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Review

Vitamin C – an Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19

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Abstract: There are limited proven therapies for the treatment of COVID-19. Vitamin C's antioxidant, anti-inflammatory and immunomodulating effects, make it a potential therapeutic candidate, both for the prevention and amelioration of COVID-19 infection, and as an adjunctive therapy in the critical care of COVID-19, supporting anti-inflammatory treatment. This literature review focuses on vitamin C deficiency in respiratory infections including COVID-19; the mechanism of action in infectious disease and adrenal function supporting the anti-inflammatory actions of glucocorticosteroids: its role in preventing and treating colds and pneumonia and its role in treating sepsis and COVID-19. The evidence to date indicates that oral vitamin C (2-8g/d) may reduce incidence and duration of respiratory infections and intravenous vitamin C (2-24g/d) has been shown to reduce mortality, Intensive Care Unit and hospital stays, time on mechanical ventilation in severe respiratory infections. Further trials are urgently warranted. Given the favourable safety profile and low cost of vitamin C, and frequency of vitamin C deficiency in respiratory infections it may be worthwhile testing patients' vitamin C status and treating accordingly with intravenous use within ICUs and orally with doses between 2 and 8g/day in hospitalised and infected persons.

Keywords: COVID-19; SARS-CoV-2; coronavirus; vitamin C; ascorbate; colds; pneumonia; sepsis; immunonutrition; supplementation

1. Introduction

Vitamin C, ascorbic acid, is an essential water-soluble nutrient. It is synthesised in plants from fructose and in almost all animals from glucose. It is not synthesized by primates, most bats, guinea pigs, and a small number of birds and fish since the final enzyme, gulonolactone oxidase (GULO), required for ascorbic acid synthesis is missing due to genetic mutations that occurred before the evolution of humans. All these species are therefore dependent on vitamin C in their food. Primates are dependent on an adequate supply provided by fruits and vegetation intake ranging from 4.5g/d

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for gorillas[1] to 600mg/d for smaller monkeys (7.5kg – a tenth of human size)[2]. The EU Average Requirement of 90mg/d for men and 80mg/d for women to maintain a normal plasma level of 50 μmol/l [3], which is the mean plasma level in UK adults{4] is sufficient to prevent scurvy but may be inadequate when a person is under viral exposure and physiological stress. The Swiss Society of Nutrition recommend everyone supplement 200mg 'to fill the nutrient gap for the general population and especially for the adults age 65 and older. This supplement is targeted to strengthen the immune system.'[5]

2. Infection Induced Vitamin C Deficiency and COVID-19

Human serum vitamin C levels decline rapidly under conditions of physiological stress including infection, trauma, surgery and burns [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] not uncommonly resulting in overt vitamin C deficiency in hospitalised patients, defined as a serum level of vitamin C ≤11 μmol/l. A survey of elderly Scottish patients hospitalized as a consequence of acute respiratory infections reported that 35% of patients had vitamin C plasma levels ≤ 11 μmol/l [18]. One study in a hospital in Paris reported that 44% of patients had vitamin C plasma levels less than 6 μmol/l[19], and in another hospital in Paris, 17% of patients had levels ≤11 μmol/l[20] . In a Canadian university hospital, it was found that 19% of patients had vitamin C plasma levels ≤ 11 μmol/l[21]. In a study of surgical patients in Australia, it was found that 21% had vitamin C plasma levels ≤ 11 μmol/l[22]. A study of patients in New Zealand with sepsis found that 40% had vitamin C ≤11μmol/l and the majority of the patients with sepsis had hypovitaminosis C (serum level < 23 μmol/l).[23] The UK's National Diet and Nutrition Survey, based on a cross section of the UK population, reports that 4% of 65+ year olds have vitamin C levels ≤11nmol/l.[24] indicating how older people with low vitamin C status may be especially susceptible to critical infection.

A study of 21 critically ill COVID-19 patients admitted to ICU in the US found a mean level of 22μmol/l thus the majority had hypovitaminosis C. The mean level for 11 survivors was 29μmol/l compared to 15 μmol/l for the 10 non-survivors with five (50%) ≤ 11μmol/l.[25] A study in an ICU in Barcelona of 18 COVID-19 adult patients meeting acute respiratory distress syndrome (ARDS) criteria found that 17 had undetectable levels of vitamin C. One patient had a low vitamin C (14μmol/l).[26]

3. Vitamin C, COVID-19 and Pneumonia

In the early literature, scurvy was associated with pneumonia which indicates in our current understanding that vitamin C may influence respiratory infections.[27] People deficient in vitamin C may be more susceptible to severe respiratory infections such as pneumonia. A meta-analysis reported a significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes.[28] However, a prospective study of 38,378 males followed over 10 years did not associates vitamin C status with community-acquired pneumonia.[29]

Since COVID-19 pneumonia and post-mortem investigations have demonstrated a secondary organising pneumonia phenomenon [30] studies investigating vitamin C in relation to pneumonia may be relevant.

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A New Zealand study reports that their patients with pneumonia had depleted vitamin C status compared with healthy controls (23 μmol/l vs 56 μmol/l, P <0.001). The more severe patients in the ICU had vitamin C ≤11 μmol/l. The total pneumonia cohort comprised 62% with hypovitaminosis C and 22% with vitamin C ≤11μmol/l, compared with only 8% hypovitaminosis C and no cases ≤11μmol/l in the healthy controls.[31]

This wealth of data demonstrates that low vitamin C levels are common in critically ill hospitalized patients with both respiratory infections, pneumonia, sepsis and COVID-19, the most likely explanation being increased metabolic consumption.[32]

4. Mechanism of action of vitamin C in infectious disease

Vitamin C has important anti-inflammatory, immunomodulating, antioxidant, antithrombotic and antiviral properties[33] [34] [35] [36] [37] Importantly, and with specific reference to the critical phase of COVID-19, it plays a critical role in downregulating cytokines, protecting the endothelium from oxidant injury[38] and has an essential role in tissue repair.[39]

The effects of vitamin C on the immune system during infection are wide-ranging and include the development and maturation of T-lymphocytes and function of phagocytosis and chemotaxis of leucocytes [40]. It also has an important homeostatic role as an antioxidant whereby phagocytes import oxidised vitamin C (dehydroascorbic acid) and regenerate it to reduced vitamin C (L-ascorbic acid) in exchange.[41] [42] It demonstrates direct virucidal activity and augments interferon production and has effector mechanisms in both the innate and adaptive immune system.[43] [44] [45] While SARS-CoV-2 downregulates the expression of type-1 interferons (the host's primary anti-viral defence mechanism)[46] ascorbic acid upregulates these key host defence proteins[47]. In GULO knockout mice vitamin C shows in vivo anti-viral immune responses at the early time of infection, especially against influenza virus, through increased production of interferon.[48] Animal studies support a beneficial role of vitamin C in reducing the incidence and severity of bacterial and viral infections[49] including increased resistance to infection of chick embryo tracheal organ cultures to infection and protection of broiler chicks against avian coronavirus.[50] [51]

The interaction between oxidative stress and the induction of genes integral to the inflammatory response, including TNFα, IL-1, IL-8, and ICAM-1 has been demonstrated to be mediated through activation of NF-κB. [52] [53] [54] Vitamin C has been shown to lessen reactive oxidative species (ROS) and inflammation via attenuation of NF-κB activation.[55]

Although there are many potential targets for vitamin C in the process of infection, viral replication and pathology in Covid-19 disease, it is noteworthy that a key protease in the virus, Mpro, whose function is to activate several viral non-structural proteins, has been proposed as a target. In a modelling study using the crystal structure of Mpro, the active site of this enzyme was found to bind magnesium ascorbate, which had the strongest binding out of 106 nutraceuticals. The authors suggested that ascorbate might, therefore, be a powerful inhibitor of the enzyme (Kumar, V.; Jena,

M. In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19. [56]

5. Mechanism of Action of Vitamin C in Sepsis and the Adrenal Response

The critical and often fatal phase of COVID-19, primarily triggered by the host's reaction to dead virus particles, occurs with the excessive generation of potent proinflammatory cytokines and chemokines, resulting in the development of multi-organ failure.[57] This can result in neutrophil migration and accumulation within the lung interstitium and broncheoalveolar space and is considered a key determinant of progression in ARDS.[58] Neutrophil extracellular traps (NETosis) is a cell death pathway different from apoptosis and necrosis that traps and inactivates pathogens.[59] This is a maladaptive response that may contribute to tissue and organ damage leading to organ failure. Vitamin C deficiency in GULO-knockout mice showed enhanced NETosis in the lungs of septic animals and increased circulating cell-free DNA suggesting that vitamin C is a novel regulator of NETosis.[60] [61] Vitamin C significantly increases superoxide dismutase, catalase and glutathione and decreases serum TNFα and IL-1β levels in a rat ARDS model.[62] These other effects of vitamin C may be due to its epigenetic regulation of various genes ie upregulation of antioxidant proteins and downregulation of proinflammatory cytokines – rather than its direct scavenging of oxidants. Furthermore, vitamin C enhances lung epithelial barrier function in an animal model of sepsis by promoting epigenetic and transcriptional expression of protein-channels at the alveolar capillary membrane that regulate alveolar fluid clearance which include cystic fibrosis transmembrane conductance regulator, aquaporin-5, the Na+/K+-ATPase pump and epithelial sodium channel.[63]

Ascorbic acid concentrations are three to ten times higher in the adrenal glands and pituitary than in any other organ [64]. It is released from the adrenal cortex under conditions of physiological stress (ACTH stimulation), including viral exposure, raising plasma levels fivefold.[65] Vitamin C enhances cortisol production [66] and potentiates the anti-inflammatory and endothelial cytoprotective effects of glucocorticoids.[67] [68] Exogenous glucocorticoid steroids are the only proven disease-modifying treatment for COVID-19.[69] There is also increasing evidence that vitamin C, which is a pleiotropic stress hormone, may be playing a critical role in mediating the adrenocortical stress response, particularly in sepsis [30] [70], and in protecting the endothelium from oxidant injury. [36] [37] Additionally, inflammatory cytokines negatively regulate an isoform of the sodium-dependent vitamin C transporter (SVCT2) resulting in depletion of intracellular vitamin C.[71]

The postulated mechanisms for vitamin C's amelioration of COVID-19 symptoms and pathology are shown in Figure 1.

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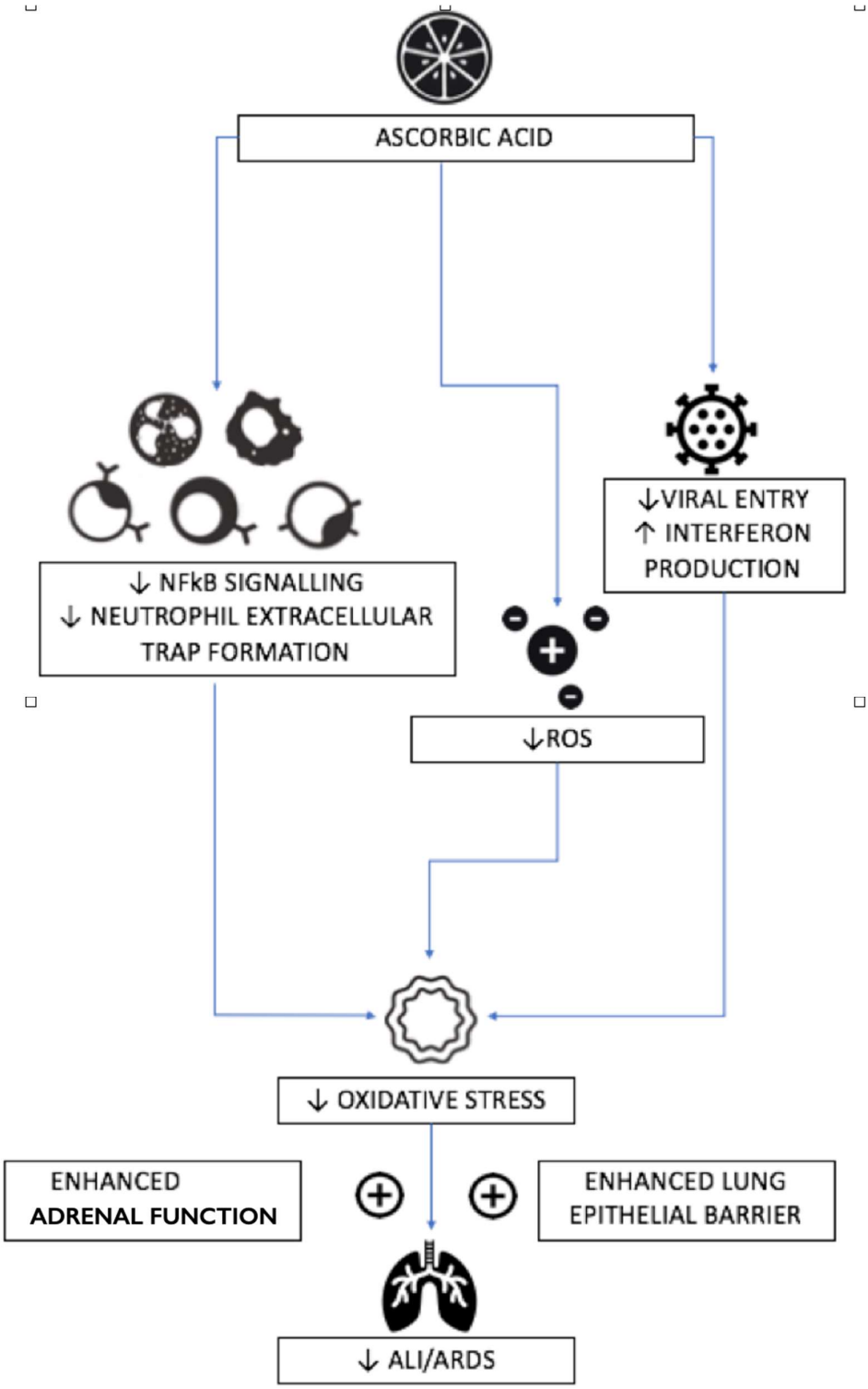

Figure 1: Postulated mechanisms for vitamin C's amelioration of COVID-19 pathology

6. Clinical Evidence for the Role of Vitamin C in Colds

Vitamin C was first synthesized in 1933. In 1951 FR Klenner investigated the effects of high doses, given intravenously, against viral diseases including pneumonia.[72] Nobel laureate, Linus Pauling

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concluded from early randomized controlled trials (RCTs) that vitamin C prevented and alleviated the common cold and as such popularised its use in the 1970s.[73] [74]

A Cochrane Review of placebo-controlled trials giving oral vitamin C for preventing and treating the common cold found that supplementation above 200mg did not reduce the incidence in the general population.[75] However, in five trials involving a total of 598 marathon runners, skiers and soldiers on subarctic exercises vitamin C reduced the incidence of colds by 52% ($P<0.0001$).[76] [77] [78] [79] [80] [81] Based on these findings, vitamin C can influence resistance to virus infections in special conditions, such as during brief periods of severe physical exercise.

Whereas trials where vitamin C has been administered only after the onset of symptoms, have not shown consistent benefits, trials which regularly administered vitamin C reduced the duration of infections in adults by 8% and in children by 14% [74] with an apparent dose-dependency up to 6-8 g/day.[82] [83] In children, 1 to 2 g/day vitamin C shortened colds by 18% with the severity of colds being reduced by regular vitamin C administration.[74]

The latest UK placebo-controlled trial best illustrates the meaningful clinical difference between the number of colds, cold duration and severity. This small trial comprised 168 volunteers who were randomized to receive a placebo or a vitamin C supplement of two 500 mg tablets daily, over a 60-day period between November and February. Compared with the placebo group, the vitamin C treatment group had fewer colds (37 vs 50, $P = 0.05$), but even fewer virally challenged 'cold' days (85 vs 178, $P=0.03$) and a shorter duration of severe symptom days (1.8 vs 3.1 days, $P = 0.03$). The number of participants who had 2 colds during their trial was significantly reduced (2/84 on vitamin C vs 16/84 in the placebo group; $P = 0.04$) [84]. This study's design does, at least, illustrate a means to report both number of colds, cold duration and severity to obtain a measure of the efficacy of vitamin C to impact on respiratory infections.

In summary, cold symptoms have been shown to be less severe and resolve more quickly with vitamin C with a dose-dependent effect. Colds, caused by over 100 different virus strains, some of which are coronaviruses, are defined by a group of symptoms similar to the majority of those who get SARS CoV-2 infection and do not convert into the acute illness phase. This similarity of symptoms and the disease-modifying effect of vitamin C across a wide range of cold-related viruses is further rationale for considering that vitamin C's effects in reducing severity and duration of infection is not virus-specific and could thus occur for SARS CoV-2 related symptoms. Each of these effects – reduced duration, severity and number of colds – could reasonably be hypothesized, in the context of SARS CoV-2, to reduce conversion from mild infection to the critical phase of COVID-19. Given the consistent effect of regular vitamin C intake on the duration and severity of colds , and the low cost and safety, it would be appropriate for patients with respiratory virus infections to have the benefits of therapeutic vitamin C assessed.

Since the disease caused by the novel coronavirus can be more severe than the ordinary virus infections, the above estimates may justify a regular increased daily intake of vitamin C for the period when the prevalence of the virus is high; when a patient suffers from a virus infection with

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active cold symptoms; in those testing PCR positive to SARS-CoV2 and in COVID-19 hospitalised patients; an oral dose of up to 6-8 g/day might be considered. Pauling's recommendation of 1 gram every hour of oral ascorbic acid during active infection. [73] has yet to be studied in a controlled trial therefore the most effective dose has yet to be determined.

7. Clinical Evidence for the Role of Vitamin C in Pneumonia

A Cochrane review on vitamin C and pneumonia identified three controlled trials that reported the number of pneumonia cases in participants who were administered oral vitamin C.[85] Each of these found a ≥80% lower incidence of pneumonia for the vitamin C group. One was an RCT, giving 2 g/day vs placebo to US Marine recruits during a two-month recruit training period and reported 1/331 cases of pneumonia in the vitamin C group vs 7/343 cases in the placebo group (P = 0.044) [86]. Another was an RCT with elderly people in the UK (mean age 81 years), who were hospitalized because of acute bronchitis or pneumonia. The study found that the plasma vitamin C level at baseline was 23 μmol/l (hypovitaminosis C) and one third of the patients had a vitamin C level of ≤11 μmol/L. [87] There was a significant difference in the effect of 0.2 g/day of vitamin C between patients who were more ill and those who were less ill when admitted to the hospital. Vitamin C reduced the respiratory symptom score in the more ill patients but not in their less ill counterparts. There were also six deaths during the study, all among the more ill participants: five in the placebo group, but only one in the vitamin C group.

The third study, in the former Soviet Union, administered two different doses, a variable high or low dose relating to the dosage of antibiotics given. [88]. The low dose vitamin C ranged from 0.25 to 0.8 g/day, and the high dose ranged from 0.5 to 1.6 g/day. The duration of hospital stay in the control group (no vitamin C supplementation) was 23.7 days. In the low dose vitamin C group the hospital stay was 19% shorter and in the high dose vitamin C group it was 36% shorter. A benefit was also reported on the normalization of chest X-ray, temperature, and erythrocyte sedimentation rate.

8. The Role of Vitamin C in Critically Ill, Septic and COVID-19 Patients

The major cause for concern regarding COVID-19 is the high frequency of ICU treatment that is needed. Meta-analyses of vitamin C supplementation in critically ill (burns, sepsis and septic shock) patients found that it may lead to vasopressor sparing effects, reduced duration of ICU stay and a reduced need for mechanical ventilation in the critically ill.[89] In six trials, orally administered vitamin C in doses of 1–3 g/day (weighted mean 2.0 g/day) reduced the length of ICU stay by 8.6% (P = 0.003). [90] In five trials including 471 patients requiring ventilation for over 10 hours, a dosage of 1–6 g/day of vitamin C shortened ventilation time on average by 25% (P <0.0001). [91]

There is clear evidence that vitamin C levels decline precipitously in critically ill patients [17], and in those with sepsis [92]. Although 0.1 g/day of vitamin C can maintain a normal plasma level in a healthy person, much higher doses (2-3 g/day) are needed to keep plasma vitamin C levels of critically ill patients within the normal range.[93] [94] Being water-soluble, and thus excreted within hours, frequency of dose is important to maintain sufficient blood levels during active infection. Limitations in bioavailability in conditions of rapid vitamin C depletion in critically unwell patients have led to the hypothesis that the required therapeutic plasma levels to optimally reduce oxidative

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stress and exert an anti-inflammatory effect, are more effectively achieved with intravenous administration than with oral administration alone.[95] [96]

Clinicians using intravenous vitamin C in severely ill COVID-19 patients have reported clinical effect giving 3 grams every 6 hours together with steroids and anti-coagulants.[97] However, clear evidence for the most effective dose and frequency has not yet been determined. A four-group randomized pharmacokinetic trial testing 2 or 10 g/day, either delivered as a twice-daily bolus infusion or continuous infusion found that the 2 g/day dose was associated with normal plasma concentrations, and the 10 g/day dose was associated with supranormal plasma concentrations, increased oxalate excretion, and metabolic alkalosis. The study's authors concluded that sustained therapy is needed to prevent hypovitaminosis. [98]

Vitamin C has been reported to reduce mortality in sepsis patients requiring vasopressor treatment randomly assigned to be given 25 mg/kg intravenous ascorbic acid every 6 hours versus placebo. Mortality at 28 days was significantly lower in the ascorbic acid than the placebo group (14.28% vs. 64.28%, respectively; P = 0.009).[99]

In the largest trial of intravenous vitamin C in ARDS associated with sepsis, the CITRIS-ALI trial, patients were given vitamin C at a dose of 50mg/kg every 6 hours for 4 days, thus providing 15g/day for a 75 kg person, or placebo. Patients in the vitamin C group did not have significantly improved markers of inflammation, vascular injury or organ dysfunction which were the primary outcomes.[100] However, there was statistically significant benefit on mortality (P = 0.03) and duration of ICU (P = 0.03) and hospital-free days (P = 0.04). Marik and Payen criticized the paper for excluding mention of the significant mortality reduction and the absence of side-effects. [101] Hemilä and Chalker pointed out that in the CITRIS-ALI trial there were only 4 clinically relevant outcomes: mortality, duration of ICU stay, hospital stay, and ventilation.[102] Vitamin C showed statistically significant benefit on 3 of the 4 and they argued that it was not reasonable to dismiss these significant effects on clinically relevant outcomes on the basis that vitamin C did not have a significant effect on less important clinical biomarkers. Furthermore, Hemilä and Chalker showed that there was statistically significant differences between the vitamin C and placebo groups over the follow-up. In the vitamin C group, during the 4-day vitamin C administration, mortality was 81% lower, but after the cessation of vitamin C administration, there was no difference between the two trial groups. By the end of the 4-day vitamin C administration, the mortality rate was 22.9% (19/83) in the placebo group and 4.8% (4/84) in the vitamin C group (P = 0.0007). This difference of 18.1 percentage points corresponds to the number needed to treat equal to 5.5. Furthermore, the study authors, in recognition of the exclusion of SOFA scores in deceased patients, reported in a post hoc analysis assigning deceased patients a SOFA score of 20 and discharged patients a SOFA score of 0, that there was a 60% probability that any random patient from the placebo group had a higher SOFA score than any random patient from the vitamin C group (P = 0.03) at 96 hours.[103] The effect of vitamin C in relation to duration of vitamin C treatment may also be a limitation of this study as studies giving vitamin C for 4 days or less have tended to be ineffective compared with those of more than 4 days.[104]

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Another trial randomized 216 patients to low-dose intravenous vitamin C (1.5g every 6 hours thus providing 7.5 g/day), thiamine, and hydrocortisone up to 10 days or until septic shock resolved, with a mean of 3.4 days, versus hydroxycortisone alone and found no effect on the primary outcome of vasopressor-free time to 7 days or on 90-day mortality.[105] Two limitations of this study are the delay in giving vitamin C [106], and the absence of a vitamin C only arm [107], hence, this study only shows that the addition of vitamin C, possibly too late in the disease process and for too short a time, to hydroxycortisone treatment added no treatment advantage.

9. Vitamin C's Relevance to COVID-19

Given the potential role of vitamin C, in oral doses of 2-8 g, to reduce duration and severity of the common cold, pneumonia, sepsis and ARDS, there is gathering interest as to whether early oral supplementation could be beneficial in preventing conversion from mild infection to more critical COVID-19 infection and, if given intravenously to those with critical COVID-19 symptoms, in reducing mortality and ICU stay, thus speeding up recovery.

One pilot RCT has been completed, three are underway, and case reports of different protocols including vitamin C have been reported, as summarized below:

In the first RCT to test the value of vitamin C in critically ill COVID-19 patients, 54 ventilated patients in Wuhan, China were treated with a placebo (sterile water) or intravenous vitamin C at a dose of 24 g/day for 7 days. [108] After the 7-day treatment period, the ratio of PaO_2/FiO_2 in the vitamin C group was 228.52 mmHg and 150.70 mmHg in the control group ($P = 0.01$), and also improved over time in the vitamin C group, but fell in the control group. On day 7 the IL-6 level was lower in the vitamin C group than in the placebo group: 19.42 vs. 158.00 ($P = 0.04$). Patients with SOFA scores ≥3 in the vitamin C group exhibited a trend for reduction in 28-day mortality: 18% vs. 50% ($P = 0.06$) in univariate survival analysis (see Figure 2b). These effects of treatment on the ratio PaO_2/FiO_2 and on IL-6 are clinically important, but further studies are needed to see if the trend in lower mortality can be confirmed. The trial was designed with 140 subjects thus was underpowered with 54 due to no new admissions..

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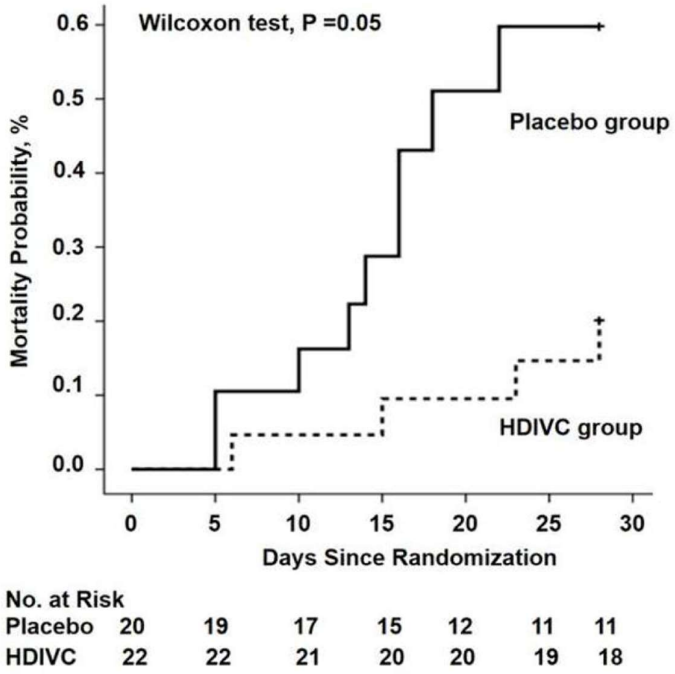

B Kaplan-Meier analysis was used to estimate the 28-day mortality and survival curves were compared with the Wilcoxon test(P=0.05) among severe COVID-19 patients (baseline SOFA score≥3). Cox regression was used as multiple comparisons (P=0.06, HR, 0.32[95%CI, 0.10-1.06]). Abbreviations:
HDIVC: high dose intravenous vitamin C; COVID-19, coronavirus disease 2019; SOFA: sequential organ failure assessment.

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Figure 2 – Figure 2b,reproduced from Zhang J et al., High-dose vitamin C infusion for the treatment of critically ill COVID-19, (ResearchSquare preprint; DOI: 10.21203/rs.3.rs-52778/v1)

A high dose (10 g/day) vitamin C cohort study is in progress in Palermo, Italy.[109]

A vitamin C arm of the REMAP-CAP study has been added giving placebo or intravenous vitamin C at a dose of 50 mg/kg every 6 hours for 16 doses, equivalent to 15 g/day for a 75 kg man, to ICU patients with COVID-19 pneumonia. The study design provides further rationale for the use of vitamin C in COVID-19 patients.[110] Also the LOVIT (Lessening Organ Dysfunction With VITamin C - COVID) trial in Canada is recruiting 800 patients who will be randomly assigned to vitamin C (intravenous, 50 mg/kg every 6 hours or placebo for 16 doses (96 hours). Daily assessments will occur for organ function, inflammation, infection, and endothelial injury biomarkers on days 1, 3, 7 and at 28 days and 6 months for mortality and HRQoL.[111] There is concern, however, that the study designs limit the use of vitamin C to four days which may be inadvisable in acutely ill patients due to potential return of symptoms if the inflammation is not resolved. This issue is illustrated by the CITRIS-ALI trial which showed marked reduction in mortality compared to placebo on day 4, final day of vitamin C administration but no significant reduction after 28 days.

In the UK the Chelsea and Westminster hospital ICU, where adult ICU patients were administered 1 g intravenous vitamin C every 12 hours, [112] together with anticoagulants, has reported 29%

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mortality [113], compared to the average 41% reported by the INARC (Intensive Care National Audit and Research Centre) for all UK ICUs.[114] While the authors have stated that the addition of an antioxidant in the form of ascorbic acid could have contributed to lower mortality it should be noted that other clinical factors and procedures could also account for the improved mortality and that the Chelsea & Westminster ICU serves a more affluent sector of the population with less deprivation on the Index of Multiple Deprivation (IMD). Deprivation, while a risk factor for COVID-19 mortality, is also a predictor of low vitamin C status. In the UK an estimated 25% of men and 16% of women in the low-income/materially deprived population are deficient with vitamin C ≥11 μmol/l.[115]

The Frontline COVID-19 Critical Care Expert Group, a group of emergency medicine experts, have reported, with the combined use of 6 g/day IVC - 1.5 g every 6 hours, plus steroids and anticoagulants, mortality[94] of 5.1% in two ICUs in the US (United Memorial Hospital in Houston, Texas and Norfolk General Hospital in Norfolk, Virginia) and posted the lowest mortality in their respective counties.[116]

A case report of 17 COVID-19 patients who received 1 g IV vitamin C every 8 hours for 3 days reported a mortality rate of 12% with 17.6% rates of intubation and mechanical ventilation and a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO_2 requirements.[117]

Other case reports of unexpected recovery following high dose intravenous vitamin C have been reported.[118]

While these case reports are subject to confounding and are not prima facie evidence of effect, they do illustrate the feasibility of using vitamin C for COVID-19 with no adverse effects reported.

10. Safety of oral and intravenous vitamin C

The US DRI, having thoroughly considered the wide literature on vitamin C and many kinds of speculated harms, stated that the safe range is up to 2 g/day[119]. The European Food Safety Authority state that the lowest observable adverse effect level is 3-4g/day (in relation to gastrointestinal effects).[120] Injectable vitamin C phials state "there are no contraindications to the administration of ascorbic acid. As much as 6 grams has been administered parenterally to normal adults without evidence of toxicity."[121]

Three concerns have been raised regarding high doses of vitamin C - namely diarrhoea, kidney stones and kidney failure in the case of intravenous vitamin C if high doses can't be cleared, and unsuitability for those with specific genetically inherited metabolic issues that affect vitamin C utilisation. The latter relates to those with glucose-6-phosphate deficiency (G6PD) and also haemochromatosis and thalassaemia due to enhanced iron absorption with vitamin C. G6PD deficiency is not considered an exclusion criterion in the use of up to 6 g/day orally or intravenously[122]. The FLCCC report that 3 g every 6 hours appears to be safe in patients with G6PD. It may be wise for those with haemochromatosis or thalassaemia to avoid high dose vitamin C taken with iron-rich foods or supplements and short-term high dose vitamin C to be medically monitored.[123]

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A survey of 9,328 patients given an average intravenous dose of 24 g of vitamin C every 4 days primarily for cancer, infection or fatigue reported 101 had side effects, mostly minor, including lethargy/fatigue in 59 patients, change in mental status in 21 patients and vein irritation/phlebitis in 6 patients.[124]

Looser bowels, or diarrhoea, rarely occurs below 3 g/day and tolerance is increased considerably when fighting a viral infection.[125] Diarrhoea has not been reported as a complication in hospital-based oral treatment and does not occur, in any event, with intravenous vitamin C administration.

Regarding kidney stone formation the Kidney Stone Research Laboratory of the University of Cape Town conducted a controlled trial in which ten volunteer subjects were required to ingest 4 g of vitamin C per day for five days. Unlike the earlier studies, they simply put a preservative in the urine collection bottles to prevent the conversion of ascorbate to oxalic acid. These were rigorously analysed for a host of independent physicochemical risk factors, all of which are regarded as powerful indicators of the risk of kidney stone formation. The results showed that these risk factors were not significantly altered. The authors concluded that ingestion of large doses of vitamin C does not increase the risk of forming kidney stones and earlier trials had faulty study design involving unpreserved urine samples.[126] A prospective cohort study of 85,557 women with no history of kidney stones, with 1078 incidence of kidney stones over 14 years reported that vitamin c was not associated with risk.[127]A systematic review of studies giving vitamin C found a correlation between ascorbic acid supplementation and the incidence of kidney stones in men, but not women,. [128] A study administering intravenous ascorbic acid in doses ranging from 0.2 to 1.5 g/kg body weight measured urinary oxalic excretion during and over 6 hours from infusion. The authors conclude that less than 0.5% of a very large intravenous dose of ascorbic acid is recovered as urinary oxalic acid in people with normal renal function. [129] A cautious position would be to exclude those with a history of kidney stones or kidney disease from high dose oral or intravenous vitamin C unless medically supervised, as is being done in the REMAP-CAP study. Short-term high dose vitamin C in the region of 2-8 g/day is unlikely to be of significant concern.

11. Conclusions

Vitamin C's potential benefits, low cost and safety profile and multiple disease-modifying actions including antioxidant, anti-inflammatory and immunomodulating effects make it an attractive therapeutic candidate in reducing viral load with oral supplementation in the range of 6-8 g/day to prevent the conversion to the critical phase of COVID-19. Likewise, vitamin C has potential benefits in treating acute respiratory infections and mitigating inflammation in critical COVID-19 patients with intravenous vitamin C infusion in the range of 6-24 g/day both for correcting disease-induced deficiency, reducing oxidative stress, enhancing interferon production and supporting the anti-inflammatory actions of glucocorticosteroids, especially given the high level of fatality for patients with COVID-19 and septic shock.

Given the remarkable safety of vitamin C, frequent deficiency among infected patients and extensive evidence of potential benefit current treatment is justified on compassionate grounds until more

COVID-19 clinical trial data becomes available, both for intravenous use within ICUs, but also orally with doses between 2 and 8 g/day in hospitalised patients due to increased need when fighting a viral infection as concluded by three recent reviews. [130] [131] [132]

People in high-risk groups for COVID-19 mortality, and at risk of vitamin C deficiency, should be encouraged to supplement with vitamin C daily to ensure vitamin C adequacy at all times, and to increase the dose when virally infected to up to 6-8 g/day [133]. Whether or not this will prevent conversion to the critical phase in COVID-19 has yet to be determined.

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