

Exhibit 417

Vitamin C in the Prevention & Treatment of Covid-19

Richard Z. Cheng, MD, PhD

Cheng Integrative Health Center Columbia, SC, USA BaoAn

Central Hospital Shenzhen, Guangdong, China

International Society for Orthomolecular Medicine (ISOM)

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Can early and high intravenous dose of
vitamin C prevent and treat coronavirus
disease 2019 (SOVID-19)?

Richard Z. Cheng. M,

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Richard Z. Cheng, M.D., Ph.D.

Cheng Integrative Health Center

Columbia, SC, USA

BaoAn Central Hospital

Shenzhen, Guangdong, China

International Society for Orthomolecular
Medicine (ISOM)



Richard Z. Cheng, M.D., Ph.D *Richzcg@gmail.com*

Conflict of Interest Disclosure

I have nothing to disclose.

Disclaimers:

The opinions expressed in this talk purely represent that of mine and of the International Society for Orthomolecular Medicine (ISOM) and do not represent that of the NIH.

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Key Pathologies of Covid-19

Covid-19 primarily affects the respiratory system, causing pneumonia, some of whom may develop acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), sepsis, septic shock & multi-organ failure.¹⁻²

- Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS) (17%);³
- Requiring mechanical ventilation (4%) ;³
- And septic shock (~4%).³

1. Peng ZY et al. Vitamin C infusion for the treatment of severe 2019-nCov infected pneumonia. <https://www.clinicaltrials.gov/ct2/show/NCT04264533>

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3. Chen, N. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 395 (2020)

Increased Oxidative Stress/ Cytokine Storm Underlying ALI/ARDS

ALI, ARDS, and sepsis **are nonspecific pathologies** shared by many viral infections including Covid-19 infection and other pathogens. Cytokine storm or increased oxidative stress is the key underlying common mechanism. Therapeutic agents, primarily antioxidants, including prototypical vitamin C, targeting increased oxidative stress/cytokine storm holds promises.

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3. [Markos G. Kashiouris](#),^{1,*} [Michael L'Heureux](#),¹ [Casey A. Cable](#),¹ [Bernard J. Fisher](#),¹ [Stefan W. Leichtle](#),² and [Alpha A. Fowler](#)¹ The Emerging Role of Vitamin C as a Treatment for Sepsis. [Nutrients](#). 2020 Feb; 12(2): 292. PMID: [31978969](#)
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VC Deficiency, a Key Finding of ICU Patients

Vitamin C deficiency is common among patients with acute and chronic diseases.¹⁻⁵

- 40% ICU patients with septic shock have blood VC levels approaching zero, diagnostic of scurvy (<11.3 umol/L),¹
 - with the remainder of ICU sepsis patients have hypovitaminosis C (<23 umol/L).¹
- ~50% non-septic ICU patients also have hypovitaminosis C.¹
- Low plasma VC levels are associated with more severe organ failure and increased mortality.⁶

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High-Dose IVC Prevents and Improves Pneumonia

☒

- 148 animal studies show VC can alleviate or prevent bacterial, viral and protozoan infections.
- VC cuts the risks of colds by 50% in physically active adults, although this is not always observed in the general population.
- 2 RCTs show a dose-dependent response in the therapeutic effects of VC in common colds.
- 3 RCTs found VC can prevent pneumonia.
- 2 RCTs found VC improve pneumonia treatment.
- 1 RCT found VC beneficial in the treatment of tetanus.

Hemilä H. *Nutrients*. 2017 Mar 29;9(4). pii: E339. doi: 10.3390/nu9040339. Vitamin C and Infections.

High-Dose IVC Shortens Mechanical Ventilation

High-dose IV Vit C (HDIVC) has been used in the treatment of pneumonia, sepsis and ARDS successfully. A recent meta-analysis pooled the data from 9 qualified trials and the analysis found strong evidence that HDIVC improves patient outcome:

- HDIVC shortens patients time on mechanical ventilation by 14% to 25% (when VC dose is 1,000 mg – 6,000 mg).

[Hemilä H. J Intensive Care.](#) 2020 Feb 7;8:15. doi: 10.1186/s40560-020-0432-y. eCollection 2020. Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. PMID 32047636

▣ High-Dose IVC Prevents Multi-Organ Failure

A 2014 study found very low plasma VC levels, approaching scurvy levels. HDIVC at 200 mg/kg body weight showed a dose-dependent effect of preventing multi-organ failure.

HDIVC group showed plasma VC levels of 3 mM/L on day 4, more than 40 times the average plasma VC level (~70 uM/L for people on balanced diet. For scurvy, VC < 11.3 uM/L).

[Vincent JL](#)¹, [Moreno R](#), [Takala J](#), [Willatts S](#), [De Mendonça A](#), [Bruining H](#), [Reinhart CK](#), [Suter PM](#), [Thijs LG](#). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. [Intensive Care Med.](#) 1996 Jul;22(7):707-10.

HDIVC Reduces ARDS Mortality

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The first HDIVC on ARDS trial was reported in 1989 where 32 patients were divided into 2 groups, 16 each. HDIVC group received VC 1,000 mg + NAC + Selenium + Vit E, every 6 hours.

HDIVC group showed a 47% reduction in mortality. The mortality in the HDIVC group was 37%, compared to 71% in the control group.¹

A 2016 study of 96 septic patients showed HDIVC (6,000 mg VC + hydrocortisone + thiamine cut the mortality by 31.9%.²

1. Sawyer M.A.J., Mike J.J., Chavin K., Marino P.L. Antioxidant therapy and survival in ARDS. Crit. Care Med. 1989;17:S153.

[2. Marik P, et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock. 2017. Chest PMID: 27940189](#)

CITRIS-ALI, the Largest Trial on Sepsis and ARDS

CITRIS-ALI trial is a multi-center RCT, enrolled a total of 167 patients of sepsis and ARDS. HDIVC group was receiving VC 50 mg/kg body weight, every 6 hours for 4 days (3,500 mg IVC for a 70 kg person over 6 hours for 4 days).

- On day 28, HDIVC group showed a reduction of mortality by 35% (HDIVC 29.8% vs. control group 46.3%).
- HDIVC group also had a shortened duration on mechanical ventilation, as well as
- Average of 3-day reduction in ICU stay.

[Kashiouris MG](#)¹, [L'Heureux M](#)¹, [Cable CA](#)¹, [Fisher BJ](#)¹, [Leichtle SW](#)², [Fowler AA](#)¹.

[Nutrients](#). 2020 Jan 22;12(2). The Emerging Role of Vitamin C as a Treatment for Sepsis. PMID 31978696

HDIVC on Covid-19

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HDIVC has been used in different settings in China during this pandemic.

- ~50 cases of moderate to severe Covid-19 pneumonia were treated with HDIVC (10,000 mg - 20,000mg/day) out of a total of 358 confirmed cases at the Shanghai Public Health Center.
- HDIVC group had a shorter hospital stay of ~5 days, compared to the 30-day average hospital stay. HDIVC patients also improved faster with no fatality. There were 3 fatalities of 358.
- One of the patient had rapidly deteriorating oxygenation index. This patient received an additional bolus of 50,000 mg VC over 4 hours. Real time improvement of the oxygenation index was observed.

Personal communication on Mar. 17th, 2020 with Dr. EQ Mao, Prof and Chief of Emergency Medicine, Ruijing Hospital, Jiaotong University, Shanghai, China

Richard Z. Cheng, M.D., Ph.D *Richzc@gmail.com*

HDIVC on Covid-19



HDIVC has been used in different settings in China during this pandemic.

- A Zhongnan Hospital, Wuhan University team announced world's 1st HDIVC clinical trial on Covid-19 infection.
- A total of ~40 confirmed Covid-19 patients have been enrolled. HDIVC group received 24,000 mg/day IVC.
- A preliminary analysis shows HDIVC group showed significantly improved inflammatory markers and organ function tests. The final data analysis and report are being prepared.

Personal communication on April 6th, 2020 with Dr. ZY Peng, principal investigator of the world's first HDIVC on Cogi-19 trial, prof and chief of critical medicine, Zhongnan Hospital, Wuhan University, Wuhan China.

HDIVC Included in the Covid-19 Treatment by Shanghai and Guangdong Province

[Shanghai Expert Panel Consensus on Covid-19 Treatment](#)

<https://mp.weixin.qq.com/s/bF2YhJKiOfel1yimBc4XwOA>

Guangdong Expert Panel Consensus on Covid-19 Treatment

http://wsjkw.gd.gov.cn/zwyw_gzdt/content/mpost_2924849.html

Oral VC May Prevent Colds

A recent large study of 1,444 South Korean army recruits, average age 21.7 years, were divided into 2 groups, VC group received 6,000 mg VC daily.

At the end of the 30-day training, the VC group showed a 0.8-fold reduction in risks of developing common cold.

Kim et al., Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. *BMJ Mil Health* 2020;0:1-7. PMID:32139409

Oral VC Reduces Duration and Symptoms of Colds and May Prevent Colds

A 2013 meta-analysis of 29 qualified clinical trials (mostly double blind RCTs) totaling 11,306 subjects, found:

- VC 200 mg daily reduces cold duration in adults by 8%
- VC 200 mg daily reduces cold duration in children by 14%
- VC 1,000 mg - 2,000 mg daily reduces cold duration in children by 18%
- Reduced severity of common cold
- Better results at 8,000 mg daily or higher

[Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2013 Jan 31. PMID 23440782](#)

High-dose Oral VC Reduces Cold symptoms

715 college students, aged 18-32, were divided into 2 groups, test group or control group. Those developed cold symptoms were given: VC in the test group and pain relievers and nasal decongestant in the control group. Those in the test group without symptoms were given VC 1,000 mg 3 times daily. Authors concluded:

- High-dose VC (1,000 mg/hour x 6 hours, then followed by 1,000 mg 3 times daily, reduced the cold symptoms by 85%.
- High-dose VC (1,000 mg 3 times daily) also reduced the risks of catching cold.

[Gorton HC, Jarvis K.](#) The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. [J Manipulative Physiol Ther.](#) 1999 Oct;22(8):530-3. PMID 10543583

HDIVC is Safe without Significant Side Effects

HDIVC (up to 1,500 mg/kg body weight) has been generally well tolerated in clinical trials.¹⁻⁹

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https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq#cit/section_6.1

Vit C is Safe without Significant Side Effects

- Renal failure after IVC has been reported occasionally in patients with pre-existing renal disorders.¹
- Patients should be screened for G6PD deficiency. HDIVC should be avoided in Patients with G6PD deficiency.²⁻⁴
- HDIVC may increase bioavailability of iron, and high doses of IVC are not recommended for patients with hemochromatosis.⁵

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Mechanisms of VC's Anti-Viral and Anti-Inflammatory Effects

- VC's role in prevention and treatment of common cold was proposed as early as 1971 by Dr. Pauling.¹
- Hydrogen peroxide (H₂O₂) production of VC upon its oxidation may have direct virucidal effects.²⁻⁶
- Immunomodulation Effects⁶⁻⁷
 - Increases neutrophil phagocytosis and chemotaxis
 - Increases macrophage migration
 - Affects production of interferon
 - Enhances T&NK cell proliferation and modulates their functions
- Affects replication of viruses⁶⁻⁷
- Powerful antioxidant, can protect cells from oxidative damages during infection from increased oxidative stress.⁸⁻⁹

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EFSA Officially Endorses these VC Effects (1)

European Food Safety Authority (EFSA) concluded that

1. A **cause and effect** relationship between the dietary intake of vitamin C and contribution to the normal function of the immune system has been established.

Article 14 of the Regulation (EC) NO 1924/2006

EFSA Officially Endorses these VC Effects (2)

European Food Safety Authority (EFSA) concluded that

2. In persons exposed to severe physical stress, it has been established that regular vitamin C intake above 200 mg/d exerts a **cause and effect** relationship with
 - the protection of DNA
 - proteins and lipids from oxidative damage
 - normal collagen formation
 - normal function of the nervous system
 - normal function of the immune system

EFSA Journal 2009; 7(9):1226

Summary

- A percentage of Covid-19 infection develops into pneumonia, ALI/ARDS, sepsis and death.
- ALI and ARDS are nonspecific pathologies caused by cytokine storm/ significantly increased oxidative stress.
- HDIVC has immune boosting effects and probably direct virucidal effects.
- HDIVC seems to prevent pneumonia and reduce pneumonia severity.
- HDIVC seems to improve ARDS and sepsis and reduce ARDS/Sepsis related mortality.
- HDIVC is safe without significant side effects in doses up to 1,500 mg/kg body weight. The doses used for pneumonia, sepsis and ARDDS are often lower.
- HDIVC is a promising non-specific anti-viral as well as therapeutic agent for oxidative stress induced ARDS.
- Given VC's safety profile and its nonspecific antiviral effect and its role in oxidative stress induced ARDS, further research is warranted to establish **VC as a universal and nonspecific agent in the prevention and treatment of Covid-19 and future epidemics/pandemics.**



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ORTHOMOLECULAR MEDICINE

Richard Z. Cheng, M.D., Ph.D

Richzc@gmail.com

Summary

I asked in my article in the journal of Medicine in Drug Discovery (Mar 26, 2020).

Can early and high intravenous dose of vitamin C prevent and treat coronarvirus disease 2019 (COVID-19) ?

My answer is **YES. Early and Large Dose VC** is the key to prevention and treatment of Covid-19.

Richard Z. Cheng. Can early and high intravenous dose of vitamin C prevent and treat coronarvirus disease 2019 (COVID-19) ? Medicine in Drug Discovery. Mar. 26th, 2020. <https://www.sciencedirect.com/science/article/pii/S2590098620300154>



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ORTHOMOLECULAR MEDICINE

Richard Z. Cheng, M.D., Ph.D

Richzc@gmail.com

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This presentation is a collective effort from the many doctors, scientists at the [International Society of Orthomolecular Medicine \(ISOM\)](#) and its [Orthomolecular Medicine News Service \(OMNS\)](#) editorial board. These scholars have been tirelessly and unselfishly discussing the scientific evidence of vitamin C, educating the public and the healthcare professionals of vitamin C and other natural or orthomolecular molecules, in the global fight against Covid-19.

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INTERNATIONAL SOCIETY FOR
ORTHOMOLECULAR MEDICINE

Richard Z. Cheng, M.D., Ph.D

Richzcc@gmail.com

Thank You



Richard Z. Cheng, M.D., Ph.D.

www.DrWLC.com

www.DrWLC.com/China

richzc@gmail.com

1(803)233.3420 (USA)

173-1716-9336 (China)



INTERNATIONAL SOCIETY FOR
ORTHOMOLECULAR MEDICINE

Richard Z. Cheng, M.D., Ph.D

Richzc@gmail.com



Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?



The COVID-19 (SARS-2-Cov) pandemic, first reported in Wuhan, China, is now spreading to many continents and countries, causing a severe public health burden. Currently, there is no vaccine or specific antiviral drug for this deadly disease. A quick, deployable and accessible, effective and safe treatment is urgently needed to save lives and curtail the spreading. Acute respiratory distress syndrome (ARDS) is a key factor of fatality. Significantly increased oxidative stress due to rapid release of free radicals and cytokines is the hallmark of ARDS which leads to cellular injury, organ failure and death. Early use of large dose antioxidants, such as vitamin C (VC) may become an effective treatment for these patients. Clinical studies also show that high-dose oral VC provides certain protection against viral infection. Neither intravenous nor oral administration of high-dose VC is associated with significant side effect. Therefore, this regimen should be included in the treatment of COVID-19 and used as a preventative measure for susceptible populations such as healthcare workers with higher exposure risks.

Coronaviruses and influenza are among the pandemic viruses that can cause lethal lung injuries and death from ARDS [1–3]. Viral infections could evoke “cytokine storm” that leads to lung capillary endothelial cell activation, neutrophil infiltration and increased oxidative stress (reactive oxygen and nitrogen species). ARDS, characteristic of severe hypoxemia, is usually accompanied by uncontrolled inflammation, oxidative injury and damage to the alveolar-capillary barrier [4]. Increased oxidative stress is a major insult in pulmonary injury including acute lung injury (ALI) and ARDS, two clinical manifestations of acute respiratory failure with substantially high morbidity and mortality [5,6].

In a report of 29 patients with COVID-19 pneumonia, 27 (93%) showed increased hsCRP, a marker of inflammation and oxidative stress [7]. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. VC, an important component of the cellular antioxidant system [8], is beneficial to critical care management [9]. Cytokine storm is observed in both viral and bacterial infections [3] and results in increased oxidative stress via a common and non-specific pathway. Since the prevention and management of oxidative stress could be realized by large dose of antioxidants, this approach may be applicable to COVID-19 with intravenous high-dose VC based on the outcome of three previous clinical studies involving a total of 146 patients with sepsis [10].

Hemila and colleagues reported that various high-dose intravenous VC infusions (e.g., 200 mg/kg body weight/day, divided into 4 doses) shortened the intensive care unit (ICU) stay by 7.8% [11], accompanied

by a significant reduction in the mortality rate [12]. Such an experience was reproduced among patients ill with severe influenza [13,14]. Indeed, dietary antioxidants (VC and sulforaphane) were shown to decrease oxidative stress induced acute inflammatory lung injury in patients receiving mechanical ventilation [15]. In addition, oral VC (e.g., 6 g daily) was able to reduce viral infection risk [16] or to improve symptoms [17].

1 High-dose intravenous VC has also been successfully used in the treatment of 50 moderate to severe COVID-19 patients in China. The doses used varied between 10 g and 20 g per day, given over a period of 8–10 h. Additional VC bolus may be required among patients in critical conditions. The oxygenation index was improving in real time and all the patients eventually cured and were discharged [18]. In fact, high-dose VC has been clinically used for several decades and a recent NIH expert panel document states clearly that this regimen (1.5 g/kg body weight) is safe and without major adverse events [19].

Because the development of efficacious vaccines and antiviral drugs takes time, VC and other antioxidants are among currently available agents to mitigate COVID-19 associated ARDS. Given the fact that high-dose VC is safe, healthcare professionals should take a close look at this opportunity. Obviously, well-designed clinical studies are absolutely needed to develop standard protocols for bedside use.

Conflict of Interest

The authors declare no conflict of interest

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