Promising Therapies for Covid-19 Patients?

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Objectives

- Discuss the clinical stages and presentation of COVID-19
- Become familiar with therapies currently in use or in development for COVID-19
- Discuss the treatment options of COVID-19 patients

CME Disclaimers & Disclosures

- **HIPAA Disclaimer** – All patient information and identifiers have been altered or removed or from published studies
  - Any similarities to real patient cases are purely coincidental
- **Financial Disclosures** – none
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COVID-19 Background

- Virus origin
  - SARS-CoV-2 identified in Wuhan, Hubei Province, China, in December 2019
  - Thought to transmitted to humans from animals sold illegally markets
  - SARS-CoV-2 is thought to be similar to other coronavirus in bats
- There is likely an intermediate host
  - Pangolin
  - Scaly anteater, which is illegally trafficked

Assessment of Evidence for COVID-19-Related Treatments: Updated 5/28/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

Public access is currently available to AHFS Drug Information® (https://www.ahfscdi.com/login) with the username "ahfs@ashp.org" and password "covid-19." ASHP's patient medication information is available at http://www.safemedication.com/.

Visit our website for the latest information on current drug shortages.

Select entries were updated on 5/28/2020; these can be identified by the date that appears in the Drug(s) column.

TABLE OF CONTENTS

ANTIVIRAL AGENTS

- BALOXAVIR
- UPDATED CHLOROQUINE PHOSPHATE
- FAVIPIRAVIR (Avigan®, Favilavir)
- HIV PROTEASE INHIBITORS (e.g., LPV/RTV, Kaletra®)
- UPDATED HYDROXYCHLOROQUINE (Plaquenil®)
- NEURAMINIDASE INHIBITORS (e.g., oseltamivir)
- UPDATED REMDESIVIR
- UMIFENOVIR (Arbidol®)

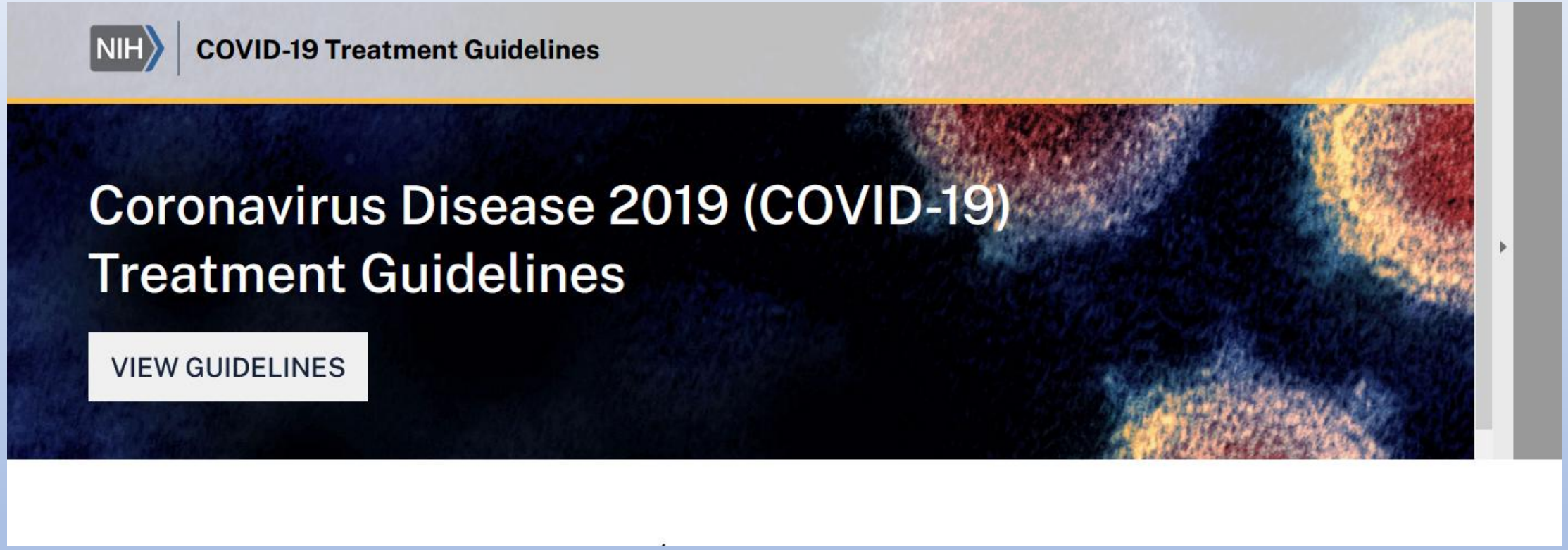
SUPPORTING AGENTS

- UPDATED ANAKINRA
- ASCORBIC ACID
- UPDATED AZITHROMYCIN
- BARICITINIB (Olumiant®)
- COLCHICINE
- CORTICOSTEROIDS (general)
- UPDATED EPOPROSTENOL (inhaled)
- NEW INTERFERONS
- METHYLPREDNISOLONE (DEPO-Medrol®, SOLU-Medrol®)
- UPDATED NITRIC OXIDE (inhaled)
- RUXOLITINIB (Jakafi®)
- SARILUMAB (Kefzara®)
- SILTUXIMAB (Sylvant®)
- UPDATED SIROLIMUS (Rapamune®)
- TOCILIZUMAB (Actemra®)

OTHER

- ACE INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)
- ANTICOAGULANTS (low molecular weight heparin [LMWH], unfractionated heparin [UFH])
- COVID-19 CONVALESCENT PLASMA
- FAMOTIDINE
- HMG-CoA REDUCTASE INHIBITORS (statins)
- IMMUNE GLOBULIN (IGIV, IVIG, γ-globulin)
- IVERMECTIN
- NEBULIZED DRUGS
- UPDATED NICLOSAMIDE
- UPDATED NITAZOXANIDE
- NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIAs)
- TISSUE PLASMINOGEN ACTIVATOR

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx



https://covid19treatmentguidelines.nih.gov/

NON FDA APPROVED

- You hear of some agents here first BUT
- This is informational only
- None are FDA Approved for COVID-19
- **NOT RECOMMENDING ANY OF THESE THERAPIES**
- **SHOULD NOT BE USED OUTSIDE OF CLINICAL TRIALS**

Time Dated Material
Data as of 06/01/20*
Changing ALL THE TIME

Please note many of suggested medications
Are in current clinical trials

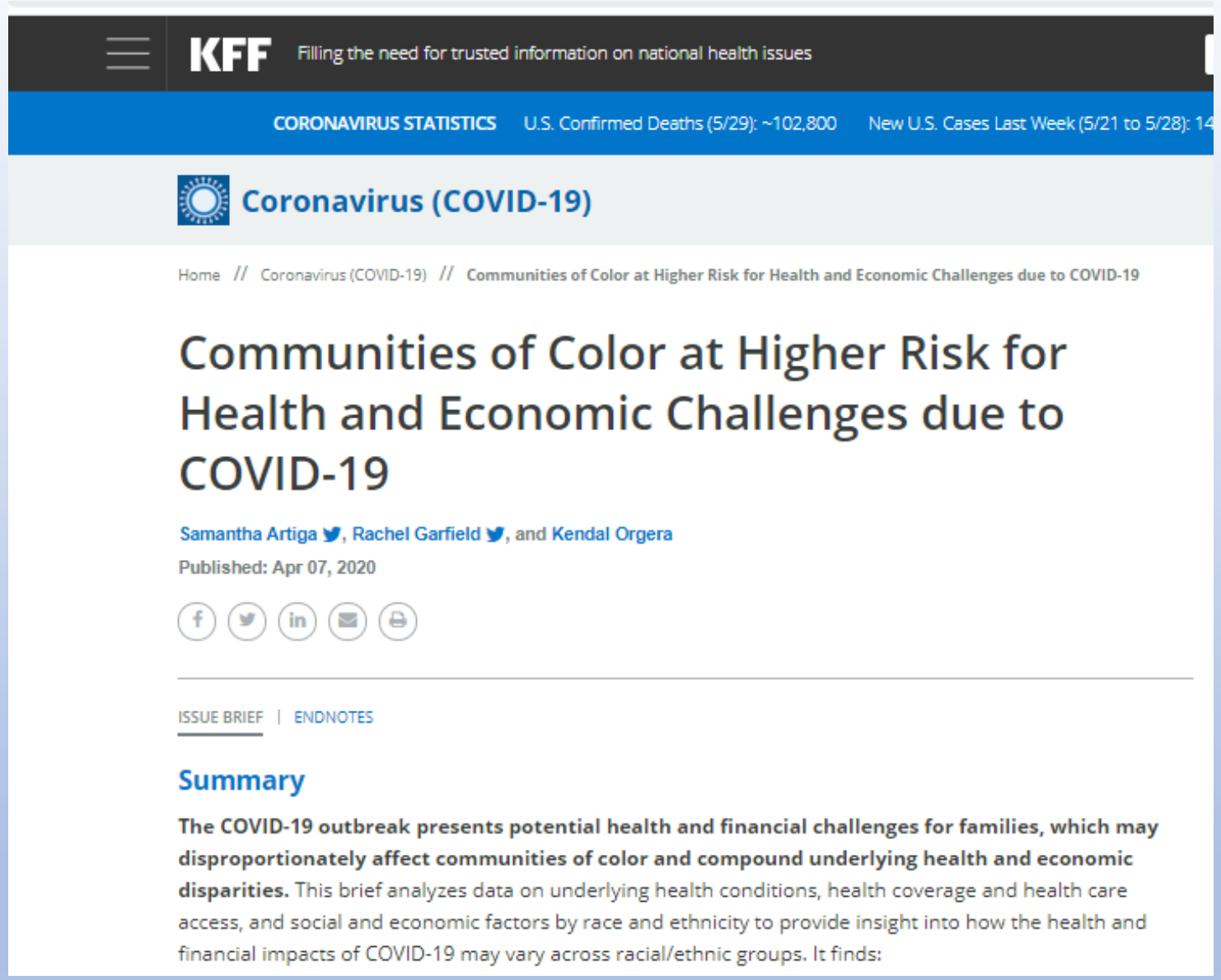
Many are NOT randomized control trials

Many of studies are preliminary and published online to get
Information out but increases risk

Many agents being used based on theoretical or
in vitro activity

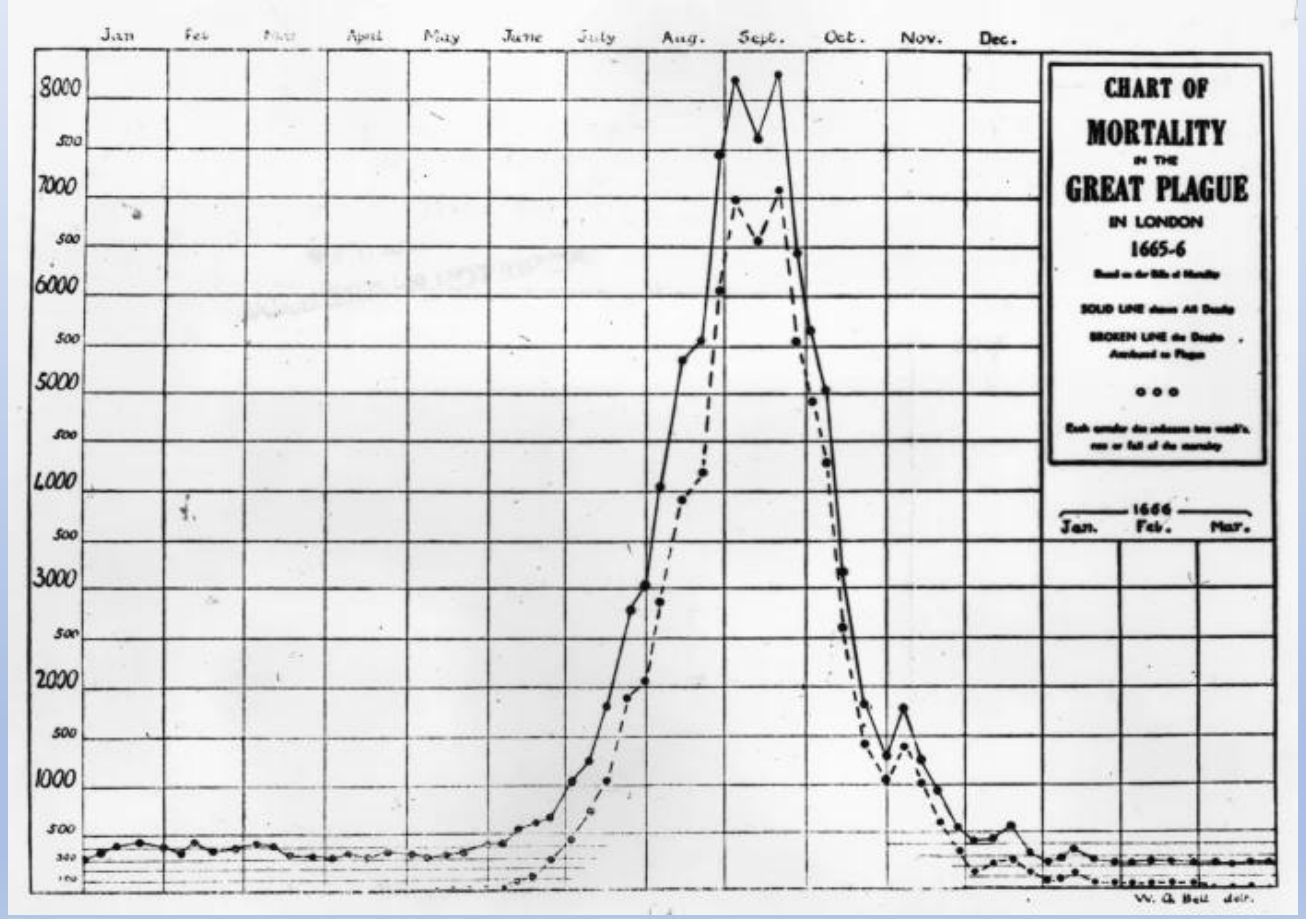
THIS LECTURE IS INFORMATIONAL ONLY

ALL OF THESE AGENTS SHOULD BE USED IN CLINICAL TRIALS
ONLY IF AT ALL
*Efforts made to have most up to date but new data may be available



https://www.kff.org/coronavirus-covid-19/issue-brief/communities-of-color-at-higher-risk-for-health-and-economic-challenges-due-to-covid-19/

Great Plague of London 1665-1666



https://www.history.com/topics/middle-ages/pandemics-timeline

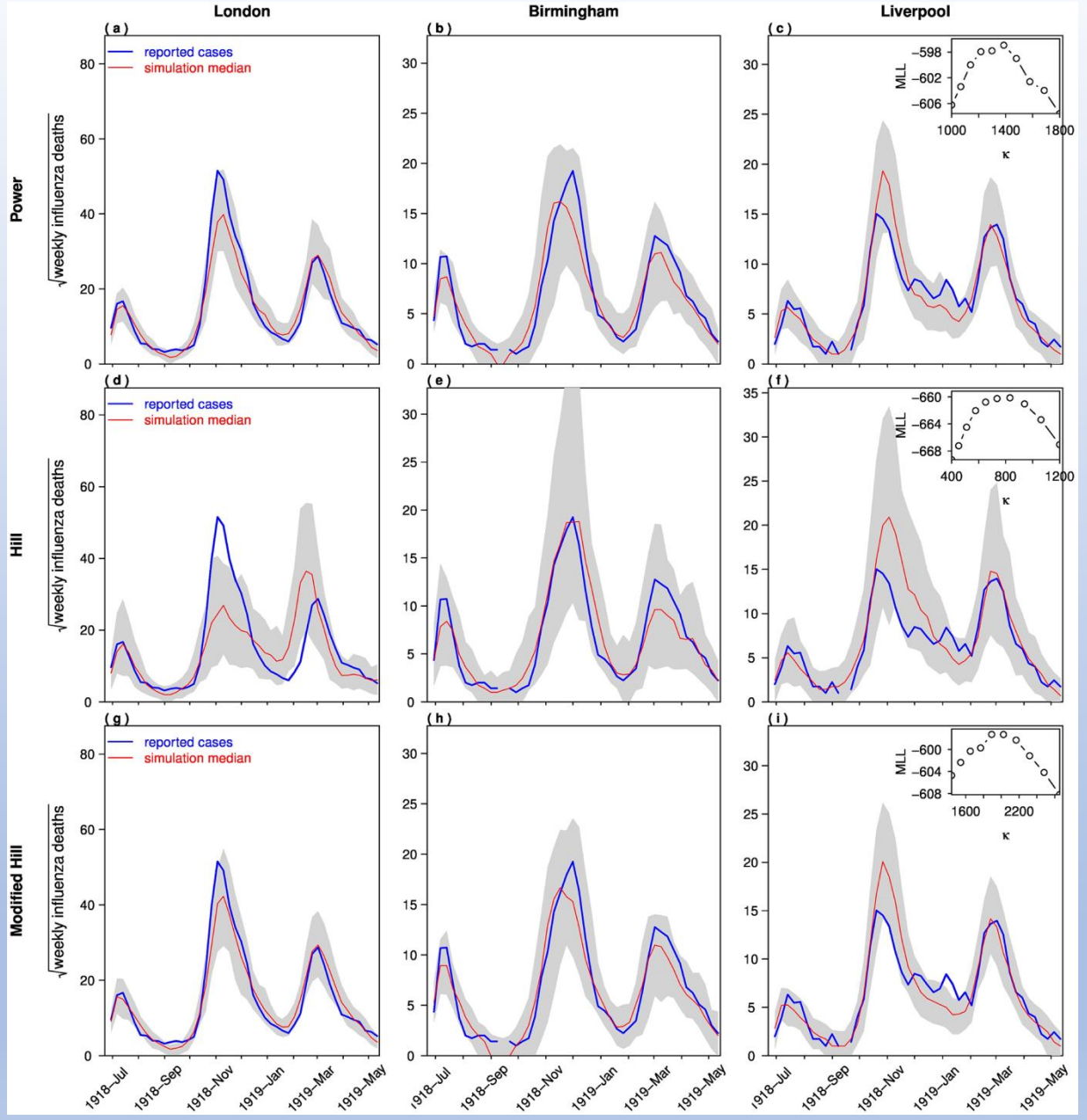
Effects of social distancing on 1918 flu deaths

As the first cases of the 1918 flu were reported in Philadelphia in September 1918, authorities played down the significance and allowed public gatherings to continue. Closures in Philadelphia were only enacted once the virus had spread. The first cases in St. Louis were reported in early October, with measures to contain the spread enacted two days later. This resulted in a slower spread and lower mortality rate.

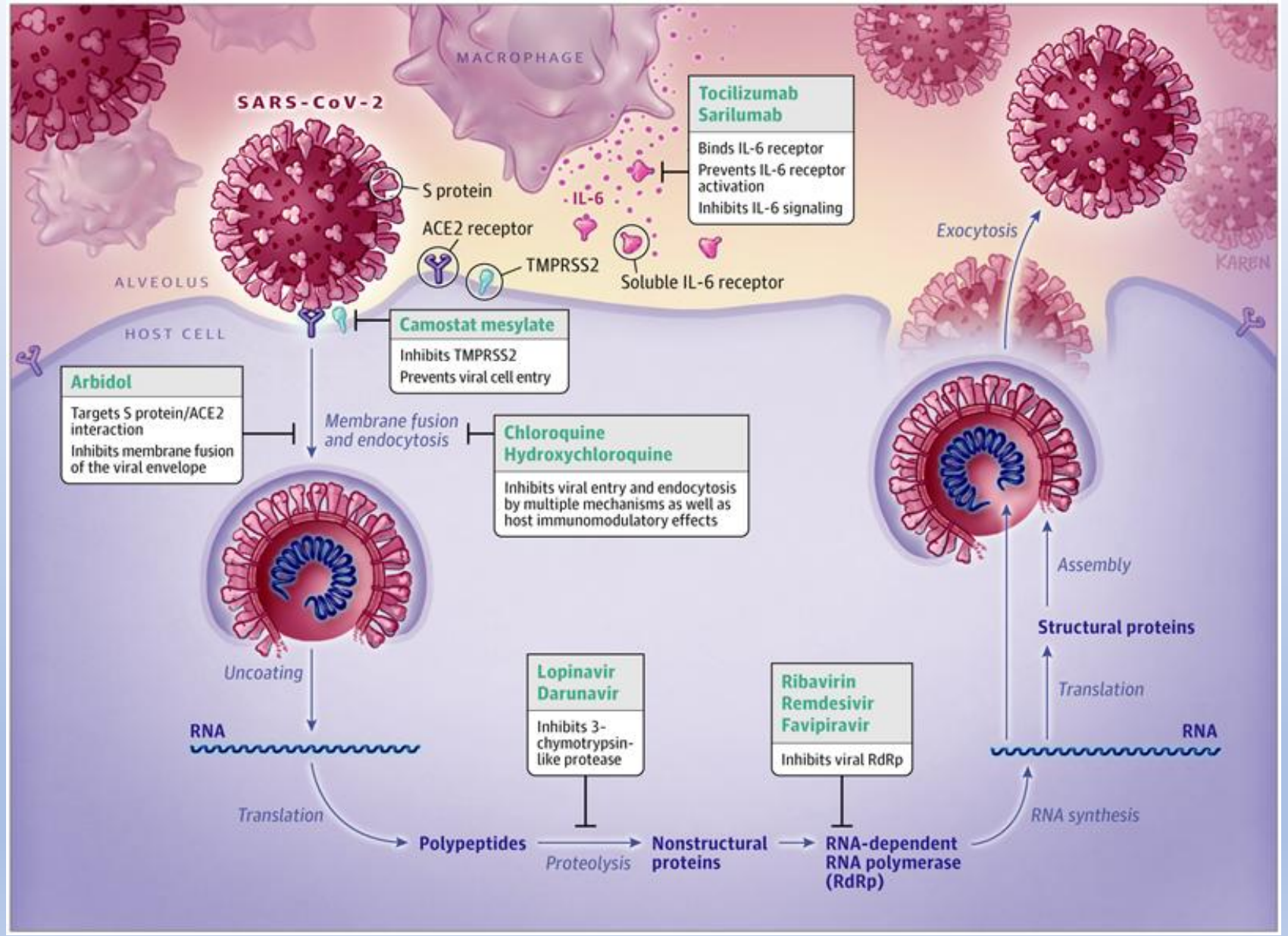
Sources: "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007. Data derived from "Public health interventions and epidemic intensity during the 1918 influenza pandemic" by Richard J. Hatchett, Carter E. Mecher, Marc Lipsitch, Proceedings of the National Academy of Sciences May, 2007.

TIM MEKO/THE WASHINGTON POST

https://www.washingtonpost.com/health/2020/03/10/social-distancing-coronavirus/



https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0180545



https://jamanetwork.com/journals/jama/fullarticle/2764727

COVID-19

- Enveloped positive sense RNA coronavirus
- Spike protein binds to angiotensin-converting enzyme-2 (ACE2) receptor
- ACE2 in multiple types of cells
  - Type II alveolar cells
  - Intestines, kidney, heart, and blood vessels
- Incubation period ranges from 1 to 14 days
- Typically 4 to 5 days
- Onset and duration of viral shedding is currently unknown

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?
Fang L, et al.

Published:March 11, 2020DOI:https://doi.org/10.1016/S2213-2600(20)30116-8

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by Xiaobo Yang and colleagues[1] were cerebrovascular diseases (22%) and diabetes (22%). Another study[2] included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23·7%), diabetes mellitus (16·2%), coronary heart diseases (5·8%), and cerebrovascular disease (2·3%). In a third study,[3] of 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% had diabetes. Notably, the most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors; however, treatment was not assessed in either study.

Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[4] The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs).[4] Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2.[5] ACE2 can also be increased by thiazolidinediones and ibuprofen. These data suggest that ACE2 expression is increased in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.

If this hypothesis were to be confirmed, it could lead to a conflict regarding treatment because ACE2 reduces inflammation and has been suggested as a potential new therapy for inflammatory lung diseases, cancer, diabetes, and hypertension. A further aspect that should be investigated is the genetic predisposition for an increased risk of SARS-CoV-2 infection, which might be due to ACE2 polymorphisms that have been linked to diabetes mellitus, cerebral stroke, and hypertension, specifically in Asian populations. Summarising this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism.

We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs. Based on a PubMed search on Feb 28, 2020, we did not find any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients.

We declare no competing interests.

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1 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; published online Feb 24. https://doi.org/10.1016/S2213-2600(20)30079-5.

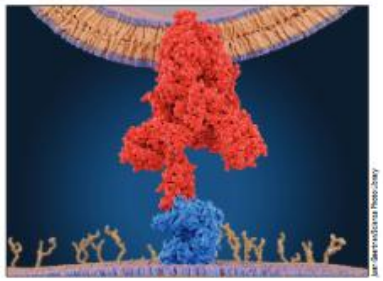
2 Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; published online Feb 28. DOI:10.1056/NEJMoa2002032.

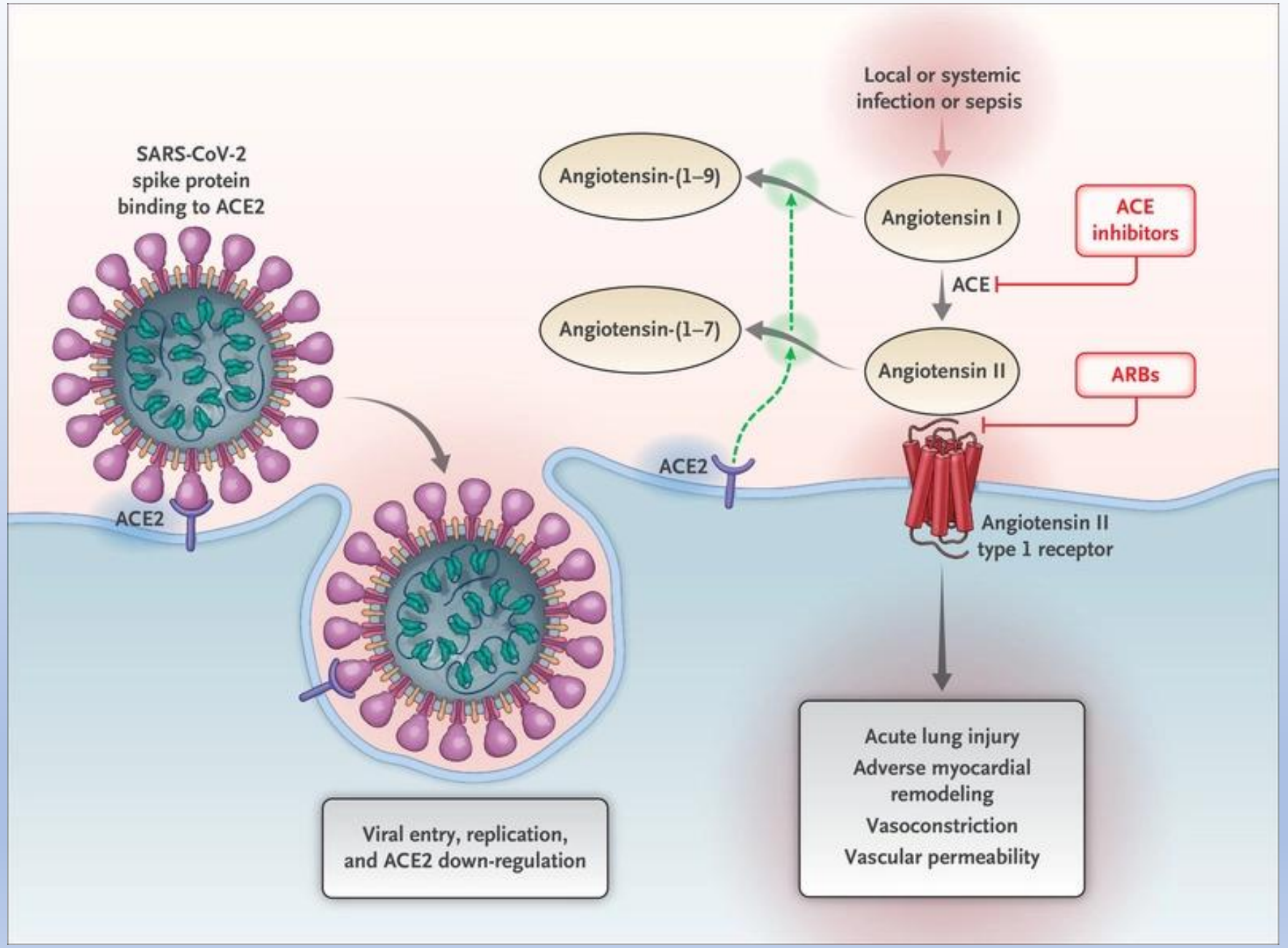
3 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy* 2020; published online Feb 19. DOI:10.1111/all.14238.

4 Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virology* 2020; published online Jan 29. DOI:10.1128/JVI.00127-20.

5 Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res* 2017; 125: 21–38.

Published Online March 11, 2020 https://doi.org/10.1016/S2213-2600(20)30116-8

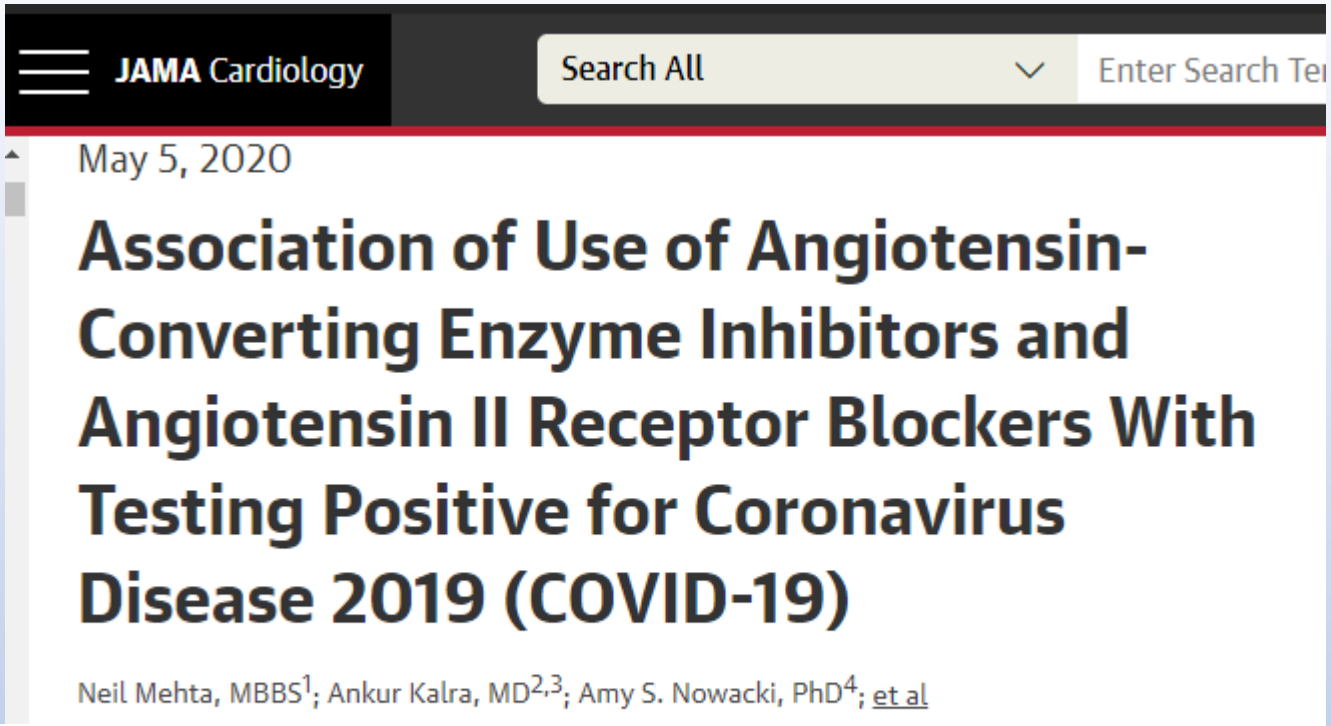




https://www.nejm.org/doi/pdf/10.1056/NEJMsr2005760

ACE Inhibitors and ACE Receptor Blockers (ARBs)

- ACEIs and ARBs increase expression of ACE2 receptors
  - This could increase the risk of infection
  - Some suggest these medications may be protective
- Increased mortality with hypertension and diabetes
- Clinical Data has some data showing beneficial and other showing worse outcomes
- The European, Canadian, and United States cardiovascular societies and others do not currently recommend discontinuing these medications in patients



https://jamanetwork.com/journals/jamacardiology/fullarticle/2765695?guestAccessKey=ab9ada9a-e796-4ae8-891c-4bb318235c24&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=050520

Brief Report

ONLINE FIRST FREE

April 23, 2020

Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China

Juyi Li, MD[1]; Xiufang Wang, MS[2]; Jian Chen, BS[3]; et al

» Author Affiliations | Article Information

JAMA Cardiol. Published online April 23, 2020. doi:10.1001/jamacardio.2020.1624

https://jamanetwork.com/journals/jamacardiology/fullarticle/2765049

NSAIDs

- Similar to ACEIs and ARBs
- NSAIDs may increase expression of ACE2 receptors
- NSAIDs have been suggested to prolong illness and result in recurrence of acute respiratory tract infections
- Currently no data on effect of NSAIDs in COVID-19
- WHO initially recommended against use
- As of March 18th, 2020, the official WHO Twitter feed does not recommend against the use of ibuprofen
- May consider using acetaminophen as initial antipyretic

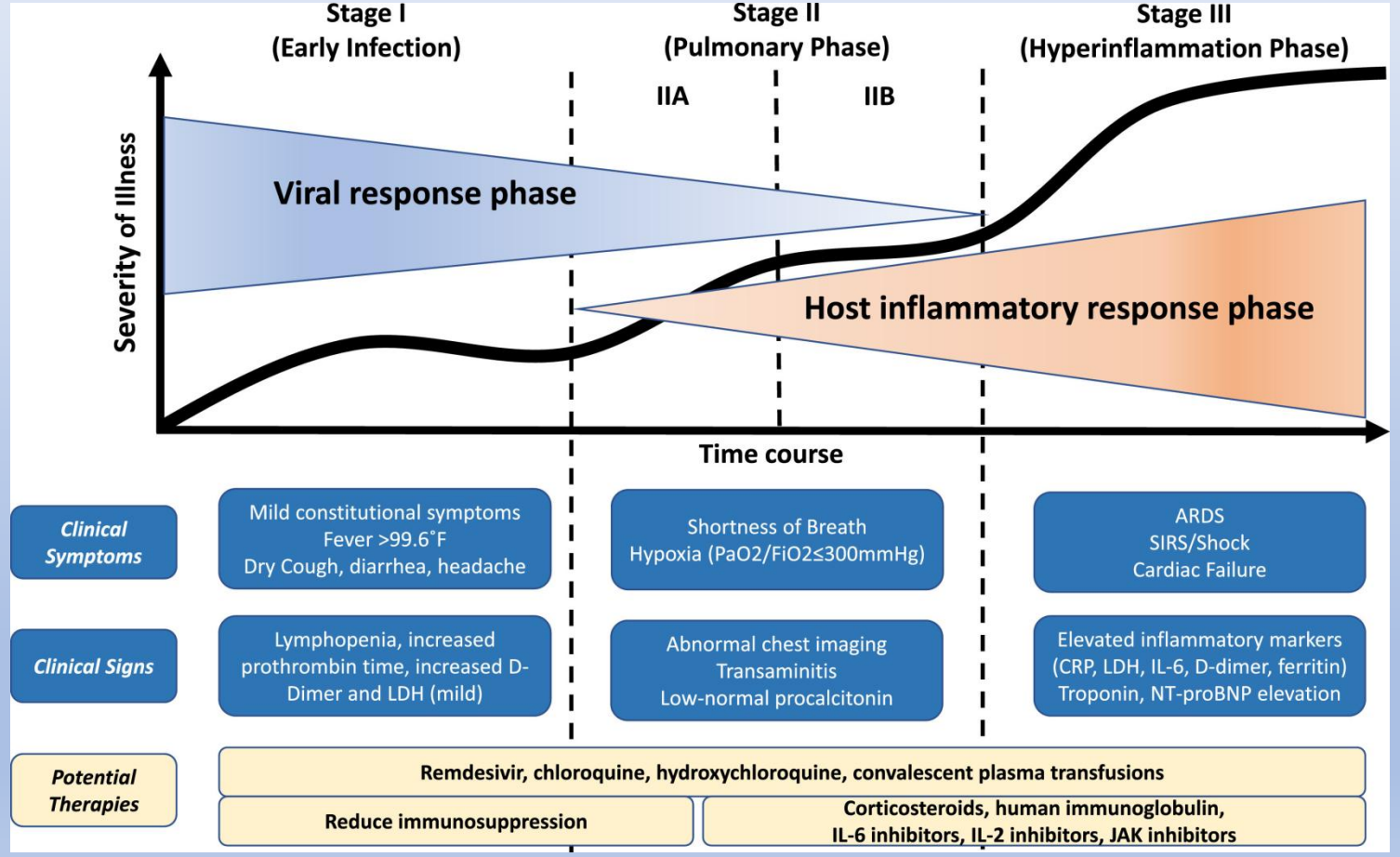
Risk Factors

- Patients with underlying comorbidities tend to have a more severe clinical course. In particular, patients with the following have had more severe courses
  - Cardiovascular disease
    - Hypertension
    - CAD
  - Pulmonary disease
  - Diabetes

Laboratory Abnormalities

- Lymphocytopenia is present in 70%-80% of patients
  - Patients with more severe disease tend to have more prominent lymphocytopenia and leukopenia
- Prolonged prothrombin time
- Elevated lactate dehydrogenase
- Elevated ferritin
- Thrombocytopenia
- Elevated C-reactive protein
- D-dimer is elevated in a significant percentage of patients with COVID-19
  - Levels over 2500 ng/mL have been associated with poor prognosis

Inflammatory Markers



https://www.jhltonline.org/article/S1053-2498(20)31473-X/fulltext

Pulmonary Presentation

- Dyspnea may be a sign of more severe illness
  - Data from China shows often patients with dyspnea at admission later developed severe disease
  - However, dyspnea was present in only 15% that never developed severe disease
- Severe hypoxia but tolerate well
  - HAPE? No not same
- Severe cases progress to acute lung injury about 15%
  - May occur up to 12 days after symptom onset

Pulmonary Presentation

- Pneumonia
  - Bilateral patchy infiltrates
  - Antibiotics? Generally used
- Acute Respiratory Disease Syndrome?
  - Different types of patients
- Pulmonary embolism

Thrombotic Complications

- Thrombotic complications are common in critically ill COVID-19 patients
- Pulmonary embolism
- Venous thromboembolism
- Extremities
- Thrombosed small vessels
- Arterial thrombosis less common
- Anticoagulation and thrombolysis
  - There are reports of critically ill patients treated with heparin apparently having a better prognosis than non-treated patients
  - Thrombolysis
  - The non-random nature of the study and other methodological issues make extrapolation of this data unclear.

In a rapid communication to be published online April 29 in the New England Journal of Medicine, investigators report five cases of large vessel stroke over a 2-week period in COVID-19 patients under age 50 years

This represents a sevenfold increase in what would normally be expected

The five cases had either no, or mild, COVID-19 symptoms

"It's been surprising to learn that the virus appears to cause disease through a process of blood clotting," Oxley told Medscape Medical News.

https://www.medscape.com/viewarticle/929345

Asthma and COPD Increased Risk?

- Asthma may not increase risk of COVID or complications
- Could be not enough data to demonstrate risk of having asthma
- CDC does consider moderate to severe asthma a risk factor
- COPD data mixed with some data showing increased risk of more severe disease and death and other data showing no increased risk
- **However, patients with either asthma or COPD with COVID or suspected COVID present with an exacerbation including beta-agonists and steroids should be used at regular doses if the indication is for the asthma or COPD exacerbation**

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DOI: 10.1111/all.14238

ORIGINAL ARTICLE

Epidemiology and Genetics

Allergy WILEY

Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China

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Abstract

Background: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been widely spread. We aim to investigate the clinical characteristic and allergy status of patients infected with SARS-CoV-2.

Methods: Electronic medical records including demographics, clinical manifestation, comorbidities, laboratory data, and radiological materials of 140 hospitalized COVID-19 patients, with confirmed result of SARS-CoV-2 viral infection, were extracted and analyzed.

Results: An approximately 1:1 ratio of male (50.7%) and female COVID-19 patients was found, with an overall median age of 57.0 years. All patients were community-acquired cases. Fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal symptoms (39.6%) were the most common clinical manifestations, whereas hypertension (30.0%) and diabetes mellitus (12.1%) were the most common comorbidities. Drug hypersensitivity (11.4%) and urticaria (1.4%) were self-reported by several patients. Asthma or other allergic diseases were not reported by any of the patients. Chronic obstructive pulmonary disease (COPD, 1.4%) patients and current smokers (1.4%) were rare. Bilateral ground-glass or patchy opacity (89.6%) was the most common sign of radiological finding. Lymphopenia (75.4%) and eosinopenia (52.9%) were observed in most patients. Blood eosinophil counts correlate positively with lympho-

https://onlinelibrary.wiley.com/doi/epdf/10.1111/all.14238

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis

Wei-jie Guan, Wen-hua Liang, Yi Zhao, Heng-rui Liang, Zi-sheng Chen, Yi-min Li, Xiao-qing Liu, Ru-chong Chen, Chun-li Tang, Tao Wang, Chun-quan Ou, Li Li, Ping-yan Chen, Ling Sang, Wei Wang, Jian-fu Li, Cai-chen Li, Li-min Ou, Bo Cheng, Shan Xiong, Zheng-yi Ni, Jie Xiang, Yu Hu, Lei Liu, Hong Shan, Chun-liang Lei, Yi-xiang Peng, Li Wei, Yong Liu, Ya-hua Hu, Peng Peng, Jian-ming Wang, Ji-yang Liu, Zhong Chen, Gang Li, Zhi-jian Zheng, Shao-qin Qiu, Jie Luo, Chang-jiang Ye, Shao-yong Zhu, Lin-ling Cheng, Feng Ye, Shi-yue Li, Jin-ping Zheng, Nuo-fu Zhang, Nan-shan Zhong, Jian-xing He

Please cite this article as: Guan W-jie, Liang W-hua, Zhao Y, *et al*. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00547-2020).

https://erj.ersjournals.com/content/erj/early/2020/03/17/13993003.00547-2020.full.pdf

The Medical Journal of Australia - Preprint only - Version 2, updated 1 April 2020

Consensus statement: Safe Airway Society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group

David J Brewster[1], Nicholas C Chrimes[1], Thy BT Do[1], Kirstin Fraser[1], Chris J Groombridge[1], Andy Higgs[1], Matthew J Humar[1], Timothy J Leeuwenburg[1], Steven McGloughlin[2], Fiona G Newman[1], Chris P Nickson[1], Adam Rehak[1], David Vokes[1], Jonathan J Gatward[1]

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Free, open access resources to accompany this article can be found at:

https://www.safeairwaysociety.org/covid19/

https://www.mja.com.au/system/files/2020-04/Preprint%20Brewster%20updated%201%20April%202020.pdf

Albuterol

- Nebulized medications, eg, albuterol
- There is a theoretical risk of viral spread with nebulized medications.
- Limited data related to viral transmission of SARS-CoV with nebulized medications showed conflicting results
- Metered-dose inhalers should be used as an alternative in patients with suspected or confirmed COVID-19
- Can consider parenteral medications eg, terbutaline, epinephrine but need to use with caution

COVID-19 and the cardiovascular system

Ying-Ying Zheng[1,2], Yi-Tong Ma[3]✉, Jin-Ying Zhang[1,2]✉ and Xiang Xie[3]✉

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells through ACE2 receptors, leading to coronavirus disease (COVID-19)-related pneumonia, while also causing acute myocardial injury and chronic damage to the cardiovascular system. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19.

In December 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, Hubei province, and has spread rapidly throughout China, with an ongoing risk of a pandemic[1]. After virus identification and isolation, the pathogen for this pneumonia was originally called 2019 novel coronavirus (2019-nCoV)[2] but has subsequently been officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the WHO. On 30 January 2020, the WHO declared the outbreak of SARS-CoV-2 a Public Health Emergency of International Concern. Compared with the SARS-CoV that caused an outbreak of SARS in 2003, SARS-CoV-2 has a stronger transmission capacity. The rapid increase in confirmed cases makes the prevention and control of COVID-19 extremely serious. Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients have severe cardiovascular damage[3]. In addition, some patients with underlying cardiovascular diseases (CVDs) might have an increased risk of death[3]. Therefore, understanding the damage caused by SARS-CoV-2 to the cardiovascular system and the underlying mechanisms is of the greatest importance, so that treatment of these patients can be timely and effective and mortality reduced.

SARS-CoV-2 and ACE2

Angiotensin-converting enzyme 2 (ACE2) is a membrane-bound aminopeptidase that has a vital role in the cardiovascular and immune systems[4]. ACE2 is involved in heart function and the development of hypertension and diabetes mellitus. In addition, ACE2 has been identified as a functional receptor for coronaviruses[5], including SARS-CoV and SARS-CoV-2. SARS-CoV-2 infection is triggered by binding of the spike protein of the virus to ACE2, which is highly expressed in the heart and lungs[4]. SARS-CoV-2 mainly invades alveolar epithelial cells, resulting in respiratory symptoms. These symptoms are more severe in patients with CVD, which might be associated with increased secretion of ACE2 in these patients compared with healthy individuals. ACE2 levels can be increased by the use of renin–angiotensin–aldosterone system inhibitors. Given that ACE2 is a functional receptor for SARS-CoV-2, the safety and potential effects of antihypertension therapy with ACE inhibitors or angiotensin-receptor blockers in patients with COVID-19 should be carefully considered. Whether patients with COVID-19 and hypertension who are taking an ACE inhibitor or angiotensin-receptor blocker should switch to another antihypertensive drug remains controversial, and further evidence is required.

Acute cardiac injury

Reports suggest that the Middle East respiratory syndrome related coronavirus (MERS-CoV) can cause acute myocarditis and heart failure[6]. SARS-CoV-2 and MERS-CoV have similar pathogenicity, and the myocardial damage caused by infection with these viruses undoubtedly increases the difficulty and complexity of patient treatment. Myocardial injury associated with the SARS-CoV-2 occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, which mainly manifested as an increase in high-sensitivity cardiac troponin I (hs-cTnI) levels (>28 pg/ml)[3]. In this study, four of five patients with myocardial injury were admitted to the intensive-care unit (ICU), which indicates the serious nature of the myocardial injury in patients with COVID-19. Blood-pressure levels were significantly higher in patients treated in the ICU than in those not treated in the ICU (mean systolic blood pressure 145 mmHg versus 122 mmHg, $P<0.001$)[3]. In another report of 138 patients with COVID-19 in Wuhan, 36 patients with severe symptoms were treated in the ICU[1]. The levels of biomarkers of myocardial injury were significantly higher in patients treated in the ICU than in those not treated in the ICU (median creatine kinase (CK)-MB level 18 U/l versus 14 U/l, $P<0.001$; hs-cTnI level 11.0 pg/ml versus 5.1 pg/ml, $P=0.004$), suggesting that patients with severe symptoms often have complications involving acute myocardial injury[1]. In addition, among the confirmed cases of SARS-CoV-2 infection reported by the National Health Commission of China (NHC), some of the patients first went to see a doctor

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https://doi.org/10.1038/s41569-020-0360-5

https://www.nature.com/articles/s41569-020-0360-5

Cardiovascular

- Acute cardiac injury with elevated troponin seen
- Abnormal EKGs and echocardiography in severe cases
- Acute coronary syndrome seen
  - May be from inflammatory response causing plaque rupture
  - May be from hypercoagulable state
  - Influenza has increased risk for acute myocardial infarction
  - PCI recommended over thrombolytics
- Myocarditis
- Pericarditis
- Myopathy

Radiology

Reviews and Commentary
Images in *Radiology*

Free Access

COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features

Neo Poyiadji, Gassan Shahin, Daniel Noujaim, Michael Stone, Suresh Patel, Brent Griffith

Author Affiliations

Published Online: Mar 31 2020 | https://doi.org/10.1148/radiol.2020201187

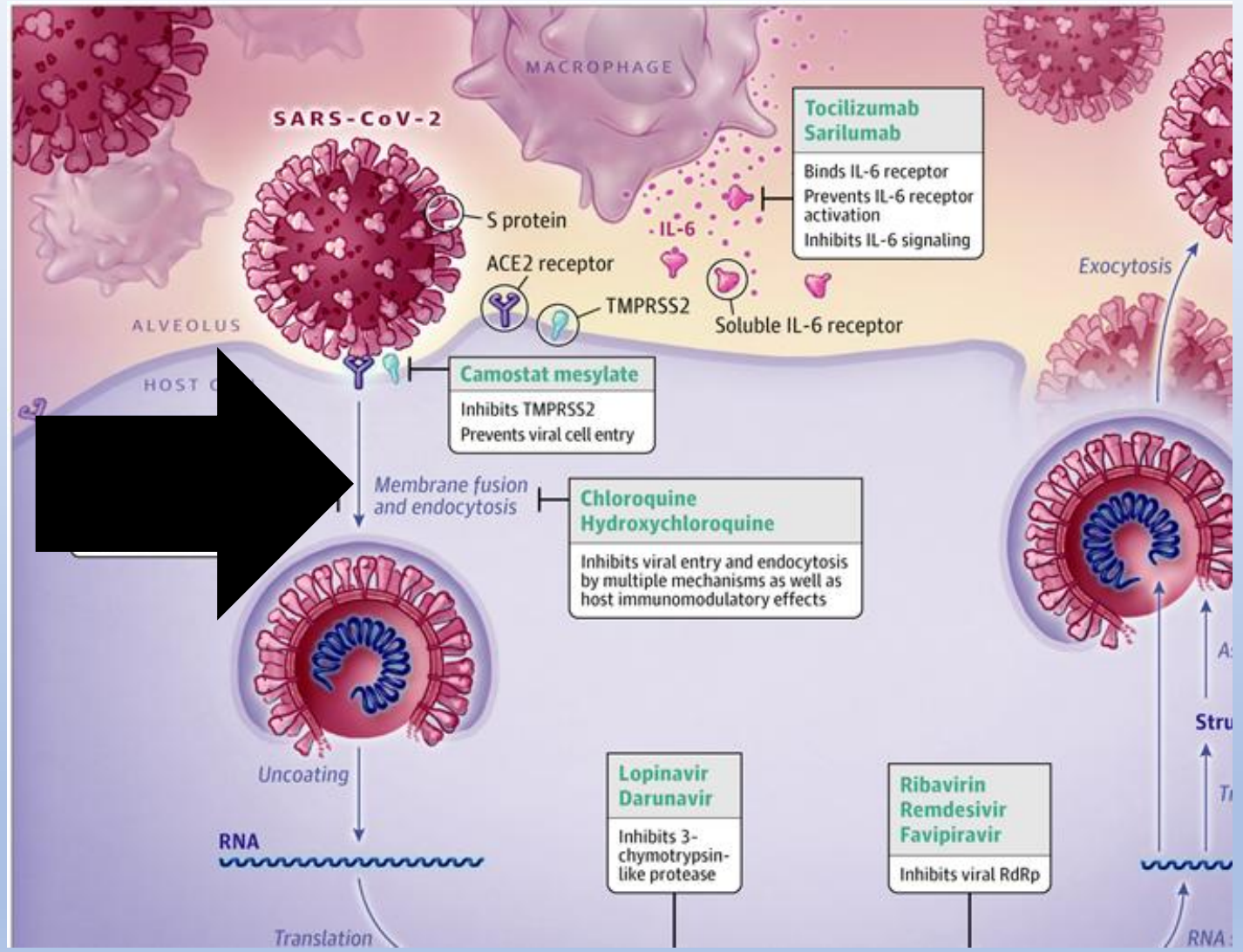
https://pubs.rsna.org/doi/10.1148/radiol.2020201187

Neurologic and Gastrointestinal

- Neurologic
  - Altered mental status and encephalopathy reported
  - Acute necrotizing encephalopathy in COVID-19 patients has also been reported with influenza and other viral illnesses, which may be secondary to cytokine storm
- Gastrointestinal
  - Preliminary, non-peer reviewed data from a Chinese study noted that digestive symptoms (anorexia, diarrhea, vomiting, and abdominal pain) were common

Chloroquine and Hydroxychloroquine

- Anti-malarials with immuno-modulatory activity and may have anti-inflammatory benefits
- Increases pH of cytoplasm
- Decreases virus binding to cell
- Decreases virus replication
- in vitro activity against MERS, COVID-19
- Concerns with QTc prolongation and retinopathy
  - Electrolyte abnormalities, congenital, drug interactions
- Acute poisonings very dangerous



https://jamanetwork.com/journals/jama/fullarticle/2764727

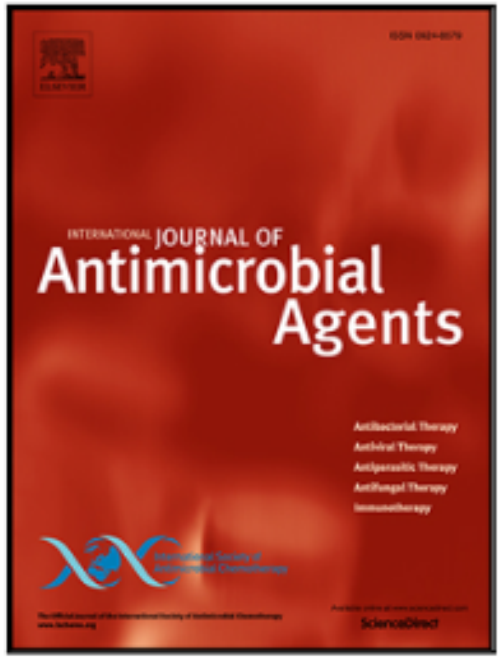
Azithromycin

- Azithromycin is a macrolide antibiotic with some antiviral and anti-inflammatory effects
  - in vitro activity against H1N1, Zika
- Suggested to be synergistic with hydroxychloroquine
- Drug shortages affecting ability to treat CAP
- QTc prolongation

Journal Pre-proof

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

Philippe Gautret , Jean-Christophe Lagier , Philippe Parola , Van Thuan Hoang , Line Meddeb , Morgane Mailhe , Barbara Doudier , Johan Courjon , Valérie Giordanengo , Vera Esteves Vieira , Hervé Tissot Dupont , Stéphane Honoré , Philippe Colson , Eric Chabrière , Bernard La Scola , Jean-Marc Rolain , Philippe Brouqui , Didier Raoult



PII: S0924-8579(20)30099-6
DOI: https://doi.org/10.1016/j.ijantimicag.2020.105949
Reference: ANTAGE 105949

To appear in: *International Journal of Antimicrobial Agents*

Hydroxychloroquine and Azithromycin

- 26 patients varying severity of illness treated with hydroxychloroquine compared to 16 controls
- 6 patients in the control arm also received azithromycin
- Notably, this study did not assess clinical benefit
- Viral clearance on day 6 of treatment was noted to be:
  - 100% in the hydroxychloroquine and azithromycin group (6 patients)
  - 57% in the hydroxychloroquine group
  - 12.5% in the control group

TITLE PAGE

Title: Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial

Running title: Hydroxychloroquine for COVID-19

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Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19

Joseph Magagnoli, M.S.[1,2,*], Siddharth Narendran, M.D.[4,5,*], Felipe Pereira M.D.[4,5,*], Tammy Cummings, Ph.D.[1], James W. Hardin, Ph.D.[3], S. Scott Sutton, Pharm.D.[1,2], Jayakrishna Ambati, M.D.[4,5,6,7]

https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

ABSTRACT

BACKGROUND

Hydroxychloroquine has been widely administered to patients with Covid-19 without robust evidence supporting its use.

METHODS

We examined the association between hydroxychloroquine use and intubation or death at a large medical center in New York City. Data were obtained regarding consecutive patients hospitalized with Covid-19, excluding those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline). The primary end point was a composite of intubation or death in a time-to-event analysis. We compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score.

RESULTS

Of 1446 consecutive patients, 70 patients were intubated, died, or discharged within 24 hours after presentation and were excluded from the analysis. Of the remaining

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CONCLUSIONS

In this observational study involving patients with Covid-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death. Randomized, controlled trials of hydroxychloroquine in patients with Covid-19 are needed. (Funded by the National Institutes of Health.)

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2012410?articleTools=true

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6·1%; 2·369, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; 3·561, 2·760–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretation We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

Funding William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

Interpretation We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

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Original Investigation

ONLINE FIRST FREE

May 11, 2020

Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg, PhD[1]; Elizabeth M. Dufort, MD[2]; Tomoko Udo, PhD[1]; et al

» Author Affiliations | Article Information

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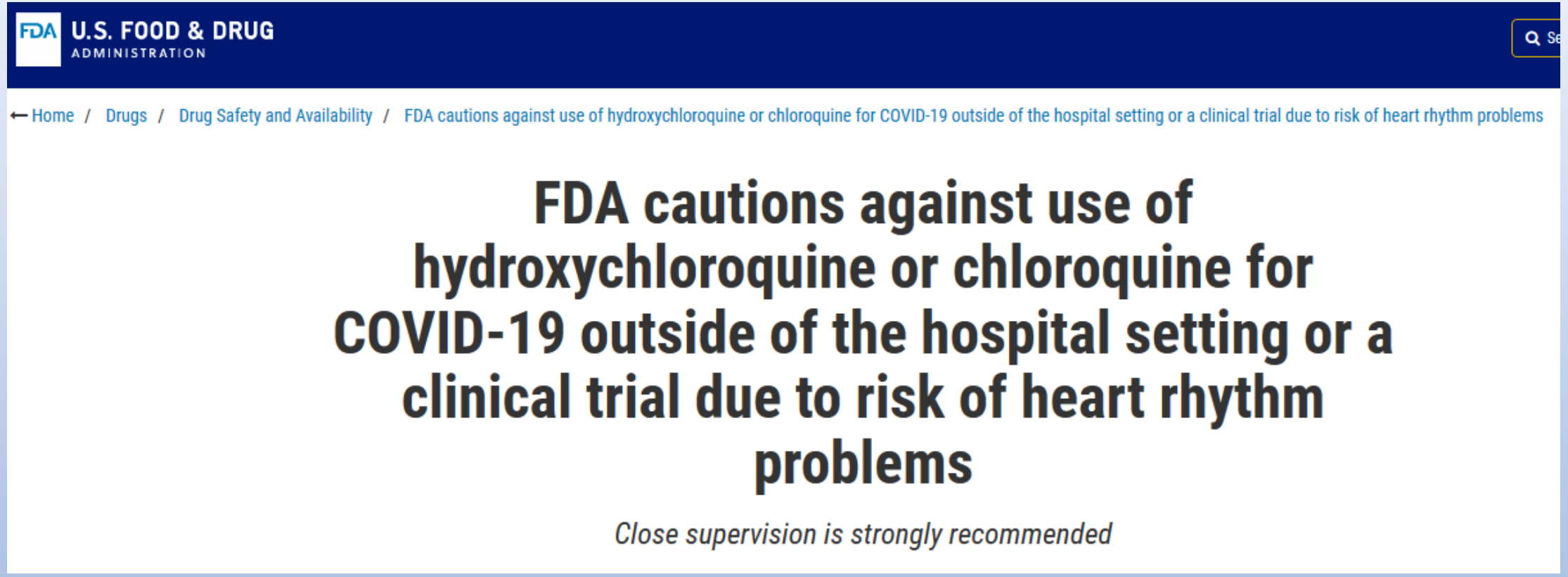
azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]). In logistic models, compared with patients receiving neither drug cardiac arrest was significantly more likely in patients receiving hydroxychloroquine+ azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]), but not hydroxychloroquine alone (adjusted OR, 1.91 [95% CI, 0.96-3.81]) or azithromycin alone (adjusted OR, 0.64 [95% CI, 0.27-1.56]), . In adjusted logistic regression models, there were no significant differences in the relative likelihood of abnormal electrocardiogram findings.

Conclusions and Relevance Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, the interpretation of these findings may be limited by the observational design.

https://jamanetwork.com/journals/jama/fullarticle/2766117

What About Zinc?

- Binds with RNA-dependent RNA polymerase
- Theory cannot make more viral proteins
- Increase pH facilitates
- Excessive doses can cause copper deficiency
- Magnesium?



https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

ABSTRACT

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treat-

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DOI: 10.1056/NEJMoa2007016

Remdesivir

- Investigational anti-viral agent
- Has in vitro and in vivo activity against Ebola, MERS, SARS and in vitro against COVID-19
- No longer providing for compassionate use ie, clinical trials
- Nucleotide analog inhibits RNA-dependent RNA polymerase
- Safety not established

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-

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*A complete list of members of the ACTT-1 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events

CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

This article was published on May 22, 2020, at NEJM.org.
DOI: 10.1056/NEJMoa2007764

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

ABSTRACT

BACKGROUND

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.

RESULTS

A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir–ritonavir group, and 100 to the standard-care group. Treatment with lopinavir–ritonavir was not associated with a

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Drs. Cao, Y. Wang, Wen, W. Liu, Jingli Wang, Fan, L. Ruan, Song, Cai, and M. Wei and Drs. D. Zhang and C. Wang contributed equally to this article.

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DOI: 10.1056/NEJMoa2001282

https://www.nejm.org/doi/full/10.1056/NEJMoa2001282

Lopinavir/Ritonavir

- FDA approved for treatment of HIV
- in vitro activity against other novel coronaviruses by inhibiting 3-chymotrypsin-like protease
- Has been used clinically in SARS and MERS
- Thought would be of most benefit early, 7-10 days, during peak viral replication
- NEJM study199 adult patients with severe COVID-19, lopinavir-ritonavir had no observed benefit
- Although unknown if could be beneficial in different subgroups or different regimens

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial

Ivan Fan-Ngai Hung, Kwok-Cheung Lung, Eugene Yuk-Keung Tso, Raymond Liu, Tom Wai-Hin Chung, Man-Yee Chu, Yuk-Yung Ng, Jenny Lo, Jacky Chan, Anthony Raymond Tam, Hoi-Ping Shum, Veronica Chan, Alan Ka-Lun Wu, Kit-Man Sin, Wai-Shing Leung, Wai-Lam Law, David Christopher Lung, Simon Sin, Pauline Yeung, Cyril Chik-Yan Yip, Ricky Ruiqi Zhang, Agnes Yim-Fong Fung, Erica Yuen-Wing Yan, Kit-Hang Leung, Jonathan Daniel Ip, Allen Wing-Ho Chu, Wan-Mui Chan, Anthony Chin-Ki Ng, Rodney Lee, Kitty Fung, Alwin Yeung, Tak-Chiu Wu, Johnny Wai-Man Chan, Wing-Wah Yan, Wai-Ming Chan, Jasper Fuk-Woo Chan, Albert Kwok-Wai Lie, Owen Tak-Yin Tsang, Vincent Chi-Chung Cheng, Tak-Lun Que, Chak-Sing Lau, Kwok-Hung Chan, Kelvin Kai-Wang To, Kwok-Yung Yuen

Summary

Background Effective antiviral therapy is important for tackling the coronavirus disease 2019 (COVID-19) pandemic. We assessed the efficacy and safety of combined interferon beta-1b, lopinavir–ritonavir, and ribavirin for treating patients with COVID-19.

Methods This was a multicentre, prospective, open-label, randomised, phase 2 trial in adults with COVID-19 who were admitted to six hospitals in Hong Kong. Patients were randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group). The primary endpoint was the time to providing a nasopharyngeal swab negative for severe acute respiratory syndrome coronavirus 2 RT-PCR, and was done in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT04276688.

Findings Between Feb 10 and March 20, 2020, 127 patients were recruited; 86 were randomly assigned to the combination group and 41 were assigned to the control group. The median number of days from symptom onset to start of study treatment was 5 days (IQR 3–7). The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010). Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. One patient in the control group discontinued lopinavir–ritonavir because of biochemical hepatitis. No patients died during the study.

Interpretation Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted.

Funding The Shaw Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and Sanming Project of Medicine.

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See Comment page 1670

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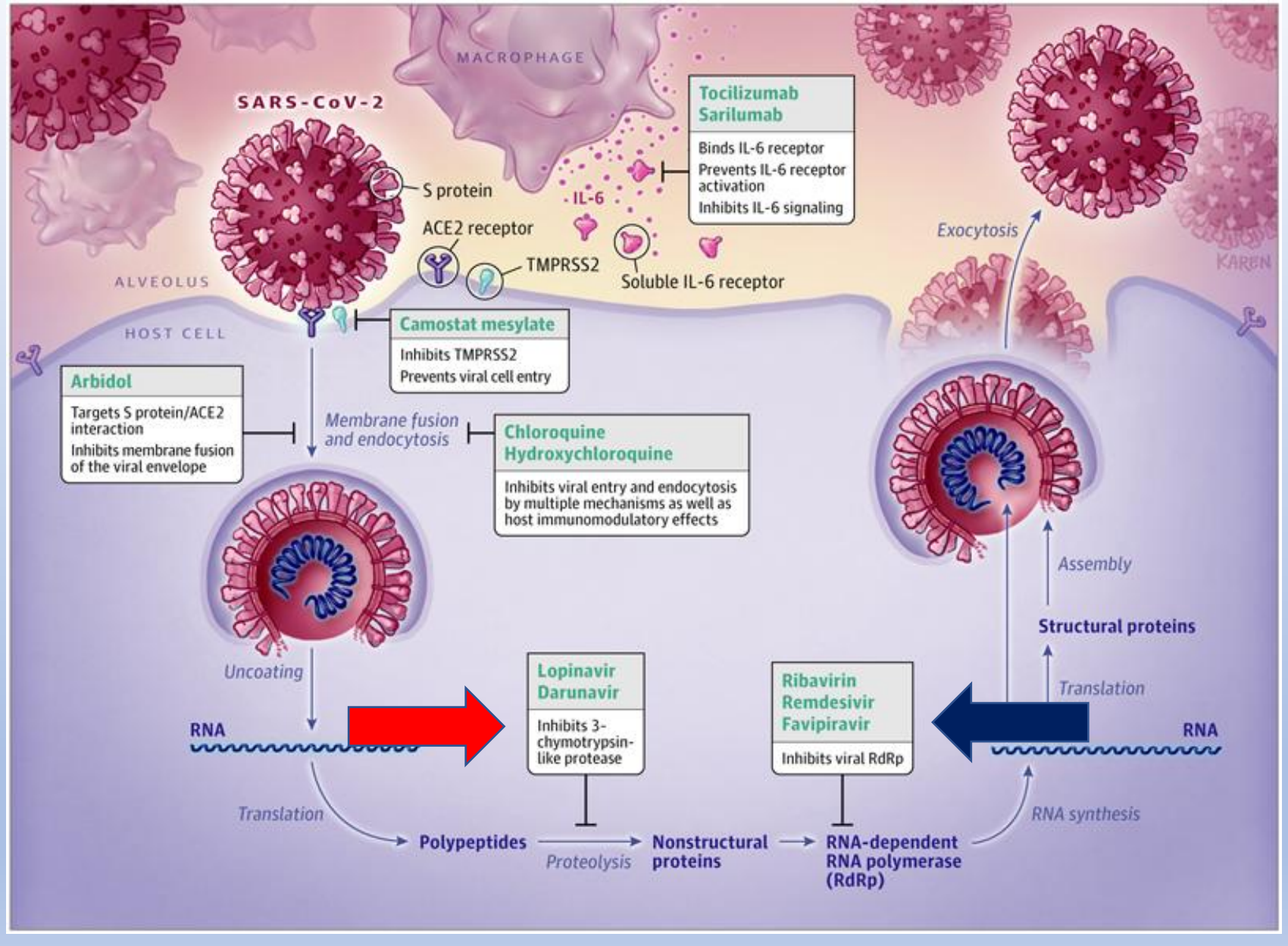
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext

Ribavirin

- Antiviral guanine analog inhibits viral RNA-dependent RNA polymerase
- Has *in vitro* activity against SARS but required high concentrations
- Did not show clinical benefit in SARS or MERS
- Severe dose-dependent hematologic toxicity eg, hemolytic anemia
- More than 60% of patients required blood transfusion
- Elevated transaminases
- Probably not beneficial, possibly as combination



https://jamanetwork.com/journals/jama/fullarticle/2764727

Communication

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Drug treatment options for the 2019-new coronavirus (2019-nCoV)

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[3] Department of Infectious Disease, Huashan Hospital Affiliated to Fudan University, Shanghai, China.

SUMMARY As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (2019-nCoV) have been reported in 25 provinces (districts and cities) in China. At present, there is no vaccine or antiviral treatment for human and animal coronavirus, so that identifying the drug treatment options as soon as possible is critical for the response to the 2019-nCoV outbreak. Three general methods, which include existing broad-spectrum antiviral drugs using standard assays, screening of a chemical library containing many existing compounds or databases, and the redevelopment of new specific drugs based on the genome and biophysical understanding of individual coronaviruses, are used to discover the potential antiviral treatment of human pathogen coronavirus. Lopinavir /Ritonavir, Nucleoside analogues, Neuraminidase inhibitors, Remdesivir, peptide (EK1), arbidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine, such ShuFengJieDu Capsules and Lianhuaqingwen Capsule, could be the drug treatment options for 2019-nCoV. However, the efficacy and safety of these drugs for 2019-nCoV still need to be further confirmed by clinical experiments.

Ostemalivir

- Oseltamivir neuraminidase inhibitor
- Antiviral properties against influenza viruses
- COVID-19 has overlapping features of influenza
- First described in influenza season 2019
- Patients treated for suspected flu
- Widely used in China but not shown to be clinically beneficial
- No data to support use in COVID-19

Ni et al. Critical Care (2019) 23:99
https://doi.org/10.1186/s13054-019-2395-8

Critical Care

RESEARCH Open Access

The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis

Yue-Nan Ni[1], Guo Chen[2], Jiankui Sun[3], Bin-Miao Liang[1*] and Zong-An Liang[1]

Abstract

Background: The effect of corticosteroids on clinical outcomes in patients with influenza pneumonia remains controversial. We aimed to further evaluate the influence of corticosteroids on mortality in adult patients with influenza pneumonia by comparing corticosteroid-treated and placebo-treated patients.

Methods: The PubMed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and Information Sciences Institute (ISI) Web of Science databases were searched for all controlled studies that compared the effects of corticosteroids and placebo in adult patients with influenza pneumonia. The primary outcome was mortality, and the secondary outcomes were mechanical ventilation (MV) days, length of stay in the intensive care unit (ICU LOS), and the rate of secondary infection.

Results: Ten trials involving 6548 patients were pooled in our final analysis. Significant heterogeneity was found in all outcome measures except for ICU LOS ($I^2 = 38\%$, $P = 0.21$). Compared with placebo, corticosteroids were associated with higher mortality (risk ratio [RR] 1.75, 95% confidence interval [CI] 1.30 ~ 2.36, $Z = 3.71$, $P = 0.0002$), longer ICU LOS (mean difference [MD] 2.14, 95% CI 1.17 ~ 3.10, $Z = 4.35$, $P < 0.0001$), and a higher rate of secondary infection (RR 1.98, 95% CI 1.04 ~ 3.78, $Z = 2.08$, $P = 0.04$) but not MV days (MD 0.81, 95% CI − 1.23 ~ 2.84, $Z = 0.78$, $P = 0.44$) in patients with influenza pneumonia.

Conclusions: In patients with influenza pneumonia, corticosteroid use is associated with higher mortality.

Trial registration: PROSPERO (ID: CRD42018112384).

Keywords: Corticosteroids, Influenza pneumonia, Mortality

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Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

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https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Original Investigation

ONLINE FIRST FREE

March 13, 2020

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

Chaomin Wu, MD[1,2,3]; Xiaoyan Chen, MD[3]; Yanping Cai, MD[2]; et al

» Author Affiliations | Article Information

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Corticosteroids

- Previous experience use in influenza, MERS and SARS
- Steroids in viral pneumonias
  - Potential harm
    - Prolonging viremia, increasing virus shedding and delaying viral clearance, ultimately increasing the risk of mortality
- Methylprednisolone
  - May be a mortality benefit for COVID-19 with ARDS treated with methylprednisolone.
  - Current evidence should be interpreted with caution: data are from one small study that examined the sickest patients.
- For adults with COVID-19 and refractory shock, some data suggests low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy

Corticosteroids

SSCCM Recommendations

- In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), do not recommend routine use of systemic corticosteroids (weak recommendation, low quality evidence)
- In mechanically ventilated adults with COVID-19 **and ARDS**, suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence)

https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

COVID-19: consider cytokine storm syndromes and immunosuppression

As of March 12, 2020, coronavirus disease 2019 (COVID-19) has been confirmed in 125 048 people worldwide, carrying a mortality of approximately 3·7%,[1] compared with a mortality rate of less than 1% from influenza. There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.[2] Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections[3] and occurs in 3·7–4·3% of sepsis cases.[4] Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.[3] A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α.[4] Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297·6 ng/ml in non-survivors vs 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001),[4] suggesting that mortality might be due to virally driven hyperinflammation.

As during previous pandemics (severe acute respiratory syndrome and Middle East respiratory syndrome), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury.[2] However, in hyperinflammation, immunosuppression is likely to be beneficial. Re-analysis of data from a phase 3 randomised controlled trial of IL-1 blockade (anakinra) in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events.[5] A multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin (ng/ml)	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The HScore™ generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.[11] HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 92 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Table: HScore for secondary HLH, by clinical parameter

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For the **HScore calculator** see https://saintantoine.aphp.fr/score/

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RESEARCH ARTICLE

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Tocilizumab treatment in COVID-19: A single center experience

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Abstract

Tocilizumab (TCZ), a monoclonal antibody against interleukin-6 (IL-6), emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms recently. In the present study, we aimed to discuss the treatment response of TCZ therapy in COVID-19 infected patients. The demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after TCZ therapy and clinical outcome in the 15 COVID-19 patients were retrospectively assessed. Totally 15 patients with COVID-19 were included in this study. Two of them were moderately ill, six were seriously ill and seven were critically ill. The TCZ was used in combination with methylprednisolone in eight patients. Five patients received the TCZ administration twice or more. Although TCZ treatment ameliorated the increased CRP in all patients rapidly, for the four critically ill patients who received an only single dose of TCZ, three of them (No. 1, 2, and 3) still dead and the CRP level in the rest one patient (No. 7) failed to return to normal range with a clinical outcome of disease aggravation. Serum IL-6 level tended to further spiked firstly and then decreased after TCZ therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in these four patients who failed treatment. TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. And for these critically ill patients with elevated IL-6, the repeated dose of the TCZ is recommended.

KEYWORDS

COVID-19, cytokine storms, interleukin-6, SARS-CoV-2, Tocilizumab

What is Role of IL6 in COVID?

- When virus infects cell eg, in alveolus starts cascade of proinflammatory chemicals eg, interleukins, TNF, interferons
- In COVID IL6 is predominant interleukin
- Makes blood vessels more permeable leading to cytokines moving into blood stream and increased pro inflammatory response
- Cytokine release syndrome “cytokine storm”
- Clinically see fever, hypotension, tachycardia, capillary leak, ARDS, MSOF

Tocilizumab

- Humanized monoclonal antibody specific for IL6 receptor blocks IL6 binding and systemic response
- FDA approved for
  - Giant cell arteritis
  - Rheumatoid arthritis
  - Cytokine release syndrome
- Adverse effects
  - Increased risk of infections
  - Hepatotoxicity
  - Leukopenia, thrombocytopenia

Article type: Original Research (Meta-Analysis)
Word count (without headers): 2842 (body), 199 (abstract)

Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis

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https://www.medrxiv.org/content/10.1101/2020.03.30.20048058v1.full.pdf

Tocilizumab

- Studies from China
- Recent meta analysis, non peer-reviewed
- Six studies included, 4 retrospective, 2 prospective, non randomized or controlled
- Tocilizumab showed clinically and mortality benefit
- All receiving other therapies but not uniform
- Questions about selection bias
- Promising

Janus Kinase (JAK) Inhibitors

Baricitinib as potential treatment for 2019-nCoV acute respiratory disease

Given the scale and rapid spread of the 2019 novel coronavirus (2019-nCoV) acute respiratory disease, there is an immediate need for medicines that can help before a vaccine can be produced. Results of rapid sequencing of 2019-nCoV, coupled with molecular modelling based on the genomes of related virus proteins,[1] have suggested a few compounds that are likely to be effective, including the anti-HIV lopinavir plus ritonavir combination.

BenevolentAI's knowledge graph is a large repository of structured medical information, including numerous connections extracted from scientific literature by machine learning.[2] Together with customisations bespoke to 2019-nCoV, we used BenevolentAI to search for approved drugs that could help, focusing on those that might block the viral infection process. We identified baricitinib, which is predicted to reduce the ability of the virus to infect lung cells.

Most viruses enter cells through receptor-mediated endocytosis. The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells (figure). These AT2 cells are particularly prone to viral infection.[3] One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles.[4]

Of 378 AAK1 inhibitors in the knowledge graph, 47 have been approved for medical use and six inhibited AAK1 with high affinity. These included a number of oncology drugs such as sunitinib and erlotinib, both of which have been shown to inhibit viral infection of cells through the inhibition of AAK1.[5] However, these compounds bring serious side-effects, and our data infer high doses to inhibit AAK1 effectively. We do not consider these drugs would be a safe therapy for a population of sick and infected people.

By contrast, one of the six high-affinity AAK1-binding drugs was the janus kinase inhibitor baricitinib, which also binds the cyclin G-associated kinase, another regulator of endocytosis.[6] Because the plasma concentration of baricitinib on therapeutic dosing (either as 2 mg or 4 mg once daily) is sufficient to inhibit AAK1, we suggest it could be trialled, using an appropriate patient population with 2019-nCoV acute respiratory disease, to reduce both the viral entry and the inflammation in patients, using endpoints such as the MuLBSTA score, an early warning model for predicting mortality in viral pneumonia.[7]

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAI, and has consulted with Lansdowne partners, Vitruvian, and Social Impact Capital; he now sits on the Board of Directors for

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How can these be beneficial in COVID?

- COVID-19 binds to ACE2 receptor enters cell through endocytosis
- There are regulators of endocytosis including AP2 Associated Protein Kinase 1 (AAK 1) and G-Associated Kinase
- Baricitinib FDA-approved oral JAK inhibitor used in the treatment of rheumatoid arthritis
  - In addition to being a JAK inhibitor baricitinib inhibits AAK 1 and GAK
- By blocking both kinases can block entry into cell and intracellular assembly of viral proteins

What about JAK Inhibition and COVID?

- JAK 1/JAK intracellular tyrosine kinase mediates cytokine signaling leading to inflammation
- Baricitinib and another JAK inhibitor ruxolitinib block JAK 1/JAK 2 preventing cytokine signaling
- This is thought to be of benefit as prevents cytokine storm but not specific like ILR6 antagonists
- May be of benefit a prevents more types of cytokines
- There are concerns some cytokines eg, IFN alpha may be beneficial and should not be blocked

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

Giulio Cavalli, Giacomo De Luca, Corrado Campochiaro, Emanuel Della-Torre, Marco Ripa, Diana Canetti, Chiara Oltolini, Barbara Castiglioni, Chiara Tassan Din, Nicola Boffini, Alessandro Tomelleri, Nicola Farina, Annalisa Ruggeri, Patrizia Rovere-Querini, Giuseppe Di Lucca, Sabina Martinenghi, Raffaella Scotti, Moreno Trevisiol, Fabio Ciceri, Giovanni Landoni, Alberto Zangrillo, Paolo Scarpellini, Lorenzo Dagna

Summary

Background Mortality of patients with coronavirus disease 2019 (COVID-19), acute respiratory distress syndrome (ARDS), and systemic inflammation is high. In areas of pandemic outbreak, the number of patients can exceed maximum capacity of intensive care units (ICUs), and, thus, these individuals often receive non-invasive ventilation outside of the ICU. Effective treatments for this population are needed urgently. Anakinra is a recombinant interleukin-1 receptor antagonist that might be beneficial in this patient population.

Methods We conducted a retrospective cohort study at the San Raffaele Hospital in Milan, Italy. We included consecutive patients (aged ≥18 years) with COVID-19, moderate-to-severe ARDS, and hyperinflammation (defined as serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both) who were managed with non-invasive ventilation outside of the ICU and who received standard treatment of 200 mg hydroxychloroquine twice a day orally and 400 mg lopinavir with 100 mg ritonavir twice a day orally. We compared survival, mechanical ventilation-free survival, changes in C-reactive protein, respiratory function, and clinical status in a cohort of patients who received additional treatment with anakinra (either 5 mg/kg twice a day intravenously [high dose] or 100 mg twice a day subcutaneously [low dose]) with a retrospective cohort of patients who did not receive anakinra (referred to as the standard treatment group). All outcomes were assessed at 21 days. This study is part of the COVID-19 Biobank study, which is registered with ClinicalTrials.gov, NCT04318366.

Findings Between March 17 and March 27, 2020, 29 patients received high-dose intravenous anakinra, non-invasive ventilation, and standard treatment. Between March 10 and March 17, 2020, 16 patients received non-invasive ventilation and standard treatment only and comprised the comparison group for this study. A further seven patients received low-dose subcutaneous anakinra in addition to non-invasive ventilation and standard treatment; however, anakinra treatment was interrupted after 7 days because of a paucity of effects on serum C-reactive protein and clinical status. At 21 days, treatment with high-dose anakinra was associated with reductions in serum C-reactive protein and progressive improvements in respiratory function in 21 (72%) of 29 patients; five (17%) patients were on mechanical ventilation and three (10%) died. In the standard treatment group, eight (50%) of 16 patients showed respiratory improvement at 21 days; one (6%) patient was on mechanical ventilation and seven (44%) died. At 21 days, survival was 90% in the high-dose anakinra group and 56% in the standard treatment group (p=0·009). Mechanical ventilation-free survival was 72% in the anakinra group versus 50% in the standard treatment group (p=0·15). Bacteraemia occurred in four (14%) of 29 patients receiving high-dose anakinra and two (13%) of 16 patients receiving standard treatment. Discontinuation of anakinra was not followed by inflammatory relapses.

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See Comment page e310

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Interpretation In this retrospective cohort study of patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients. Confirmation of efficacy will require controlled trials.

Introduction

As of April 29, 2020, the coronavirus disease 2019 (COVID-19) pandemic has affected 3 018 681 people worldwide, causing the death of 207 973.[1] Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the main cause of death.[2] Mortality in patients with COVID-19 and ARDS who are admitted to the intensive care unit (ICU) is high: a study of 24 patients reported that 50% had died at 14 days,[3] whereas mortality in other reports ranges from 28% to 78%.[2,4] Mortality is increased in patients with pronounced systemic inflammation.[2]

In areas where the COVID-19 pandemic is overwhelming, the number of patients with COVID-19 and ARDS can exceed the maximum capacity of ICUs.[5] As a shortage of ICU beds has emerged, with an unsettling

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext

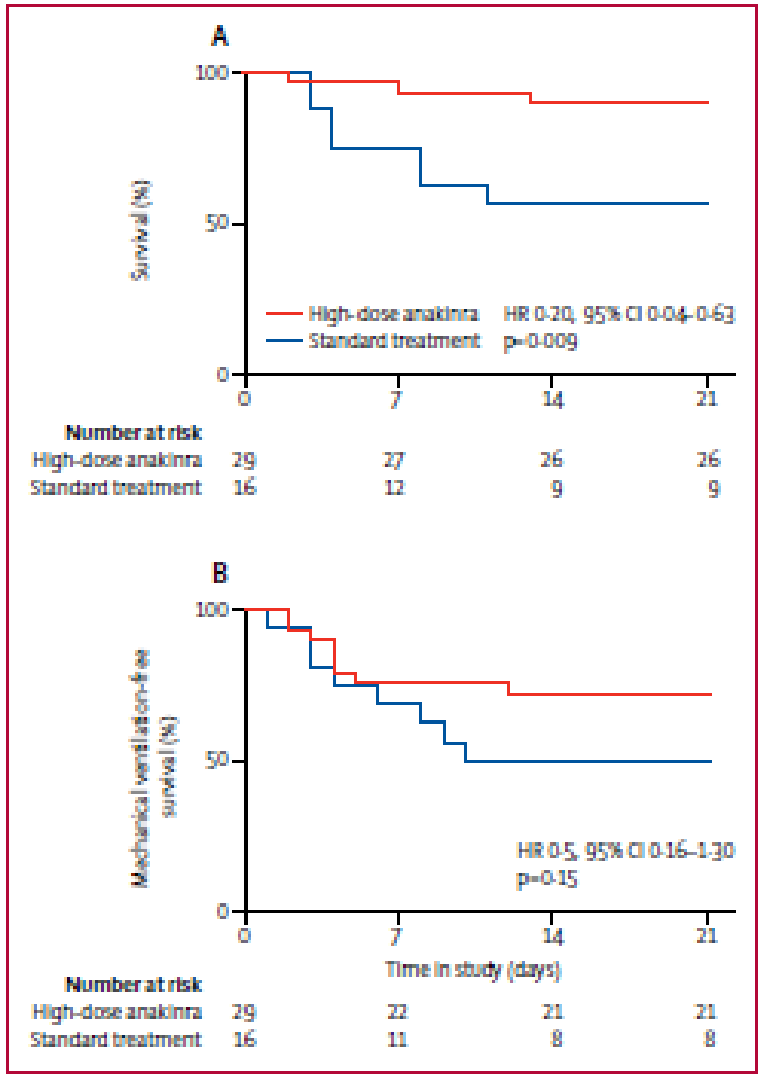

Figure 1: Survival and mechanical ventilation-free survival at 21 days
Plots show survival (A) and mechanical ventilation-free survival (B) at 21 days of patients with COVID-19, ARDS, and hyperinflammation managed outside the intensive care unit with CPAP and high-dose anakinra (n=29) or receiving CPAP and standard treatment only (n=16). For mechanical ventilation-free survival (B), death and mechanical ventilation were considered equivalent to treatment failure. COVID-19=coronavirus disease 2019. ARDS=acute respiratory distress syndrome. CPAP=continuous positive airway pressure. HR=hazard ratio.

IVERMECTIN

Antiviral Research
Available online 3 April 2020, 104787
In Press, Journal Pre-proof

The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

Leon Caly [1], Julian D. Druce [1], Mike G. Catton [1], David A. Jans [2], Kylie M. Wagstaff [2]

Show more

https://doi.org/10.1016/j.antiviral.2020.104787

https://www.sciencedirect.com/science/article/pii/S0166354220302011

IVERMECTIN
In vitro Studies

Positive Sense RNA

- West Nile
- Dengue (in vivo, but not clinical)
- SARS
- MERS
- SARS CoV-2 ?
- *Zika*
- *Chikungunya*
- HIV
- Hep C

Negative Sense RNA

- Ebola
- Hanta
- **Newcastle** (avian)
- **Influenza** (in vivo)

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Original Article

The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design

Spyridon G. Deftereos [1,*], Gerasimos Siasos [1], Georgios Giannopoulos [2], Dimitrios A. Vrachatis [1,3], Christos Angelidis [1], Sotiria G. Giotaki [1], Panagiotis Gargalianos [4], Helen Giamarellou [1,5], Charalampos Gogos [6], Georgios Daikos [1,7], Marios Lazanas [8], Pagona Lagiou [1], Georgios Saroglou [1,9], Nikolaos Sipsas [1], Sotirios Tsiodras [1], Dimitrios Chatzigeorgiou [10], Nikolaos Moussas [4], Anastasia Kotanidou [1], Nikolaos Koulouris [1], Evangelos Oikonomou [1], Andreas Kaoukis [2], Charalampos Kossyvakis [2], Konstantinos Raisakis [2], Katerina Fountoulaki [11], Mihalis Comis [11], Dimitrios Tsiachris [4], Eleni Sarri [1],

https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2395-8

Colchicine

- Inhibitor of microtubule polymerization and leukocyte infiltration used for gout and pericarditis
- Anti-inflammatory action may be beneficial for COVID
- NLRP3 inflammasome inhibitor
- Colchicine inhibits inflammasome
  - Inhibits P2X7 receptor activation
  - Inhibits ASC polymerization
  - Decreases interleukin production
  - Unknown if this is beneficial or detrimental

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journal homepage: www.elsevier.com/locate/lifescie

COVID-19: Melatonin as a potential adjuvant treatment

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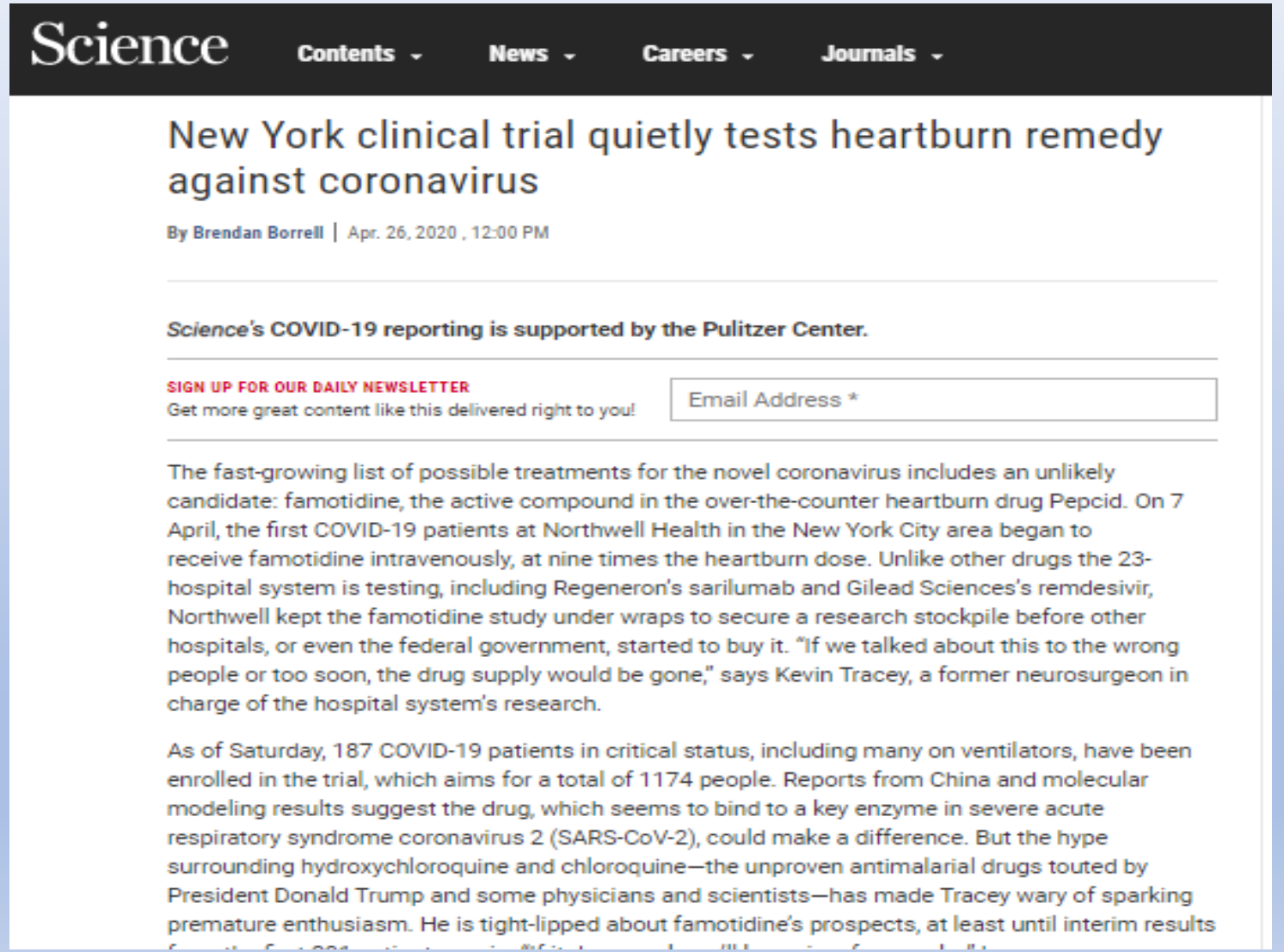
ABSTRACT

This article summarizes the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis. The recent outbreak of COVID-19 has become a pandemic with tens of thousands of infected patients. Based on clinical features, pathology, the pathogenesis of acute respiratory disorder induced by either highly homogenous coronaviruses or other pathogens, the evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response very likely contribute to COVID-19 pathology. This leads to a cytokine storm and subsequent progression to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and often death. Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against ALI/ARDS caused by viral and other pathogens. Melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients. Notably, melatonin has a high safety profile. There is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients. Additional experiments and clinical studies are required to confirm this speculation.

Melatonin

- Anti-oxidant
- Anti-inflammatory
- Safe
- May decrease interleukin
- Inhibits pro-interleukins
- Unknown if this is beneficial or detrimental

Famotidine



Science Contents News Careers Journals

New York clinical trial quietly tests heartburn remedy against coronavirus

By Brendan Borrell | Apr. 26, 2020 , 12:00 PM

Science's COVID-19 reporting is supported by the Pulitzer Center.

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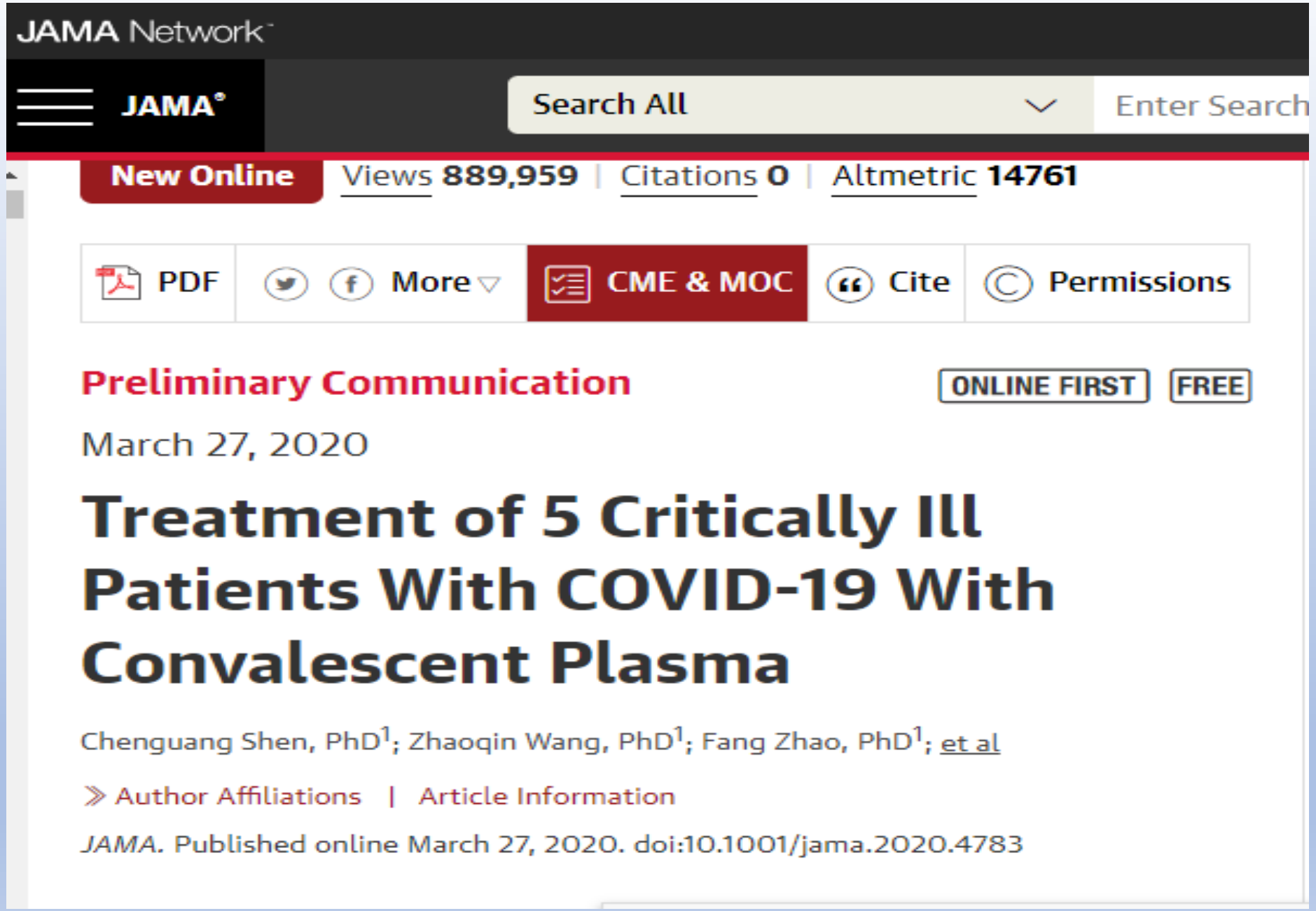
The fast-growing list of possible treatments for the novel coronavirus includes an unlikely candidate: famotidine, the active compound in the over-the-counter heartburn drug Pepcid. On 7 April, the first COVID-19 patients at Northwell Health in the New York City area began to receive famotidine intravenously, at nine times the heartburn dose. Unlike other drugs the 23-hospital system is testing, including Regeneron's sarilumab and Gilead Sciences's remdesivir, Northwell kept the famotidine study under wraps to secure a research stockpile before other hospitals, or even the federal government, started to buy it. "If we talked about this to the wrong people or too soon, the drug supply would be gone," says Kevin Tracey, a former neurosurgeon in charge of the hospital system's research.

As of Saturday, 187 COVID-19 patients in critical status, including many on ventilators, have been enrolled in the trial, which aims for a total of 1174 people. Reports from China and molecular modeling results suggest the drug, which seems to bind to a key enzyme in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could make a difference. But the hype surrounding hydroxychloroquine and chloroquine—the unproven antimalarial drugs touted by President Donald Trump and some physicians and scientists—has made Tracey wary of sparking premature enthusiasm. He is tight-lipped about famotidine's prospects, at least until interim results



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Passive Immunity

- Have large amount of experience with passive immunity
  - Including animal exposures
- Rabies immunoglobulin (Human)
- Rattlesnake antivenom (horse, sheep)
- Convalescent plasma for infections

Convalescent Plasma

- Immunoglobulins from recovered person to infected person
- Passive immunity
- Prophylactically
- Treatment
- Has been used for over one hundred years

How Does Convalescent Plasma Work

- Recovered person donates blood
- Plasma containing IgG antibodies removed from whole blood
- Administer to infected person
  - does not have enough or any IgG of own
- IgG ideally neutralizes the virus
  - may have other actions
- Though short-lived may allow ill person to clinically improve potential role in high-risk patients following exposure

Why Should We Consider Convalescent Plasma in COVID?

- SARS-CoV2 is a novel virus
- Humans do not have immunity until exposed and recovered
- No current proven medical therapies or vaccines available
- Large number of critically-ill patients making convalescent plasma an attractive potential therapy

History of Convalescent Plasma

- First used in late 1890s sporadically
- Given in Spanish Influenza in early 1900s
- Has been used in measles, mumps, polio, others
- More recent use in H1N1 influenza and Ebola
- Has also been used for other coronaviruses
  - including SARS and MERS

JAMA

Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma

- Case series of five patients
- Patients had lab confirmation of COVID-19
- Three men, two women, ages 36-73 years, on mechanical ventilation
- All received other therapies including antivirals
- Had clinical improvement and decreased viral load
- Caveat: small numbers, not randomized, one institution

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REVIEW

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Convalescent plasma transfusion for the treatment of COVID-19: Systematic review

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Abstract

The recent emergence of coronavirus disease 2019 (COVID-19) pandemic has reassessed the usefulness of historic convalescent plasma transfusion (CPT). This review was conducted to evaluate the effectiveness of CPT therapy in COVID-19 patients based on the publications reported till date. To our knowledge, this is the first systematic review on convalescent plasma on clinically relevant outcomes in individuals with COVID-19. PubMed, EMBASE, and Medline databases were searched upto 19 April 2020. All records were screened as per the protocol eligibility criteria. We included five studies reporting CPT to COVID-19 patients. The main findings from available data are as follows: (a) Convalescent plasma may reduce mortality in critically ill patients, (b) Increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy, and (c) Beneficial effect on clinical symptoms after administration of convalescent plasma. Based on the limited scientific data, CPT therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality. Well-designed large multicenter clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients.

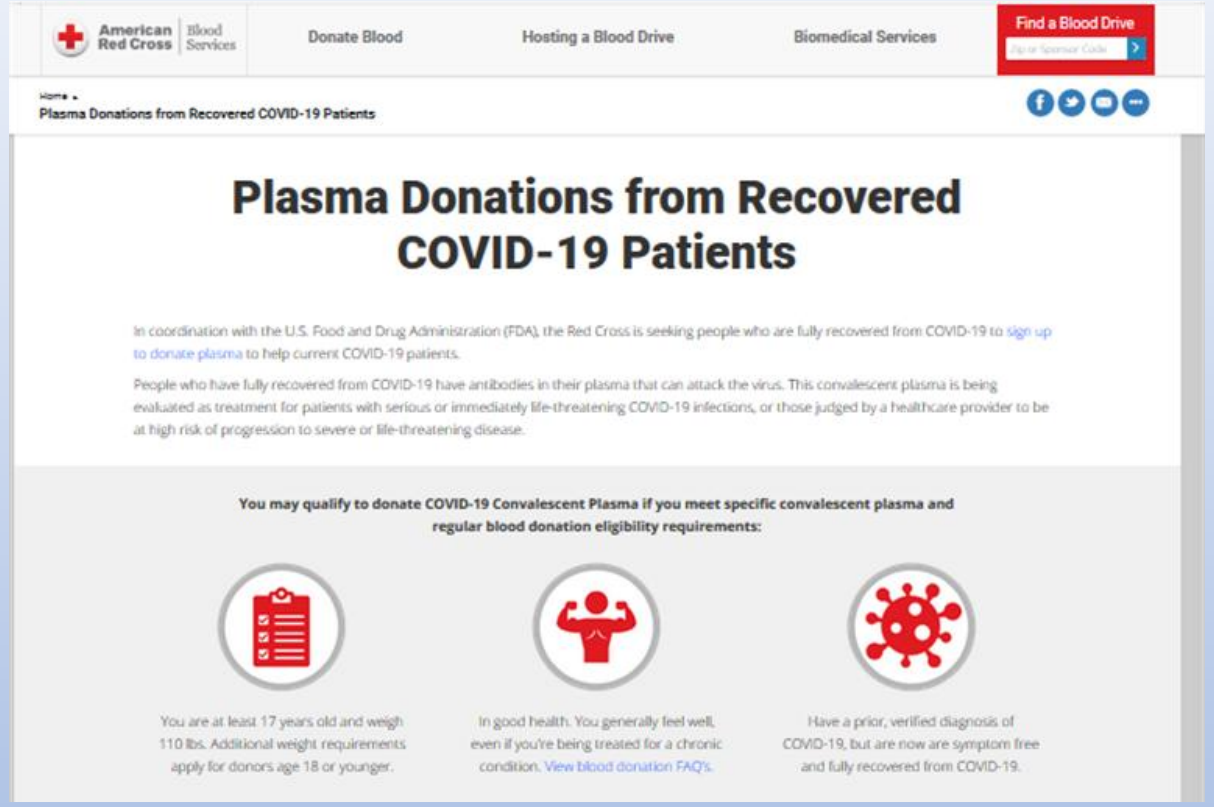
convalescent plasma. Based on the limited scientific data, CPT therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality. Well-designed large multicenter clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/jmv.25961

Are There Risks With Administration of Convalescent Plasma?

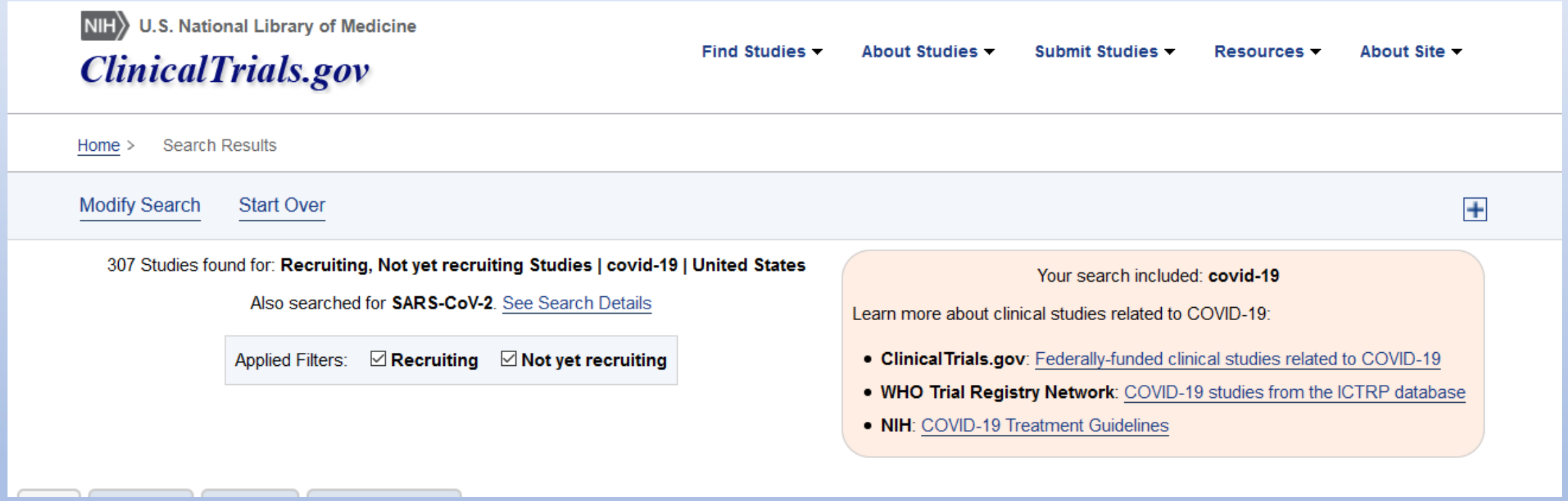
- Lack of large randomized controlled trials
- As blood product risk of transmission of blood-borne pathogens to receiving patient
  - Widespread screening of pathogens greatly reduces this risk
- May impair recipients ability to fight infection over long term
- Serum sickness
- Transfusion reactions

How Does Covid-Recovered Patient Donate or Clinician Obtain Convalescent Plasma?



- https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html

ClinicalTrials.gov

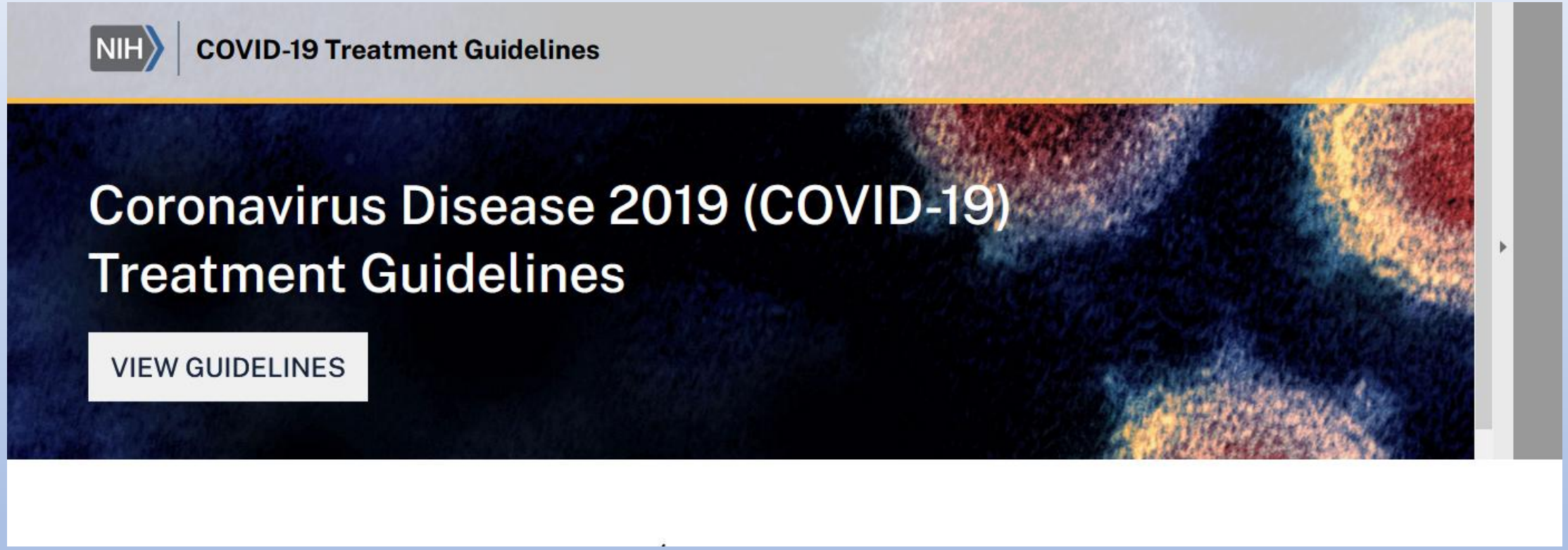


https://clinicaltrials.gov/ct2/results?recrs=ab&cond=covid-19&term=&cntry=US&state=&city=&dist=

As of 06/01/20

Conclusion

- COVID-19 complex disease
- No widespread immunity
- Many medications being considered but none proven or FDA approved
- These agents should be used only as part of clinical trials
- Data changing all the time
- Refer to websites CDC, ASHP, WHO, FDA



https://covid19treatmentguidelines.nih.gov/

NIH | COVID-19 Treatment Guidelines

Home / What's New

What's New

Introduction

What's New in the Guidelines

Last Updated: May 12, 2020

Remdesivir:

- On the basis of preliminary clinical trial data, the Panel recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO_2 ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation **(BI)**.
    - Remdesivir is not approved by the Food and Drug Administration (FDA); however, it is available through an FDA emergency use authorization for the treatment of hospitalized adults and children with COVID-19. Remdesivir is also being investigated in clinical trials, and it is available through an emergency access program for children and pregnant patients.
- The Panel **does not recommend remdesivir** for the treatment of mild or moderate COVID-19 outside the setting of a clinical trial **(AIII)**.

Chloroquine/Hydroxychloroquine:

- The Panel **recommends against** using **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**, because the high dose carries a higher risk of toxicities than the lower dose.
- The FDA warning that cautioned against the use of chloroquine or hydroxychloroquine for COVID-19 outside the setting of a hospital or clinical trial was added to this section.

https://covid19treatmentguidelines.nih.gov/whats-new/

What's New in the Guidelines

Last Updated: May 12, 2020

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

The following key changes were made to this section:

Convalescent Plasma and Immune Globulins:

- New information has been added to the section on convalescent plasma and SARS-CoV-2-specific immune globulins.
- A new section for non-SARS-CoV-2 intravenous immune globulin (IVIG) was created, in which the Panel **recommends against** the use of **non-SARS-CoV-2-specific IVIG** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Interleukin-6 Inhibitors:

- New data from an interim review of a Phase 2/3 clinical trial for sarilumab have been included.
- New preliminary results from a clinical trial for tocilizumab (CORIMUNO-TOCI) have been added.
- There is no change to the Panel's recommendation for IL-6 inhibitors. There are insufficient data to recommend either for or against the use of **IL-6 inhibitors** (e.g., **sarilumab, siltuximab, tocilizumab**) for the treatment of COVID-19 **(AIII)**.

https://covid19treatmentguidelines.nih.gov/whats-new