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VITAMIN C IN TERMS OF COVID-19, CURRENT TRENDS

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Abstract: The role of vitamin C in the prevention and treatment of pneumonia andsepsis has been investigated for past decades. This reviewaimsto translatethese findings into patients with severe coronavirus disease (COVID-19). It has indicatedthat patients with pneumonia and sepsis have low vitamin C status and elevated oxidative stress.Additional oral or intravenous (IV) vitamin C administered patients with pneumonia can mitigate the severity and course ofthe disease. Severely ill patients with sepsis need for intravenous administration of amounts counted in grams ofthe vitamin to achieve adequate plasma levels, an intervention that some studies suggest reduces mortality.The vitamin has physiological functions like pleiotropic, many of which are closely connected to COVID-19.These are its antioxidant, anti-inflammatory, antithrombotic and immunomodulatory functions.Previous observational studies found out low vitamin C status in critically ill patients with COVID-19.A number of randomized controlled trials (RCTs) conductedworldwideevaluate intravenous vitamin C as monotherapy in patients with COVID-19. Optimization of the intervention protocolsin future trials, e.g., earlier and continuously administration, is justified to potentially improve itsefficacy. In order to the excellent safety profile, low cost, and potential for rapid enlargement of production,administration of vitamin C to patients, especially with hypovitaminosis C and severe respiratory infections,e.g., COVID-19, appears warranted. In addition, there are few new ways of concurrent using vitamin C and other manipulations or medications.

Keywords:COVID-19; Vitamin C; pneumonia; sepsis; acute respiratorydistress syndrome; randomized controlled trials;SARS-CoV-2.

Since late 2019, the world had faced a major public healthchallenge against the novel coronavirus disease termed COVID-19 caused by the severe acute respiratorysyndrome coronavirus 2 (SARS-CoV-2) [1]. As of November 14th, there are over fifty-five million confirmed cases of COVID-19 and more than1300,000 deaths globally [2].The first known case of COVID-19 hadroots in the city ofWuhan in Hubei Province, China. From there, it has spread to every inhabited continentworldwide.

Vitamin C (ascorbic acid) is a water-soluble vitamin, which has been partof cultural practice consuming when suffering with a cold or flu for almost half of a century. This began after research publishedby Nobel prize winner Linus Pauling (1970) theorizing how vitamin C aids to treat colds [3, 25].An analysis of 29 studies including 11,306 participants concluded that supplementing with 200 mg ormore of vitamin C does not minimize the risk of contracting a cold [4,5]. Despite this, regular vitamin Csupplements had several advantages, including:

- Reduced cold severity: They reduced the manifestations of a cold, making it less severe.

- Reduced cold duration: Supplements contracted the recovery time by 8% in adults and 14% inchildren, on average [5, 37].

Vitamin C provides various pharmacologicalactivities to the human body: immunemodulatingactivity, anti-oxidants activity, antimicrobialactivity, anti-viral activity, anti-parasiticactivity, anti-fungal activity, etc. [6].

For decades, it has been known that patients with greater gravity of illness, including those with sepsis and multiple organ failure, have dramatically low vitamin C status. Moreover, these critically ill patients have higher requirements for vitamin C, withdoses counted in gramsnecessaryfor normalizing their blood levels, 20–30 times more than is required for the average population. However, critically ill patients with sepsis continue to be administered amounts of vitamin C measured in milligrams,which is insufficient to replete their vitamin C level [7].

Administration of vitamin C in advanced stage of the disease process, e.g., when acute respiratory distress syndrome (ARDS) has developed,probably mitigates its effectiveness. Clinical trials conducted earlier have indicated that vitamin Cadministered to patients with pneumonia can improve the severity of the respiratory symptoms, notably of themost gravity ill patients, and the duration of hospital stay. Thus, administration of vitamin Cas early as possible in the respiratory infection process may prevent its progression to severe stage (sepsis) [7-9].Neutrophilextracellular traps or NETosis is a cell death pathway different from necrosis andapoptosis that trapsand kills pathogens. An excessive NETosis response is a maladaptive response that causes totissue damage, organ injury, and leads to multi-organ failure (MOF) [8].There is evidence to suggest that vitamin C is anovel regulator of this process [10].

Vitamin C reduces therelease of proinflammatory cytokines which possibly play a rolein improving cytokine stormin SARS-CoV-2 infection whichleads to lessen of tissue damage due to inflammatory-induction[12].In fact,SARS-CoV-2 infection has a notably impact on theimmune system. It leads to lymphopenia and reduced numbersof natural killer cells concurrently inducing immoderate releaseof inflammatory mediators leading to cytokine storm and tissuedamage [7-11]. According on the findingsabove, vitamin Cmight have the possible way to ameliorate the deleterious effect on one's immunityduring SARS-CoV-2 infection which could makeit a useful treatment option in COVID-19.

Numerous evidencesdiscover that vitamin C has a potent antioxidanteffect. It acts right as a scavenger of oxygen-freeradicals [32]. Moreover, it helps to save other cellular anti-oxidantssuch as tetrahydrobiopterin and vitamin E. Vitamin C carries redox integrityof the cells, which staves off lungs against oxidativestress due to infection and inflammation [9].Indeed, proinflammatory andpro-oxidant states are the main destructive processes whichleads to development of ARDS. Therefore,vitamin C might be a potential option in resolving of pneumonia,prevention and treatment of ARDS in patients withCOVID-19 [30, 32]. Despite it,

doctors administering high doses of vitaminC in treatment of COVID-19-related pneumonia and ARDSshould keep careful watch for possible danger or difficulties as high doses of vitamin Ccan have a pro-oxidant effect [12, 29, 31]. Another possible disadvantage is stone forming. Khusid, J. A. et all. [36] informed vitamin C supplementation at doses>1000 mg/d should be used with caution, especially inmen, and patients should be monitored with 24-h urinestudies for hyperoxaluria. Therefore, RCTs on the benefitsof vitamins C for COVID-19 and potential sequelae of its use for this indication, such as nephrolithiasis, arecritically needed.

Some authorshave point of view as vitamin C could potentially worsening one's condition. The reason is vitamin C increases the body'sability to absorb more Fe2+ from food and convert itto the blood. And excessive Fe level is considered as one of the most harmful factors to one's body [41].Vitamin C supplements might be recommended in the course of the acute stage of infection for restoringadequate vitamin Ccontents [13, 42]. This is because it is noticed vitamin C deficiency in association withpneumonia [40]. In fact, vitamin C levels is depleted in people with acute presentation of chest infection due to oxidative stress and elevated physiological demand [14].Vitamin C and zinc supplementsdecreased incidence and enhanced outcome ofpneumonia more remarkably in children [4]. On the top of that, findingsfrom three clinical trials provided that prophylactic supplementsof vitamin C decreased incidence of pneumonia [15, 26, 35].Based on the above facts, vitaminC could have a significant place in prevention and treatment of COVID-19-related pneumonia.

The burden of sepsis is growing worldwide. 8 million global deaths each year is due to it. At the present time, treatment options are limited to antimicrobials and supportive cure such as IV fluids, vasopressors, mechanical ventilation, and renal replacement therapy. In the shortage of successful in producing a desired result therapies specifically aiming the dysregulated immune response, prolonged utilizing of these life-sustaining therapies can lead to really hard times. A growing foundation of evidence suggesting that vitamin C, a cheap and widely available intervention, is potentially beneficial in sepsis. IV vitamin C may be initial therapy to attenuate the dysregulated chain of events that leads to sepsis. As it was noticed above, vitamin C deficiency is common in significantly ill patients, sepsis is not an exclusion. On top of that, patients with septic shock have notably lowered vitamin C levels in comparison with nonseptic patients [16]. Indeed, there is an inverse correlation between serum vitamin C level in beginning of a sepsis and measures of multi-organ dysfunction [33]. Vitamin C deficiency in critically ill patients is associated with enlarged vasopressor needs, multi-organ failure and more mortality [25]. Vitamin C has an anti-sepsis action by inhibiting inflammatory reaction and oxidative stress as well as reducing immunological dysfunction, which are the ground pathophysiological mechanisms of sepsis [17, 28].Once proven effective, vitamin C could be used widely and significantly change outcomes in high- and low-income settings alike.

Administering of IV vitamin C for treatment of COVID-19 inChina has provided promising outcomes. Using of highdose of IV vitamin C decreased the risk of appearing ofcytokine storm within the course of the late stage of COVID-19 infection[12, 25, 28]. Facts showed that nutritional support could have a role in cure of COVID-19 [34, 43]. Vitamin Cin concurrent with curcumin and glycyrrhizic acid (VCGplus regime) stimulated innate antiviral immunologicalreaction and prevented excessive inflammatory reactionwhich reduced the risk of inflammation-induced tissuedamage.A non-hospitalized patient with COVID-19received a traditional Chinese medicine with a steroid-likeeffect called diammonium glycyrrhizinate in

couplewith vitamin C [18]. This administration resulted in significantreduction of the patient's symptoms. As vitamin C potentiatesthe pharmacological effect of flavonoid, the concurrentuse of vitamin C and Quercetin (a flavonoid drug) mighthave a synergistic antiviral effect [19, 38, 42]. In other words,there is a suggestion that vitamin C and Quercetin can beused as an additional treatment to other promising drugs,such as remdesivir, in cure of COVID-19 [18]. Burninjury causes oxidative stress and generation of free radicalswhich cause of endothelial damage and elevated capillarypermeability. Vitamin C administration in management ofburn patients helped to renew endothelial function (ratherthrough its potent anti-oxidant effect) and mitigatedresuscitative IV fluid requirements [27]. Severe SARSCoV-2 infection leads to endothelial damage and dysfunctionwhich, as a result, elevates the risk of development ofwidespread micro- and macrovascular thrombosis and multiorganfailure [44]. As vitamin C has the ability to renewendothelial function, it could help to decrease the risk ofappearance of this complication if used early duringcure of COVID-19. Treatment with IV vitaminC, as a monotherapy, might help to diminish lung inflammationand lung injury in COVID-19 [20, 25, 26].All the statements given above support idea of using high dose of IV vitamin C as a part of the supportive cure of severe COVID-19.

Accuracy of the glucometer measurement of blood glucose level might be interfered with high dose of vitamin C treatment, the reason is vitamin C and Glucose have comparable molecular structure, which could result in false high blood glucose readings, and the diagnosis of clinically significant hypoglycemia can be easily missed [21, 22]. Therefore, clinicians should rely on laboratory blood samples or venous blood gases for measurement of blood glucose in patients treated with excessive dose of vitamin C to not missing the diagnosis of hypoglycemia or worse, unnecessary insulin treatment based on inappropriate glucometer readings resulting in increasing the risk of hypoglycemia[23]. A dose adjustment of vitamin C is preferable in patients with renal impairment [24]. Taking into account that, excessive dose vitamin C should be administered with caution because risk of vitamin C toxicity might be increased due to impaired renal excretion. In addition, cure with excessive dose of vitamin C should be restricted in patients with glucose-6-phosphate dehydrogenase deficiency as it can lead to acute hemolysis [25]. Based on the above, the side effects of excessive dose of vitamin C for short-term use are approximately negligible [24]. Therefore, the advantage of using high dose of vitamin C as element of the supportive management of COVID-19 vastly outweighs the risk of development of unfavorableafter-effects.

Until May 2020 there were no comprehensive RCTs evaluating the effect of vitamin C in patientswith COVID-19 [39].For November 2020 there are a number of clinical trials registered globally assessing vitamin C effectiveness as monotherapy or in combination with other medicines or interventions in COVID-19 patients. Some of them are listed below (Table 1).Following to current trends of using supplements such as vitamin C and zinc Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh decided to conduct a trial to accurately assess influence of these supplementations to COVID-19 severity (NCT04558424). They aim to clearly assess the major clinical manifestations such as fever, cough, fatigue, muscle/body aches, headache, new loss of taste, newloss of smell, congestion/runnynose, nausea, vomiting, diarrhea within the period of 28 days after hospitalization. There are will be a group taking 1g vitamin C concurrently with 220mg zinc gluconate orally daily and a group taking a placebo in addition to standard therapy.In a trial which is conducted in Saudi Arabia (NCT04468139) with recruitment

of 60 patients it is searched a potential way of COVID-19 treatment improvement through administration of a combination of medicines (Quercetin 500mg, Bromelain 500mg, zinc 50mg and vitamin C 1000mg) taking orally.

It is well known that a quality sleep is vital for keeping one's body healthy and sooner recovery from a disease. It became more prominent during the COVID-19 pandemic because of additional factors interrupting adequate sleeping such as ongoing stress and panic summon up with the quarantine measures.Partially for evaluation this a group of researchers from Lancaster General HealthLancaster, Pennsylvania, USA began a randomized double-blind placebo-controlledtrial (NCT04530539). They planned to recruit 150 patients in outpatient department, randomize to groups and administer to one of the groups 10mg melatonin and 1000mg vitamin C with a goal of evaluating disappearance of existing symptoms.They hypothesized melatonin in couple with vitamin C improves the symptoms' vanishing.

Taking Over-The-Counter (OTC) agents could stave offdeterioration and hospitalization for COVID19, it could stop the great damage wrought by the pandemic. A few OTC agents have pre-clinical and clinical background for utility, especially famotidine. For trial conducted by Pykonsult headquartersNew Fairfield, Connecticut, USA (NCT04565392), 216 subjects get assigned to open-label treatment by birth day of the month; if odd, 1 tab famotidine per day; if even, 1 tab famotidine twice daily. All also take 2000 IU (International Units) vitamin D3 daily and 1 gram (1000 mg) vitamin C twice a day.

There are two multicenter concealed-allocation parallel-group blinded randomized controlled trials conducted in the same place in Canada, with involving 800 hospitalized critically ill patients, including sepsis,with COVID-19 (NCT04401150) and with or without(NCT03680274). These studies aimed to identify death or persistent organ dysfunction (Time Frame: Both assessed at 28 days), number of deceased participants or with persistent organ dysfunction (dependency on mechanical ventilation, new renal replacement therapy, or vasopressors).Vitamin C will be administered intravenously 50mg/kg of weight every 6 hours for 96 hours (16 doses).

Based on the information given above, vitamin C seems warrant in treatment of COVID-19 in both inpatient and outpatient conditions, resulting in a positive effect in patients with different severity clinical manifestations: mild symptoms, severe pneumonia, sepsis and ARDS. Therefore, it is preferable to add vitamin C to the national treatment guidelines of COVID-19 specifically in case the ongoing double-blinded RCTs will provide notably positive results.

Table 1. Ongoing vitamin C related trials, as registered on https://clinicaltrials.gov/. Search carried out on 14November 2020.

№	Interventions	Study design	Conditions	Estimated enrollment (*n*)	Phase	Country	Clinical Trial ID
1	220 mg zinc gluconate and 1g Vitamin C for 10 days in addition to their standard treatment	Randomized double-blind placebo Controlled	Hospitalized patients with COVID-19	50	Not yet recruiting	Bangladesh	NCT04558424
2	Quercetin 500 mg orally once daily in the morning before breakfast for 5-10 days or patient improves or discharged Bromelain 500 mg orally daily zinc 50 mg orally daily vitamin c 1000 mg orally daily	Single Group Assignment Open-label	Hospitalized patients with COVID-19	60	Recruiting	Saudi Arabia	NCT04468139
3	Vitamin C 2-hour infusion daily (for 6 days), escalating dose (0.3g/kg, 0.6g/kg, 0.9g/kg)	Single-center, prospective, randomized, open-label	Hospitalized patients with COVID-19	66	Not yet recruiting	USA	NCT04363216
4	10mg melatonin, at bedtime. 1000mg Vitamin C, at bedtime.	Randomized double-blind placebo controlled	COVID-19	150	Not yet recruiting	USA	NCT04530539
5	IV Vitamin C (Sodium Ascorbate) 50mg/kg every 6hrs on day 1 followed by 100mg/kg every 6hrs (4x per day; 400mg/kg/day) for 7 days (average 28g/day; maximum dose of 50g/24hrs for those weighing more than 125kg). Can be converted to 1 gram three times per day PO on hospital discharge) Outpatients: Vitamin C Outpatient trial: 200mg/kg x1 IV, then 1 gram PO three times	Randomized investigator-double blinded controlled	Hospitalized patients with COVID-19	200	Recruiting	Australia	NCT04395768

	per day for 7 days; Plus Active Comparator treatment						
6	A 20-mg tablet of Famotidine, 1000 IU vitamin D3 and 1000 mg vitamin C in the morning with breakfast and a 20-mg tablet of Famotidine, 1000 mg vitamin C in the evening with supper	Proof-of-concept Open-label Randomized Dose-response Comparison	Hospitalized patients with COVID-19	216	Not yet recruiting	USA	NCT04565392
7	Infrared Energy with a wavelength of 5 - 20 microns, 60 minutes exposure. IV vitamin C 10 grams daily	Single Group Assignment Open-label	Hospitalized patients with COVID-19	400	Not yet recruiting	Canada	NCT04584437
8	10 gr of IV vitamin C daily in addition to conventional therapy	Single Group Assignment Open-label	Hospitalized patients with COVID-19	500	Recruiting	Italy	NCT04323514
9	IV vitamin C: 50 mg/kg of weight administered every 6 hours for 96 hours (16 doses)	Multicenter concealed-allocation parallel-group blinded randomized controlled	Hospitalized patients with COVID-19	800	Recruiting	Canada	NCT04401150
10	IV vitamin C: 50 mg/kg every 6 hours for 96 hours	Multicenter concealed-allocation parallel-group blinded randomized controlled	Hospitalized patients with or without COVID-19	800	Recruiting	Canada	NCT03680274

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