Rationale for Vitamin C Treatment of COVID-19 and Other Viruses

by the International Society Of Orthomolecular Medicine, Olufemi Kofoworola Dada B.Sc. Microbiology and John Adeyanju B.Sc. Microbiology, PGD Education.
Peer reviewed and supervised by Dr Gregory Agbonvihele Okoh-Oboh M.B.B. S, M.Sc. Epidemiology & Biostatistics, Ph.D.
|Email address/LinkedIn profile:
dadaolufemi91@gmail.com, Olufemi Dada. johnadeyanju30@gmail.com, John Adeyanju.
Dr Gregory Agbonvihele Okoh-Oboh.

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Epidemics seem to be on the rise: in a total of 98 epidemics in the 200 years of 19th and 20th centuries, there were 14 epidemics with 1000 or more deaths. However, in the last 20 years, in a total of 63 epidemics, there have already been 11 epidemics with more than 1,000 deaths. With the recent COVID-19 pandemic, the trend is concerning as our modern world becomes more connected by high-speed travel. [1-5]

Vaccines

Research and development of vaccines and virus specific drugs takes at least a few years to develop and deploy for worldwide use -- if indeed possible. There has never been a vaccine available to stop an ongoing major pandemic in the history of mankind. We didn't have vaccine for SARS, nor MERS. We can't expect a vaccine for most of the worldwide people anytime soon for COVID-19. Likely this trend will continue for the foreseeable future. This is due to the nature of the process: vaccines are always in reaction to a new outbreak, and R&D of vaccines takes a long time. Even if a vaccine for COVID-19 does become available, it will be too late and the world will likely be affected by major chaos with lives lost and economies damaged. It's clear that although a vaccine strategy is desirable, with the current R&D process, it's not practical. [4,5]

Integrative medicine is effective and practical

The world's political, scientific, medical and industrial leaders need to consider this very carefully. We must face the reality of the current crisis and look elsewhere for more proactive, effective and practical ways for preventing and stopping major pandemics like COVID-19. The integrative medical approach, that employs safe supplements of vitamin C, vitamin D, and zinc and other nutrients is highly relevant. This approach is a proactive, effective and eminently practical way to deal with the present pandemic. Treatment with high-dose vitamin C has been widely utilized by hospital ERs and ICUs to prevent death from SARS-associated pneumonia. [6-21] This treatment needs due attention paid, and most definitely warrants further studies. If there is one good thing out of this world-wide tragedy of COVID-19, maybe it has prepared us for future pandemics.

Role of vitamin C in the body

Vitamin C is the main systemic extracellular antioxidant, and when given at high doses, either orally (3-10 g/day) or IV (10-50 g/day, etc.), can function as an antioxidant to prevent toxicity from ROS (Reactive oxygen species) and viruses. When oxidized through donating an electron to reduce an ROS, it can be regenerated through a variety of mechanisms, including reducing enzymes and other antioxidants.

Vitamin C can support intracellular antioxidants such as GSH (glutathione) and catalase when the load of ROS is severe. Vitamin C can regenerate GSH when depleted by severe stress. The role of catalase is mainly to reduce hydrogen peroxide and it can function along with SOD and vitamin C to protect cells. However catalase and SOD are large molecules and do not serve the same role as vitamin C (ascorbate) which is a small molecule and can donate electrons to any ROS that it contacts, including oxidized vitamin E and many other molecules that may get damaged by ROS -- in either the intracellular or extracellular space. [22]

Vitamin C also empowers the immune system, promoting chemotaxis, growth, and activity of some immune cells (macrophages, lymphocytes, natural killer cells) allowing the body to more effectively fight an infection. [22]

Vitamin C has many other roles in which it functions as a specific co-factor for biochemical reactions, for example, in the synthesis of aggrecan and collagen in which it is necessary for the crosslinking of long fibers into a 3D matrix, in the absorption of iron, in the metabolism of many essential biochemicals including carnitine and neurotransmitters (e.g. norepinephrine, serotonin). Thus it is essential for recovery from damage caused by viral or bacterial infections, as well as for the normal functioning of the brain and many essential biochemical pathways. [22]

In addition, when the body is under severe stress, for example, recovering from toxin exposure, surgery, or SARS, the level of vitamin C can be depleted so that it cannot perform its direct or indirect antioxidant functions or its many other specific co-factor roles in biochemical metabolism. This can in turn deplete the other antioxidants, e.g. GSH and vitamin E, which can cause severe oxidative damage inside cells that normally they would prevent.

In high-dose intravenous vitamin C (IVC) therapy, vitamin C is thought to be a pro-oxidant in selective cell types, which allows it to kill specific cell types. This role may function in some types of cancer and also immune hyperinflammation. [23-30]

Overall, vitamin C has a variety of effects (i.e. "pleiotropic") that are not duplicated by intracellular antioxidants. It supports intracellular antioxidants and is necessary as a specific co-factor in many critical biochemical reactions in many organs of the body.

Dosage of vitamin C: effects

IVC can supply much higher blood plasma levels than oral doses. However, the vitamin C levels from IVC peak and fall rapidly. Although IVC can be given continuously, this is performed less often than IVC doses given at intervals. Oral doses taken regularly (i.e. in divided doses throughout the day) can maintain an even (but lower) level. [25-30]

The lower level of vitamin C produced by oral dosing is commonly thought to provide an anti-oxidant function. However, higher doses provided by IVC are considered to cause a pro-oxidant state within cells such as cancer cells that lack antioxidant enzymes, where the high vitamin C level generates H_2O_2 (hydrogen peroxide) and other free radicals and causes cell death.

Since vitamin C has a similar structure to glucose (sugar), cancer cells, which have a high metabolic rate and transport large amounts of sugar into the cell, will also transport large amounts of vitamin C. This is thought to be one of the mechanisms through which high-dose vitamin C is effective against cancer. [23-30]

In other types of cell that have a lower metabolic rate but also have antioxidant enzymes, the same high dose of vitamin C is thought not to cause a pro-oxidant state, but to maintain an anti-oxidant state. Thus the same bloodstream level of vitamin C is thought to function differently in different cell types.

Absorption of oral doses of vitamin C is modulated by the blood level. When the blood level is high, absorption from the gut is low, but can increase during illness when the blood level drops because of oxidative stress. In addition, the blood level from low oral doses of vitamin C (100-200 mg) is regulated by level-dependent active transport in the kidneys that maintains a threshold plasma level (50-100 µM or µmol/L), and the remainder is excreted in the urine. For higher oral doses (500 - 5,000 mg or more), absorption can be much lower (50% down to 10% or less), depending on the blood level and oxidative stress. The blood level from an oral dose may take up to several hours to reach its peak. Therefore, higher oral doses taken at intervals throughout the day (e.g. 3,000-10,000 mg/day in divided doses) can produce higher plasma levels (200-400 µmol/L). But IVC (1-200 g) can produce plasma concentrations of up to 20 mmol/L (up to 100-fold greater than possible by oral dosing) within 1-2 h of administration. However, after a single IVC transfusion, the higher peak level falls by half every half-hour. Therefore, to maintain a relatively constant high level from IVC requires transfusions at short intervals or continuous IVC. For a comparison, blood glucose typically varies from 4 mmol/L to 6 mmol/L for individuals without diabetes. [25-27]

Therefore, the levels achieved from a single high-dose of IVC can apparently go through anti-oxidant and pro-oxidant phases after administration. With this knowledge, treatments for cancer can adjust the doses and timing of IVC administration to maintain the pro-oxidant effect for cancer cells. Even a transient rise in the vitamin C level from an IVC transfusion can have a prolonged physiological effect, such as direct viral inactivation and up-regulation of immune cascades.

Prevention of viral infections

To prevent infection by viruses and bacteria, vitamin C (capsules of ascorbic acid, or crystals of ascorbic acid or sodium ascorbate) dissolved in water or juice has been taken at low and high oral doses (200 mg/d to 10,000 mg/d). The upper limit for an oral dose is defined by the "bowel tolerance" above which the dose is not absorbed in the gut and causes a laxative effect. This dose is set by the body's need to absorb vitamin C from the gut into the bloodstream. Since the level of vitamin C in the body varies according to the level of oxidative stress, the amount of vitamin C absorbed by the gut also varies. [27-30]

Typically many individuals can tolerate 1000-3000 mg/day in divided oral doses, which can then maintain a relatively constant level of vitamin C in the bloodstream. Some organs (e.g. liver, brain, eyes, etc) actively transport vitamin C to maintain a higher level than provided by the blood. This state of a relatively high maintained level of vitamin C throughout the body is thought to lower the risk of viral infection by assisting the immune system in detecting and destroying foreign microbes such as viruses that attack the nasopharynx and lungs. In addition, oral doses of vitamin C can directly denature viruses. [29]

Liposomal C

Liposomal vitamin C is absorbed by a different mechanism in the gut. The liposomes containing vitamin C can bind directly to the gut cells to release their content of vitamin C which therefore does not require active transport. Thus the maximum level achievable with oral doses of liposomal vitamin C is higher than for regular vitamin C. However, since the absorption mechanism for liposomal vitamin C differs from the active transport of regular vitamin C, both forms can be taken together to increase the level in the bloodstream (up to 400-600 μM), greater than either oral form alone. [29]

High-dose IVC: treatment of severe stress

With severe shock, trauma, or sepsis, ascorbate blood levels typically drop to near zero. To restore the ascorbate level, several grams of vitamin C must be administered. [30] To treat pneumonia and hyper-inflammation caused by COVID-19, vitamin C has been given at high doses, both oral and IVC.

Some IVC protocols have specified doses of 1000-3000 mg as necessary at intervals throughout the day. Other IVC protocols have specified doses as high as 10-20 grams daily for several days or weeks, and even as high as 50-100 grams daily, when necessary for several days. [6-21]

In severe lung infections, a "cytokine storm" generates reactive oxygen species (ROS) that can be effectively treated with doses of 30-60 g of vitamin C. At the same time the relatively high level of vitamin C can promote an enhanced chemotaxis of white blood cells (neutrophils, macrophages, lymphocytes, B cells, NK cells). [14-20]

High-dose oral C

When the body is stricken with severe stress, oral vitamin C supplements of 20,000 mg/day or even 50,000-100,000 mg/day, in divided doses, can be surprisingly well tolerated because it becomes depleted by helping to alleviate a critical inflammation, e.g. SARS pneumonia. In this case, the level of vitamin C in the bloodstream will not rise much above 200-300 μmol/L, even though under normal circumstances a much lower oral dose would produce the same blood level. The reason is that the vitamin C is oxidized in the process of attacking the inflammatory agent, e.g. viral infection, so that more vitamin C can be absorbed from the gut than normally possible. In this range of high oral doses, vitamin C is considered to function as an anti-oxidant. [27-30]

I**ron: pro-oxidant**

Iron can act in conjunction with vitamin C to cause a powerful oxidation reaction (the "Fenton reaction") that generates free radicals. For individuals who are iron-overloaded, vitamin C can cause this problem and can generate hydrogen peroxide throughout the body. Normally this type of reaction is limited by the "catalase" enzyme that degrades hydrogen peroxide. However, some viruses contain an iron atom that in the presence of vitamin C may denature the virus. As mentioned above, vitamin C can cause a similar reaction when it is taken up at high levels into cancer cells. Therefore it is thought that vitamin C can act as an anti-oxidant for some organs and cell types, and as a pro-oxidant for other cell types and e.g. viruses. Yet vitamin C is also thought to be capable of "neutralizing" viruses since their binding sites contain free radicals. [29,31]

Pro-oxidant vs. anti-oxidant

This dual function of anti- vs. pro-oxidant is thought to be dose- and level-dependent. What dose should be the best, given that a low IV dose is thought to provide anti-oxidation, but a high dose is thought to provide pro-oxidation? Which action is working best against a virus? This question is at the cutting edge of current research. The specific cancer-killing dose is thought to be in the high pro-oxidant range. But it is not known what range of oral or IVC doses is the best for treatment of viruses. Apparently, a single relatively low dose IVC treatment can raise bloodstream levels only transiently, and generate blood levels that range from the anti-oxidant to the pro-oxidant, and then back to anti-oxidant -- which may target different target cell types. Continuous or short-interval IVC dosing may allow taking advantage of all the direct and indirect antiviral mechanisms of ascorbate. For example, doses of 10g every 6 hours might fit this purpose.

Vitamin D, zinc

Many studies have shown the efficacy of vitamin D (2000-5000 IU/d) for preventing viral infections. Vitamin D has been shown to assist the body in preventing viral infections. The level of vitamin D in patients with flu is lower than healthy individuals. For those who do not take supplements of vitamin D, the level of vitamin D is the lowest in the body in the winter and early spring -- which is flu season. In a study of hospitalized older patients, those with with pneumonia more often had a severe vitamin D deficiency. [32-43] Further, zinc supplements (20-50 mg/d) are known to assist the immune system in fighting viral infections, especially by inhibiting viral replication. [22,44]

Optimal doses for prevention and treatment of COVID-19

The theme of dose-dependent action of vitamin C may be important for prevention and treatment of relatively innocuous viral infections and also for treatment of severe critical SARS pneumonia from COVID-19 and other flu-like infections. In the treatment of COVID-19, we likely need both the anti-viral and antioxidant effects of vitamin C. We know high-dose vitamin C may have pro-oxidant activity, but if the dosage is too high (And what defines too high?), would this add a pro-oxidant effect to an already elevated oxidative stress? With protocols specifying 30-50 grams of IVC, how can this dose be scientifically justified?

Further, the existing data from many decades of studies show that oral vitamin C can prevent viral infection. It would be helpful for an NIH panel

to further study the prevention of COVID-19 with oral vitamin C by pushing the oral dose higher. COVID-19 infection seems to linger around for a longer time than the common cold. Several COVID-19 patients who have improved on high-dose vitamin C have not healed quickly, implying that the high doses should be continued beyond their hospital stay.
Many studies of the effect of vitamin C on infections and cancer have been hampered by an ineffective dose, duration, or dose frequency. For the maximum effect, relatively high oral vitamin C doses (10,000-50,000 mg/d in divided doses) must be continued for several (or many) days, and the dose frequency must be adequate to supply a relatively continuously high level in the bloodstream. Further, early treatment of a viral infection is important. Oral vitamin C (1000 mg at 1-2 hour intervals) should be started immediately upon noting symptoms of an infection. For severely ill patients with pneumonia, early initiation of an IV vitamin C protocol can be critical. [14-19] Studies that have not observed these precautions have often not found much benefit.

Conclusion

Supplemental vitamin C, both oral and IV is an excellent and relatively simple and inexpensive treatment for both uninfected individuals at home, and critically-ill individuals in the hospital. It has been proven to be effective in treating many different viral infections, including SARS pneumonia. With early and high dosing at regular intervals, vitamin C can effectively fight against sepsis, hyper-inflammation, and high virus titer to allow ICU patients to recover quickly. Combined with an overall integrative approach to health management, vitamin C, vitamin D, zinc, and other essential vitamins and minerals can effectively prevent and treat COVID-19.
However, the mechanisms and relative benefits of different doses, both oral/liposomal and IV need further study.
Side effects and precautions
Intravenous ascorbic acid
Most IVC is given as an isotonic solution of sodium ascorbate. However, ascorbic acid can also be given IV with careful precaution -- it may sting a bit -- and can be given with magnesium sulfate or magnesium chloride, the most used form is sodium ascorbate. Compatible diluents: 0.9% Sodium Chloride (Normal Saline or NS), 0.45% Sodium Chloride (half-Normal Saline), Lactated Ringer's (LR), Dextrose/Saline combinations or Dextrose/LR solutions. However, dextrose solutions should be discouraged because they will compete for transport of vitamin C into cells, since both of these molecules are imported by the same membrane transporter. For IV infusion: Add to a large volume of diluent and infuse slowly. A faster rate of infusion and less diluent have also been used. [14-19]
IV Osmolarity
From experience, we know that the osmolarity of an IV transfusion is more important than the pH (until it goes paravenous of course). Advice written to our Italian colleague two weeks ago: Do give IVC in addition to oral vitamin C. (It is a paradoxical thing that patients generally tolerate more oral C on the day they receive IVC). We calculate the osmolarity for such infusions. It's important for people under oxidative stress. If the osmolarity of the IV is outside the normal serum range, it can cause a collapsed or thrombosed vein.

The total milli-Osmoles in an infusion is the sum of all the mOsmoles of the components. Total Osmolarity mOsm/ml is Total mOsm/Total volume. This should be within the range 0.28 to the value for the vein size. A 20 gram infusion is nearly at the borderline to add both calcium gluconate and bicarbonate.

Side effects of IVC treatment

High dose intravenous AA may lower blood glucose, potassium, calcium.
A fluid overload from a series of IVs can cause congestive heart failure.
Glucometer readings of glucose level can be falsely raised by vitamin C since it is similar in shape to vitamin C. [25]
It is important to monitor blood glucose (not by glucometer), and Na, K, Ca levels if the patient is symptomatic after high dose ascorbate (acid or buffered).
There is no need to check the serum ascorbate for safety; there is no maximum above which it is unsafe. The rationale for checking serum ascorbate is to make sure of an effective level -- which depends on the severity of the clinical picture.
The side effects of high-dose IVC appear minimal. In one study, of ~9000 patients surveyed, only ~1% reported minor side effects that included lethargy, fatigue, change in mental status and vein irritation. More recent safety trials of high dose IVC show only minor side effects and no adverse events beyond what could be expected from the underlying disease or chemotherapy. [25]
Oxalate from vitamin C
Although the body metabolizes vitamin C to produce small quantities of oxalate, for individuals with normal kidney function IV vitamin C does not contribute to calcium oxalate kidney stones. [25,45] More important sources of oxalate for most individuals are the amount of cruciferous vegetables, tea, and other sources in the diet. These oxalates bind with the excess calcium that is in our dairy, fortified foods, and supplements. To prevent oxalate stones, in general, and when taking oral vitamin C, it is important to drink adequate amounts of fluid and avoid excessive calcium levels in the diet. In addition, magnesium supplements (300-500 mg/day, in malate, citrate, or chloride form) can prevent calcium from precipitating with oxalate to form stones. [46,47]
G6P6 deficiency, hemochromatosis
For some individuals with a mutation in the Glucose-6 phosphate dehydrogenase gene, high levels of vitamin C in their bloodstream can cause anemia and lysis of their red blood cells. This genetic issue is found mos

commonly in individuals with African or Middle Eastern descent. If you have this rare disorder, you may want to limit your dosage of vitamin C. Moderate doses are thought to be acceptable. Before taking vitamin C supplements or IVC therapy, you may want to discuss this issue with your doctor. [25, 48]

Vitamin C treatment for HIV

The research of Linus Pauling, just in the years before he died was on HIV. With private funds and a grant from the Shipbuilding Industry Foundation in Japan, he started an in vitro experiment into the effect of vitamin C in HIV. In 1990 he published the results: the replication (multiplication) of HIV was reduced by more than 99% by vitamin C. [49]
One of the co-authors, Raxit Jariwalla, said they compared the effect of vitamin C with that of the HIV inhibitor AZT. In this in vitro test, the cell cultures were pretreated with ascorbic acid (vitamin C) or with AZT . It was found that the artificially induced enzyme activity, which is a measure of HIV replication, was greatly reduced by vitamin C (the higher the concentration, the stronger the effect). The HIV drug AZT did not show a significant result [50].

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Nutritional Medicine is Orthomolecular Medicine
Orthomolecular medicine uses safe, effective nutritional therapy to fight illness.