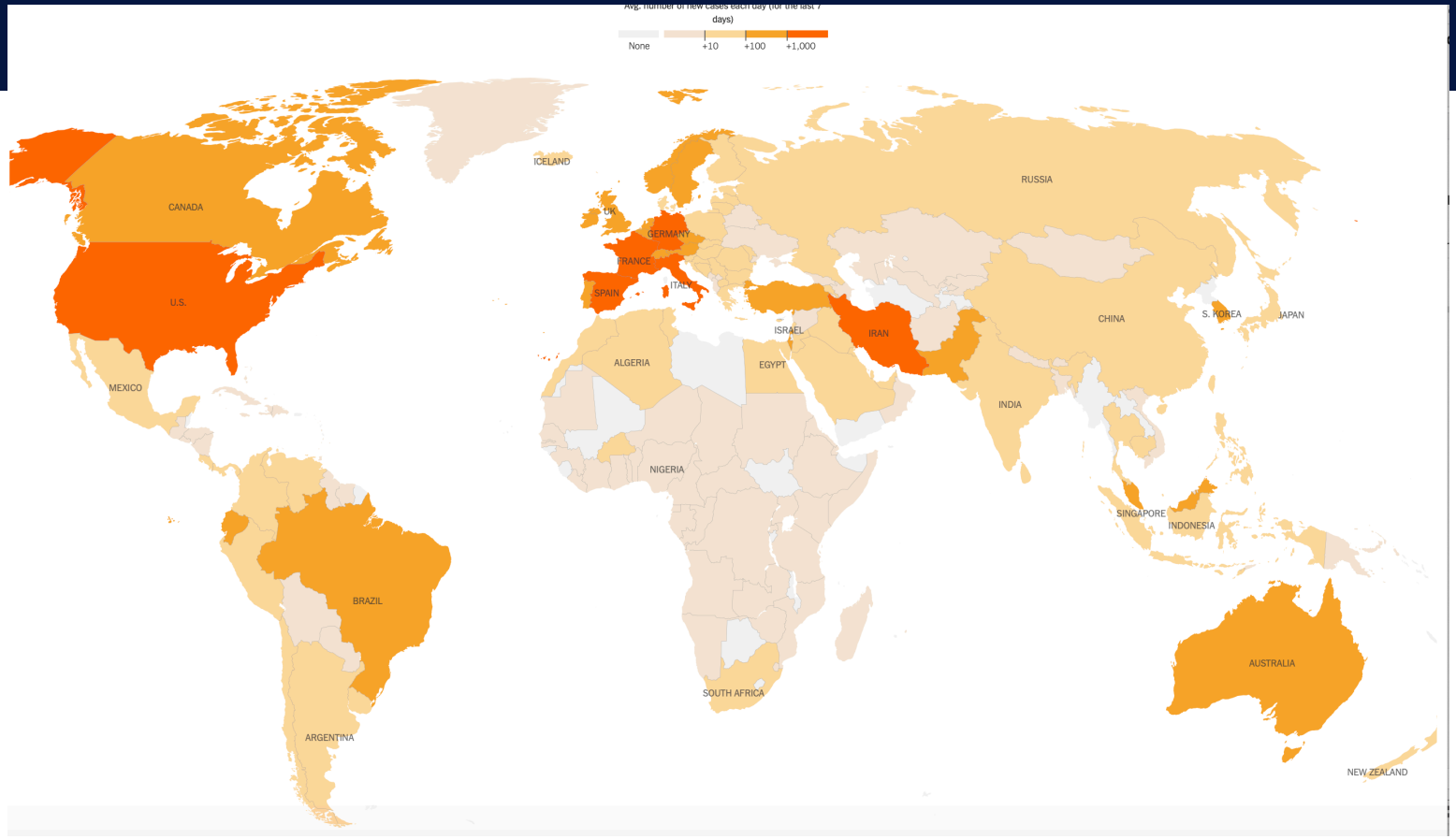
- 6,820 deaths Italy
- 3,160 deaths **Hubei** China
- 2,991 deaths Spain
- 1,934 deaths Iran
- 1,100 deaths France
- 422 deaths United Kingdom
- 276 deaths Netherlands
- 192 deaths New York City, New

Total Recovered
108,573

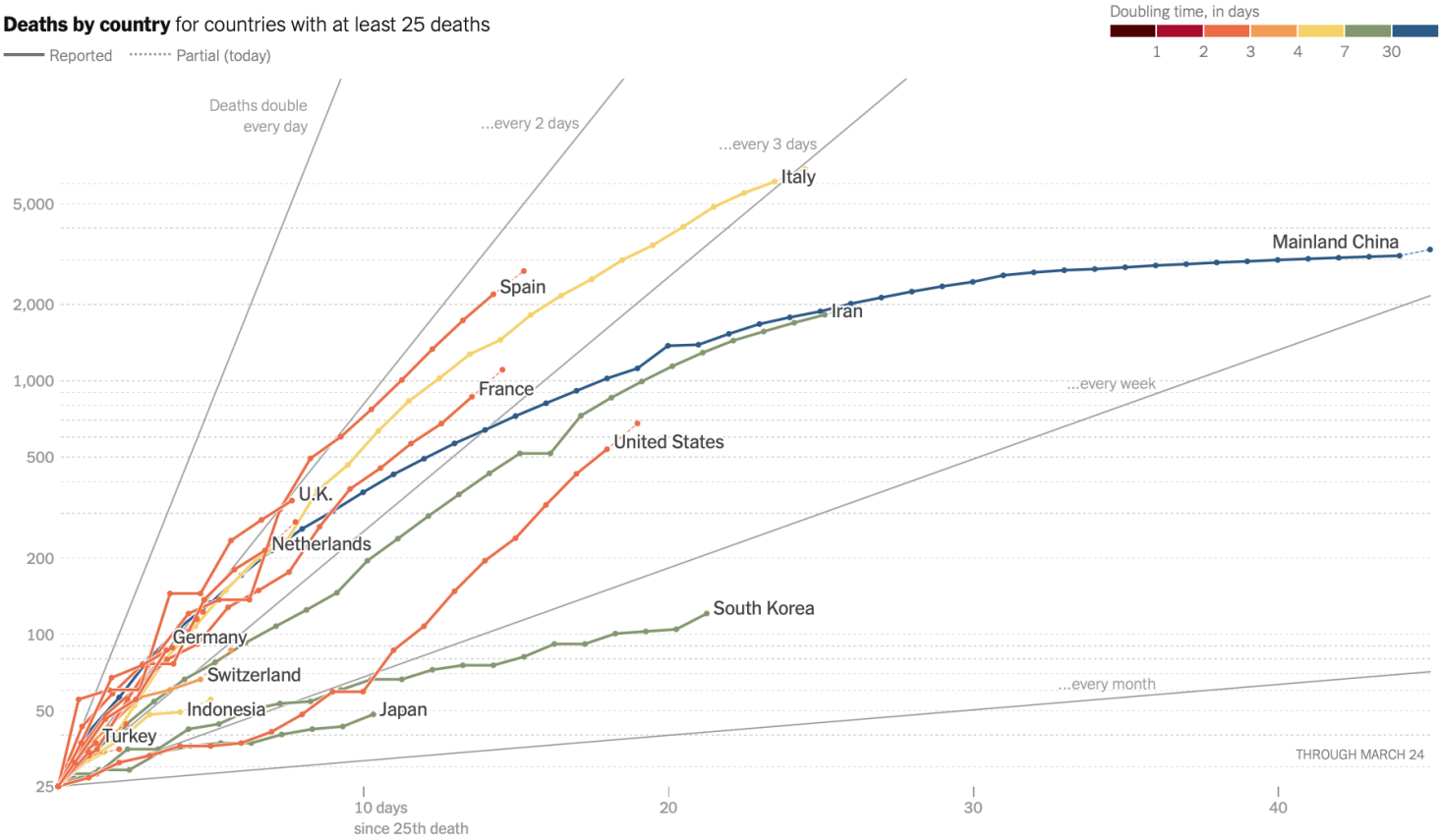
- 60,324 recovered **Hubei** China
- 8,913 recovered Iran
- 8,326 recovered Italy
- 3,794 recovered Spain
- 3,730 recovered Korea, South
- 3,290 recovered Germany
- 3,281 recovered France
- 1,333 recovered Guangdong China



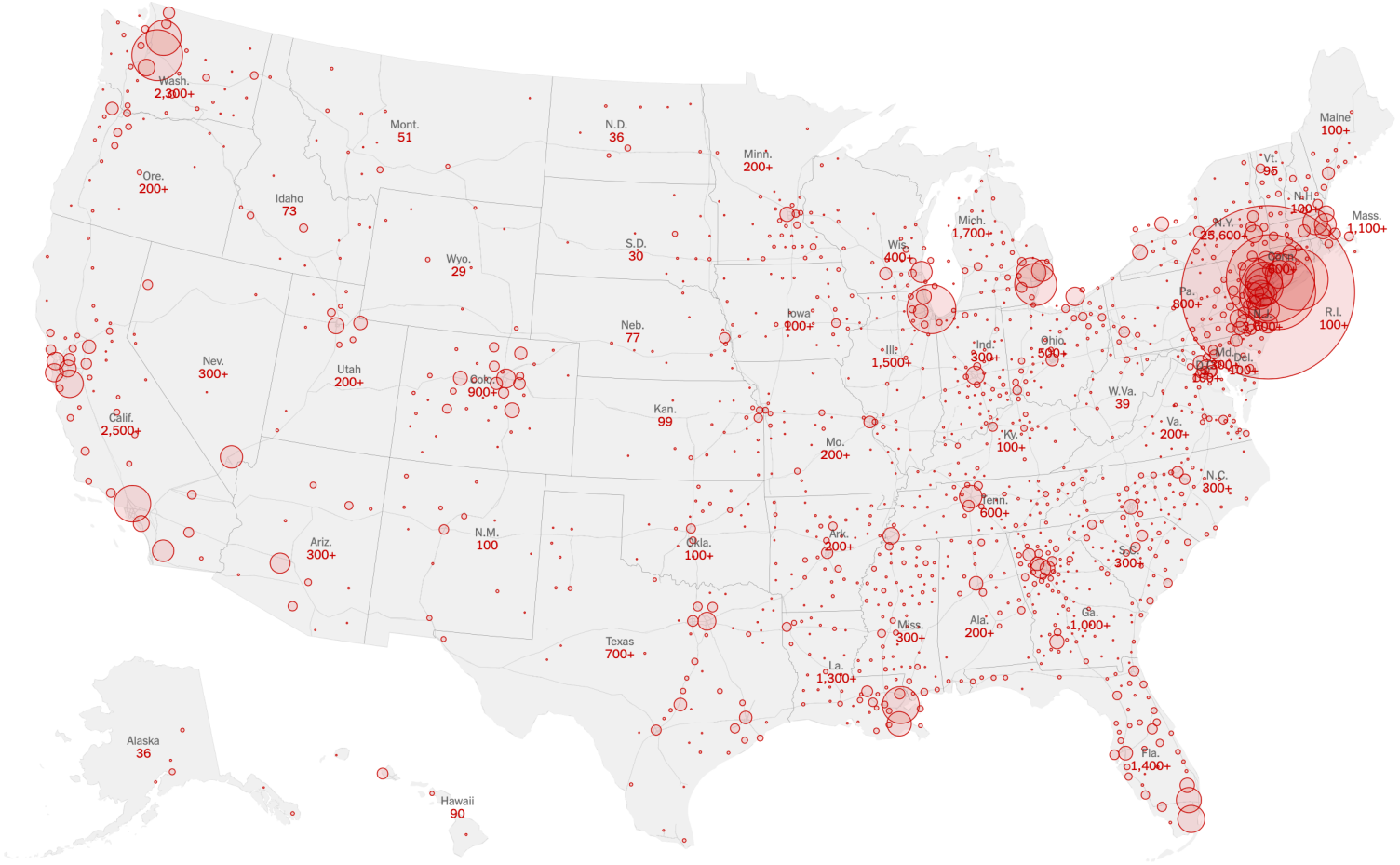
Confirmed | Daily Increase



NY Times March 24, 2020

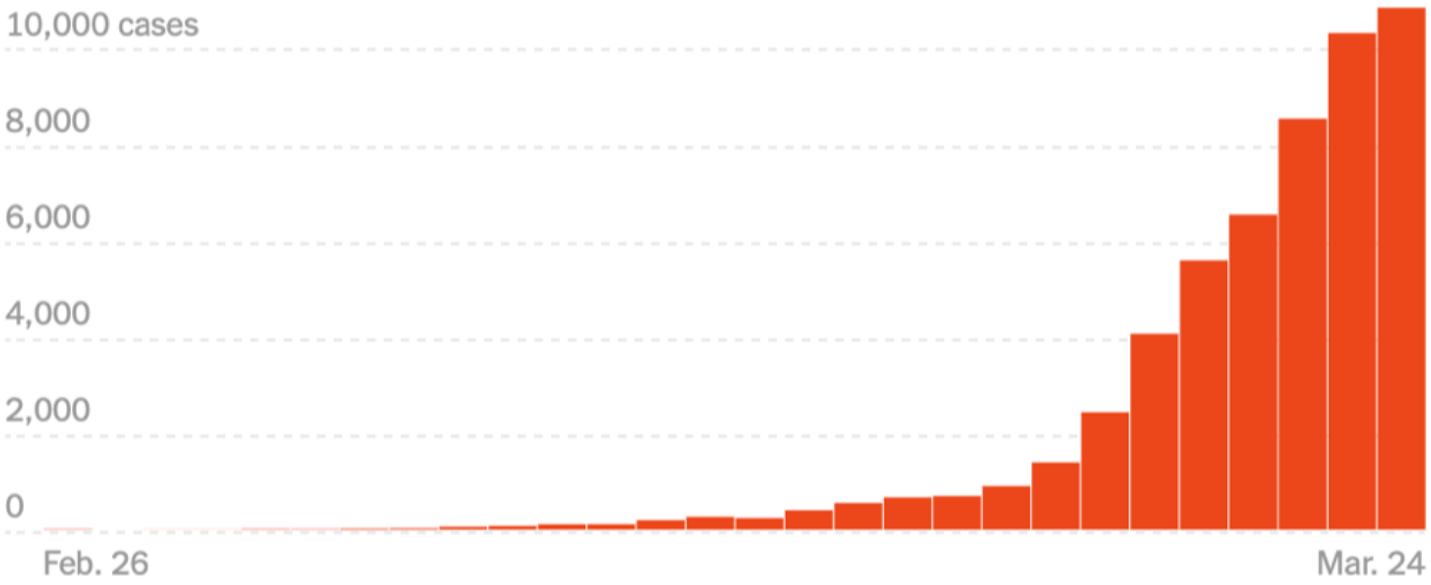


NY Times March 24, 2020



NY Times March 24, 2020

New coronavirus cases announced in the U.S. each day



Source: C.D.C., state and local health agencies, hospitals.

NY Times March 25, 2020

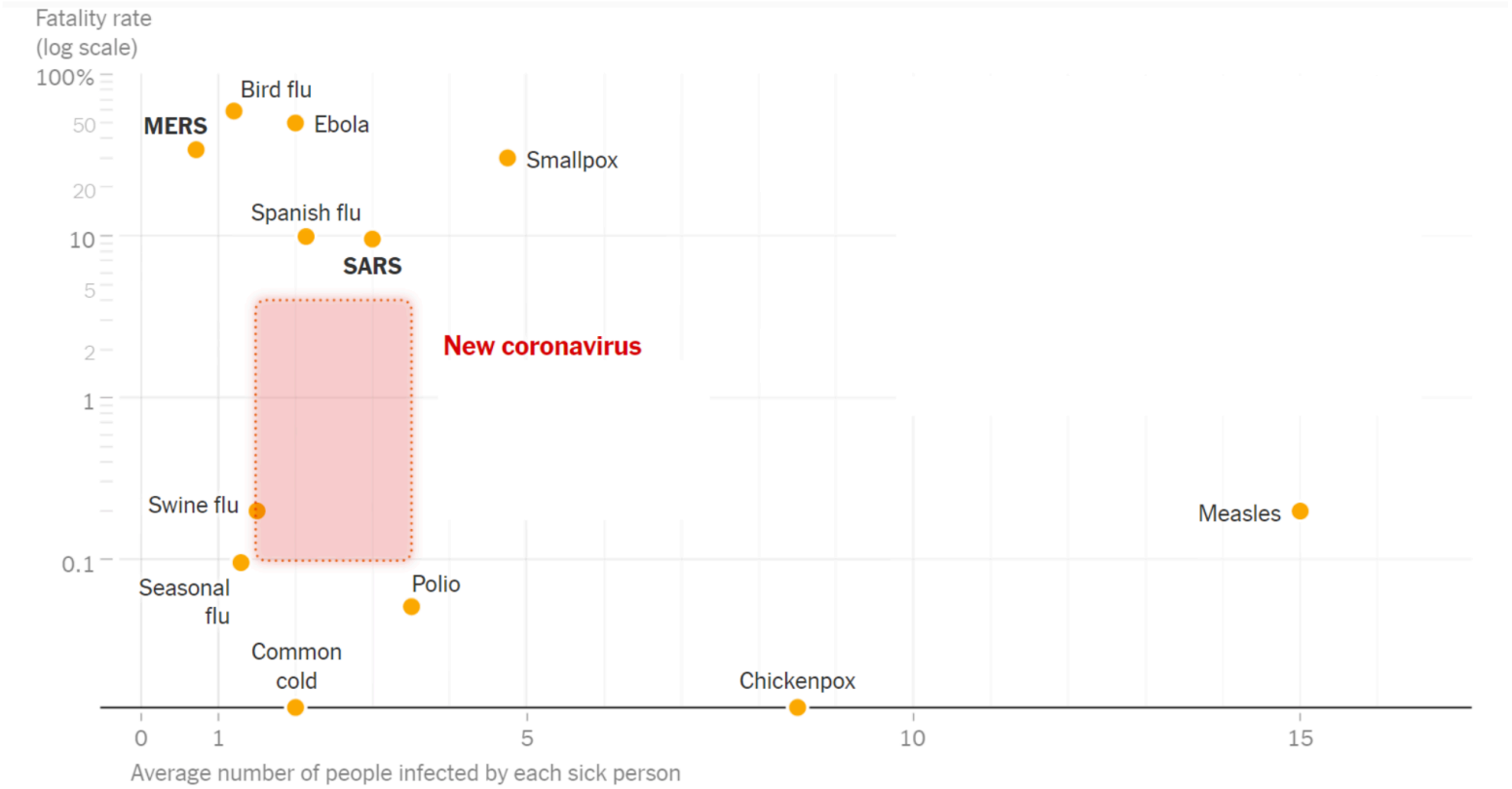
STATE	CASES	DEATHS
New York	30,811	285
New Jersey	3,675	44
California	2,648	56
Washington	2,469	123
Michigan	1,783	24
Illinois	1,535	16
Florida	1,456	19
Louisiana	1,388	46
Massachusetts	1,159	11
Georgia	1,097	38

NYT Times March 25, 2020

- Human coronavirus 229E (HCoV-229E) - 1960s
- HCoV-OC43 - 1960s
- SARS-CoV-1 - 2003 (Severe Acute Respiratory Syndrome Coronavirus 2)
- HCoV-NL63 - 2004
- HCoV-HKU1 - 2005
- MERS-CoV - 2012
- **SARS-CoV-2 – 2019 - (Wuhan, China; December 2019)**

- COVID-19 - **co**rona**vi**rus **d**isease of 20**19**.

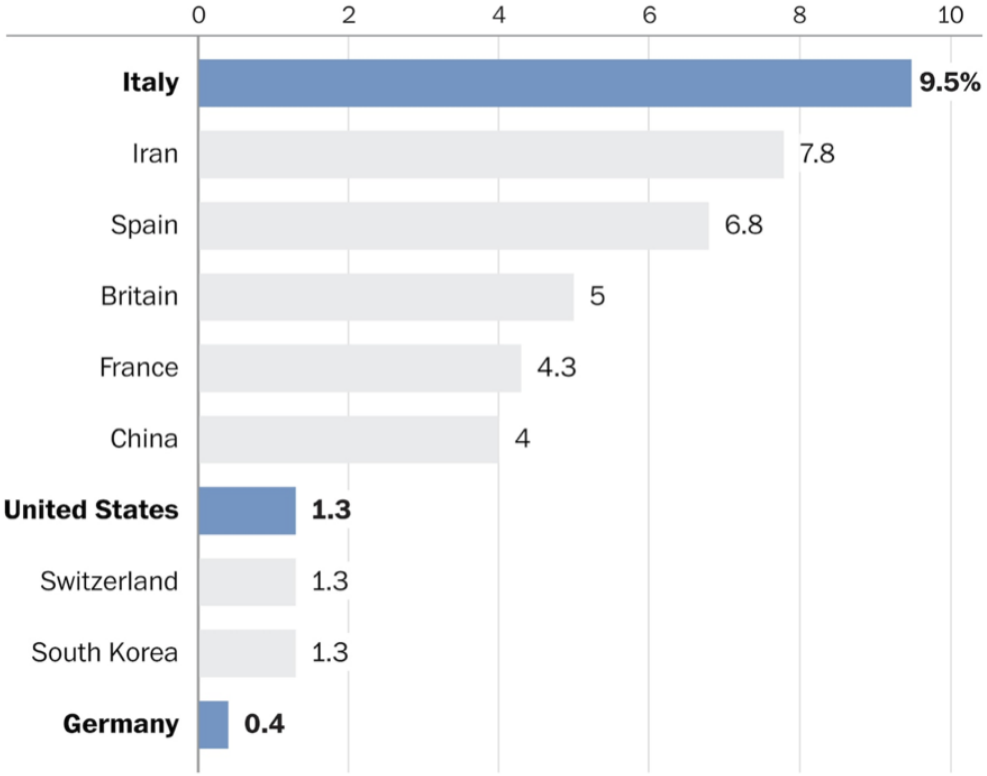
Fatality Rate vs Avg # of people infected by each sick person



NY TIMES March 24, 2020

Coronavirus death rates

Among the 10 countries with the most confirmed cases of the coronavirus, Germany has the lowest death rate.



Data as of March 24

Source: Johns Hopkins Coronavirus Resource Center

THE WASHINGTON POST

March 24, 2020 - Hospital Guideline for Treatment of COVID-19

Severity	Definition for Confirmed Positive or Highly Suspected COVID-19	Recommendation
Mild	Defined as fever, malaise, cough, headache, sore throat, myalgia, nasal congestion, diarrhea, mild SOB without hypoxemia	• Supportive care • Antiviral therapy NOT recommended
Mild with risk factors+	• Symptoms listed above for "Mild" plus • Risk Factors: ➢ Age ≥ 65, coronary artery disease, diabetes, hypertension, transplant or immunosuppression	Treat as below for "Moderate"
Moderate+	Defined as a non-intubated patient with >1 of the following: • Any symptom listed above for "Mild" • SpO2 <90% and/or requiring supplemental oxygen • Radiographic imaging (chest x-ray or lung ultrasound) with bilateral ground glass opacities or bilateral consolidations	**Antiviral Therapy per ID or Critical Care Consult:** • Supportive Care, and • Hydroxychloroquine* 400 mg PO BID x2 doses, then 200 mg PO BID x8 doses (4 days) ➢ QTc prolonging medication. Baseline EKG recommended. Do not use if QTc >500msec
Severe/Critical+	Meets Moderate Criteria plus Mechanical Ventilation and may have ≥ 1 of the following: • Radiographic imaging (chest x-ray or lung ultrasound) with bilateral ground glass opacities or consolidations • ARDS • Lymphopenia • IL-6 >40 pg/mL[2] or CRP >10 mg/L or elevated D-Dimer with no other suspected cause • Septic Shock • Multi-Organ Failure • Altered Consciousness	**Antiviral Therapy per ID or Critical Care Consult:** • Supportive Care, and • Hydroxychloroquine as stated above; May consider up to 10 days duration if needed. --- or ---- • [NOT a first-line agent] Tocilizumab (Actemra®) 4-8 mg/kg (usual dose 400 mg; max 800 mg) IV x1; may repeat x 1 in 12 hours if necessary; max of 2 doses ➢ IL-6 testing and other inflammatory marker testing prior to start (CRP, Ferritin, D-Dimer)

* Chloroquine has been used for treatment but not readily available thus hydroxychloroquine is recommended given the evidence that both agents have activity against SARS-CoV2. If available, can use Chloroquine 500 mg bid for pts 50 kg or greater. For patients <50 kg 500 mg BID on days 1 and 2, then 500 mg once daily days 3-7 if available.

+In case antibiotics must be provided for suspected bacterial superinfection, consider adding **azithromycin** (given its possible synergistic effect with hydroxychloroquine) with particular caution for interaction and QT prolongation – daily EKG monitoring. Azithromycin suggested dose: 500 mg PO x1, then 250 mg PO daily x4 days.

Cortegiani et al.
Journal of Critical Care
2020

Liu et al. *Cell Discovery* (2020)6:16
https://doi.org/10.1038/s41421-020-0156-0

Cell Discovery
www.nature.com/celldisc

CORRESPONDENCE Open Access

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

Jia Liu[1], Ruiyuan Cao[2], Mingyue Xu[1,3], Xi Wang[1], Huanyu Zhang[1,3], Hengrui Hu[1,3], Yufeng Li[1,3], Zhihong Hu[1], Wu Zhong[2] and Manli Wang[1]

Dear Editor,

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/2019-nCoV) poses a serious threat to global public health and local economies. As of March 3, 2020, over 80,000 cases have been confirmed in China, including 2946 deaths as well as over 10,566 confirmed cases in 72 other countries. Such huge numbers of infected and dead people call for an urgent

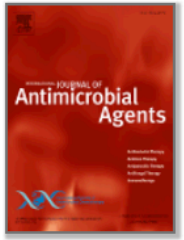
trial drugs in the Guidelines for the Diagnosis and Treatment of COVID-19 (sixth edition) published by National Health Commission of the People's Republic of China.

CQ (N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine) has long been used to treat malaria and amebiasis. However, *Plasmodium falciparum* developed widespread resistance to it, and with the development of new antimalarials, it has become a choice for the pro-

International Journal of Antimicrobial Agents

Available online 12 March 2020, 105938

In Press, Journal Pre-proof



New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?

Christian A. Devaux [a, b, c], Jean-Marc Rolain [a, c], Philippe Colson [a, c], Didier Raoult [a, c]

Show more

https://doi.org/10.1016/j.ijantimicag.2020.105938

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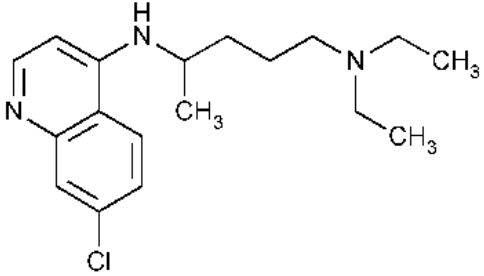
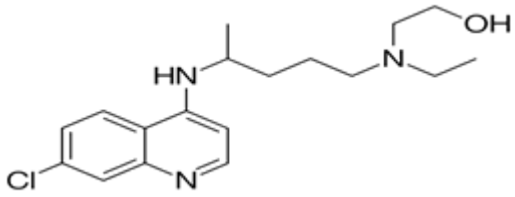
- Form of quinine that was synthesized in Germany by Bayer (1934) and emerged approximately 70 years ago as an effective substitute for natural quinine.
- Quinine is found in the bark of *Cinchona* trees native to Peru
- For decades, was a front-line drug for the treatment and prophylaxis of malaria
- Efficacy gradually declined due to chloroquine-resistant *P. falciparum*

Source CDC



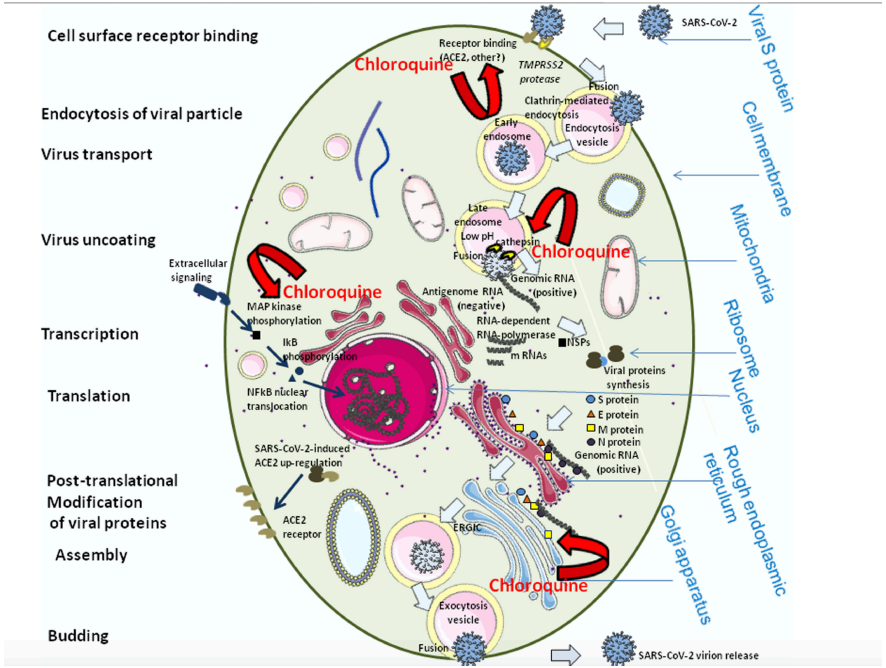
Hydroxychloroquine

- Derivative of chloroquine
- Synthesized in 1946 and was demonstrated to be much less (~40%) toxic than chloroquine in animals
- Available to treat auto-immune diseases, such as Lupus and Rheumatoid Arthritis

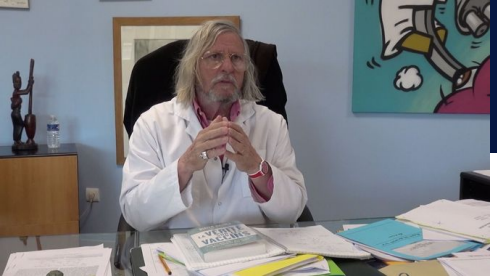


Some Proposed Mechanisms of Chloroquine

- Interferes with ACE2 receptor glycosylation, preventing SARS-CoV-2 binding to target cells.
- Limit the biosynthesis of sialic acids that may be required for cell surface binding of SARS-CoV-2.
- Modulate the acidification of endosomes thereby inhibiting formation of the autophagosome.
- Inhibit virus replication through reduction of cellular mitogen-activated protein (MAP) kinase activation.
- Alter M protein maturation and interfere with virion assembly and budding.
- Possible other immunomodulatory actions



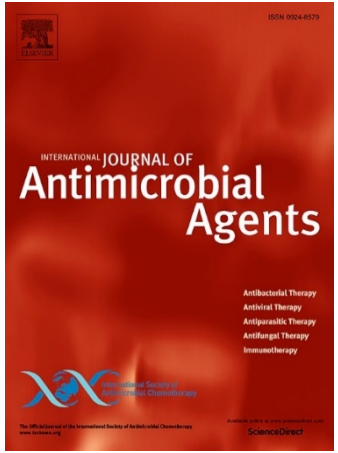
Devaux CA[1], Rolain JM[2], Colson P[2], Raoult D[2]. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020 Mar 11:105938.

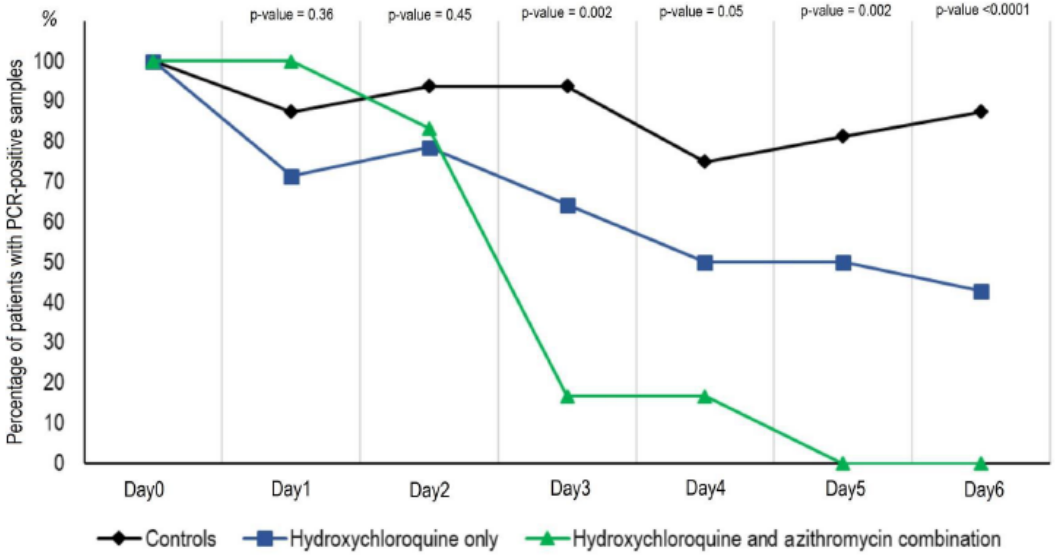


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret[a,b$], Jean-Christophe Lagier[a,c$], Philippe Parola[a,b], Van Thuan Hoang[a,b,d], Line Meddeb[a], Morgane Mailhe[a], Barbara Doudier[a], Johan Courjon[e,f,g], Valérie Giordanengo[h], Vera Esteves Vieira[a], Hervé Tissot Dupont[a,c], Stéphane Honoré[i,j], Philippe Colson[a,c], Eric Chabrière[a,c], Bernard La Scola[a,c], Jean-Marc Rolain[a,c], Philippe Brouqui[a,c], Didier Raoult[a,c*].

[a]IHU-Méditerranée Infection, Marseille, France.





Facts First

Nigeria records chloroquine poisoning after Trump endorses it for coronavirus treatment

By Stephanie Busari and Bukola Adebayo, CNN

Updated 5:06 AM ET, Mon March 23, 2020

CNN.COM

U.S.

MARCH 23, 2020 / 7:48 PM / UPDATED 14 HOURS AGO

Arizona man dies after taking chloroquine for coronavirus

Deena Beasley

3 MIN READ

NEWS

Sales of fish tank additive skyrocket after studies say it could treat coronavirus

By Tamar Lapin

March 19, 2020 | 4:49pm

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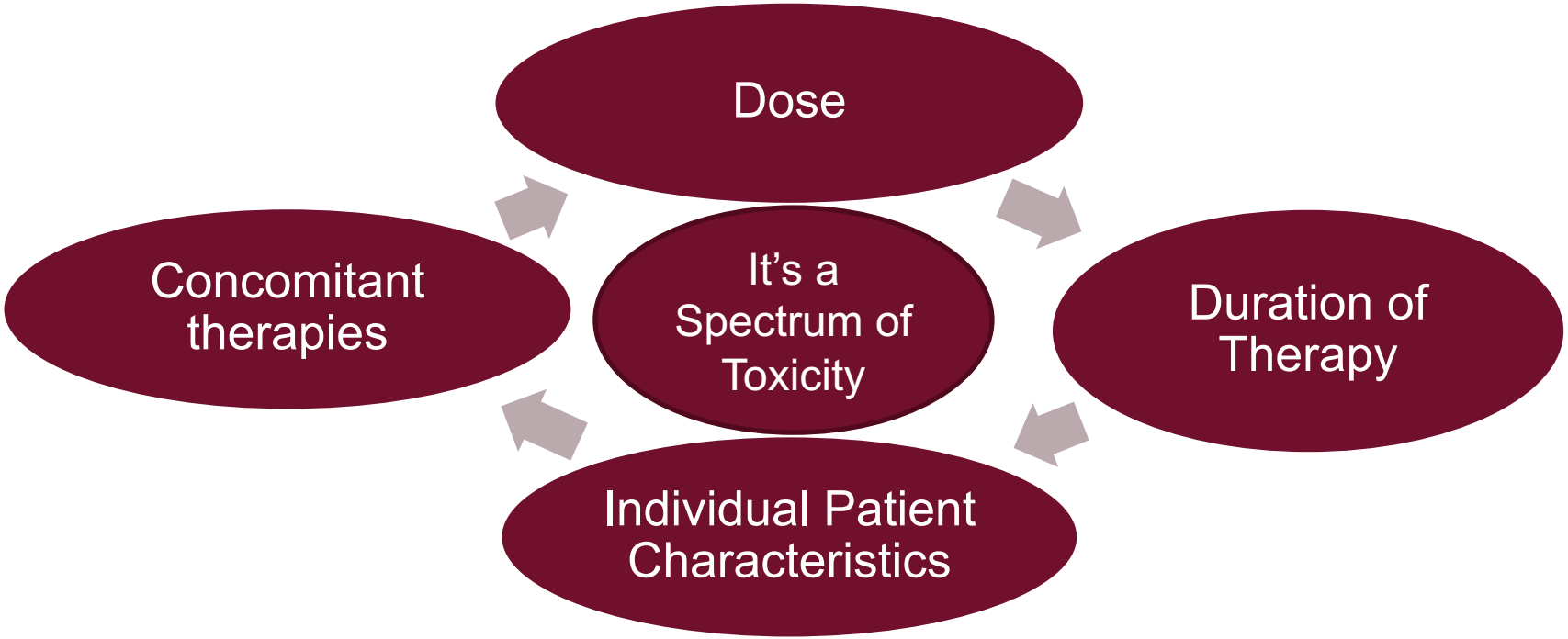
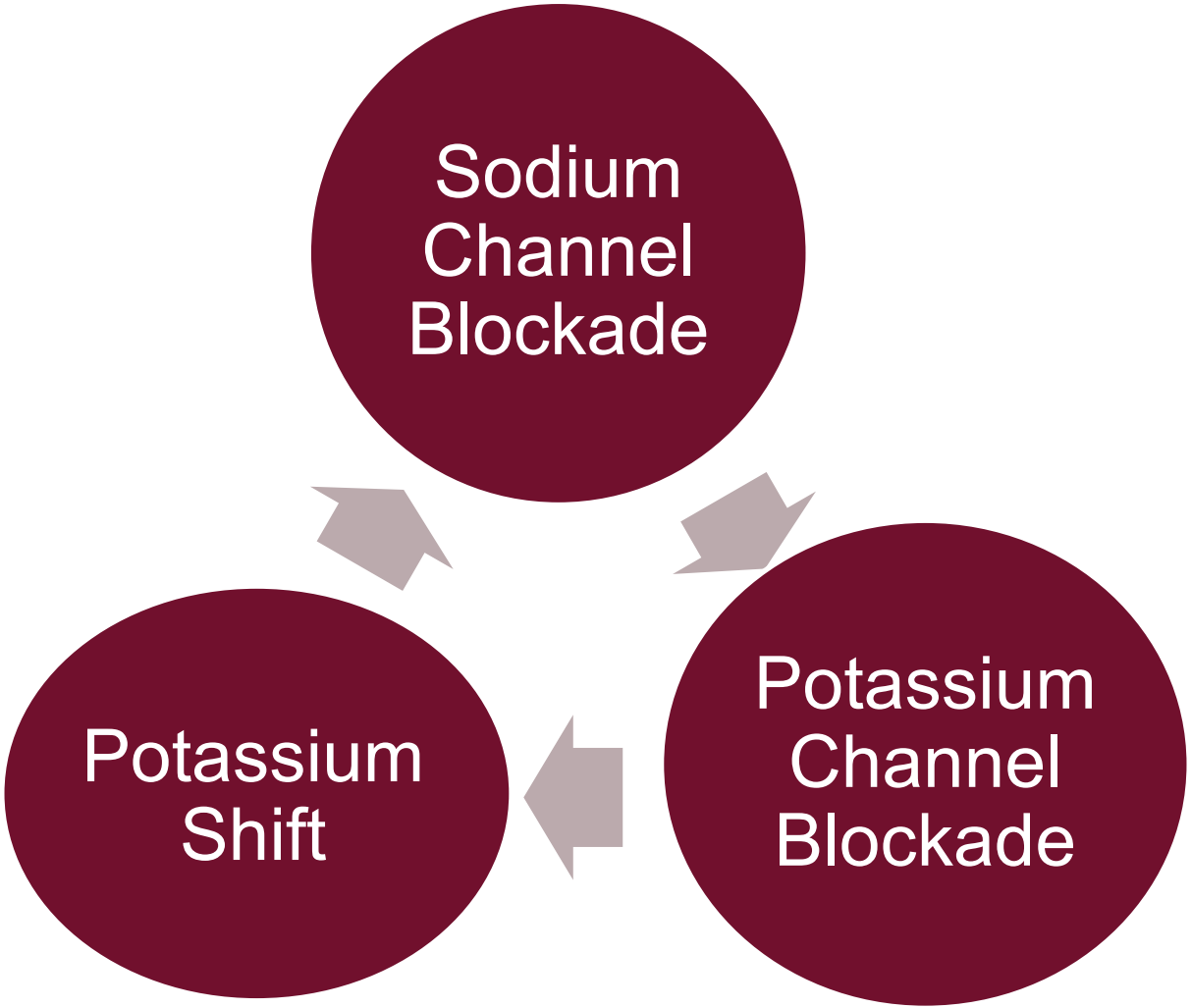
New Life Spectrum Ich Shield Medicated Powder 50g - Chloroquine Phosphate

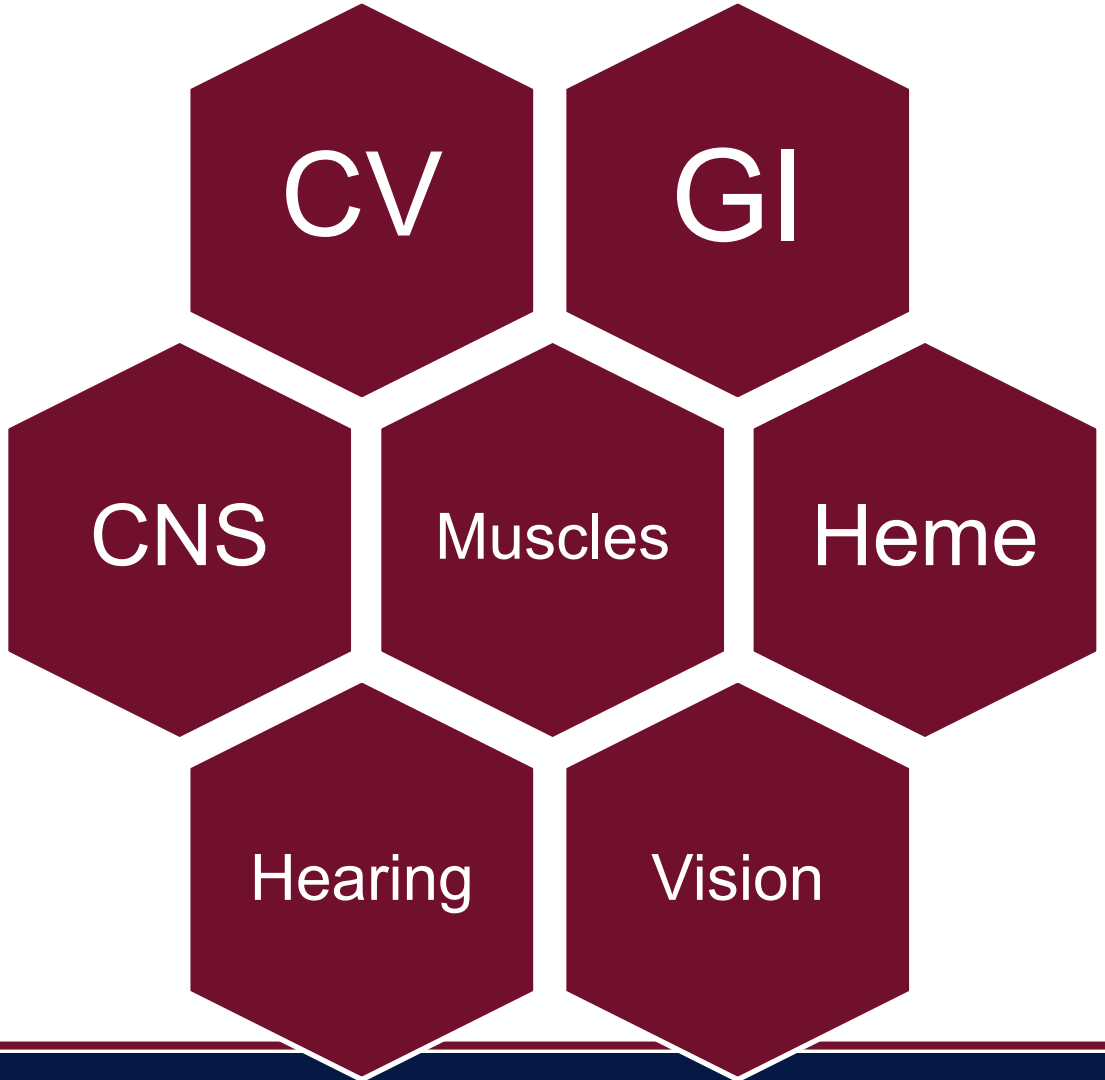
Out of stock

https://www.championlighting.com/new_life_spectrum_ich_shield_powder_50g.html

Adverse Effects at Therapeutic Doses, Supratherapeutic Doses and in Overdose




Sodium Channel Blockade
Potassium Channel Blockade
Potassium Shift


CV
GI
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Muscles
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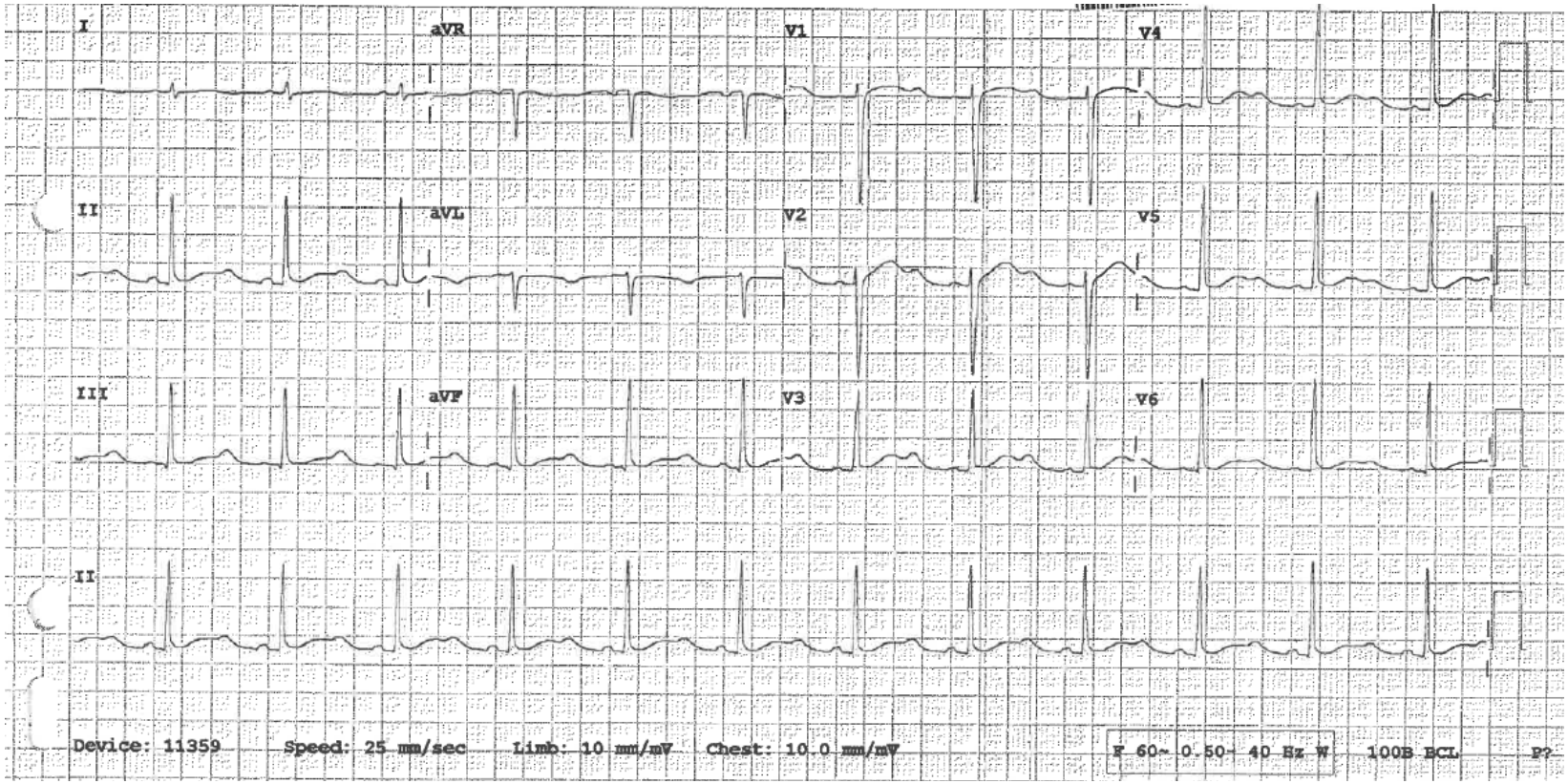
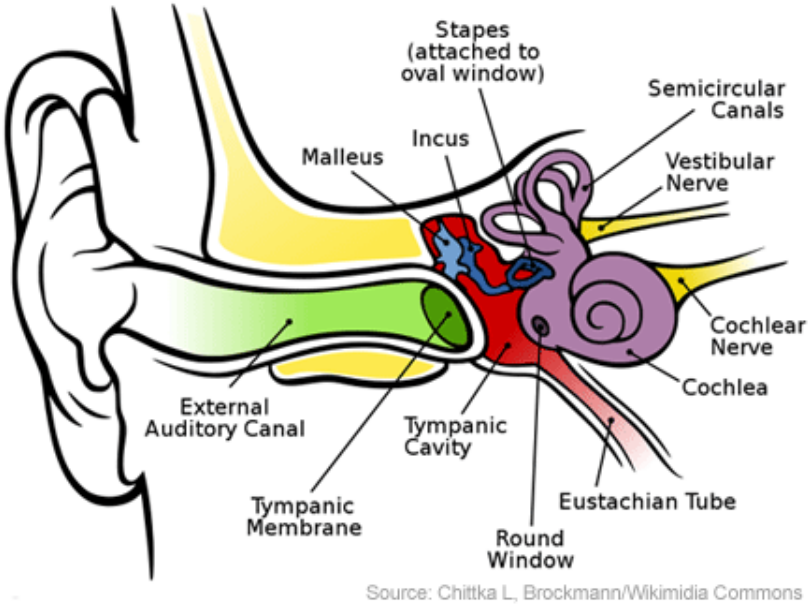
Vision

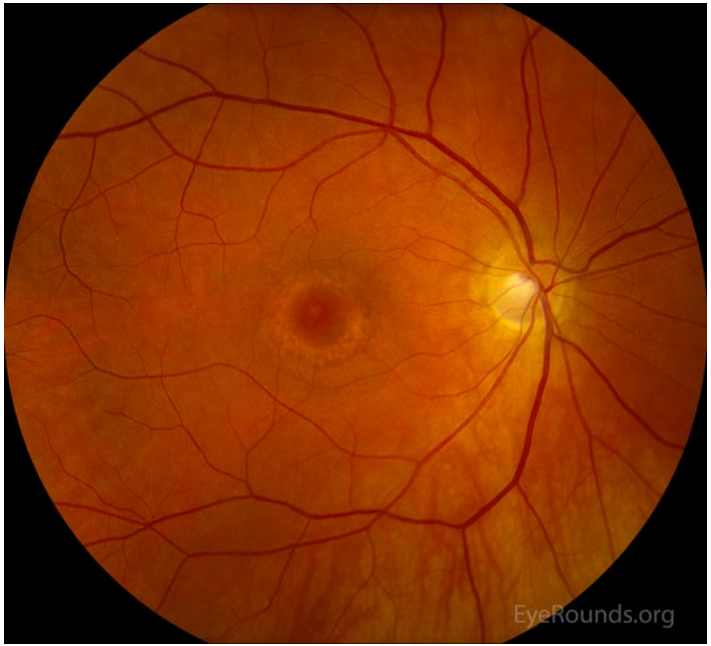
Cardiac Effects QT Prolongation



Adverse Effects on Hearing and Vision

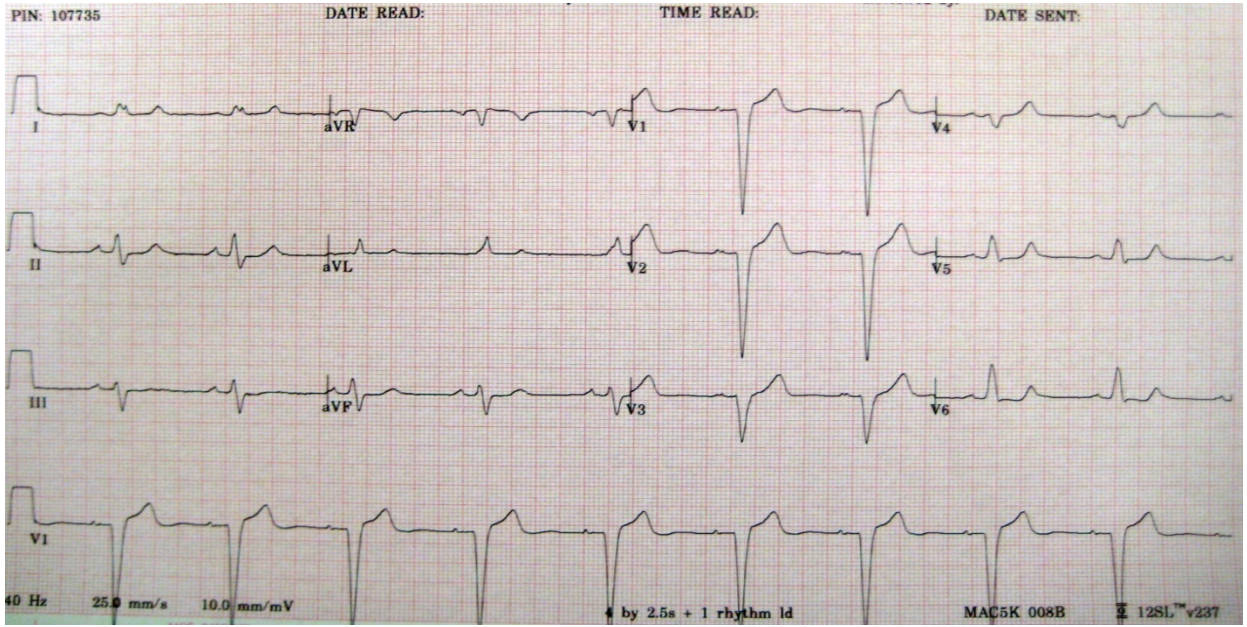


Source: Chittka L, Brockmann/Wikimidia Commons



Ophthalmic Atlas Images by EyeRounds.org, The University of Iowa are licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License.

Cardiac Effects
Myopathy and Conduction Blocks



Left Bundle Branch Block and Irregular Rhythm
By Steven Fruitsmaak - Own work, CC BY-SA 3.0,
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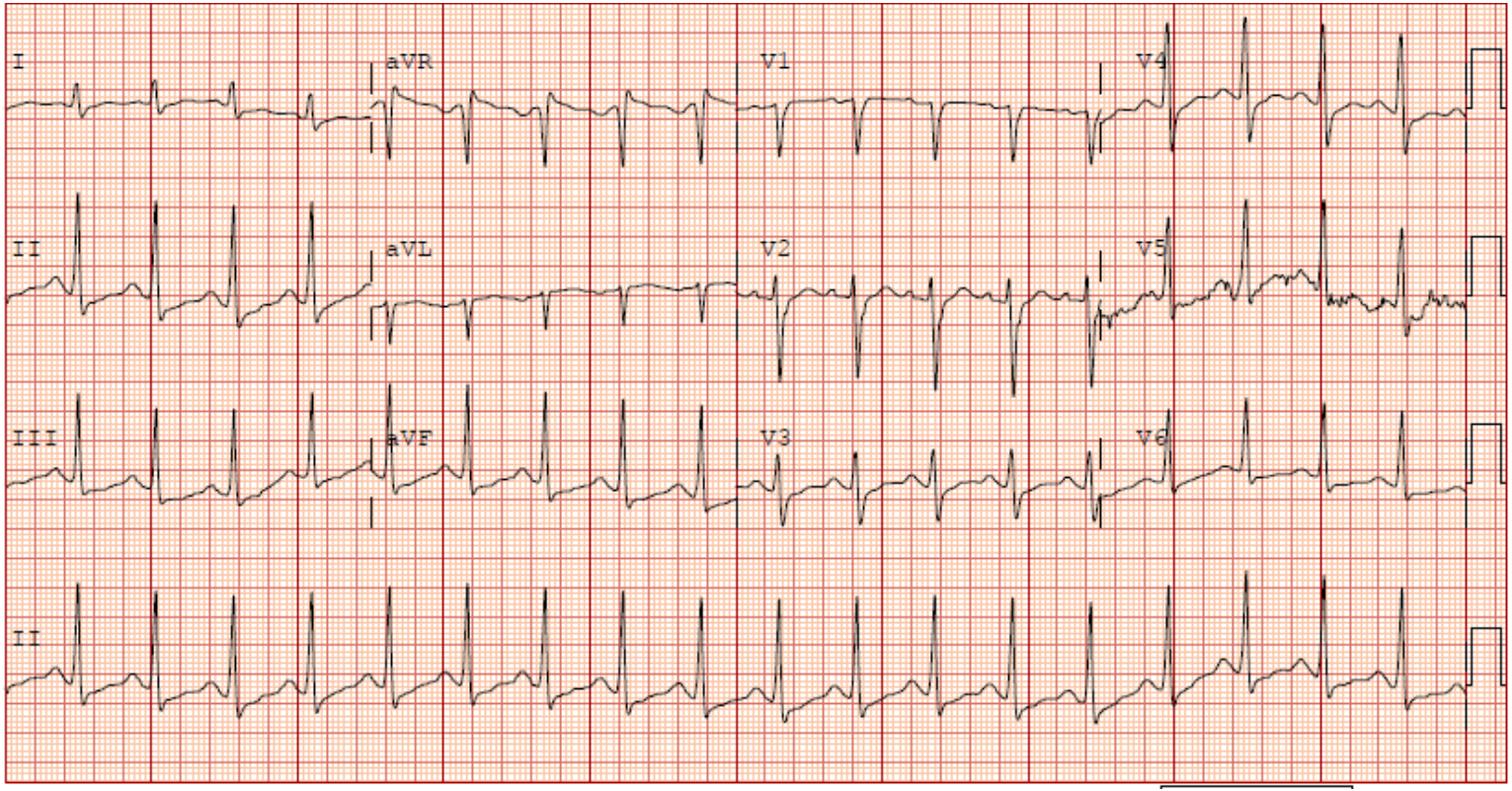
EKG of an Acute Hydroxychloroquine Overdose



High-Dose Epinephrine Infusion

Diazepam Bolus and Infusion

Risk-Based Aggressive Supportive Care

Judicious Potassium Replacement

Sodium Bicarbonate

RELEVANT PUBLIC HEALTH CONSIDERATIONS DURING A PANDEMIC

- Lack of clinical guidelines for off-label use in COVID-19
  - Vulnerable patients including health care providers and emergency responders
  - Special populations (children, pregnancy, breastfeeding)
  - Drug-drug interactions
- Limited ability to monitor for adverse effects during an emergency
- Limited supply of the pharmaceutical and prescribing rules
  - Potential use of non-pharmaceutical products

SUMMARY POINTS

- Chloroquine and hydroxychloroquine are currently used for malaria. Hydroxychloroquine is also used for rheumatoid arthritis and SLE
- They are being used in some patients with COVID19 infections as an off-label use or as part of a research study
- Both drugs are associated with several adverse effects affecting the heart, the gastrointestinal tract, hearing, and vision. Other effects include myopathy, neuropathy, neuropsychiatric events, and hypoglycemia
- Acute overdoses can be associated with severe toxicity in different organs or systems including the heart (cardiac conduction), brain and serum potassium levels

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