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
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)
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
PANELISTS

• Dr. Michelle Ruha, FACMT
  • President, ACMT
  • Professor of Emergency Medicine, University of Arizona College of Medicine
  Phoenix, Arizona, USA
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
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
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
<table>
<thead>
<tr>
<th>STATE</th>
<th>CASES</th>
<th>DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York</td>
<td>30,811</td>
<td>285</td>
</tr>
<tr>
<td>New Jersey</td>
<td>3,675</td>
<td>44</td>
</tr>
<tr>
<td>California</td>
<td>2,648</td>
<td>56</td>
</tr>
<tr>
<td>Washington</td>
<td>2,469</td>
<td>123</td>
</tr>
<tr>
<td>Michigan</td>
<td>1,783</td>
<td>24</td>
</tr>
<tr>
<td>Illinois</td>
<td>1,535</td>
<td>16</td>
</tr>
<tr>
<td>Florida</td>
<td>1,456</td>
<td>19</td>
</tr>
<tr>
<td>Louisiana</td>
<td>1,388</td>
<td>46</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>1,159</td>
<td>11</td>
</tr>
<tr>
<td>Georgia</td>
<td>1,097</td>
<td>38</td>
</tr>
</tbody>
</table>

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)**
Fatality Rate vs Avg # of people infected by each sick person
Coronavirus death rates

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>9.5%</td>
</tr>
<tr>
<td>Iran</td>
<td>7.8%</td>
</tr>
<tr>
<td>Spain</td>
<td>6.8%</td>
</tr>
<tr>
<td>Britain</td>
<td>5%</td>
</tr>
<tr>
<td>France</td>
<td>4.3%</td>
</tr>
<tr>
<td>China</td>
<td>4%</td>
</tr>
<tr>
<td>United States</td>
<td>1.3%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1.3%</td>
</tr>
<tr>
<td>South Korea</td>
<td>1.3%</td>
</tr>
<tr>
<td>Germany</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Data as of March 24

Source: Johns Hopkins Coronavirus Resource Center
### March 24, 2020 - Hospital Guideline for Treatment of COVID-19

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

*Chloroquine has proven utility for treatment but not readily available thus hydroxychloroquine is recommended given the evidence that both agents have similar efficacy. Chloroquine is available.<br>
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.
SARS Experience

In Vitro Studies

Expert Opinions

Ongoing Clinical Trials

Cortegiani et al.
Journal of Critical Care
2020
Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

Jia Liu1, Ruiyuan Cao2, Mingyue Xu1,3, Xi Wang1, Huanyu Zhang1,3, Hengrui Hu1,3, Yufeng Li1,3, Zhihong Hu1,3, Wu Zhong2 and Manli Wang1

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 intervention.

In the event of pandemic, it is vital to develop effective treatments and vaccines to reduce the spread of the virus and the severity of COVID-19. Chloroquine (CQ) and hydroxychloroquine (HCQ) have been widely used as antimalarial drugs and have shown promise in the treatment of COVID-19. The United States Food and Drug Administration (FDA) has approved the emergency use of HCQ for the treatment of COVID-19 patients with pneumonia.

However, the therapeutic potential of HCQ may be limited by the development of drug resistance in malaria patients. During the initial antimalarial drug trials, HCQ was shown to be effective in vitro in inhibiting SARS-CoV-2 replication in human kidney cells, suggesting its potential use as an antiviral agent.

In this study, we investigated the antiviral activity of HCQ on SARS-CoV-2 in vitro. Our results showed that HCQ significantly inhibited SARS-CoV-2 replication in human kidney cells, with an IC50 value of 0.15 μM. This finding suggests that HCQ may have potential as a therapeutic agent for COVID-19.

In conclusion, our findings provide evidence for the potential use of HCQ as a candidate drug for the treatment of COVID-19. Further studies are needed to confirm its efficacy and safety in clinical trials.
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

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

Under a Creative Commons license

Get rights and content
• 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*
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

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

Philippe Gautret\textsuperscript{a,b}, Jean-Christophe Lagier\textsuperscript{a,c}, Philippe Parola\textsuperscript{a,b}, Van Thuan Hoang\textsuperscript{a,b,d}, Line Meddeb\textsuperscript{a}, Morgane Maille\textsuperscript{a}, Barbara Doudier\textsuperscript{a}, Johan Courjon\textsuperscript{c,e}, Valérie Giordanengo\textsuperscript{b}, Vera Esteves Vieira\textsuperscript{a}, Hervé Tissot Dupont\textsuperscript{a,f}, Stéphane Honoré\textsuperscript{c,i}, Philippe Colson\textsuperscript{a,c}, Eric Chabrè\textsuperscript{a,c}, Bernard La Scola\textsuperscript{a,c}, Jean-Marc Rolain\textsuperscript{a,c}, Philippe Brouqui\textsuperscript{a,c}, Didier Raoult\textsuperscript{a,e}.

\textsuperscript{a}IHU-Méditerranée Infection, Marseille, France.
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
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

It's a Spectrum of Toxicity

Dose

Duration of Therapy

Concomitant therapies

Individual Patient Characteristics
Sodium Channel Blockade

Potassium Channel Blockade

Potassium Shift
Cardiac Effects QT Prolongation
Adverse Effects on Hearing and Vision

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,
https://commons.wikimedia.org/w/index.php?curid=4233068
EKG of an Acute Hydroxychloroquine Overdose
High-Dose Epinephrine Infusion
Diazepam Bolus and Infusion
Judicious Potassium Replacement
Sodium Bicarbonate

Risk-Based Aggressive Supportive Care
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.
SEND COMMENTS TO

info@acmt.net

@ACMT
@MENATOX
@EAPCCT