The prophylaxis and treatment potential of supplements for COVID-19

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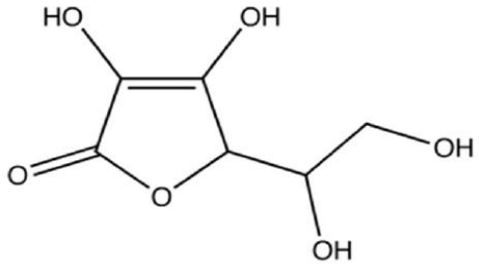
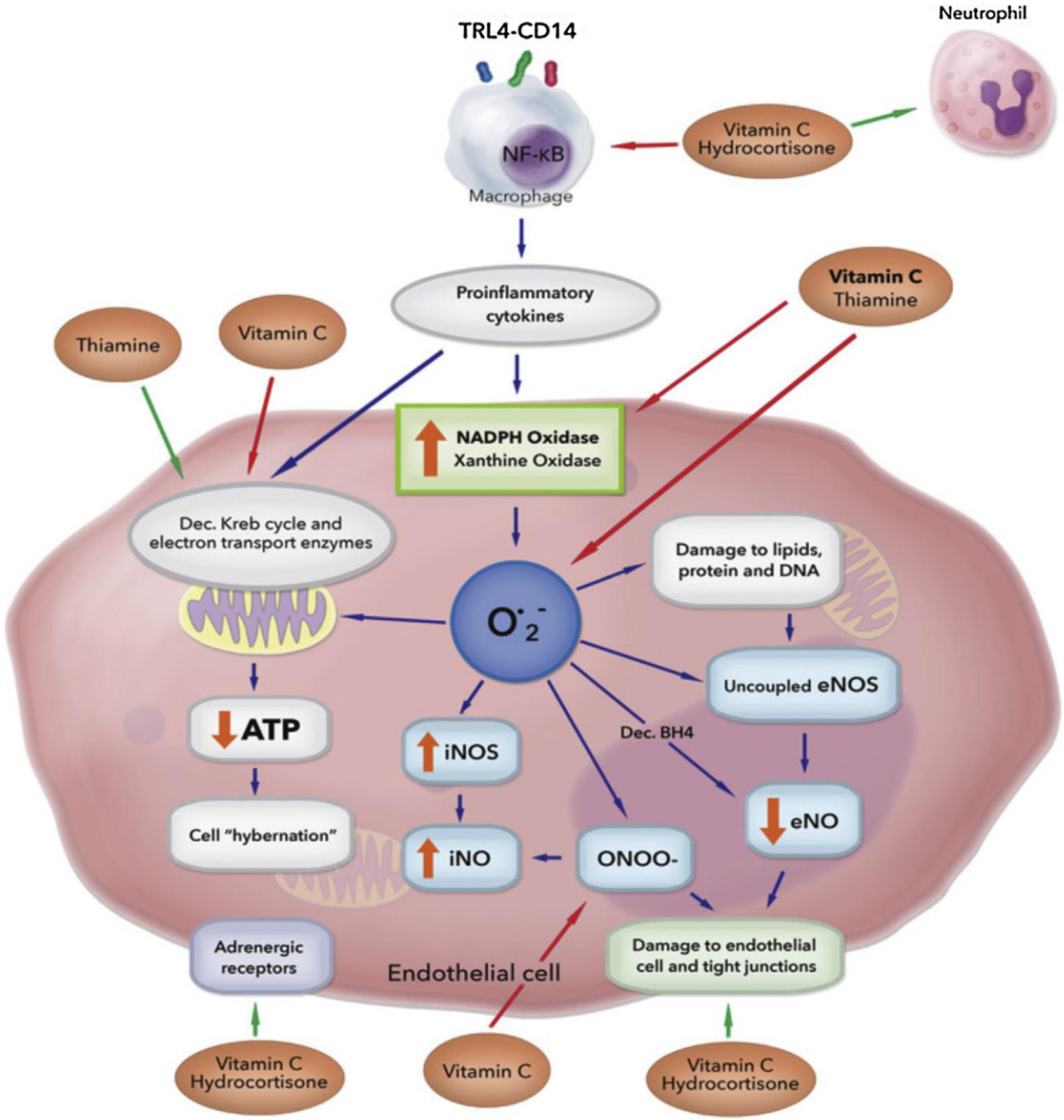
Vitamin C



- Vitamin C, also known as ascorbic acid , is an essential water-soluble nutrient, required as a cofactor for a number of enzymatic reactions
  - required in norepinephrine biosynthesis,
  - Amidation of peptide hormones,
  - collagen hydroxylation,
  - carnitine biosynthesis,
  - tyrosine metabolism,
  - histone demethylation.
- Its effects on the immune system during infection is wide ranging and includes
  - the promotion of phagocytosis and chemotaxis of leucocytes
  - development and maturation of T-lymphocytes.
  - has homeostatic antioxidant role,
  - may play a role in mediating the adrenocortical stress response, particularly in sepsis

The most studied supplement in the acute care setting


TRL4-CD14
Neutrophil
NF-κB
Macrophage
Vitamin C
Hydrocortisone
Proinflammatory
cytokines
Vitamin C
Thiamine
Thiamine
Vitamin C
NADPH Oxidase
Xanthine Oxidase
Dec. Kreb cycle and
electron transport enzymes
Damage to lipids,
protein and DNA
$O^{\cdot}_2^-$
Uncoupled eNOS
ATP
iNOS
Dec. BH4
eNO
Cell "hybernation"
iNO
ONOO-
Adrenergic
receptors
Endothelial cell
Damage to endothelial
cell and tight junctions
Vitamin C
Hydrocortisone
Vitamin C
Vitamin C
Hydrocortisone

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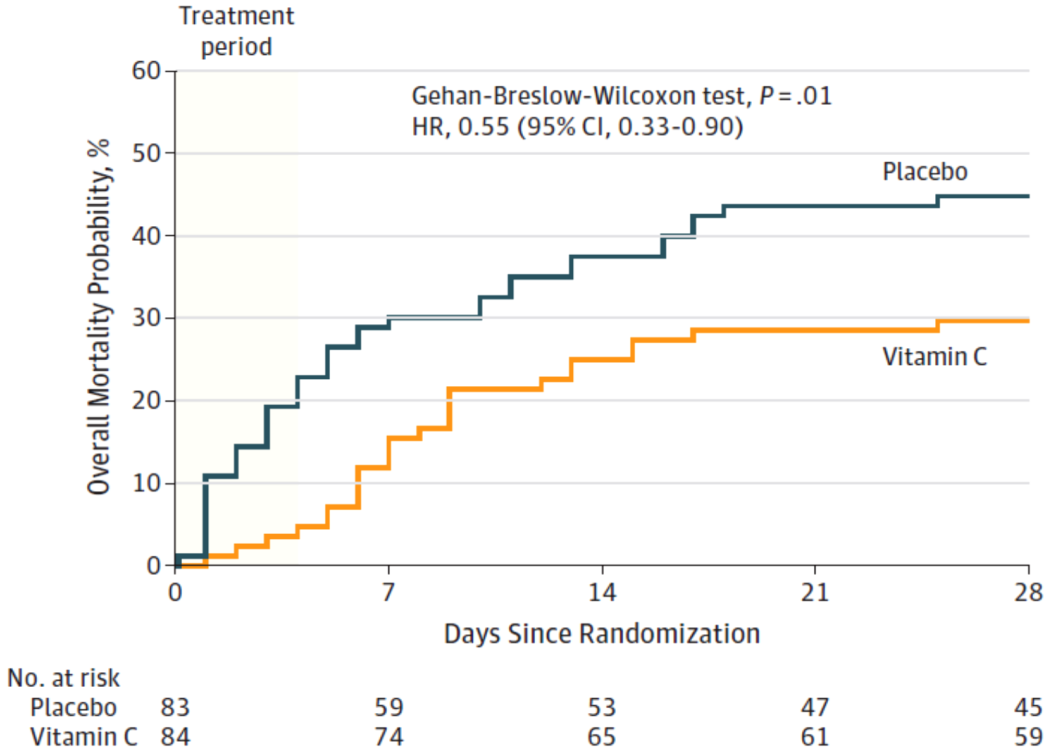
Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure

The CITRIS-ALI Randomized Clinical Trial

- INTERVENTIONS Patients were randomly assigned to receive intravenous infusion of vitamin C (50mg/kg in dextrose 5%in water, n = 84) or placebo (dextrose 5%in water only, n = 83) every 6 hours for 96 hours.
- MAIN OUTCOMES AND MEASURES The primary outcomes were change in organ failure as assessed by a SOFA score from baseline to 96 hours, and plasma biomarkers of inflammation (C-reactive protein levels) and vascular injury (thrombomodulin levels) measured at 0, 48, 96, and 168 hours.
- RESULTS There were no significant differences



Vit C

- A meta-analysis published in 2019, reviewed **18 trials** to evaluate the effect of vitamin C on intensive care unit (ICU) **length of stay** and **duration of mechanical ventilation**.
  - Of 12 trials containing **1766 patients**, **IV** administered vitamin C reduced the length of ICU stay by 7.8%.
  - **Orally** administered vitamin C in doses of **1–3 g**/day was evaluated in 6 studies and was associated with reduced length of ICU stay by 8.6% (*p*=0.003).
  - Of the 3 studies evaluating patients requiring mechanical ventilation for >24 h, vitamin C reduced the duration of mechanical ventilation by 18.2% (95% CI: 7.7–27; *p*=0.001).

Hemilä H., Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. *Nutrients*. 2019;11(4):708.

- These authors also performed a meta-regression analysis in critically ill patients receiving mechanical ventilation
  - in 5 studies consisting of 471 patients, vitamin C (1–6 g/ day) was most beneficial in reducing ventilation time by an average of 25% ($p<0.0001$)

- These findings can serve as a foundation for analyzing the role of vitamin C in potentially reducing the time spent on mechanical ventilation in patients with COVID-19.

Hemilä H, Chalker E. Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. *J Intensive Care*. 2020;8:15.

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Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock

The VITAMINS Randomized Clinical Trial

- **Design, setting, and participants:** Multicenter, open-label, randomized clinical trial conducted in 10 intensive care units that recruited 216 patients fulfilling the Sepsis-3 definition of septic shock. The first patient was enrolled on May 8, 2018, and the last on July 9, 2019.
- **Interventions:** Patients were randomized to the intervention group (n = 109), consisting of intravenous vitamin C (1.5 g every 6 hours), hydrocortisone (50 mg every 6 hours), and thiamine (200 mg every 12 hours), or to the control group (n = 107), consisting of hydrocortisone (50 mg every 6 hours) alone until shock resolution or **up to 10 days**.
- **Main outcomes and measures:** The primary trial outcome was duration of time alive and free of vasopressor administration up to day 7. Ten secondary outcomes were prespecified, including 90-day mortality.
- **Results:** Time alive and vasopressor free up to day 7 was 122.1 hours in the IG and 124.6 hours in the control group; (P = .83). Of 10 prespecified secondary outcomes, 9 showed no statistically significant difference
- **Conclusions and relevance:** In patients with septic shock, treatment with intravenous vitamin C, hydrocortisone, and thiamine, compared with hydrocortisone alone, did not significantly improve the duration of time alive and free of vasopressor administration over 7 days. The finding suggests that treatment with vitamin C, hydrocortisone, and thiamine **does not lead to a more rapid resolution of septic shock** compared with hydrocortisone alone.

Table 2. Primary and Secondary Outcomes

Outcomes	Intervention (n = 107)	Control (n = 104)	Difference (95% CI)	*P* Value
Primary Outcome				
Time alive and free of vasopressors, median (IQR), h	122.1 (76.3 to 145.4)	124.6 (82.1 to 147.0)	-0.6 (-8.3 to 7.2)[a]	.83
Secondary Outcomes				
28-d Mortality, No. (%)	24 (22.6) [n = 106]	21 (20.4) [n = 103]	2.3 (-8.9 to 13.4)	.69
90-d Mortality, No. (%)	30 (28.6) [n = 105]	25 (24.5) [n = 102]	4.1 (-8.0 to 16.1)	.51
ICU mortality, No. (%)	21 (19.6)	19 (18.3)	1.4 (-9.2 to 11.9)	.80
Hospital mortality, No. (%)	25 (23.4)	21 (20.4) [n = 103]	3.0 (-8.2 to 14.1)	.60
28-d Cumulative vasopressor-free days, median (IQR)	25.6 (17.8 to 26.8) [n = 106]	25.8 (19.6 to 26.8) [n = 103]	-0.2 (-1.7 to 1.2)	.66
28-d Cumulative mechanical ventilation-free days, median (IQR)	25.3 (5.2 to 28.0) [n = 106]	24.8 (9.5 to 28.0) [n = 103]	0.4 (-2.6 to 3.4)	.73
28-d Renal replacement therapy-free days, median (IQR)	28.0 (23.5 to 28.0) [n = 105]	28.0 (21.0 to 28.0) [n = 103]	0.0 (-0.6 to 0.6)	.71
Change in SOFA score at day 3, median (IQR)[b]	-2 (-4 to 0) [n = 82]	-1 (-3 to 0) [n = 75]	-1.0 (-1.9 to -0.1)	.02
28-d ICU-free days, median (IQR)	21.9 (0 to 25.8) [n = 106]	22.1 (3.9 to 25.8) [n = 103]	-0.2 (-4.1 to 3.7)	.66
Hospital length of stay, median (IQR), d	12.3 (6.2 to 26.0)	12.3 (6.2 to 26.1) [n = 103]	0.0 (-4.9 to 4.9)	.75
Prespecified Exploratory Outcome				
Acute kidney injury, No. (%)				
Stage 1	18 (16.8)	14 (13.5)	3.4 (-6.3 to 13.0)	.80
Stage 2	18 (16.8)	22 (21.2)	-4.3 (-14.9 to 6.2)	
Stage 3	39 (36.4)	39 (37.5)	-1.1 (-14.1 to 12.0)	

› Am J Med. 2020 May;133(5):635-638. doi: 10.1016/j.amjmed.2019.07.054. Epub 2019 Aug 28.

Vitamin C and Thiamine for Sepsis and Septic Shock

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Affiliations + expand

PMID: 31469984 DOI: 10.1016/j.amjmed.2019.07.054

Abstract

Background: Sepsis and septic shock are medical emergencies resulting in significant morbidity and mortality. Intravenous (IV) vitamin C, thiamine, and hydrocortisone have shown promise in reducing hospital mortality. The Memphis Veterans Affairs Medical Center (VAMC) similarly implemented this regimen, called the vitamin C protocol, for patients presenting in sepsis or septic shock in the intensive care unit (ICU).

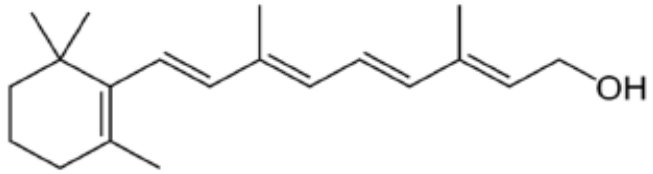
Methods: This retrospective study in Veteran ICU patients with sepsis or septic shock compared outcomes of patients treated with IV vitamin C, thiamine, and hydrocortisone (treatment) with those who received IV hydrocortisone alone (control). Data was propensity matched to ensure comparability at baseline. The Sequential Organ Failure Assessment (SOFA) score was calculated at day of diagnosis (day 0) and daily for 3 subsequent days. At the 24-month follow-up, 12 months after the 1-year-intervention, survival and measures of mental and physical health were collected by telephone interviews.

Results: Hospital mortality, the primary outcome, did not differ significantly between groups. Secondary outcomes including ICU, 28-day, and 60-day mortality were also not different, nor were vasopressor duration or hospital length of stay. However, ICU length of stay was significantly reduced in the treatment group compared to control (7.1 vs 15.6 days, respectively, P = 0.04).

Conclusions: Although no significant mortality benefit was observed, the vitamin C protocol was not associated with patient harm. In this Veteran population, there was reduced ICU length of stay, suggesting possible benefit. Though further investigation is warranted, utilization of IV vitamin C, thiamine, and hydrocortisone in patients with sepsis or septic shock may be a treatment option worth considering.

- Vit C for outpatient
- Dosing
- Side effect

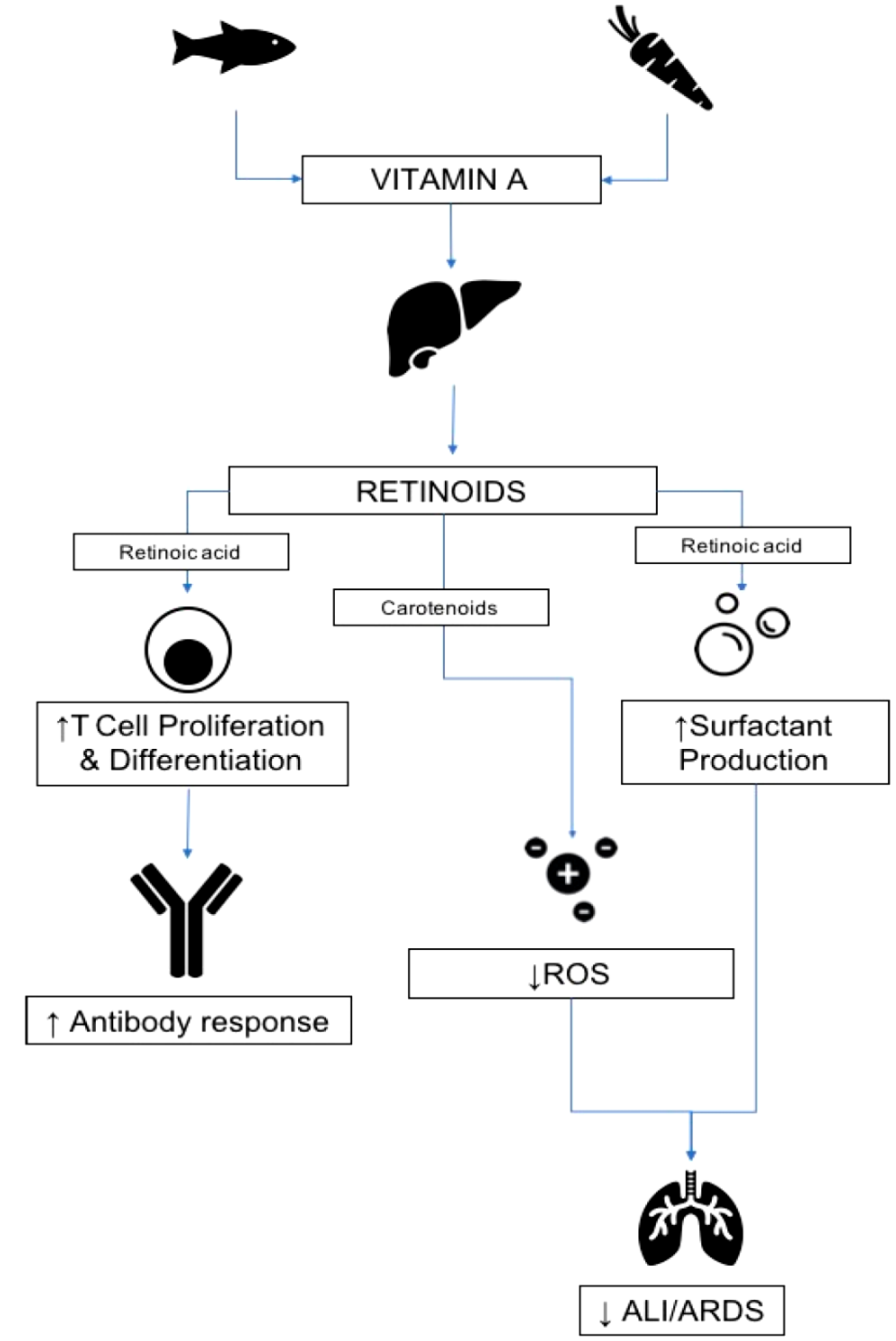
Vitamin A



- The sources of these are found commonly in animal food sources, such as meat, fish, and eggs.
- The carotenoids, generally in the form of alpha/beta/gamma carotene, are more likely to found in fruit and vegetables; β-carotene specifically contributes to the orange color of food and is typically associated with carrots. These provitamin carotenoids are converted to retinoids in body
- The most active retinoid has been found to be retinoic acid.
- The biological functions of retinoids are
  - gene transcription (more than 500 genes by its binding mechanism)
  - vision maintenance and health (in the form of retinal)
  - epithelial and membrane regulation (from skin to mucous to teeth) to bone metabolism
  - antioxidative properties
  - a major role in immune system modulation
  - promote proliferation of T-lymphocytes (through the increase of IL-2)
  - promote their differentiation, especially into regulatory T cells.
  - used as an adjunct to vaccine use, including tetanus, diphtheria, measles, influenza, rabies, and malaria,

Relevance to COVID-19

- Retinoids have been implicated in the development of an innate immunity against measles virus in vitro through an interferon-mediated mechanism
- increase the effect of antibody responses to the corona vaccine in animal model
- It was found increasing host susceptibility to influenza and SARS-CoV with a lower concentration of vitamin A in several disease models.
- In light of its pulmonary and immunological roles, oral supplementation of vitamin A is currently being investigated in the treatment of COVID-19 alongside a host of other antioxidants



- 1 unit = 0.3 mcg retinol
- Dosing in
  - deficiency: 100,000 U for 3 days then 50,000 U for 2 weeks
  - Prevention of deficiency especially in patients with severe infection: 200,000 U q6month

Oslo University Hospital trial

Experimental: Cod liver oil supplementation for 6 months	Dietary Supplement: Cod liver oil 5 ml of cod liver oil as a source of 10 ug of vitamin D and 1.2 g of long-chained n-3 polyunsaturated fatty acids (DHA 0,6g and EPA 0,4g) per day for 6 months x 1 time/day together with the first meal of the day. 5ml of Cod liver oil also contains 250ug **vitamin A** and 10 mg vitamin E.
Placebo Comparator: Corn oil (placebo)supplementation for 6 months	Dietary Supplement: Corn oil (placebo)5 ml of corn oil per day for 6 months x 1 time/day together with the first meal of the day

فهرست مواد غذایی بر پایه اندازه ویتامین آ

میزان نیاز روزانه

۱ میکروگرم رتینول برابر با ۳/۳ واحد بین المللی

- کودکان، ۴۰۰ تا ۶۰۰ میکروگرم ۱۳۰۰-۲۰۰۰ واحد
- خانم‌ها، ۷۰۰ میکروگرم ۲۳۰۰ واحد
- مادران شیرده، ۱۳۰۰ میکروگرم ۴۳۰۰ واحد
- آقایان، ۹۰۰ میکروگرم ۳۰۰۰ واحد

نام ماده غذایی	در ۱۰۰ گرم (gمیکروگرم (µ
هویج خام	۸۳۵
زردآلو آب گرفته شده (کم رطوبت) و نپخته	۶۳۳
کدو تنبل باترنات پخته یا تنوری بدون نمک	۵۵۸
شلغم تنوری، آب‌پز یا فریزری بدون نمک یا با نمک	۵۳۸
کلم کالی خام	۵۰۰
اسفناج خام	۴۶۹
جعفری تازه	۴۲۱
شوید تازه	۳۸۶
زرده تخم مرغ خام یا فریزری	۳۱۶
چغندر (لبو) خام	۳۱۶

Vitamins B

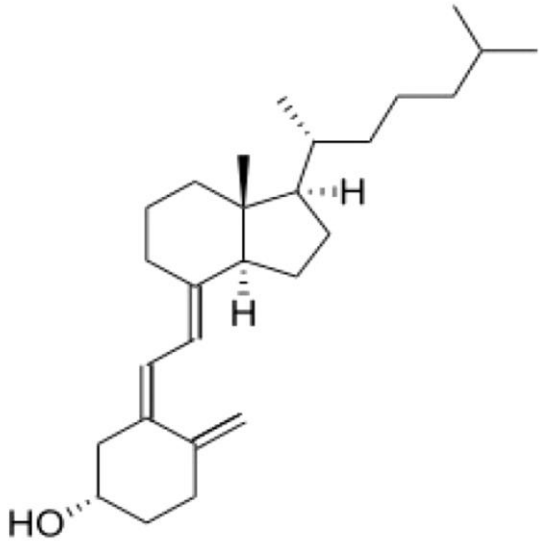
- Thiamin act as a cofactor for pyruvate dehydrogenase ,
- Thiamine and niacin is also needed for the generation of NADPH and glutathione cycling, which is an important antioxidant pathway.
- B6 , B12 and folate (B9) contribute in immune responses and contributing to the normal function of the immune system . deficiencies in these vitamins can impair immune functions.
- Vitamin B6 reduces the function and proliferation of T-lymphocytes and inhibits cytokine/chemokine release.
- Vitamin B9 (folate) deficiency has been reported to lead to megaloblastic anemia, and infections due to combined immunodeficiency with an impaired T-cell proliferation response, pan-hypogammaglobinemia, and an altered proinflammatory cytokine profile, which are reversed with folate therapy.
- Vitamin B12 (cobalamin) deficiency is particularly common in the elderly due to reduced absorption, and induces an imbalance in the cytokine and growth factor network in the CNS.
  - It was shown Lower levels of folate and vitamin B12 in COPD patients, but there is little evidence of the role of supplementation on improving symptoms, hospitalization, or pulmonary function.

Relevance to COVID-19

- The coronavirus polyprotein encodes two proteases, called 3-C-like protease (M-pro) and a papain-like protease (PL-pro), which were previous targets for drug discovery in the SARS and MERS
- A recent study utilized the available crystal structure of SARS-CoV-2 protein M-pro to screen existing approved drugs to see if they could be repurposed to combat COVID-19.
    - This study, based on docking scores, ligand efficiency, lipophilic, and hydrogen bonding interactions to predict the more powerful binding drugs, found that **niacin (B3), folate (B9), and B12** being possible contenders.
- EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL
- CORRECT DEFICIENCY

Clinical situations in which vitamin deficiency syndromes occur	
Mechanism	Examples
Poor intake	Poverty, older adults, alcoholics, restrictive diets (eg, vegan)
Abnormal losses	Hemodialysis, chronic diarrhea
Abnormal metabolism	Genetic polymorphisms, alcoholism (increases folate metabolism)
Inadequate synthesis	Vitamin D (Northern climates, homebound, little exposed skin)

Vitamin D



- In addition to its well-recognized roles in calcium and bone homeostasis, the physiological roles of vitamin D also include
  - immunomodulation and in critically ill patients,
  - associations between vitamin D deficiency and infection rates , renal and respiratory failure, sepsis, and mortality.
  - there is association between vitamin D deficiencies with immunological disorders, such as MS, IBD

- It has been hypothesized that vitamin D exerts its antimicrobial effects in three main ways:
  1. Through augmenting natural protective barriers,
  2. enhancing innate cellular immunity, through promoting the release of defensins and cathelicidins,
  3. Boosting adaptive immunity

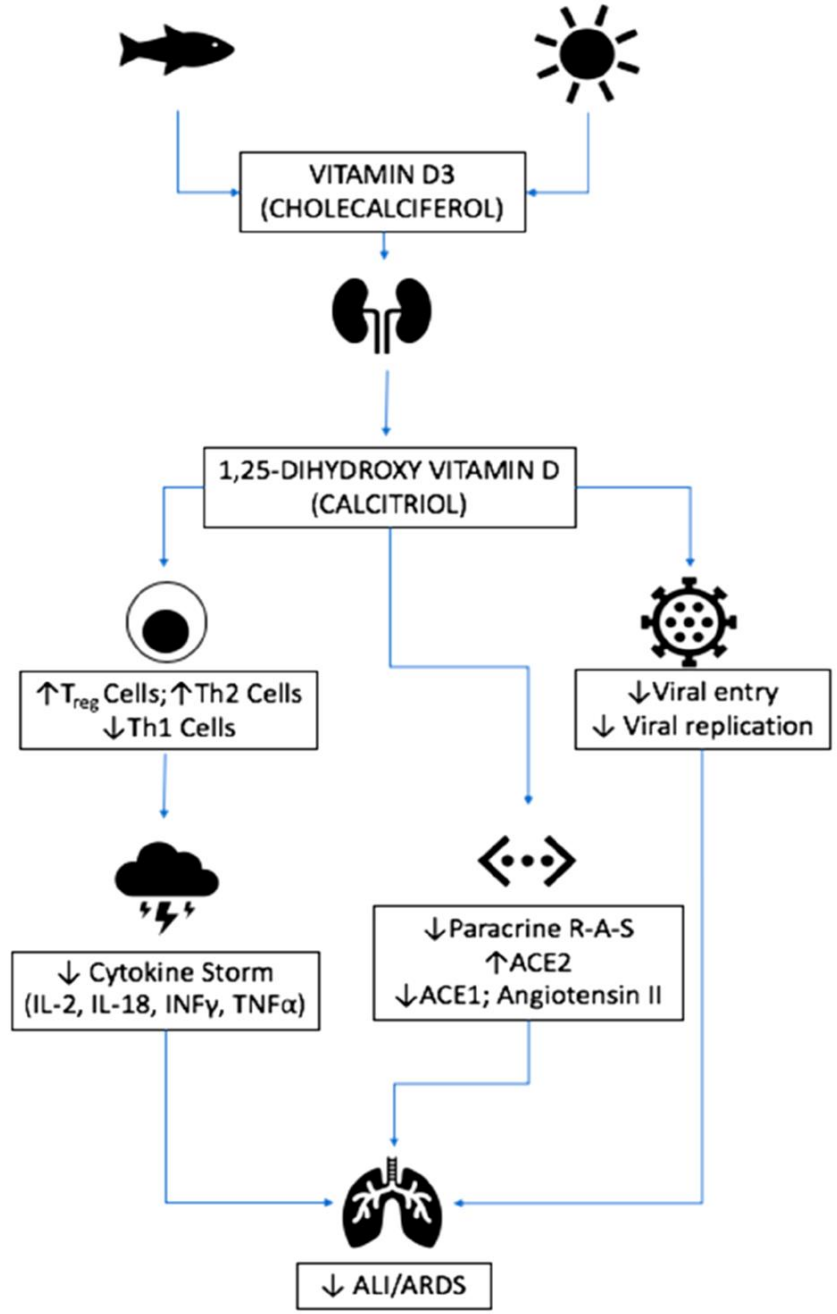
- Vitamin D deficiency in particular has been recognized as a direct contributor to ARDS in the aftermath of bacterial sepsis

- Vitamin D also upregulates the expression of some antioxidant genes, such as glutathione reductase, reducing the free radicals generated in inflammation, leads to the decreasing development of ARDS

- **(3rd NHANES study)** Results from a meta-analysis of vitamin D supplementation and risk of acute (bacterial and viral) respiratory tract infection show a 12% overall protective effect of vitamin D supplementation. This increased to 19% with a daily or weekly regimen compared to a monthly bolus regimen. Furthermore, a 70% protective effect was observed when deficiency was corrected

- **Two randomized clinical trial with no effect in rate of URTI (2012 and 2013)**

- Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; (risks for worse outcome in COVID)
- In observational studies, low vitamin D levels have been associated with an increased risk of CAP in older adults and children.
- In a meta-analysis of randomized clinical trials, vitamin D supplementation was shown to protect against acute respiratory tract infection.
- However, in 2 randomized, double-blind, placebo-controlled trials, high doses of vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the **mortality** rate compared to placebo. *(JAMA 2014, N Engl J Med. 2019)*
- High levels of vitamin D may cause hypercalcemia and nephrocalcinosis.


VITAMIN D3
(CHOLECALCIFEROL)
1,25-DIHYDROXY VITAMIN D
(CALCITRIOL)
↑T_{reg} Cells;↑Th2 Cells
↓Th1 Cells
↓Viral entry
↓ Viral replication
↓ Cytokine Storm
(IL-2, IL-18, INFγ, TNFα)
↓Paracrine R-A-S
↑ACE2
↓ACE1; Angiotensin II
↓ ALI/ARDS

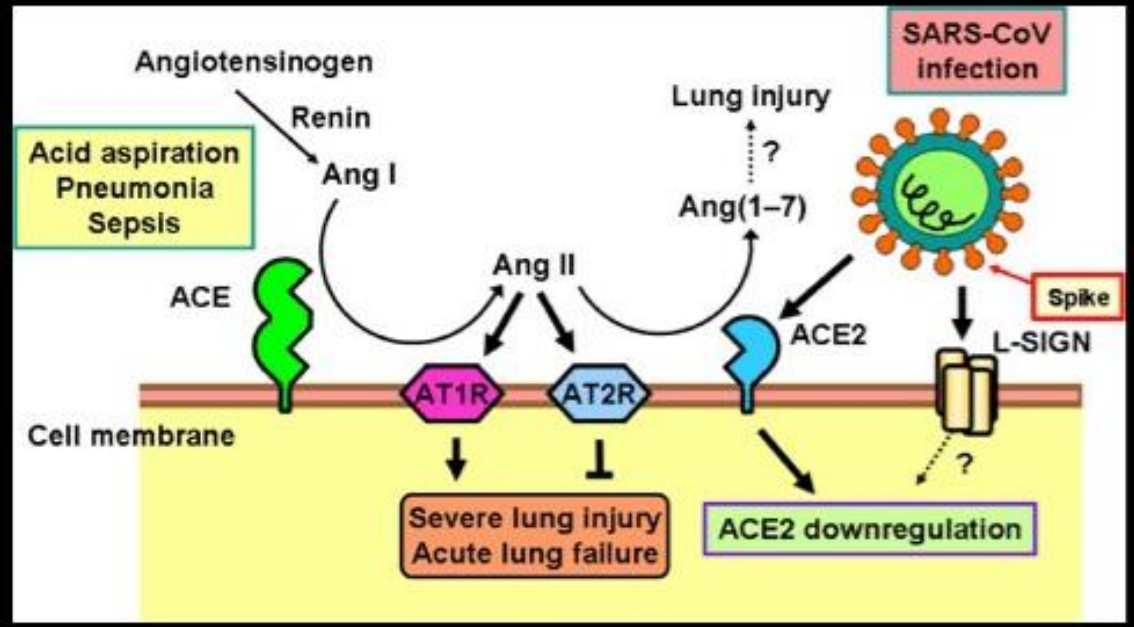
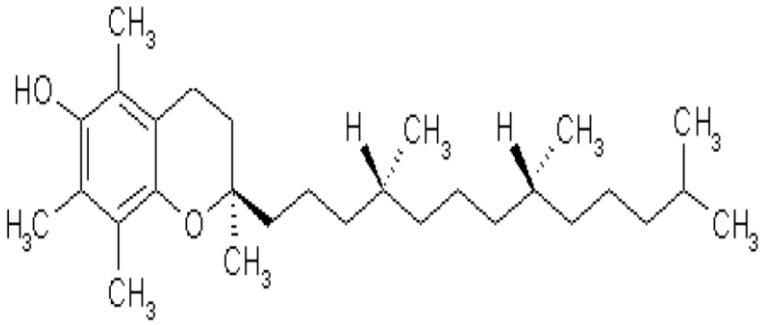
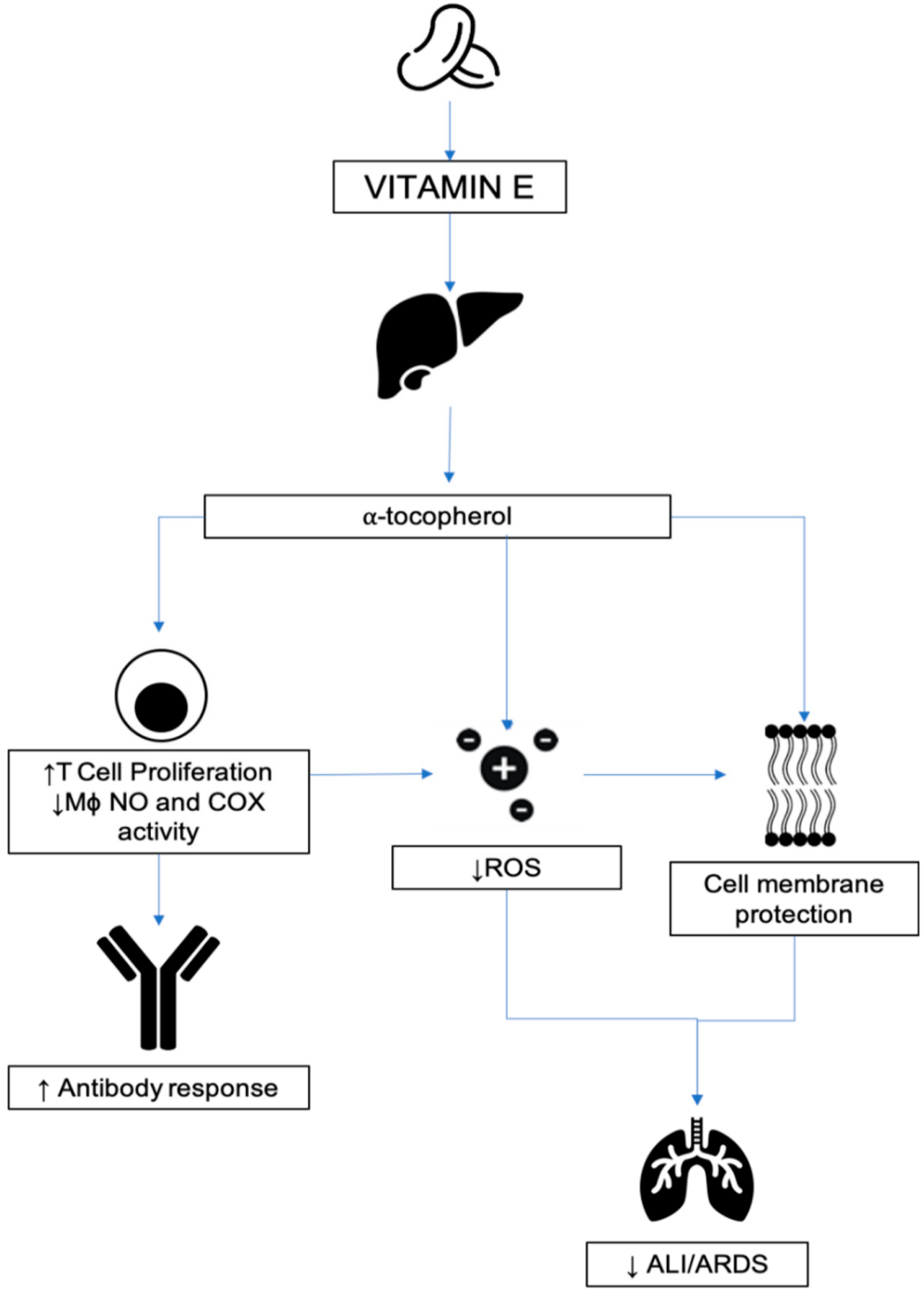


Figure 3 Schematic diagram of the role of the renin–angiotensin system in acute lung failure and proposed SARS-CoV action In acute lung injury, such as acid aspiration, pneumonia or sepsis, the generation of Ang II from Ang I is enhanced by ACE, and Ang II induces acute lung failure through stimulation of the AT_1R, while ACE2 and AT_2R negatively regulate this pathway and protect from acute lung failure. In contrast, SARS-CoV infection is mediated through binding of the SARS Spike protein to ACE2 or liver/lymph node-specific intercellular adhesion molecule-3-grabbing nonintegrin (L-SIGN) and downregulates the protective molecule ACE2, thus leading to severe lung injury and acute lung failure.

Vitamin E



Almonds, hazelnuts, peanuts; avocados and sunflower seeds



Vitamin E and Respiratory Tract Infections in Elderly Nursing Home Residents

A Randomized Controlled Trial

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Gerard E. Dallal, PhD
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Maria Fiatarone Singh, MD
Davidson H. Hamer, MD

Context Respiratory tract infections are prevalent in elderly individuals, resulting in increased morbidity, mortality, and use of health care services. Vitamin E supplementation has been shown to improve immune response in elderly persons. However, the clinical importance of these findings has not been determined.

Objective To determine the effect of 1 year of vitamin E supplementation on respiratory tract infections in elderly nursing home residents.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled trial was conducted from April 1998 to August 2001 at 33 long-term care facilities in the Boston, Mass, area. A total of 617 persons aged at least 65 years and who met the study's eligibility criteria were enrolled; 451 (73%) completed the study.

Intervention Vitamin E (200 IU) or placebo capsule administered daily; all participants received a capsule containing half the recommended daily allowance of essential vitamins and minerals.

Main Outcome Measures Incidence of respiratory tract infections, number of persons and number of days with respiratory tract infections (upper and lower), and number of new antibiotic prescriptions for respiratory tract infections among all participants randomized and those who completed the study.

Results Vitamin E had no significant effect on incidence or number of days with infection for all, upper, or lower respiratory tract infections. However, fewer participants receiving vitamin E acquired 1 or more respiratory tract infections (60% vs 68%; risk ratio [RR], 0.88; 95% confidence interval [CI], 0.76-1.00; $P=.048$ for all participants; and 65% vs 74%; RR, 0.88; 95% CI, 0.75-0.99; $P=.04$ for completing participants), or upper respiratory tract infections (44% vs 52%; RR, 0.84; 95% CI, 0.69-1.00; $P=.05$ for all participants; and 50% vs 62%; RR, 0.81; 95% CI, 0.66-0.96; $P=.01$ for completing participants). When common colds were analyzed in a post hoc subgroup analysis, the vitamin E group had a lower incidence of common cold (0.67 vs 0.81 per person-year; RR, 0.83; 95% CI, 0.68-1.01; $P=.06$ for all participants; and 0.66 vs 0.83 per person-year; RR, 0.80; 95% CI, 0.64-0.98; $P=.04$ for completing participants) and fewer participants in the vitamin E group acquired 1 or more colds (40% vs 48%; RR, 0.83; 95% CI, 0.67-1.00; $P=.05$ for all participants; and 46% vs 57%; RR, 0.80; 95% CI, 0.64-0.96; $P=.02$ for completing participants). Vitamin E had no significant effect on antibiotic use.

Conclusions Supplementation with 200 IU per day of vitamin E did not have a statistically significant effect on lower respiratory tract infections in elderly nursing home residents. However, we observed a protective effect of vitamin E supplementation on upper respiratory tract infections, particularly the common cold, that merits further investigation.

JAMA. 2004;292:828-836 www.jama.com

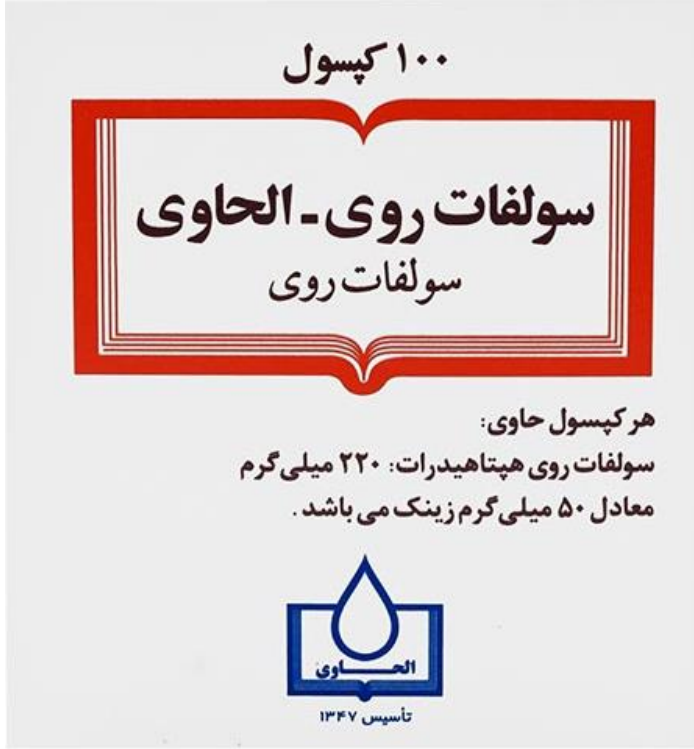
INFECTIONS, PARTICULARLY RESPIRATORY tract infections, are common in elderly individuals, resulting in decreased daily activity, prolonged recovery times, increased health care service use, and more frequent complications, including death.[1-11] In the United States, an estimated 43% of elderly persons will be admitted to a nursing home, with more than 85% of them admitted to long-term (>1 year) care facilities.[12] Infections occur more frequently in nursing home residents than among independent-living elderly,[2-10,13] and respiratory tract infections are a major cause of morbidity and mortality.[9,14,15] Contributing to the increased incidence of infection with age is the well-described decline in immune response.[16] For example, those who have diminished delayed-type hypersensitivity skin test responses have higher morbidity and mortality from cancer, pneumonia, and postoperative complications.[17-19]

Nutritional status is an important determinant of immune function.[20,21]

Zinc

- Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses.
    - Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog*. 2010;6(11):e1001176
- Zinc has been shown to enhance cytotoxicity and induce apoptosis when used *in vitro* with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake *in vitro*.
    - Chloroquine is a zinc ionophore. PLoS One. 2014;9(10):e109180

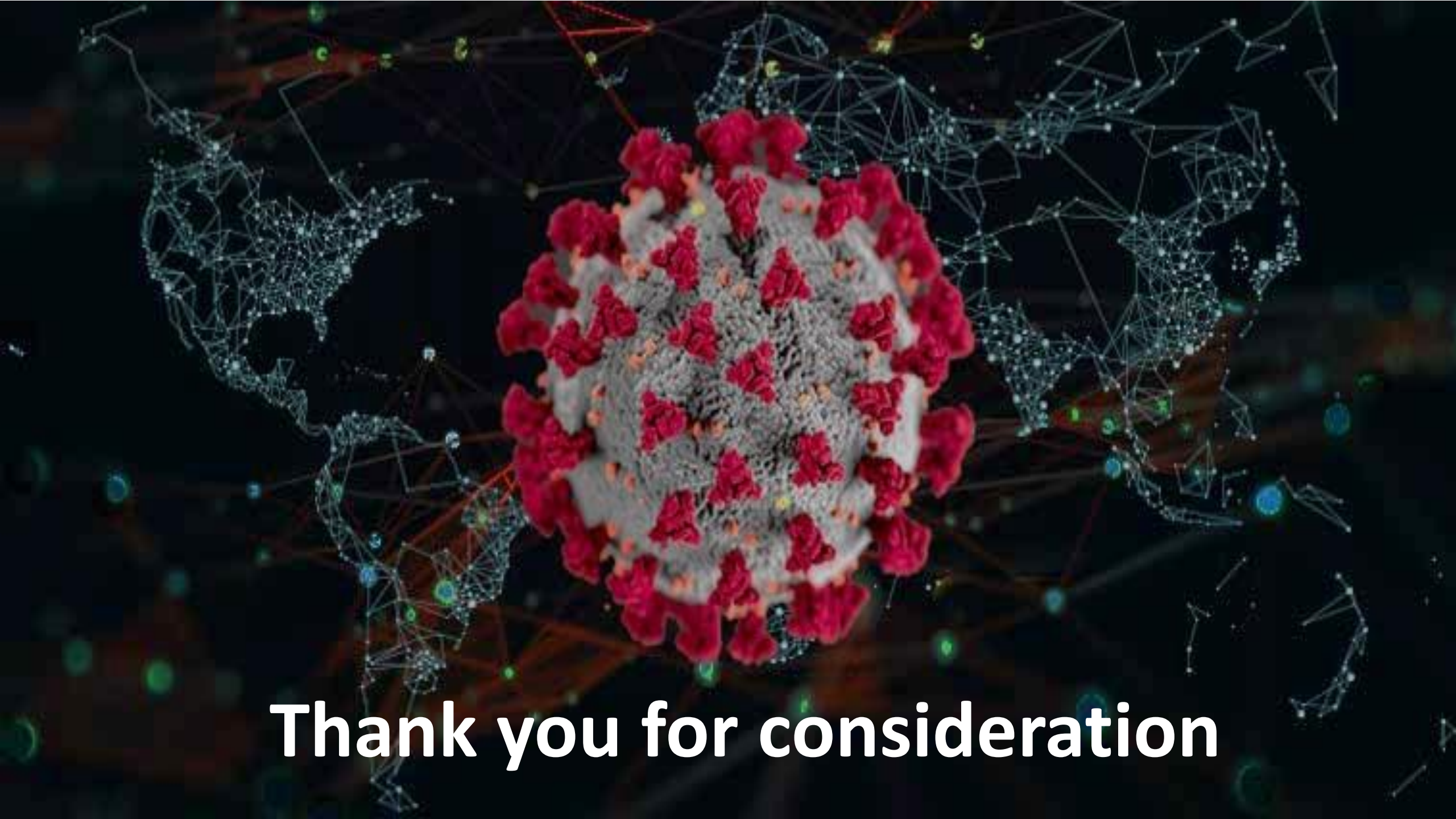
Zinc



- Zinc supplementation alone or in combination with HQC for prevention and treatment of COVID-19 is currently being evaluated in clinical trials.
- Dose?
- Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).
- Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency. In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.
- Because zinc has not been shown to have clinical benefit and may be harmful, the **recommendations are against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial

Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv. 2020;Preprint.

- A total of 932 patients were included in this analysis; 411 patients received zinc, and 521 did not.
- In univariate analysis, no differences were observed between the two groups in
  - duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO2.
- In bivariate logistic regression analysis, zinc supplementation was associated with a decreased mortality rate or rate of transfer to hospice; however, the association with a decreased mortality rate was no longer significant when analysis was limited to patients who were treated in the ICU.


Thank you for consideration