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Cover Page Footnote

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Acute Induced Scurvy: Implications for COVID-19 and the Cytokine Storm

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Abstract: Using an evolutionary genetic disease model, this review considers Vitamin C (VC) and its potential for treating COVID-19 (CV-19). The model's validity rests on VC's potent antioxidant property and the mutation sustained by the primate ancestor (est.) 61 MYA that left humans unable to produce VC. The result is humans cannot -by diet or oral supplementation- achieve plasma VC concentrations typical of vitamin C synthesizers. This may leave humans chronically vulnerable to infectious disease (hypoascorbemia). VC deficiency can become more acute during severe disease (anascorbemia) and, because of the relationship between disease severity and oxidative stress, can intensify the oxidative load and associated inflammation. During acute disease, oxidative stress becomes oxidative distress when highly reactive oxidants are produced at a rate faster than normal homeostatic mechanisms can quench them, such as with the inflammatory cytokine storm characteristic of severe CV-19. Cytokine storms directly underly the most severe complications of CV-19, e.g., acute respiratory distress syndrome (ARDS), sepsis, and multiple organ dysfunction syndrome (MODS). Infusions of VC into the plasma achieve concentrations that can exceed those of VC synthesizing species. At such concentrations, VC's action as a non-rate limited antioxidant may lower the probability of a cytokine storm and the risk of tissue injury. I suggest that VC may prove a useful treatment in such contexts. In advance of the resulting ongoing clinical trials, this review will extrapolate a picture of VC's potential therapeutic impact on the inflammatory cytokine storm and severe complications possible with CV-19.

Keywords: Vitamin C, COVID-19, anascorbemia, evolutionary medicine

Introduction

Vitamin C (VC) deficiency and its manifestation as scurvy are most widely known as the disease of sailors during the Age of Discovery (Lamb 2016). However, the symptoms of scurvy have been documented since the classical period (Magiorkinis 2011). More recently, bioarcheologists have found skeletal evidence for scurvy and VC deficiency throughout the past, including ancient Egypt (Pitre et al. 2016) and The Great Irish Potato Famine (Geber & Murphy 2012). In fact, recent reports of clinical cases of scurvy (Fortenberry et al. 2020, Yule et al. 2021) make it clear that VC deficiency is still with us, but do not capture its full impact.

Acute scurvy appears to be more common than previously thought, not so much as a dietary deficiency but as the impact of other severe diseases. Sustained oxidative stress is characteristic of severe disease (Kehrer & Klotz 2015), as is acute scurvy (de Grooth et al. 2014). Oxidative stress typical of severe disease appears to create such a draw on VC stores as to deplete the diseased tissue (Carr et al. 2017) and, eventually, the blood and the body, creating acute systemic scurvy or anascorbemia (Cathcart 1981). Thus, symptoms of acute scurvy may both be induced by- and manifest with severe disease, creating, in effect, a disease within a disease. This review will explore the therapeutic use of VC and the implications of anascorbemia in the context of COVID-19 (CV-19). However, before considering VC as a treatment for CV-19, CV-19 and the evolutionary medicine (EM) of VC will be discussed.

COVID-19

CV-19 is an infection caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chary et al. 2020). Its symptoms mirror those of influenza, including fever, chills, coughing, difficulty breathing, myalgia, and sore throat. With CV-19, however, difficulty breathing, and fatigue are more commonly reported (Maragakis 2020) and, unique to CV-19, the loss of smell and taste (CDC 2020a).

In 2020, CV-19 was the third leading cause of death in the US, behind only heart disease and cancer (Wolf et al. 2021). As of January 31st 2021, there have been 103,514,297 reported cases of CV-19 and 2,237,252 deaths (Worldometer 2021). On March 11th, 2020, the World Health Organization (WHO) classified CV-19 as a pandemic (WHO 2020). It has so far spread to over 219 countries and territories around the world (Worldometer 2021).

Although the FDA has approved two vaccines to date for use against CV-19 (CDC 2020b), advances in pharmacotherapeutics are ongoing and typically take 12 or more months to develop fully. Given the threat CV-19 posed at the onset of the pandemic, doctors turned to alternative therapies, including treatment with VC. By March 2020, hospitals in the Northwell Hospital System (New York) were using VC "widely" to help treat severe CV-19 cases (Mongelli and Golding 2020).

The adoption of VC as a treatment option stemmed from Shanghai, China, where it was documented to successfully treat CV-19 (Mongelli and Golding 2020). Dr. Enqiang Mao, the chief of the emergency medicine department at Ruijing Hospital in Shanghai reported treating 50 moderate-to-severe cases of CV-19 with high dose intravenous VC (I-VC) (10,000 mg – 20,000 mg/day for 7-10 days). All 50 patients improved, and averaged hospital stays that were 3-5 days shorter than untreated patients. Further, no deaths or side effects were reported (Cheng 2020). As a result, by August 2nd, 2020, there were 28 studies worldwide (nine in the US) which either isolated VC as a treatment option or used it as part of a drug or nutrient cocktail (ClinicalTrials.gov 2021).

VC and COVID-19

Presently, there is limited information about the impact of VC on the treatment of CV-19. There is, however, a body of evidence VC's impact on the severe complications that define CV-19, e.g., acute respiratory distress syndrome (ARDS) (e.g., Fowler et al. 2017); sepsis, severe sepsis, and septic shock (Li 2018; Li et al. 2020); and multiple organ dysfunction syndrome (MODS) (Fowler et al. 2014; Fowler et al. 2019), and death (Wang et al. 2019). VC's therapeutic value lies not on its effect on the complications themselves but on the acute inflammatory response that underlies and unifies them. The severity of these complications and associated mortality are not a function of the SARS-CoV-2 virus *per se* but can be traced to the so-called inflammatory cytokine storm (ICS), the most cited pathological theory of CV-19 (Wu 2020).

The ICS is mediated by a dysregulated homeostatic redox state in which highly reactive oxidants are produced at a rate faster than normal homeostatic mechanisms can quench them (Camini et al. 2017). Such oxidative distress underlies the ICS and the ICS, in turn, directly underlies the most morbid complications of CV-19, i.e., sepsis, severe sepsis, septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and mortality (Zabetakis et al. 2020; Fu et al. 2020).

Through its anti-inflammatory property, VC may moderate the inflammatory response and, in so doing, keep the level of inflammation within the scope and tolerance of the pre-existing homeostatic redox system. By avoiding runaway inflammation, VC may inhibit the morbidity and mortality of the most severe complications of CV-19.

The Evolutionary Medicine of VC

Although VC is defined as a vitamin, that is true for only a few mammal species. In all but a small subset, VC is a hepatic metabolite (Stone, 1966a). As such, it is part of the endogenous antioxidant system and subject to the homeostatic redox mechanisms that regulate it (Sies and Jones 2007). Via feedback mechanisms, most mammals produce and regulate VC production in response to biochemical needs, such as oxidative stress.

Humans, however, cannot synthesize VC - nor can any other primate anthropoids (infraorder Simiiformes) (Drouin et al. 2011; LaChapelle and Drouin 2010). This loss of capacity stems from a mutation sustained by primate ancestors approx. 61 MYA. All descendants carry a defective gene that results in the absence of the hepatic enzyme L-gulonolactone oxidase (GLO), the end-stage enzyme necessary for VC synthesis. As a result, humans are entirely dependent on non-metabolic sources of VC, e.g., dietary intake or supplements.

As a point of comparison, rats not only synthesize their own VC but, through a redox feedback mechanism, can up- or downregulate production. If stressed, they can up VC production 3-fold from 70 mg per kilogram of bodyweight per day to 215 mg (Salomon and Stubbs, 1961; Conney et al. 1961). In a human 70 kg adult, that converts to about 4,000 to 15,000 mg of **plasma VC** synthesized per day (Stone, 1966b). The range's upper bound translates to a peak VC plasma concentration of approximately 5.722 mmol/L (Kashiouris et al. 2020). In comparison, were a human to ingest 18,000 mg daily in doses of 3,000 mg every 4 hours, the peak plasma concentration would be about 0.22 mmol/L, a 26-fold difference.

In humans, pharmacokinetic modeling predicts that 50 and 100-gram I-VC administrations can yield VC concentrations of 13.350 mmol/L and 15.380 mmol/L, respectively (Padayatty et al. 2004). More broadly, intravenous VC administrations achieve plasma concentrations 30- to 70-fold higher than oral ones (Padayatty et al. 2010). Compensating orally for *direct-to-plasma* VC concentrations is not possible.

On the assumption that the human primate ancestor's diet approximated that of great apes, Pauling (1970) estimated, fifty years ago, that ancestral humans would only have ingested 2.3 - 9.5 grams of VC per day. The ingestion of 15,000 - 18,000 mg of VC is not possible without modern supplements. Thus, before the advent of modern medicine, the disparity between *direct-to-plasma* VC concentrations and ingested concentrations would have been that much more pronounced.

Despite the handicap of obtaining VC from the diet, the mutation responsible for the cessation of VC synthesis in humans persisted in the primate lineage. This may reflect two factors: 1) Natural selection is more intense on the young (the pre-reproductive) than on the old. The average human life span may have been short enough, and VC sources of food plentiful enough to minimize the fitness liability of the loss; 2) All other things being equal, the aged sustain more net oxidative damage than the young (Liguori et al. 2018). In that sense, the liability may have been late enough in the life span to escape the influence of natural selection.

Furthermore, the loss of VC production may not have been a total liability. As Pauling noted, it did save the body the cost of having to produce VC (1968). Further, it may have triggered an increased ability of the kidney to pump VC back into the plasma of certain cells, e.g., white blood cells, intestinal epithelial cells, to extract VC from circulation (Bergsten et al. 1990; Rivas et al. 2008). Still, humans can benefit therapeutically from oral doses of 100,000 mg + a day when severely ill (Cathcart 1981)¹. This is especially true with IV administration which can more readily duplicate the plasma VC concentrations reached had humans been able to synthesize VC (Stone 1979).

The impact of VC on human illness is consistent with the difference in the outcome of infection in mice with and without the ability to synthesize VC. Gulo (-/-) knockout mice², mice who have had their VC synthesizing ability removed (Li et al. 2006; Kim et al. 2013), fare much worse than normal mice when infected with the H3N2 or H1N1 influenza viruses. Compared to normal mice, over the course of a week, 0% of the former survived after infection (Kim et al. 2013). Relative to normal mice, gulo (-/-) mice had significantly higher virus titers of H3N2 in the lungs and evidenced lower production of the anti-viral cytokine interferon (IFN)- α/β . They also had higher lung inflammatory cell densities and increased production of proinflammatory cytokines. More tissue injury was also present (Li et al. 2006). These effects did not occur in gulo (-/+) mice, gulo (-/-) mice supplemented with VC before virus exposure.

The end-stage enzyme responsible for VC synthesis in humans, L-gulono- γ -lactone oxidase (GLO), is defective (Hickey and Roberts 2004). All the other necessary enzymes are present in the liver. As such, the loss of VC synthesis in humans may be characterized as a genetic disease (Stone, 1966a). The disease, hypoascorbemia, is analogous to other genetic diseases in which a missing or defective enzyme causes a pathologic syndrome, e.g., phenylketonuria, galactosemia, and alkaptonuria.

Fully correcting for the missing enzyme would entail supplying VC in amounts the liver would be synthesizing had the mutation not occurred. The disparity between this condition and merely supplying enough VC to forestall scurvy is by Stone's (1966a) conception equivalent to subclinical scurvy. An ongoing deficit of VC is created when acute scurvy, a potentially fatal condition, is prevented. Humans, however, remain chronically vulnerable to disease, especially acute forms. Acute scurvy, as discussed, can also be induced by the presence of acute disease (Evans-Olders et al., 2010; de Grooth et al. 2014).

The assumption is that human VC requirements are not significantly different, pound for pound, from that of mammals capable of VC synthesis (Stone, 1966a; Pauling 1986). Accordingly, like most mammals, the required VC amounts in humans would vary consistent with metabolic demands and thus vary consistent with the variation in endogenous production observed in mammals (Ginter 1981).

Scaled up pound for pound to the average human adult (154 lbs.), oral VC recommendations for non-human anthropoids (e.g., *Macaca mulatta*: Rhesus macaques; *Macaca fascicularis*: Crab-eating macaques; *Chlorocebus aethiops*: the grivet; and *Callithrix jacchus*; the common marmoset) extrapolate to 583 – 5,636 mg of VC per day (National Research Council 1962, 1972 2003)³. This overlaps with Pauling's (1970) estimate of the optimum oral daily intake of VC for human beings: 2,300 – 9,500 mg. It corresponds to $6x$ - $62x$ the adult human male US recommended daily VC allowance (US-RDA) and $7x$ - $75x$ the adult human female VC US-RDA, respectively.

US-RDA VC recommendations are designed to provide antioxidant protection through near-maximal neutrophil VC concentrations and the minimal urinary excretion of VC⁴. The oral RDA judged sufficient to meet that standard, for (97% -98%) of healthy adults in the US, is 75 and 90 mg/day of VC for women and men (Institute of Medicine (US) 2000)⁵, respectively.

The upper-end of the VC recommended range for non-human anthropoids reflect an intake of VC appropriate to prevent atherosclerosis in squirrel monkeys (Portman et al. 1967) and, inasmuch as it may be a potentiating factor in the context of vitamin B₆ deficiency, atherosclerosis, dental caries, and hepatic cirrhosis in rhesus macaques (Rinehart and Greenberg 1956).

Given a 1:1 comparison in the vein of the human US-RDA standard, the recommended range scaled to a human adult for a non-human anthropoid (that of the rhesus macaque and the marmoset- the only data available)

extrapolate to 777 - 1,400 mg of VC or 8x - 15x the adult human male US recommended daily VC allowance (US-RDA) and 10x - 18x the adult human female VC US-RDA (National Research Council 1972, 2003). Thus, the deviation from the scaled human US-RDA values and the actual US-RDA values reveals an inconsistency between the ways human and non-anthropoid VC recommendations are considered.

COVID-19: Hyperinflammation and Oxidative Distress

Oxidative Distress

Oxidative stress (OS) is an “an imbalance between oxidants and antioxidants in favor of oxidants, leading to a disruption of redox signaling and control and/or molecular damage” (Sies and Jones 2007, 45). If oxidative stress becomes too intense and supraphysiological, the term **oxidative distress** is used (Sies 2019). In this state, oxidation leads to tissue damage. This stems from the power of oxidants to denature the physiology, function, and structure of lipid membranes, proteins, and DNA (Valko et al. 2007), which can result in the overall deterioration of these constituents extending into- and including cell death and organ failure (Wu 2020). As such, oxidative distress is a state associated with acute disease, including systemic hyperinflammation (Evans-Olders et al. 2010).

Inflammation, Oxidative Distress, and CV-19

All inflammation begins with tissue injury. In the case of severe CV-19, this is typically the epithelial cells in the lungs. SARS-CoV-2 viruses kill these cells, causing them to break apart, and DAMP⁶ release their contents (Reinhart et al. 2012). These contents include oxidants, which play a role in signaling for- and activating white blood cells (WBC's) (e.g., macrophages, neutrophils, and dendritic cells, to phagocytotically engage the virus).

These WBC's, in turn, signal for- and recruit, through the release of proinflammatory (pro-oxidant) cytokines, T-lymphocytes to the site of the infection. (Deramautd et al. 2013). Cytokines deploy oxidants to further consolidate the inflammatory response, and oxidants, in turn, play a role in mediating the action of cytokines (Deramautd et al. 2013).

Normally at this point, the inflammation starts to destroy, dilute, and segregate the virus and injured tissue but, because of the high viral load, T-lymphocytes become damaged and release more proinflammatory cytokines, all of which potentiate the inflammatory response further, upregulating oxidant production, and creating more T-cell involvement. The cycle then perpetuates itself (Deramautd et al. 2013).

The resulting local inflammation reaction may metastasize to a systemic reaction and create what's known as a *cytokine storm*. The acute increase in oxidant and cytokine production amplifies and dysregulates the inflammatory response inducing a state of oxidative distress. The result is tissue damage and injury, both by the oxidative distress and the inflammation itself (LeBaron et al. 2020).

Severe cases of CV-19 can lead to escalating cross-mediation between the inflammatory response and oxidative distress that, if left unchecked, results in an uncontrolled local and systemic inflammatory reaction. This can generate a complex of consolidating conditions: cytokine storms, sepsis, septic shock, acute respiratory distress syndrome (ARDS), multiple organ failure, and often death (Zabetakis et al. 2020; Fu et al. 2020) (see Figure 1).

(next page)

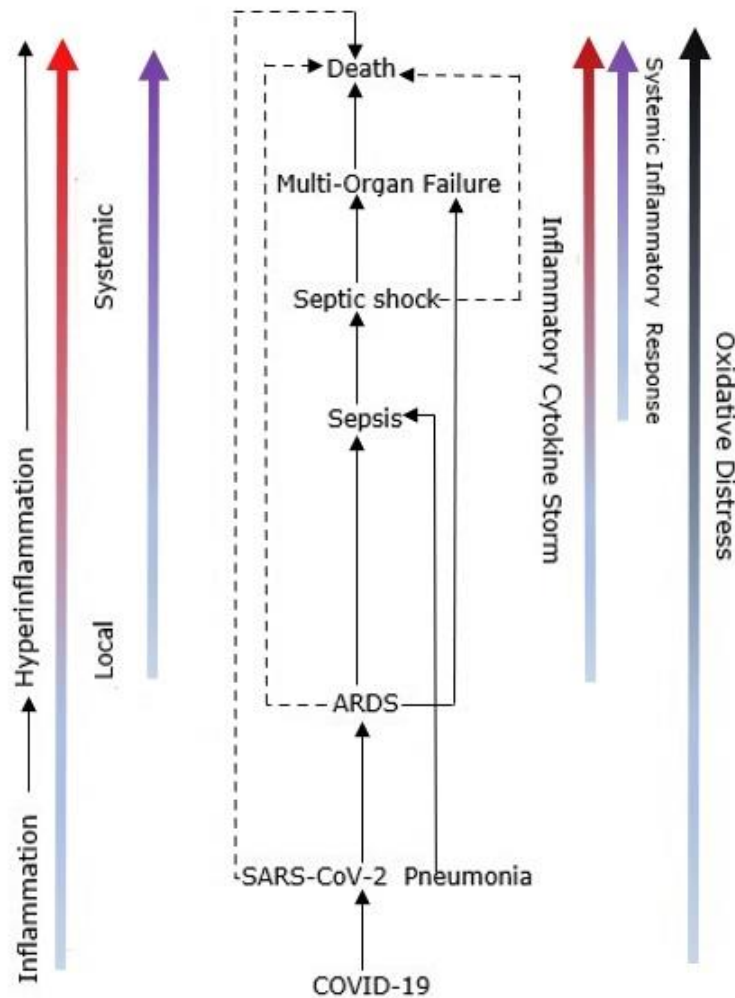


Figure 1: Oxidative Distress, the ICS, Hyperinflammation, and the Severe Complications of COVID-19

* Dashed arrows mean the connection is not subject to the conditions implied by the block arrows on either side of the figure.

** Clinical progressions of severe CV-19 do not necessarily adhere to the progression depicted in the center of the figure.

The Impact of VC on Hyper-Inflammation⁷

During oxidative distress, highly reactive oxidants are produced at a rate exceeding the rate at which antioxidant enzymes can quench them. When ascorbic acid (VC) is completely oxidized, dehydroascorbic acid is formed. If the ascorbic acid/dehydroascorbic acid (AA/DHA) ratio is kept high⁸ until DHA is reduced, the redox reaction can be recycled. Provided it is supplied in sufficient quantities, VC's ability to reduce oxidation is not rate-limited. Since VC itself is virtually nontoxic, even at very high doses, it may be given in the amounts necessary to maintain a reducing redox state in the tissue, even in conditions where highly reactive oxidants are produced at high rates, e.g., during an ICS (Hickey & Roberts 2004).

At high intakes, VC has a half-life of about 30 minutes (Hickey et al. 2005). If VC is not administered orally or intravenously, in a way that compensates for this short half-life, plasma levels decline fairly quickly. IV administrations mitigate these concerns because of direct entry into plasma and the repeated and extended nature of administration. Pharmacokinetics are important for oral administrations as plasma levels are limited by gut absorption and therefore less potent in impacting acute conditions like severe CV-19.

At any rate, unlike VC, which can be administered in virtually any quantity and rate, enzymatic antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase (Sharma 2014), are rate-limited and can't be

produced fast enough to keep up with the oxidative distress typical of a hyper-inflammatory state. The redox systems of enzymatic antioxidants, as a result, can become displaced and dysregulated.

Thus, VC administration is hypothesized to mitigate hyper-inflammation by inducing a reducing redox state in the tissue and modifying oxidant signaling so as to inhibit the dysregulation of the inflammatory response and, in turn, the potential for tissue injury (Hickey & Roberts 2004). Severe viral infections generate elevated amounts of oxidants and AA/DHA ratios of ≤ 1 . Patients experiencing a CV-19 cytokine storm are likely similarly situated (Akaike et al. 1998). AA/DHA ratios of ≤ 1 are also concomitant with acute scurvy. Accordingly, Stone (1972) defines the AA/DHA ratio as a *morbidity index*. The lower the ratio, the higher the oxidative burden, and the higher the likelihood of tissue damage.

Drs. Robert F. Cathcart and Frederick R. Klenner, whose 60 years of combined clinical experience with VC includes over 30,000 patients (ISOM, 2007; Saul 2007), determined that VC helps mitigate and/or more quickly resolve a variety of toxic and disease conditions, e.g., among others, cholera, meningitis, mononucleosis, burns, and chemical poisonings (Cathcart 1981; Klenner 1971). Because of VC's strong antioxidant effect, especially at high IV doses, they interpreted its wide spectrum of efficacy as evidence that conditions such as viral infections, allergic responses, and burns have a basis in the escalation of oxidative stress. Thus, they suggest that VC should be used more widely as a therapy - especially given its safety and low toxicity (Padayatty 2010; Cathcart 1981, 1985).

The Impact of VC on the Severe Complications of CV-19

Acute Respiratory Distress Syndrome (ARDS)

ARDS involves inflammatory injury to the alveolo-capillary membrane, the locus of gas exchange in the lungs. The result is respiratory insufficiency and hypoxemia (Badia 2012). ARDS develops most commonly as a complication of severe pneumonia (Matthay et al. 1999), e.g., SARS-CoV-2 pneumonia, though it can occur with severe sepsis as well. The mortality rate for ARDS is approximately 40% (Coperchini et al. 2020). The inflammatory injury associated with ARDS results from a cytokine storm where the uncontrolled over-production of proinflammatory cytokines attracts immune cells, e.g., WBC's, to the loci of inflammation (Coperchini et al. 2020).

VC and ARDS

Studies on the use of VC to treat ARDS, strictly defined, are confined to three case reports, Fowler et al. (2017), Kim et al. (2017), and Bharara et al. (2016). I-VC trials, however, are underway to test the impact of VC on ARDS qua severe CV-19 (Clinical trials.gov 2021). Cases are tabulated; see Table 1.

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Table 1: Adjunctive Use of VC in ARDS cases

	Patient	Admission Criteria	Mechanical Ventilation	I-VC Dosage	Other Treatment	Clinical Progression
Case 1 (Fowler et al. 2017)	20-year-old female	Diffuse bilateral opacities, dyspnea, and severe hypoxemia	Day 3: Yes, but ventilatory support failed.	Day 3-5 : 50 mg/kg every 6 hours Day 6: 25 mg/kg every 6 hours Day 7: 12.5 mg/kg every 6 hours	Day 1: Antibiotics vancomycin, piperacillin-tazobactam and levofloxacin initiated. Day 3: Due to the failure of conventional ventilatory strategies, extracorporeal membrane oxygenation (ECMO), and antibiotics were also initiated. Day 5: Furosemide initiated Day 8: 4 L/min nasal oxygen for 48 h	Day 1: Chest X-ray reveals diffuse bilateral opacities. Day 3: Chest imaging reveals dense bilateral opacities with central air bronchograms. Day 5: Chest X-ray reveals additional improvement in bilateral lung opacities. Day 6: Chest X-ray imaging reveals significant improvement in bilateral lung opacities. Day 7: ECMO and mechanical ventilation discontinued. Day 12: Patient discharged
Case 2 (Kim et al. (2017)	34-year-old male	Generalized tonic-clonic seizure followed by vomiting and aspiration of gastric contents following a morning meal	Yes, but ventilatory support failed	Day 2-5 : 50 mg/kg every 6 hours Day 6-7: 25 mg/kg every 6 hours Day 8: I-VC discontinued	Day 1: Venovenous ECMO instituted; hydromorphone and propofol infusions administered for analgesia and sedation; vancomycin and piperacillin-tazobactam administered as antibiotic therapy. Day 2: Methylprednisolone (2 mg/kg every 6 hours) initiated; furosemide infused to maintain a negative fluid balance. Day 11: Ceftriaxone was initiated	Day 1: CT reveals near-complete opacification of bilateral hemithoraces present with modest preservation of aeration of the middle lobe, lingula, and apical upper lobe segments. Day 2: Patient's lung function and lung imaging improved significantly. Day 6: Lung imaging revealed significantly less opacification. Day 7: Patient liberated from ECMO; chest imaging with anterior-posterior chest X-ray continues to reveal substantial radiographic improvement. Day 11: Repeat respiratory cultures continue to demonstrate MRSA. Day 13: Mechanical ventilation ceased. Day 19: Patient was discharged.

Table 1: Adjunctive Use of VC in ARDS cases (cont....)

	Patient	Admission Criteria	Mechanical Ventilation	I-VC Dosage	Other Treatment	Clinical Progression
Case 3 (Bharara et al. 2016)	31-year-old female	Fever, myalgia, and tachycardia complicated by Cronkhite-Canada syndrome (two admissions, AD 1 & AD 2)	AD 1/Day 3: Yes	AD 1/Day 4-5: 50 mg/kg every 6 hours	AD 1/Day 1: Four liters of intravenous volume resuscitation with 0.9% saline was administered; norepinephrine infusion was initiated and vancomycin and piperacillin/tazobactam were given. AD 1/Day 2: noninvasive positive pressure ventilation (NIPPV) was initiated	AD 1/Day 1: Patient dyspneic, hypotensive, hypoxemic, and tachycardic AD 1/Day 2: Patient experiences worsening dyspnea and hypoxemia; repeat chest imaging reveals more opacities. AD 1/Day 3: Hypoxemia and radiographic abnormalities more significant AD 1/Day 5: Chest imaging and oxygenation improve. AD 1/Day 7: Patient extubated and released
			AD 2/Day 1: Yes	AD 2/Day 4-6: 50 mg/kg every 6 hours	AD 2/Day 3: Neuromuscular paralysis (cisatracurium) required to accommodate high-pressure ventilation and ventilator desynchrony	(6 weeks post) AD 2/Day 1: Patient admitted to medical ICU and intubated for respiratory failure; oxygen deteriorates and criteria for ARDS again met. AD 2/Day 3: Oxygenation still severely depressed (PaO ₂ /FiO ₂ = 100). AD 2/Day 6: Chest imaging dramatically improves; oxygenation improves: AD 2/Day 10: Patient weaned and successfully extubated.

Sepsis

Sepsis results from a systemic inflammatory response to an infection (Gül et al. 2017) and begins early with the onset of the cytokine storm (Boomer et al. 2011). Hence the term systemic inflammatory response syndrome (SIRS). SIRS is the exaggerated response of the immune, autonomic, endocrine, and hematological systems to an irritant or stressor - be it a virus, bacterium, or equivalent (Chakraborty and Burns 2021). It is widely accepted that with sepsis, the oxidative stress produced during the inflammation response plays a role in symptoms such as general vasodilatation, hypo-responsiveness to therapeutic vasoconstrictor agents, tissue death, and multi-organ failure (Prauchner 2017).

Presence of Anascorbemia.

Of a sample of twenty-four septic shock patients admitted into the ICU, 40% of them presented with VC serum levels diagnostic of scurvy (<11.3 u/mol/l) (Carr et al. 2017). Despite receiving standard enteral and/or parenteral nutritional VC therapy (mean 125 mg/d of VC), the balance of the sample had serum levels characteristic of C-hypovitaminosis, a milder form of scurvy (< 23 u/mol/l).

Multiple organ dysfunction syndrome (MODS)

MODS is defined as “the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention” (Bone et al. 2009:1646). The cytokine storm is identified as the prime cause of MODS (Wang and Ma 2008). MODS is composed of an early and late phase, each of which is defined by a cytokine storm. The second usually marks the point of organ failure (Wang and Ma 2008).

Presence of Anascorbemia

In a cohort of 51 ICU patients admitted with mixed diagnoses (major trauma, sepsis, major neurological disease and ‘other’), early plasma VC deficiency correlated with acute kidney injury, multiple organ dysfunction, the need for increased vasopressor support, and mortality (de Grooth et al. 2014). VC deficiency (< 20 μ mol/l) and severe VC deficiency (< 11 μ mol/l) occurred, respectively, in 41 % and 14 % of patients on day 1, and in 59 % and 16 % on day 3. Severe VC deficiency was associated on day three with ensuing mortality in the ICU (OR 8.5; 95 % CI 1.4-50; $p = 0.019$). No causality between oxidative stress and antioxidant depletion was established, but severe VC deficiency appears to contribute to organ dysfunction and failure.

Mortality

The role of oxidants in mediating mortality reflects the conditions discussed above, the role of oxidants in those conditions, and their high mortality rates. **The mortality rate associated with the inflammatory cytokine storm outright is not readily isolatable.** However, the mortality rate for ARDS is approximately 40% (Coperchini et al. 2020); for septic shock (the lethal form of sepsis), 40 - 60% (Gerlach 2016); and for MODS, 44 -76% (Angus et al. 2001). Since most cytokine storm-related deaths are related to multi-organ failure, the MODS mortality rate is a suitable proxy (Wang and Ma 2008).

Treatment with I-VC

Treatment of Sepsis

In a consolidation of two meta-analyses examining the efficacy of VC in the treatment of sepsis, Li (2018), pooling a total of three studies ($n=146$), observed: 1) a significant reduction in mortality associated with the VC group (odds ratio (OR) = 0.17, 95% confidence interval (CI) 0.07–0.40; $p < 0.001$), and 2) a significant reduction in the duration of vasopressor administration in the VC group (SMD = -1.57 , 95% CI -2.03 to -1.11 ; $p < 0.001$). However, no significant reduction in length of hospital stay was observed (SMD) = -0.30 , 95% CI -0.83 to 0.23 ; $p = 0.27$.

I-VC dosing in these studies ranged from a dose of 1.5 grams/every 6 hours (Marik et al. 2017) to relative doses of 25 mg/kg every 6 hours (Zabet et al. 2016) or 50 mg/kg/day (Low VC condition) or 200 mg/kg/day (High VC condition) (Fowler et al. 2014). All patients received a diagnosis of severe sepsis or septic shock. Zabet et al. (2016) extended the condition of septic shock to require the presence of a mean arterial pressure (MAP) of > 65 mmHg (drug-treated). Only Fowler et al. (2014) and Zabet et al. (2016) were randomized, double-blind, placebo-controlled clinical trials. Marik et al. (2017) was a before-after study with a propensity score adjustment.

A more recent study by Li et al. (2020) looked at 117 subjects with sepsis. Subjects were randomly divided into a control group (CG) ($n= 56$) and VC group (VC-G) ($n=61$). In addition to standard therapy, the CG and VC-G's received, respectively, an IV of 5% dextrose (100 ml/time, two times/day) and an IV of 5% dextrose (100 ml/time, two times/day) with 3 grams of dissolved VC (100 ml/time, two times/day).

The VC-G had a significantly lower mortality rate at 28 days than the CG group, (27.93% vs. 42.97%) ($p < 0.05$), a significantly higher negative change in (SOFA)⁹ scores at 72 hrs. post-ICU admission (4.2 vs. 2.1), a significant higher procalcitonin clearance rate (PCT)¹⁰ (79.6% vs 61.3%) ($p < 0.05$), and a significant lower application of vasoactive drugs, however, (25.6 vs. 43.8) ($p < 0.05$).

Overall, evidence suggests that sepsis patients demonstrate VC plasma levels consistent with scurvy and benefit from I-VC therapy in the form of significantly lower mortality rates and SOFA scores, and significantly higher procalcitonin clearance rates.

Treatment of MODS

Two studies to date, Fowler et al. (2014) and Fowler et al. (2019), have investigated the impact of I-VC on MODS. In Fowler et al. (2014), 24 ICU patients with severe sepsis were randomized 1:1:1 to receive IV infusions every six hours for four days: Low VC: (50 mg/kg/24 h, n=8), or High VC (200 mg/kg/24 h, n = 8), or Placebo (5% dextrose/water, n = 8). Organ failure was measured using the Sequential Organ Failure Assessment (SOFA)¹¹ (Vincent et al. 1996). Scores were assessed at enrollment and at 24-, 48-, 72-, and 96-hours post.

No significant differences in SOFA scores were exhibited across groups (Placebo – 13.3 ± 2.9 , Low VC – 10.1 ± 2.0 , and High VC 10.8 ± 4.4 , NS). However, SOFA scores in both VC groups declined significantly across the 4-day study period ($p < 0.05$, slopes significantly non-zero). Compared to the placebo group, the High VC group exhibited a significantly faster decline in the regression slopes of delta daily total SOFA scores over time (-0.043 vs. 0.003 , $p < 0.01$). The placebo group exhibited a gradual *increase* in their SOFA scores. VC appeared to have an attenuating effect on the severity of SOFA scores.

In the other study, Fowler et al. (2019), 167 patients were randomized 1:1 to receive IV infusions of ascorbic acid every six hours for four days: VC: (50 mg/kg/24 h, n=84), or placebo (5% dextrose/water, n = 83). As in Fowler et al. (2014), organ failure was measured using the Sequential Organ Failure Assessment (SOFA). No significant differences were exhibited between groups in mean modified SOFA scores from baseline to 96 hours in the VC group (SOFA: 9.8 to 6.8, -3 points) and in the placebo group (SOFA: 10.3 to 6.8, -3.5 points).

Both studies employed VC infusions of 3,500 mg/24 hrs, but only Fowler et al. (2014) also included a high dosage group, 14,000 mg /24 hrs. This high dosage group was the only one to reveal a significantly quicker recovery from organ failure. This is consistent with VC's ability to quench the oxidants that index the severity of organ failure more quickly, helping resolve the condition.

Treatment of Mortality

Wang et al. (2019) performed a meta-analysis to investigate the impact of VC on mortality among critically ill adults. The analysis consolidated trials of patients with- or recovering from burn shock, sepsis, and septic shock, critical injury, post-operation recovery and trauma, and ICU patients in need of contrast-enhanced CT. The meta-analysis did not discriminate with respect to dose or the co-administration of other antioxidant agents.

The meta-analysis included 12 studies (n=1210) that used I-VC administration exclusively. The main finding was that medium IV doses (3–10 g/d) of VC were associated with a 25% reduction in mortality (OR 0.25; 95% CI (0.14–0.46); $p < 0.001$; $I^2 = 0.0\%$). In contrast, low (< 3 g/d) and high doses (≥ 10 g/d) were not, respectively (OR 1.44; 95% CI (0.79–2.61); $p = 0.234$; $I^2 = 0.0\%$ versus OR 1.12; 95% CI (0.62–2.03); $p = 0.700$; $I^2 = 0.0\%$). Why only medium doses were associated with decreased mortality is not clear. The authors suggest that the outcome may have been influenced by the timing of- and duration of therapy together with varying post-treatment intervals for recording mortality.

Together with the sepsis and MODS mortality data, this meta-analysis suggests I-VC may blunt the mortality rate associated with sepsis and MODS by limiting the degree of systemic inflammation. Overall, VC was associated with a decreased duration of both vasopressor support and mechanical ventilation. Both measures militate against the steep drops in blood pressure and organ failure characteristic of severe systemic hyperinflammation (Gül et al. 2017)

Implications for Treatment

As discussed, the inflammatory response does not escalate without the mediation of oxidants. The rapid up-regulation of the inflammation response generates a level of oxidative distress that disrupts the inflammatory response's ability to regain homeostasis, thus precipitating the inflammatory cytokine storm. The evidence presented suggests that VC helps lower the probability of the inflammatory cytokine storm and the resulting tissue injury and damage by maintaining a reducing redox state in the tissue. As such, it constitutes a promising treatment for the complications reviewed here, as initially suggested by Dr. Mao's pilot results (Cheng 2020).

However, more research needs to be performed to properly define and standardize VC's therapeutic use for severe disease. The I-VC dosages used to date vary widely and confound a clearer interpretation of the results. Cathcart's (1981) clinical experience supports calibrating I-VC dosing to the oxidative toxicity of the disease. The best proxy for such toxicity is the *morbidity index* discussed earlier, the AA/DHA ratio of reduced VC (AA) to oxidized VC (DHA).

Healthy controls have AA/DHA ratios of up to 14 (Stone 1972). Chakrabarti and Banerjee (1955) and Stone (1972) derived and tracked the AA/DHA ratios of various diseases based on the current severity of- and specific disease condition. In acute pneumonia, meningitis, and tetanus cases, they were as low as 1, which usually means death.

AA/DHA ratios rise as patients recover from disease. Standardizing dosing protocols in accordance with this measure might lead to more uniform clinical guidelines in the I-VC treatment of specific diseases. However, individual VC requirements vary considerably when healthy or ill. Ideally, the protocols will include built-in levels of freedom that track patients' biochemical individuality (Williams and Deason 1967; Pauling 1986). Clinically speaking, titrating to bowel tolerance (Cathcart 1981) has been used to make adjustments with oral dosing.

Conclusion

Given modern medical care, the absence of VC synthesis in humans brings with it a set of liabilities that, on balance, seem adequately compensated. However, the fact remains that modern medicine does not directly account for- and treat disease-induced scurvy. It is simply not standard practice to account for the possibility of scurvy in the context of acute disease or any condition defined by oxidative distress, e.g., traumatic injury or burns.

It stands to reason that medical care would be better to recognize and integrate acute induced scurvy within its treatment practices. Evolutionary medicine (EM) may be the conduit for that consideration. A better understanding of the evolutionary context of humans would likely yield a more open-minded posture with regard to the examination of VC's role in human health.

The lack of consideration of VC may reflect a failure to incorporate evolutionary medicine into medical school curricula and mainline medical practices (Balasubramanian 2019). Medical doctors, as a result, often fail to consider the role of human evolution in shaping the physiology and health of human beings. This paper may help reinforce the potential of such consideration.

At this juncture, the threat of CV-19 may well be controlled by the end of 2021. CV-19 vaccines have already been developed. Still, the early inertia at the beginning of the pandemic opened a window to the implications of the loss of VC synthesis. Given acute scurvy is a characteristic of severe disease and VC's role as a nontoxic, non-rate limited antioxidant oxidant scavenger, the evidence presented here suggests that I-VC in appropriate amounts may be effective in mitigating the hyperinflammation characteristic of the severe complications of CV-19. This potential efficacy has influenced the commissioning of 51 studies worldwide, all of which either isolate VC as a treatment option or as part of a drug or nutrient cocktail (ClinicalTrials.gov 2021).

Furthermore, through its ability to maintain a reducing redox state in the tissue, VC may prove an inexpensive therapeutic in the mitigation and treatment of a variety of other severe diseases as well. Much more than a treatment for COVID-19 hinges on the results of ongoing VC trials.

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Notes

No other studies to date have documented the administration of oral dosages in the 100+ gram range.

² (-/-) denotes mice un-supplemented with VC who have had their VC synthesizing ability removed.

³ Compared to the VC US - RDA standard, the stated dose range -though far from meeting the hypoascorbemic plasma standard described- more closely approaches it.

⁴ The minimal urinary excretion standard is problematic and, additionally, beyond the scope of the paper to address. See (Hickey et al. 2005)

⁵ Estimates of median dietary intakes of VC for adults are 102 mg/day in the United States (Institute of Medicine (US) 2000) and thus exceed the VC US - RDA.

⁶ The damage-associated molecular pattern (DAMP). In addition, the viruses are detected by the immune system by virtue of their pathogen-associated molecular pattern (PAMP) (Reinhart et al. 2012)

⁷ In the interest of length, VC's other effects on the immune system will not be covered in the review.

⁸ High as in the ratio of AA/DHA reflects a reducing redox state in the tissue, i.e., the AA/DHA ratio is ≥ 1 .

⁹ The study has concurrent bearing in the MODS section.

¹⁰ The degree of induction of PCT is a positive index of severity of systemic infection in sepsis and the extent of organ dysfunction.

¹¹ The higher the score, the higher the level of multi-organ failure.

References

- Akaike, Takaaki, Moritaka Suga, and Hitoshi Maeda.
1998. "Free Radicals in Viral Pathogenesis: Molecular Mechanisms Involving Superoxide and NO." *Proceedings of the Society for Experimental Biology and Medicine* 217: 64–73.
- Angus, Derek C., Walter T. Linde-Zwirble, Jeffrey R. Lidicker, Gilles Clermont, Joseph A. Carcillo, and Michael R. Pinsky.
2001. "Epidemiology of Severe Sepsis in the United States: Analysis of Incidence, Outcome, and Associated Costs of Care." *Critical Care Medicine* 29: 1303–10.
- Badia, Joan R.
2012. "Acute Respiratory Distress Syndrome and Acute Lung Injury." In *Encyclopedia of Intensive Care Medicine*, edited by Jean-Louis Vincent and Jesse B. Hall, 79–83. Berlin, Heidelberg: Springer Berlin Heidelberg.
- Balasubramanian, Anupama.
2019. "Does Evolutionary Medicine Have a Place in Medical Schools? |." <http://frontiersmag.wustl.edu/2019/04/08/does-evolutionary-medicine-have-a-place-in-medical-schools/>.
- Bergsten, P., G. Amitai, J. Kehrl, K. R. Dhariwal, H. G. Klein, and M. Levine.
1990. "Millimolar Concentrations of Ascorbic Acid in Purified Human Mononuclear Leukocytes. Depletion and Reaccumulation." *The Journal of Biological Chemistry* 265 (5). United States: 2584–87.
- Bharara, Amit, Catherine Grossman, Daniel Grinnan, Aamer A. Syed, Bernard J. Fisher, Christine DeWilde, Ramesh Natarajan, and Alpha A. Berry Fowler.
2016. "Intravenous Vitamin C Administered as Adjunctive Therapy for Recurrent Acute Respiratory Distress Syndrome." *Case Reports in Critical Care* 2016.
- Bone, Robert C., Robert A. Balk, Frank B. Cerra, Richard Phillip Dellinger, Alan M. Fein, William A. Knaus, Roland M. H. Schein, and William J. Sibbald.
2009. "Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992." *Chest* 136 5 Suppl: e28.
- Boomer, Jonathan S., Kathleen To, Kathy C. Chang, Osamu Takasu, Dale F. Osborne, Andrew H. Walton, Traci L. Bricker, et al.
2011. "Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure." *JAMA* 306 (23): 2594–2605.
- Camini, Fernanda Caetano, Camila Carla da Silva Caetano, Letícia Trindade Almeida, and Cintia Lopes de Brito Magalhães.
2017. "Implications of Oxidative Stress on Viral Pathogenesis." *Archives of Virology* 162 (4): 907–17.
- Carr, Anitra C., Patrice C. Rosengrave, Simone Bayer, Steve Chambers, Jan Mehrrens, and Geoff M. Shaw.
2017. "Hypovitaminosis C and Vitamin C Deficiency in Critically Ill Patients despite Recommended Enteral and Parenteral Intakes." *Critical Care* 21 (1): 300.
- Cathcart, Robert F.
1981. "Vitamin C, Titrating to Bowel Tolerance, Anascorbemia, and Acute Induced Scurvy." *Medical Hypotheses* 7 (11): 1359–76.
- _____.
1985. "Vitamin C: The Nontoxic, Nonrate-Limited, Antioxidant Free Radical Scavenger." *Medical Hypotheses* 18 1: 61–77.
- CDC.
2020a. "Coronavirus Disease 2019 (COVID-19) – Symptoms." *Centers for Disease Control and Prevention*. May 13. <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.
-

- 2020b. "Different COVID-19 Vaccines." *Centers for Disease Control and Prevention*. February 11. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html>.
- Chakrabarti, B., and Sachchidananda Banerjee.
1955. "Dehydroascorbic Acid Level in Blood of Patients Suffering from Various Infectious Diseases." *Proceedings of the Society for Experimental Biology and Medicine* 88: 581–83.
- Chakraborty, Rebanta K., and Bracken Burns.
2021. "Systemic Inflammatory Response Syndrome." In *StatPearls*. Treasure Island (FL): StatPearls Publishing.
- Chary, Michael A., Alexander F. Barbuto, Sudeh Izadmehr, Bryan D. Hayes, and Michele M. Burns.
2020. "COVID-19: Therapeutics and Their Toxicities". *Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology*, April, 1–11.
- Cheng, Richard.
2020. "Hospital Treatment of Serious and Critical COVID-19 Infection with High-Dose Vitamin C." *Cheng Integrative Health Center Blog*. March. <http://www.drwlc.com/blog/2020/03/18/hospital-treatment-of-serious-and-critical-covid-19-infection-with-high-dose-vitamin-c/>.
- ClinicalTrials.gov.
2020. "Search of: Vitamin C | Recruiting, Not yet Recruiting, Active, Not Recruiting, Enrolling by Invitation Studies | COVID-19 - Results on Map - ClinicalTrials.Gov." <https://clinicaltrials.gov/ct2/results/map/click?map.x=1261&map.y=280&term=Vitamin+C&recrs=abdf&cond=COVID-19&mapw=1345>.
-
2021. "Search of: Vitamin C | Recruiting, Not yet Recruiting, Active, Not Recruiting, Enrolling by Invitation Studies | COVID-19 - Results on Map - ClinicalTrials.Gov." <https://clinicaltrials.gov/ct2/results/map/click?map.x=1261&map.y=280&term=Vitamin+C&recrs=abdf&cond=COVID-19&mapw=1345>.
- Conney, A. H., G. A. Bray, C. Evans, and J. J. Burns.
1961. "Metabolic Interactions between L-Ascorbic Acid and Drugs." *Annals of the New York Academy of Sciences* 92 (April): 115–27.
- Coperchini, Francesca, Luca Chiovato, Laura Croce, Flavia Magri, and Mario Rotondi.
2020. "The Cytokine Storm in COVID-19: An Overview of the Involvement of the Chemokine/Chemokine-Receptor System." *Cytokine & Growth Factor Reviews* 53: 25–32.
- Council, National Research.
1962. *Nutrient Requirements of Domestic Animals, Number 10. Pub. 990*. Washington, D.C: National Academy of Sciences.
-
1972. *Nutrient Requirements of Laboratory Animals: Cat, Guinea Pig, Hamster, Monkey, Mouse, Rat: Second Revised Edition, 1972*. Washington, DC: The National Academies Press.
-
2003. *Nutrient Requirements of Nonhuman Primates: Second Revised Edition*. Washington, DC: The National Academies Press.
- Deramaudt, Therese B., Courtney D. Dill, and Marcel Bonay.
2013. "Regulation of Oxidative Stress by Nrf2 in the Pathophysiology of Infectious Diseases". *Medecine et Maladies Infectieuses* 43 3: 100–107.
- Drouin, Guy, Jean-Rémi Godin, and Benoît Pagé.
2011. "The Genetics of Vitamin C Loss in Vertebrates." *Current Genomics* 12 (5). Bentham Science Publishers Ltd: 371–78.
- Evans-Olders, Rebecca, Shaun Eintracht, and L. John Hoffer.
2010. "Metabolic Origin of Hypovitaminosis C in Acutely Hospitalized Patients." *Nutrition* 26 (11): 1070–74.
- Fortenberry, Megan, Heather Rucker, and Katelyn Gaines.
2020. "Pediatric Scurvy: How an Old Disease Is Becoming a New Problem." *The Journal of Pediatric Pharmacology and Therapeutics : JPPT : The Official Journal of PPAG* 25 (8). Pediatric Pharmacy Advocacy Group: 735–41.

- Fowler, Alpha A. Berry, Amer A. Syed, Shelley Knowlson, Robin Sculthorpe, Don E. Farthing, Christine DeWilde, Christine A. Farthing, et al.
2014. "Phase I Safety Trial of Intravenous Ascorbic Acid in Patients with Severe Sepsis." *Journal of Translational Medicine* 12: 32–32.
- , Christin Kim, Lawrence Lepler, Rajiv Malhotra, Orlando Debesa, Ramesh Natarajan, Bernard J Fisher, et al.
2017. "Intravenous Vitamin C as Adjunctive Therapy for Enterovirus/Rhinovirus Induced Acute Respiratory Distress Syndrome." *World Journal of Critical Care Medicine* 6 (1). Baishideng Publishing Group Inc: 85–90.
- , Jonathon D Truwit, R. Duncan Hite, Peter E Morris, Christine Dewilde, Anna Priday, Bernard Fisher, et al.
2019. "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." *JAMA* 322 (13). American Medical Association: 1261–70.
- Fu, Leiwen, Bingyi Wang, Tanwei Yuan, Xiao-ting Chen, Yunlong Ao, Thomas Fitzpatrick, Peiyang Li, et al.
2020. "Clinical Characteristics of Coronavirus Disease 2019 (COVID-19) in China: A Systematic Review and Meta-Analysis". *The Journal of Infection* 80: 656–65.
- Geber, Jonny, and Eileen Murphy.
2012. "Scurvy in the Great Irish Famine: Evidence of Vitamin C Deficiency from a Mid-19th Century Skeletal Population." *American Journal of Physical Anthropology* 148 (4). Wiley Subscription Services, Inc., A Wiley Company: 512–24.
- Gerlach, Herwig.
2016. "Agents to Reduce Cytokine Storm." *F1000Research* 5 (December). F1000Research: 2909–2909.
- Ginter, E.
1981. "Endogenous Ascorbic Acid Synthesis and Recommended Dietary Allowances for Vitamin C." *The American Journal of Clinical Nutrition* 34 (7): 1448–49.
- Grooth, HJS de, AME Spoelstra-de Man, and HM Oudemans-van Straaten.
2014. "Early Plasma Vitamin C Concentration, Organ Dysfunction and ICU Mortality." In *Intensive Care Medicine*, 40:S199–S199.
- Gül, Fethi, Mustafa Kemal Arslantas, İsmail Cinel, and Anand Kumar.
2017. "Changing Definitions of Sepsis." *Turkish Journal of Anaesthesiology and Reanimation* 45 3: 129–38.
- Hickey, D., H. Roberts, and R. Cathcart.
2005. "Dynamic Flow: A New Model for Ascorbate." *Journal of Orthomolecular Medicine* 20 (December).
- Hickey, Steve, and Hillary Roberts.
2004. *Ascorbate: The Science of Vitamin C*. Napa (California): Lulu Press.
- Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds.
2000. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington (DC): National Academies Press. <https://www.ncbi.nlm.nih.gov/books/NBK225483/> doi: 10.17226/9810.
- ISOM.
2007. "Robert Cathcart III: Independent Vitamin Safety Review Panel Statement." *ISOM*. <https://isom.ca/profile/robert-cathcart/>.
- Kashiouris, Markos G, Michael L'Heureux, Casey A Cable, Bernard J Fisher, Stefan W Leichtle, and Alpha A Fowler.
2020. "The Emerging Role of Vitamin C as a Treatment for Sepsis." *Nutrients* 12 (2). MDPI: 292.
- Kehrer, James P., and Lars-Oliver Klotz.
2015. "Free Radicals and Related Reactive Species as Mediators of Tissue Injury and Disease: Implications for Health." *Critical Reviews in Toxicology* 45: 765–98.
- Kim, Christin, Orlando debesa, Patricia Nicolato, Bernard Fisher, Ramesh Natarajan, and Alpha Fowler.
2017. "Vitamin C Infusion for Gastric Acid Aspiration-Induced Acute Respiratory Distress Syndrome (ARDS)" 4 (December): 33–37.

- Kim, Yejin, Hyemin Kim, Seyeon Bae, Jiwon Choi, Sun Young Lim, Naeun Lee, Joo Myung Kong, Young-II Hwang, Jae Seung Kang, and Wang Jae Lee.
2013. "Vitamin C Is an Essential Factor on the Anti-Viral Immune Responses through the Production of Interferon- γ At the Initial Stage of Influenza A Virus (H3N2) Infection." *Immune Network* 13: 70–74.
- Klenner, F. R.
1971. "Observations on the Dose and Administration of Ascorbic Acid When Employed Beyond the Range of a Vitamin in Human Pathology." *Journal of Applied Nutrition* 23 (3 & 4): 61–88.
- Lachapelle, Marc Y., and Guy Drouin.
2010. "Inactivation Dates of the Human and Guinea Pig Vitamin C Genes." *Genetica* 139: 199–207.
- Lamb, Jonathan.
2016. *Scurvy: The Disease of Discovery*. Princeton, NJ : Princeton University Press, [2016]
- LeBaron TW, McCullough ML, and Ruppman KH.
2020. "A Novel Functional Beverage for COVID-19 and Other Conditions: Hypothesis and Preliminary Data, Increased Blood Flow, and Wound Healing". *Journal of Translational Science* 6 (January).
- Li, Jing.
2018. "Evidence Is Stronger than You Think: A Meta-Analysis of Vitamin C Use in Patients with Sepsis." *Critical Care* 22.
- Li, Rong, Chao Guo, Yu Li, Zuqian Qin, and Wenjun Huang.
2020. "Therapeutic Targets and Signaling Mechanisms of Vitamin C Activity against Sepsis: A Bioinformatics Study." *Briefings in Bioinformatics*, no. bbaa079 (May).
- Li, Wei, Nobuyo N. Maeda, and Melinda A. Beck.
2006. "Vitamin C Deficiency Increases the Lung Pathology of Influenza Virus-Infected Gulo^{-/-} Mice." *The Journal of Nutrition* 136 10: 2611–16.
- Liguori, Ilaria, Gennaro Russo, Francesco Curcio, Giulia Bulli, Luisa Aran, David Della-Morte, Gaetano Gargiulo, et al.
2018. "Oxidative Stress, Aging, and Diseases." *Clinical Interventions in Aging* 13 (April). Dove Medical Press: 757–72.
- Magiorkinis, Emmanuil, Apostolos Beloukas, and Aristidis Diamantis.
2011. "Scurvy: Past, Present, and Future." *European Journal of Internal Medicine* 22 (2). Netherlands: 147–52.
- Maragakis, Lisa L.
2020. "Coronavirus Disease 2019 vs. the Flu." <https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/coronavirus-disease-2019-vs-the-flu>.
- Marik, Paul Ellis, Vikramjit Khangoora, Racquel Rivera, Michael H. Hooper, and John D. Catravas.
2017. "Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before/After Study." *Chest* 151: 1229–38.
- Matthay, Michael A., Thomas Geiser, Sadis Matalon, and Harry Ischiropoulos.
1999. "Oxidant-Mediated Lung Injury in the Acute Respiratory Distress Syndrome." *Critical Care Medicine* 27 9: 2028–30.
- Mongelli, Lorena, and Bruce Golding.
2020. "New York Hospitals Treating Coronavirus Patients with Vitamin C." March 24. <https://nypost.com/2020/03/24/new-york-hospitals-treating-coronavirus-patients-with-vitamin-c/>.
- Padayatty, Sebastian J, Andrew Y Sun, Qi Chen, Michael Graham Espey, Jeanne Drisko, and Mark Levine.
2010. "Vitamin C: Intravenous Use by Complementary and Alternative Medicine Practitioners and Adverse Effects." *PLoS One* 5 (7). Public Library of Science: e11414–e11414.
- , He Sun, Yaohui Wang, Hugh D. Riordan, Stephen M. Hewitt, Arie Katz, Robert A. Wesley, and Mark Levine.
2004. "Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use." *Annals of Internal Medicine* 140 (7): 533.
- Pauling, L.
1968. "Orthomolecular Psychiatry." *Science* 160: 265–71.

-
1970. "Evolution and the Need for Ascorbic Acid." *Proceedings of the National Academy of Sciences of the United States of America* 67 (4): 1643–48.
-
1986. *How to Live Longer and Feel Better*. New York: Avon Books.
- Pitre, Mindy C., Robert J. Stark, and Maria Carmela Gatto.
2016. "First Probable Case of Scurvy in Ancient Egypt at Nag El-Qarmila, Aswan." *International Journal of Paleopathology* 13 (June): 11–19.
- Portman, Oscar W., Manfred Alexander, and Cesar A. Maruffo.
1967. "Nutritional Control of Arterial Lipid Composition in Squirrel Monkeys: Major Ester Classes and Types of Phospholipids." *The Journal of Nutrition* 91 (1): 35–46.
- Prauchner, Carlos André.
2017. "Oxidative Stress in Sepsis: Pathophysiological Implications Justifying Antioxidant Co-Therapy." *Burns : Journal of the International Society for Burn Injuries* 43 3: 471–85.
- Reinhart, Konrad, Michael Bauer, Niels Riedemann, and Christiane S. Hartog.
2012. "New Approaches to Sepsis: Molecular Diagnostics and Biomarkers." *Clinical Microbiology Reviews* 25: 609–34.
- Rinehart, J. F., and L. Greenberg.
1956. "Vitamin B6 Deficiency in the Rhesus Monkey; with Particular Reference to the Occurrence of Atherosclerosis, Dental Caries, and Hepatic Cirrhosis." *The American Journal of Clinical Nutrition* 4 4: 318–25; discussion, 325–28.
- Rivas, C I, F A Zúñiga, A Salas-Burgos, L Mardones, V Ormazabal, and J C Vera.
2008. "Vitamin C Transporters." *Journal of Physiology and Biochemistry* 64 (4). Dordrecht: Springer Netherlands: 357–75.
- Salomon, Lothar L., and Donald W. Stubbs.
1961. "Some Aspects of the Metabolism of Ascorbic Acid in Rats*." *Annals of the New York Academy of Sciences* 92 (1): 128–40.
- Saul, Andrew W.
2007. "Hidden In Plain Sight: The Pioneering Work of Frederick Robert Klenner, M.D." *Journal of Orthomolecular Medicine* 22 (1): 31–38.
- Sharma, Neeti.
2014. "Free Radicals, Antioxidants and Disease." *Biology and Medicine* 6 (October): 2–6.
- Sies, H., and D. Jones.
2007. "Oxidative Stress*." In *Encyclopedia of Stress (Second Edition)*, edited by George Fink, 45–48. New York: Academic Press.
-
2019. "Chapter 13 - Oxidative Stress: Eustress and Distress in Redox Homeostasis". In *Stress: Physiology, Biochemistry, and Pathology* edited by George Fink, 153–63. Academic Press.
- Stone, Irwin.
1966a. "Hypoascorbemia, the Genetic Disease Causing the Human Requirement for Exogenous Ascorbic Acid." *Perspectives in Biology and Medicine* 10 (1): 133–34.
-
- 1966b. "On the Genetic Etiology of Scurvy." *Acta Geneticae Medicae et Gemellologiae* 15 4: 345–50.
-
1972. *The Healing Factor: "Vitamin C" Against Disease*. New York: Grosset & Dunlap.
-
1979. "Homo Sapiens Ascorbicus, A Biochemically Corrected Robust Human Mutant." *Medical Hypotheses* 5: 711–22.
- Valko, Marian, Dieter Leibfritz, Jan Moncol, Mark T. D. Cronin, Milan Mazur, and Joshua Telser.

2007. "Free Radicals and Antioxidants in Normal Physiological Functions and Human Disease." *The International Journal of Biochemistry & Cell Biology* 39 (1). Netherlands: 44–84.
- Vincent, Jean Louis, Rui Moreno, Jukka Takala, Sheila M. Willatts, Arnaldo de Mendonca, Hajo A. Bruining, Carmen M. Reinhart, Peter Suter, and Lambertius G. Thijs.
1996. "The SOFA (Sepsis-Related Organ Failure Assessment) Score to Describe Organ Dysfunction/Failure." *Intensive Care Medicine* 22: 707–10.
- Wang, Houli, and Sui Ma.
2008. "The Cytokine Storm and Factors Determining the Sequence and Severity of Organ Dysfunction in Multiple Organ Dysfunction Syndrome." *The American Journal of Emergency Medicine* 26 (6). United States: 711–15.
- Wang, Ying Hong, H. C. Lin, Bing-wen Lin, and Jian-dong Lin.
2019. "Effects of Different Ascorbic Acid Doses on the Mortality of Critically Ill Patients: A Meta-Analysis." *Annals of Intensive Care* 9.
- WHO.
2020. "WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 3 March 2020". <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020>.
- Williams, R., and G. Deason.
1967. "Individuality in Vitamin C Needs." *Proceedings of the National Academy of Sciences of the United States of America* 57 6: 1638–41.
-
1998. *Biochemical Individuality: The Basis for the Genetotropic Concept*. Connecticut, R.I.: Keats Publishing.
- Woolf, Steven H., Derek A. Chapman, and Jong Hyung Lee.
2021. "COVID-19 as the Leading Cause of Death in the United States." *JAMA* 325 (2): 123–24.
- Worldometer.
2021. "Coronavirus Update (Live): Worldometer." <https://www.worldometers.info/coronavirus/>.
- Wu, Jun.
2020. "Tackle the Free Radicals Damage in COVID-19". *Nitric Oxide* 102. Elsevier BV: 39–41.
- Yule, Summer, Jillian Wanik, Elizabeth M. Holm, Mary Beth Bruder, Ellen Shanley, Christina Q. Sherman, Megan Fitterman, et al.
2021. "Nutritional Deficiency Disease Secondary to ARFID Symptoms Associated with Autism and the Broad Autism Phenotype: A Qualitative Systematic Review of Case Reports and Case Series." *Journal of the Academy of Nutrition and Dietetics* 121 (3). United States: 467–92.
- Zabet, Mohadeseh Hosseini, Mostafa Mohammadi, Masoud Ramezani, and Hossein Khalili.
2016. "Effect of High-Dose Ascorbic Acid on Vasopressor's Requirement in Septic Shock." *Journal of Research in Pharmacy Practice* 5: 94–100.
- Zabetakis, Ioannis, Ronan Lordan, Catherine Norton, and Alexandros Tsoupras.
2020. "COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation". *Nutrients* 12 (5).
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