**REVIEW**

# Overview of the possible role of vitamin C in management of COVID-19

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## Abstract

The mainstay of management of coronavirus disease 2019 (COVID-19) is mainly supportive as to date there is no effective antiviral treatment, apart from remdesivir which has been approved by Food and Drug administration (FDA) for treatment of COVID-19, or vaccine. Supplementation with micronutrients, such as vitamins and minerals, has gained an increasing interest as part of the supportive management of COVID-19. Vitamin C levels in serum and leukocytes are depleted during the acute stage of infection owing to increased metabolic demands. High-dose vitamin C supplement helps to normalise both serum and leukocytes vitamin C levels. Vitamin C has multiple pharmacological characteristics, antiviral, anti-oxidant, anti-inflammatory and immunomodulatory effects, which make it a potential therapeutic option in management of COVID-19. The use of high dose of intravenous vitamin C for management of COVID-19 in China and the United Stated has shown promising results. There were no reported adverse reactions with the short-term use of high dose of vitamin C. Given the fact that vitamin C is cheap, available and safe drug with beneficial effects in management of viral infections and critically ill patients reported in previous clinical trials, it is sensible to add it to COVID-19 management protocol particularly if the current ongoing clinical trials testing the effect of vitamin C in management of COVID-19 show positive results.

**Keywords**  Vitamin C · COVID-19 · SARS-CoV-2 · Beneficial effects · Management

## Abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| FDA | Food and Drug Administration |
| ARDS | Adult respiratory distress syndrome |
| EBV | Epstein–Barr virus |
| CMV | Cytomegalovirus |
| HSV-1 | Herpes simplex virus-1 |
| HIV | Human immunodeficiency virus |
| RCT | Randomised controlled trial |
| IV | Intravenous |
| VZV | Varicella zoster virus |
| URTI | Upper respiratory tract infection |
| SOFA | Sequential organ failure assessment |
| ICU | Intensive care unit |
| AIDS | Acquired Immune Deficiency Syndrome |

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## Introduction

Since the start of coronavirus disease 2019 "COVID-19" pandemic, multiple treatment regimens have been tried under the compassionate use indications. So far, no specific antiviral drug has been proven to be effective, apart from remdesivir which showed promising results and has gained an emergency approval by Food and Drug Administration (FDA) to be used in the treatment of COVID-19 [1, 2]. That is why supportive treatment, including supplementation of micronutrients such as vitamin C, has become a crucial part in management of COVID-19. It is noticed that serum and leukocyte levels of vitamin C is depleted during the acute stage of the infection [3, 4]. Previous clinical trials found that supplementation with high dose of vitamin C decreased the severity and duration of respiratory viral infections [5]. Based on these findings, vitamin C might be used in management of COVID-19 as it might improve the immunological response against the novel coronavirus (SARS-CoV-2).

The pathological damage induced by SARS-CoV-2 infection is partially due to the direct viral virulence effect, but the main part is caused by massive host immune response and oxidative stress secondary to release of free radicals

[5]. SARS-CoV-2 infection induces excessive release of proinflammatory cytokines, leading to cytokines storm, and increases production of reactive oxygen species which both cause significant lung damage which leads to subsequent development of adult respiratory distress syndrome (ARDS) [6, 7]. ARDS can lead to further deterioration and development of septic shock which both are the common cause of intensive care unit (ICU) admission and mortality particularly in patients older than 60 years [8, 9]. There is evidence showed that vitamin C is a potent anti-oxidant and has immunomodulatory effect [10–12]. Therefore, vitamin C can be used for treatment and prevention of complications of COVID-19.

In this review, we will discuss the various pharmacological effects of vitamin C which could make it a potential option for prevention and treatment of COVID-19 (Fig. 1). In addition, we will discuss whether administration of high dose of vitamin C is safe or leads to development of adverse reactions.

## Antiviral properties of vitamin C

There is multiple evidence from in vitro studies, animal experiments and clinical trials showed that vitamin C might have an antiviral effect. It is argued that high dose of vitamin C might have a virucidal effect because it inactivated viral multiplication in vitro [13]. In fact, this effect was related to catalytic reaction to the copper-containing media and not due to virucidal activities of vitamin C [13]. This conclusion is supported by the fact that the virucidal effect of vitamin C cannot be confirmed in vivo [10]. Vitamin C decreased activation of Epstein–Barr virus (EBV) early antigen, and supressed EBV viral load [14]. Pre-treatment of human foreskin fibroblast and endothelial cells, infected with cytomegalovirus (CMV), with vitamin C in combination with antiviral drugs such as ganciclovir and foscarnet, decreased viral replication, whereas treatment of the infected cells with antiviral drugs alone did not have a significant effect on viral replication [15]. Furthermore, vitamin C, not in combination with antivirals, supressed viral replication of herpes simplex virus-1 (HSV-1), influenza type A virus, poliovirus type 1 and rhinovirus [16, 17]. In another in vitro study, a nutrient mixture, including vitamin C, had a dose-dependent suppression effect on production of influenza viral nucleoproteins and neuraminidase activity [18]. Interestingly, exposure of chick embryo tracheal organ to vitamin C increased resistance of infection to coronavirus [19]. The same observation was noticed with broiler chicks in which resistance to infection with avian coronavirus was dependent on the dose of vitamin C [20]. In an animal experiment, treatment of Gulo knockout mice, which cannot synthesise vitamin C like human, with vitamin C had an in vivo antiviral immune response against influenza virus (H3N2) by increasing the production of interferon alpha and beta [21]. In another study, treatment of monkeys infected with poliomyelitis
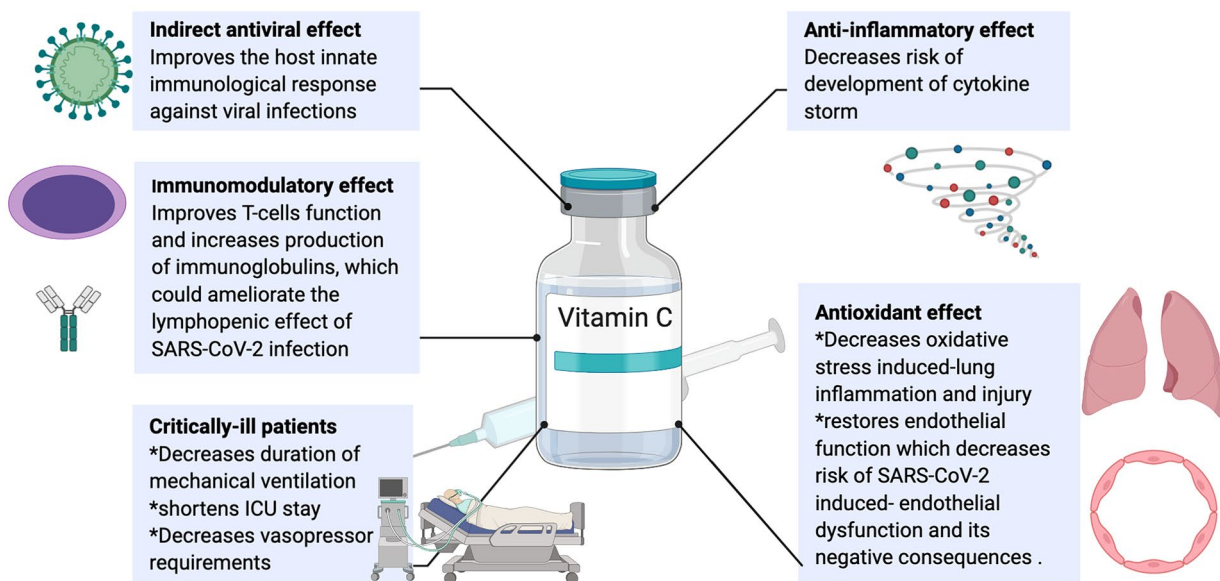


Fig. 1 The possible beneficial effects of vitamin C in management of COVID-19 (created with BioRender.com)

with vitamin C reduced the risk of paralysis and improved survival [22]. The above pre-clinical data showed that vitamin C might have an antiviral effect against both DNA and RNA viruses. However, whether vitamin C has direct effect against viral replication in vivo cannot be confirmed. Alternatively, we believe that the antiviral effect of vitamin C is secondary to improved host immune response against viral infection as shown in Gulo knockout mice experiment [21].

The beneficial antiviral effect of vitamin C has been proven in many clinical studies. Low vitamin C level has been detected in patients with post-herpetic neuralgia [23]. A randomised controlled trial (RCT) showed that treatment of patients who had post-herpetic neuralgia with three doses of intravenous (IV) vitamin C (50 mg/kg/day) on days 1, 3 and 5 improved the pain [23]. Treatment of acute varicella virus (VZV) infection in another RCT with IV vitamin C (5 g/day) on days 1, 3 and 5 had no effect on improvement of acute pain. However, it significantly decreased the incidence of post-herpetic neuralgia [24]. In a retrospective study, it was found that the concentration of vitamin C in aqueous humour in the anterior chamber of the eye increased following oral supplementation of vitamin C [25]. Moreover, prophylactic oral antiviral and vitamin C decreased the recurrence rate of herpes simplex keratitis. It is argued that regular use of vitamin C supplement reduced the duration of common cold symptoms [26]. There is a conceptual believe that 1–2 g/day of vitamin C prevents upper respiratory tract infection (URTI) [27]. As this dose cannot be obtained from diet, oral vitamin C supplement might be recommended for people at risk of respiratory tract infection. It is hypothesised that a combined oral and inhalational vitamin C supplement maintain high level of vitamin C in bronchial epithelium and respiratory secretions which could have a protective antiviral effect against influenza virus [28]. Twenty-nine meta-analyses involving 11,077 participants showed that routine prophylaxis of high dose of vitamin C in normal population did not decrease the incidence of common cold [29]. However, six RCTs showed that vitamin C supplement decreased the incidence of common cold in 642 marathon runners, soldiers and skiers by 50% [29]. The difference in the finding could be because the participants in the RCTs are exposed to more physical stress, which increases risk of infection compared with normal population, and that is why the prophylactic benefit of vitamin C has been detected in this high-risk group. An RCT showed that regular supplement of 1 g of vitamin C decreased the duration of illness but did not decrease the frequency of common cold [30]. This result was consistent with the finding of a meta-analysis which showed that oral vitamin C supplement between 500 mg and 2 g/day did not decrease the incidence of viral URTI, but shortened the duration of illness by 1.6 days in children younger than 6 years [31]. In addition, a larger number of RCTs showed that daily supplement of 1 g vitamin C and

30 mg zinc decreased the duration and severity of symptoms in common cold [29]. A meta-analysis found that vitamin C supplement of more than 0.2 g/day in adults and 1–2 g/day in children reduced duration and severity of common cold [32]. However, once the symptoms of common cold started, treatment with vitamin C did not have an effect on severity or duration of common cold [32]. In fact, when vitamin C was given in a higher dose (3 g/day), it improved the symptoms of common cold even if it was started after the onset of symptoms [33]. Furthermore, a meta-analysis of nine RCTs showed that extra-therapeutic dose of vitamin C at the onset of symptoms in addition to routine vitamin C supplement relieved common cold symptoms and decreased duration of illness [34]. Interestingly, oral and IV treatment with mega-dose of vitamin C (50–200 g/day) ameliorated symptoms in patients with Acquired Immune Deficiency Syndrome (AIDS), and reduced severity of opportunistic infections [35]. Based on the evidence from the above clinical studies, we can conclude that vitamin C might be effective in treatment of respiratory viral infections as well as other viral infections, such as HSV-1, VZV and human immunodeficiency virus (HIV), and its effect is dose dependent. The results of the studies which showed the antiviral effect of vitamin C in prevention and treatment of viral infections are summarised in Tables 1 and 2.

## Immunomodulatory effect of vitamin C

Vitamin C could have a role in improving the function of innate immunity and enhancing cellular and humoral immune response. Evidence showed that inadequate intake of micronutrients, including vitamin C, decreases resistance to infection and increases disease complications [36]. Vitamin C improves epithelial barrier integrity, which is the first line of defence against external pathogens [37]. Administration of vitamin C in high oral dose (60 mg/kg) enhanced natural killer cell activity, which play an important role in the innate immunity against viral infection [38]. Apparently, vitamin C accumulates intracellularly in neutrophils which might suggest that vitamin C has a role in maintaining the normal function of leukocytes [39]. Furthermore, it appears that leukocyte vitamin C level as well as neutrophil function decline with age [40]. Administration of 1 g/day of IV vitamin C for 6 months to asthmatic children significantly improved neutrophil chemotaxis [41]. The same effect on neutrophil chemotaxis was observed in healthy volunteers when treated with vitamin C for 3 weeks in a weekly increasing-dose regime: 1 g for the first week, 2 g for the second week and 3 g for the third week [42]. Interestingly, multiple studies showed that the effect of vitamin C on phagocytic function of neutrophil is dose dependent. Vitamin C supplement in a dose of 200 mg to 1 g daily for 1–4 months

**Table 1** Summary of the results of the studies which used vitamin C for prevention of viral infections

| References | Viral infection | Type of study | Intervention | Effect |
|---|---|---|---|---|
| Davelaar et al. [20] | Avian coronavirus | Pre-clinical (animal study) | Treatment of broiler chicks with different doses of vitamin C (ranging from 7 mg/kg to 1320 mg/kg) | Early vitamin C supplement of 300–330 mg/kg ↑↑ resistance of chicks to avian coronavirus infection |
| Kim et al. [25] | Herpes simplex | Retrospective cohort study | Oral vitamin C treatment (1000 mg twice a day) | ↓↓ recurrence rate of herpes simplex keratitis |
| Hemila et al. [32] | Common cold | Meta-analysis (based on the analysis of 29 RCT results) | Regular supplement of vitamin C (≥0.2 g/day) | No ↓↓ in incidence of common cold in normal population |
| Hemila et al. [32] | Common cold | Meta-analysis (based on the analysis of five RCT results) | Regular supplement of vitamin C (≥0.2 g/day) | ↓↓ incidence of common cold in 642 marathon runners, soldiers and skiers by 50% |
| Anderson et al. [30] | Common cold | RCT | Oral vitamin C supplement (1.0 g/day for 3–4 months) | No ↓↓ in frequency of incidence of common cold |
| Vorilhon et al. [31] | Viral URTI | Meta-analysis | Oral vitamin C supplement (500 mg to 2.0 g/day) | No ↓↓ in incidence of viral URTI in children |
| Peter et al. [57] | Viral URTI | RCT | Oral vitamin C supplement (600 mg/day) | ↓↓ incidence of URTI after ultra-marathon race |
| Hemila et al. [66] | Pneumonia | Meta-analysis (based on the analysis of three prophylactic RCT results) | Oral vitamin C supplement (dose ranging between 50 mg/day and 2.0 g/day) | ↓↓ incidence of pneumonia |

improved neutrophilic phagocytic activity [43, 44]. However, administration of 2 g of vitamin C on a daily basis for 2 weeks impaired bacterial killing activity of neutrophil [45]. In addition, vitamin C might have an anti-apoptotic effect on peripheral blood neutrophils. Treatment of post-operative septic patients with 450 mg/day of IV vitamin C for 6 days significantly reduced serum markers of neutrophil apoptosis [46]. As vitamin C improves epithelial barrier integrity, natural killer cell activity, neutrophil chemotaxis and phagocytosis, regular supplement of vitamin C could enhance the innate immune response against SARS-CoV-2 infection.

Multiple studies showed that experimentally induced vitamin C deficiency leads to impaired cellular and humoral immune response [47]. Age-related vitamin C deficiency is associated with low IgG and IgM serum levels [43]. Evidence showed that vitamin C enhances proliferation, differentiation and maturation of T lymphocytes in vitro [48, 49]. Supplementation of 1000 mg of vitamin C daily for 42 days significantly reduced free radical-induced DNA damage in peripheral blood lymphocytes [50]. Intramuscular injections of vitamin c (500 mg/day for 1 month) improved T lymphocyte proliferation and cell-mediated immunity in elderly [40]. The same finding was observed in elderly women treated with a higher dose of vitamin C and vitamin E for longer period: 1 g vitamin C daily plus 200 mg of vitamin E for 16 weeks [44]. An in vitro evidence showed that vitamin C increased production of immunoglobulins by peripheral blood lymphocytes [51]. Moreover, vitamin C supplement of 200 mg/day for 1–3 months increased IgG and IgM serum levels and improved

humoral immune response in elderly [43]. An animal study showed that vitamin C inhibited the negative immunoregulatory effect of T regulatory cells, which in turn enhanced T cell-medicated response leading to improvement of sepsis and sepsis-induced multi-organ failure [11]. Vitamin C modulates the release of various inflammatory mediators. Vitamin C supplement in mice increased release of interferon [52], which has an important role in enhancing cellular immune response against viral infection. Furthermore, vitamin C reduces the release of proinflammatory cytokines which might play a role in mitigating cytokine storm in SARS-CoV-2 infection which leads to reduction of inflammatory-induced tissue damage [53]. In an animal study, vitamin C supplement reduced lung inflammation induced by influenza A virus and proinflammatory cytokine production in Gulo knockout mice [54]. In fact, SARS-CoV-2 infection has a significant negative impact on the immune system. It leads to lymphopenia and reduced numbers of natural killer cells in addition to inducing excessive release of inflammatory mediators leading to cytokine storm and tissue damage [6, 53]. Based on the above findings, vitamin C might have the potential to ameliorate the deleterious immunological effect of SARS-CoV-2 infection which could make it a feasible treatment option in COVID-19.

## Anti-oxidant effect of vitamin C

Multiple evidence reveal that vitamin C has a potent anti-oxidant effect. It acts directly as a scavenger of oxygen-free radicals. It also helps to restore other cellular anti-oxidants

**Table 2** Summary of the results of the studies which used vitamin C for treatment of viral infections

| References | Viral infection | Type of study | Intervention | Treatment outcome |
|---|---|---|---|---|
| Jungeblut et al. [22] | Poliomyelitis | Pre-clinical (animal study) | Treatment of monkeys infected with polio-myelitis with subcutaneous injections of vitamin C (5–100 mg/day for 2 weeks) | *↓ risk of paralysis<br>*↑ survival |
| Chen et al. [23] | Post-herpetic neuralgia | RCT | Treatment with three doses of IV vitamin C (50 mg/kg/day) | Improvement of pain in patients with post-herpetic neuralgia |
| Kim et al. [24] | Acute VZV infection | RCT | Treatment with three doses of IV vitamin C (5.0 g/day) | *No improvement of acute pain<br>*↓ incidence of post-herpetic neuralgia |
| Anderson et al. [30] | Common cold | RCT | Oral vitamin C supplement (1.0 g/day for 3–4 months) | ↓ duration of illness |
| Vorilhon et al. [31] | Viral URTI | Meta-analysis | Oral vitamin C supplement (500 mg to 2.0 g/day) | ↓ duration of URTI by 1.6 days in patients <18 years |
| Hemila et al. [32] | Common cold | Meta-analysis | Oral vitamin C supplement (>0.2 g/day in adults and 1–2 g/day in children) | ↓ duration and severity of common cold if the supplement was started before onset of symptoms |
| Gorton et al. [33] | Common cold | RCT | Oral vitamin C supplement (3.0 g/day) | Prevention and improvement of common cold symptoms even if the supplement was started after the onset of symptoms |
| Ran et al. [34] | Common Cold | Meta-analysis (based on the analysis of nine RCT results) | Regular oral vitamin C supplement (≤1.0 g/day) PLUS extra-therapeutic daily dose (>1.0 g/day) started at onset of illness | *Relieve of common cold symptoms<br>*↓ duration of illness |
| Cathcart et al. [35] | AIDS | Preliminary clinical evidence | Mega-high dose of vitamin C (50–200 g/day) | *Ameliorated symptoms of AIDS<br>*↓ severity of opportunistic infections |
| Peter et al. [57] | Viral URTI | RCT | Oral vitamin C supplement (600 mg/day) | ↓ severity and duration of URTI after ultramarathon race |
| Hunt et al. [63] | Acute respiratory infections, e.g. acute bronchitis and pneumonia | RCT | Oral vitamin C supplement (200 mg/day for 4 weeks to hospitalised elderly patients) | *↓ severity of illness<br>*↓ mortality rate |
| Hemila et al. [64] | Pneumonia | RCT (findings of Kimbarowski 1967 study) | Oral vitamin C supplement (0.3 g/day) | ↓ duration of hospital stays |
| Khan et al. [65] | Pneumonia | RCT | Oral vitamin C supplement (200 mg/day) | ↓ duration of severe pneumonia in children <5 years |

such as tetrahydrobiopterin and vitamin E [10]. In addition, vitamin C potentiates the anti-oxidant effect of polyphenols, such as flavonoids [55]. Vitamin C maintains redox integrity of the cells [29], which protects lungs against oxidative stress caused by infection and inflammation [56]. Vitamin C supplement of 600 mg daily reduced incidence, severity and duration of URTI after ultramarathon race [57]. This might indicate that vitamin C decreases oxidative stress during strenuous physical activity through its anti-oxidant effect, which results in improved immunity. In another experiment, a single injection of paraquat (a herbicide) induced lung fibrosis in male mice by increasing the oxidative stress. Treatment of paraquat-induced lung fibrosis by vitamin C was beneficial, which was evident by detecting elevated levels of superoxide dismutase and catalase, natural anti-oxidant enzymes, in bronchoalveolar lavage fluid following treatment with vitamin C [58]. In fact, proinflammatory and pro-oxidant states are the main pathological processes which leads to development of ARDS [59]. Moreover, evidence from an animal study showed that anti-oxidants reduced viral-induced lung inflammation and injury [60]. Therefore, vitamin C could be a potential option in treatment of pneumonia, prevention and treatment of ARDS in patients with COVID-19. However, doctors using high doses of vitamin C in treatment of COVID-19-related pneumonia and ARDS should remain vigilant as high concentrations of vitamin C can have a pro-oxidant effect [12].

## The role of vitamin C in prevention and treatment of pneumonia

Vitamin C deficiency has been detected in association with pneumonia [61]. In fact, vitamin C body store is depleted in patients with acute presentation of chest infection because of oxidative stress and increased physiological demand [62]. Therefore, vitamin C supplements might be required during the acute stage of infection to restore normal vitamin C levels. An RCT showed that supplementation of 200 mg/day of oral vitamin C for 4 weeks to hospitalised elderly patients with acute respiratory infections, e.g. acute bronchitis and pneumonia, improved the clinical outcome (reduced severity of illness and lowered mortality rate) [63]. The significant clinical improvement was noticed amongst the more severely ill patients [63]. Vitamin C supplements decreased duration of hospital stay in patients with pneumonia. The duration of hospital stay was shorter in patients receiving higher doses of vitamin C [64]. Treatment of children younger than 5 years diagnosed with pneumonia by 200 mg of vitamin C once daily decreased duration of severe pneumonia. This was evident by a statistically significant quicker improvement in oxygen saturation and tachypnoea by 1 and 4 days, respectively in patients treated with vitamin C compared

with placebo group [65]. It is argued that vitamin C has a role in prevention of pneumonia. Vitamin C and zinc supplements decreased incidence and improved outcome of pneumonia particularly in children [29]. In addition, results from three clinical trials showed that prophylactic supplements of vitamin C decreased incidence of pneumonia [66]. Based on the above evidence, we can conclude that vitamin C might be effective in prevention and treatment of COVID-19-related pneumonia.

## The role of vitamin C in management of ARDS, sepsis, septic shock and critically ill patients

Vitamin C deficiency is commonly seen in patients with sepsis [67]. Furthermore, patients with septic shock have significantly depleted vitamin C levels compared with non-septic patients [68]. In fact, there is an inverse correlation between serum level of vitamin C in early sepsis and measures of multi-organ dysfunction [67]. In addition, vitamin C deficiency in critically ill patients is associated with increased vasopressor requirements, multi-organ failure and increased mortality [69]. Vitamin C has an anti-sepsis effect by reducing inflammatory response and oxidative stress as well as suppressing immunological dysfunction, which are the main pathophysiological mechanisms of sepsis [70]. Pre-clinical evidence showed that vitamin C supresses excessive cytokine release leading to sepsis-induced organ dysfunction [67]. Sepsis leads to cellular immunosuppression. Treatment of mice with high dose (200 mg/kg) of IV vitamin C inhibited the negative immunoregulatory effect of T regulatory cells, which in turn enhanced T cell-mediated cellular immune response, and resulted in improvement of sepsis and sepsis-induced multi-organ dysfunction syndrome [11]. Therefore, vitamin C could be beneficial as a supportive treatment of sepsis and septic shock, which are common complications associated with COVID-19.

In phase I RCT, 24 patients with severe sepsis were treated with high doses of IV vitamin C (50–200 mg/kg/24 h) for 4 days. Following the treatment, there was a reduction in sequential organ failure assessment (SOFA) score, a significant reduction in proinflammatory biomarkers (C-reactive protein and procalcitonin), and no significant rise in thrombomodulin which indicates less vascular injury [71]. In case of sepsis-induced ARDS, high-dose vitamin C treatment did not improve the clinical outcome. In a clinical trial, patients with sepsis-related ARDS requiring invasive mechanical ventilation received vitamin B1 (200 mg/day) and vitamin C (2 g/day). The median duration of the treatment was 6 days. This regime did not improve mortality, and did not reduce the number of ventilator and intensive care unit (ICU)-free days [72]. In a multi-centre RCT, patients

with sepsis and ARDS with less than 24-h onset treated with 50 mg/kg/6 h of IV vitamin C for 96 h. There was no change in multi-organ failure score after the treatment. Furthermore, there were no improvement neither in markers of inflammation (C-reactive protein) nor in markers of vascular injury (thrombomodulin). However, the mortality rate was significantly less in patients treated with high dose of IV vitamin C compared with placebo group [73]. Plasma cell-free DNA level was significantly lower after 48 h following treatment with high dose of IV vitamin C compared with placebo [74]. Apparently, high level of plasma cell-free DNA is associated with increased mortality in critically ill patients [74]. The significant improvement in mortality rate could be explained with the higher dose of vitamin C treatment used in the multi-centre RCT [73] compared with the other clinical trial [72]. A case report showed that treatment of 20-year-old patient presented with viral-induced ARDS with IV vitamin C (200 mg/kg/24 h) in addition to ventilatory support resulted in rapid resolution of acute lung injury without long-term sequelae of ARDS, such as lung fibrosis [75]. The improvement in the clinical outcome in this case is most likely because of the young age of the patient and the absence of severe sepsis.

In a clinical trial, treatment of septic shock patients with high dose of IV vitamin C decreased vasopressor requirements and improved mortality [76]. Vitamin C is a cofactor for endogenous synthesis of catecholamines and adrenal steroid hormones, and this explains the reduced vasopressor requirements in patients with septic shock treated with high dose of vitamin C [77]. In another RCT, early treatment of septic shock with IV vitamin C 1.5 g/6 h reduced vasopressor requirements, shortened the duration of ICU stay, but unlike the previous study, did not improve mortality [78]. The combination of vitamin C with hydrocortisone and thiamine (HAT therapy) decreased morbidity and mortality in patients with severe pneumonia, sepsis and septic shock [79, 80]. In the VITAMINS Randomized Clinical Trial, the combination of hydrocortisone, thiamine and IV vitamin C (HAT therapy) 1.5 g/6 h did not lead to rapid improvement in septic shock compared with hydrocortisone alone [81]. This might indicate that HAT therapy is not superior to hydrocortisone alone in management of septic shock. However, the slight delay in the time-to-intervention of more than 30 h (after the onset of septic shock) could have an influence on the results of the study.

Vitamin C could play an important role in supportive management of critically ill patient. In fact, anti-oxidant treatment with vitamins C and E decreased duration of mechanical ventilation and shorten the length of ICU stay in critically ill surgical patients [82]. Meta-analysis showed that vitamin C as an adjuvant treatment shortened the duration of mechanical ventilation and ICU stay in non-surgical critically ill patients [83, 84]. Although an individual study

showed that treatment of septic patients requiring mechanical ventilation with IV vitamin C (6 g/day) did not improve mortality rate [85], a meta-analysis which enrolled 1210 patients from different clinical trials showed that treatment of critically ill patients with a dose ranging between 3 and 10 g/day of IV vitamin C decreased mortality rate [86]. In conclusion, all the above observations support the idea of using high dose of IV vitamin C as a part of the supportive management of severe COVID-19.

## The beneficial effect of vitamin C in management of COVID-19

The use of IV vitamin C for treatment of COVID-19 in China has shown promising results. Administration of high dose of IV vitamin C reduced the risk of development of cytokine storm during the late stage of COVID-19 infection [12]. Evidence showed that nutritional support might have a role in management of COVID-19 [87]. Vitamin C in combination with curcumin and glycyrrhizic acid (VCG plus regime) promoted innate antiviral immunological response and prevented excessive inflammatory response which decreased the risk of inflammation-induced tissue damage [88]. A non-hospitalised patient with COVID-19 received a traditional Chinese medicine with a steroid-like effect called diammonium glycyrrhizinate in combination with vitamin C [89]. This regime resulted in significant relieve of the patient's symptoms. As vitamin C potentiates the pharmacological effect of flavonoid [55], the combined use of vitamin C and Quercetin (a flavonoid drug) could have a synergistic antiviral effect [90]. Having said that, there is a suggestion that vitamin C and Quercetin can be used as an adjunctive treatment to other promising drugs, such as remdesivir, in management of COVID-19 [90]. Burn injury causes oxidative stress and generation of free radicals which lead to endothelial damage and increased capillary permeability [91]. The use of vitamin C in management of burn patients helped to restore endothelial function (possibly through its potent anti-oxidant effect) and decreased resuscitative IV fluid requirements [91]. Severe SARS-CoV-2 infection leads to endothelial damage and dysfunction which consequently increases the risk of development of widespread micro- and macrovascular thrombosis and multi-organ failure [92]. As vitamin C has the ability to restore endothelial function, it might help to reduce the risk of development of this complication if used early in the course of management of COVID-19. Treatment with IV vitamin C, as a monotherapy, might help to reduce lung inflammation and lung injury in COVID-19 [93]. An expert group on clinical treatment of COVID-19 in Shanghai advised that high dose of IV vitamin C is recommended to prevent cytokine storm in patients with mild or general symptoms

of COVID-19 [94]. In fact, the use of high dose of IV vitamin C has been implemented in Chinese hospitals to treat hospitalised patients with COVID-19 [95]. Physicians in China stated that they have successfully treated 50 patients with moderate-to-severe COVID-19 with high dose of IV vitamin C: 10 g daily for moderate cases, and 20 g daily for severe case for 7–10 days. This treatment improved the clinical outcome. Compared with untreated group, this treatment regime shortened the duration of hospital stay by 3–5 days, and there was no mortality reported in the treatment group [96]. A pulmonary and critical care physician in the United States stated that he treated COVID-19 patients admitted to his ICU with high dose of IV vitamin C (1500 mg, 4 times a day). A significant improvement was noticed compared with patients who did not receive IV vitamin C treatment [26]. Cheng et al. recommended early administration of high dose of vitamin C for treatment of COVID-19 pneumonia [97]. There is an ongoing clinical trial registered on clinicaltrials.gov website (NCT04264533) testing the effect of using mega high dose of IV vitamin C (24 g/day for 1 week) in treatment of severe COVID-19-related pneumonia. The study will be completed by the end of September 2020. There are few other trials still in the recruitment stage registered on clinicaltrials.gov testing the effect of high dose of vitamin C for treatment of hypoxic COVID-19 patients (NCT04357782), treatment of sepsis of any cause, including COVID-19 (NCT03680274) and prevention of acute lung injury in COVID-19 (NCT04344184). Another registered trial with the reference number (NCT04342728) is testing the effect of vitamin C and zinc supplement in improving symptoms in patients with mild COVID-19. Based on the above evidence, vitamin C seems to have a role in treatment of COVID-19 in both inpatient and outpatient settings, leading to a beneficial effect in patients with mild symptoms, as well as patients with severe pneumonia, sepsis and ARDS. Therefore, we recommend to add vitamin C to the national treatment guidelines of COVID-19 particularly if the ongoing double-blinded RCTs provide promising results.

## The safety profile of vitamin C

The recommended daily allowance of vitamin C for adults is 90 mg/day [98]. During acute infection, a higher dose of vitamin C is required to meet the increased metabolic demand. According to the United States nutritional recommendation, the tolerable upper limit of the daily dose of vitamin C is 2 g [99]. Doses higher than 2 g/day can cause diarrhoea, abdominal pain and nausea, which are self-limited once the dose is reduced [99, 100]. There is a concern that high dose of vitamin C (10 g/day) could lead to a supraphysiological level of vitamin C which causes oxaluria and increases the risk of oxalate nephropathy and oxalate

kidney stone [101, 102]. In a randomised, crossover, controlled study, vitamin C supplement of 1000 mg twice a day increased urinary oxalate in 40% of the participants, which in turn increases the risk of oxalate kidney stone [103]. Interestingly, in sepsis clinical trials, no series adverse effects, including kidney stones, have been reported to date [104]. This can be explained by the fact that vitamin C is water soluble, therefore, intoxication due to excessive intake of vitamin C is unlikely as the concentration of vitamin C which exceeds the body daily requirement will be excreted by the kidneys [47].

Treatment with high dose of vitamin C might interfere with the accuracy of the glucometer measurement of blood glucose level, as both vitamin C and Glucose have similar molecular structure, which could lead to false high blood glucose readings, and the diagnosis of clinically significant hypoglycaemia can be easily missed [105, 106]. Therefore, clinicians should rely on laboratory blood samples or venous blood gases for measurement of blood glucose in patients treated with high dose of vitamin C to avoid missing the diagnosis of hypoglycaemia or increasing the risk of hypoglycaemia caused by unnecessary insulin treatment based on inaccurate glucometer readings [104]. A dose adjustment of vitamin C might be required in patients with renal impairment [107]. Therefore, high-dose vitamin C should be used with caution as impaired renal excretion of vitamin C might increase risk of vitamin toxicity. Moreover, treatment with high dose of vitamin C should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency as it can lead to acute haemolysis [108]. In summary, the side effects of high dose of vitamin C for short-term use are almost negligible [107]. Therefore, the benefit of using high dose of vitamin C as part of the supportive management of COVID-19 hugely outweighs the risk of development of adverse reactions.

## Conclusion

The mainstay of the management of COVID-19 at present is supportive. An important part of the supportive management is a nutritional support, and this includes micronutrient supplement including vitamin C. Vitamin C might have an antiviral effect against multiple respiratory viruses in addition to other DNA and RNA viruses, such as HSV-1, EBV and HIV. This effect is most likely secondary to enhanced immunological response against viral infections rather than a direct effect against viral replication. Vitamin C has potent anti-oxidant and anti-inflammatory effects which reduce the chance of oxidative stress-related tissue damage and suppress excessive inflammatory response, known as cytokine storm. Vitamin C improves the host antiviral immune response by increasing the production of interferon and

stimulating proliferation of lymphocytes. In previous clinical trials, vitamin C improved survival, decreased vasopressor requirements and shortened the length of ICU stay in critically ill patients and patients with severe sepsis and septic shock. Interestingly, treating COVID-19 patients with high dose of IV vitamin C in China and the United States have shown promising results. In addition, there were no reported adverse effects with short-term use of high dose of vitamin C. Therefore, given the pharmacological characteristics of vitamin C and its safe profile on high doses, we suggest to add vitamin C to the treatment protocol of COVID-19 particularly if the ongoing RCTs which are registered on clinicaltrials.gov provide positive results in the near future.

## Compliance with ethical standards

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