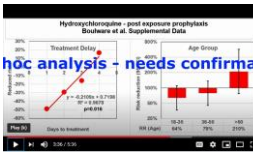

5 min video

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Rapid Deployment Reduce Load & Secondary Peak, multi stage, population nuanced, COVID-19 Strategy

Dear Colleague, 071020-v9.9

We **already** have drugs to **improve medical** and **economic outcomes** and **CHANGE THE CURVES**

I am a /pharmacist (UK) and PhD in Experimental Pathology and run a medical R&D company producing high quality data. Adopting the **NIH's** method of **critical review and synthesis of available data**, we believe that:

We have NOW observational, front-line and other data that support a population- and time- nuanced, multi-stage strategy using common agents to accelerate medical and economic recovery

1. Late stage **dexamethasone** use reduces mortality in patients requiring oxygen or ventilation (by 35%). Earlier use of methylprednisolone and heparin in hospitalized patients may reduce **death rate from >25% to <10%,** along with reductions in intubation and hospital load. Hydroxychloroquine may enhance this effect.
2. **Use of zinc and low toxicity antioxidant ionophores** for pre-emption and prevention and treatment of mild symptoms. Low dose hydroxychloroquine (**with zinc**) for moderate cases, under medical **supervision**.
3. RCT data suggest hydroxychloroquine given **<1 day** post exposure reduces disease in **young** subjects.

This proposed strategy is **Rapidly Deployable to Reduce** resource **Load and disease** escalation at every stage. Our treatment-with-study protocols can be implemented by governments, communities and businesses.

Zinc disturbances may partly **determine** COVID-19 **severity** associated with **high risk** conditions and high-risk **African-American** and **Hispanic** communities. We propose enhancing **zinc**'s antiviral and other actions with natural, **antioxidant**, **ionophore** and **antiviral** agents**,** used **within current indications.**

We have one enemy only: COVID-19 - Please join me in a non-partisan team to execute this strategy.

David Wiseman PhD, MRPharmS. President, Synechion, Inc.

FAST UPDATE v9.9

>> A large randomized study showed use of dexamethasone reduces mortality in late stage patients. Published and anecdotal reports of **reduced death and intubation** with **early hospital** use of **methylprednisolone** may berelated to a combined effect with hydroxychloroquine..
>> A large UK randomized study supports our stance that hydroxychloroquine **ALONE** (HCQ) is **unlikely** to be effective for treatment. **Zinc must be added**. Working through a different mechanism, HCQ **likely** prevents or pre-empts given early in **younger subjects**, with the opportunity for **age-nuanced** COVID-approach.
>> **Reduced death** and **ventilation** with **early** use of **ZINC with HCQ** and azithromycin in an NYU observational study supports early case reports. Other studies report no effect of these drugs **used without zinc**.
>> Early RCT data suggest HCQ given <1 day after exposure reduces disease in younger people.
>> **Zinc and its natural ionophores** for prophylaxis and treatment of mildly symptomatic patients are included in a number of published recommendations and protocols.
>> COVID-19 severity may be related to disturbances in Zn associated with the virus and comorbid conditions.
>> Prospective meta-analyses are needed to confirm promising trends emerging from individual trials.
>> Please see our 5 minute video summary

Executive Summary pages 2 to 4 – Protocol Outlines page 26

1 EXECUTIVE SUMMARY

1.1 Basic hypothesis

- Deployment of this plan will link improvements in **medical** outcomes to **economic** outcomes.
- A multi-stage **age-**, **population- and time- nuanced,** strategy is required.
- *"how bad a person's COVID-19 will be, is partly governed by how zinc metabolism is disturbed,"*
    - *"giving zinc **and** drugs to get where it is needed, will reduce COVID-19"*

1.2 Strategy Summary to Reduce Load and Improve Outcomes

1. Dexamethasone reduces death in late-stage patients requiring oxygen (20%) or ventilation (35%). Earlier use of methylprednisolone and LMW heparin in moderate and severe hospitalized patients appears to **cut death rate from >25% to <10%,** as well as intubation need. Hydroxychloroquine (HCQ) may be additive.
2. Early use of **low dose** hydroxychloroquine and azithromycin **WITH ZINC** in moderately symptomatic patients appears to cut **death rate by about 50%** as well as intubation need. Early data suggest that HCQ given **shortly** (<1 day) after exposure may reduce disease in **younger** patients.
3. **Use of zinc** and **low toxicity antioxidant ionophores** is justified by low toxicity and high potential benefit. **P**re-exposure prophylaxis; **P**re-emption of infection after exposure; **P**reventing worsening of mildly symptomatic patients; **P**rotecting at-risk workers and at-risk disease/ minority populations

Strategy must:

• **<u>reduce secondary peaks</u>** and **Open up America**	• be scientifically sound
• be rapidly deployable, no waiting for long studies	• be low risk, high potential benefit
• use available drugs within current indications	• Include study protocols (see p 26)

Multi-Stage Strategy

Stage	**Pre-**	**At Risk**	**Exposed**	**Home**	**Hospital**	**Hospital**	**ICU**
Goal	**Prevent**	**Prevent**	**Preempt**	**Treat**	**Treat**	**Treat**	**Treat**
Symptoms	**None**	**None**	**None**	**Mild**	**Mild**	**Moderate**	**Severe**
Nutrition	***Provide supplements including: Zinc, Vitamins B, C, D***						
Drugs							
VACCINE	None	None	None				
Currently used	Nothing	Nothing	Nothing	Supportive	Supportive	Supportive	Supportive
Zinc + ionophores	Low Zn	Aggressively treat: diabetes obesity heart, elderly, smoking. Avoid Zn depletors ARB.ACE for H/T	YES	YES			
Famotidine-replace omeprazole				Unknown	YES	For SUP?	For SUP?
Remdesivir				Unknown	Unknown	YES	YES
HCQ/AZI alone	HCQ?		HCQ-early/ young		NO	NO	NO
Zinc+LD HCQ (+AZI?)				Supervised	YES	YES	Unknown
Methylprednisolone, LMW heparin						YES	YES
Dexamethasone							YES

1.3 It goes without saying that…

- <u>Always consult you doctor about treatment, preferably within ongoing studies (e.g. HCQ/Zn, steroids)</u>
- Clinical studies are still needed to confirm effectiveness of this strategy.
- Zinc status will be one of many factors in the development of COVID-19.
- Drugs (even "silver bullets") useful in one stage of COVID-19 may not work, or may be detrimental in another.
- A nuanced strategy targeting specific age, disease and ethnic groups at specific times will likely be needed.
- This strategy complements social distancing and hygiene measures.

1.4 Rapid Implementation in One of Two Models

a) Top Down implementation at Federal / State level, including management of drug supply, reduce hoarding.
b) Grass Roots implementation by businesses, local communities, faith- and disease-based organizations.

1.5 Scientific Overview (see below for detail and references)

- Late stage use of dexamethasone reduces mortality in patients requiring oxygen (by 20%) or ventilation (by 35%).

Patients must always consult with their doctor before starting or changing any medical treatment.

- Clinical data is emerging regarding the success of early use of methylprednisolone (with heparin) in hospitalized patients in reducing death rates and reliance on ventilators. This work is now supported by published[1] and anecdotal reports Detroit (Ramesh, p/c; Marik[2]), as well as from France.[3] Several studies are underway.
- Zinc (Zn) is a mineral essential for many biological processes. It is an antioxidant. Zn supplements are used to treat many conditions and to optimize immunity.
- Zn disturbances (not necessarily deficiency) are found in the elderly and in many diseases/conditions including immune deficiency, susceptibility to viruses, diabetes, obesity, heart disease and sickle cell anemia. Zn disturbances may make COVID-19 worse in these conditions and in populations where common.
- Some drugs cause Zn loss (e.g. omeprazole, losartan). Zn loss may worsen lung damage from smoking.
- Zn is anti-viral and is helpful in treating the common cold. Its action against other types of corona virus in test tubes has been boosted using ionophores, drugs that "open the door" for Zn to enter cells.
- A large UK RCT found hydroxychloroquine (HCQ) ineffective for **treating** COVID-19.[4] HCQ may be effective in young subjects when given within one day of exposure to COVID-19.(supplement to [5] see 4.4.3).
- Most studies report HCQ/AZI **ineffectiveness in treating COVID-19,**[6-9] possibly because it **must be used early and with Zn,** evidenced by preprinted observations from NYU of reduced death/hospice and ventilation need and increased discharges.[10] This supports anecdotal reports (Cardillo, Los Angeles, Armstrong, TX) and an uncontrolled case series of 405 severe COVID-19 patients (Zelenko, NY) using **lower** HCQ doses.
- 92 year old Dr. Ananda Prasad, the foremost expert on zinc[11-15] (including its effects on viruses[16-18]) (along with his wife) recovered from COVID-19 after self-treatment with HCQ and Zn. There is other support for using Zn in COVID-19,[19,20] adding it to HCQ/CQ[17,21-24] or other drugs.[22] A trial is underway (4/30/20).
- HCQ may work partly as a Zn "door-opener," allowing normal body Zn to get into cells where it can inhibit the virus. Zn is also an antioxidant which could limit oxidative stress.
- HCQ and AZI have **severe side, particularly cardiac,**[4,7,25] **effects, interact** with other drugs and each other.[7,26] They must be used under medical supervision. It is unclear if AZI is needed.[27]
- **Much less toxic** than HCQ and AZI are **natural antioxidants** that are also Zn "**door openers**" such as the catechins (green tea, cocoa, other foods), quercetin (many vegetables) and pomegranate extracts.
- Quercetin and the catechins were in the top 200 of 50,000 drugs screened by the Oak Ridge National Laboratory's supercomputer for their theoretical ability to interfere with the action of the SARS-Cov-2 virus.
- In test tubes some of the natural "door openers" boosted zinc's effect against viruses.
- Zn and these less toxic "door openers" are inexpensive and readily available without prescription as nutritional supplements. Most of this plan seeks merely to optimize Zn nutritional status within **current indications and** should not require regulatory approval any more than a recommendation to exercise or lose weight.
- Zn plus natural "door openers" might limit COVID-19 severity, especially in at-risk patients with likely low Zn.
- Quercetin, zinc and other agents have been proposed[28] by the U of Arizona's Andrew Weil Center, E Virginia Medical School[29] and others for prophylaxis and treatment of mildly symptomatic patients. A growing number of ongoing studies employ zinc (see 13.6).
- Our hypotheses require testing in clinical trials.
- COVID-19 variants (e.g. D614G) may contribute to variations in morbidity and responsiveness to treatment.[30-32]
- The effect of proposed treatments may vary in newly infected but previously exposed patients.

1.6 Justification for Fast-Tracking within accepted treatment decision tools

Treatment guidelines have historically been based on a quality of evidence"[33] ranked by the type of trial used to test the treatment. The highest quality evidence comes from Randomized Clinical Trials (RCT), followed by observational and other study designs, expert opinion and basic research. New assessment systems[34] can now[35] integrate RCT and observational evidence, especially when statistical methods rarefy "wrong" conclusions.

Although similar to others, the "new" SARS-CoV-2 causes a "new" disease – COVID-19 - with little high-quality evidence about how to treat it. Of the 2315 (6/25/20) NIH registered studies, only 158 are complete (no results) and 748 are not yet recruiting patients. Treatment protocols are rapidly evolving and basic assumptions challenged such as whether ventilators may be harmful. That these reports often appear first in the media (e.g. WebMed) and on pre-peer review sites (e.g. medrxiv), highlights the weakness of an otherwise (mostly) robust system for making medical decisions.[36] Research perfection must be sacrificed for exigency.[37,38]

Accordingly, the NIH COVID-19 Treatment Guidelines[39] depart from convention in two major ways. a) they revert to a simpler method of evaluating quality of evidence. b) they rely *"heavily on experience with other diseases, supplemented with evolving personal clinical experience with COVID-19, and incorporated the rapidly growing published scientific literature on COVID-19."*

We have adopted the same approach, paying close attention to *in-the-trenches front-line* intelligence and emerging observational studies. With the appearance (6/29/20) of secondary waves,[40] the exigency certainly justifies these departures, as does the low risk and high potential benefit of this proposed plan.

There is a scene in the movie Apollo 13, in which failing carbon dioxide filters on the spacecraft must be fixed in short order. Engineers dump on the table duplicates of everything that is on the spacecraft.

With no time for tests, they must use their knowledge to solve the problem with *"nothing but [what is on the table]."*

This is our Apollo 13 moment.[a]

We have NOW data to support the nuanced use of readily available drugs to accelerate our medical and economic recovery from COVID-19.

2 SCIENTIFIC ABSTRACT, BIO AND CONFLICT OF INTEREST

2.1 Scientific Abstract

Wiseman, DM. Rapid Deployment Reduce Load & Secondary Peak, multi stage, population nuanced, COVID-19 Strategy, based on scoping review. V9.8. Synechion, Inc., Dallas, TX.
synechion.com/COVID/RapidDeploymentReduceLoadCOVIDStrategyLATEST.pdf

Background: There are now signs of secondary peaking. Reintroducing lockdowns is economically unsustainable but there are few medical interventions for widespread and immediate use to reduce healthcare resource overload.

Objective: To formulate a rapidly deployable, multi-stage, population nuanced COVID-19 strategy to: a) reduce resource load; b) reduce secondary peaks; c) protect essential workers, high-risk disease and minority groups; d) reduce escalation of exposed or early stage patients; e) improve the speed and quality of treatment guideline making; f) accelerate medical and economic recovery; g) reduce long-term consequences in recovered COVID-19 patients; h) apply knowledge gained to other therapeutic areas.

Methods: This strategy was devised from a critical (scoping, per PRISMA) review and synthesis (as used in NIH's COVID-19 Treatment Guidelines) of medical literature, observational studies, case reports and clinical judgments of front-line physicians.

Results: A low-risk, rapidly deployable multi-stage, nuanced strategy was devised:

1. Late stage use of dexamethasone reduces mortality in patients requiring oxygen (by 20%) or ventilation (by 35%).
2. For moderate and severe hospitalized patients. early use of methylprednisolone and LMW heparin may reduce death rate from >25% to <10%, along with reductions in intubation and hospital load. HCQ is likely at least additive.
3. For moderate cases, zinc must be added to low dose hydroxychloroquine (HCQ, possibly with azithromycin), and administered early. Early HCQ alone may preempt after exposure, especially in young subjects.
4. For pre-exposed, exposed and mildly symptomatic cases, use of zinc is proposed in a low risk strategy for prevention, pre-emption and treatment of mild symptoms. Zinc's antiviral and other actions may be enhanced with natural, antioxidant, antiviral agents that are also ionophores ("door openers") that help zinc get to where it is needed. These agents are inexpensive, readily available and used within current indications as nutritional supplements.
5. Zinc dysregulation by COVID-19 and comorbidities may partly determine severity associated with high risk conditions such as diabetes, obesity, heart disease and old age and may play an additional role in high-risk African-American and Hispanic communities. Zinc supplementation may be provided along with intensive medical and dietary efforts to assist these high-risk groups, reduce their risks for serious COVID-19, and contribution to healthcare workload.
6. Machine-learning algorithms to predict COVID-19 outcomes may be adapted to reduce confounding in observational data, enhancing their utility and accelerating the formulation of treatment guidelines.
7. Novel screening and tele-medicine technology will further contribute to economic and medical recovery.

Conclusion: Currently available observational, front-line and other data support this low risk nuanced strategy to accelerate medical and economic recovery from COVID-19. The strategy includes clinical study protocol outlines for tracking with methods for rapid data collection. These may be implemented at a government or community level, or by businesses wishing to protect their employee, customers and to drive economic recovery from COVID-19.

We seek: Government, business or community (city, faith- or condition-based) partners to implement this strategy and to track outcomes using scientifically established tools and systems for rapid data collection, analysis and dissemination of treatment guidelines that will accelerate medical and economic recovery from COVID-19.

[a] I incorporated this note on 4/12/20 and was later informed that Commander Lovell had just been on TV to commemorate the mission's 50th anniversary. That next morning, I was struck by the coincidence that it was on that same night of April 13 that the mission went awry.

2.2 Brief personal background

My degree was in pharmacy with First Class Honors in Pharmacology (U Manchester). I am a pharmacist (UK) and trained at the Royal London Hospital. My PhD (Experimental Pathology, U Manchester) and post-doc (Northwestern U) were in lymphocyte and macrophage function, angiogenesis and cytokine signaling. I was lead author on a paper that first described the effect of TGFβ on monocyte chemotaxis and induction of TNFα expression and angiogenesis. This was one of the most exquisitely sensitive effects ever described with fewer than 20 molecules of TGFβ needed for effect.

My work (Google Scholar) has focused on adhesions and fibrosis, women's health, surgical therapeutics and pain. I was one of only 60 Research Fellows at Johnson & Johnson where I headed up a research program. Since 1996, my company Synechion has provided R&D services for medical companies including pre-clinical and clinical studies for product development, FDA submission or peer-reviewed publication. I constructed predictive correlations between animal and clinical adhesion prevention outcomes. Much of our work is performed at the VA Hospital, Dallas and we have a long-standing collaboration with the Pathology Department, U Texas Southwestern Medical Center. My work has included the effect of zinc, other antioxidants and iron on inflammation and fibrosis. I described the relationship between adverse reactions to an iron-based medical device and patients with various genetic or acquired iron-overload propensities.

I have been a reviewer for Cochrane and various journals. I founded the International Adhesions Society, for patient advocacy and research, described *Complex Abdominal and Pelvic Pain Syndrome* (CAPPS) and co-founded the world's first clinic for its treatment at Celebration Health, FL. I pioneered the use of a device for pelvic and abdominal pain and related conditions. I have conducted large, internet and patient-based studies to support public policy initiatives related to informed consent, opioid use and pain, much of which has been presented to FDA, CDC, NIH or AHRQ.

2.3 Conflict of Interest Statement

This document has not been solicited by any other company. I am also the President of KevMed, LLC., which distributes an ultrasound device for the treatment of pain and has a Texas license to distribute *"Multiple Products with Non-Prescription Drugs."* Due to our position that this strategy should be part of public policy that includes control of the products described here, we have refrained from obtaining inventory of these products, but are prepared to do so if conditions change. I am the President of Zaide Reuven's Esrog Farm, LLC., that sells seasonal plant products for non-medical or nutritional use. Although these contain compounds possibly useful in the treatment of COVID-19, there are no current plans to exploit this aspect of those products.

3 ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
AZI	Azithromycin
CI	Confidence Interval
CRP	C Reactive Protein
CQ	Chloroquine
DEX	Dexamethasone
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
HCP	Health Care Personnel
HCQ	Hydroxychloroquine
LDH	Lactate dehydrogenase
LMW	Low molecular weight
MPD	Methylprednisolone
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Clinical Trial
SARS	Severe acute respiratory syndrome

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Rapid Deployment Reduce Load & Secondary Peak, multi stage, population nuanced, COVID-19 Strategy, based on a scoping review

Protect essential workers & high-risk groups/ Reduce escalation of exposed or early stage patients

4 STRATEGY DETAIL AND SCIENTIFIC RATIONALE

4.1 Goals, methodology and project evolution

As the COVID-19 pandemic began accelerate in the Spring of 2020, our primary objective was to determine what pharmacological agents could be deployed immediately. Based on an initial review of what was known about COVID-19 in late March 2020, there appeared to be an associated between acquired or genetic zinc deficiency or dysregulation and high risk COVID with age, obesity, diabetes, heart disease, and African-American and other minorities. Our initial working hypothesis of:

"how bad a person's COVID-19 will be, is partly determined by their zinc levels,"

was the basis for a literature exploration of what might form the basis of therapeutic intervention. What may be more important is how Zn metabolism is disturbed both by the virus and by co-morbid conditions. As we began to explore this hypothesis, it became obvious that any treatment would need to form part of a multi-stage, population nuanced, attack on COVID-19. Further, we would need to link scientific data and economic outcomes. Accordingly, we considered more broadly other modalities for rapid deployed in a multi-stage, low risk strategy to:

a) reduce resource load; b) reduce secondary peaks; c) protect essential workers, high-risk disease and minority groups; d) reduce escalation of exposed or early stage patients; e) improve the speed and quality of treatment guideline making; f) accelerate medical and economic recovery; g) reduce long-term consequences in recovered COVID-19 patients.

The review of the literature on which this work is based is a "scoping review", defined[41] as:
"a type of knowledge synthesis, follow[ing] *a systematic approach to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps."* To conform with methodological quality and reporting we have used the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist.

Using the method described in the NIH Treatment Guidelines, we synthesized literature, observational and case reports, adding four elements. 1. We obtained in-the-trenches intelligence from front-line physicians and study authors. 2. We reviewed at some level the 35,000 some COVID preprint or pubmed papers (6/29/20). 3. We scrutinized buried supplemental and underreported data. 4. We formed strategy as we often do in drug development, from incomplete data.

Additional discussion is included addressing technical and methodological challenges confronting the execution of studies that will test our hypotheses. We were able to offer a number of suggestions to enhance the quality of some manuscripts, we contributed to information presented at a Senate Committee hearing, and prompted an enhancement to a treatment protocol at a major institution. We have submitted a letter to NEJM. This is a work in progress.

By its urgent nature and the expanding understanding of COVID-19, this review cannot be exhaustive and a number of areas have been flagged as particularly requiring expansion; thus [expand].

4.2 Strategy

Reduce health resource **overload**, improve outcomes, by limiting escalation from one stage to the next: *exposure -> mild symptoms -> requiring hospitalization*.

- Late stage use of dexamethasone reduces mortality in patients requiring oxygen (by 20%) or ventilation (by 35%).[42]
- **Early** use of methylprednisolone and heparin in moderate and severe hospitalized patients appears to **cut death rate from >25% to <10%,**[1] as well as intubation need. See also anecdotal report[2] regarding the Marik/MATH+ protocol), Methylprednisolone, Ascorbic acid, treatment with Heparin and other agents (Zn,

thiamine, Vit D[43]), now includes famotidine for SUP and possible anti-COVID activity -5/14/20). Zn depleting drugs such as omeprazole might be avoided.

- Early use of low dose hydroxychloroquine (HCQ) and azithromycin (AZI) **WITH ZINC** in moderately symptomatic patients appears to cut **death rate cut by about 50%** as well as intubation need. (see 4.5.2),[10]
- **Pre-exposure Prophylaxis** Provide Zn supplements (+- flavonoids) at normal daily dose (10-15mg) to pre-exposure subjects.
- **Pre-empt** development of infection in exposed but asymptomatic subjects with normal dose Zn (10-15mg) plus flavonoids. HCQ given early and alone may preempt after exposure in **younger** people (see.4.4.3)
- **Prevent progression** of mildly symptomatic patients to need **diminishingly effective and available** health resources. Zn lozenges or higher dose Zn (50mg) plus flavonoids. Treat with HCQ/AZI **and** Zn only if necessary.
- **Protect** at-risk populations (e.g. diabetics, elderly, smokers, minorities – **African American** and other highly affected **minorities**), reduce their impact on resource load. Use loading dose Zn followed with maintenance, plus flavonoids. Where possible provide education/monitoring. Vitamin D and nutrition to stabilize underlying conditions – e.g. glucose levels in diabetics, smoking cessation nicotine substitution.

- Being that the strategy is based largely on a scoping review, synthesizing of observational, case report and other literature. It must be implemented along with controlled clinical study elements to test the hypotheses on which the strategy is based. See for section 5 protocol outlines.
- Strategy must be in the context of an intensive primary and self-care effort to control disease in those groups most vulnerable. A number of measures (on line services, mobile apps) along these lines related to diabetes are discussed by the Center for Evidence-based Medicine.
- Consider providing nutritional supplements to residents of impoverished and densely populated areas. The City of Dallas has established a free milk initiative. Initiate community wide efforts to encourage exercise, weight reduction, appropriate nutrition, development of lung capacity through deep breathing exercises and integrative approaches etc. Employment of suitably apt but currently unemployed people as community-based "health facilitators" would further this goal and provide a source of income that will help restart the economy.
- Strategy should be implemented along with distancing and hygiene measures.
- Although preliminary data concerning remdesivir, are positive, its initial use may be limited to certain patient categories and not available to wider populations. Accordingly, there will remain a need for parallel strategies.

4.3 Late Stage Strategy: Steroids, Heparin

4.3.1 Use of Steroids for moderate and severe COVID-19

- The guidelines of NIH (6/11/20)[44] were:

The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without ARDS **(BIII)**.
• In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication.
• For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid **(BII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

The guidelines were amended (6/25/20)[39] following the recent announcement[42]]

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI).
• The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI).

- A of 6/24/20, there are 26 studies registered at clinicaltrials.gov involving methylprednisolone.

4.3.1.1 Observational Studies

- Despite this, there is a pre-print Chinese report[45] as well as anecdotal reports[2], that based on non-COVID-19 ARDS,[46] **earlier, timed** use of corticosteroids may help to reduce fulminant oxidative stress and reduce

significantly the need for mechanical ventilation. Further discussion of the use of steroids can be found in PulmCrit a popular critical care blog.

- Dr. Ramesh and colleagues in Detroit, using a pre-test post-test semi-prospective quasi-experimental design, found that prior to using **methylprednisolone (MP)**, the 14+ day death rate among hospitalized patients was 26% (n=81). After employing the protocol this reduced to 14% (n=132) (OR 0.45 CI 0.22 – 0.91, p=0.024).[1] The pre (70%) and post- (79%) were both treated with HCQ, the post-group being treated generally earlier. Dr. Ramesh kindly relayed (personal communication 5/6/20):
  - "These data included late-presenting patients and that for administrative delays some patients in the pre-protocol arm were treated with steroid, and some in the post-protocol arm were not.
  - The OR was about 0.45 in composite and also similar OR in each of the individual component of the primary endpoints including mortality. When we studied any steroids vs no steroids, the OR did get even better close to 0.3 for mortality, but we felt that was not our primary intention to study. We did not have data on 30-day mortality at submission. We have subsequently, and the data remains strong with KM curves separating out early in hospitalization of the post-protocol cohort.
  - With earlier treatment, the death rate is less than about 2%. Dr. Ramesh also reported that he is aware of hundreds of patients in the Detroit area being treated similarly with similar results. Floor and ICU units are gradually closing down.
  - See discussion of this study at Pulmcrit.
- A pre-printed French retrospective observational study in 70 patients with pneumonia-related respiratory failure, with propensity score matching found associated with steroid (unspecified) use a reduction of risk of intubation from 65% to 18% by 47.1% (95% CI -71.8% to -22.5%).[3]
- In a sub cohort of 201 patients in a retrospective cohort study (C Wu) from Wuhan, 84 patients developed ARDS. Of the 50 that were treated with MP 23 (46%) died, compared to 21/34 (62%) deaths for non-treated patients (HR, 0.38; 95% CI, 0.20-0.72, p =0.003).[47] These data were not subject to propensity score matching, and the authors note that patients treated with MP were generally sicker than those not treated.
- A Spanish retrospective study[48] found a reduction in mortality associated with steroids from 24% [16/67] to 14% [55/396] (OR 0.51, 0.27 - 0.96, p= 0.044), (RRR 0,42 [0.048 to 0.65). (further discussion [49] with Fadel[1] paper).
- A pre-printed retrospective observational study (J Wu) in 1514 Chinese patients[50] has found an **increase** in mortality associated with the use of corticosteroids (unspecified).[50] The patients in this study appear (PE Marik, pers comm) to be at a more advanced stage of disease than those in the French[3] and Detroit[1] studies (Table 2) and there appears to be a worsening of response once patients are in the ICU or have mechanical venthilation (Table 1). The doses uses appear lower than those in the Detroit[1] study and the Marik/EVMS Protocol.

Table 1: Abstraction of data from J Wu Chinese study[50] on the effects of steroids in COVID patients.

Association of systemic corticosteroid use and in-hospital mortality in COVID-19 patients in multivariable Cox regression analysis.

From: Wu et al., 2020	**Before matching**				**Inverse probability of treatment weighted**		**Propensity score matching**	
Variables	**Cox**		**Time-varying Cox**		**Time-varying Cox**		**Time-varying Cox**	
	Adjusted HR (95% CI)	***P* value**	**Adjusted HR (95% CI)**	***P* value**	**Adjusted HR (95% CI)**	***P* value**	**Adjusted HR (95% CI)**	***P* value**
Systemic corticosteroid use				**SEVERE**				
Yes	1.77 (1.08, 2.89)	0.023	2.83 (1.72, 4.64)	<0.001	1.43 (0.82, 2.49)	0.201	1.55 (0.83, 2.87)	0.166
				CRITICAL				
Yes	2.07 (1.08, 3.98)	0.028	3.02 (1.59, 5.73)	0.001	3.34 (1.84, 6.05)	<0.001	2.90 (1.17, 7.16)	0.021

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval.

- A number of differences in the timing, dose, type of steroid and degree of progression of disease may be critical factors in the efficacy of steroids for COVID-19. Use of (unspecified) corticosteroids in 248 Chinese patients in a retrospective study was associated with adverse outcomes[51] as was the case in 132 non-severe Chinese patients.[52]

- A meta-analysis[53] concluded that the use of corticosteroids *"in critically ill patients with COVID-19 did not improve or worsen mortality."* Another literature review could not *"fully support the routine use of corticosteroids in COVID-19, but some findings suggest that methylprednisolone could lower mortality rate"*[54]
- A systems biology analysis of gene expression in SARS-Cov-2 infected tissue, and various cell lines suggests that methylprednisolone (and to a slightly lesser extent prednisolone) may be uniquely suited for treatment of cytokine storm in severe COVID-19 compared with other members of its class (hydrocortisone, prednisone, dexamethasone).[55] This approach also predicted the inability of HCQ to act in these same pathways. Effects of Zn on these pathways [expand] [56,57]
- Use of steroids in previous outbreaks of SARS may be associated with development osteonecrosis of the femoral head.[58]
- Use of steroids (but not TNFa antagonists) by IBD patients appears to be associated with increased adverse COVID-19 outcomes.[59] A Portuguese study also found higher incidence of COVD-19 associated with chronic steroid use in rheumatological patients.[60]
- Other differences between the actions of corticosteroids have been discussed[expand][61-63] [different effects on inflammasome - expand][64]

Table 2: Comparison of observational studies involving steroids in COVID-19

	J Wu[50]	J Wu[50]	Fadel[1]	Bani-Sadr[65]	Chroboczek[3]	C Wu[47]	Cruz[66]
N	1514 N=531 steroid	249 N=159 steroid	81 pre-steroid 132 steroid	85 pre-steroid 172 steroid	70	84	396 steroids 67 no steroids
Definition	Severe Required O2	Critical MV or ICU or shock	Required O2 (moderate) or MV (severe)	Needs oxygen or more	Severe – required O2	Severe - ARDS	Hosp patients with COVID pneumonia
CRP mg/l	14 no steroid 36 steroid	47 no steroid 88 steroid	98 pre 88 post	98 pre 89 post	170	83	122 no steroid 141 steroid
Dose	MP equiv 40mg/d	MP equiv 40mg/d	MP – 0.5-1mg/kg/d	MP or Pred 1mg/kg/d	Not stated	Not stated	1 mg/kg/d MPE, but also also pulses
Drug	DEX, MP, HYDRO – not specified	DEX, MP, HYDRO – not specified	MP	MP, or Prednisone	Not stated	MP	MP or equivalent
Started	<24h Dx as severe, median 2.2h	<24h Dx as severe, median 0.1h	From presentation Pre-test 5d Post-test 2d	On SOB	13d after symptom onset	Not stated	10d after symptom onset
Length of Tx	6d (iqr3-10)	5d (3-7)	3d mod, 3-7d severe	3-4 w, with last week taper	Not stated	Not stated	
Mortality	28d 21% steroid 3.7% no steroid (corrected	28d 51% steroid 17% no steroid	>14d 26% pre 14% post	20% no steroid 18% steroid, before Cox adjustment	28d 1/70 (all study patients)	62% 21/34 No MP 46% 23/50 MP	13.9% vs 23.9%
HR/OR/RR CI is 95%	HR=1.43, 0.82-2.49, p=0.201 in IPTW/Time vary HR=1.55, 0.83-2.87, p=0.166 in	HR=3.34, 1.84-6.05, p<0.001 in IPTW/Time vary HR=2.90, 1.17-7.16, p=0.021 in	Death OR 0.45, 0.22 – 0.91, p=0.024 OR 0.3 steroid/non-steroid	Death: After: HR 0.86; 0.47-1.56; p=0.62) – bivariate But adj for age NEWS etc. HR = 0.47; 0.23 - 0.97; p=0.04)	Reduced risk of intubation from 65% to 18% by 47.1% (-71.8% to -22.5%). RR – 0.22	Death HR, 0.38; 0.20-0.72; p = 0.003	OR 0.51 [0.27 - 0.96], p= 0.044). reduced mortality by 41.8% (RRR 0,42 [0.048 to 0.65).

Design	Retrospective, observational, propensity matched/ time vary	Retrospective, observational, propensity matched/ time vary	Semi Prospective, Pre/post quasi-experimental	Retrospective, Pre-post	Retrospective, observational propensity matched	Retrospective, observational **NOT** propensity matched	Retrospective, observational, propensity matched
HCQ/AZI use	NR		HCQ - 70.4 (SOC), 78.8% steroid group AZI – yes, but NR	HCQ 13.3% pre/ 6% post	HCQ 17% AZI 41%	NR	Almost all received HCQ 50-60% AZI

NR Not reported

- Early reviews[67] and guidelines,[68] including from WHO[69] did not support the use of steroids in COVID-19. These conclusions may not have considered the importance on the timing of treatment.
- Although advocated by some for many years,[70] the subject of using steroids in sepsis patients is not without controversy. A Cochrane review[71] concluded:
  "Overall, low-quality evidence indicates that corticosteroids reduce mortality among patients with sepsis. Moderate-quality evidence suggests that a long course of low-dose corticosteroids reduced 28-day mortality without inducing major complications and led to an increase in metabolic disorders."
- A UK observational study found that high serum cortisol was associated with COIVD-19 mortality.[72]
- Other discussion and review.[54,67,73-77]
- Other smaller observational studies with: favorable (methylprednisolone[78-80], with LMW heparin[81]) (dexamethasone[82], various[83]), mixed,[84] neutral[85] or negative findings related to use of steroids.

4.3.1.2 Possible Synergy of MPD with HCQ

(excerpted from letter submitted to Int J Infect Dis, see also 4.4.1.5)

A study ("Arshad") from the Henry Ford Health System (HFHS) ostensibly reported the early effect of HCQ. [86] The 2541 consecutive COVID-19 subjects included (M Ramesh p/c) over seven weeks from 3/10/20 included 213 consecutive patients, starting 3/12/20 for two weeks, in a previously reported pre/post quasi-experiment [1]. Fadel's conclusion that *"early short course of methylprednisolone* [MPD] *in … moderate to severe COVID-19 … improved clinical outcomes"* did (M Ramesh p/c) guide treatment protocols for the remaining five weeks of Arshad. Comparing the two studies (Table 1Table 3):

1. *A similar "control" (~26%) mortality*
   (Row A) Late 70% HCQ use + late 57% steroid use, sicker (needing at least oxygen) patients
   = (Row C) No use HCQ + "mostly early" 36% steroid use, sicker plus less sick patients
2. *A similar treatment mortality (~13.5%):*
   (Row B) Early 79% HCQ use + early 68% steroid use, sicker patients
   = (Row D) Early 100% HCQ use + mostly early 79% steroid use, sicker plus less sick patients

With much lower HCQ usage, a similar pre/post study [65] found steroid-associated reduced mortality, but only after multivariate adjustment. These studies support the early combined in-hospital use of HCQ and MPD to reduce mortality and need for ventilation. This contrasts with an effect of dexamethasone limited to more advanced disease [87] possibly reflecting between-steroid pharmacological differences [55]. Early use of MPD is supported by other studies, some of which [79] also involve HCQ with possible synergy via a lysosomal mechanism [88]. HCQ given alone at this stage, may require zinc [10]. In Arshad's less sick and comorbid (propensity matched) patients, HCQ's steroid requirement appears reduced. For early post-exposure prophylaxis in young subjects ([5], supplement), HCQ requires neither zinc nor steroid.

Table 3: Comparison of related studies involving hydroxychloroquine and steroids in COVID-19

Row	Study	Group	Data type	n	HCQ Use%	Days	HCQ + AZI Use %	Steroid Use %	Days	Mortality % (HR)	HR. Cox

A	Fadel	Standard	Crude	81	70.4	3 (1-4)	in HCQ	Late 56.8	5 (3-7)	26.3	
B	Fadel	Steroid	Crude	132	78.8	1 (0-2)	in HCQ	Early 68.2	2 (1-3)	13.6 (0.52)	
C	Arshad	None	Crude	409	0	NA	0	35.7	NA	26.4	
D	Arshad	HCQ	Crude	1202	100	1 (1-2)	0	78.9	NK	13.5 (0.51)	0.34
E	Arshad	None/AZI	Propensity	190			0	44.2	NK	NK	-
F	Arshad	HCQ ± AZI	Propensity	190			100	44.2	NK	NK	0.487
G	Arshad	AZI	Crude	147	0	NK	100	38.8	NK	22.4(0.85)	1.05
H	Arshad	HCQ/AZI (severe)	Crude	783	100	NK	100	74.3	NK	20.1 (0.76)	0.294
I	Bani-Sadr	Standard	Crude	85	13.3	NK	0	12.9	At SOB	20	-
J	Bani-Sadr	Steroid	Crude	172	6	NK	0	69.2	At SOB	18 (0.9)	0.47

NK Not known (information not supplied in paper)
Days Median days (IQR) to drug use

4.3.1.3 Inhaled Steroids

- A rapid review of the available literature concerning the use of inhaled corticosteroids by patients with asthma or COPD concluded that there was insufficient evidence to support the withdrawal of treatment, or increased dosing, in these patients.[89] The inhaled corticosteroid ciclesonide [90] inhibited SARS-CoV-2 replication in vitro, and successfully treated one[91] and three patients.[92] It was used in 8 patients (no outcome described) on a cruise ship.[93]
- A large cohort study of UK health records found that patients receiving inhaled steroids with COPD (HR 1.38) or asthma (1.52) had a higher risk of death form COVID-19 than those taking beta agonists or muscarinic antagonists; this may be due to differences in disease severity.[94]
- Successful use of budesonide, given by nebulized, plus oral aspirin, clarithromycin and zinc has been described in two patients.[95] In vitro, in combination with a β2 agonist and a muscarinic antagonist, budesonide interfered with the activity of a common cold coronavirus.[96]

4.3.1.4 Randomized Studies

- In a large RCT "RECOVERY Trial" in UK,[87], 2104 and 4321 patients were randomized to dexamethasone 6 mg od (po or iv x 10 days) or usual care alone. Dexamethasone reduced 28-day mortality by one-third in ventilated patients (from 41% - ageadjRR 0.65, 0.51 - 0.82; p=<0.001) and by one fifth in other patients receiving oxygen only (from 25% - ageadj0.80 [0.70 to 0.92]; p=0.002). There was no benefit among those patients who did not require respiratory support (from 13% - ageadj1.22 [0.93 to 1.61]; p=0.14)." These findings dovetail with those from the observational studies that suggest that early, rather than late MPD is effective in reducing progression of patients to requiring ventilation. Overall mortality was reduced 17% (age adjusted RR 0.83; 0.74-0.92 <0.001). The effect was greatest (RR0.64; 0.52−0.78) in younger (<70) patients, and when given late (RR0.68; 0.58−0.80)(> 7 days from symptom onset). [data corrected from announced[42] version which inadvertently reported 99%CI as 95% CI]
- A small Spanish study involving methylprednisolone showed reduction in a composite endpoint. This was mainly driven by ICU admission although the results were challenging to interpret given the partial randomization.[97]

4.3.1.5 Steroid – zinc interactions

- In addition to the well-known effects of steroids on calcium metabolism,[ref] there are interactions[98-102] between steroids and zinc homeostasis that may have implications for COVID-19. These interactions are likely part of a wider homeostatic system involving Zn and Vitamin D (6.9).

4.3.2 Use of heparin in moderate and severe COVID-19

- Early administration of low molecular weight heparin is advocated to reduce the effects of coagulopathy and COVID-19 induced endothelial cell dysfunction. [I have briefly discussed with Dr. Marik the wisdom of exploring the use of low dose aspirin in mildly symptomatic patents at home – expand] Favorable hypoxia

and survival [103] as well as immunological (increased lymphocyte count, reduced IL6)[104] in COVID-19 patients have been reported. [expand]

- A pre-printed observational study found a 79% reduction in death in therapeutically anticoagulated (mainly heparin and enoxaparin) COVID-19 ICU patients (HR 0.209, 0.10 -0.46, p <0.001).[105]
- Heparin has other properties that make It suited for use in COVID-19 patients.[106] Further, based on computer simulations[107] borne out by in vitro studies, heparin,[108] other glycosaminoglycans (e.g. heparan sulfate[109]) and sulfated polysaccharides[110] are potential ligands for the spike protein and/or docking complex. Unfractionated heparin was more effective than LMW forms were more effective in inhibiting binding of spike protein to RT4 urinary bladder transitional carcinoma cells expressing ACE2 and TMPRSS2 proteases, a possible in vitro model of viral interactions with host cells.[111] Heparin inhibited invasion of SARS-Cov-2 into Vero cells in vitro.[112] Heparin[108] as well as LMW heparin enoxaparin[112] may act partly by inducing a conformational change in the spike protein. See review[113] for actions of heparin and others GAGS in COVID-19.
- Plasma heparanase, believed to contribute to vascular damage via degradation of endothelial glycocalyx, and heparan sulfate were raised in COVID-19 patients and associated with disease severity. Prophylactic LMW heparin was associated with reduced heparinase activity.[114]
- There is some discussion about the best dose and type of heparin to be used.[115]
- A new section on antithrombotic therapy was added (5/12/20) to the NIH COVID-19 Treatment Guidelines.[116] See further discussion at PulmCrit.
- Pixatimod is a synthetic sulfated inhibitor of heparinase with a number of anti-cancer, anti-inflammatory and antiviral properties. It binds to spike protein S1 receptor binding domain (RBD), inhibits binding of S1 RBD to Vero cells expressing ACE2 receptor, infection of Vero cells.[117]
- A blood purification device continaing heparin-bound beads, has been proposed for use in COVID-19.[118]

4.3.3 Use of ascorbic acid in moderate and severe COVID-19

- High dose ascorbic acid is also being used based on work by Dr. Marik and others in sepsis. According to the PulmCrit blog, that work was: "*perhaps the most polarizing publication in recent memory*," partly because despite the finding in a related study by other workers of reduced mortality (a secondary endpoint), certain peculiarities of the protocol design and execution gave rise to controversy. This controversy may have clouded the consideration of the MATH+ protocol for COVID-19.
- The use of ascorbic acid has been proposed both for its anti-viral and immunomodulatory properties, as well as a synergy with quercetin which may include preventing the pro-oxidant "quercetin paradox effect."[29]

Table 4: Proposed ascorbic acid and quercetin regime for COVID-19 from[29]

	Quercetin	Vitamin C
Prophylaxis	250–500 mg BID	500 mg BID
Mild cases	250–500 mg BID	500 mg BID
Severe Cases*	500 mg BID	3 gr q6 for 7 days

**ARDS-like presentation, require assisted ventilation/intubation, ICU hospitalization.*

4.4 Hydroxychloroquine – without and with zinc

4.4.1 Therapeutic use of Hydroxychloroquine (+- AZI) but without Zn

- On 6/15/20 FDA announced that it had revoked[4] its Emergency Use Authorization (EUA) of HCQ/CQ, citing primarily the as yet unpublished results of the RECOVERY trial (see 4.4.1.6).
- Based on this, NIH recommendations (6/16/20[119] revised from[116]) are:
  - The Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial

4.4.1.1 Mechanism of action

- Several mechanisms of direct anti-viral activity of CQ and HCQ have been proposed,[44,120,121] Both HCQ and CQ were able to inhibit SARS-Cov-2 infection in vitro.[122,123]
- Other mechanisms for HCQ have been proposed, including immunomodulation,[123,124] modulaiton of iron homeostasis[125] (see 6.10.8) and, based on in silico observations, interactions with the spike protein, docking complex[107,126] other viral proteins[127] and related attachment[128] sites complementary to virus sites targeted by

AZI.[128] Using a pseudotype virus, HCQ and CQ bound to ACE2, with an equivalent suppression of entry of the virus into cells expression high ACE2.[129]

- Differences in response may be due to differences in disease stage which may have pharmacodynamic as well as pharmacokinetic consequnces.[130]
- It has been suggested that HCQ may interfere with trained immunity, i.e. the innate immune response residing mainly within macrophages and NK cells.[131]
- HCQ also has hypoglycemic properties and is approved in India for patients with uncontrolled diabetes.[128]
- See further discussion in 4.4.3.
- HCQ acts as a Zn ionophore, allowing normal body Zn to enter cells where it can inhibit the viral replicase. Zn is also an antioxidant which could limit oxidative stress. Differences in Zn levels/dysregulation among different populations may partly explain differences in outcomes observed.

4.4.1.2 Pharmacokinetics

- The unusual and poorly understood pharmacokinetics of HCQ (and CQ) (see 7.1.2, 7.1.3) with a long half-life and large and variable volume of distribution likely results in wide variations in blood/plasma levels of HCQ[132] and may account for variations in susceptibility to cardiac events, as well as efficacy. There are emerging pharmacokinetic models and data for HCQ in COVID-19 patients[123,133-136] and HCQ regimes vary widely in clinical practice as well in in clinical trials (reviewed by [137]), including whether or not a loading dose is used. Some dosing regimens may well predispose to toxicity.
- In simulations, reduction in lung pH (that may occur in COVID-19) led to 20, 4.0- and 2.7-fold increases in levels as well as dwell time of CG, HCQ and AZI respectively. When combined with renal failure, these increases were 30-, 8.0- and 3.4-fold respectively. Although systemic exposure increases 20-30%, [138], these sorts of increases may contribute to HCQ/AZI toxicity when administered later in disease progression.
- A small study, part of the UK REOVERY trial, evaluated HCQ levels in seven COVID-19 patients after dosing with 800mg q6h apart (sic), then 400mg q6h later followed by 400mg q12h subsequently. Based on modeling, HCQ concentrations were lower than expected.[139]

4.4.1.3 Adverse Effects

- Cardiac related-events were associated with the use of HCQ and/or AZI for COVID-19[7,25,140,141] (Table 5). An observational and partly self-controlled cohort multinational study using data from over 1.8 million patients from multinational electronic health and claim records concluded that: "*Short-term hydroxychloroquine treatment is safe, but addition of azithromycin may induce heart failure and cardiovascular mortality, potentially due to synergistic effects on QT length.*"[142] HCQ+AZI risk of 30d cardiovascular mortality (CalHR 2.19, 1.22- 3.94]), chest pain/angina (CalHR 1.15, 1.05-1.26]), and heart failure (CalHR 1.22, 1.02- 1.45).
- Other observational studies report increased mortality when AZI is added to HCQ.[143,144]
- HCQ is generally regarded as being less toxic than CQ. CQ is known to increase the risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and is accordingly contraindicated.[145] Caution has been expressed regarding the use of CQ by asymptomatic carriers of genes predisposing to G6PD.[146] G6PD is regarded as less of a concern with HCQ, however there has been a case reported of hemolytic anemia in a COVID-19 patient with G6PD[147] (see 6.10.1).
- Although adverse events occurred in a preemption study involving HCQ, none were serious.[5]
- In patient telemetry has been used to monitor patients taking HCQ/AZI[148] and an inexpensive patch-based sensor that detects changes in the QT interval is being eveloped.
- A meta-analysis of adverse events reported in nine RCTs involving HCQ for any indication found an increase risk of skin pigmentation (OR, 4.64; 1.13 - 19.00), with other AEs as non-significant: rash, GI effects, headache, dizziness, fatigue; and visual AEs. Cardiac toxicity was not reported.[149]

4.4.1.4 Effect on Viral Load

[expand]

In a small Russian study, HCQ had no effect on viral load in nasopharynx of patients being treated for mild COVID-19.[150]

4.4.1.5 Observational Studies

- With early Chinese reports using CQ,[151] a small, single arm study with parallel controls from another institution conducted in France examined the effect of HCQ/AZI in COVID-19 patients. With several design and interpretation issues, this study sparked much interest in HCQ/AZI[152,153] and has since been expanded.[154,155]

- Other small observational studies have report success with HCQ/AZI. A Lebanese group report success with early use of HCQ/AZI in 21 patients.[156] In a small respective cohort study from S. Korea, treatment of moderately severe patients with HCQ and antibiotics including AZI, was associated with improved outcomes (viral clearance, hospital stay, symptom resolution) compared to lopinavir-ritonavir plus antibiotics or conservative treatment.[157]
- A Chinese retrospective study found that low dose HCQ reduced mortality in critical patients from 47% to 19%. IL6 levels were also reduced in treated patients, but not in untreated patients.[27] After Cox regression was used to adjust for other factors, the adjusted HR for fatality was 0.36 (95% CI: 0.18–0.75; P=0.006). Propensity score matching was not performed. Earlier (< 5d vs > 5d after admission) treatment with HCQ was associated with a lower mortality (9% -1/11 vs 22% - 8/37) than later treatment. The authors attribute the lack of cardiotoxicity to the low dose of HCQ used and the non-use of AZI.
- A number of mostly pre-peer review observational studies, have shown mostly minimal[158] or detrimental effects of HCQ or HCQ/AZI[6,7 140,159] (see [58,116,160-166] for reviews or meta-analyses, see [167] for reviews made involving ROBINS-I[35,144] quality assessment). Although a number of these studies used statistical methods such as propensity score matching to account for the possibility that the patients given HCQ/AZI were the sicker patients who were more likely to have poorer outcomes, these methods cannot completely rule out this possibility, as suggested by the discussion of the Geleris study[6] by Yu.[27]
- One systematic review and meta-analysis[144] found a decreased mortality with use of HCQ (bit not with AZI) among European and Asian, but not American studies.
- When comparing study outcomes, especially in observational studies, it is important to define the stage in the disease at which patients began treatment. Although statistical techniques such as propensity matching may help to reduce confounding due to differences in disease stage etc., they cannot completely eliminate them. A retrospective Spanish study of patients with rheumatological conditions found no difference between patients taking or not taking HCQ on the incidence of confirmed or suspected COVID-19 cases.[168] A similar conclusion was drawn from an Italian study.[169] These studies have a number of limitations, including the inability to control for any differences in disease exposure.
- The apparent (mostly reported) ineffectiveness of HCQ (no Zn) is now also being reported as an incidental finding in a number of observational studies primarily directed at other questions.[3,170]
- (see also 4.3.1.2) A large observational study found a benefit of HCQ over no treatment (see Table 5 Arshad[86]) with a HR reduction of 66% for HCQ and 71% for HCQ+AZI 71% compared to neither treatment ($p < 0.001$). This study included patients from the quasi-experimental study involving methylprednisolone [1] and suggests a synergistic effect of HCQ and steroids. In a propensity score matched subgroup with lower steroid use (44.2%), HCQ still provided a benefit – this was mainly with less-sick patients. Steroids were used to varying degrees in a number of the other studies involving HCQ (Table 5) which may have affected the results. Unusual about this study was that both steroids and HCQ were given early after admission. Through a lysosomal mechanism, CQ likely exerts an anti-inflammatory effect synergistic with steroids.[88]

Table 5: Observational Studies involving HCQ, AZI with and without Zinc. (selected see also [58,116,140,160])

Study	Geleris[6]	Rosenberg[7]	Magagnoli[159]	Yu[27]	Ip[158]	Arshad[86]	Carlucci[10]
Location	NY	NY	VA	China	NJ	MI	NYU
Steroid use	26.6% HCQ 10.1% Contr	NR	NR	NR	NR	35.7% No treat 78.9% HCQ, 28.8% AZI, 74.3% HCQ/AZI	9.7% Zn 9% No Zinc
N	HCQ=811 AZI = 486 None = 274 (propensity match)	HCQ/AZI =735 HCQ = 271 AZI = 211 Neither = 221	HCQ = 97 HCQ+AZI = 113 None = 158	HCQ 48 None 502 Critical, needing MV	No HCQ 598 HCQ (all) 1914	2541	HCQ/AZI/Zn =411 77.1% discharge HCQ/AZI = 521 68.3% discharge
Type	OBS, Cox+PM	OBS, Cox	OBS, Fine/Gray model, PM	OBS	OBS, Cox + PM	OBS, Cox, PM	OBS, multivariate regression
EKG changes	Not reported	Adj. log regr, no sig differences in relative likelihood of abnormal EKG	Not reported		Not reported	None, patients, prescreened for lengthened Qt interval and excluded. No torsades des pointes	Not examined ##

		Abnormal ECG HCQ/AZI 27.1% HCQ 27.3% AZI 16.1% Neither 14%					
Cardiac events	Not reported	Log. models, cardiac arrest: HCQ/AZI 15.5% (adjusted OR, 2.13, 1.12-4.05) HCQ 13.7% (adj OR, 1.91, 0.96-3.81) AZI 6.2% (adj OR, 0.64, 0.27-1.56) Neither 6.8%	Not reported		Deaths attrib to cardiac causes: HCQ cohort, 89/432 (21%) 19/115 (16%) in non-HCQ cohort.		Not examined ##
HCQ Dose	600 mg bid day 1, then 400 mg sid x 5d (median)	400mg bid (modal), duration NK	Not reported	200 mg bid x 7-10 d	Modal: 800 mg d1, 400 mg d2-5		400mg stat, 200mg bid x 5d
AZI Dose	500mg day 1, 250mg sid x 4d	500mg sid (modal) , duration NK	Not reported	NONE	Not reported		500mg sid
Zinc dose	NONE	NONE	NONE	NONE	NONE	NONE	ZnSO4 220mg bid
Outcome	COMP	Mortality	Death/ venthilation	Mortality	Mortality	Mortality	Discharge/Mortality
HCQ	HR 1.04 (0.82 - 1.32) HR 0.97 other method	HR 1.08 (0.63-1.85) / 18.9%	Death: adHR 2.61 (1.10 - 6.17; P=0.03) Ventilation: Ad HR 1.43 (0.53 - 3.79; P=0.48)	Death:d that HCQ 19% (9/48) (p<0.001). Cox adHR: 0.36; 0.18–0.75; P=0.006	HR, 1.02 (0.83-1.27) 30d Mortality 25%	HCQ alone, 162/1202 (13.5% [11.6%-15.5%])	
AZI	HR 1.03 (0.81-1.31)	HR 0.56 (0.26-1.21 / 10.9%	Not done	Not done	HR 0.89 (0.72-1.1) 30d Mortality 20%	AZI alone, 33/147 (22.4% [16.0%-30.1%]),	
HCQ+AZI	Data reported for HCQ & AZI separately, some patients received both	HR 1.35 (0.76-2.40) / 22.5%	Death: adHR 1.14 (0.56 - 2.32; P=0.72) Ventilation: adHR 0.43 (0.16 - 1.12; P=0.09)	Not done	HR 0.98 (0.75-1.28). 30 mortality 18%	HCQ+AZI, 157/783 (20.1% [17.3%-23.0%]),	Discharge: +Zn OR 1.53 (1.12-2.09) Transfer to hospice /Mortality: +Zn OR 0.449 (0.271-0.744) (only patients not admitted to ICU **
No treat		17.8%		47% (238/502) No drug	30 mortality 20%	108/409 (26.4% [22.2%-31.0%])	

- MCL Macrolide antibiotic
- OBS Observational
- PM Propensity matched
- COMPOSITE Endpoint – Intubation or death
- Where RR, HR or OR ratios shown – 95% CI are in parentheses
- ## Dr. Rahimian informed us that these parameters were not examined

- **Discharge figures do not include 40 (Zn cohort) and 46 (non-Zn) patients who were discharged to rehab and similar facilities. These all survived (P. Carlucci, personal communication) to give an adjusted OR of 1.789 (1.233-2.59, p = 0.002 – our estimate)

Continuation table

Study	Membrillo[171]	Guérin[172]	Oteo[173]	Mikami[174]	Sbidian[143]	Mehra[25] (see and letter[175] Concern[176] & retraction[177])
Steroid use	Yes, but n NR	NR	NR	NR	HCQ 17% HCQAZI 18.9% None 10.5%	Yes, but n NR
Location	Spain	France	Spain	NY, Mt. Sinai Syst	France	Multination
N	164	88/57	80	3708, Hospitalized	624 HCQ 227 AZI 3792 none	1868 CQ 3783 CQ + MCL 3016 HCQ 6221 HCQ +MCL 81144 None
Type	OBS, not PM	OBS	OBS	OBS, Cox	OBS	OBS, Cox, PM, Tipping point
EKG changes	NR	No cardiac tox noted	2 with lengthened QTc interval	NR	Increase mortality in HCQ/AZI, not HCQ	Risk of in hospital de-novo ventricular arrhythmia vs. control (0.3%) HCQ (6.1%; 2.369, 1.935–2.900) HCQ + MCL (8.1%; 5.106, 4.106–5.983), CQ (4.3%; 3.561, 2.760–4.596), CQ + MCL (6.5%; 4.011, 3.344–4.812)
Cardiac events				NR		
HCQ Dose	Early Tx HCQ 800mg stat, 400mg od	AZI, AZI+HCQ	HCQ 400 mg x2 loading, 200 mg bid x5d AZI 500 mg stat, then 250mg od x5d	NR	HCQ 600mg stat, 400mg od x9d AZI 500mg stat, 250mg od x4d	
AZI Dose				Also used, NR		
Zinc dose				No		
Outcome	22% death HCQ, 48% death no HCQ	Recovery time No Tx 25.8d AZI 12.9d HCQ/AZI 9.2d Similar data in case-control analysis	No deaths (30d)	Death	28d mortality HCQ vs. no adHR 1.05 (0.77 -1.33). HCQ/AZI vs. no HR 1.40 (0.98 -1.81, ;p=0.062) 28d discharge HCQ(1.25;1.07-1.42]). HCQ/AZI 1.00 (0.77-1.23)	Risk of mortality vs control (as HR)
HCQ				Adju HR		HCQ (18%; HR 1.335; 1.223–1.457)

				0.53 (0.41–0.67), includes unk AZI use		CQ(16.4%; 1.365, 1.218–1.531)
AZI						
HCQ+AZI						HCQ + MCL (23.8%; 1.447; 1.368–1.531) CQ + MCL (22.2%; 1.368, 1.273–1·469)
No treat						9.3%
	Hospitalized for COVID-19	Early stage	Moderate	Hospitalized	Hospitalized mode- severe	

- A large observational study appearing in The Lancet of records from 96,032 mainly North American patients[25] using Cox regression, propensity score match and tipping point analysis found an increase in risk of mortality or arrythmia with use of HCQ or CQ with or without macrolide (e.g. AZI) antibiotics. Pursuant to an open letter[175] which challenged the reliability of the source data, the Lancet (6/3/20) published an Expression of Concern[176] and the paper **was retracted**.[177]

4.4.1.6 Randomized studies with HCQ

- The UK RECOVERY Pragmatic RCT was terminated at an additional interim analysis that showed the 28-day death rate in COVID-19 patients was similar to usual hospital care (25.7% n=1542 vs. 23.5% n= 3132; HR 1.11, 0.98-1.26; P=0.10).[178] (results not published but announced on study web site).
- A RCT involving 150 Chinese patients with mild to moderately severe COVID-19 found similar rates of conversion to a negative PCR test in HCQ-treated (85.4%, 73.8% -93.8%) and standard of care (81.3%, 71.2% - 89.6%) groups. 21/70 (30%) of HCQ-treated patients had adverse events compared with 7/80 (9%) of the control group patients. Two of the HCQ-treated patients had serious (unspecified) events that did not involve cardiac arrhythmia such as prolonged QT interval. The HCQ dose was 1200 mg sid x 3d then 800 mg sid for two weeks (mild) or three weeks (moderate or severe).[179]
- A small Chinese RCT involving 48 moderate COVID-19 patients found shorter times to recovery, and faster times to viral negativity with CG and HCQ than control patients. With limited evaluation, No cardiac abnormalities were observed. [180]
- A small (n=37) RCT, conducted along with an small (n=37 retrospective study) found no shortening of viral shedding in mild to moderate cases with HCQ.[181]

4.4.2 HCQ use with other drugs – AZI and Doxycycline

- AZI's immunomodulatory and antioxidant actions have been reviewed.[182,183] Although for the most part, AZI has been considered alongside HCQ, there is some support for using it (Table 5) or other macrolides[184] alone.
- Doxycycline, an antibiotic used also to treat malaria, has been proposed[185] for use against COVID-19 as an alternative to AZI with fewer HCQ interactions and side effects. In a small open-bale single arm cohort report,[186] 54 patients in long term care facilities with sudden onset of fever, cough, and shortness of breath, presumed to have COVID-19 were treated with either doxycycline (100 mg po bid x 7d) and HCQ (200 mg pp tid x 7d or 400 mg po bid x1d, then 400 mg sid x6d). 3/54 of the patients died. 46/54 (85%) patients recovered. Of the six others, two were hospitalized and then returned to the facility, two were transferred to hospital but outcome is unknown, another is in the ICU and one patient had a seizure due to HCQ and was continued on doxycycline.

4.4.3 Pre-emptive and Prophylactic use of Hydroxychloroquine use with AZI but without Zn

- An observational cohort study examined the effect of voluntary use of HCQ by HCP who had been on duty for one month at an Indian teaching hospital prior to a cluster outbreak there of COVID-19 among HCP.[187] Following the outbreak, HCP were tested for SARS-CoV-2 by rtPCR and those with confirmed exposure to a COVID-19 (per Indian National CDC[188]) patient and agreeing to participate in the survey were stratified according to whether or not they had adequate taken at least a loading dose of HCQ (400mg bid day 1, then weekly for seven weeks) according to an Indian Ministry of Health advisory.[189] HCP in both groups had a similar mean number of contacts (3) as well as age, gender, comorbidities, type and degree of exposure. Examining all types of exposure, those HCP taking HCQ had fewer (4/54, 7,4%) COVID-19 positive results than those not (20/52, 38.5%) (RR 0.19, CI 0.07-0.52). Most exposures were of the face-to-face variety which

showed a similar reduction. The average age was similar in the two groups (HCQ 26.46; non-HCQ 27.71 years).

- An observational study involving all records from the Portuguese National Health Service electronic database fund reduced incidence (7.45% to 5.96%, adjOR 0.51, 0.37-0.70) of COVID-19 among patients taking long term HCQ for rheumatological conditions.[60]
- An RCT[5] published in the NEJM of HCQ used pre-emptively after health care or household exposure to COVID-19 concluded: *"the incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving HCQ (49/414 [11.8%]) and those receiving placebo (58/407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P=0.35). Side effects were more common with HCQ than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported."* Outcomes were all self-reported and the actual incidence of cardiac anomalies is unknown.
- The web site of the University of Minnesota, summarizes the study findings that "*Hydroxychloroquine Has No Benefit Over Placebo in Preventing COVID-19,*" describing them as "conclusive." The NEJM editorial described this study as *"more provocative than definitive"* and examination of the supplementary data and correspondence with the primary author, reveals a number of interesting aspects to the study. It is important to note the statistical challenges of sub-group analysis[190], accordingly the trends noted below require further multivariate analysis and confirmation by a suitably powered prospective study.

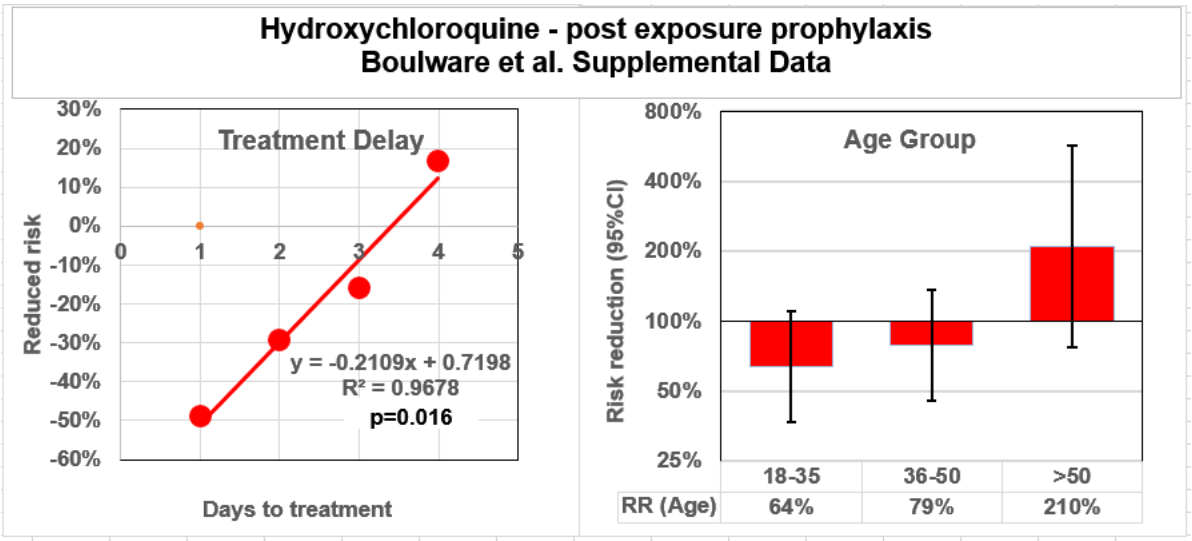
    - Was the placebo inactive?
      The study employed folate as the placebo. A recent study found, using in silico molecular docking analysis, that folic acid binds tightly to M^{pro} of SARS-Cov-2[191] and also has affinity for the spike protein as well as the spike protein-ACE2 docking complex.[107] A recent observational study found that blood folic acid levels were significantly lower in severe COVID-19 patients.[192] A brief literature search indicates that for some other viruses at least there may be an association between folate deficiency/ supplementation and disease severity/ amelioration/prevention - Zika[193]; HPV[194,195]; HIV[196]. Until further consideration, it cannot be assumed that the control group is a true control. Indeed, it may turn out that folate supplementation may be a worthy low-risk strategy to reduce COVID-19 infectivity. Use of methotrexate, a folate blocker, does not appear to influence COVID-19,[197] although patients taking methotrexate are likely to be taking folic acid supplementation.
    - Was the study realistically powered?
      The study was powered to reduce development of COVID-19 by 50% in all patients. Since this was a "pragmatic" clinical trial, where effect sizes are typically lower than under tightly controlled "explanatory" trial conditions,[198] and with greater heterogeneity, this may have been over-ambitious. The overall reduction was 17%. Based on CDC (6/8/20) likely underestimates of 71768 COVID-19 cases among HCP in the USA, this would have translated, in a suitably powered study, to a reduction of about 12,000 cases. This may be both clinically meaningful and may have impacted modeling of COVID-19 trajectory and health resource estimates that drive decisions on lockdowns and social distancing. Among some subgroups, the reduction of COVID-19 was much higher.
    - Type of exposure
      Severity of exposure was defined as exposure (i.e. one time) to a person with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure, 87.6% of subjects) or while wearing a face mask but no eye shield (moderate-risk exposure). These definitions do not discriminate between the numbers of exposures or durations longer than 10 minutes. In the placebo group, there is much lower illness rate in the healthcare group than the household group. (OR 0.5291, 95%CI 0.2987-0.9371, p = 0.031).
      There was only 7.8% reduction in COVID-19 using HCQ in the healthcare subgroup (about 66.4% of subjects) but 30.9% in the household group (RR 0.691, CI 0.398-1.2, p=0.24). This may reflect:
        - Lower age in the healthcare group
        - Higher exposure risk in household contacts who may have been likely to use masks/shields (and likely N95 masks) than the health care group or less able than trained health workers to practice and implement hygiene practices better (touching face, disinfecting surfaces etc.). The exposure levels described in the Indian HCP cohort study[187] were much higher. Differences between in-hospital exposure risk related to type of assignment, ethnicity and likely use of PPE in a UK study likely accounts for differences in rates of COVID-19 among hospital workers, with household exposure contributing to a higher incidence of COVID-19.[199]

      (see Swedish study stratifying seropositivity and symptoms with type of patient exposure[200] 19% of hospital workers were seropositive of whom 91% had symptoms of varying degrees. 74% of

seronegative workers also had symptoms, but included much less taste/small disturbances, fever, cough and malaise)

- Exposure to Treatment Lag
  Figure 1 shows from our post hoc analysis a significant negative correlation between time from exposure to treatment and reduction in COVID-19. When treated within one day, the reduction in risk may be as much as 49% (RR 0.51, CI 0.176-1.46, p=0.249).

Figure 1: Post-Exposure Prophylaxis with HCQ: Time Lag and Age Dependency



Our post hoc analysis based on supplemental data provided in[5].
Regression calculated using vassarstats.net/corr_big.html. (Slope -0.211, 95%CI -0.328—0.094, p=0.016, rho CI -1 to -0.42)

- Age
  There were 36% and 21% reductions in COVID-19 when HCQ was used by 18-35 and 36-50 year old sub groups respectively, with an increase of 110% for patients over 110%. This is consistent with the findings of the observational prophylaxis study involving mainly young HCP in India.[187]
- Zinc and Vitamin C
  A number of patients reported taking zinc and/or vitamin C supplements. Observational data is presented that for Vitamin C, there is a higher incidence of symptoms when Vitamin C is used, both without (20.8% vs 11.2%, p=0.014) and with (14.3 vs. 10.6%, p=0.33) HCQ. For Zn there is a similar relationship in the HCQ group, but not in the placebo group. since details about timing, dose and reasons for self-medicating with these agents are unknown, these observational data confound the overall findings and require further examination if possible.
- Adverse events
  More adverse events did occur in patients taking HCQ, but none were serious.
- Hospitalizations
  There were no hospitalizations. With an estimated attack rate of 10% after exposure and 10% progression to hospitalization among HCP[201]), the 8 or so expected hospitalizations among the 107 COVID-19 cases (8/107 vs 0/107 Fisher's exact test p = 0.007) may not have occurred due to the generally lower age of the participants.
- Mechanism
  A number of mechanisms of action for HCQ have been proposed (see 4.4.1.1). At early stages such as here, and consistent with incubation period estimates of 3-8 days[202], HCQ alone may be effective in pre-emption because it interferes with viral attachment and initial infectivity. Using zinc (or Vitamin C) here may be futile, ineffective or counterproductive in otherwise healthy individuals with no Zn dysregulation. This may be sufficient in young people, however once infection has occurred, HCQ's actions as an ionophore may be more important, and require the presence of zinc for viral inhibition. A similar argument may be made for other ionophores that may also interfere with viral attachment.

Use of zinc in early stages may be futile or counterproductive, accordingly, low Zn does are proposed here.

- It has been reported in the press that a Spanish study NCT04304053 prophylaxis study, as failed to detect significant differences in the rate of COVID-19 development with HCQ, with no other details given.
- HCQ when used prophylactically in two Indian studies by 166[203] 297[204] health workers did result in a number of adverse events, mostly of a GI nature, but no serious cardiovascular events were reported.

4.4.4 Hydroxychloroquine use WITH Zn

- HCQ's **ineffectiveness** may be due to late treatment onset and/or omission of Zn. It appears that **Zinc must be added** to HCQ/AZI **and given early** as reported in preprinted observational findings of reduced death, ventilation need and increased discharges[10] (Table 5). This is supported by anecdotal reports (Dr. Cardillo, Los Angeles; Dr. Armstrong, TX) and a large uncontrolled case series of 405 patients. (Table 6)
- 92 year old Dr. Ananda Prasad, the foremost expert on zinc[11-15] (including it's effects on viruses[16-18]) was reported (along with his wife) to have recovered from COVID-19 after self-treatment with HCQ and Zn. Support for adding Zn to HCQ has been published.[21-23] A trial in the US at St. Francis Hospital, NY is underway, along with others involving Zn (see 13.6).
- In vitro, HCQ and AZI together are viricidal to SARS-CoV-2 at concentrations achieved in the lung.[205]

- There is instructive discussion within a number of papers[19,20,22,206-208] and blogs on the issue of zinc and COVID-19:
  - C Masterjohn PhD, Nutritional Sciences
    Are Chloroquine and Hydroxychloroquine Zinc Ionophores?
    What Is the Best Dose of Zinc for COVID-19 Prevention?
  - University Colorado – UC Health
    Coronavirus: To zinc or not to zinc?
  - F Cusimano PhD, Nutrition and Metabolic Biology
    Zinc supplementation for COVID-19

Table 6: Anecdotal reports of use of Zinc with HCQ/AZI

Doctor	Location	
Armstrong	The Resort, Texas City, TX	56 residents, 33 staff at nursing home. One death
Cardillo	Los Angeles CA	
Zelenko	Monroe, NY	405 (4/17/20 largely untested patients with severe COVID-19 symptoms using half the HCQ doses used elsewhere (200mg bid x 5d) . Two patients died and four needed ventilators, now recovered 699 patients in another report (3/31/20) Study reported using 141 PCR positive patients only.[209]

- Of the 2315 COVID-19 related studies registered in clinicaltrials.gov (6/24/20) 259 involve HCQ or chloroquine. Of these only 10 also involve Zn (see 13.6).
- Whether HCQ+Zn is as effective as the combination with AZI is unknown, and whether its use is necessary (or harmful) when used with HCQ.[27]
- There is some questions as to whether zinc reduces the GI absorption of the tetracyclines.[210] Doxycycline may be influenced less than tetracycline itself.[211] Zinc does form complexes with the tetracyclines,[212] which may contribute to their potential utility in COVID-19.
- In vitro, AZI as well as ciprofloxacin displayed a number of actions similar to those of chloroquine.[213]

4.5 Zinc and natural antioxidant ionophores: effects on viral infection

The effect of zinc on the action of hydroxychloroquine is described above (4.4).

4.5.1 Zinc and viruses

Viruses differ widely in composition, modes of transmission and pathogenicity. Their interactions with Zn biology are highlighted below. The effects found in one virus may not be found in others.

- Zn deficiency has been associated with a number of viral infections[214] [215] and implicated in susceptibility to H1N1 virus.[16] Some papilloma viruses have evolved mechanisms to exploit Zn homeostasis.[215]
- Virally mediated intracellular Zn dysregulation has been reported to favoring a viral function in a papilloma virus.[216] Zn dysregulation induced by other viruses does not appear to have been described. (Whether COVID-associated hypogeusia is due to a virally induced hypozincemia is unclear). Acute-phase cytokine-mediated hypozincemia[217] may contribute to a reduction in zinc availability for replicase inhibition.
- Zn inhibits viral RNA replicase and is active against a number of viruses,[215,218] including SARS-Cov-1.[218]
- A review of 13 studies involving various Zn formulations of Zn lozenges concluded *"This study shows strong evidence that the zinc lozenge effect on common cold duration is heterogeneous so that benefit is observed with high doses of zinc but not with low doses. The effects of zinc lozenges should be further studied to determine the optimal lozenge compositions and treatment strategies."*[219]
- A meta-analysis[220] comparing the efficacy of zinc acetate and gluconate lozenges in the common cold concluded *"Properly composed zinc gluconate lozenges may be as effective as zinc acetate lozenges… Common cold patients may be encouraged to try zinc lozenges for treating their colds."* In reporting unsatisfactory results using a particular zinc acetate lozenge, the same group[221] discussed the importance of lozenge formulation on effectiveness and affirmed the validity of their previous findings.
- A 2011 Cochrane review[222] of 15 trials involving various Zn lozenge or syrup formulations, concluded that *"zinc administered within 24 hours of onset of symptoms reduces the duration and severity of the common cold in healthy people.*" An updated 2013 Cochrane review[223] that considered 18 studies concluded that *"Zinc administered within 24 hours of onset of symptoms reduces the duration of common cold symptoms in healthy people but some caution is needed due to the heterogeneity of the data."* The authors further noted *"Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data. When using zinc lozenges (not as syrup or tablets) the likely benefit has to be balanced against side effects, notably a bad taste and nausea."* A 2015 version of this review,[224] later withdrawn,[b] drew the same conclusion.
- A Cochrane review on the effects of Zn supplementation in children found a risk ratio (RR) of 0.86 (95% CI 0.64 to 1.15, three studies, moderate-quality evidence) for mortality due to lower respiratory tract infection (all causes). The RR for incidence of lower respiratory tract infection was 1 (95% CI 0.94 to 1.07, 12 studies, moderate-quality evidence). The authors concluded *"In our opinion, the benefits of preventive zinc supplementation outweigh the harms in areas where the risk of zinc deficiency is relatively high."*[226]
- A meta-analysis of ten clinical trials found that zinc supplementation reduced the incidence of acute lower respiratory infections in 49,450 children in developing countries[227] [IRR 0.65; 0.52-0.82] when specific criteria were employed. Using less specific criteria the effect was not seen [IRR 1.01; 0.91-1.12). Quoting only this one study concerning zinc, a brief review[228] on the possible utility of nutritional supplements concluded that" *"The evidence in the scientific literature to support vitamin supplements is pretty dreadful ... I would say there's absolutely no data to support most of them, with only two or three possible exceptions. One exception would be zinc," he explains, "but that data which allows any supplement with a trace of zinc to make health claims is about 20 or 30 years old and hasn't been updated so it could be flawed."*

- There are a number of potential sites of action of Zn, alone and with HCQ, in the response to SARS-Cov-2.[22]
- Zn supplements were associated with an increased risk of developing HIV/AIDS[229] with poorer survival.[230]
- A small (n=4) uncontrolled case series reported positive outcomes of treatment of COVID-19 with oral Zn.[231]

4.5.2 Zinc Ionophores and antiviral activity

- The antiviral activity *in vitro* of Zn SARS-CoV-1 is potentiated by the ionophore pyrithione[218] Zn-pyrithione was active in an in vitro pseudovirus assay.[232]
- In addition to their antioxidant properties, plant polyphenol flavonoids (quercetin[233], green tea[233,234] and punicalagin - pomegranate extract[235]) are less toxic Zn ionophores. Catechin, quercetin or its derivatives were active against to Influenza Virus (or complications) in clinical or laboratory settings[236,237] and against

[b] The Cochrane Database of Systematic Reviews (cochrane.org) publishes comprehensive reviews to facilitate health decisions. Each review undergoes rigorous peer-review and quality control scrutiny. Reviews are periodically updated. The 2015 version of the review, "Zinc for the common cold," was withdrawn over allegations of text and data plagiarism from a different review by Hemila (2011). Although the Cochrane Database clearly notes the withdrawal of the 2015 versions (and not the 2011 or 2013 versions), a retraction issued in reference to a JAMA version references the 2013 Cochrane review as being the withdrawn version.225. Das RR, Singh M. Notice of Retraction: Das RR, Singh M. Oral Zinc for the Common Cold. JAMA. 2014;311(14):1440-1441. JAMA 2016;316:2678. We contacted Dr. Singh for clarification of this issue.

murine norovirus[238] and other viruses *in vitro*.[239] A product containing quercetin, catechin (as well as selenium and cinnamon and liquorice extracts) has been proposed as a treatment for COVID-19.[240] Pyrithione and another ionophore, hinokitiol were active in vitro against picornavirus infection.[241]

- The use of Zn with natural ionophores and related agents has been advocated in the context of an Integrative Medicine approach.[28]
- Use of these ionophores could reduce the dose requirements of HCQ and AZI.
- Differences in the ionophoric mechanisms of HCQ and the flavonoids may affect their action in COVID.

4.5.2.1 Quercetin

- Quercetin is found in a number of vegetables including capers, dill, cilantro and red onion. It is contained in Huashi Baidu, a traditional Chinese medicine, being used ot treat COVID-19.[242]
- Quercetin-3-β-O-D-glucoside has been effective against Zika virus *in vitro* and in mice[243] and against Ebola virus in mice.[244] It is undergoing evaluation in COVID-19 (here, here). Rutin, a quercetin glycoside, was found in in silico studies to inhibit the main protease (M^{pro}/ $3CL^{pro}$) of SARS-Cov-2.[245,246] [247,248]
- Quercetin and the catechins displayed moderate to high theoretically ability to interfere with the SARS-Cov-2 Spike Protein-ACE2 receptor complex, being in the top 200 of over 50,000 drugs, plant extracts and other chemicals screened by the SUMMIT supercomputer at the Oak Ridge National Laboratory.[107] It is noted that the predicted interaction may be one that stabilizes the Spike Protein-ACE2 receptor complex. Analyzing the interaction just with the spike protein, various quercetin and catechin derivatives had a moderate interaction, being placed in the top 3000-6000 ranked compounds.
- In another in silico analysis, various quercetin glycosides interfered strongly with Mpro and ACE2.[249]
- Quercetin and the catechins may therefore be useful because of least three facets of their mechanism of action: as antioxidants, and zinc ionophores and as agents possibly interfering with viral-cell attachment.
- Quercetin chelates Zn ions.[250]
- Other actions of quercetin have been reviewed[29] including the proposed need for co-administration of ascorbic acid to avoid the "quercetin paradox" in which pro-oxidant quercetin derivatives may form.
- Quercetin occurs as the free aglycone as well as in glycosidated forms. The aglycone appears to have very low bioavailability, which is improved as a glycoside.[251,252] In humans the terminal half- life of the aglycone, quercetin-4'-O-glucoside and quercetin-3-O-rutinoside was about 11 hours.

4.5.2.2 Catechins, green tea extracts

- Green tea catechins are a family of derivatives of catechin variously esterified with gallic acid.[253] The main active components include epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and epicatechin gallate. EGCG is the most abundant and has highest potency as an antioxidant.[254]
- As with quercetin in the SUMMIT analysis, catechins interreacted in silico with the spike protein-ACE2 receptr complex as well as the spike protein itself.[107]
- In silico activity against M^{pro} [246] [255-258]
- Various catechins showed interactions, in silico, to various spike protein sites that were in some cases superior to that of HCQ.[256,259]
- Green tea extracts inhibited in vitro infection of BHK21 cells by CoV, SARS, MERS, and SARS-2 pseudoviruses, likely by inhibiting the interaction between the spike protein and ACE2 receptor.[260]
- These compounds have a complex metabolism, including distribution to the lung, with elimination half-lives of between 2-8 hours.[254,261,262] As with any naturally derived product, the source, season of collection and extraction method will greatly influence the composition of green tea extracts commercially available. The total catechin content in a number of commercially available green teas varied from 26-103 mg per gram of tea.[263] Although highly variable, there are a number of studies that have associated the delay or reduction of various cancers with the consumption of green tea; generally in the range of 5-10 cups per day.[263,264] Another study[265] concluded in the context of preventative actions against various (including lung) cancers that *"it is safe for healthy individuals to take green tea polyphenol products in amounts equivalent to the EGCG content in 8–16 cups of green tea once a day or in divided doses twice a day for 4 weeks."*

4.5.2.3 Punicalagin, Pomegranate extract

- Punicalagin is synergistic with Zn against HSV *in vitro*.[235]

4.5.2.4 Luteolin

- Another compound highly ranked in the SUMMIT analysis is luteolin, a flavonoid found in a number of vegetables including celery, broccoli, green pepper, [expand] with antioxidant and immunomodulatory properties. [expand] Luteolin chelates Zn ions.[250]
- Luteolin scored highly in an in silico analysis of interaction with Mpro.[266]
- Complex Zn dysregulation occurs in Alzheimer's disease with both positive and negative effects.[267] [268] Luteolin has been investigated as a possible modulator of Zn dysregulation in Alzheimer's disease either as a chelation agent[250] or via other mechanisms.[269,270]

4.5.2.5 Resveratrol

- Resveratrol, also an antioxidant, influences Zn homeostasis, and may enhance Zn accumulation and antioxidant ability by other mechanisms.[271]

4.5.3 Anti-oxidant and other activity

- The use of antioxidants for prevention and treatment of respiratory viruses is well described.[236,272,273]
- Zn is an antioxidant[14] that along with HCQ and azithromycin[182,183] may limit the fulminant oxidative stress of ARDS evoked by COVID. Zn overload may contribute to oxidative stress and production of ROS.
- From the SUMMIT analysis, a number of other natural compounds were identified with antioxidant and other immunomodulatory actions, possibly useful in treating COVID-19.[274]
- Another useful compound identified by this analysis is eriodictyol, found in a number of fruits, including citrus. [expand] Quercetins and catechins, as well as other potentially useful compounds are found in the leaves of *Myrtus communis*.[275] [expand]
- There is discussion about the use (alone or in addition to Zn and ionophores) of Vitamin C (ascorbic acid)[276,277] as well as Vitamin D[207,228,278,279] (see also 8) and other agents for COVID-19. As with Zn and the other agents discussed here where there are no randomized clinical trials to support their use, there is discussion [expand] in favor of the use of Vitamin C (or at least neutral for normal, non-high, doses). The Marik/EVMS protocol uses high doses of intravenous Vitamin C to suppress cytokine storm (see review [280,281]). Further studies are underway.
- There is some basis for the use of melatonin based on its antioxidant and other properties.[282-285] It is also included in the Marik/EVMS protocol.
- Zinc (as iodide for its antimicrobial properties) along with DMSO (for its antioxidant and antiinflamatory properties) has been advocated.[286]
- Glutathione deficiency has been proposed as a factor in COVID-19 development, along with use of glutathione (as N Acetyl cysteine) for its treatment.[287-289]

4.5.4 Reviews of possible use of multi-action natural compounds in COVID-19

- See discussion by Alschuler et al.[28] and others[290] related to use of Zn, antioxidants, related agents as well as the importance of nutrition in general[291-293] for COVID-19.
- Quercetin, hesperidin, rutin, naringin, naringenin,[294] catechins luteolin, myricetin and others[295]

5 PROTOCOL OUTLINES

5.1 PROTOCOL: Pre-exposure prophylaxis for SARS-Coronavirus-2 using zinc and natural ionophores

Objective: To determine if pre-exposure prophylaxis with zinc and natural ionophores is effective for the prevention of COVID-19 disease.

Standard of care: Social distancing and hygiene measures. There is no approved treatment or prophylaxis for COVID-19.

Inclusion criteria: Health and essential workers, general public.

See standard inclusion/ exclusion criteria (5.6) and disease categories (5.7).

Exclusion criteria: Patients who have:

- Been in contact with someone known or suspected as having COVID-19. Patients coming into contact with a person known or suspected of having COVID-19 may, at their option enter the "pre-emption" study
- Developed symptoms of COVID-19 within last 14 days: Cough, fever or chills, shortness of breath, diarrhea, nausea, sputum production, headache, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.
- Known active COVID-19 disease

- Known prior suspected or confirmed COVID-19 disease, but now tested negative by PCR is not an exclusion

Estimated number of patients: 3000
Interventions: Zinc supplement (as 10-15mg elemental zinc) and/or either quercetin or green tea extract (at recommended daily dose).
Design: (modeled on NCT04328467)
Patients will be randomized to treatment or no treatment. In addition, outcomes will be compared with references populations within COVID-19 Symptom Tracker.
Primary outcomes: Percent of participants in each arm who are COVID-19-free at the end of study treatment
Secondary outcomes:

- Incidence of confirmed SARS-CoV-2 detection
- Incidence of possible COVID-19 symptoms
- Incidence of all-cause study medicine discontinuation
- Disease maximum severity if COVID-19 diagnosed at study end
- Incidence of hospitalization for COVID-19 or death
- Incidence of study medication-related side effects

Stratification: Subjects will be stratified by age and risk type:

- Type and intensity of COVID-19 contact – health (subtype), EMT, grocery and essential services workers, comorbidities, possible ethnic and genetic factors. Patients taking zinc-depleting drugs (e.g. omeprazole) will be informed about the possible issues with this drug and advised to speak with their doctor about switching to famotidine, if medically appropriate.
- At-risk patients with known co-morbidities

Data collection: COVID-19 Symptom Tracker.- self or proxy reported
Other: Patients developing symptoms at any time must seek medical advice.

5.2 PROTOCOL: Post-exposure prophylaxis/ pre-emption for SARS-Coronavirus-2 using zinc and natural ionophores

Objective: To determine if post-exposure prophylaxis with zinc and natural ionophores is effective for the prevention of COVID-19 disease.
Standard of care: Observation and quarantine after exposure to COVID-19. There is no approved treatment or prophylaxis for COVID-19.
Inclusion criteria: See standard inclusion/ exclusion criteria (5.6) and disease categories (5.7).
Asymptomatic health and essential workers, general public who have come into contact with a person known or suspected as having COVID-19.
Exclusion criteria: Patients who have:

- Developed symptoms of COVID-19 within last 14 days: Cough, fever or chills, shortness of breath, diarrhea, nausea, sputum production, headache, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.
- Known active COVID-19 disease
- Known prior suspected or confirmed COVID-19 disease, but now tested negative by PCR is not an exclusion

Estimated number of patients: 3000
Interventions: Zinc supplement (as 10-15mg elemental zinc) and/or either quercetin or green tea extract (at recommended daily dose).
Design: Modeled on NCT04308668
Patients will be randomized to treatment or no treatment. In addition, outcomes will be compared with references populations within COVID-19 Symptom Tracker.
Primary outcomes: Percent of participants in each arm who are COVID-19-free at the end of study treatment
Secondary outcomes:

- Incidence of confirmed SARS-CoV-2 detection
- Incidence of possible COVID-19 symptoms
- Incidence of all-cause study medicine discontinuation
- Disease maximum severity if COVID-19 diagnosed at study end
- Incidence of hospitalization for COVID-19 or death
- Incidence of study medication-related side effects

Stratification: Subjects will be stratified by age and risk type:

- Type and intensity of COVID-19 contact – health (subtype), EMT, grocery and essential services workers, comorbidities, possible ethnic and genetic factors.
- At-risk patients with known co-morbidities.
- Patients taking zinc-depleting drugs (e.g. omeprazole) will be informed about the possible issues with this drug and advised to speak with their doctor about switching to famotidine, if medically appropriate.

Data collection: COVID-19 Symptom Tracker.- self or proxy reported
Other: Patients developing symptoms at any time must seek medical advice.

5.3 PROTOCOL: Treatment of mildly symptomatic patients with known or suspected COVID-19

Objective: To determine if treatment of mildly symptomatic patients with zinc and natural ionophores is effective for the remission of symptoms, prevention of progression of more severe COVID-19 disease.
Standard of care: There is no approved treatment of COVID-19.
Inclusion criteria: Mildly symptomatic health and essential workers, general public.
See standard inclusion/ exclusion criteria (5.6) and disease categories (5.7).
Exclusion criteria: Patients who have:

- Asymptomatic patients
- Patients with moderate, severe or critical disease

Estimated number of patients: 3000
Interventions: Zinc supplement (as 50mg elemental zinc) and/or either quercetin or green tea extract (at recommended daily dose).
Patients may take OTC medicines such as acetominophen, as recommended by CDC and their doctor.
Design: Patients will be randomized to treatment or no treatment. In addition, outcomes will be compared with references populations within COVID-19 Symptom Tracker.
Primary outcomes: Percent of participants in each arm who are symptom-free free at the end of study treatment
Secondary outcomes:

- Incidence of confirmed SARS-CoV-2 detection
- Incidence of possible COVID-19 symptoms
- Incidence of all-cause study medicine discontinuation
- Disease maximum severity if COVID-19 diagnosed at study end
- Incidence of hospitalization for COVID-19 or death
- Incidence of study medication-related side effects
- Time to resolution of symptoms

Stratification: Subjects will be stratified by age and risk type:

- Type and intensity of COVID-19 contact – health (subtype), EMT, grocery and essential services workers, comorbidities, possible ethnic and genetic factors.
- Patients taking zinc-depleting drugs (e.g. omeprazole) will be informed about the possible issues with this drug and advised to speak with their doctor about switching to famotidine, if medically appropriate.
- At-risk patients with known co-morbidities

Data collection: COVID-19 Symptom Tracker.- self or proxy reported
Other: Patients developing more severe symptoms at any time must seek medical advice, immediately.

5.4 PROTOCOL: Use of machine learning algorithms in place of propensity score matching and other statistical techniques for observational studies to emulate an RCT in COVID-19.

Objective: To determine if machine learning algorithms may be used in place in place of propensity matching and other statistical techniques to emulate an RCT in COVID-19.
Background: Observational studies suffer a number of well-known drawbacks related to the presence of a known and unknown confounding factors which prevent the direct comparison of treatment cohorts. The effect of confounding may be reduced but not entirely eliminated using statistical techniques such as multivariate regression analysis and propensity score matching. Recently machine-learning algorithms have been developed that may predict mortality risk in patients with COVID-19.
Design: Reassessment of data from observational studies using machine-learned algorithms to assess mortality risk in treatment cohorts. Risk will be compared with data obtained through propensity matching using standard techniques such as assessment of accuracy, precision and sensitivity.

5.5 PROTOCOL: Prospective Meta-analysis

A number of studies are being conducted with essentially similar study designs. Taken separately, each study may have a number of potential subgroups (age, time, degree of exposure etc.) that can provide valuable information about COVID-19 and its treatment. However, conclusions will be limited by statistical considerations related to small subgroup size, multiple end point examination, post hoc analysis (data fishing) etc. This problem may be partly solved by initiating a prospective meta-analysis.[296,297]

5.6 Standard inclusion/ exclusion criteria

Patients over 18 giving informed consent and consulting with doctor, no known intolerance to planned interventions, taking drugs with known interactions to interventions, no pregnant or nursing women, patients with diagnosis of cancer and/or receiving chemotherapy. etc.

5.7 Definition Disease categories

The definitions used by NIH[116] will be used:

- Asymptomatic or Pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 but have no symptoms
- Mild Illness: Individuals who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal imaging (dysgeusia, anosmia added to NIH list).
- Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) >93% on room air at sea level
- Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 /FiO2) <300, or lung infiltrates >50% ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2)
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

6 DISEASES AND CONDITIONS ASSOCIATED WITH ZINC DYSREGULATION: COVID-19 IMPLICATIONS

6.1 General

- Zinc (Zn) is an essential mineral,[298] facilitating immune function[13,299 300-302] and other processes.[274] A comprehensive review of the history of Zn biology is given.[274] The global prevalence of inadequate zinc intake has been estimated.[303,304]
- Numerous diseases are associated with Zn deficiency (dysregulation?).[298,305 306 307] In obesity[308-310] (other mechanisms in obesity also proposed[311]) and the conditions discussed further below it may contribute to a high risk of serious COVID. Zinc deficiency is also present in Crohn's disease[312] but whether this is a risk factor for COVID-19 is unknown. There is much we do not know about COVID-19 and the susceptibility of different groups is likely multifactorial. Zn depletion may contribute to poor COVID-19 outcomes in poorer communities as well as in diabetes, heart disease, obesity and smokers, the highest risk groups for COVID-19 (all of these are interrelated).
- Zinc nutritional supplementation is the subject of a number of global initiatives[313] conducted or supported by numerous governmental and philanthropic organizations such as International Zinc Nutrition Consultative Group (IZiNCG). Zinc deficiency is believed to contribute to morbidity and mortality from a variety of causes in children.[314,315] Supplementation programs appear effective for diarrhea[314,316] and pneumonia[316] [no/less evidence for pneumonia, malaria, TB[314] - expand] Another study in children in Burkina Faso failed to find an effect of various Zn supplements on diarrhoea, malaria, fever, and lower and upper RTI.[317]

6.2 Zn deficiency or dysregulation?

- It is important to understand that any changes in overall levels of Zn must be viewed in the context of the changes that exist at the tissue or compartment level. Although the term "deficiency" has been widely used here (until version 9.6), based on the papers quoted, it is rather imprecise and "dysregulation" may be more accurate. This would encompass changes in storage, transport, distribution and mobilization of Zn.
- A negative correlation was found between estimates of the prevalence of Zn deficiency based on nutritional intake,[303] and the numbers of COVID-19 cases and deaths in different European countries.[318] This study did not account for other differences, such as comorbidity differences, that could contribute to COVID-19.

Nevertheless, Zn **deficiency** may not be a factor, rather, Zn **dysregulation** associated with the disease itself, or comorbidities.

- Zn deficiency is associated with smell and taste disturbances, especially in the elderly.[307] Whether this is related to the hypogeusia and anosmia in COVID-19 in unknown.
- The raised level of procalcitonin found in COVID-19 patients[319-321] may further suggest Zn dysregulation in COVID-19 as calcitonin (along with PTH) have effects on Zn homeostasis.[322-324] (see also discussion on Vitamin D 6.9). Procalcitonin is generally used as a marker for bacterial infection,[325] and it has been suggested that elevated procalcitonin in COVID-19 is indicative of a bacterial coinfection.[320]
- Hypozincemia occurs in sepsis,[326,327] likely as a mechanism to deprive pathogens of zinc, associated with acute-phase changes such as elevated CRP.[328] Citing studies showing reduced cytokine response to infection in animal and human malnutrition, it has been suggested that infection may "*exert less of a confounding effect on plasma zinc concentration in malnourished individuals*."[328] Further, early studies with leukocytic endogenous mediator (now named, in purified form IL1) mediates zinc redistribution/sequestration in the early response to infection,[329-331] although this response may be less pronounced in viral infections.[332] Inflammation, assessed by CRP, in apparently healthy HIV+ adults, as associated with lowered plasma Zn, as well as resistance to Zn elevation after micronutrient supplementation.[333] A high background of subclinical infection in a population, evidenced by CRP levels, will like depress plasma Zn levels, confounding estimates of zinc deficiency in that population.[334,335]
- There appear to be ethnic differences between Caucasian and East Asian populations in the taste and smell disturbances associated with COVID-19.[336] Since Zn deficiency is associated with these sorts of disturbances, could this indicate differences in Zn metabolism that may account for different responsiveness to apparently Zn-dependent drugs, such as HCQ.
- Plasma Zn levels were noted as being an insensitive predictor of zinc status in volunteers[337] and in children with sickle cell disease.[338] They may not be indicative of short term changes of Zn supplementation.[339] The threshold plasma level for Zn deficiency based on the development of acrodermatitis enteropathica has been estimated at 50ug/dL.[340]
- The value of plasma Zn levels to as an indicator of Zn status is dependent on a number of diurnal, age, gender and genetic factors.[341,342] Other markers of Zn levels have been proposed.[342]

6.3 Diabetes

- Zincuria, hypozincemia and Zn deficiency/dysregulation may contribute to diabetes,[343] which may contribute to severe COVID-19 risk.
- Although it does not appear to prevent type 2 diabetes in adults with insulin resistance,[344] Zn supplements may improves glycemic control in diabetes.[344,345] The American Diabetes Association has suggested (April 2020) that the *"risk of getting very sick from COVID-19 is likely to be lower if…diabetes is well-managed."* This has subsequently been born out by an observational study from China involving 7300 patients with Type II diabetes,[346] also reviewed with other evidence.[347]
- The Center for Evidence Based Medicine have stated (4/8/20)
    - *"There is no evidence on whether people with diabetes are more likely to contract COVID-19.*
    - *People with diabetes appear to be at increased risk of having a more severe COVID-19 infection, though evidence quantifying the increased risk is highly uncertain.*
    - *The extent to which clinical and demographic factors moderate the relationship between diabetes and COVID-19 severity is entirely unclear due to a paucity of data."*
- No doubt accounted for by cultural as well as genetic factors, prevalence of all diabetes in the USA varies by race and ethnicity, with varying estimates (**Table 7** [348] , also [349]).
- There has been a pre-print report from mouse studies of a potential fatal drug interaction of HCQ (or chloroquine) with metformin, a drug taken by some diabetics.[350] HCQ has hypoglycemic properties.[128]

Table 7: Prevalence of diabetes in various adult populations 2011-16 (data from [348], see text)

Cohort	Prevalence*	Undiagnosed diabetes
non-Hispanic white	12%	4%
non-Hispanic black	20%	5%
Hispanic (all)	22%	7.5%
Mexican	25%	
Puerto Rican	22%	
Cuban/Dominican	21%	

Central American	19%	
South American subgroups	12%	
non-Hispanic Asian (all)	19%	7.5%
East Asian	14%	
South Asian	23%	
Southeast Asian subgroups	22%	

- A number of genes / SNPs have been associated with a higher risk of Type 2 diabetes across ethnicities[351,352] [expand – look at function]. (see also 6.10.3.1).
- One link between Zn and diabetes relates to SLC30A8, (also known as ZNT8 - Zinc transporter 8) whose polymorphic forms confer altered susceptibility to diabetes in a Chinese Han[353] population but not in an Indian family from Tamil Nadu.[354]
- Presence of autoantibodies to ZNT8 is associated with type 1 diabetes.[355] [expand – tissue distribution and population prevalence]
- Other ZnT8 variants also associated with type 2 diabetes were associated with differences in Zn levels within peripheral blood mononuclear cells from diabetic patients, as well as differences in expression of other Zn-transport related genes and release of cytokines after LPS challenge.[356]
- In a preprinted observational study[357] of 832 S Korean patients with COVID-19 and diabetes, compared with patients not taking these drugs, those taking dipeptidyl peptidase-4 (DPP4) inhibitors (sitagliptin etc.) had better clinical outcomes in terms of severe treatment or death (adOR 0.362; 0.135-0.971). Patients taking RAS blockers (ACE inhibitors or ARBs) also had reduced, but not statistically significant outcomes (adOR 0.599; 0.251-1.431). Others[358] have proposed the use of DDP-4 inhibitors. As with MERS-CoV, SARS-Cov-2 may be using the DPP4 receptor as a co-receptor for cell entry, after initial binding to ACE2.[359]
- New onset diabetes has been observed associated with COVID-19.[360] Whether this is related to zinc dysregulation is unknown.

6.4 Kidney Disease, Renin-Angiotensin-Aldosterone System (RAAS)

- The SARS-Cov-2 virus enters the cell by attachment of its spike glycoprotein to the ACE2 receptor.[361]
- According to the National Kidney Foundation: *"People with kidney disease and other severe chronic medical conditions are at higher risk for more severe* [COVID] *illness."* Although this is true for a variety of reasons, kidney disease may influence the expression of ACE2 in lung tissue, facilitating entry of SAR-CoV-2.
- In an Icelandic population, increases serum ACE2 was associated with smoking, obesity, diabetes. Serum ACE2 was reduced in males.[362] An Italian study found no evidence of association between ACE2 expression and disease severity or sex bias.[363]
- A pre-printed review and meta-analysis found that kidney disease is a risk factor for COVID-19, which may also damage the kidney.[364]
- ACE2 is a Zn-dependent protein along with other angiotensin receptors.[365] It is possible that through ACE2, the virus exploits other nexi between the Angiotensin II system and Zn similar to a described mechanism of smooth muscle cell senescence.[366]
- Kidney disease leads to a variety of changes in RAAS and studies in humans and animals have variously described both up[c]-and down regulation of ACE2 and some dependence on disease severity and treatment. However, most of these studies have only examined renal system tissue[368,369]
- ACE2 polymorphism has implications for heart disease and hypertension.[370] and may also play a role in explain ethnic and other differences in COVID-19,[371-374] An autopsy series of 67 COVID-19 patients the presence of an ACE2 endothelial phenotype mainly in brain and lung, but not kidney correlated with pathologic and clinical findings.[375]
- ACE2 polymorphisms did not appear to play a role in disease related to SARS-Cov-1 in Vietnamese[376] and Hong Kong-Chinese[377] populations. Studies of ACE2 variations between animal species may be instructive.[378]
- In primary cultures of human cells, ACE2 expression and infection by SARS-Cov-1 appears related to their state of differentiation.[379] In humans it is highly expressed in oral mucosal epithelium.[380]

[c] The upregulation of ACE2 by an exercise regimen has led to the recent suggestion that *"while exercise is clearly associated with improved cardiovascular outcomes in chronic situations, exercise may contribute to a greater risk of SARS-CoV-2 infection."* This may explain the COVID-19 susceptibility of a number of apparently healthy individuals.367. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol 2020;318:H1084-H90.

- In rats, age and sex differences in ACE2 expression were found in various lung epithelial and vascular tissues.[381] The significance to COVID-19 of gender differences in surface expression and circulating levels of ACE2 and other components of RAAS[382,383] is unclear.
- Based on earlier studies in a murine model of lung injury,[384] studies are underway to evaluate soluble ACE2 for the treatment of COVID-19.
- The relationship between sickle cell and kidney disease is discussed in 6.10.2.1.
- Small bowel ACE2 expression is reduced in active Crohn's disease.[385] How this related to COVID-susceptibility is unclear.
- The correlation of nicotinic receptor gene expression with ACE2 in airway epithelial cells as well as with BMI has been proposed as an underlying cause for high COVID-19 risk in obesity.[386]
- The use of metformin in COVID-19 has been proposed based, inter alia, on its antiviral effect (it was originally developed as an anti-influenza drug)[387] and on its effect on AMP Kinase which phosphorylates the ACE2 receptor, possibly hindering it sterically for binding to SARS-Cov-2.[388]
- Zn dysregulation occurs in renal disease. This may be linked to iron dysregulation as well as comorbidities such as obesity and cardiovascular disease.[389-391]

6.4.1 Drugs acting on the RAAS

- RAAS and implications for its pharmacological manipulation based on the role of angiotensin converting enzyme-2 (ACE2) as a receptor for the SARS-CoV-2 into the lungs have been reviewed[367] (see also 6.12 for discussion regarding losartan).
- Because SARS-CoV-2 uses ACE2 to enter cells (see also 6.4), manipulation of RAAS using Angiotensin Receptor Blockers (ARBs) such as losartan, has been suggested as an approach to treating COVID. Due to the complexity of RAAS with its feedback loops and upregulation of ACE2 by losartan, the proposed mechanisms of action do not appear fully understood[392] with early caution being expressed[367,393,394] Further, losartan depletes Zn.[395] Trials of losartan should include a Zn supplement arm. Existing losartan patients might also be given Zn.
- A pre-printed observational study from medical record data in the UK failed to find an association between COVID-19 status and the use of ARB/ACE inhibitors (studied as a group). [396]
- A large observational [now retracted[177]] study of records from 96,032 mainly North American patients[25] found a reduced risk associated with the use of ACE inhibitors (HR 0.566, 0.514–0.624, n=7949) and statins (HR 0.793, 0.736–0.855, n=9245) but not ARBs (0.989, 0.914–1.071, n=5849). A similar finding was made in a separate meta-analysis.[397]
- Another meta-analysis[398] found a similar risk of mortality or serious illness in patients taking ARB/ACE. However, examining just hypertensive patients, these drugs was associated with significantly lower mortality (OR 0.64, 0.45-0.89) and lower but not statistically significant severe/critical illness (OR (0.76, 0.52-1.12; p=0.16), a finding essentially replicated in another meta-analysis.[399]
- Looking at just hypertensive patients, another meta-analysis found a 35% reduced mortality risk (RR=0.65, 95% CI: 0.45-0.94) in patients taking RAAS inhibitors.[400]

Figure 2: The renin angiotensin system (from South[367])

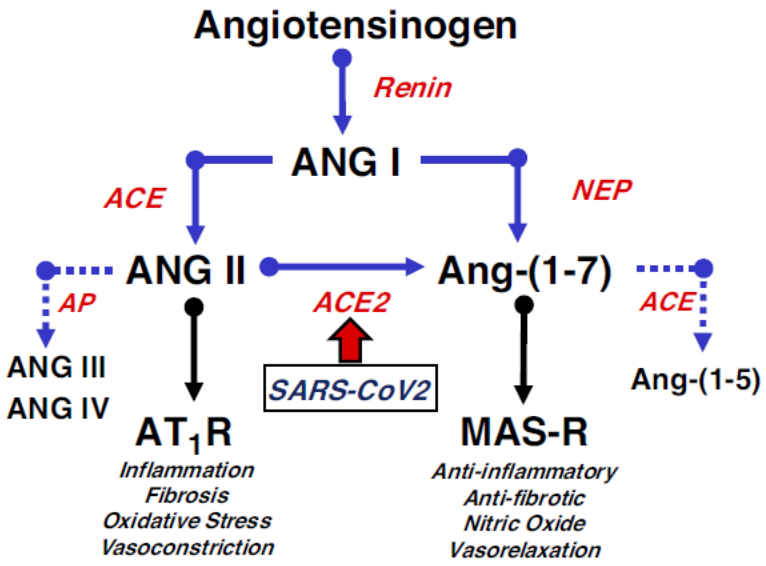


Fig. 1. Processing and functional scheme of the renin-angiotensin system. The protease renin converts the precursor angiotensinogen to angiotensin I (ANG I), which is subsequently converted to ANG II by dipeptidyl carboxypeptidase angiotensin-converting enzyme (ACE). ANG II binds to the ANG II type 1 receptor (AT_1R) to stimulate inflammation, fibrosis, oxidative stress, and an increase in blood pressure. ANG II is metabolized to ANG III and ANG IV through various aminopeptidases (APs). ANG I and ANG II are converted to Ang-(1–7) via endopeptidases (NEP) and the monocarboxypeptidase ACE2, respectively. Ang-(1–7) binds to the Mas receptor (Mas-R) to exert anti-inflammatory and antifibrotic actions, stimulate the release of nitric oxide, and reduce blood pressure. Ang-(1–7) is metabolized to Ang-(1–5) by ACE. Major forming and degrading pathways are depicted by solid and dashed lines, respectively. SARS-CoV-2 binds to ACE2 to stimulate internalization of both the virus and peptidase that may remove ACE2 from this pathway.

- Vitamin D may modulate the RAAS in a number of ways beneficial to the treatment of COVID-19.[401]

6.5 Heart Disease

The prevalence of acute myocardial infarction was inversely correlated with serum Zn levels.[402] [expand]
The role of zinc dysregulation and supplementation in heart disease has been reviewed.[403]

6.6 Smoking and Vaping

- Smoking appears to be associated with negative COVID outcomes.[404]
- Alteration in Zn homeostasis by cadmium present in cigarette smoke[405] and Zn depletion in smokers may contribute to lung damage from smoking.[406] Initial reports from COVID-19 tracker (4/7/20, Steves, C) are: *"In this U.K. data, smoking significantly increases the risk of self-diagnosed COVID-19 given classical symptoms (fever and persistent cough) by about 26%. Other studies indicate the risk of severe disease is probably even higher."* The investigators further recommend *"If you or one of your loved ones is going to quit, it's a good idea to get a form of nicotine replacement. I wouldn't suggest vaping, as there is some evidence that might also not be good, but patches, gum or inhalators work really well."*
- According to the Center for Evidence-Based Medicine *"smoking increased both the risk of getting an [acute respirator] infection. Quitting smoking during an acute respiratory infection reduces the risk of developing serious complications. Even if someone has smoked for decades, quitting smoking can lead to almost immediate improvements in the cardiovascular and respiratory system. Within one to two days of quitting smoking, positive effects can be observed in blood pressure, heart rate, vasoconstriction and oxygen levels."* Since Zn has been used to treat cadmium toxicity[407] it may be appropriate, that in addition to smoking cessation, zinc supplementation be initiated. Smoking may also increase hand-to-mouth transmission, according to WHO, who provide additional discussion on tobacco use and COVID. as do Cochrane.

- Initiatives to encourage smoking-cessation would certainly have long-term benefits, if not short-term ones relating to COVID-19.
- A recent study found that ACE2 expression is upregulated in smokers and patients with CPOD in the lower respiratory tract, possibly contributing to an increased risk of severe COVID-19.[408]
- In contrast to the above, some have argued that smoking is not a risk factor for COVID-19.[409] and two recently (4/23/20) reported French studies[410] suggest [needs further review] that smoking may be a *protective* factor for becoming infected. It is hypothesized that in additional to entering cells via ACE2, SARS-Cov-2 may also access cells via the nicotinic acetylcholine receptor,[411] which may mediate other aspects of the inflammatory response to SARS-Cov-2.[412,413] Additionally, ACE2 expression may be partly regulated by the nicotinic receptor.[386] One possible source of protection, if any, may be nitric oxide present in cigarette smoke.[414]
- Further discussion.[415-417]
- Among hundreds of other compounds, rutin, a quercetin glycoside, is found in tobacco. Differences in rutin or other content of tobacco among brands[418] used in France and elsewhere may partly explain the contrasting reports regarding smoking and COVID-19, consistent with the finding that daily quercetin supplements reduced a number of cardiovascular risk factors in a study of 92 Korean smokers.[419]
- There appears to be an association between vaping and increased susceptibility to COVID-19 and death.[420][expand]

6.7 Alcohol Use

Alcohol abuse is associated with low Zn status due to reduced intestinal absorption and increased urinary excretion.[302] [expand]
In a case-controlled study alcohol was associated with higher rates of infection.[421]

6.8 Other possible environmental factors

[expand all]

- Air quality, climate
- The fluoridation of water (see CDC national fluoridation information) to prevent tooth decay, may have additional benefits in reducing other diseases whose patients are at higher risk of severe COVID-19 [ref, any associations?]. [effects of Zn and F?] [422]

6.8.1 Subway pollutants and spread of COVID-19: iron and zinc dysregulation

- PM2.5 (Particulate Matter < 2.5um) particles generated by friction between subway train wheels and tracks, as well as during braking, appear to adhere to SARS-Cov-2 virions, facilitating their deep penetration into the lung. PM2.5 levels may be tens of times higher on subway platforms than at the surface and correlate with the number of stations and the length of the rail network. The percentage COVID-19 mortality for a given city correlated significantly with both minimum and maximum levels of subway PM2.5.[423] In addition to PM2.5, subway trains generate significant amount of Black Carbon.[424] This effect is likely multifaceted and ethnic differences in ridership and employment across the whole system, and differences in levels of pollutants in stations serving particular neighborhoods, may contribute to ethnic differences in COVID-19 prevalence.
- PM2.5 contain significant amounts of iron, with smaller contributions from manganese and chromium which could contribute to oxidative stress and adverse oxidative consequences to biological tissues.[425] One reason why these effects have at best translated equivocally into clinically relevant health consequences[426,427] is the failure to take into account particular susceptibilities on sub-populations prone to iron overload (see 6.10.8 for further discussion).

6.9 Zinc-associated calcium dysregulation in viral infection, Vitamin D

- In addition to its role in calcium regulation, Vitamin D has a large influence on immune function.[279,428] Chemically, Vitamin D is a sterol, and like glucocorticoids, mineralocorticoid, estrogen, androgen and progestogen steroids, is derived from cholesterol. The Vitamin D receptor is in the same nuclear receptor superfamily, and there is are a number of points of interaction between Vitamin D and the various steroid hormones.[429,430]
- Viroporins, transmembrane viral proteins that form ion channels in host membranes, have a role in virally-induced calcium dysregulation.[431,432] It is possible that these viroporins may also dysregulate Zn, or may be the target of Zn treatment.[expand] A small retrospective study found that hypocalcemia was common among severe COVID-19 patients and associated with poor outcomes.[433]
- Examination of COVID-19 epidemiological data, historical data on Vitamin D levels in the elderly, a previously established inverse relationship between CRP (C reactive protein, a marker of inflammation) levels and

Vitamin D levels, and the presumption that CRP levels are a marker for severe COVID-19 disease, has led to the suggestion that Vitamin D status may in part determine an individual's response to COVID-19,[434] particularly in diabetics.[435] A similar inverse relationship exists between CRP and Zn levels in acutely ill elderly patients.[436] Zn has been shown to reduce CRP levels in the elderly.[437]

- Although contradicted by a large observational German study involving respiratory disease and the elderly,[438] Swiss[439] and Israeli[440] studies, analysis of UK Biobank data could not "support a potential link between vitamin D concentrations and risk of COVID-19 infection" nor explain ethnic differences in COVID-19 infection by differences in Vitamin D levels.[441-443] Another, smaller UK observational study found an association between low Vitamin D levels and admission to ICU.[444] Correlations were also observed for countrywide Vitamin d deficiency and COVID-19 mortality.[445]
- Social distancing measures may certainly result in lower sunlight exposure. Geographical (latitude[446]), cultural (degree of body covering), skin pigmentation (blocking effective of sunlight on Vitamin D production), age (efficiency of skin to product Vitamin D) differences may contribute to COVID-19 risk.[43,279]
- Although mentioned in the EVMS/MATH+ protocol[43], and proposed by others[447,448] including a Lancet editorial,[449] some caution has been expressed about Vitamin D (see 8). The suggestion of Zn dysregulation associated with elevated procalcitonin (see 6.1), does prompt consideration of how use Vitamin D might be used. Vitamin D is known to influence Zn (and other trace element) metabolism.[450]
- A small (n=43) preprinted cohort observational study in hospitalized COVID-19 patients over 50 found that oral vitamin D3 1000 IU OD, magnesium 150mg OD and vitamin B12 500mcg OD reduced the need for oxygen (17.6% vs 61.5%, P=0.006, OR 0.13, 0.03 − 0.59) and ICU therapy (OR 0.15, 0.03 − 0.93).[451]
- Fusion and infectivity of two other coronaviruses -MERS and SARS-Cov-1 – with the host cell is promoted by calcium ions. It is possible that Zn could interfere with this process as one anti-viral mechanism.[452]

6.10 Diseases and Conditions - Higher Prevalence in Racial/Ethnic Groups: implications for Zn & COVID-19

The higher prevalence of a number of diseases or conditions have been associated with various racial and ethnic groups. In addition to the above discussion, cultural or socio-economic factors (beyond the scope of this document[453]), the following genetic factors may contribute further to an increased risk of COVID-19 severity. Zinc dysregulation may or may not be involved.

Environmental, cultural and other factors may modulate differences in COVID-19 severity between racial/ethnic groups within the USA and their contemporary counterparts in their geographic region of origin.

6.10.1 Glucose 6 Phosphate Dehydrogenase Deficiency

About 400 million people worldwide have G6PD, more frequently in Africa, Asia, the Mediterranean, and the Middle East, with about 10% of African American males affected.[454] (see 4.4 for discussion regarding HCQ and CQ). It has been suggested that G6PD may be a risk factor for COVID-19.[455,456]

6.10.2 Factors Possibly Affecting the African-American Population

- A study of the development of COVID-19 in New York City found that: "*Areas with large proportions of Black/African American residents are at markedly higher risk that is not fully explained by characteristics of the environment and pre-existing conditions in the population.*""[9] Similar conclusions were drawn in a pre-printed UK study regarding blacks, Asians and other non-white groups.[457]
- Differences between in-hospital exposure risk related to type of assignment, ethnicity and likely use of PPE in a UK study likely accounts for differences in rates of COVID-19 among hospital workers, with household exposure contributing to a higher incidence of COVID-19.[199]
- Particularly in African-American, but also in Hispanic children in Atlanta,[458] highly prevalent Zn deficiency (and anemia) were found. It is not unreasonable to suppose that this reflects the nutritional status of the adults.

6.10.2.1 Sickle Cell Disease, Sickle Cell Trait

- Sickle Cell Anemia/ Disease (SCD) occurs in homozygotes for the variant β globin gene.
- Zn deficiency has been noted in sickle cell disease (SCD).[11] Infection contributes significantly to morbidity and mortality in SCD through a variety of mechanisms.[459,460] *In vitro*, Zn loading of sickle erythrocytes improves their filterability.[461]
- Zn supplementation, proposed to mitigate aspects of immune compromise and susceptibility to infection in SCD,[301] enhanced immune function and reduced hospitalizations due to bacterial (including respiratory tract) infections in 32 adult SCD patients.[12] A study is ongoing to examine the effect of Zn supplements on infection (including respiratory tract) rates in Ugandan children with SCD.[462] An Indian study failed to show a benefit of Zn supplements against bacterial pneumonia in children (not with SCD).[463] A Cochrane review[464] found

that *"people with sickle cell disease who received zinc supplements …had fewer sickle cell crises and infections*."

- We speculate that Zn depletion is one mechanism by which SCD confers resistance to malaria, as Zn was found to accumulate within the malaria parasite *Plasmodium falciparum* as it matured inside human erythrocytes *in vitro*.[465] Despite lowered plasma Zn levels in 689 pre-school children (SCD status unstated) during acute falciparum malaria[466] and despite Zn supplements having no beneficial effect[467] on fever in a larger population (n=1087) from which this observation was made, no detrimental was apparent.
- The heterozygous Sickle Cell Trait (SCT) trait occurs in about 8% of African-American.[468] Although historically considered a benign condition, SCT is associated with extreme exertional collapse and sudden death in athletes and servicepeople (Exercise Collapse Associated with Sickle cell Trait - ECAST) due to hypoxia-induced sickling.[468] In a review of other conditions associated with SCT,[469] conditions suggestive of immune compromise or susceptibility to infection do not appear prominent.
- Most relevant to COVID-19 perhaps is that in a 25 year study of 1995 African Americans, SCT (6.8% of the cohort) was found not to be an independent risk factor for developing hypertension, diabetes, or metabolic syndrome.[470] However, in an analysis of over 15000 patients from five studies, SCT was associated with a higher risk of kidney disease in African-Americans,[471] with a proposed mechanism of sickling-induced ischemia and infarction of the renal tubules.
- It appears unknown whether Zn dysregulation occurs in SCT that may contribute to immunocompromise and susceptibility to viral infections.
- The higher risk of kidney disease in SCT may manifest itself in the form of attenuated alterations in levels of ACE2 and other RAAS components seen in children with sickle cell anemia and proteinuria.[472] Along with changes in inflammatory markers[473] the mechanisms of kidney damage may have parallels in COVID-associated lung damage (see 6.4).
- COVID-19 recommendations have been issued by the Sickle Cell Disease Association of America and the American Society of Hematology.

6.10.2.2 PIEZO1 E756del variant

- The gene PIEZO1 codes for the Piezo1 protein, a stretch-activated non-selective cation channel found in many tissues including erythrocytes and lung epithelium. Calcium influx triggers another channel, the Gardos channel, which removes intracellular sodium and potassium ions.[474] The PIEZO1 E756del variant is associated with xerocytosis. Erythrocytes from xerocytosis patients become dehydrated and shrink, due to changes in cation flux kinetics.[475]
- This variant was found in 36% of a sample of 25 otherwise healthy African-American volunteers, who were all heterozygous for this allele. Their erythrocytes displayed the shrunken morphology found in xerocytosis patients and showed reduced susceptibility to infection with *Plasmodium falciparum in vitro*.[476] Further, in an animal model of xerocytosis consisting of mice modified to carry the E756del allele, erythrocytes were also dehydrated and showed reduced growth of a rodent malarial parasite. Further, these mice displayed a higher survival rate than their wild-type counterparts.[476] In Gabonese children, heterozygosity for this allele did appear to confer protection against malarial severity.[477] There was no additive protection for E756del heterozygotes who also had sickle cell trait and there was an increased risk of severe disease in E756del homozygotes, evincing complex epistatic regulation.
- Since there are other instances of Zn transported via calcium channels,[478] it is not unreasonable to speculate that Zn transport may also be altered in variants of the PIEZO1 channel. Further, since Piezo1 is also found in lung epithelium,[479] it is suggested that E756del status may affect epithelial Zn status and therefore the response to COVID-19 and/or Zn ionophores used to treat it.

6.10.3 Factors Possibly Affecting the Hispanic/Latino Population

6.10.3.1 Diabetes

- People identifying as "Hispanic" and/or "Latino" have diverse Native American, European and African origins with particular ancestry proportions correlating with susceptibilities to breast cancer, hypertension, diabetes[480] and obesity.[481] There are strong overlapping associations between diabetes and heart disease, obesity,[481] and kidney disease, as well as with certain genetic polymorphisms. In genome wide associated studies (GWAS), a number of gene variants and SNPs were associated with diabetes in Mexican Americans[351] or other Hispanic/Latino cohorts[352] (HNF1a[482,483]; SLC16A11[483,484], IGF2[483 68]).

6.10.3.2 Asthma in Puerto Ricans

- Puerto Ricans, in whom asthma is highly prevalent, have European, African and Native American ancestry. An increased risk of asthma was found in those of European ancestry but low socio-economic status (SES),

but a lowered risk associated with African ancestry. This relationship was reversed in cohorts with higher SES.[485] The increased risk of asthma in Puerto Ricans appears associated with the 5q23.3 region with a possible contribution from 13q13.3.[486] [expand – genetic basis and susceptibility to lung infection]

6.10.4 Factors Possibly Affecting the Jewish Population

- A UK government study found a higher age-adjusted risk (1.5-2.5 times) of mortality among Jewish, Hindu, Muslim and Sikh people compared with Christians, even when adjusted for a number of confounding variables.[487] After adjusted for other variables, Jewish people had the highest risks of the religious groups examined.
- SNPs near the promotor region coding for Hepatocyte Nuclear Factor-4α (HNF4α) were associated with diabetes (type 2) as well as in Ashkenazi families in two studies.[488,489] HNF4*α* is involved in the regulation of lipid transport and metabolism and its variants are associated with a variant of diabetes (Maturity-Onset Diabetes of the Young – MODY). [expand – prevalence etc.].
- Zn supplementation in a murine model of alcoholic liver disease enhanced hepatic regeneration associated with an increase in HNF4α.[490] Whether this indicates that Zn supplementation would be particularly beneficial in diabetic patients with lowered HNF4*α* activity requires further investigation. [expand].
- See 6.10.7 for discussion of thalassemia which is also found in Sephardi Jewish populations.
- See 6.10.5 for discussion on Familial Mediterranean Fever.
- With the recent popularity of genealogical DNA testing, the admixture Sephardi (North African, Mediterranean, Middle Eastern) Jewish ancestry within Ashkenazim (East and North-Eastern Europe) populations is becoming more evident. Consequently, conditions such as Thalassemia and Familial Mediterranean Fever have been found among Jews who had no oral tradition of a Sephardi ancestry [expand].

6.10.5 Familial Mediterranean Fever

- Familial Mediterranean Fever (FMF) is characterized by bouts of fever, arthritis, various pains or aches. It is found in Sephardi Jews as well as those of North African, Arab, Armenian, Turkish, Greek, Italian or Sephardi Jewish descent. FMF is associated with one of over 80 variations of the MEFV gene coding for pyrin, whose presence in inflammasome NLRP3 restrict the inflammatory response in monocytes and other leukocytes and in "non-professional" immune response cells [expand].[491] The NLRP3 inflammasome in peritoneal mesothelial cells can be activated by Zn deficiency, and inhibited by Zn supplementation.[492]
- The role of an over-exuberant inflammatory response in FMF patients or carriers with COVID-19, as well as its modulation with Zn is unknown. [expand]
- Prevalence in population of FMF [expand]

6.10.6 Factors Possibly Affecting other Racial/Ethnic/ Disease Groups

This review is not exhaustive. Further review is required on factors affecting the COVID-19 susceptibility of other groups including Native Americans[349] and people of Asian ancestry. [348,349] [353] related to diabetes and conditions. [expand]

6.10.7 Hemoglobinopathies

- The thalassemias are a group of genetic disorders related to blood hemoglobin production, found in people of Mediterranean, African and South-East Asian origin. Mineral deficiency, including Zn, may occur and should be monitored,[493] A Cochrane review[464] found *"no evidence from randomised controlled trials to indicate any benefit of zinc supplementation with regards to serum zinc level in patients with thalassaemia. However, height velocity was noted to increase among those who received this intervention."*
- Thalassemia patients may be at higher risk of viral (Including possibly COVID-19) and other infections, through a number of mechanisms, including iron overload.[460]
- COVID-19 related guidance has been issued by the American Society of Hematology and the Thalassemia International Federation.
- After attempting to control for a number of variables including disease trajectory in three Italian regions, a retrospective study suggested that the prevalence of beta thalassemia heterozygosity is inversely associated with the prevalence of COVID-19.[494]
- Sickle Cell Disease and Trait are discussed below (6.10.2.1).

6.10.8 Iron Overload Conditions

- Since free iron contributes to generation of ROS, oxidative stress may be more pronounced in patients with poor iron handling such as those with premenopausal hysterectomy and people of Irish-Scottish ancestry

(about 25% of the US population).[495] This ethnicity has a high prevalence of Hereditary Hemochromatosis (HHC) and even carriers of the HFE mutations show attenuated forms of iron overload which manifest under stress. Also, HHC (including carriers) has a higher incidence of diabetes. Men also carry a higher iron load, and this may contribute to the gender imbalance in COVID. Although obviously multifactorial, the trajectory data currently shown for Ireland (4/8/20) indicate a slightly initial higher case acceleration compared to a number of other countries.

- Iron, present in PM2.5 particulate pollutants in underground transit systems (see 6.8.1), may pose an additional propensity for iron overload in susceptible individuals, superimposed on the iron dysregulation that occurs in COVID-19.[496-498] Among other mechanisms, HCQ has been proposed to act by modulating iron homeostasis during viral infection.[125]
- Iron overload may induce changes in Zn distribution[499,500] [expand] Conversely, Zn deficiency may result in iron accumulation[501] and Zn treatment may protect against iron overload.[502,503]

6.10.9 Hemoglobin and Iron

- In a review of observational studies of COVID-19, there was a reduction in Hb level with increased age, comorbidity and disease severity. Ferritin increased with increased male proportion in any study and Hb. A lower Hb and higher ferritin was associated with disease severity. Lower ferritin was associated with survival.[504]

6.11 Other Diseases and Conditions with implications for COVID-19

6.11.1 The elderly

- Age has repeatedly been associated with a higher of poorer COVID-19 outcomes. A pre-printed study suggests that "(i) frailty is not a good discriminator of prognosis in COVID-19 and (ii) pathways to mortality may differ in fitter compared with frailer older patients."[505]
- In addition to higher prevalence of comorbidities, the effects of aging on the immune system, there are a number of special considerations (beyond the scope of this paper) that apply to the elderly in terms of overall care, protection from exposure to family members and care givers, assistance with grocery shopping, and mental wellbeing.[506]

6.11.2 Pediatric Kawaski-like disease in COVID-19

- There are increasing numbers of reports of pediatric cases of COVID-19, including some post COVID-19 cases, of vasculitis, pericarditis and abdominal pain, which resemble Kawasaki Disease.[507] Differences in the immune system as well as the expression of COVID-19 related receptors throughout the body may well account for some of these differences. Vasculitis, pericarditis and abdominal pain, may indicate a similar SARS-CoV-2 mediated injury to the related endothelial and (pericardial, peritoneal serosal) mesothelial systems. An "activated" peritoneum may place a patient at increased long-term risk of adhesions, abdominal and pelvic pain, as related conditions of interstitial cystitis, IBS and pudendal neuralgia.[495] Early intervention with heparin (eg LMW heparin) and other drugs used in adhesion-prevention strategies[508] may be a suitable approach worthy of investigation, not only to treat the immediate disease, but also to attempt to mitigate long term effects. [expand] (see also 10.3)

6.12 Drugs that Modulate Zinc Metabolism

- If Zn deficiency is associated with immunocompromise and susceptibly to oxidative stress, patients taking Zn-depleting drugs may be at higher risk of developing serious COVID. Similarly, the effectiveness of drugs such as HCQ whose action may depend on Zn, may be compromised. Thus, any trial of HCQ should stratify not only by comorbidity, but also concomitant medications and Zn levels.
- Patients taking Zn depleting drugs such as omeprazole and Angiotensin Receptor Blockers (ARB) such as losartan[395] may also fall into the high-risk COVID-19 categories of obesity and heart disease.[170]
- A number of anti-hypertensive drugs also deplete Zn.[509] It is unclear if this effect is independent of hypertension associated with Zn deficiency.[510,511]

6.12.1 Gastric acid-lowering drugs – omeprazole, famotidine

- Although not all studies agree, appears to reduce Zn GI absorption.[512] Omeprazole was associated with lowered serum Zn levels in men,[513] Possibly,[514] but arguably[515] by reducing intestinal absorption. *In vitro*, this drug increased the anti-HSV activity of acyclovir.[516]
- A review of over 6200 patient records in China, suggested a lower death rate (14% vs 27%) in elderly patients taking famotidine (H2 antagonist) rather than omeprazole. Based on this observation, as well as a computer

modelling study of the viral papain-like protease (necessary for replication), a clinical study was initiated to examine the effects of high iv doses of famotidine[d] in COVID-19 patients.[517] The reason for using high iv doses is unclear. Whether the difference between the omeprazole and famotidine-treated patients was due to a positive effect of the famotidine, or a negative effect of omeprazole, is unclear. Both famotidine and omeprazole were found to have at least moderate potential to interfere with the spike protein or the ACE2 docking complex in the SUMMIT simulation.[107]

- A retrospective study[170] (now published[518]) of patients in New York, not requiring *"urgent or semi-urgent intubation"* and testing positive by PCR for SARS-Cov-2 by PCR found:
    - **For famotidine - a reduction** in the HR for death (0.30; 0.11-0.80) in 84 patients receiving famotidine compared with 420 propensity score-matched patients not receiving it. This association was not found in patients who did not test positive for the virus.
    - Famotidine was associated with lowered ferritin levels, a surrogate marker of cytokine storm. A number of possible mechanisms for the action of famotidine, are reviewed in this NY paper, including its theoretical ability to inhibit 3-chymotrypsin-like protease (3CLpro), needed for SARS-CoV-2 replication.
    - This study also found that the *"relationship between famotidine and the composite death/ventilation outcome remained similar among 930 patients who used HCQ (HR for famotidine 0.35; 0.14-0.85) and among 690 patients who did not use HCQ (HR for famotidine 0.55; 0.18-1.75)."* The study may not have sufficient power to discern any difference, but if famotidine works partially by redistributing Zn, this may be sufficient to provide enough Zn to facilitate some efficacy of HCQ.
      As relayed by its principal author (Freedberg, personal communication 5/12/20), *"The confidence intervals widely overlap on the stratified analysis and a test for a HCQ-famotidine interaction was non-significant."*
    - The reasons for the use of famotidine in the Freedberg paper are not completely clear. Dr. Freedberg relayed that: *"15% famotidine use was documented on medication reconciliation but medication reconciliation is inaccurate, especially for OTC medications. On chart review of a subset of charts, 55% of patients either had famotidine mentioned as a home medication on the intake history or a diagnosis of GERD. Our assumption is that famotidine was continued as a home med, but we cannot prove this."* Further: *"Our study did not include ICU patients receiving famotidine for SUP. Anecdotally, famotidine does not seem to have benefit in these patients."* The findings are supported by a small prospective case series in non-hospitalized patients.[519]
    - For proton pump inhibitors (e.g. omeprazole), an **increased** risk (HR=1.34, 1.06-1.69) for the composite endpoint of death or intubation (even after adjustment for age, BMI, diabetes, hypertension, and baseline oxygen requirement). PPIs are used in ICUs for Stress Ulcer Prophylaxis (SUP).[520,521e] This is contradicted by the finding of a preprinted retrospective case-controlled study of a lower risk (OR 0.44, 0.23- 0.82, p=.0053)) of COVID-19 infection associated with the use of proton pump inhibitors in 179 patients at a geriatric hospital in France.[421]. The drugs used were mostly pantoprazole, lansoprazole and esomeprazole, less so omeprazole, and rabeprazole. [differences in Zn depletion among PPIs?]

- A population-based (n=53,130 subjects), online survey with 3,386 (6.4%) reporting a positive COVID-19 test, found after multivariable logistic regression that included consideration of BMI, that use of PPIs once (OR 2.15; 1.90–2.44) or twice daily (OR 3.67; 2.93–4.60) had higher odds for reporting a positive COVID-19 test than non-use of PPIs. Once (OR 0.85, 0.74–0.99, p = 0.032) and twice (OR 0.86, 0.66–1.11) daily use of H2 antagonists was associated with reduced odds Almario – GET REF
- The expert COVID-19 recommendations are silent on the use of PPIs,[522] and the extent to which they are being used in COVID-19 patients is not known [expand].
- The H2 antagonists cimetidine, ranitidine and famotidine reduce Zn absorption (as plasma levels) in healthy volunteers, presumably by increasing gastric pH.[523,524] In their discussion of the Sturniolo[107] study, Henderson et al.,[106] suggested that cimetidine, but not famotidine is a Zn ligand. Zn-famotidine complexes have however been formed, albeit under lab conditions.[525] As with other drugs, the use of Zn supplements along with famotidine, may be warranted.
- Cimetidine has been shown to enhance mitogen-induced lymphocyte proliferation associated with incorporation of Zn (and Mg) into lymphocytes from treated volunteers. There appeared to be a differential effect on helper and suppressor populations.[526] In rats, cimetidine changed, in a sex-dependent manner, the

[d] It is noted that famotidine is being compared with HCQ, and uses a control arm consisting of patients treated earlier in the outbreak.

[e] I am grateful to my daughter Jennifer Wiseman, a third-year medical student, for pointing this out. I questioned Dr. Marik about this, who included it in the EVMS protocol.

tissue distribution of Zn, copper iron, calcium, magnesium and sodium, with a reduction in fecal excretion of the divalent ions.[527]

- Carnosine is an endogenous dipeptide with numerous biological actions. Its actions on vascular smooth muscle may occur in a Zn-dependent manner via the H1 receptor. Its actions via H2 do not appear Zn dependent.[528]
- A 110 patient case uncontrolled series of patients with severe to critical symptoms reported the use of famotidine, along with a H! blocker, cetirizine.[529]

6.12.2 Drugs acting on RAAS
See 6.4

7 PHARMACOKINETICS, CHEMISTRY

[**expand**]

7.1.1 Zinc Formulations

Consideration should be given to the effect of formulations and dose forms on bioavailability.[530] The acetate,[523] citrate, gluconate[531] and sulfate salts have better absorption than the oxide.

[**expand – more detail on acetate**]
Factors affecting absorption [expand][298]

7.1.2 Hydroxychloroquine

Wide variations in the volume of distribution give rise to wide variations in blood concentration.[132] See discussion in 4.4.

From https://www.drugs.com/pro/plaquenil.html and
https://pubchem.ncbi.nlm.nih.gov/compound/hydroxychloroquine#section=Metabolism-Metabolites

Single 200 mg oral dose of HCQ to healthy male volunteers:
C_{max} (blood) 129.6 ng/mL after 3.26 hours, $t_{1/2}$ 537 hours (22.4 days).
C_{max} (plasma) 50.3 ng/mL reached in 3.74 hours, $t_{1/2}$ 2963 hours (123.5 days).
Urine HCQ was still detectable after 3 months with approximately 10% of the dose excreted was parent drug.

Single dose of a 200 mg tablet vs. i.v. infusion (155 mg)
$t_{1/2}$ ~ 40 days, large Vd.
C_{max} (blood) of metabolites observed at the same time as peak levels of HCQ.
Mean fraction of the dose absorbed = 0.74.

Single 155 mg and 310 mg intravenous doses,
C_{max} 1161 ng/mL - 2436 ng/mL (mean 1918 ng/mL) following the 155 mg infusion and 6 months following the 310 mg infusion. Pharmacokinetic parameters were not significantly different over the therapeutic dose range of 155 mg and 310 mg indicating linear kinetics.
(ignores effects of metabolites)

Differential activity of enantiomers?[532,533]

Pharmacokinetic modeling of HCQ action in COVID-19.[534]

Activity and metabolism of metabolites [expand]

7.1.3 Chloroquine

From:
https://pubchem.ncbi.nlm.nih.gov/compound/chloroquine#section=Biological-Half-Life
Estimates of half life vary widely and may be dose dependent. After a single 250mg oral dose, half-life was 3.1 hr, reaching 312 hr for a 1g dose. Other estimates have been up to 60 days.

7.1.4 Ascorbic Acid

Liposomal ascorbic acid – enhanced absorption? –[expand]

8 SAFETY ISSUES

8.1 Adverse Effects

The use of any drug, is not without risk and patients be provided with the usual cautions. Patients should always be advised to consult with their doctor regarding the use of these products, especially for at-risk patients such diabetics. Particular areas to highlight are:

- Long term use, copper depletion, overdose and the effects of foods high in phytates on Zn absorption.[535]
- Very high doses (500 and 1000 mg/kg/d) of one of the green tea catechins - Epigallocatechin-3-gallate (EGCG), were found to induce cardiac fibrosis in mice.[536]
- See discussion by Alschuler et al.[28] related to cautious use of related agents (including Elderberry *Sambucus nigra*; and Vitamin D)[228] at different stages in the progression of COVID-19.
- Zn supplements were associated with an increased risk of developing HIV/AIDS with poorer survival.

8.2 Drug Interactions

Using Drug Interactions Checker: [expand]

Drug 1	Drug 2	Drug interaction	Food/alcohol
Zinc sulphate or gluconate	Quercetin	None	None
Zinc acetate	Quercetin	None	Effect of cerain foods on Zn absorbtion
Zinc sulphate or gluconate	Green tea	None	None
Zinc acetate	Green tea	None	Effect of cerain foods on Zn absorbtion

There were no entries for pomegranate extracts.

Both HCQ and AZI have a number of significant interactions with other drugs and with each other [expand].

9 OTHER THERAPEUTIC APPROACHES

High level evidence concerning the utility of some treatments will take some time to appear and be analyzed by the medical community. Some reviews and meta-analyses are beginning to emerge (5/4/20).[537]

Several general reviews of possible drug approaches to COVID-19 have appeared.[207,208,538-545]

An extensive review of patent activity related to treatment of coronavirus diseases.[546]

A number of review have appeared in the integrative medicine literature, which variously discuss the use of Zn, Vitamins B, C and D, quercetin and other plant based agents to address different phases of COVID-19.[28 547]

Bio.org has an excellent COVID PipelineTracker

9.1 Remdesivir

- Inhibits viral RNA-dependent RNA polymerase
- NEJM RCT[548]. Hospitalized patients. Median recovery time of 11 d (95%CI, 9 - 12), vs 15 d (95%CI, 13-19) placebo. (RR 1.32; 95%CI, 1.12 -1.55; P<0.001). 14d mortality 7.1% vs 11.9% (HR 0.70; 95%CI, 0.47 - 1.04).

9.2 Other antiviral mechanisms

- M^{pro} 3-Chymotrypsin like protease is a key viral enzyme involved in replication and transcription. Inhibitors include Lopinavir and ritonavir etc. reviews[549]
- Neuropilin receptors as targets[550]
- TMPRSS2 (Transmembrane protease, serine 2) – is present on cell surface and is upregulated by androgens prostate cancer cells. In COVID-19, it is believed to activate the spike protein in the entry process after initial recognition by ACE2. Camostat mesylate 9sued in pancreatitis, esophagitis and some cancers), an inhibitor of TMPRSS2, inhibited SARS-CoV-2 into a lung cancer cell line in vitro.[551] An Italian study suggested an association between TMPRSS2 variants and disease.[363]

- Bromhexine (mucolytic, anti-tussive) which inhibits TMPRSS2 inhibitor has been proposed for use in COVID-19.[280]
- General review of specific anti-viral mechanisms and approaches[552]
- Review of compounds derived from fungi with anti-viral (anti-protease) and immunomodulatory activity of potential use in COVID-19.[553]
- Drugs affecting other coronaviruses may be effective against SARS-Cov-2, for example
    - MERS – inhibition of viral fusion[554], or helicase,[555]
    - Feline infectious peritonitis virus (FIPV) - 3CL^{pro} [556]

9.3 Other drug approaches

9.3.1 Immunotherapy

BCG vaccine[557,558] – effect on viral immunity
Convalescent plasma[559]
Tocilizumab[158]

9.3.2 Inflammation modulating

Colchicine[560-562]
NSAIDs, Acetominophen[563]
No apparent effect of using ibuprofen on death of respiratory support in small observational study.[564]
Silibinin, regulator of STAT3 and inhibitor of viral RNA-dependent RNA polymerase (RdRp)[565]
Inhalation anesthetics – effect on immune function[566]
Leronlimab - CCR5 antagonists
Noscapine (non-narcotic, anti-tussive opiate), via modulation of bradykinin response[567]
Pentoxifylline[568-570]
Cannabidiol[571], Cannabinoids[572]
PPAR-γ agonists (peroxisome proliferator-activated receptors (PPARs) - transcription factors part of the ligand-activated nuclear hormone receptor (NR) superfamily which regulate inflammation.[573] - Drugs and phytochemical (including curcuma, lemongrass, and pomegranate)
Renalse [expand]

9.3.3 Antifibrotic

Pirfenidone[574,575]

9.3.4 Inorganic-based, metal ions

Copper[289,576]
Gold-containing drugs -auranofin - inhibits SARS-COV-2 replication in vitro.[577]
Lithium[578]
Nitric oxide[579] [expand] Prevention protocol.[414,580]
Oxygen/ozone[581]
Selenium[582]

9.3.5 Anti-infectives

Dapsone[185]
Ivermectin[583]
Metronidazole[584]
Nitazoxanide/azithromycin[585]
Chlorpromazine[586] (as antiviral)

9.3.6 Phytochemical

Andrographis paniculata[587]
Curcumin[588]
Ginkgolic acid from Ginkgo biloba.[589]
Glycyrrhizin[590-592]
Hesperidin[593,594]

9.3.7 Other

Anti-Gaucher drugs
5- Hydroxymethylfurfural – nutritional supplement – effect on Hb-O_2 affinity[595]
Chicken soup (actual and metaphorical)[596]
Purinergic receptor antagonists - dipyridamole[597]
Vasoactive Intestinal Peptide[598]
Probiotics[599], reduction in mortality risk with fermented vegetables[600]
Statins[601]

9.4 *In vitro or in silico* screening for compounds

Table 8: In vitro or in silico screening for compounds useful in COVID-19

Compounds	Target	Reference
50,000 drugs, phytochemicals and other compounds	Spike protein and ACE2 docking complex	SUMMIT super computer[107]
Turmeric (Curcuma longa) compounds	M^{Pro}	602
Curcumin (from turmeric)	spike glycoproteins, nucleocapsid phosphoprotein, membrane glycoprotein, nsp10, RdRp	603
Essential oils (isothymol, thymol, limonene) from Ammoides verticillate, an Algerian plant	Inhibitors of ACE2	604
Various essential oils: farnesene, farnesol etc.	M^{Pro}, endoribonucleoase - Nsp15/NendoU), ADP-ribose-1″-phosphatase – ADRP, RdRp, spike protein, hACE2	605
Rutin, hesperidin	M^{Pro}	245
Neohesperidin	Tmprss2	258
Plants from India and Pakistan (includes luteolin)	M^{Pro}	266
African medicinal plants	$3CL^{pro}$	606
Saikosaponins from Chinese medicinal plants	NSP15 Endoribonuclease and spike protein	607
318 phytochemicals from 11 plants	M^{Pro}, ACE2	249
Compounds inhibiting enzymes sharing similarity to MPro	DPP-4 inhibitors; HCV protease inhibitors; SARS-CoV-2; a-thrombin inhibitors	608
Andrographolide	M^{Pro}	587
1615 FDA approved drugs	M^{Pro}	609
Hispidin, Lepidine, folic acid	M^{Pro}	191
67 compounds from Moroccan medicinal plants, includes several from M communis	M^{Pro}	610
	Drugs interacting with proteins whose genes are co-expressed with ACE2.	611
61 reported antiviral agents	Various SARS-Cov-2 protein structures	612
FDA approved anti-viral, plus database of other compounds	$3CL^{pro}$ High hits: Remdesivir, Saquinavir, Darunavir and two flavone and coumarin derivatives	613
Chinese herbal medicines	PL^{pro}, $3CL^{pro}$ and spike proteins Included quercetin (vs PL^{pro}, $3CL^{pro}$)	247,248
Protease inhibitors from public libraries: PubChem, zinc.docking.org	M^{Pro}	614
4153 phytochemicals	E protein ion channel	615
1403 FDA approved compounds	Pseudovirus in vitro assay	232
Novel keotamides	M^{Pro}, 3C protease	616
Vitamin C, curcumin and glycyrrhizic acid in combination	Systems biology approach targeting NOD-like and Toll-like signaling pathways to promote IFN, activation and balance of T cells and inflammatory response by inhibiting PI3K/AKT, NF-κB and MAPK pathways	617

Flavonoids, incl. quercetin, catechins, hesperidin, myricetin, luteolin	SARS-CoV 3Cl^{pro}	246
In silico design of peptides	Spike protein	618
Indian medicinal plant - *Azadirachta indica* (neem)	Inhibitors of SARS-CoV-2 Membrane (M) and Envelope (E) proteins	619
Antimalarial drugs	M^{pro}	620
Benzylidene-chromanones, (related to the flavones) found in *Hyacinthaceae* and *Caesalpinioideae* (also antioxidant and other actions)	M^{pro}	621
GC376, a drug used against feline coronaviruses, via M^{pro}	M^{pro} of SARS-Cov-2	622
100 fungal metabolites, flaviolin	3CL^{pro}	623
HCQ, CQ, remdesivir, arbidol	ACE2 RdRp, NSP12, NSP16 (replication, and viral latency)	127
14064 Marine natural products	M^{pro}	624
Compounds within Anthocephalus Cadamba	M^{pro}	625
FDA approved antivirals, active phytochemicals from Indian medicinal plants (includes epicatechin)	M^{pro}	255
FDA approved antivirals, ant malarials	M^{pro}	626
154 phytochemicals with analogous structure from limonoids and triterpenoids: top hits include Glycyrrhizic acid, limonin, Obacunone (from citrus)	3CLpro (main protease), PLpro (papain like protease), SGp-RBD (spike glycoprotein-receptor binding domain), RdRp, ACE2	627
14010 phytochemicals from Indian medicinal plants	TMPRSS2 and cathepsin L	628
FDA approved drugs: top hits: lumefantrine (antimalarial), dipyridamole (coronary vasodilator), dihydroergotamine (migraine), hexoprenaline (antiasthmatic), vitamin B2, B5	M^{pro}	629
Phytochemicals: top include hesperidine, cannabinoids, pectolinarin, epigallocatechin gallate, rhoifolin	M^{pro} and spike glycoprotein	256
Hesperidin, other citrus flavonoids	Various	Review[630]
	Water interactions with ACE2-Spike protein complex	631
Possible effect of heparin (positive) and TMPRSS2 inhibitors (negative) in viral clearance	TMPRSS2	632
Cinnamon compounds. Top hits: Tenufolin (TEN) and Pavetannin C1 (PAV)	M^{pro} and spike glycoprotein	633
Moringa oleifera flavonoids	15 peptides from SARS-Cov-2	634
Melaleuca cajuputi, SE Asia, member myrtle family Terpineol, Guaiol, Linalool, Cineol, β-Selinenol, α-Eudesmol, γ-Eudesmol	M^{pro}, ACE2	635
Modeling of open and closed conformations of spike fully spike protein		636
Geranium (Citronellol, geraniol, and neryl acetate) and lemon (limonene) essential oils	ACE2 inhibition in epithelial cells, immunoblotting, qPCR. Citronellol and limonene downregulated ACE2 expression in epithelial cells.	637

FDA approved drugs, statins, antivirals	M^{pro}	638

The target designation is as described in the paper. M^{pro} is also called $3CL^{pro}$ [639]
RdRp (RNA dependent RNA polymerase

Bioinformatics techniques (DrugBank, NCATS Pharmaceutical Collection -NPC, COVID-KOP, Chemotext, QSAR) were used to select 73 combinations of 32 drugs with potential synergistic or antagonistic activity against SARS-CoV-2. These were tested in a viral-Vero cell assay in vitro. 16 synergistic and 8 antagonistic combinations were identified with combinations of nitazoxanide and remdesivir, amodiaquine and umifenovir having significant synergry against SARS-CoV-2.[640]

9.5 Other proposed approaches

Neuromodulation –dysfunction in autonomic tone related cytokine release syndrome? [641]
Mesenchymal cells[642] and secretome[643]
Saline nasal irrigation and gargling
Povidone-iodine oral rinse (for oral procedures[644]) and nasal spray[645]
Hydrogen peroxide as oral disinfectant[646]
Mouthwashes containing chlorhexidine or (Citrox) citrus-derived broad spectrum antimicrobial bioflavonoids.[647]

Ultra-shortwave diathermy[648]
Chewing gum containing ACE2-coated nanoparticles.[649]
Photobiomodulation and Photodynamic therapy.[650]

Heated [651] humidified[652] air.

10 CLINICAL, PATHOLOGY

10.1 Clinical Summary

- There are a number of descriptions of the history, clinical, comorbidity, immunological characteristics of COVID-19 patients,[319,653-655] including deceased[656] patients.
- A good summary of COVID-19 may be found in the Internet book of Critical Care: COVID-19.
- Urinary frequency as a symptom of viral cystitis.[657]
- Neurological symptoms,[658-661] [expand] Guillain-Barré Syndrome [662]. Possible mediation by demyelinating MMP activity?[663]
- SARS-Cov-2 mutations, genotypes and geographic differences. [expand][664,665]
- The expression of a number genes related to the entry of SARS-Cov-2 is altered in patients with various comorbidities.[666]
- Comparison of SARS, MERS and COVID-19[667] [get more extensive reference]
- Transmission through ocular surface.[668]

10.2 Immune System Changes

- Review of pathophysiology[669]
- Blue-green neutrophil and monocyte inclusions INN COVID-19.[670] Lipofusion-like substance? Relationship to these inclusions as harbingers of mortality in liver disease.[671,672]
- High fluorescent lymphocytes in COVID-19.[673]
- Infection of lymphocytes via spike protein.[674]
- Atypical lymphocytes.[675]
- Disease progression marked by cytokine changes[543,676,677] as well as lymphocyte changes[677-680]
- Activation of macrophages by oxidized-LDL (and prevention with pioglitazone?) to initiate cytokine storm.[681]
- Possible contribution of CD169+ macrophages to spread of SARS-Cov-2, hyperinflammation and lymphocyte death.[682]
- in silico analysis of binding of all SARS-Cov-2 peptides to MHC class I sites within HLA -A, -B, and -C genotypes was conducted to determine the potential for cross -protective immunity conferred by prior exposure to other coronaviruses[665] HLA -B*46:01 (high prevalence in China) had the fewest binding

peptides suggesting increased vulnerability (as with SARS) with HLA -B*15:03 the highest. [expand ethnic distribution]

- Reduction in perforin expression with age/disease and ability to kill infected cells.[683][expand]

10.3 Endothelial dysfunction and fibrinolysis

- Endothelial dysfunction in COVID-19[684,685] [expand]
- There is paradoxical (reviewed[686,687]) perturbation of the normal balance of coagulation and fibrinolysis in COIVD-19. On the one hand microthrombi give rise to extensive organ failure. On the other hand there is hyperfibrinolysis evidenced by elevated D dimer, with elevated plasmin(ogen). It is believed to enhance SARS-Cov-2 infectivity and virulence.[688] For these reasons the use of fibrinolysis inhibitors has been proposed.[688]
- Nafamostat a drug used in Japan for DIC has strong antifibrinolytic and weak anticoagulation actions. Its use together with heparin has been proposed to address coagulopathy and may be particularly attractive because of its inhibition of viral-host membrane fusion.[689]
- To prevent fibrin deposition in the lungs, to improve oxygenation and to lessen the risk of fibrosis, use of tPA[690-692], including by nebulization[693] has been proposed and is now part of the EVMS protocol (5/25/2).. Improvements in oxygenation and other clinical signs were noted in 13 patients after inhalation of freeze-dried plasminogen.[694] Giving tPA in this way may be justified in later stage disease when oxygenation rather than infectivity is more of a priority.
- Consequences for adhesions?[695] SARS-Cov-2 was detected in ascites of one COVID-19 patient[696] in the peritoneal dialysate of another[697] but not in the peritoneal fluid or peritoneal washings of another.[698]
- Presence of SARS-CoV-2 examined in patients with COVID-19 undergoing abdominal surgery. Found in feces in ¾ patients and duodenal wall of patient with perforated peptic ulcer. Not detected in wall of small intestine, appendix, and gallbladder, bile, liver, urine, omentum and abdominal subcutaneous fat.[699]
- Abdominal pain has been reported in PCR positive patients with no CT[700] or ultrasound[701] abdominal abnormality.
- ACE2 and TMPRSS2 expression in intestine[702] *ACE2* or *TMPRSS2* were not found significantly expressed in normal human myometrium, uterus, ovarian, fallopian tube, or breast tissue.[703]
- Expression of ACE2 in the female reproductive tract – consequences for adhesions?[expand][704]
- See also section on heparin (4.3.2) and review on use of antithrombotics n COVID-19. [705]

10.4 Other

- Association of blood-type with COVID risk – an Italian-Spanish GWAS: A had a higher risk (OR=1.45, 1.20 - 1.75, P=1.48x10-4) with a protective effect for group O (OR=0.65, 0.53 - 0.79, P=1.06x10-5).[706] Directionally, a similar conclusion was reached in a meta-analysis.[707]
- Rapid production of hyaluronic acid (HA) and the sequestration of water is postulated to contribute to terminal demise in COVID-19 patients and other respiratory distress syndromes. The inhibition of HA by (4-methylumbelliferone) a drug available in some European countries has been proposed as a treatment for COVID-19.[708] Changes in HA and GAG metabolism have been proposed to contribute to the ground-glass opacities.[709]
- Modulation of chondroitin sulfates, chondroitin sulfotransferases, and chondroitin sulfatases by Angiotensin II (and chloroquine) under conditions of hypoxia may contribute to respiratory morbidity in COVID-19.[710]
- Role of angiogenesis as a marker for COVID?[711]
- Possible role of adipose tissue as a reservoir for viral spread and immune hyperstimulation.[712]
- Role of epicardial fat as a source of inflammatory mediators, possibly mediated by downregulation of ACE2, [713] directly supplying the myocardium.[714] Presence of SARS-Cov-2 in pericardial fluid.[715]

11 POST-COVID-19 SYNDROME

- Long term, post viral fatigue,[716] postintensive care syndrome (PICS), pain[717]
- Long term fibrosis [expand][718-720] FIB-4 a marker of liver fibrosis was associated with worse COVID-19 outcomes.[721] Association of cirrhosis and COVID severity.[722,723]
- SARS-CoV-2 contributes to altering post-transcriptional gene regulation – implications for long-term effects.[724]

12 DISEASE AND ECONOMIC MODELS

There is much discussion on the mechanism of transmission, true infection rate[725,726] and timeline of COVID-19, as well as the selection of different mathematical models.[727] This has implications for disease modelling and the establishment of social distancing and economic measures.

Wharton School, U. Pennsylvania.
Risk model for predicting severe COVID-19 to inform lockdown strategy.[728]
Epidemic Calculator
Worldometer Stats
Hospital Resource Calculator
CDC COVID-19 Pandemic Planning Scenarios
CDC Cases in US – Update

13 TRACKING, STUDY DESIGN AND STATSTICAL METHODS

Consider controlled study version of this strategy to provide definitive data on dose, formulation variation etc. Study should account for the effect of clustering – e.g. all residents of one nursing home vs those of another, all workers in one ICU vs those of another, etc., grocery store workers etc.

13.1 Clinical Study Design

- Pragmatic pRCT vs. explanatory RCT.[729,730]. Real World Evidence[731], likely need to increase sample size based on RWE effect size.[198]
- Comparison of UK recovery and EU Discovery trials designs[732]

13.2 Rapid and Centralized Data Collection

- Until very recently, there has been no central / open source method of collecting and crunching large amounts of data in real time for rapid decision-making. COVID-Symptom Tracker is gaining traction with over 3 million subjects participating with the ability to link to other ongoing studies. This system has now formulated several recommendations concerning reliance on symptoms and the use of nicotine patches in smokers.
- Other systems are:
    - ISARIC.[733] Their CRF has provision for daily/repeat case follow up, but is limited in the treatment component. Further, there are only 2000 or so patients in the database most of whom are from the UK. The database is designed for use of professionals who are no doubt focused on patient care.
    - The CDC's COVIDView may be insufficient for the needs of this strategy.
- Electronic medical records held by hospital systems in data warehouses have been an emerging source of retrospective observational studies. These have varied in quality and extent of analysis. Very often the warehouse is interrogated about only one particular drug treatment, when in fact useful information can be provided about many drugs. From our communications with the authors of those studies, funding and time - allocation appears to be limited, and deeper analysis not possible. The need for national health information technology infrastructure has been discussed in the context of COVID-19.[734]

13.3 Establishing baseline – Testing vs. Symptoms/ Endpoints

- Regarding the collection of data in observational vs. trial conditions, statistical analytical challenges remain, including knowing whether a person entering any evaluation is COVID-19 positive or not to establish a baseline. Tests are poorly available and take time to perform. Further, as reported in a preprint,[735] viral mRNA could only be detected in nasal swabs from 53.6%~73.3% of severe and mild cases of confirmed novel coronavirus pneumonia during the first 14 days after illness onset. Despite some obvious challenges in understanding this the significance of this report, since our goal is to reduce resource overload, and since that is driven by presentation of symptoms rather than presentation of a positive PCR, symptom-based entry criteria may be appropriate.
- Initial data from the COVID-19 Symptom tracker suggest that: *"When combined with other symptoms, people with loss of smell and taste appear to be three times more likely to have contracted COVID-19 according to our data, and should therefore self-isolate for seven days to reduce the spread of the disease."* Our contention that symptom-based criteria be used as is further supported by the recommendation of COVID-19 tracker: And that *"Given the circumstances, the best advice for anyone noticing loss of smell or taste is to treat yourself as being infectious."* (accessed 4/8/20). This is born out in a prospective study of symptom development among household members of patients with COVID-19.[736] A model to predict COVID-19 infection with nearly 80% accuracy was developed from observations of over 2.6 million people based on

age, gender, loss of taste or smell, presence of severe or persistent cough, presence of severe fatigue or skipped meals.[737]

- There appear to be ethnic differences between Caucasian and East Asian populations in the taste and smell disturbances associated with COVID-19.[336]
- Council of State and Territorial Epidemiologists, Standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19), April 5 2020.[738]
- A similar argument can be made regarding endpoint. However, the current priority is to reduce health resource overload. Accordingly, having severe enough symptoms to require a medical intervention (family doctor, hospital etc.) would be as useful and valid endpoint as would "no longer requiring intervention." Since cases of influenza would be presumptive COVID-19 cases and would also contribute to resource load, it matters less if the patient has been tested for SARS-Cov-2.

- Remote vital sign sensors, especially if tied into to the COVID-19 Symptom Tracker, may provide additional ability to collect large datasets rapidly. One device under development is the Vital device and app which can measure, HR, RR, BP, SpO_2 and temperature. The BVue app, undergoing testing in Canada. uses artificial intelligence to compute the same parameters via images collected from a smartphone camera.

- Using data from the COVID-19 Symptom Tracker, an Artificial Intelligence-based tool is being developed to predict the likelihood of COVID-19 without testing, based on symptoms.

- There are various scoring systems for clinical evaluation of patients: [expand]
  - SOFA [739] and qSOFA[740]
  - APACHE II [741]
  - SOFA vs APACHE II [742]
  - NEWS[743]

- A one minute breath test has been developed that assesses the resonance of the virus in a breath sample.
- A chip IR-based detection method has been proposed.[744]
- Other biosensor[745] technology for COVID-19 mass testing.[746,747]
- A wearable wireless sensor of respiratory rate and tidal volume may provide an early warning for COVID progression.
- Small portable PCR and biomarker instrument, providing results in 1-1.5hrs[748]
- Use of quantitative assessment of taste and smell [expand]

13.4 Non-Randomized, Observational Studies

13.4.1 Non-Randomized, Observational Studies

- There is a need for observational studies, when experimentation may be inappropriate or unethical.[749] The limitations of observational studies are well-known. Although regression, propensity-score matching, tipping-point analysis and other statistical methods may reduce (but not completely eliminate) the effect of confounding due to lack of prospective randomization. A finding that worse outcomes are associated with a particular drug may simply mean that sicker patients, who were more likely to experience poorer outcomes, were given that drug.
- An observational study on the use of HCQ was recently published in NEJM[6] (see there for statistical methods, including propensity[750] models) and editorial rationale for publication.[751]

  Guidelines do exist for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[752,753] Although they are endorsed by many leading journals, including for example PLoS Medicine,[754] the lack of enforcement and awareness have been proposed as reasons for their infrequent use.[755,756]

- The report by Fadel et al.,[1] used a pre-test post-test quasi experimental design, a hybrid of observational and experimental methods.[757] and appropriate for disaster scenarios[758-760] We offered the authors the following suggested context for this design (since modified):

  "Given the pandemic nature of the disease a pragmatic quasi-experimental NRSI design was used with its main limitations[760] of possible regression to the mean and maturation. In the Canadian Task Force Classification,[761] the "quality of evidence" offered by this study would fall between Level II-1 (well-designed

cohort or case-control analytic studies) and Level II-2 (comparisons between times or places with or without the intervention). Our semi-prospective, quasi-experimental design combines both observational and experimental methods.[757]

Although systems to rate the quality of evidence[33] have historically relied on the study type, the recognition that assessing the risk of bias is the main determinant of quality has led to the widely used methodology of the GRADE Working Group[762]. This group has recently developed a tool (ROBINS-I) to asses risk of bias in NRSIs, allowing their data to be integrated with that from randomized studies into a body of evidence whose certainty can now be rated.[35] [763] (see here and here for online tools). This type of method has been used in the context of treatment switching strategies for individuals.[764]

The value of rapidly conducted observational studies in pandemic situations[751] has been recently acknowledged with the publication of two non-experimental, non-randomized, retrospective, observational studies on the effects on hydroxychloroquine in COVID-19 patients where confounding was estimated using Cox regression models with[6] and without[7] propensity score matching. In our quasi-experimental, semi-prospective design, we further attempted to estimate the effects of confounding by performing the additional analyses described here. "

13.4.2 Machine learning and other predictive algorithms

A number of studies have tried to correlate clinical or lab parameters with poor outcomes (mortality of admission to ICU),[765] attempting to narrow down the main predictive parameters such as high CRP and high SOFA score.[766] Another study used clinical observations (age, fever, tachypnoea, chest crackles to predict ICU admission.[767]

A machine learning tool was developed that was able to predict poor outcomes ten day in advance in COVID-19 patients based on levels of lactate dehydrogenase (LDH), C reactive protein (CRP) and lymphocyte counts.[768] A modified version of this approach was proposed that accounted for interaction between the biomarkers.[769] It may be possible retroactively to assess the propensity of individual patients for poor outcomes and then to compare those outcomes after different treatments. A meta-analysis of 52 studies reporting changes in markers of liver function in COVID-19 (including LDH and CRP) has been released in pre-print form.[770] The most common elevated lab values found in COVID-19 were for ESR, CRP and LDH.

- Five factor[771] machine learning algorithms were almost as good as 20 factor versions in predicting mortality. The most predictive factors were age and minimum oxygen saturation. Other key factors were maximum temperature, health care encounter type (inpatient vs. outpatient and telehealth) and use of HCQ, which was likely reflective of the general treatment practices in place during the study period.

- A more complex machine learning model was used to predict ICU admission, mechanical ventilation and mortality.[772]

Table 9: Other papers discussing predictive biomarker parameters

End point	Parameters	Reference
Severity	LDH, also LC, including subtypes. Correlated of LDH and CRP.	773
Severe COVID-19	CRP alone	774
Respiratory failure	LDH, CRP	775
Severity	Neutrophil/LC (esp CD8[519])	677,776,777
Negative conversion	Neutrophil/LC (CD4)	778
Non-severe / severe COVID-19	Symptom and chemistry-based (including LDH and CRP) parameters	779
Mortality, hospital	Neutrophil:lymphocyte ratio of > 11.75	780
Severity	Procalcitonin	321
Severity, mortality	IL6 and TNFα	676

Mortality	LOW-HARM score (Lymphopenia, Oxygen saturation, White blood cells, Hypertension, Age, Renal injury, and Myocardial injury)	[781]
Mortality	high-sensitivity cardiac troponin (hs-cTn) – cardiac injury	[782]
Severity	Neutrophil extracellular traps - markers: cell-free DNA, myeloperoxidase(MPO)-DNA, and citrullinated histone H3 (Cit-H3)	[783]
Severity	IL6, IL10 (correlated with CRP)	[784]
Severity	Lymphopenia	[785,786]
Severity	HGF – hepatocyte growth factor Also M-CSF, IL-8 and SCF – healthy vs asymptomatic/mild	[787]
Severe resp failure	Solublae urokinase plasminogen activator receptor (suPAR)	[788]
Mortality	Viral load	[789]
Recovery	BDNF, brain derived neurotrophic factor	[790]

Reviews on use of predictive and diagnostic biomarkers.[791]

- Biomarker profiles obtained from NMR analysis of UK Biobank plasma samples gathered 2007-2010 were tested for association with severe pneumonia and with severe COVID-19. A multi-biomarker score based on 25 biomarkers, developed for risk of severe pneumonia followed a similar association for COVID-19, even after adjusting for BMI and other comorbidities.[792]

13.4.3 Statistical Issues

- Estimation of mean and SD from median and interquartile range.[793]
- A number of multivariate regression methods exist to reduce the effect of confounding, especially in non-randomized studies. Propensity score matching is often utilized.[794-800] These procedures must be conducted diligently as there are a number of ways to conduct them which could inject further bias into a study.
- Use of statistics in battlefield command and control.[801]
- Bayesian or "pseudo-Bayesian" and adaptive study designs may be appropriate to trial therapies as quickly as possible.
- It should be noted that the integrity of many of the studies listed is limited, since subjects within any study may not be randomly clustered with non-study participants of unknown infectivity. [expand]
- A number of statistical issues, mainly related to sample size calculations have been identified in COVID-19-related studies indexed in PubMed to 3/25/20.[802]
- Prospective meta-analyses should be performed to resolve an a number of issues related to sub-group analyses.[296,297] (see 5.5)
- Covariate adjustment--equivalent to 9-21% reductions in the required sample size to increase powerwith sample sizes of >200.[803]

13.5 Research Questions and Further Notes

13.5.1 Research questions sent by Dr. Zelenko, related to the use of HCQ/AZI/Zn

As a family physician, Dr. Vladimir Zelenko is not equipped to run clinical trials, but rather has sent us the following questions for further investigation by those who are.

a) What is the optimal length of treatment of the HCQ/AZI/Zn regime – 5 days, 10 days?
b) When should higher ICU type dosing be used in the outpatient setting?
c) Which other antibiotics (besides AZI) may be useful or even better (doxycycline, levaquin, cefdiner etc.)?

What should the guidelines be for dose and length of prophylactic treatment? Dr. Zelenko reports that he currently recommends HCQ 200mg every day for five days, and then once per week, and zinc on the same schedule.

13.5.2 Other Research Questions

- Does drug-induced or disease (condition)-induced Zn depletion contribute to worse COVID-19 outcomes?
    - How does this vary by drug, disease or condition?

- Are patients with sickle-cell trait at higher risk of worse COVID-19 outcomes?
- Are patients carrying PIEZO1 E756del at higher risk of worse COVID-19 outcomes?
- Are patients carrying FMF – MEFV variants at higher risk of worse COVID-19 outcomes?
- Do patients with genetic polymorphisms respond differently to treatment?
- Do SCT or E756del modulate the anti-COVID-19 response to HCQ, Zn and other ionophores?
- Are patients at risk of iron-overload at higher risk for worse COVID-19 outcomes?
- Can restoration of Zn status improve COVID-19 outcomes?
- Does further Zn depletion occur in already at-risk patients infected with 2019-nCoV?
    - Can this be assessed by monitoring urinary Zn levels?
- Does Zn depletion/dysregulation/change in distribution occur in otherwise not at-risk patients infected with 2019-nCoV?
- Do Zn levels predict susceptibility to COVID-19 in at risk patients? Would a Zn testing program help target those patients most in need?
- Is COVID-associated hypogeusia related to Zn depletion?
- Is ACE2 regulation altered in COVID?
    - Are there differences in ACE2 lung epithelial expression in the various at-risk groups?
- Can the use of Zn alone reduce the progression of COVID?
    - Can Zn injection alone limit oxidative stress in severe COVID-19 cases?
    - Can Zn be used to accelerate recovery from smoking-related toxicity?
    - Should Zn supplements be provided to patients taking Zn-depleting drugs?
    - Will the use of Zn with ACEII antagonists limit infection with and progression of COVID.

- Is the additional use of Zn ionophores more effective than Zn alone in reducing the progression of COVID?
    - Which ionophores are effective?
    - In addition to accounting for pharmacokinetic differences, how should administration of Zn be timed in relation to that of its ionophores?
    - What dose route is appropriate (oral, lozenge, injection, inhalation etc.)?
    - Can use of flavonoid ionophores in combination with HCQ, reduce HCQ dose and risk of toxicity?
        - Would a reduced HCQ dose/flavonoid Zn combination reduce the risk of HCQ toxicity to the point that its use would be appropriate for pre-emption and prophylaxis?
    - Is ingestion of Zn and ionophore-rich foods as effective (by patent type) as pharmaceutical preparations?
- Can the use of Zn and its ionophores be uses pre-emptively and prophylactically?
- What other nutritional supplementation is beneficial?
- How can Zn supplementation be effectively monitored in diabetes where its administration would likely necessitate careful monitoring of glycemia?
- Can COVID-19 Tracker be used to obtain rapid data that can facilitate real-time decisions?
- Can patient records be mined and flagged as at-risk for early testing using AI-based algorithms, followed by intervention?
- What can we learn from COVID-19 about other conditions?

13.5.3 Lab and Animal models

Animal models of COVID/ARDS [expand][804-812]
Syrian hamster[813,814]
Macaque[814]
Murine humanized lung[815 816] – transgenic hACE2 expressing mice[817]
Zinc measurement[818,819] [expand]
Antibodies, antigens and reagents
Multi-Cell Type Lung Organoids[820]

13.5.4 Additional Notes on Diabetes and other Zn depleted groups

Using diabetes as an example there are three sets of premises:

a) Glycemic control and COVID
    - Diabetes is a high-risk factor for serious complications of COVID-19 requiring intensive Zinc resources.
    - *"risk of getting very sick from COVID-19 is likely to be lower if…diabetes is well-managed."* (ADA)[346]

b) Zinc and viruses

- Zn deficiency is associated with immunocompromise
- Zn is helpful in treating respiratory viruses

c) Zinc and diabetes
- Zn deficiency in present in diabetics.
- *"some studies have shown that Zn improves glycaemic control in …diabetes."*[344]

Our question can be phrased as:
If Zn contributes to viral control and it is also valid method of controlling glycemia
Will the use of Zn in diabetics contribute to more positive outcomes (to be defined) in COVID?

We spoke with an endocrinologist specializing in diabetes who agreed with the guidance of ADA related to COVID-19 and agreed that any method of glycemic control to a particular patient should be valuable. Normally zinc would not be the highest priority method (after diet, exercise, insulin etc.) and whether zinc would have any additional advantages would remain to be seen.

Subject to an individual patient's physician, there is some basis for proposing Zn nutritional supplementation in diabetes.

There are other examples of Zn deficiency where a parallel argument can be advanced:
- Patients taking omeprazole or ACEII inhibitors where Zn depletion is known are also likely to fall into the high-risk categories of obesity and heart disease.

13.6 Clinical Trials Underway

- As of 4/4/20 there were only a few other studies that address pre- (NCT04328467, NCT04329923) and post (NCT04308668, NCT04318444, NCT04318015) exposure prophylaxis or preemptive treatment of mild symptoms (NCT04308668). These mostly involve HCQ with or without AZI but not Zn.
- Update 6/25/20: There are 15 studies involving Zn, and one involving quercetin and one with Acai berry (contains catechins)
-

Table 10: NIH registered trials involving pre-exposure, or post-exposure prophylaxis or pre-emptive treatment.

Study Title	Interventions	Location	Number
HCQ and Zn With Either AZI or Doxycycline for Treatment of COVID-19 in Outpatient Setting	HCQ, AZI, Zn Sulfate, Doxycycline	St Francis Hosp, Roslyn, NY	NCT04370782
A Study of HCQ and Zn in the Prevention of COVID-19 Infection in Military Healthcare Workers	HCQ, HCQ (placebo), Zn, Zn (Placebo)	Military Hosp of Tunis, Tunisia	NCT04377646
Impact of Zn and Vit D3 Supplementation on the Survival of Aged Patients Infected With COVID-19	Zn gluconate, 25-OH cholecalciferol	Univ Hosp, Lille, France	NCT04351490
A Randomised Controlled Trial of Early Intervention in COVID-19: Favipiravir vs. HCQ & AZI & Zn vs. standard care	Favipiravir, HCQ, AZI, Zn Sulfate, Other: Standard of care management	Chelsea and Westminster and W Middlesex U Hosp, London, UK	NCT04373733
A Study of HCQ, Vit C, Vit D, and Zn for the Prevention of COVID-19 Infection	HCQ, Vit C, Vit D, Zn	ProgenaBiome, Ventura, CA	NCT04335084
COVID-19 Prophylaxis With HCQ Associated With Zn For High-Risk Healthcare Workers	HCQ, Zn sulfate	Federal Univ of Ceara (UFC), Fortaleza, Brazil	NCT04384458
Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zn Supplementation	Ascorbic Acid, Zn Gluconate, Ascorbic Acid and Zn Gluconate, Other: Standard of Care	Cleveland Clinic, FL, OH	NCT04342728
Proflaxis Using HCQ Plus Vits-Zn During COVID-19 Pandemia	Plaquenil 200Mg Tablet, Zn	Istinye University Med Sch, Istanbul, Turkey	NCT04326725
New Antiviral Drugs for Treatment of COVID-19	Combination of Nitazoxanide, Ribavirin and Ivermectin, Zn	Mansoura Univ, Mansoura, Egypt	NCT04392427
A Study of Quintuple Therapy to Treat COVID-19 Infection	HCQ, AZI, Vit C, Vit D, Zn	ProgenaBiome, Ventura, CA	NCT04334512

Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19	oral nutrition supplement (ONS) enriched in a number of supplements including 205 mg Vitamin C and 5.7 mg Zn	King Saud University, Saudi Arabia	NCT04323228
Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, Vitamin B12 With or Without Vitamin C, a Multi-centre, International, Randomized Trial: The International ALLIANCE Study	Vitamin C, HCQ, AZI, Zinc Citrate, VitD3, Vit B12	National Institute of Integrative Medicine, Australia	NCT04395768
Evaluation of the Relationship Between Zinc Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women	Measurement of Serum zinc, vitamin d vitamin b12 levels	Kanuni Sultan Suleyman Training and Research Hospital, Turkey	NCT04407572
Prevalence of Diabetes Among Hospitalized Patients With Covid-19 in West of Algeria	HCQ 200 mg po tid x 10d, AZI 500 mg stat then 250 mg od x 4d ZnSO4 220 mg od x5d. Lopinavir/ritonavir 200 mg/50 mg, oral 2 capsules bds x 5-7d	Tlemcen, Algeria	NCT04412746
A Preventive Treatment for Migrant Workers at High-risk of Covid-19	HCQ 400mg stat, 200mg od x 42d Ivermectin tablet 12mg Zn 80 mg/vitamin C 500mg odx42 Povidone-iodine throat spray Vitamin C 500mg od x 42d	National University Hospital, Singapore	NCT04446104
The Possible Effect of Quercetin on Prophylaxis and Treatment of COVID-19	quercetin (500mg)	Kanuni Sultan Suleyman Training and Research Hosp, Istanbul, Turkey	NCT04377789
Randomized Clinical Trial of Açaí Palm Berry Extract as an Intervention in Patients Diagnosed With COVID-19	Açaí palm berry extract	U Toronto	NCT04404218

- COVID-19 host genetics initiative (covid19hg.org is a global collaboration to study the genetic determinants of COVID-19 susceptibility, severity, and outcomes.
- UK based study to track COVID-19 – COVIDENCE

14 IMPLEMENTATION

This strategy sent to government officials is **Rapidly Deployable** in one of several implementation models:

a) Top Down Leadership Approach - Implementation team at Federal / State level

- Issue recommendations for treatment at all stages. Coordinate among medical professional societies.
- Establish rapid front-line intelligence system to monitor treatment progress and fine tune
- Establish, exploit, accelerate existing methods of trials and large-scale data collection and analysis
- Conduct initial and ongoing medical and regulatory review
- Ensure orderly supply of drugs, reduce hoarding
- Intensive efforts to improve health among the most vulnerable, and general population.
- Incorporate into **Opening Up America** strategy to reduce impact of possible **secondary peaks**.
- Legislation and funding to encourage and expedite investment in repurposing drugs.[821]

b) Grass Roots Approach

- Build coalition of physicians, constituency stake-holders e.g.
  - Professional medical organizations
  - Condition-based organizations – Diabetes, Kidney disease etc.
  - Health and welfare philanthropic organizations
  - Minority-focused organizations – faith and neighborhood

  - Essential businesses
  - Local neighborhood and city/county organizations.
- Provide recommendations and resources for self-implementation
- Define protocols and execute coalition-initiated rapid evaluation plan.

A team to implement strategy would include:

- Medical: critical care, infectious disease, internal medicine
- Pharmacology, Pharmacy, Nursing
- Statistics, epidemiology
- Database set up, entry and maintenance
- Programming
- Logistics
- Procurement and Distribution
- Legal and Compliance
- Coordination with other agencies
- PR, social media, web

15 THE NEED TO COLLABORATE

The COVID-19 crisis has had a number of effects on the attitudes to national and international authorities, government figures or establishment institutions. Mainly divided along party lines, there are supporters and critiques of the way the crisis has been handled. Injected into this from both sides are conspiracy theories and efforts from across the political and business spectrum to shore up, or carve out future positions. These efforts include the accidental (or otherwise) dissemination of misinformation and disinformation.[822] Paradoxically, there is the making of strange bedfellows. By way of example only, and not to express any endorsement or opposition to the following position, one medical doctor professing to be a life-long socialist-communist stated that he believed that President Trump was doing a fair (or even good) job and that the virus and any negative consequences to its response were not his fault. This opinion would no doubt find support from a more politically conservative outlet sch as American Spectator.

From a medical and scientific perspective, COVID-19 is complex enough without trying to navigate media hype[823] and the political maze. A recent editorial in Nature opined:[824] *"The increased connectivity of our digital times means that it is easier to engage directly and disseminate knowledge in simple, digestible bites. However, maintaining an honest working balance with politics and media is also crucial, given that science does not operate in a vacuum. Rebutting misinformation and pseudoscience quickly and emphatically is essential."*

Accordingly, our goal is to keep our approach as non-partisan as possible and steer away from the sort of debate that has bogged down progress in understanding whether or not HCQ has a role in COVID-19.

A situation like this has never arisen in world history. There is no one who is an expert at this. Decisions that are made with the best available information will in hindsight turn out to be incorrect. Some decisions made for the wrong reasons, will turn out to have been good ones.

All sorts of people on both sides have made all sorts of innocent mistakes, but there have been many good decisions and many heroic actions by people at every level and from every walk of life.

This unprecedented crisis has exposed unknown or under-appreciated weaknesses in the established (otherwise generally robust) system of how medicine is practiced, how data is gathered and analyzed and how medical decisions are made[37,38] and overly influenced by media.[825] From a certain viewpoint, one respected critical care blog penned an article whose title encapsulates one aspect of the problem: *"American research infrastructure is killing us: The misbegotten battle between the ivory tower academics and the rogue cowboys"* The good news is that the crisis has stimulated innovation in the way we conduct research to make our decision-making more efficient.[36]

The way we can begin to address these is to show that it is possible to implement a fast-track, risk-managed, scientifically-based, approach as presented here.

But above all, we must work together.

Patients must alwa ***ny medical treatment.***

I am grateful to Mr. Paul Sluss for his artistic talents

16 UPDATE NOTES

V9.9	7/10/20	• Possible interactions between MPD and HCQ: Arshad, Fadel and Bani-Sadr studies • Updated information on inhaled steroids • 832 references
V9.8	6/30/20	• Oxford Recovery Study, dexamethasone, add to strategy. • Updated NIH Treatment guidelines 6/16/20 and 6/25/20 • Abbreviation list • Clarification of strategy – low Zn for prevention see 4.4.1.14.4.3 • Further clarification of Zn deficiency vs. dysregulation • Expanded discussion of iron overload and Zn. • Stress population- and time- nuanced nature of strategy • Critique of study design, pragmatic vs. explanatory trial design. • Discussion of post-exposure HCQ prophylaxis study, post hoc analysis • PRISMA-ScR checklist completed for scoping review • Reorganized section 4.5.2 • 779 references
V9.7	6/15/20	• Explanation of goals and methodology • Diagnostic test • Update to latest NIH Guidelines[44] • Correction in Table 2. • Update on data within Fadel study, now accepted for publication[1] • Update scientific abstract • Update on discussion on Zn levels and measurement • Expand on fibrinolysis • Doxycycline, other approaches, table for in silico studies • Table for anecdotal reports • Update on ACE2 polymorphism; disease prediction from symptoms, diagram of RAAS • Additional HCQ studies, U MN – Boulware, Singh • Additional machine learning algorithms • Update document structure, many references added. • Goals, methodology and project evolution added • Zn deficiency vs dysregulation • Current with ~30,963 papers in pubmed, mdrxiv/biorxiv, arxiv and preprints • Search strategy included • 670 references
V9.6	5/20/20	• Protocol outlines • Written as multi-stage strategy, to include later stages • Observational studies on HCQ, with and without zinc, famotidine • Discussion of NIH rating methods for COVID-19 • Cardiac events with HCQ/AZI • Further notes on steroids, Ramesh, Chroboczek and Wu studies • Further notes on calcium dysregulation, Vit D • Notes on AZI • Review of other drug approaches • SOFA, APACHE, NEWS scores • Observational Studies, RoB, STROBE Statement • RAAS update • Extensive heading reorganization, consolidation

		• Abstract added • 273 references
V9.5	5/1/2020	• Style, layout • Pediatric COVID-19 • 179 references
V9.4	4/30/20	• Discussion on famotidine, H2 antagonists • Integration with later stage strategies, discussed of critical care protocols • Procalcitonin, viroporins • Update on need to collaborate • 176 references
V9.3	4/27/20	• Update personal background • French smoking study • HCQ-AZI interaction • Zn and F • Research questions from Dr. Zelenko • Typos, layout and consolidation • The need to collaborate • 155 references
V8	4/21/20	• Update: Front Line Protocol and Integrative Approaches added • "It should go without saying" section added. • By its urgent nature this review is not exhaustive and a number of areas have been flagged as requiring review and expansion, as [expand]. • Further discussion of diabetes, especially in Hispanic/Latino populations. Preliminary addition of discussion of Asian and Jewish populations. Additional linkage between Zn and diabetes. • Discussion of asthma in Puerto Ricans. • Notes on Thalassemia, Familial Mediterranean Fever. • Strategy Summary added. • Added note on implementation • Typos, stylistic and grammatical errors. Consolidation of concepts. • Note on hypertext. • Acknowledgements added • 144 references
V7	4/14/20	• Discussion of possible sources of apparent susceptibility of African-American population to COVID: ○ SCD, SCT, Zn handling; kidney disease and RAAS including ACE2. • Corrections and clarifications on details of RAAS; MOA of losartan. • Research questions and hypothesis. • Justification for fast track. • Pharmacokinetics • Table of contents, heading structure • Typos, stylistic and grammatical errors. Consolidation of concepts. • 108 references
V6	4/10/20	60 references
V5	4/8/20	54 references
V4	4/6/20	Expanded background, citations added 50 references
V3	4/5/20	COI statement added
V2	4/4/20	
V1	4/2/20	

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18 PRISMA-SCR CHECKLIST

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist[41]

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	PAGE #	
TITLE				
Title	1	Identify the report as a scoping review.	4, 9	Rapid Deployment Reduce Load & Secondary Peak low risk, multi stage COVID-19 Strategy based on a scoping review
ABSTRACT				
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	4	
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4, 9	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4 9	
METHODS				
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Click here to enter text.	No *a priori* protocol exists, although Search strategy and methodology included from version 9.7 (6/15/20) onwards
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Search strategy page 63	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Search strategy page 63	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Search strategy page 63	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Search strategy page 63	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Click here to enter text.	In some cases data from several topically related studies were tabulated (e.g. Table 2, Table 5, Table 6, Table 9) In several instances author were contacted directly by phone or email to seek clarification of protocols or data ([5, 1,2,7,10,170,708]225,826-828)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	PAGE #	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Click here to enter text.	see Table 2, Table 5, Table 6, Table 9
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Click here to enter text.	Studies likely to support or refute were selected for more detailed review on the basis of their ostensible level of evidence 9eg RCT, type of observational study). Supplemental data was examined if available, and authors contacted, if possible, for clarification. This information was included in the review.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Click here to enter text.	Tabular and/or narrative data summaries were formulated.
RESULTS				
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	See page 63	Search strategy and current numbers of papers screened, also reasons for selection. Papers with only abstracts and no full-text available online were generally not used, except to provide a references to a general point being made, where no more complete source had been found.
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Click here to enter text.	As provided in text
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.	See item 12.
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Click here to enter text.	Throughout text
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Click here to enter text.	See executive summary (page 2), abstract (page 4),
DISCUSSION				
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Click here to enter text.	See executive summary (page 2), abstract (page 4), and outline (page 9).
Limitations	20	Discuss the limitations of the scoping review process.	Page 9	Being that the strategy is based largely on a scoping review, synthesizing of observational, case report and other literature. It must be implemented along with controlled clinical study elements to test the hypotheses on which the strategy is based. See for section 5 protocol outlines. Limitations are also discussed in section 1.6.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	PAGE #	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Click here to enter text.	The devised strategy (page 2 and 9) is the output of the objectives. Implementation is discussed page 53 with clinical protocol outlines page 26.
FUNDING				
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	5	This is self funded. See Conflict of Interest statement

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

19 REFERENCES

This document:
URL: http://synechion.com/COVID/RapidDeploymentReduceLoadCOVIDStrategyLATEST.pdf

19.1 General resources, Internet articles of a review or non-peer revised nature

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)[829]

Zinc Nutrient Initiative of the International Zinc Association.

Internet book of Critical Care: COVID-19

Our World in Data: Coronavirus Pandemic (COVID-19)

Coronavirus Disease Research Community - COVID-19 - Zenedo

COVID-19: living map of the evidence – maps COVID research by category from UK NIHR

Folding@home distributed Exascale computer[830]

COVID-19 Molecular Structure and Therapeutics Hub self-description:
"This site provides a community-driven data repository and curation service for molecular structures, models, therapeutics, and simulations related to computational research related to therapeutic opportunities for COVID-19 (caused by the SARS-CoV-2 coronavirus)."

COVID-KOP:[831] COVID linked in Knowledge Oriented Pathways. Biomedical reasoning system combining the knowledge existing in the ROBOKOP knowledge graph and data collected about the COVID-19 pandemic.

National Center for Advancing Translational Sciences (NCATS) Building a COVID-19 Analytics Platform to Turn Clinical Data into Knowledge

CORD-19: COVID-19 Open Research Dataset from Semantic Scholar team at the Allen Institute for AI

CORDITE: The Curated CORona Drug InTERactions Database for SARS-CoV-2[832]

COVID-19 related studies at Clinicaltrials.gov - U.S. National Library of Medicine.

European Union Clinical Trials Registe

Individual hypertext links have been used to reference general lay articles from reliable sources such as CDC, NIH etc.

19.2 Excerpted Personal Bibliography

Google Scholar: https://scholar.google.com/citations?hl=en&user=XGvjyC8AAAAJ

Research Gate: https://www.researchgate.net/profile/David_Wiseman

Government Agency Submissions
Wiseman D. CDC guideline for prescribing opioids for chronic pain, 2016: comments of the International Adhesions Society [Available from: https://www.regulations.gov/document?D=CDC-2015-0112-4341 https://www.regulations.gov/contentStreamer?documentId=CDC-2015-0112-4341&attachmentNumber=1&disposition=attachment&contentType=pdf

Wiseman D. Comments on The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evidence Report/Technology Assessment: Agency for Healthcare Research and Quality Publication No. 14-E005-EF [Available from: effectivehealthcare.ahrq.gov/sites/default/files/related_files/chronic-pain-opioid-treatment_disposition-comments.pdf (search within document)

Wiseman, DM, 2012. Adhesiolysis: A reanalysis of the AHRQ report on chronic pelvic pain. http://www.adhesions.org/IAS2012-AHRQAdhesiolysis.pdf

Wiseman D. 2013. Impact of approved drug labeling on chronic opioid therapy; public hearing; request for comments: docket FDA-2012-N-1172 [Available from: regulations.gov/#!documentDetail;D=FDA-2012-N-1172-0223.

19.3 Search Strategy

The search strategies shown below were used to identify papers related to COVID. A review of all titles was conducted to identify English-language papers for further review mainly relating to:

- Treatment and prevention of COVID, particularly related to agents that may act through zinc modulating mechanisms
- Use of zinc, quercetin, catechins and other phytochemicals
- Use of biomarkers
- Methodology for clinical trial design, logistics, statistics etc.

Additional searches were carried out in pubmed and within reference lists to identify possible genetic variations that may account for differences in COVID-19 susceptibility of ethnic or other subgroups. Genetic variations that may have a bearing on zinc metabolism were examined more closely. Internet search engine searches were also used. Other searches were conducted as needed to examine specific issues that may have a bearing on the design of studies to test the hypotheses generated by this work. This is a work in progress.

Search strategies

Database	Search Terms	Date	Hits	Last
Medrxiv/biorxiv	Pre-tagged preprints relating to COVID-19 SARS-CoV-2	7/10/20	6289	Riiser
Pubmed (includes some medrxiv/biorxiv from 6.9/20)	(("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND 2019/12[PDAT] : 2030[PDAT]) OR 2019-nCoV[All Fields] OR 2019nCoV[All Fields] OR COVID-19[All Fields] OR SARS-CoV-2[All Fields]	7/10/20	32,050	Lin
Preprints.org	Pre-tagged preprints relating to COVID-19 SARS-CoV-2	7/10/20	8 pages (abt 85/p)	Brooks
Arxiv	PresetQuery: order: -announced_date_first; size: 200; page_start: 600; include_cross_list: True; terms: AND title=COVID-19; OR abstract=SARS-CoV-2; OR abstract=COVID-19; OR title=SARS-CoV-2; OR title=coronavirus; OR abstract=coronavirus	7/10/20	1622	Boaz Barak

Search term consolidation (6/8/20)
Prior to 6/820, two sets of pubmed terms were used.

A. COVID 19
B. SARS-Cov-2 OR coronavirus NOT "COVID 19" (limit to 2020)

On 6/7/20, pubmed provided a comprehensive search term as:

C. ((wuhan[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND 2019/12[PDAT] : 2030[PDAT]) OR 2019-nCoV[All Fields] OR 2019nCoV[All Fields] OR COVID-19[All Fields] OR SARS-CoV-2[All Fields]

This yielded the same number of hits as Term A. When combined as A NOT C, or C NOT A, there were zero hits. When combined as A OR C.

D. Combining as B NOT A, gave 1232 hits, as B NOT C

The modified term
(("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND 2019/12[PDAT] : 2030[PDAT]) OR 2019-nCoV[All Fields] OR 2019nCoV[All Fields] OR COVID-19[All Fields] OR SARS-CoV-2[All Fields]

Gave 21254 hits, which is slightly more than the total for the total of D plus A (or C).
Pubmed's LitCOVID collection was not used, as it had a similar (smaller) number of hits.

Other searches:

https://www.ncbi.nlm.nih.gov/pubmed/?term=(resveratrol+OR+quercetin+OR+catechin+OR+epicatechin+OR+pomegranate)+AND+zinc+AND+(virus+OR+viral+OR+influenza+OR+cold)
14 hits, 4/6/20 , repeated 6/25/20 same results

19.4 Selected medical/scientific literature

Please note that papers whose journal is noted as "preprints", arxiv, chemrxiv, medrxiv or biorxiv are considered pre-prints and have not undergone peer-review.

1. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. Clin Infect Dis 2020.
2. Marik P, Varon, J. Frontline Covid19 Critical Care Working Group The MATH+ Protocol Will Likely Have the Most Dramatic Impact on Survival. 2020 June 16. (Accessed 20202 June 17, at https://covid19criticalcare.com/wp-content/uploads/2020/06/STEROID-STUDY.pdf.)
3. Chroboczek T, Lacoste M, Wackenheim C, et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRxiv 2020:2020.05.08.20094755.
4. Hinton D. Letter to Dr. GL Disbrow, revoking EUA for hydroxychlroquine, June 15. In: (BARDA) BARaDA, ed. Rockville, MD: Food and Drug Administration; 2020.
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19. Skalny AV, Rink L, Ajsuvakova OP, et al. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). International journal of molecular medicine 2020;46:17-26.
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