COVID-19: Prevention, Diagnosis, Treatment Options AONM



June 11th, 2020



Dr. Richard Horowitz,

 Medical Director HVHAC, Hyde Park, N.Y., Board Certified Int Medicine Member, HHS Tick-Borne Disease Working Group 2017-2019
 Co-chair, HHS Other Tick-borne Diseases and Co-infections, 2017-2019
 Member, HHS Babesia and Tick-borne Pathogens Subcommittee, 2019

Disclaimer/Conflicts of Interest

Conflicts of Interest:

- St Martin's Press: royalties for two books: "Why Can't I Get Better?" and "How Can I Get Better?"
- Xymogen Board of Advisors, stock, honorariums
- Grants: Bay Area Lyme Foundation, MSIDS Research Foundation
- Disclaimer: The views expressed in this presentation do not represent the views of the Tick-Borne Disease Working Group, HHS or the United States

CORONAVIRUSES: OVERVIEW

- Coronaviruses (COVs): first characterized in the 1960s, they are a large family of enveloped, positive-strand RNA viruses with spike glycoproteins that cause a substantial proportion of URT inf's in children and adults
- 7 CoVs are known to cause human disease, either of low or highly pathogenic potential
- Kahn JS, McIntosh K. History and Recent Advances in Coronavirus Discovery. Pediatr Infect Dis J. 2005;24(11):S223. doi:10.1097/01.inf.0000188166.17324.60
- Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. Cell Stress. March 2020. doi:10.15698/cst2020.04.216
- To KKW, Hung IFN, Chan JFW, Yuen K-Y. From SARS coronavirus to novel animal and human coronaviruses. J Thorac Dis. 2013;5 Suppl 2:S103-108. doi:10.3978/j.issn.2072-1439.2013.06.02

3 HIGHLY PATHOGENIC COV'S

- SARS coronavirus (SARS-CoV, now named SARS-CoV-1)
- The Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV)
- SARS-CoV-2, the agent of COVID-19, identified in patients in Wuhan, China w/severe PN
- Xu J, Zhao S, Teng T, et al. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. Viruses. 2020;12(2):244. doi:10.3390/v12020244
- Bigging HO | Severe Acute Respiratory Syndrome (SARS). WHO. https://www.who.int/csr/sars/en/.
- Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814-1820. doi:10.1056/NEJMoa1211721
- He F, Deng Y, Li W. Coronavirus disease 2019: What we know? J Med Virol. n/a(n/a). doi:10.1002/jmv.25766

Viral shedding and Incubation

- The median incubation period is 4-5 days
- After becoming infected, 97.5% of people will have symptoms within 11.5 days
- Viral shedding can happen up to 3 days before becoming symptomatic, & 40% to 50% of cases are likely transmitted from asymptomatic individuals

- Gandi R, et al. Mild or Moderate COVID-19. NEJM, Apr 24, 2020
- https://www.nejm.org/doi/pdf/10.1056/NEJMcp2009249



Early Prodromal Symptoms

Anosmia, hyposmia and dysgeusia = 88%

- Followed days later by fever (91.7%), chills, cough (75.0%), SOB, fatigue (75.0%), GI symptoms including N+, V+, diarrhea (39.6%).
- A sore throat, headache, myalgias and rarely conjunctivitis, hemoptysis have been reported
- Coronavirus Disease 2019: Resources. American Academy of Otolaryngology-Head and Neck Surgery. https://www.entnet.org/content/coronavirus-disease-2019-resources. Published March 15, 2020. Accessed March 29, 2020.
- Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. February 2020. doi:10.1111/all.14238
- Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-286. doi:10.1007/s12098-020-03263-6

Significance of Anosmia

- Very few diseases cause a sudden loss or decreased sense of smell and/or taste: 1*: trauma, rhinosinusitis/nasal polyps, viral inf's
- 5% of people exhibit functional anosmia (age)
- 25% of people > 50 y.o. have impaired smell
- Also seen in early neurodegenerative dx (Alzheimers, PD, Lewy body dementia)
- Hummel T, Landis BN, Hüttenbrink K-B. Smell and taste disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2012;10. doi:10.3205/cto000077
- Murphy C, Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Prevalence of Olfactory Impairment in Older Adults. JAMA. 2002;288(18):2307-2312. doi:10.1001/jama.288.18.2307
- Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. Science. 1984;226(4681):1441-1443. doi:10.1126/science.6505700
- Hüttenbrink K-B, Hummel T, Berg D, Gasser T, Hähner A. Olfactory Dysfunction: Common in Later Life and Early Warning of Neurodegenerative Disease. Dtsch Ärztebl Int. 2013;110(1-2):1-7.

5 Categories of Derm Manifestations with COVID-19

- 5 Skin manif's: pseudo-chilblain (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapules (47%), and livedo or necrosis (6%)
- Pseudo-chilblain lesions affect younger patients with less severe disease (bottom left)
- Vesicular lesions: affect middle age, intermediate severity
- Urticarial, maculopapular, and livedoid/necrotic lesions were all associated with more severe disease
 DID British Journal of Dermatology







ORIGINAL ARTICLE

Free Access

Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases

'COVID TOES': Early Sx, ? Only Sx "Purple lesions" on Feet (or hands)



Early Prodromal CNS Symptoms: Confusion, ANE, Stroke

- Altered brain function can be an early sign: HA's, confusion, seizures, tingling & numbness
- Worst complication: Acute Necrotizing Encephalopathy (ANE)

Large Vessel Stroke in the Young

Figure 2a: MRI images demonstrate T2 FLAIR hyperintensity within the bilateral medial temporal lobes and thalami (A, B, E, F) with evidence of hemorrhage indicated by hypointense signal intensity and rim enhancement on postcontrast images (D, H).



- Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. New England Journal of Medicine. 2020;0(0):e60. doi:10.1056/NEJMc2009787
- Neo Poyiadji et al., COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Images in Radiology. Published Online:Mar 31 2020https://doi.org/10.1148/radiol.2020201187

Neuroinflammation & Blood Brain Barrier Disruption: COVID PCR + On LP Welcome, M., Inflammopharmacology 2020, Springer Nature

Neuropathophysiology of coronavirus disease 2019: Neuroinflammation and blood brain barrier disruption are critical pathophysiological processes that contribute to the clinical sym...

Preprint · May 2020

SARS-CoV-2 possesses neurotropic properties (Wu et al. 2020b) and has been implicated in

neurological diseases including Guillain-Barré syndrome, Miller Fisher syndrome, polyneuritis

cranialis and epilepsy (Gutiérrez-Ortiz et al. 2020; Zhao et al. 2020b) as well as cerebral stroke

Other Neuro Complications: GBS, MS, Acute Disseminated Encephalomyelitis *ADEM

- Post-infectious, immune-mediated complications in the convalescent period are possible
- Viral RNA can be found within brain tissue & CSF
- Meningitis, encephalitis, acute flaccid paralysis
- Direct neuronal injury in brainstem cardiorespir centers
- Autoimmune inflammatory and demyelinating syndromes seen in susceptible individuals
- Carlos A. Pérez, MD. Looking ahead: The risk of neurologic complications due to COVID-19. NeurClinPrac. DOI: 10.1212. CPJ.00000000000836

SEVERE COMPLICATIONS

- Severe complications include: Novel Coronavirus Pneumonia (NCP) with or without acute respiratory distress syndrome (ARDS) and respiratory failure
- Organ function damage with cardiac injury and fulminate myocarditis, pneumothorax, liver dysfunction & acute kidney injury
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. March 2020. doi:10.1007/s00134-020-05991-x
- 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;0(0). doi:10.1016/S2213-2600(20)30079-5

Cardiac Complications: Acute COVID-19 CV Syndrome (ACovCS)

Description and Proposed Management of the Acute COVID-19

Cardiovascular Syndrome

Running Title: Hendren et al.; Acute COVID-19 Cardiovascular Syndrome

Nicholas S. Hendren, MD1; Mark H. Drazner, MD, MSc1; Biykem Bozkurt, MD, PhD2;

Leslie T. Cooper, Jr., MD3

- Due to cytokine storm: myocarditis, microvascular injury, stress rel cardiomyopathy
- Cardiac arrythmias, clinical CHF can result
- 个 Troponin, CV stable → no need for extensive cardiac imaging

1/3 Pts Have Liver Abnormalities: Higher % on Lopinovir/Ritonavir

PANCREAS, BILIARY TRACT, AND LIVER

Clinical Features of COVID-19-Related Liver Functional Abnormality



Zhenyu Fan,^{*,a} Liping Chen,^{*,a} Jun Li,^{*} Xin Cheng,^{*} Jingmao Yang,^{*} Cheng Tian,^{*} Yajun Zhang,^{*} Shaoping Huang,^{*} Zhanju Liu,[‡] and Jilin Cheng^{*}

*Department of Gastroenterology and Hepatology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China; and [‡]Department of Gastroenterology, The Shanghai Tenth People's Hospital of Tongji University, Shanghai, China

BACKGROUND & AIMS:	Some patients with SARS-CoV-2 infection have abnormal liver function. We aimed to clarify the features of COVID-19-related liver damage to provide references for clinical treatment.
METHODS:	We performed a retrospective, single-center study of 148 consecutive patients with confirmed COVID-19 (73 female, 75 male; mean age, 50 years) at the Shanghai Public Health Clinical Center from January 20 through January 31, 2020. Patient outcomes were followed until February 19, 2020. Patients were analyzed for clinical features, laboratory parameters (including liver function tests), medications, and length of hospital stay. Abnormal liver function was defined as increased levels of alanine and aspartate aminotransferase, gamma glutamyl-transferase, alkaline phosphatase, and total bilirubin.
RESULTS:	Fifty-five patients (37.2%) had abnormal liver function at hospital admission; 14.5% of these patients had high fever (14.5%), compared with 4.3% of patients with normal liver function ($P = .027$). Patients with abnormal liver function were more likely to be male, and had higher levels of procalcitonin and C-reactive protein. There was no statistical difference between groups in medications taken before hospitalization: a significantly higher proportion of patients

Acute kidney injury (AKI) in patients hospitalized with COVID-19



Hirsch JS, et al. Nephrology COVID-19 Research Consortium, ACUTE KIDNEY INJURY IN PATIENTS HOSPITALIZED WITH COVID-19, Kidney International (2020), doi: <u>https://doi.org/10.1016/j.kint.2020.05.006</u>.

How Many People Will Get Sick From COVID? Look at Risk Factors



Risk Factors COVID-19

- Advanced age (≥ 65), male gender, race (African-American), obesity, smoking history
- Prior medical histories: HTN, DM, CV and respiratory disease (asthma, emphysema), Hemorrhagic or ischemic strokes, immunosuppression, cancer, chronic kidney and liver disease & secondary infections
- Shi Y, et al. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care. 2020;24. doi:10.1186/s13054-020-2833-7
- Garg S. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69. doi:10.15585/mmwr.mm6915e3
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl. March 2020.

ACEI/ARB Therapy: No 个 Risk

Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study

Francisco J de Abajo, Sara Rodríguez-Martín, Victoria Lerma, Gina Mejía-Abril, Mónica Aguilar, Amelia García-Luque, Leonor Laredo, Olga Laosa, Gustavo A Centeno-Soto, Maria Ángeles Gálvez, Miguel Puerro, Esperanza González-Rojano, Laura Pedraza, Itziar de Pablo, Francisco Abad-Santos, Leocadio Rodríguez-Mañas, Miguel Gil, Aurelio Tobías, Antonio Rodríguez-Miguel, Diego Rodríguez-Puyol, on behalf of the MED-ACE2-COVID19 study group*

Summary

Background Concerns have been raised about the possibility that inhibitors of the renin–angiotensin–aldosterone system (RAAS) could predispose individuals to severe COVID-19; however, epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19.

Methods In this case-population study, we consecutively selected patients aged 18 years or older with a PCRconfirmed diagnosis of COVID-19 requiring admission to hospital from seven hospitals in Madrid, who had been admitted between March 1 and March 24, 2020. As a reference group, we randomly sampled ten patients per case, individually matched for age, sex, region (ie, Madrid), and date of admission to hospital (month and day; index date), from Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP), a Spanish primary health-care database, in its last available year (2018). We extracted information on comorbidities and prescriptions up to the month before index date (ie, current use) from electronic clinical records of both cases and controls. The outcome of interest was admission to hospital of patients with COVID-19. To minimise confounding by indication, the main analysis focused on assessing the association between COVID-19 requiring admission to hospital and use of RAAS inhibitors compared with use of other antihypertensive drugs. We calculated odds ratios (ORs) and 95% CIs, adjusted for age, sex, and cardiovascular comorbidities and risk factors, using conditional logistic regression. The protocol of the study was registered in the EU electronic Register of Post-Authorisation



Published Online May 14, 2020 https://doi.org/10.1016/ 50140-6736(20)31030-8 See Comment page 1671 *Listed at the end of the Article Clinical Pharmacology Unit (Prof F I de Abajo PhD. S Rodriguez-Martin PhD, V Lerma RN, A Rodriguez-Miguel PhD) and Department of Nephrology (Prof D Rodríguez-Puyol PhD), University Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain; Department of **Biomedical Sciences** (Pharmacology Section)

Lancet 2020; 395: 1705-14

↑ HbA1c: **↑** Risk Inflammation, Hypercoagulability, Poorer Prognosis



Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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



International Diabetes Federation



Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients



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ARTICLE INFO

Article history: Received 3 May 2020 Accepted 7 May 2020

ABSTRACT

Background: Diabetes is a risk factor for the progression and prognosis of coronavirus disease (COVID-19), but the relationship between glycosylated hemoglobin (HbA1c) level, inflammation, and prognosis of COVID-19 patients has not been explored. Methods: This was a retrospective study of COVID-19 patients who underwent an HbA1c test. Their demographic data, medical history, signs and symptoms of COVID-19, laboratory test results, and final outcomes of COVID-19 treatment were collected and analyzed.

Varmanda

Is Low T A Risk Factor in Older Men?

https://www.sciencetimes.com/articles/25685/20200514/men-hypogonadism-leading-low-testosterone-levelsmore-die-coronavirus-study.htm

- Of the 35 male COVID-19 patients in an ICU at a German hospital, > than 68% had low levels of test
- The majority of female patients had elevated testosterone levels. Of all the participants in the study, nine men and three women died
- Sex hormones are involved in the process of how the immune system starts an inflammatory response to pathogens
- Need a larger, controlled study
- FU: 71-79% men in 2 Spanish studies admitted to hospitals had low T

Bald Men At Higher Risk Of Severe **Coronavirus Symptoms**

o//www.forbes.com/stec/martan/ling/2020/06/06/bald-main-at-Nation-Six of severa-nearus-senutran/K24cdSbl225e4



Genetic Risks: Type A Blood, Gene Loci on Chromosome 3 (CCL-2 SNP) Lower risks: Type O Blood (23 & Me)

Genes May Leave Some People More Vulnerable to Severe Covid-19

Geneticists have turned up intriguing links between DNA and the disease. Patients with Type A blood, for example, seem to be at greater risk.

https://www.nytimes.com/2020/06/03/health/coronavirus-blood-typegenetics.html?campaign_id=154&emc=edit_cb_20200604&instance_id=19100&nl=coronavirusbriefing®i_id=103987437&segment_id=30119&te=1&user_id=a2c3fadde0fc78562ace8fa1d14b7b07



Risk in Children: Rare Cases of Kawasaki Dx: Inflammation Bl. Vessels, Toxic Shock

https://www.nytimes.com/2020/05/05/nyregion/children-Kawasaki-syndrome-coronavirus.

15 Children Are Hospitalized With Mysterious Illness Possibly Tied to Covid-19

The health authorities in New York City issued an alert saying that the children had a syndrome that doctors do not yet fully understand.



Pregnancy: The Placenta Can Be Affected

A small study of 16 pregnant women w/ Covid-19 found evidence of injury to the placenta: insufficient blood flow from the mother to the fetus and blood clots in the placenta. ? Need to test the O2 delivery of the placenta during pregnancy and follow the intrauterine growth via ultrasounds, although the babies were healthy

Covid-19 appears to attack placenta during pregnancy, study says

By Sandee LaMotte, CNN Updated 4:32 PM ET, Fri May 22, 2020



Now Playing Fear, panic as women navigate pregnancy during a pandemic

Risk Is Lower At High Altitudes

https://www.wvgazettemail.com/washington_post/international/from-the-andes-to-tibet-the-coronavirusseems-to-be-sparing-populations-at-high-altitudes/article_e2c145af-f774-51fd-ae0b-e4d6597eabc3.html

- From the Andes to Tibet, COVID-19 seems to be sparing populations at high altitudes
- May be due to a combination of an ability to cope with hypoxia and a natural environment hostile to the virus — dry mountain air, high levels of UV radiation and the possibility that lower barometric pressure reduces the virus's ability to linger in the air
- Also, acclimatization to oxidative stress at high altitude and ↑ GSH levels may play a role: After 13 months at ↑ altitude, plasma total antioxidant status (TAS) improved by 21% & glutathione levels by 32.8%

https://pubmed.ncbi.nlm.nih.gov/16351564/

Risk Is Increased With Air Pollution

First nationwide study linking exposure to PM 2.5 to COVID death rates (Harvard, in peer review)



Exposure to air pollution and COVID-19 mortality in the United States: A nationwide cross-sectional study

View ORCID ProfileXiao Wu, View ORCID ProfileRachel C. Nethery, Benjamin M. Sabath, Danielle Braun, Francesca Dominici **doi:** https://doi.org/10.1101/2020.04.05.20054502

Inflammation: common denominator in environmental toxin exposure & chronic disease

Horowitz, R.I., The Global Rise of Chronic Diseases: Why Broaden the Paradigm to Include Tick-borne Illness and Environmental Toxin Exposure? Arch Med Case Rep. 2019, Volume 1, Issue 1.

The 3 l's: Infection, Immune Dysfunction, Inflammation



https://www.scientificarchives.com/journal/archives-of-medical-case-reports

Archives of Medical Case Reports

Short Communication

The Global Rise of Chronic Diseases: Why Broaden the Paradigm to Include Tick-borne Illness and Environmental Toxin Exposure?

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RISKS BY THE NUMBERS: April 2020

- April 2020: As of April 11, 2020 almost 1.7 million people worldwide had been infected
- Global mortality rates over time are around
 5.7% converging with current WHO estimates
- US: Based on death certificates, % of deaths attributed to PN, influenza or COVID-19 (PIC) ranged from 14.6%-23.6% during week 16-17
- Coronavirus. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed April 12, 2020.
- Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020;0(0). doi:10.1016/S1473-3099(20)30195-X
- https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Risks By the Numbers: May 22, 2020

- More than 5 million people have now been infected with COVID 19 worldwide: This translates into 1 million new infections in 2 weeks (NYT, May 22, 2020)
- New coronavirus cases have emerged in northeast China, Iran & US states that have loosened restrictions. Now at 100k, 5/28



WHO Worldwide: Almost At 7 Million, 400,000 Deaths, June 9th



WHO Numbers: June 9, 2020 Coronavirus disease (COVID-19)

Situation Report – 139

Data as received by WHO from national authorities by 10:00 CEST, 07 June 2020

Situation in numbers (by WHO Region)

Total (new cases in last 24 hours)

Globally	6 799 713 cases (136 409)	397 388 deaths (4 586)
Africa	131 324 cases (4 763)	3 148 deaths (86)
Americas	3 234 875 cases (79 505)	179 394 deaths (3 227)
Eastern Mediterranean	623 684 cases (18 658)	14 326 deaths (302)
Europe	2 268 311 cases (18 312)	183 732 deaths (604)
South-East Asia	350 542 cases (13 965)	9 672 deaths (356)
Western Pacific	190 236 cases (1 206)	7 103 deaths (11)

NYT: June 11th, 2020: Daily Country Curves

How new cases are changing by day



Putting the Risk of Covid-19 in Perspective The New York Times, David C. Roberts, May 22, 2020

- A useful way to understand risks is by comparing them with a "micromort," which measures a one-in-amillion chance of dying (aver risk/day = 1 micromort)
- General anesthesia in the US (5 micromorts)
- Skydiving (7 micromorts per jump)



- Driving a motorcycle 44 mi every day (11 micromorts per day)
- Giving birth in the United States (210 micromorts)
- An individual living in New York City has experienced roughly
 50 additional micromorts of risk per day because of Covid-19
- If you're infected with the virus, your odds of dying jump dramatically: 1% case fatality rate = 10,000 micromorts

Establishing a Clinical Risk Score:

Age, CXR, Dyspnea, Hemoptysis, Unconsciousness, Co-morbidities, Cancer, Neutrophil/lymphocyte ratio, LDH, Direct Bilirubin JAMA Intern Med. Published online May 12, 2020

Research

JAMA Internal Medicine | Original Investigation

Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19

Wenhua Liang, MD; Hengrui Liang, MD; Limin Ou, MD; Binfeng Chen, MD; Ailan Chen, MD; Caichen Li, MD; Yimin Li, MD; Weijie Guan, MD; Ling Sang, MD; Jiatao Lu, MD; Yuanda Xu, MD; Guoqiang Chen, MD; Haiyan Guo, MD; Jun Guo, MD; Zisheng Chen, MD; Yi Zhao, MD; Shiyue Li, MD; Nuofu Zhang, MD; Nanshan Zhong, MD; Jianxing He, MD; for the China Medical Treatment Expert Group for COVID-19

IMPORTANCE Early identification of patients with novel corona virus disease 2019 (COVID-19) who may develop critical illness is of great importance and may aid in delivering proper treatment and optimizing use of resources.

OBJECTIVE To develop and validate a clinical score at hospital admission for predicting which patients with COVID-19 will develop critical illness based on a nationwide cohort in China.

DESIGN, SETTING, AND PARTICIPANTS Collaborating with the National Health Commission of China, we established a retrospective cohort of patients with COVID-19 from 575 hospitals in 31 provincial administrative regions as of January 31, 2020. Epidemiological, clinical, laboratory, and imaging variables ascertained at hospital admission were screened using

Supplemental content

Establishing a Clinical Risk Score: LDH, Lymphocyte Ct, HS-CRP !

machine intelligence

ARTICLES

Check for updates

An interpretable mortality prediction model for COVID-19 patients

Li Yan^{1,10}, Hai-Tao Zhang^{2,10}, Jorge Goncalves^{3,4,10}, Yang Xiao², Maolin Wang², Yuqi Guo², Chuan Sun², Xiuchuan Tang⁵, Liang Jing¹, Mingyang Zhang², Xiang Huang², Ying Xiao², Haosen Cao², Yanyan Chen⁶, Tongxin Ren⁷, Fang Wang¹, Yaru Xiao¹, Sufang Huang¹, Xi Tan⁸, Niannian Huang⁸, Bo Jiao⁸, Cheng Cheng², Yong Zhang⁹, Ailin Luo⁸, Laurent Mombaerts⁰³, Junyang Jin⁷, Zhiguo Cao², Shusheng Li¹¹², Hui Xu¹¹⁰, and Ye Yuan¹¹²

The sudden increase in COVID-19 cases is putting high pressure on healthcare services worldwide. At this stage, fast, accurate and early clinical assessment of the disease severity is vital. To support decision making and logistical planning in healthcare systems, this study leverages a database of blood samples from 485 infected patients in the region of Wuhan, China, to identify crucial predictive biomarkers of disease mortality. For this purpose, machine learning tools selected three biomarkers that predict the mortality of individual patients more than 10 days in advance with more than 90% accuracy: lactic dehydrogenase (LDH), lymphocyte and high-sensitivity C-reactive protein (hs-CRP). In particular, relatively high levels of LDH alone seem to play a crucial role in distinguishing the vast majority of cases that require immediate medical attention. This finding is consistent with current medical knowledge that high LDH levels are associated with tissue breakdown occurring in various diseases,

Establishing a Clinical Risk Score: Key Numbers for LDH, hs-CRP, lymph's



Lymphocytopenia, Low CD4/CD8 counts: Key Clinical Indicators of Severe Dx

IL-6, IL-8 also 个

Cite this article as: Zhang, X. et al. Viral and host factors related to the clinic outcome of COVID-19. *Nature* https://doi.org/10.1038/ s41586-020-2355-0 (2020).

Article

Viral and host factors related to the clinical outcome of COVID-19

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Xiaonan Zhang^{1,7}, Yun Tan^{2,7}, Yun Ling^{1,7}, Gang Lu^{2,7}, Feng Liu^{2,7}, Zhigang Yi^{1,4,7}, Xiaofang Jia¹, Min Wu¹, Bisheng Shi¹, Shuibao Xu¹, Jun Chen¹, Wei Wang¹, Bing Chen², Lu Jiang², Shuting Yu², Jing Lu², Jinzeng Wang², Mingzhu Xu¹, Zhenghong Yuan⁴, Qin Zhang⁵, Xinxin Zhang³, Guoping Zhao⁶, Shengyue Wang², Saijuan Chen², Hongzhou Lu¹

In December 2019, the Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus SARS-CoV-2, emerged in Wuhan, Hubei province, China¹ and soon spread across the world. In this ongoing pandemic, public health concerns and the urgent need for effective therapeutic measures require a deep understanding of its epidemiology, transmissibility and pathogenesis. Here we analyzed the clinical, molecular and immunological data from 326 confirmed cases of COVID-19 in Shanghai. Genomic sequences of SARS-CoV-2 assembled from 112 quality samples together with sequences in the Global Initiative on Sharing All Influenza Data (GISAID) showed a stable evolution and suggested two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Nevertheless, they exhibited similar virulence and clinical outcomes. Lymphocytopenia, especially the
APACHE II Score ≥ 17 Predicts Death

Critical Care Medicine: May 01, 2020 - Volume Online First - Issue doi: 10.1097/CCM.00000000004411

Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019

Xiaojing Zou, MD¹; Shusheng Li, MD¹; Minghao Fang, MD¹; Ming Hu, MM²; Yi Bian, MD¹; Jianmin Ling, MM¹; Shanshan Yu, MD¹; Liang Jing, MD¹; Donghui Li, MM¹; Jiao Huang, PhD³

Objectives: Coronavirus disease 2019 has emerged as a major global health threat with a great number of deaths in China. We aimed to assess the association between Acute Physiology and Chronic Health Evaluation II score and hospital mortality in patients with coronavirus disease 2019, and to compare the predictive ability of Acute Physiology and Chronic Health Evaluation II score, with Sequential Organ Failure Assessment score and Confusion, Urea, Respiratory rate, Blood pressure, Age 65 (CURB65) score.

Design: Retrospective observational cohort.

Setting: Tongji Hospital in Wuhan, China.

Subjects: Confirmed patients with coronavirus disease 2019 hospitalized in the ICU of Tongji hospital from January 10, 2020, to February 10, 2020.

Interventions: None.

Measurements and Main Results: Of 178 potentially eligible patients with symptoms of coronavirus disease 2019, 23 patients (12.92%) were diagnosed as suspected cases, and one patient (0.56%) suffered from cardiac arrest immediately after admission. Ultimately, 154 patients were enrolled in the analysis and 52 patients (33.77%) died. Mean Acute Physiology and Chronic Health Evaluation II score (23.23±6.05) was much higher in deaths compared with the mean Acute Physiology and Chronic Health Evaluation II score of 10.87±4.40 in survivors (p < 0.001). Acute Physiology and Chronic Health Evaluation II score was independently associated with hospital mortality (adjusted bazard

strated better discriminative ability (area under the curve, 0.966; 95% Cl, 0.942–0.990) than Sequential Organ Failure Assessment score (area under the curve, 0.867; 95% Cl, 0.808–0.926) and CURB65 score (area under the curve, 0.844; 95% Cl, 0.784–0.905). Based on the cut-off value of 17, Acute Physiology and Chronic Health Evaluation II score could predict the death of patients with coronavirus disease 2019 with a sensitivity of 96.15% and a specificity of 86.27%. Kaplan-Meier analysis showed that the survivor probability of patients with coronavirus disease 2019 with Acute Physiology and Chronic Health Evaluation II score less than 17 was notably higher than that of patients with Acute Physiology and Chronic Health Evaluation II score greater than or equal to 17 ($\rho < 0.001$).

Conclusions: Acute Physiology and Chronic Health Evaluation II score was an effective clinical tool to predict hospital mortality in patients with coronavirus disease 2019 compared with Sequential Organ Failure Assessment score and CURB65 score. Acute Physiology and Chronic Health Evaluation II score greater than or equal to 17 serves as an early warning indicator of death and may provide guidance to make further clinical decisions. (*Crit Care Med* 2020; XX:00–00)

Key Words: Acute Physiology and Chronic Health Evaluation II score; coronavirus disease 2019; mortality; risk factor; severe acute respiratory syndrome coronavirus 2

5 Support Targets For COVID-19:

Foundation, Antioxidant/Anti-inflammatory, Support NK/Th1

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery Yanuck et al. Immuno-physiological Approach to COVID-19. Integrative Medicine, Vol. 19, No. S1 Epub Ahead of Print

Figure 1. Five Targets of Support as they apply to the four Phases in the time course of disease. It's essential that if the patient moves from the Infection Phase to the Escalating Inflammation Phase, the emphasis shifts to downregulation of the potentially life-threatening inflammatory process.



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ARTICLE INFO

Keywords: COVID-19 Cytokine storm syndrome Macrophage activation syndrome Pneumonia ARDS DIC N-Acetyl-cysteine Glutathione NF-xB

ABSTRACT

Purpose: Asymptomatic or minimally symptomatic infection with COVID-19 can result in silent transmission to large numbers of individuals, resulting in expansion of the pandemic with a global increase in morbidity and mortality. New ways of screening the general population for COVID-19 are urgently needed along with novel effective prevention and treatment strategies.

Hypothesis: A hypothetical three-part prevention, diagnostic, and treatment approach based on an up-to-date scientific literature review for COVID-19 is proposed. Regarding diagnosis, a validated screening questionnaire and digital app for COVID-19 could help identify individuals who are at risk of transmitting the disease, as well as those at highest risk for poor clinical outcomes. Global implementation and online tracking of vital signs and scored questionnaires that are statistically validated would help health authorities properly allocate essential

Pathogenicity of COVID-19

- "Cytokine storm syndrome" with ARDS is the primary cause of death. Also:
- Fulminant myocarditis w/ multiorgan dys(f)
- Uncontrolled systemic inflammatory response
 ↑ large amounts of pro-inflammatory
 cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18,
 IL-33, TNF-α, TGFβ, etc.) & chemokines
 (CXCL9, CXCL10, etc.) by immune effector cells
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
- Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. March 2020. doi:10.1016/j.jpha.2020.03.001

Pathogenicity of COVID-19:

- We also can see: Secondary hemophagocytic lymphohistiocytosis (sHLH), also known as Macrophage Activation Syndrome (MAS)
- This is a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure
- Seen in approximately 4% of cases triggered by viral infections and/or sepsis
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-1034.
- Adult haemophagocytic syndrome The Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61048-X/fulltext. Accessed April 12
- Karakike E, Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. Front Immunol. 2019;10. doi:10.3389/fimmu.2019.00055

Cardinal features of sHLH/MAS*

- Unremitting fever, cytopenia's, low or absent natural killer (NK) cell activity, HSM, hepatobiliary dysfunction (HBD), coagulopathy, high ferritin levels (≥500 ng/ml), fasting triglycerides ≥265 mg/dl w/ fibrinogen ≤150 mg/dl
- Pulmonary involvement with ARDS can occur in up to 50% of patients. All these are seen in fatal complications from COVID-19
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-1034.
- Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. Chest. 2016;149(5):1294-1301. doi:10.1016/j.chest.2015.11.004

Macrophage Activation Syndrome

- MAS has been reported in AI disorders & viral inf's
- Pathogenesis: ↑ activation of macrophages and NK cells → ↑↑ interleukin (IL)-1β over-secretion leads cytokine storm of IL-6, IL-18, ferritin, and IF-gamma
- High ferritin levels = diagnostic hallmark of MAS
- Ferritin measurements within the first 24 hours can be used as a diagnostic biomarker of MAS
- IL-18 also can promote human MAS
- Karakike E, Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. Front Immunol. 2019;10
- Rosado FGN, Kim AS. Hemophagocytic LymphohistiocytosisAn Update on Diagnosis and Pathogenesis. Am J Clin Pathol. 2013;139(6):713-727.
- Rosário C, et al. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013;11:185

Pulmonary involvement in HLH/MAS

- Dyspnea and cough were the most common symptoms at the onset of the disease
- CXR's: interstitial infiltrates w/ centrilobular nodules,
- Ill-defined consolidation
- Ground-glass opacities
 (GGO, crazy paving pat)



Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. Chest. 2016;149(5):1294-1301.



Figure 2: Chest CT findings of COVID-19 pneumonia on transaxial images. (a) GGO; (b) crazy-paving pattern (GGO with superimposed inter- and intralobular septal thickening); (c) Consolidation. All images have the same window level of -600 and window width of 1600.



Acute Resp Distress Syndrome (ARDS)

- 81% of critically ill COVID-19 patients develop life-threatening ARDS, hypoxemic respiratory failure → mechanical ventilation, and/or hypotension requiring vasopressor treatment
- ARDS is caused by lung inflammation & ↑ alveolar endothelial and epithelial permeabilities → protein-rich pulmonary edema w/ severe hypoxemia and ↓ CO2 excretion
- Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a singlecentered, retrospective, observational study – The Lancet Respiratory Medicine <u>https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/fulltext</u>
- Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically III Patients in the Seattle Region Case Series. N Engl J Med. 2020;0(0):null.

Etiology of ARDS Lung Injury

- Neutrophil & platelet-dependent damage to the endothelial and epithelial barriers of the lung, frequently caused by pneumonia
- Neutrophils become activated → ↑ toxic mediators including reactive oxygen species (ROS), proinflammatory cytokines (TNF-α, IL-6, IL-8) & procoagulant molecules
- Synergistic interaction w/ platelets ↑ damage
- Matthay MA, Zemans RL. The Acute Respiratory Distress Syndrome: Pathogenesis and Treatment. Annu Rev Pathol. 2011;6:147-163.
- Looney MR, et al. Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. J Clin Invest. 2009;119(11):3450-3461.

Procoagulant Effect/Coagulopathy

- A procoagulant effect with coagulopathy and anti-phospholipid antibodies has recently been reported in patients with Covid-19
- These abnormal coagulation parameters are associated with a poorer prognosis in patients with novel coronavirus pneumonia (NCP)
- Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020;0(0):null.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847. doi:10.1111/jth.14768

What Can We Do To Lower The Risk of Dying on a Ventilator?



Deep down in my heart, I am terrified, I am afraid that the old lady cannot tolerate HFNC and her condition will continue to worsen...

NCP: Control Inflammation with Steroids, IV Vitamin C, Heparin?

https://covid19criticalcare.com/wp-content/uploads/2020/04/MATHPressRelease.pdf

Front Line COVID-19 Critical Care Working Group Urges Immediate Adoption of "MATH+"—Early Intervention Protocol for Any ER or Hospitalized Patient Developing Breathing Difficulty

A Treatment Strategy Directed at Suppressing Hyper-Inflammation to Reduce the Need for Ventilators & Save Lives

Intravenous Methylprednisolone • High Dose Intravenous Ascorbic Acid (Vitamin C) • Full Dose Low Molecular Weight Heparin • PLUS optional Treatment components

NEW YORK, NY: Leading critical care specialists at five academic or major hospitals who together have formed the *Front Line COVID-19 Critical Care Working Group*, have released MATH+ —a protocol for treating patients who arrive in hospitals with COVID-19.



Based on available research, the experience in China

reflected by the Shanghai expert commission, and their decades-long professional experiences in Intensive Care Units around the country, the five experts strongly urge fellow physicians to immediately adopt a change in strategy by using MATH+; delivering powerful therapies earlier in the disease course, prior to admission to the ICU or the need for a mechanical ventilator.

Based on early experiences with this more aggressive approach, they predict that early adoption of MATH+ will reduce ICU admissions, obviate the need for mechanical ventilators, and most importantly, save many lives.

"If you can administer intravenous corticosteroids and ascorbic acid starting in the Emergency Room and every 6 hours thereafter while in the hospital, the mortality rate of this disease and the need for mechanical ventilators will likely be *greatly* reduced," says Dr. Pierre Kory, the Medical Director of the Trauma and Life Support Center and Chief of the Critical Care Service at the University of Wisconsin in Madison.

Anticoagulation (AC) May Help Lower Mortality Rates on Ventilators in COVID

- 2,773 patients were hospitalized with COVID-19: 786 (28%) received systemic AC (oral, SQ, IV) median 3 d
- Patients who received AC were more likely to require invasive mechanical ventilation & had 个 PT/PTT, LDH, hsCRP, ferritin, D-dimers at baseline: in-hospital mortality was 29.1% with a median survival of 21 days w/ AC, 62.7% with a median survival of 9 days w/o AC
- Longer duration of AC treatment was associated with a reduced risk of mortality (p<0.001).</p>
- Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S, Nadkarni GN, Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19, Journal of the American College of Cardiology (2020), doi: https://doi.org/10.1016/j.jacc.2020.05.001.

CCB's May Decrease Ventilator Mortality: Retrospective Study 65 Pts: 50% survived vs 14.6%

Cureus

Open Access Original Article

DOI: 10.7759/cureus.8069

Nifedipine and Amlodipine Are Associated With Improved Mortality and Decreased Risk for Intubation and Mechanical Ventilation in Elderly Patients Hospitalized for COVID-19

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Abstract

Dihydropyridine calcium channel blockers (CCB) are typically used agents in the clinical management of hypertension. Yet, they have also been utilized in the treatment of various

Noninvasive Oxygenation: Lower Mortality With COVID-19

NIV, similar to IMV, probably reduces mortality : https://www.acpjournals.org/doi/10.7326/M20-2306

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure A Systematic Review and Meta-analysis

Bruno L. Ferreyro, MD; Federico Angriman, MD, MPH; Laveena Munshi, MD, MSc; Lorenzo Del Sorbo, MD; Niall D. Ferguson, MD, MSc; Bram Rochwerg, MD, MSc; Michelle J. Ryu, MLIS; Refik Saskin, MSc; Hannah Wunsch, MD, MSc; Bruno R. da Costa, MSc, PhD; Damon C. Scales, MD, PhD

IMPORTANCE Treatment with noninvasive oxygenation strategies such as noninvasive ventilation and high-flow nasal oxygen may be more effective than standard oxygen therapy alone in patients with acute hypoxemic respiratory failure.

OBJECTIVE To compare the association of noninvasive oxygenation strategies with mortality and endotracheal intubation in adults with acute hypoxemic respiratory failure.

DATA SOURCES The following bibliographic databases were searched from inception until April 2020: MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and LILACS. No limits were applied to language, publication year, sex, or race.

STUDY SELECTION Randomized clinical trials enrolling adult participants with acute hypoxemic respiratory failure comparing high-flow nasal oxygen, face mask noninvasive ventilation, helmet noninvasive ventilation, or standard oxygen therapy.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted individual study data and evaluated studies for risk of bias using the Cochrane Risk of Bias tool. Network meta-analyses using a bayesian framework to derive risk ratios (RRs) and risk differences along with 95% credible intervals (CrIs) were conducted. GRADE methodology was used to

Editorial

Supplemental content

Supportive Measures for ARDS

- Attention to fluid balance,

 transfusions,

 sedatives & neuromuscular blocking agents
- Inhaled bronchodilators & prostacycline
- Vasoconstrictors & anti-inflammatory agents including steroids (no benefit, cause harm)
- These confer short term improvement, but have no proven effect on survival
- Why? ROS overwhelm endogenous antioxidants resulting in oxidative cell damage
- Pierrakos C, Karanikolas M, Scolletta S, Karamouzos V, Velissaris D. Acute Respiratory Distress Syndrome: Pathophysiology and Therapeutic Options. J Clin Med Res. 2012;4(1):7-16. doi:10.4021/jocmr761w
- Martin TR. Lung cytokines and ARDS: Roger S. Mitchell Lecture. Chest. 1999;116(1 Suppl):2S-8S

Addressing ROS & Inflammation: Block NF-kappaB, Stimulate Nrf2

- Activation of NF-kappaB is required for transcription of the genes → ↑ proinflammatory mediators associated w/ ARDS
- NF-kB plays a key role in the orchestration of the multifaceted inflammatory response, in the pro-inflammatory phase and later in the the resolution of inflammation when antiinflammatory genes are expressed (ARE)
- Gasparini C, Feldmann M. NF-kB as a target for modulating inflammatory responses. Curr Pharm Des. 2012;18(35):5735-5745. doi:10.2174/138161212803530763
- Rahman A, Fazal F. Blocking NF-κB. Proc Am Thorac Soc. 2011;8(6):497-503. doi:10.1513/pats.201101-009MW

Blocking NF-kB: Antioxidant Tx

- Antioxidants including N-acetyl-cysteine (NAC), alpha lipoic acid (ALA) and glutathione (GSH), have all been published to inhibit activation of NFKappaB
- Both NAC and alpha-lipoic acid upregulate and regenerate glutathione production in vivo
- Brocard H, Charpin J, Germouty J. [Multicenter, double-blind study of oral acetylcysteine vs. placebo]. Eur J Respir Dis Suppl. 1980;111:65-69.
- Zhang WJ, Frei B. Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells. FASEB J Off Publ Fed Am Soc Exp Biol. 2001;15(13):2423-2432.
- Cho S, Urata Y, Iida T, et al. Glutathione downregulates the phosphorylation of I kappa B: autoloop regulation of the NF-kappa B-mediated expression of NF-kappa B subunits by TNF-alpha in mouse vascular endothelial cells. Biochem Biophys Res Commun. 1998;253(1):104-108.



N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why

Giancarlo Aldini, Alessandra Altomare, Giovanna Baron, Giulio Vistoli, Marina Carini, Luisa Borsani & Francesco Sergio

To cite this article: Giancarlo Aldini, Alessandra Altomare, Giovanna Baron, Giulio Vistoli, Marina Carini, Luisa Borsani & Francesco Sergio (2018) N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why, Free Radical Research, 52:7, 751-762, DOI: <u>10.1080/10715762.2018.1468564</u>

To link to this article: https://doi.org/10.1080/10715762.2018.1468564



Primary Roles of Glutathione

- Antioxidant/Anti-inflammatory activity of GSH: neutralize potentially dangerous molecules (ROS, RNS), xenobiotics, metals
- Regulates cell processes: metabolism, proliferation, differentiation, apoptosis
- Regulates immune response: the concentration of GSH and its oxidized form, glutathione disulfide (GSSG), mainly determines the redox state of the cell
- Viruses alter the intracellular redox state to pro-oxidant conditions, contributing to viral pathogenesis
- Dickinson DA, et al. Cellular glutathione and thiols metabolism. Biochem Pharmacol. 2002 Sep; 64(5-6):1019-26.
- Forman HJ, et al. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. 2009 Feb-Apr; 30(1-2):1-12.

Other Roles of GSH: Glutathionylation in Infection & Inflammation





Review

Role of Glutathionylation in Infection and Inflammation

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Abstract: Glutathionylation, that is, the formation of mixed disulfides between protein cysteines and glutathione (GSH) cysteines, is a reversible post-translational modification catalyzed by different cellular oxidoreductases, by which the redox state of the cell modulates protein function. So far, most studies on the identification of glutathionylated proteins have focused on cellular proteins, including proteins involved in host response to infection, but there is a growing number of reports showing

Glutathionylation: Antiviral Activity

Checconi P, et al. Role of Glutathionylation in Infection and Inflammation. Nutrients. 2019;11(8):1952. Published 2019 Aug 20

- Glutathionylation is the formation of mixed disulfides between protein cysteines and (GSH) cysteines
- Microbial proteins undergo glutathionylation, with modification of their functions
- Viruses alter the intracellular redox state to prooxidant conditions, which is an alteration that contributes to viral pathogenesis
- Redox signaling: potential target for antiviral strategies
- Palamara AT, et al. Evidence for antiviral activity of glutathione: in vitro inhibition of herpes simplex virus type 1 replication. Antiviral Res. 1995 Jun; 27(3):237-53.
- Palamara AT, et al. Glutathione inhibits HIV replication by acting at late stages of the virus life cycle. Res Hum Retroviruses. 1996 Nov 1; 12(16):1537-41.
- Ciriolo MR et al. Loss of GSH, oxidative stress, and decrease of intracellular pH as sequential steps in viral infection. J Biol Chem. 1997 Jan 31; 272(5):2700-8.

Other Beneficial Antioxidants: Nrf2 Stimulation & Vitamin C

Stimulation of Nrf2 blocks the macrophage inflammatory response: 4 nutraceuticals: curcumin, sulforaphane glucosinolate (broccoli seed extract), resveratrol, EGCG (green tea)

Vitamin C: can ↓ the duration of mechanical ventilation in critically ill patients

- Hemilä H. Vitamin C and Community-acquired Pneumonia. Am J Respir Crit Care Med. 2011;184(5):621-622.
- Kobayashi EH, Suzuki T, Funayama R, et al. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun. 2016;7.
- Yadav VS, Mishra KP, Singh DP, Mehrotra S, Singh DVK. Immunomodulatory Effects of Curcumin. Immunopharmacol Immunotoxicol. 2005;27(3):485-497
- Subedi L, Lee JH, Yumnam S, Ji E, Kim SY. Anti-Inflammatory Effect of Sulforaphane on LPS-Activated Microglia Potentially through JNK/AP-1/NF-κB Inhibition and Nrf2/HO-1 Activation. Cells. 2019;8(2)

Other Potentially Beneficial Therapies: Zinc

- Zinc plays a central role in the immune system
- Mediates nonspecific immunity, affecting neutrophils & natural killer (NK) cells
- Zinc-deficiency ↑ susceptibility to pathogens
- After zinc supplementation $\rightarrow \downarrow$ incidence of infections, \downarrow TNF-α & oxidative stress markers
- Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr. 1998;68(2 Suppl):447S-463S.
- Prasad AS, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am J Clin Nutr. 2007;85(3):837-844.
- Prasad AS, et al. Antioxidant effect of zinc in humans. Free Radic Biol Med. 2004;37(8):1182-1190.

Other Potentially Beneficial Therapies: Zinc

- Zn inhibits induction of TNF-α and IL-1β mRNA in mononuclear cells (MNCs)
- Provides protection against TNF-α—induced nuclear factor—κβ activation in mononuclear cells
- Macrophages are adversely affected by zinc deficiency, which can dysregulate intracellular killing and cytokine production
- Prasad AS, Beck FWJ, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am J Clin Nutr. 2007;85(3):837-844.
- Prasad AS, Bao B, Beck FWJ, Kucuk O, Sarkar FH. Antioxidant effect of zinc in humans. Free Radic Biol Med. 2004;37(8):1182-1190.

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneu-monia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

Respiratory Medicine Case Reports 30 (2020) 101063



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Case report

Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases



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ARTICLE INFO

Keywords: COVID 19 Pneumonia ARDS N-acetyl-cysteine Glutathione NF-kB

ABSTRACT

Purpose: Infection with COVID-19 potentially can result in severe outcomes and death from "cytokine storm syndrome", resulting in novel coronavirus pneumonia (NCP) with severe dyspnea, acute respiratory distress syndrome (ARDS), fulminant myocarditis and multiorgan dysfunction with or without disseminated intravascular coagulation. No published treatment to date has been shown to adequately control the inflammation and respiratory symptoms associated with COVID-19, apart from oxygen therapy and assisted ventilation. We evaluated the effects of using high dose oral and/or IV glutathione in the treatment of 2 patients with dyspnea secondary to COVID-19 pneumonia.

Low Blood Glutathione Levels in Healthy Aging Adults

Lang, C. et al., Jnl Lab and Clin Med. VOLUME 120, ISSUE 5, P720-725, NOVEMBER 01, 1992

- Test the hypothesis that blood GSH levels are 1 in aging human subjects. Took 39 men and 130 women, 20 to 94 years old, who were healthy
- Reference group was comprised of the 20- to 39-yo's, whose RBC blood GSH levels were 547 ± 53.5 µg
- Cutoff: 440 µg/10 10 erythrocyte cutoff
- The incidence of low blood GSH in the older subjects increased significantly, particularly in the 60- to 79year-old group. Their RBC GSH levels were 452 ± 86.8 µg/, 17% lower than the reference group (p < 0.001).</p>

Other Researchers Believe GSH Deficiency Is Of Primary Importance

Polinokov, A. Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in patients with the novel coronavirus infection (COVID-19): a hypothesis based on literature data and own observations, Pre-print, April 2020

Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in patients with the novel coronavirus infection (COVID-19): a hypothesis based on...

Preprint · April 2020		
DOI: 10.21626/vestnik		
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	Alexey V Polonikov Kursk State Medical University 198 PUBLICATIONS 1,900 CITATIONS SEE PROFILE	

- Two cases: both pts w/ hx of LD & co-inf's (Anaplasma, babesia; Bart, RMSF) presented w/ symptoms & signs of COVID-19 PN w/ SOB
- Pt 1: Significant autoimmune/inflammatory markers (ANA, RF, anticardiolipin AB), Hg, low T, low normal cortisol, normal hs-CRP & ferritin levels
- Pt 2: hx improvement post tx LD & Bartonella

- Shared symptoms: anosmia, dysgeusia, severe fatigue, myalgias, chills, night sweats, HA, sore/scratchy throat, cough, SOB, chest tightness, nausea, diarrhea, dizziness, brain fog, chronic insomnia
- Patient 1: symptoms started one week before testing returned positive for COVID-19
- Patient 2: sudden onset fevers, cough, SOB, anosmia, diarrhea. Testing unavailable in ER

- Pt 1, Symptoms: After several months of treatment with antibiotics during the time period of 2011 to 2012, the patient remained in relatively good health until 8 years later
- January 2020 symptoms relapsed w/ moderate fatigue, insomnia (sleeping 6 hours per night), occasional migratory pain in the muscles and joints, including low back, shoulders, ankles and feet, mild tremors & mild cognitive dysfunction

- Labs Patient 1: Lyme C6 ELISA was negative, IgM and IgG Immunoblot were negative with a negative PCR for *Borrelia burgdorferi*, along with negative Babesia testing and negative testing for other tickborne co-infections
- Complement levels were 1 with 1 C4a, & 1 immune complex detection by C-1 Q binding
- RF 个 (154), ANA 个 (1:320). All other AI markers were negative

- Labs Patient 1: Hg level in the blood was elevated at 15.3 (normal range < 10 ug/L), Lead level was 1 (normal range 0 – 4 ug/dL)
- Uric acid was sl. ↑ at 7.4 (normal range less than 7 mg/deciliter) with a normal hemoglobin A1c at 5.3 (normal range less than 6.0).
- A CBC and CMP were WNL, as were immunoglobulin levels (IGA, IgM and IgG) and mineral levels (iodine, zinc, copper, mag)

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

Symptoms Patient 1: presented with anosmia, dysgeusia with a metallic taste, low-grade fevers (99.5 to 100.5 Fahrenheit), sweats (day and night occasionally interfering with sleep), body aches with flulike symptoms, low back pain, a dry cough with labored breathing, scratchy throat, severe headache, brain fog and diarrhea

Symptoms started 1 week prior when testing returned + for COVID-19. ER: CXR was negative
Potential Pharmaceuticals for COVID-19

- Hydroxychloroquine +/- azithromycin, Chloroquine
- Alinia (nitazoxanide), Ivermectin +/- doxycycline
- Remdesivir (illness by 4 days), itolizumab (monocl)
- Protease inhibitors lopinavir and ritonavir + rib/interf
- Melatonin, mercaptopurine, and sirolimus

Antibody-rich plasma of recovered COVID-19 pts

- Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6(1):16.
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Mycoplasma pneumoniae has been found in 26.5% of COVID-19 pts: ? Use Doxy or Zithromax Check Ratio CRP/Procalcitonin: Predictive Mycoplasma

International Journal of Clinical Medicine (2020) Volume 11, in press, 6 May.

COVID-19 Coronavirus: Is Infection Along with Mycoplasma or other Bacteria Linked to Progression to a Lethal Outcome?

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Received: 28 April 2020

Influenza A Co-inf w/COVID-19: ?Tamiflu Poor Sensitivity COVID RT PCR Nasopharygeal Swab: BALF +

? Broader Viral Panel Testing Needed in Difficult Cases

RESEARCH LETTERS

Co-infection with SARS-CoV-2 and Influenza A Virus in Patient with Pneumonia, China

Xiaojing Wu, Ying Cai, Xu Huang, Xin Yu, Li Zhao, Fan Wang, Quanguo Li, Sichao Gu, Teng Xu, Yongjun Li, Binghuai Lu, Qingyuan Zhan

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DOI: https://doi.org/10.3201/eid2606.200299

We report co-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza A virus in a patient with pneumonia in China. The case highlights possible co-detection of known respiratory viruses. We noted low sensitivity of upper respiratory specimens for SARS-CoV-2, which could further complicate recognition of the full extent of disease.

Tn December 2019, a series of cases of nneumonia

count of 2.18 × 10° cells/L (reference range 1.1–3.2 × 10° cells/L). Chest computed tomography revealed a mass, ground-glass consolidation in the right inferior lobe of the lungs (Figure, panel A). Because of the patient's travel history, he was isolated for suspected coronavirus disease (COVID-19).

We obtained a nasopharyngeal swab specimen and conducted real-time reverse transcription-PCR (rRT-PCR) for SARS-CoV-2 by using reagents provided by Shanghai BioGerm Medical Technology Co., Ltd. (http://www.bio-germ.com), and Da An Gene Co., Ltd. (Sun Yat-Sen University, http:// en.daangene.com), on a LightCycler 480 (Roche, https://lifescience.roche.com). However, both tests returned negative results 8 hours later. We obtained another nasopharyngeal swab specimen for detection of SARS-CoV-2 and for differentiation of influenza A and B and respiratory syncytial viruses by using Xpert Flu/RSV Xpress assay (Cepheid, https:// www.cepheid.com). The sample was negative for SARS-CoV-2 but positive for influenza A. The patient was discharged with oral oseltamivir and instructed to stay home for isolation.

On January 30 the nationt returned to the her

Efficacy of GSH in Relieving Dyspnea Associated w/COVID-19 Pneumonia

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020, <u>https://www.sciencedirect.com/science/article/pii/S2213007120301350?via%3Dihub</u>

- Patient 1, Treatment: Hydroxychloroquine as a loading dose of 400 milligrams BID × 2 days, followed by 200 milligrams TID × 8 days, nitazoxanide 500 milligrams PO BID, and Zithromax 250 milligrams BID × 10 days
- No Hx QT prolongation on an EKG
- Albuterol inhaler: no help with SOB
- Immune and nutritional support (NS): Zinc, Vit C, 3,6 Beta glucan, curcumin, sulforaphane glucosinolate, NAC, ALA, GSH, probiotics (acidophilus, lactobacillus, bifidobacterium and Saccharomyces boulardii)

Dosing Nutritional/Immune Support

- Zinc 40 milligrams per day (40-50 mg/d)
- Vitamin C 1-2 grams, TID (↑ dose for PN)
- 3, 6 beta glucan (500-1000 milligrams per day)
- Curcurmin 1 gm twice a day (can 个 2-4 gm BID)
- Sulforaphane glucosinolate 100 mg twice a day
- NAC 600 milligrams BID (can 1.2 gm BID)
- Alpha lipoic acid 600 milligrams BID (?hypoglycemia)
- Glutathione 2, 500 mg capsules BID, can ↑ to 2 grams all at once prn for acute respiratory distress. Repeat up to 6 gm/d. Use w/alkalinizing

Clinical Course Patient 1

Day 11 postexposure, 4 days into the antibiotic regimen (day 4 of nitazoxanide) the patient began to clinically improve, although he still complained of anosmia, dysgeusia, poor appetite, a cough, significant shortness of breath, debilitating fatigue and several episodes of diarrhea per day with dehydration. Pulse oximetry's remained at 95% or higher

- A trial of 2 grams of oral GSH was tried for the moderate SOB → significantly improved his dyspnea within 1 hour
- A home nursing service was subsequently hired to administer IV fluids (secondary to dehydration from significant night sweats and diarrhea with difficulty keeping down fluids)
- A dose of IV GSH 2 gm in 1 liter 0.9% NS was then infused over 1 hr → again, signif. ↓ SOB, improved sense of well being

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

- 48-year-old, G4P4 female with a 15 pack-year smoking history, & hx of Lyme disease and associated tick-borne infections (*Bartonella henselae*, *Rickettsia rickettsii*, *Rickettsia typhi*]
- March 22, 2020, the patient woke up with 103°F, severe dyspnea at rest that worsened with exertion, dry cough, chest tightness, nausea, dizziness, diarrhea, severe fatigue, body pains, shallow breathing, & anosmia.

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

Went to the ER, where they performed a CXR

Showed "hazy opacities and peribronchial thickening in the left mid and lower lung field concerning for pneumonia, possible atypical". Patient was given a loading dose of 500 mg of azithromycin in the ER and discharged with a diagnosis of "Suspected 2019 Novel **Coronavirus Infection and Atypical** Pneumonia"

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

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Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

- On Monday, March 23, 2020, the patient started a loading dose of hydroxychloroquine 400 mg PO q12h, followed by maintenance doses of Plaquenil 200 mg TID × 8 days w/ azithromycin 250 mg PO q12h (No QT ↑)
- Amoxicillin/clavulanate 875-125 mg PO q12h was added for continued SOB, w/out help
- March 23-30th, 2020: cough, dyspnea at rest that worsened with exertion, diarrhea persisted

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

- On March 31, 2 g of reduced, L-glutathione PO was given with 2 Alka seltzer gold, alpha lipoic acid 600 mg, and N-acetylcysteine 600 mg PO
- The patient saw immediate improvement described as "being able to breath better and having more energy" within an hour of use
- Repeat dosing (2 gm) next am: able to ambulate, perform ADL's, without pre-syncopal episodes
- Lower dose GSH (500mg) : not as efficacious

Immune/Antioxidant Activity of GSH

- GSH ↑ innate and adaptive immunity, conferring protection vs microbial, viral and parasitic infections
- GSH ↑ (f) activity of natural killer (NK) cells and T cells
- GSH is 1° IC, except in the lung tissue: neutralizes ROS, acts as a mucolytic, combines with NO to make nitrosoglutathione, our endogenous bronchodilator
- IV NAC: Can treat ARDS (low levels GSH in lungs): ↑
 O2 delivery, ↑ lung compliance, resolves pulm edema
- Morris, D. et al. Glutathione and Infection. Biochimica et Biophysica Acta (BBA) General Subjects, Volume 1830, Issue 5, May 2013, Pages 3329-3349
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Antiviral Activity of GSH

- Glutathione has antiviral effects against HIV, HSV 1, influenza A, murine leukemia virus, dengue virus serotype 2, and hepatitis C
- Binding of the SARS-CoV-2 spike protein to ACE2, the protein it uses to attach to the cell, depends on disulfide bond formation (NAC and GSH are mucolytic)
- One of the principle roles of GSH in the extracellular fluid of the lung is to break disulfide bonds, thereby possibly slowing the rate at which the virus gets into our cells, reducing the peak viral load
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Antiviral Activity of GSH

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ANTIBODY, ANTIGEN, PCR TESTING ALL AVAILABLE AS OF MAY 10TH 2020

TESTING FOR COVID-19

Antibody Testing for COVID-19

Coronavirus Antibody Tests: Can You Trust the Results?

A team of scientists worked around the clock to evaluate 14 antibody tests. A few worked as advertised. Most did not.



Testing for COVID-19

- Antibody testing: IgA, IgM, IgG: typically takes 1-3 weeks to develop antibodies to SARS-CoV-2
- "Point of care" rapid immunological testing chips: IgM/IgG AB's (whole blood, serum or plasma)
- PCR: CDC 2019-Novel Coronavirus Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel
- Current inf requires a PCR (nasopharyngeal swab)
 Rapid tests not vetted by FDA. False +/False -

<u>https://www.cdc.gov/coronavirus/2019-ncov/faq.html#Symptoms-&-Testing</u>

Ollar, R. A Practical Approach to Testing for Coronavirus COVID-19 Should Include Both Rapid Immunological Assays, as Well as, Virological Realtime RT-PCR Assays. Echronicon, Apr 30, 2020

IgG Antibody Testing

https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-testperformance

- Sensitivity/specificity depends on the test used
- Euroimmune ELISA: 90% sensitivity, 100% specificity
- Abbott Architect: 100% sensitive/99.6% specific
- Abbott Alinity: 100% sensitive/99% specificity (real world: missed > 48% cases: CNN, Wash Post...)
- Autobio: 95.7% sensitivity/99.7% specificity
- BioRad Platelia: 92.2%/99.6%
- Chembio: IgM 77.4%/IgG 87.1% (combined 93-94%)
- Orthoclinical: 100% sensitive/100% specific
- https://www.washingtonpost.com/health/2020/05/13/abbott-test-hailed-by-president-trump-has-beendogged-by-accuracy-questions/

https://www.nytimes.com/2020/05/08/health/fda-coronavirus-spittest.html?campaign_id=154&emc=edit_cb_20200508&instance_id=18350&nl=coronavirusbriefing®i_id=103987437&segment_id=27020&te=1&user_id=a2c3fadde0fc78562ace8fa1d14b7b07

F.D.A. Clears First Home Saliva Test for Coronavirus

The Food and Drug Administration is permitting a Rutgers lab to start selling spitcollection kits to detect the coronavirus.



May 8, 2020 : A test kit was developed by a Rutgers University lab called RUCDR Infinite Biologics, in partnership with Spectrum Solutions and Accurate Diagnostic Labs, & tests should be limited to those who are symptomatic. The F.D.A. said that Rutgers had submitted data showing that testing saliva samples collected by patients themselves, under the observation of a health care provider, was as accurate as testing deep nasal swabs that the health professional had collected from them. LabCorp previously had an in-home test nasal swab approved. A time lag exists in getting in home testing back

FDA Approves 15 Min Antigen Test

https://www.washingtonpost.com/health/2020/05/09/fda-issues-emergency-approval-new-antigen-test-that-ischeaper-faster-simpler

- The Sofia 2 SARS Antigen FIA by Quidel Corp, is a nasal swab that produces results in 15 minutes
- The test cartridges can be placed in its Sofia 2 machine or manually developed on a countertop
- Less reliable than the PCR test (not as sensitive)
- Positive results are "highly accurate," but a negative result does not rule out the presence of the virus. Need AB, Ag & PCR for full evaluation

Potential Enhanced Diagnostic Practices for COVID-19: App's, Questionnaires

Horowitz, et al. Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials. Med Hypothesis. Submitted Apr 13, 2020. Accepted May 21, 2020

- Symptoms could be collected via an online questionnaire or digital app: ? Anosmia, dysgeusia, fever, sore throat, cough, chest tightness, SOB, diarrhea, N+, V+, CNS sx
- Recently, an app was developed by Israeli researchers, & has been instituted as a screening tool in Canada
- Online tracking of vital signs (temp, O2 sat% via pulse ox) & scored questionnaires that are statistically validated

Would require a randomized, controlled trial

Canadian hospital battles coronavirus outbreak with "revolutionary" app. MSN. https://www.msn.com/enca/news/technology/canadian-hospital-battles-coronavirus-outbreak-with-revolutionary-app/ar-BB12uc5c. Accessed April 13, 2020.

PREVENTION FOR COVID-19 SOCIAL DISTANCING, MASKS, HANDWASHING, ? GARGLING, ? **IONIZERS ? NEED TO AVOID INFECTED STOOL, ? GSH & PRECURSORS ? NRF2 ACTIVATION, ZINC, VIT C, BETA GLUCAN, PULSED IVERMECTIN...**

The Post Most



May 14, 2020, Washington Post: As some countries ease up, others are reimposing lockdowns amid a resurgence of coronavirus infections. Countries on at least 3 continents are renewing restrictions as new cases spike.



Prevention Practices

Physical distancing, handwashing, isolation

How important are masks? Speech droplets can be emitted at a rate of 1000's/sec, takes 8-14 min to dissipate (PNAS, May 2020, NIH study). ? Use Ionizers

www.pnas.org/cgi/doi/10.1073/pnas.2006874117

The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission

Valentyn Stadnytskyi^a, Christina E. Bax^b, Adriaan Bax^{a,1}, and Philip Anfinrud^{a,1}

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Edited by Axel T. Brunger, Stanford University, Stanford, CA, and approved May 4, 2020 (received for review April 10, 2020)

Speech droplets generated by asymptomatic carriers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are increasingly considered to be a likely mode of disease transmission. Highly sensitive laser light scattering observations have revealed that loud speech can emit thousands of oral fluid droplets per second. In a closed, stagnant air environment, they disappear from the window of view with time constants in the range of 8 to 14 min, which corresponds to droplet nuclei of *ca*. 4 µm diameter, or 12- to 21-µm droplets prior to dehydration. These observations confirm that there is a substantial probability that normal speaking causes airborne virus transmission in confined environments.

COVID-19 | speech droplet | independent action hypothesis | respiratory disease | disease transmission

t has long been recognized that respiratory viruses can be transmitted via droplets that are generated by coughing or sneezing. It is less widely known that normal speaking also produces thousands of oral fluid droplets with a broad size distribution (*ca.* 1 μ m to 500 μ m) (1, 2). Droplets can harbor a

The amount by which a droplet shrinks upon dehydration depends on the fraction of nonvolatile matter in the oral fluid, which includes electrolytes, sugars, enzymes, DNA, and remnants of dehydrated epithelial and white blood cells. Whereas pure saliva contains 99.5% water when exiting the salivary glands, the weight fraction of nonvolatile matter in oral fluid falls in the 1 to 5% range. Presumably, this wide range results from differential degrees of dehydration of the oral cavity during normal breathing and speaking and from decreased salivary gland activity with age. Given a nonvolatile weight fraction in the 1 to 5% range and an assumed density of 1.3 g-mL⁻¹ for that fraction, dehydration causes the diameter of an emitted droplet to shrink to about 20 to 34% of its original size, thereby slowing down the speed at which it falls (1, 13). For example, if a droplet with an initial diameter of 50 µm shrinks to 10 µm, the speed at which it falls decreases from 6.8 cm·s⁻¹ to about 0.35 cm·s⁻¹. The distance over which droplets travel laterally from the speaker's mouth during their downward trajectory is dominated by the total volume and flow velocity of exhaled air (8). The flow velocity varies with phonation (14) while the total volume and BRIEF REPOR

MEDICAL SCIENCES

Cloth Masks May Prevent Transmission

Ideas and Opinions22 May 2020 https://www.acpjournals.org/doi/10.7326/M20-2567

Cloth Masks May Prevent Transmission of COVID-19: An Evidence-Based, Risk-Based Approach

FREE

Catherine M. Clase, MB BChir, MSc

Edouard L. Fu, BSc

Meera Joseph, MD , ...<u>View all authors</u> Author, Article and Disclosure Information https://doi.org/10.7326/M20-2567

PPE: Non-Recommended Masks

CDC-APPROVED PPE



+He cowboy



the beanic -



the super high waisted spanx



the jokester



ne spa

the bird man



NWOID

the Lord of the Rings Freak



safe doctor

Viral Lipid Membrane Disruption by Gargling w/Listerine?

"Emerging studies increasingly demonstrate the importance of the throat and salivary

glands as sites of virus replication"

O'Donell, V., et al. Potential role of oral rinses targeting the viral lipid envelope in SARS-CoV-2 infection" Function, zgaa002. Published: 14 May 2020



Gargle twice daily—keep well—stay on the job

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Role For Air Disinfection? Filters, UV Light

JAMA Published online June 1, 2020 Airborne Spread of SARS-CoV-2 and a Potential Role for Air Disinfection

Edward A. Nardell, MD Brigham and Women's Hospital, Division of Global Health Equity, Harvard Medical School, Boston, Massachusetts.

VIEWPOINT

Ruvandhi R. Nathavitharana, MD, MPH

Beth Israel Deaconess Medical Center, Division of Infectious Diseases, Harvard Medical School, Boston, Massachusetts.

Supplemental content

An April 2, 2020, expert consultation from the National Academies of Sciences, Engineering, and Medicine to the White House Office of Science and Technology Policy concluded that available studies are consistent with the potential aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), not only through coughing and sneezing, but by normal breathing.¹ This response to a White House request for a rapid review of the literature likely contributed to the recommendation from the US Centers for Disease Control and Prevention (CDC) that healthy persons wear nonmedical face coverings, when in public, to reduce virus spread from undiagnosed infectious cases.

Although clear evidence of person-to-person airborne transmission of SARS-CoV-2 has not been published, an airborne component of transmission is likely based on other respiratory viruses such as SARS, Middle East respiratory syndrome, and influenza. While air sampling for SARS-CoV-2, in a clinical setting, has demonstrated detectable viral RNA, the extent of transmission resulting from airborne particles relative to large respiratory droplets, directly and on surfaces, is not yet known. But if fitted N95 respirators can be justified as a ing costs when intake air must be heated or cooled and dehumidified. Portable room air cleaners may be a potential solution, but depending on room volume, their specified clean air delivery rates generally add too few equivalent air changes per hour to provide adequate protection against airborne infection. In contrast, commercially available upper-room GUV air disinfection (with an effective rate of air mixing) has been shown, in clinical settings, to reduce airborne tuberculosis transmission by 80%, equivalent to adding 24 room air changes per hour.³

In resource-limited settings, where air disinfection depends on natural ventilation, upper-room GUV may be increasingly important as windows are closed due to use of ductless air conditioners in response to global warming and severe outdoor air pollution. In resourcerich settings, upper-room GUV can be retrofitted into most areas with sufficient ceiling height. GUV technology is effective against viruses that have been tested, including influenza and SARS-CoV-1.^{4,5}

Direct whole-room GUV is also used for room surface disinfection in unoccupied rooms (eg, between infectious patients), and GUV devices are being used to

RT-PCR + in Stool, Neg in Respiratory Tract Specimen: ? Indirect Transmission

(COUTD 10)

RESEARCH LETTERS

Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China

An Tang,¹ Zhen-dong Tong,¹ Hong-ling Wang,¹ Ya-xin Dai,¹ Ke-feng Li, Jie-nan Liu, Wen-jie Wu, Chen Yuan, Meng-lu Yu, Peng Li, Jian-bo Yan

Author affiliation: Zhoushan Center for Disease Control and Prevention, Zhoushan, China

DOI: https://doi.org/10.3201/eid2606.200301

We report an asymptomatic child who was positive for a coronavirus by reverse transcription PCR in a stool specimen 17 days after the last virus exposure. The child was virus positive in stool specimens for at least an additional 9 days. Respiratory tract specimens were negative by reverse transcription PCR.

We collected nasopharyngeal swab and sputum samples from the boy 15 days after the last close contact and tested these specimens for SARS-CoV-2 by using RT-PCRs targeting the open reading frame lab (ORF1ab) and nucleoprotein gene regions (4). We obtained equivocal results: cycle threshold (C_t) values were negative for ORF1ab and 37.5 for the nucleoprotein gene. However, on February 1 (17 days after his last contact), a stool specimen was positive for SARS-CoV-2 by RT-PCR. (ORF1ab C_t 32.6; nucleoprotein gene C_t 33.7). He was then hospitalized in isolation and for monitoring.

Since January 22, The area of residence for the boy had been isolated, and community physicians monitored quarantined residents twice a day for signs and symptoms including fever, cough, and myalgia. During January 9–31, the boy had no signs or symptoms.

In the hospital, a routine blood test performed on February 2 showed cell counts within reference ranges, and a computed tomography scan on February 5 showed no abnormalities. After additional stool specimens collected on February 2 (ORF1ab C, 25.6;

Plaquenil Does Not Confer Protection in SLE Patients

To cite Konig MF, Kim AHJ, Scheetz MH, et al. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-217690

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Ann Rheum Dis 2020;0:1-2. doi:10.1136/annrheumdis-2020-217690

Letter

Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19

The use of hydroxychloroquine (HCQ) in the prophylaxis and treatment of coronavirus disease 2019 (COVID-19) has received significant attention by politicians and media figures. This has occurred despite limited data supporting its efficacy in COVID-19 as well as considerable concern about its safety when used at high doses (>400 mg daily) and in combination with other QT interval prolonging drugs.¹⁻⁴

An inaccurate narrative has emerged in recent weeks that patients with systemic lupus erythematosus (SLE) who are taking HCQ as a baseline therapy are less affected by or do not develop COVID-19.5-7 This assumption has been challenged by Monti and Montecucco,8 referencing data from the COVID-19 Global Rheumatology Alliance registry on patients with rheumatic disease that previously identified 19/110 (17%) patients with SLE.9 A case series of 17 patients with lupus or antiphospholipid syndrome who developed COVID-19 on a median HCQ dose of 400 mg daily (median HCQ blood level of 648 ng/mL) has since become available.¹⁰ As of 17 April 2020, we have now identified 80 patients with SLE and COVID-19 in the global physicianreported registry. Patients were predominantly female (72/80, 90%) and less than 65 years of age (69/80, 86%). Importantly, 64% (51/80) of patients with SLE were taking an antimalarial (LICO or chloroming) prior to infaction with source agute room

epithelial lining fluid vs lung parenchyma). Even for influenza and approved antiviral drugs (oseltamivir), the direct relationship between drug concentration and in vivo activity is uncertain.18 19 Current in vitro data suggest that the concentration of HCQ at which 50% of the maximal activity against SARS-CoV-2 is obtained (EC50) is 0.72-4.51 µM (ie, -242-1515 ng/mL),14.15 similar to the EC50 observed in SARS-CoV-1 and MERS-CoV.13 Ninety per cent inhibition of SARS-CoV-2 (EC90) with HCO was achieved at -5-15 µM (-1679-5038 ng/mL), while clearance required ~20 µM (~6717 ng/mL).14 15 Importantly, both EC50 and EC90 concentrations may be insufficient to improve clinical outcomes. Instead, the concentration of HCQ required to eliminate SARS-CoV-2 may be a more meaningful target.20 Such concentrations of HCQ (ie, ~6700 ng/mL), however, are not safely achievable in whole blood, and little is known about the concomitant concentrations obtainable in lung parenchymal cells in humans (assuming this represents a critical site for antiviral activity in COVID-19). Without an understanding of effective HCQ concentrations in target tissues, effective therapeutic doses remain difficult to predict by simulation. For dosing strategies to be informed, an intricate understanding of HCO transfer constants between the blood and the lung tissue is required.

HCQ used in the treatment of SLE is typically prescribed at doses of 5.0-6.5 mg/kg, with a maximum dose of 400 mgdaily. The majority of patients with SLE on chronic HCQ treatment do not achieve whole blood concentrations of $5-15 \mu M$ (~1679-5038 ng/mL),¹⁰ ²¹ corresponding to the EC90 for SARS-CoV-2.¹⁴ ¹⁵ While pulmonary drug concentrations in mice are known to reach much higher levels than in blood, these

Yet Plaquenil May Provide Protection in Health Care Workers ?

- The case-control investigation of the ICMR reveals that consumption of 4 or more maintenance doses of hydroxychloroquine led to a significant decline in the odds of healthcare workers getting infected w/ COVID
- Reduction of risk by 80% seen w/ 6 prophylactic doses (400 mg, 1 x/ week)
- The sample size consisted of 378 symptomatic healthcare workers who tested + for COVID-19
- The registry-based analysis recorded ↑ frequencies of ventricular arrhythmias in patients receiving HCQ
- https://www.indiatoday.in/india/story/4-hydroxychloroquine-hcq-doses-coronavirus-healthcare-workersicmr-1684112-2020-06-01

No Benefit to Plaquenil in Large Controlled Clinical Trial, NEJM June 2020

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. Boulware, D. et al.

Malaria Drug Promoted by Trump Did Not Prevent Covid Infections, Study Finds

The first carefully controlled trial of hydroxychloroquine given to people exposed to the coronavirus did not show any benefit.

https://www.nytimes.com/2020/06/03/beatb/hydroxychioroguine.coronawirustromp.html?campaign_id=154&enccedit_cb_20200503&instance_id=19067&nl=coronawirustroiefing®t_id=203087437&segment_id=30023&te=1&sizer_id=a2c3fadde0fc78562.ace8fa3d14b7b0



OR IGINAL ARTICLE A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 D.R. Boulware, M.F. Puller, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skopper, A.A. Nascene, M.R. Nicol, M. Abasai, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lotber, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, L.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

TH NEW ENGLAND JOUENAL & MEDICINE

ABSTRACT

BACKGROUND

METHODS

Coronavirus disease 2019 (Govid-19) occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For persons who are exposed, the standard of care is observation and quarantine. Whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure is unknown.

The authors' full names, academic, degrees, and affiliations are listed in the Appendix. Address: report requests to Dr. Boildware at the University of Minnesota, 689 21rd Are., Minneapolis, MN 35455, or at boalw603 glurme.eMu.

 First large controlled clinical trial of Plaquenil from the Univ of Minnesota and Canada did not show any effect in preventing COVID-19 in over 800 subjects given the drug, but no serious side effects reported

Potential Enhanced Prevention Practices for COVID-19: IVERMECTIN

- No validated protocols except for physical distancing, hand washing, and isolation exist
- Ivermectin, chloroquine & hydroxychloroquine have anti-viral properties against COVID-19, but chloroquine & Plaquenil have recently been reported to have potential SE's (arrythmias...) & Plaq was ineffective
- Ivermectin: FDA approved for parasitic inf's; WHO "Essential medication"; inhibits COVID-19 in vitro & 1 dose: ~5000-fold reduction in virus at 48 h in cell culture
- Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6(1):16.
- Caly, L., et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research, Volume 178, June 2020, 104787. <u>https://doi.org/10.1016/j.antiviral.2020.104787</u>



Contents lists available at ScienceDirect

Antiviral Research

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

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro



Leon Caly^a, Julian D. Druce^a, Mike G. Catton^a, David A. Jans^b, Kylie M. Wagstaff^{b,*}

^a Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, At the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia
^b Biomedicine Discovery Institute, Monash University, Clayton, Vic, 3800, Australia

ABSTRACT

Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. We report here that Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore warrants further investigation for possible benefits in humans.

1. Introduction

Ivermectin is an FDA-approved broad spectrum anti-parasitic agent

observed for ivermectin against Zika virus (ZIKV) in mice, but the authors acknowledged that study limitations justified re-evaluation of ivermectin's anti-ZIKV activity (Ketkar et al., 2019). Finally, ivermectin
Ivermectin Decreases Ventilator Mortality

(non-randomized, non controlled study)

- In an observational study from 169 hospitals across Asia, Europe, Africa, North and South America, they evaluated 1970 critically ill hospitalized patients diagnosed with COVID-19 with lung injury requiring mechanical ventilation, between Jan-Mar 2020
- 1,609 survived hospitalization and 361 died (18.3%)
- 52 patients received Ivermectin (150 mcg/Kg) after mechanical ventilation was instituted
- Survival benefit for ivermectin was 18.6% vs 7.7%

Patel, A. et al. Ivermectin in COVID-19 Related Critical Illness. Univ. of Utah, Salt Lake City, <u>https://ssrn.com/abstract=3570270</u>

Ivermectin & Doxycycline

- A combination of Ivermectin and Doxycycline was tried on a group of 60 COVID-19 patients with respiratory problems & other symptoms of coronavirus disease
- All patients were cured within 4 days
- No side effects were reported
- Viral testing was negative post treatment

<u>https://www.firstpost.com/health/medical-team-in-bangladesh-suggests-combination-of-ivermectin-and-doxycycline-for-covid-19-treatment-8380171.html/amp</u>

Potential Enhanced Prevention Practices for COVID-19: ? Ivermectin +/- NS Horowitz & Freeman. Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials. DOI: https://doi.org/10.1016/j.mehy.2020.109851 Reference: YMEHY 109851 What if we were to do a prevention trial of once or twice a week ivermectin? (incubation phase of COVID-19: 3 days –14 days) +/- Zinc, Vit C, D, 3,6 Beta glucan, Nrf2 activators (curcurmin,

sulforaphane glucosinolate), NAC, ALA, GSH

- Anti-viral activity &
- anti-inflammatory therapies
- Randomized, controlled trial needed

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ELSEVIER	journal homopage, www.shareer.com/besile/hom
Three novel preventi- argently necessitating	on, diagnostic, and treatment options for COVID-19
Richard I. Horowitz ²⁰⁰ , Pl 100 Intens ed Tollers fulleys Inten Index Kills fraing im trace 425 48	ty QIS R. Freeman" watan Wadapan. D.C. 2020. 194 any fare Anat. Hydr And, NY LUDR. 194.
ARTICLEINFO	ABSTRACT
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Vaccine Trials: 135 Vaccines as of June 11th, NYT



- Texas A&M to lead testing of TB vaccine against COVID-19 - HoustonChronicle.com. BCG provides immune benefits, but Israeli study w/ 3064 patients: no benefit
- Operation Warp Speed" : White House's task force have honed in on 14 different vaccines? Mutations?
- https://www.medicalnewstoday.com/articles/covid-19-could-tb-vaccine-offer-protection
- https://www.drugs.com/medical-answers/bcg-vaccine-tb-covid-19-3535337/
- Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA. Published online May 13, 2020. doi:10.1001/jama.2020.8189
- Miller A, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv. Preprint posted March 28, 2020.

Will Postinfection Immunity Confer Resistance? What About Mutations

Kirkcaldy RD, et al COVID-19 and Postinfection Immunity: Limited Evidence, Many Remaining Questions

JAMA. Published online May 11, 2020

VIEWPOINT

COVID-19: BEYOND TOMORROW COVID-19 and Postinfection Immunity

Limited Evidence, Many Remaining Questions

Robert D. Kirkcaldy, MD, MPH US Centers for Disease Control and Prevention, Atlanta, Georgia.

Brian A. King, PhD, MPH

US Centers for Disease Control and Prevention, Atlanta, Georgia.

John T. Brooks, MD

US Centers for Disease Control and Prevention, Atlanta, Georgia. In the absence of effective treatment or biomedical prevention, efforts to control the coronavirus disease 2019 (COVID-19) pandemic have relied on nonpharmaceutical interventions such as personal preventive actions (eg, handwashing, face covers), environmental cleaning, physical distancing, stay-at-home orders, school and venue closures, and workplace restrictions adopted at the national, state, and local levels. In addition to these public health interventions, development of herd immunity could also provide a defense against COVID-19. However, whether immunity occurs among individuals after they have recovered from COVID-19 is uncertain. Many human infections with other viral pathogens, such as influenza virus, do not produce a durable immune response.

Understanding whether and how recovery from COVID-19 confers immunity to, or decreased severity of, reinfection is needed to inform current efforts to safely higher titers have not always been found to correlate with clinical improvement in COVID-19.^{2,3} Moreover, mild COVID-19 symptoms can resolve prior to seroconversion (as reflected by detectable IgM and IgG), although detectable IgM and IgG antibodies have preceded declines in SARS-CoV-2 viral loads.^{2,3}

What appears more certain is that viral burden typically peaks early in illness, and then declines as antibodies develop and antibody titers rise over the subsequent 2 to 3 weeks.^{2,3} Success in culturing virus from nasopharyngeal specimens declines quickly during the first week of mild illness, but the absolute duration that a patient might shed infectious virus is unknown.² Persistent detection of viral RNA many days to weeks after recovery from COVID-19 at concentrations near the detection limit of available assays likely does not represent a meaningful clinical or public health risk, especially in the absence of symptoms²; however, definitive

Moderna's Vaccine Trial: 8 Patients:

1 Plevels of neutralizing antibodies equivalent to those found in convalescent serum of those who recovered from covid-19. ? Science

Moderna's claim of favorable results in its vaccine trial is an example of 'publication by press release'



The biotechnology company Moderna is based in Cambridge, Mass. (Bill Sikes/AP) By William Haseltine, May 19, 2020 at 6:00 p.m. EDT

https://www.washingtonpost.com/opinions/2020/05/19/rush-share-good-news-covid-19-drugs-isundermining-

CanSino's Covid Vaccine Shows Promise in an Early Study: 108 pts

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial



Summary

Background A vaccine to protect against COVID-19 is urgently needed. We aimed to assess the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the spike glycoprotein of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain.

Methods We did a dose-escalation, single-centre, open-label, non-randomised, phase 1 trial of an Ad5 vectored COVID-19 vaccine in Wuhan, China. Healthy adults aged between 18 and 60 years were sequentially enrolled and allocated to one of three dose groups (5×10¹⁰, 1×10¹¹, and 1.5×10¹¹ viral particles) to receive an intramuscular injection of vaccine. The primary outcome was adverse events in the 7 days post-vaccination. Safety was assessed over 28 days post-vaccination. Specific antibodies were measured with ELISA, and the neutralising antibody responses induced by vaccination were detected with SARS-CoV-2 virus neutralisation and pseudovirus neutralisation tests. T-cell responses were assessed by enzyme-linked immunospot and flow-cytometry assays. This study is registered with ClinicalTrials.gov, NCT04313127.

Published Online May 22, 2020 https://doi.org/10.1016/ 50140-6736(20)31208-3

*Contributed equally

Beijing Institute of Biotechnology, Beijing, China (ProfW Chen PhD, Prof J-J Xu PhD, Prof L-H Hou PhD, S-PWu PhD, B-S Wang PhD); NHC Key Laboratory of Enteric Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China

Extent of Protection? Unclear

Only 50% of those who received the medium dose of developed neutralizing antibodies. Adenovirus 5 vector failed in HIV trial years ago.

Different technologies: mRNA vaccines, recombinant subunit vaccines, recombinant viral vectors, inactivated virus vaccines, virus like particle technology...

NEWS 03 JUNE 2020

Questions remain following first COVID-19 vaccine results

CanSino and Moderna are the first vaccine makers to report data on safety and neutralization, but the extent of protection these products afford remains unclear. Cormac Sheridan

https://www.nature.com/articles/d41587-020-00015_ x?utm_source=Nature+Briefing&utm_campaign=ca5b00045f-briefing-dy_ 20200602&utm_medium=email&utm_term=0_c9dfd39373-ca5b00045f-43990557



Neutralizing antibodies are the benchmark for testing SARS-CoV-2 vaccines.

TABLE 1. COVID-19 VACCINES IN CLINICAL DEVELOPMENT

Developers	Vaccine	Description	Clinical status
AstraZeneca, Oxford University (Oxford, UK)	AZD1222 (ChAdOx1 nCoV-19)	Recombinant chimpanzee adenovirus vector expressing the SARS- CoV-2 S protein	Phase 2/3
CanSino Biologics, Beijing Institute of Biotechnology (Beijing)	Ad5-nCoV	Recombinant adenovirus type 5 (Ad5) vector expressing the SARS- CoV-2 S protein	Phase 2
BioNTech (Mainz, Germany), Pfizer, Fosun Pharma (Shanghai, China)	BNT162a1, BNT162b1, BNT162b2, BNT162c1	mRNA-based vaccines expressing SARS-CoV-2 S protein or its receptor- binding domain	Phase 1/2
Novavax	NVX-CoV2373	Matrix-M-adjuvanted recombinant subunit vaccine based on SARS- CoV-2 S protein	Phase 1/2
Inovio Pharmaceuticals	INO-4800	DNA-based vaccine encoding SARS-CoV-2 S protein	Phase 1
Moderna, NIAID	mRNA-1273	mRNA-based vaccine expressing SARS-CoV-2 S protein	Phase 1

Risks of Vaccines? Endotoxins

- Horseshoe crab blood needed to check for endotoxins. Alternative test rFc (recombinant factor C) needs more study, but the European Pharmacopia has approved the alternative test
- ? Safety: Is unproven
- Endotoxins can cause
 Toxic Shock Syndrome
 with fever & death

Tests for Coronavirus Vaccine Need This Ingredient: Horseshoe Crabs

Modern medicine still depends on this animal's blood to test for bacteria in vaccines. And an alternative test requires further study.

https://www.nytimes.com/2020/06/03/science/coronavirus-vaccine-horseshoe-crabs.html



Prevention: Stress Management

- US: MD's dying on the front lines, ↓ PPE's; 个 nursing home deaths, 个 respirator deaths, job insecurity w/unemployment, 个 stress among farmers needing to kill animals (NYT, May 15), 个 domestic violence
- Russia: Russian doctors are rapidly falling ill. 180 have died so far, and thousands more are ill. Some are from suicides (NYT, 5/15/20)
- Regular stress reduction practices like meditation, yoga, T'ai Chi, etc are now not an option, but essential as part of a complete prevention/treatment program
- Stress can ↓ immune function/ability to fight viruses
- Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. N Engl J Med. 1991;325:606–612.

POTENTIAL TREATMENTS FOR COVID-19

How Best To Respond And Treat COVID-19?



First: Self Care is Important: Pay						
Ittention To Diet	:, Exercise, Sleep					
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	(see you right before bed!)					
OF THE SNACKS						
TODAY!						
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Pay Attention To Mental Health: Higher Risk of Mental Illness

McGinty et al. JAMA June 3, 2020

RESEARCH LETTER

Psychological Distress and Loneliness Reported by US Adults in 2018 and April 2020

Coronavirus disease 2019 (COVID-19) introduced stressors to mental health, including loneliness stemming from social isolation, fear of contracting the disease, economic strain, and uncertainty about the future. We fielded a national survey measuring symptoms of psychological distress and loneliness among US adults in April 2020 and compared results with national data from 2018.

Methods | We fielded the Johns Hopkins COVID-19 Civic Life and Public Health Survey from April 7 to April 13, 2020, using NORC's AmeriSpeak Panel. AmeriSpeak is a probabilitybased panel designed to be representative of the US adult population. The panel is sourced from NORC's area probability sample and from a US Postal Service address-based sample covering 97% of US households.¹ The panel has a recruitment rate of 34% and includes approximately 35 000 members. The sample for the Johns Hopkins survey was drawn from this panel and the survey was administered online. NORC obtains informed consent prior to enrolling individuals in the panel. The Johns Hopkins Bloomberg School of Public Health institutional review board deemed this study not human participants research and waived informed consent.

We measured the prevalence of symptoms of serious psychological distress in the overall sample and among demographic subgroups using the Kessler 6 Psychological Distress Scale, with the validated measure of serious distress defined as a score of 13 or higher on the 0- to 24-point scale.² We also measured the proportion of respondents who reported that Figure. Psychological Distress Among US Adults Aged 18 Years or Older Overall and by Subgroup, April 2020 vs 2018



Potential Pharmaceuticals for COVID-19

- Hydroxychloroquine +/- azithromycin, Chloroquine/Zn
- Alinia (nitazoxanide), Ivermectin +/- doxycycline
- Remdesivir (\downarrow length of illness by 4 days)
- Lopinavir and ritonavir + ribavirin + interferon 1 beta
- Melatonin, mercaptopurine, and sirolimus

Antibody-rich plasma of recovered COVID-19 pts

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- Hung, I., et al. 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. Lancet, May 08, 2020DOI:https://doi.org/10.1016/S0140-6736(20)31042-4

Mice Treated with COVID-AB's from Recovered Patients: JViral load 2500 X

Chinese doctors say they may be able to cure coronavirus without a vaccine

https://bgr.com/2020/05/19/coronavirus-cure-vaccine-treatment/



By <u>Mike Wehner</u> @MikeWehner May 19th, 2020 at 11:44 AM

A new type of coronavirus treatment could give COVID-19 patients relief.

Patients Treated with COVID-AB's: No Statistical Benefit; ? Underpowered

Li, Ling, et al. JAMA, June 2020

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19 A Randomized Clinical Trial

Ling Li, MD, PhD; Wei Zhang, MD; Yu Hu, MD, PhD; Xunliang Tong, MD, PhD; Shangen Zheng, MD; Juntao Yang, PhD; Yujie Kong, MD; Lili Ren, PhD; Qing Wei, MD; Heng Mei, MD, PhD; Caiying Hu, MD; Cuihua Tao, MD; Ru Yang, MD; Jue Wang, MD; Yongpei Yu, PhD; Yong Guo, PhD; Xiaoxiong Wu, MD; Zhihua Xu, MD; Li Zeng, MD; Nian Xiong, MD; Lifeng Chen, MD; Juan Wang, MD; Ning Man, MD; Yu Liu, PhD; Haixia Xu, MD; E. Deng, MS; Xuejun Zhang, MS; Chenyue Li, MD; Conghui Wang, PhD; Shisheng Su, PhD; Linqi Zhang, PhD; Jianwei Wang, PhD; Yanyun Wu, MD, PhD; Zhong Liu, MD, PhD

IMPORTANCE Convalescent plasma is a potential therapeutic option for patients with coronavirus disease 2019 (COVID-19), but further data from randomized clinical trials are needed.

OBJECTIVE To evaluate the efficacy and adverse effects of convalescent plasma therapy for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Open-label, multicenter, randomized clinical trial performed in 7 medical centers in Wuhan, China, from February 14, 2020, to April 1, 2020, with final follow-up April 28, 2020. The trial included 103 participants with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation). The trial was terminated early after 103 of a planned 200 patients were enrolled.

Editorial
 Supplemental content

Updated Results Plaquenil & Azithromycin, Didier Raoult, May 14, 2020

- As of May 14, 2020, 2600 patients were treated with Plaq and Zithromax: 10 died
- Mortality rate < 0.5%</p>
- Survey SERMO: > 50% of MD's using Zithromax & 44% are using Plaquenil (check G6PD, QT)
- As of May 28th, 3737 pts, 0,9% mortality rate
- https://www.youtube.com/watch?v=Xhoi1JKjClk
- <u>http://www.leparisien.fr/societe/coronavirus-didier-raoult-publie-sa-propre-etude-scientifique-pour-defendre-l-hydroxychloroquine-27-05-2020-8325003.php</u>

NYS Study on Hydroxychloroquine & Azithromycin: No Benefit

- 1438 Patients, no decrease in mortality (Zithromax hazard ratio was lower, but not stat. significant)
- Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. Published online May 11, 2020. doi:10.1001/jama.2020.8630

Research

JAMA | Original Investigation

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

Eli S. Rosenberg, PhD; Elizabeth M. Dufort, MD; Tomoko Udo, PhD; Larissa A. Wilberschied, MS; Jessica Kumar, DO; James Tesoriero, PhD; Patti Weinberg, PA; James Kirkwood, MPH; Alison Muse, MPH; Jack DeHovitz, MD; Debra S. Blog, MD; Brad Hutton, MPH; David R. Holtgrave, PhD; Howard A. Zucker, MD

IMPORTANCE Hydroxychloroquine, with or without azithromycin, has been considered as a possible therapeutic agent for patients with coronavirus disease 2019 (COVID-19). However, there are limited data on efficacy and associated adverse events.

OBJECTIVE To describe the association between use of hydroxychloroquine, with or without azithromycin, and clinical outcomes among hospital inpatients diagnosed with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Retrospective multicenter cohort study of patients from a random sample of all admitted patients with laboratory-confirmed COVID-19 in 25 hospitals, representing 88.2% of patients with COVID-19 in the New York metropolitan region. Eligible patients were admitted for at least 24 hours between March 15 and 28, 2020. Medications, preexisting conditions. clinical measures on admission. outcomes. and adverse events were

Supplemental content

BMJ: 4 French Tertiary Care Centers: Hydroxychloroquine: No Benefit Using 600 mg/d X 48 Hrs Prior to Admission

RESEARCH

COPEN ACCESS

Check for updates

Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data

Matthieu Mahévas,¹ Viet-Thi Tran,² Mathilde Roumier,³ Amélie Chabrol,⁴ Romain Paule,³ Constance Guillaud,¹ Elena Fois,¹ Raphael Lepeule,⁵ Tali-Anne Szwebel,⁶ François-Xavier Lescure,⁷ Frédéric Schlemmer,⁸ Marie Matignon,⁹ Mehdi Khellaf,¹ Etienne Crickx,¹ Benjamin Terrier,⁶ Caroline Morbieu,⁶ Paul Legendre,⁶ Julien Dang,² Yoland Schoindre,³ Jean-Michel Pawlotsky,¹⁰ Marc Michel,¹ Elodie Perrodeau,² Nicolas Carlier,¹¹ Nicolas Roche,¹¹ Victoire de Lastours,¹² Clément Ourghanlian,¹³ Solen Kerneis,¹⁴ Philippe Ménager,¹⁵ Luc Mouthon,⁶ Etienne Audureau,¹⁶ Philippe Ravaud,² Bertrand Godeau,¹ Sébastien Gallien,¹⁷ Nathalie Costedoat-Chalumeau^{2,6}

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Additional material is published online only. To view please visit the journal online.

Cita this as: RMI 2020-360-m18///

ABSTRACT OBJECTIVE

To assess the effectiveness of hydroxychloroquine in patients admitted to hospital with coronavirus disease 2019 (covid-19) pneumonia who require oxygen.

DESIGN

Comparative observational study using data collected

outcomes were overall survival, survival without acute respiratory distress syndrome, weaning from oxygen, and discharge from hospital to home or rehabilitation (all at day 21). Analyses were adjusted for confounding factors by inverse probability of treatment weighting.

RESULTS

BMJ: Hydroxychloroquine in Mild-Mod COVID-19: No Help, 个 GI Symptoms

RESEARCH

OPEN ACCESS

Check for updates

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

Wei Tang,^{1,2} Zhujun Cao,³ Mingfeng Han,⁴ Zhengyan Wang,⁵ Junwen Chen,⁶ Wenjin Sun,⁷ Yaojie Wu,⁸ Wei Xiao,⁹ Shengyong Liu,¹⁰ Erzhen Chen,¹¹ Wei Chen,^{1,2} Xiongbiao Wang,¹² Jiuyong Yang,¹³ Jun Lin,¹⁴ Qingxia Zhao,¹⁵ Youqin Yan,¹⁶ Zhibin Xie,¹⁷ Dan Li,¹⁸ Yaofeng Yang,¹⁹ Leshan Liu,²⁰ Jieming Qu,^{1,2} Guang Ning,²¹ Guochao Shi,^{1,2} Qing Xie³

For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2020;369:m1849 http://dx.doi.org/10.1136/bmj.m1849

Accepted: 6 May 2020

ABSTRACT

OBJECTIVE

To assess the efficacy and safety of hydroxychloroquine plus standard of care compared with standard of care alone in adults with coronavirus disease 2019 (covid-19).

DESIGN

Multicentre, open label, randomised controlled trial.

SETTING

16 government designated covid-19 treatment centres in China, 11 to 29 February 2020.

PARTICIPANTS

150 patients admitted to hospital with laboratory

participants who received at least one dose of hydroxychloroquine and hydroxychloroquine nonrecipients were those managed with standard of care alone.

RESULTS

Of 150 patients, 148 had mild to moderate disease and two had severe disease. The mean duration from symptom onset to randomisation was 16.6 (SD 10.5; range 3-41) days. A total of 109 (73%) patients (56 standard of care; 53 standard of care plus hydroxychloroquine) had negative conversion well before 28 days, and the remaining 41 (27%) patients (19 standard of care; 22 standard of care

Retracted Lancet Study: Hydroxychloroquine Chloroquine +/- Macrolide: 个 Mortality

- 671 hospitals on 6 continents. 96 032 patients (mean age 53 Y)
- Hydroxychloroquine (18·0%) hydroxychloroquine with a macrolide (23·8%), chloroquine (16·4%), and chloroquine with a macrolide (22·2%) were each independently associated with an increased risk of in-hospital mortality.
- Compared with the control group (0·3%), hydroxychloroquine (6·1%), hydroxychloroquine with a macrolide (8·1%), chloroquine (4·3%), and chloroquine with a macrolide (6·5%) were independently associated with an increased risk of denovo ventricular arrhythmia during hospitalisation.
- Did NOT evaluate QT intervals, nor K+, Mag++ deficiency
- ACEI (not ARB's) & Statins decreased mortality in women/pts
- Mehra, M, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Published: May 22, 2020 DOI: https://doi.org/10.1016/S0140-6736(20)31180-6

Lancet & NEJM Plaquenil Studies Retracted: June 5th, 2020

Lancet & NEJM Studies retracted for lack of transparency of data **Two Huge Covid-19 Studies Are**

Trials resumed by

WHO

THILOSOPHICAL TRANSACTIONS: CIVING SOME OMPT OF THE PRESENT Undertakings, Studies, and Labours OF THE INGENIOUS IN MANY CONSIDERABLE PARTS OFTHE WORLD Vol I. For Anno 1665, and 1666.

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Retracted After Scientists Sound Alarms

The reports, published in two leading journals, were retracted after authors could not verify an enormous database of medical records.

https://www.nytimes.com/2020/06/04/health/coronavirushydroxychloroquine.html?action=click&module=RelatedLinks&pgtype=Article



Adding Zinc to Plaquenil & Zithromax: J ICU admission, ventilation, mortality

medRxiv preprint doi: https://doi.org/10.1101/2020.05.02.20080036.this version posted May 8, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC 4.0 International license .

Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and

azithromycin alone: outcomes in hospitalized COVID-19 patients

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Role of NLRP-3 Mediated Inflammation: Inflammasomes

Nature Microbiology Vol 4, May 2019

nature microbiology ARTICLES https://doi.org/10.1038/s41564-019-0371-3

Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host

Matae Ahn[®]¹, Danielle E. Anderson[®]¹, Qian Zhang^{1,2,3}, Chee Wah Tan¹, Beng Lee Lim¹, Katarina Luko¹, Ming Wen¹, Wan Ni Chia¹, Shailendra Mani¹, Loo Chien Wang⁴, Justin Han Jia Ng¹, Radoslaw M. Sobota^{® 4,5}, Charles-Antoine Dutertre^{1,6}, Florent Ginhoux[®]⁶, Zheng-Li Shi[®]², Aaron T. Irving^{® 1*} and Lin-Fa Wang^{® 1*}

Bats are special in their ability to host emerging viruses. As the only flying mammal, bats endure high metabolic rates yet exhibit elongated lifespans. It is currently unclear whether these unique features are interlinked. The important inflammasome sensor, NLR family pyrin domain containing 3 (NLRP3), has been linked to both viral-induced and age-related inflammation. Here, we report significantly dampened activation of the NLRP3 inflammasome in bat primary immune cells compared to human or mouse counterparts. Lower induction of apoptosis-associated speck-like protein containing a CARD (ASC) speck formation and secretion of interleukin-1β in response to both 'sterile' stimuli and infection with multiple zoonotic viruses including influenza A virus (-single-stranded (ss) RNA), Melaka virus (PRV3M, double-stranded RNA) and Middle East respiratory syndrome coronavirus (+ssRNA) was observed. Importantly, this reduction of inflammation had no impact on the overall viral loads. We identified dampened transcriptional priming, a novel splice variant and an altered leucine-rich repeat domain of bat NLRP3 as the cause. Our results elucidate an important mechanism through which bats dampen inflammation with implications for longevity and unique viral reservoir status.

B ats, as the only flying mammals, have 'emerged' in both the scientific and general public arenas due to their ability to asymptomatically host a large number of high-profile viruses. Such examples include Ebola virus, Nipah virus, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses, which are capable of causing severe, and often Over-activation of the NLRP3 inflammasome has been linked to a hyper-inflammatory state and immunopathology in viral infection with minimal effect on the viral load³⁶⁻³⁹. However, nothing is known about NLRP3-mediated inflammation in bats. On the basis of the observations of increased longevity and viral asymptomaticity in bats, we hypothesize that the NLRP3 inflammasome, as a

Decreasing Inflammasome Activation: Role of Melatonin

- Inflammasomes are part of our innate immune system that sense pathogens & danger associated molecular patterns (DAMPs). The activation of inflammasomes→↑ proinfl cytokines IL-1β & IL-18
- High level activation of the NLRP3 inflammasome is essential for inducing cytokine storms & lung injury

Melatonin Inhibits NLRP3 Inflammasomes

- An NLRP3 inflammasome-triggered cytokine storm contributes to Streptococcal toxic shock-like syndrome (STSLS) <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6553798/</u>
- Regulation of the NLRP3 inflammasome and macrophage pyroptosis by the p38 MAPK signaling pathway in a mouse model of acute lung injury <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6172370/</u>
- Critical role for the NLRP3 inflammasome during acute lung injury https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4061751/
- Melatonin Alleviates Acute Lung Injury Through Inhibiting the NLRP3 Inflammasome PubMed https://pubmed.ncbi.nlm.nih.gov/26888116-melatonin-alleviates-acute-lung-injury-through-inhibiting-thenlrp3-inflammasome/

Potentially Beneficial Therapies: Melatonin

Zhang, R. et al. Melatonin as a Potential Adjuvant Treatment, Life Sciences, Mar 20, 2020

Melatonin: anti-inflammatory, anti-oxidative and immune enhancing features



Fig. 1. Pathogenesis of COVID-19 and potential adjuvant use of melatonin. We postulated that lungs infected by SARS-CoV-2, and a suppressed immune response, elevated inflammation and excessive oxidation stress proceed unabated, this results in the activation of the cytokine storm. ALI/ARDS may ensue, accompanied by a series of complications, the outcomes of which vary according to the severity of the disease. Melatonin may play a role of adjuvant medication in the regulation of immune system, inflammation and oxidation stress, and provide support for patients with ALI/ARDS and related complications. ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome.

Vitamin D and COVID-19

- Low Vitamin D may ↑ risk of COVID-19 inf and severity
- Vitamin D is needed for innate immunity, boosts immune function against viral diseases & has an immune-modulating effect lowering inflammation
- Respiratory cells in culture document some of these effects of vitamin D & patients with respiratory infections tend to have lower blood levels of 250H Vit D
- 3 Asian hospitals: risk of having low Vit D 个 risk 8 X of contracting severe disease
- Alipio, Mark, Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19) (April 9, 2020). Available at SSRN: https://ssrn.com/abstract=3571484 or http://dx.doi.org/10.2139/ssrn.3571484

Vitamin K and COVID-19: EAT CHEESE PLEASE! (Stilton, Cheddar, Gouda) Vit K involved in blood clotting. Natto \uparrow (Japan)

Vitamin K found in some cheeses could help fight COVID-19, researchers say



Dutch researchers have found a possible connection between vitamin K deficiency and death from COVID-19

https://nationalpost.com/life/food/vitamin-k-found-in-some-cheeses-could-help-fight-covid-19-



researchers-say

Network-Based Drug Repurposing for Novel Coronavirus-2019

Zhou et al. Cell Discovery (2020) 6:14



Disulfiram: ? Repurposed Drug

Targeted Oxidation Strategy (TOS) for Potential Inhibition of Coronaviruses by

Disulfiram — a 70-year Old Anti-alcoholism Drug

Luyan Xu^{1,4,5,7,8}, Jiahui Tong^{2,3,6,7,8}, Yiran Wu², Suwen Zhao^{2,3,*}, Bo-Lin Lin^{1,4,5,7,*}

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201210, China



Figure 1. Schematics illustrating the principle for target oxidation strategy (TOS): A.

Famotidine: ? Repurposed Drug

1620 patients with COVID-19, retrospective study

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study

Daniel E. Freedberg, MD, MS,¹ Joseph Conigliaro, MD, MPH,² Magdalena E. Sobieszczyk, MD, MPH,³ David D. Markowitz, MD,¹ Aakriti Gupta, MD, MS,⁴ Max R. O'Donnell, MD, MPH,⁵ Jianhua Li, MD,⁶ David A. Tuveson, MD, PhD,⁷ Zhezhen Jin, PhD,⁸ William C. Turner, MD,⁶ Donald W. Landry, MD, PhD,⁶ Timothy C. Wang, MD,¹ Kevin J. Tracey, MD,⁹ Michael V. Callahan, MD,¹⁰ Julian A. Abrams, MD, MS¹

- 21% who took Pepcid 60-240 mg/d: Decreased risk of intubation or death
- Randomized controlled clinical trial needed
- No help with PPI's.



Natural Protease Inhibitors: Curcumin, Quercetin, Oleuropein..? Helpful Tx

Article

Potential Inhibitor of COVID-19 Main Protease (M^{pro}) from Several Medicinal Plant Compounds by Molecular Docking Study

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Abstract: COVID-19, a new strain of coronavirus (CoV), was identified in Wuhan, China, in 2019. No specific therapies are available and investigations regarding COVID-19 treatment are lacking.

Potential Enhanced Treatments for COVID-19: GSH & Precursors

- COVID-19 induced inflammation & "cytokine storm syndrome" with Macrophage Activation Syndrome (MAS) have resulted in extreme morbidity & mortality (esp. w/ co-morbidities)
- Deficiency in RBC, serum and alveolar GSH has been published in the medical literature for ARDS, as well as viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress
- Gadek JE, Pacht ER. The Interdependence of Lung Antioxidants and Antiprotease Defense in ARDS. CHEST. 1996;110(6):273S-277S. doi:10.1378/chest.110.6_Supplement.273S
- Gasparini C, Feldmann M. NF-κB as a target for modulating inflammatory responses. Curr Pharm Des. 2012;18(35):5735-5745. doi:10.2174/138161212803530763

Heparin, Diamox, Sildenafil?

Horowitz, et al. Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials. Med Hypothesis. <u>https://doi.org/10.1016/j.mehy.2020.109851</u>

- High mortality rates from sepsis induced DIC due to COVID 19 infection has also been associated with thrombotic events and elevated levels of D-dimer
- Randomized controlled trials of heparin is urgently required, especially in pts on ventilators w/ sepsis induced coagulopathy (SIC) criteria. Also:
- Is a cetazolamide with or without sildenafil + heparin → may ↑ O2 delivery to vital organs through prevention of thrombosis w/ carbonic anhydrase inhibition. Sildenafil may also help breathing efficiency
- Lalande S, Snyder EM, Olson TP, et al. The effects of sildenafil and acetazolamide on breathing efficiency and ventilatory control during hypoxic exercise. Eur J Appl Physiol. 2009;106(4):509-515.

Autopsy Findings: 58% With COVID-19 Had Venous Thromboembolism

Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients (33%)

Limitation: limited sample size

Dominic Wichmann, MD et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. A Prospective Cohort Study. Ann Int Med. 6 May 2020. <u>https://doi.org/10.7326/M20-2003</u>
Non-Recommended Treatments



Non-Recommended Sports Solutions

In the absence of stadium fans, a South Korean soccer team used sex dolls

https://www.nytimes.com/2020/05/18/world/coronavirusnews.html?campaign_id=154&context=menu&emc=edit_cb_20200518&instance_id=18595&module=STYLN_live_tabs&nl=coronavirusbriefing&pgtype=Article®i_id=103987437®ion=header&segment_id=28360&state=default&te=1&user_id=a2c3fadde0fc78562ace&fa1d14b7b07 &variant=1_menu#link-33ca0865



Conclusion: Best Practice Guidelines

- COVID-19 can cause cytokine storm syndrome & MAS in susceptible individuals' w/thrombosis
- Inflammation, inflammasomes, & NFK-B activation all increase chemokines, cytokines
- These cytokines and GSH depletion have been associated with ARDS and injury to int. organs
- Using targeted antivirals like ivermectin +/- doxy with anti-oxidant therapies (NAC, ALA, GSH, curcumin, sulforaphane, melatonin, Zn, Vit C, Vit D, 3,6 B glucan)
- Published case studies show GSH rapidly helps dyspnea
- Randomized, controlled trials need to be done ASAP!

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020

Conclusion: Practice Guidelines

- In patients with significant risk factors (age, DM, Ca, immunosuppression, PN/ARDS w/dyspnea, hemoptysis, cytopenia's, \uparrow ferritin, \uparrow LDH, direct bilirubin, CRP, Ddimers) \rightarrow consider using higher doses of NAC (1800 mg -2400mg) & GSH (2000 mg 2-3 x/day, oral liposomal/IV) which have: antiviral, antioxidant, mucolytic & bronchodilatory effects, along with zinc, Vit C & Vit D, ALA, curcurmin, sulforaphane, Beta glucan, melatonin
- CRP/Procalcitonin: PN, sepsis: Ivermectin + doxy
- Samsudin I, Vasikaran SD. Clinical Utility and Measurement of Procalcitonin. Clin Biochem Rev. 2017;38(2):59-68.

In Patients With Severe COVID-PN & ARDS

- Check D-dimers, LDH, cytopenias, hs-CRP, ferritin: → Rule out Macrophage Activation Syndrome/sHLH
- Check CXR (?GGO) + home pulse ox ? < 90%: 个 risk</p>
- Check CBC & CMP, INR for liver/kidney involvement
- Follow troponin levels/ CPK for cardiac involvement
- Consider Non-invasive Ventilation (NIV) vs PEEP
- Consider heparin, IV Vitamin C, ? CCB's, ? Acetazolamide, sildenafil
- High dose GSH +/- IV NAC. Nebulized GSH?
- Ivermectin & doxycycline (check procalcitonin/CRP)
- Mild or Moderate COVID-19, NEJM, Apr 24, 2020. DOI: 10.1056/NEJMcp2009249

"Wisdom is the marriage of knowledge and experience bound by compassion."

