JOURNAL OF
ORTHOMOLECULAR
MEDICINE

OPEN ACCESS

VOLUME 35, NUMBER 1
PUBLISHED 8 MAY 2020

REVIEW ARTICLE

Nutrition Therapy for Severe Viral Infections (COVID-19): Recommendations and Considerations for Integrative Medical Treatments

Vince Ziccarelli, PhD, MSc, RD, FICN

Citation: Ziccarelli V (2020) Nutrition therapy for severe viral infections (COVID-19): Recommendations and considerations for integrative medical treatments. *J Orthomol Med*. 35(1)

ABSTRACT

Given the limited medical treatments for severe viral infections; there is a growing need for therapeutic options to help mitigate risk and improve patient outcome. Nutrition therapies show potential benefits. Marginal deficiencies of select nutrients are common, whereby zinc, vitamins C, and D are often low for many population groups that may be immune compromised. Sub-optimal nutrient status negatively affects immune functions. With novel viruses, the body's immune system may become especially taxed with exaggerated immune responses that may lead to excessive free radical damage to organs including the lung. The latter induces elevated physical stress on the body setting the stages for more overt nutrient deficiencies, compounding the nutritional risks to health. Conversely, increased intake of vitamins C, vitamin D, and zinc may work to enhance antioxidant status, limit oxidative stress, regulate immune functions, and reduce viral replication. It is highly encouraged that current medical treatments for severe viral infections consider the integration of optimal nutritional therapies. DRI levels of most essential nutrients should be provided, with optimal doses of vitamins C, D and zinc; to correct potential nutrient deficiencies while optimizing nutrition care for better recovery. This review article provides therapeutic nutrition considerations when treating severe viral infections.

INTRODUCTION

There is a growing concern about health strategies to mitigate and or potentially limit the severe complications that affect the respiratory tract during viral infections. For this reason, researchers are looking to develop vaccines for prevention of strong viral strains such as COVID-19, to hopefully limit spread throughout the population, and reduce incidence of severe complications or mortality. One major viral complication is that of pneumonia, which elevates risk of morbidity and mortality.

In the meantime, other integrative health options should be explored. Indeed, there is a large body of evidence confirming the benefits of good nutrition for supporting immunity and lung health. Since severe viral infections often lead to pneumonia-induced mortality, a good starting point of this discussion would be to review the relation between nutrition and lung health. For instance, the intake of fresh fruit has been shown in several studies to offer beneficial effects for lung function. In a relatively recent cross sectional analysis of 18,737 children in Italy, ages 6-7, that controlled for several confounders, the consumption of vitamin C-rich fruit including kiwis and or citrus fruit, offered a protective benefit for wheezing symptoms (i.e. shortness of breath, nocturnal cough, severe wheeze), particularly in those with asthma. The authors concluded that intake of vitamin C-rich fruit may benefit lung function, particularly in those that may be vulnerable (Forastiere et al., 2000).

Similar respiratory tract health findings are found by other researchers. A well-designed systematic review and meta-analysis published in *Nutrients* in 2017, stated that a reduced intake of vegetables and fruit may play a critical role in the etiology of asthma and allergies. The review demonstrated that with a greater intake of vegetables and fruit, asthma symptoms improved – including improvements with systemic and airway inflammation, in both children and adults (Hosseini et al., 2017). Also, pregnant

© 2020 International Society for Orthomolecular Medicine ISSN 0317-0209

women that consumed more vegetables and fruit were found to experience a moderate reduction in risk for upper respiratory tract infection (Li & Werler, 2010). Further, a randomized double blinded placebo controlled trial with health care professionals taking a supplemental extract of fruit and vegetables, were noted to experience a significant 20% reduction in common cold symptom-days compared with placebo (Roll et al., 2011). One of the primary antioxidants common to many fresh fruit and vegetables is vitamin C. Following is a closer review of this essential nutrient and its relevance to viral infections and pneumonia.

THE ESSENTIALITY OF VITAMIN C FOR VIRAL INFECTIONS

It is noteworthy that the concept of lung health related to nutritional status is not a novel concept. Early documentation in the literature about vitamin C found that with overt vitamin C deficiency, as in the case with scurvy, many would die of pneumonia complications. Pneumonia was a common outcome associated with scurvy, with many documented cases of morbidity and mortality (Hemilä & Pekka, 2007). ICU patients treated for pneumonia are often found to have low vitamin C status, and most ICU patients in general are found to be low in vitamin C stores, despite the commonly administered nutritional care they receive (Kim et al., 2018). Above and beyond vitamins C's anti-scurvy effects, it plays a physiological role as an antioxidant for immune cells, and is highly concentrated in phagocytes and lymphocytes – indicating an important physiological role. As an antioxidant it may serve to protect host cells from viral-induced free radical attack. Experimentally it has been shown to increase the functions of phagocytes, proliferation of T lymphocytes and the production of interferon – while reducing viral replication (Hemilä & Pekka, 2007). The redox potential of vitamin C protects host cells against the reactive oxygen species released from the immune associated respiratory burst and inflammatory response to viral infections, thereby possibly limiting viral induced complications (Wintergerst et al., 2006).

So the question at this point is whether or not vitamin C may benefit current viral pandemics, given the fact that most Western societies rarely report any cases of overt vitamin C deficiency. However, when looking closer at what many studies report, there may be more to the essentiality of vitamin C than we think.

It is well accepted that, even when body pools of this nutrient are good, vitamin C may be rapidly depleted by extra levels of emotional, or physical stress (i.e. chronic disease, infections, pollution, smoking, etc.). Vitamin C depletion elevates risk for marginal deficiency, as well as reduction of leukocyte, adrenal cortex, and plasma pools of exogenous vitamin C antioxidant potentials.

Interestingly, recent studies in Italy have suggested that the greater COVID-19 mortality cases in Northern Italy may likely be related to the higher levels of pollution compared with other Southern Italian regions. It may very well be that many Northern Italians are at a suboptimal state of vitamin C status, or even at a state of deficiency – due to pollution-induced depletions – potentially compromising nutrient associated immune functions.

The possibility of an already existing marginal and or overt vitamin C deficiency becomes more of a nutritional concern for many population groups (Basu & Dickerson, 1996). This is supported by the fact that up to 31% of the US population have been reported to be consuming dietary vitamin C below the recommended levels for adequate intake (National Nutrition Survey, 2016).

Also based on published data from the NHANES 2003-2004 survey of 7,277 American civilians, measurement of blood serum vitamin C concentrations, suggested that approximately 21 million Americans may have various forms of vitamin C deficiency, 66 million may develop a deficiency, and less than 30 million Americans have optimal levels (National Nutrition Survey, 2016).

Similar patterns are reflected in Canada. A cross sectional study of 979 young female and male non-smoking Canadian adults ages 20-29 years, showed 33% were suboptimal for vitamin C and 14% were deficient, as reflected by low serum ascorbic acid concentrations. These results suggest that 1 out of 7 young Canadian adults are vitamin C deficient, in part due to poor dietary intake (Cahill, Corey, & El-Sohemy, 2009).

It is also stated that the RDA (Recommended Dietary Allowance) for vitamin C is too low to address the increased needs for up to 35% of the American population; due to health and lifestyle factors such as smoking, select chronic conditions, and drug nutrient interactions (National Nutrition Survey, 2016).

Moreover, many pockets of the population may be at a subclinical state of vitamin C deficiency. The elderly are an example of a vulnerable group that may have more compromised immunity to begin with, and be at greater risk for severe viral complications, particularly when micronutrient status may be suboptimal (Wintergerstet al., 2006). Add to this the fact that polypharmacy may further deplete vitamin C stores of the elderly due to often-overlooked drug nutrient interactions (Basu & Dickerson, 1996). Conversely, a large number of randomized controlled intervention trials have demonstrated that supplementing elderly participants with vitamin C and zinc (up to 1000 mg vitamin C/day, and 30 mg zinc/day), resulted in significant improvements in symptoms of upper respiratory tract infections, reduction of symptom duration, and better outcome with pneumonia (Wintergerst et al., 2006). It is noteworthy that zinc is another trace element, required for supporting immune functions. Zinc intake has been found to be inadequate for many seniors 70 years of age or older (National Nutrition Survey, 2016).

Perhaps we may be overlooking or underestimating the actual prevalence of suboptimal micronutrient status, particularly vitamin C. With lower than optimal states of vitamin C nurtriture, the risk for compromised immune physiology becomes more of a possible reality.

Hypothetically, when infected with a virus, especially an unpredictable novel virus, body stores will likely deplete rapidly, as the hosts immune defences are not tailored to respond to a completely new antigen, with the potentials for an over exaggerated immune response accompanied by an excessive release of reactive oxygen species (cytokine storm).

This may create an acute scurvy like state, whereby the inert immune and endogenous antioxidant regulatory systems fail and disease-associated free radical damage may prevail, leading to various levels of organ failure. This might be a plausible explanation for what may be affecting viral infections and recovery, especially with novel viral infections.

It may be that those with better overall nutrition and reserves of vitamin C, recover better when infected with select viruses. Better nutrition may be why certain individuals may only experience mild symptoms, while others experience severe symptoms.

OTHER ESSENTIAL NUTRIENTS RELATED TO VIRAL INFECTIONS

Other nutrients related to immune physiology that have also been found to be at risk for inadequate intake include zinc, vitamin E, vitamin D, and vitamin A (Gombart et al., 2020). As per the published NHANES 2005 survey data, 93% of Americans had inadequate intake of vitamin E, 44% had inadequate intake of vitamin A, and elderly males and females had an overall inadequate intake of zinc (National Nutrition Survey, 2016). In addition to vitamin C, the nutrients zinc and vitamin D are particularly considered to be of benefit for modulating immune activities against viral infections (Gombart et al., 2020).

VITAMIN D

Vitamin D, considered the sunshine vitamin, and is more of a hormone-like vitamin. Synthesized in response to solar UV light contacting the skin, 7-dehydrocholesterol is converted in a series of biochemical reactions to the active vitamin D3 metabolite. Vitamin D is known to be intricately involved in not only bone mineral metabolism, but may serve as a valuable immune modulating cofactor (Basu & Dickerson, 1996).

During cold and flu season, when sun exposure is usually at its lowest, viral infections are typically at their peak. The increase in infections may be explained by low vitamin D levels, which hinder the immune system's ability to keep viruses at bay. Conversely, researchers have suggested that when vitamin D pools reach peak levels during the summer months, we see a rapid decline in viral infections.

Studies have shown that supplemental intake of vitamin D has helped to reduce the severity of viral infections (including incidence of pneumonia), and severity of their outcome. Although there has been conflicting results with vitamin D and upper respiratory tract infection (URTI), a recent well designed systematic review and meta-analysis of individual participant data, from 10,933 participants, from 25 randomized control trials, has shown an overall protective effect against URTI. The review showed more pronounced benefits for those that had a lower vitamin D status, and supplementation on a daily or weekly basis was better therapeutically compared with a periodic high dose bolus of vitamin D. The authors concluded that food fortification of vitamin D may be a sensible strategy to prevent URTI, and should therefore be considered by health authorities (Martineau et al., 2017).

ZINC

Zinc, a trace mineral, is another essential nutrient involved in many enzymatic reactions. It has also been shown to influence immune functions and for this reason has been evaluated for its viral protective effects. It is known that select population groups are at risk for inadequate intake of zinc (National Nutrition Survey, 2016; Gombart et al., 2020). This may hinder immune response to viral and chronic disease.

Researchers believe that improving dietary intake of zinc may benefit immune associated health. In fact human studies with up to 30 mg of supplemental zinc, show the mineral helped ameliorate symptoms, and shorten duration of URTI, including the common cold. In a recent double blinded placebo controlled trial with children, supplemental zinc was associated with a 45% reduction in incidence of acute lower respiratory tract infection. It was suggested that interventions to improve zinc intake would improve the health and survival of children in developing countries (Sazawal et al. 1998). Moreover, there were even reported benefits for reducing the incidence and the outcome of pneumonia in select populations (Wintergerstet al., 2006). It is important to note that in many of these studies zinc was supplemented with vitamin C, as the two nutrients appear to work in synergy.

VITAMIN C, VITAMIN D, ZINC AND URTI

The use of supplemental vitamin C, zinc and vitamin D for treatment of URTI is not a novel concept. Sales and consumer use of these nutrient supplements are common place throughout the world, with rare reports of adverse events, when used appropriately and sensibly. Numerous human trials have shown that supplemental doses ranging from 200 mg to 1,000 mg/day of vitamin C and up to 30 mg/day of zinc have improved URTI symptoms, reduced incidence of pneumonia, and improved URTI outcomes with common viral infections (Wintergerstet al., 2006). Daily supplemental intakes of vitamin D that have shown therapeutic potentials range from 7.5-50 ug/day (300-2000 IU) (Martineau et al., 2017).

Given the evidence supporting of the use of nutrients that may influence immunity, and potentials for coping with viral infections, it would be prudent to consider their therapeutic integration for the medical management of patients that are infected with novel viruses.

Therefore, with the increased prevalence of super virus strains such as SARS1 and now SARS2 (COVID-19), it is all the more critical that optimal nutrition be explored as an important piece of the treatment model. This form of treatment is in line with an integrative model of medical nutrition therapy, which incorporates the best of modern medicine with that of evidence based nutrition therapies.

INTEGRATIVE NUTRITION THERAPY CONSIDERATIONS FOR SEVERE VIRAL INFECTIONS

To that end, the following are recommendations should be considered for the treatment of novel viral infections, improving the potential for recovery, and reducing severe complications.

Patients should receive the DRI for all essential nutrients including selenium, zinc, vitamin E, and vitamin A – to provide foundational nutrition support for immune function. Most essential nutrients are known to offer synergetic effects for immune function and overall wellness.

Above and beyond the DRI for essential nutrients, vitamin C, vitamin D and zinc should be provided at optimal levels. Dose range for vitamin C would be from 1000 mg/day to 6000 mg/day, dependent on normalizing leukocyte ascorbic acid concentrations as a marker for required dose. Typically, it has been suggested that 6 grams daily of intravenous vitamin C (IVC) at divided daily doses may be required to replete leukocyte levels for ICU patients (Kim et al., 2018).

A recent study found significant improvements with pneumonia mortality rate, and radiologic scores for those patients receiving IVC (Kim et al., 2018). It is recommended that this clinical trial be referenced as a guidepost for IVC protocol.

Other protocols for IV vitamin C that are currently being investigated for specific treatment of COVID-19 should also be referenced. These protocols employ much larger therapeutic doses, in the range of 4,000 mg/day to 16,000 mg plus (50-200 mg/kg body weight/day), for varied cases of severity, with promising potentials (Anderson, 2020).

Optimal therapeutic dose for vitamin C therapy may largely depend on the extent of disease-associated reactive oxygen species produced, as well as the baseline levels of vitamin C plasma and tissue saturation. Leukocyte and blood plasma ascorbic acid levels may help direct the initial dose levels that should be employed, as these levels are usually a good marker for body tissue saturation (Basu & Dickerson, 1996; Anderson, 2020).

Also, plasma TBARS (thiobarbituric acid reactive substances) are an indirect method to measure vitamin C status, since elevated levels of TBARS indicate elevated levels of oxidative stress. Oxidative stress is usually associated with lower levels of, or an increased requirement for vitamin C. Alternatively, reduced TBARS may be used as a useful measure of vitamin C effectiveness (Tanaka et al., 1997).

If physicians feel that higher doses are unsubstantiated, then perhaps a lower dose of 2,000mg to 4,000 mg daily, in divided doses, may be a more reasonable middle ground for starting therapeutic dose. These doses are certainly closer to the daily tolerable upper limit level (Health Canada, 2005). Integration of the lower doses will likely offer some level of therapeutic benefit. However, many current day practitioners who employ IV vitamin C therapies advocate much larger doses to be effective. This should be noted when implementing therapeutic protocols (Anderson, 2020).

THIAMINE IS COMMONLY KNOWN TO BE DEFICIENT WITH ICU PATIENTS EXPERIENCING SEPSIS

It is important to note that high dose thiamine supplementation (200 mg BID for 4 day period), was provided in the IVC 6 gram study to help reduce the bio-conversion of glyoxylate to oxalate, in order to prevent calcium oxalate nephropathy (Kim et al., 2018). None of the treated IVC participants developed renal dysfunction (Kim et al., 2018). Thus, supplemental thiamin should be considered to prevent potential risk for high dose ascorbic acid induced renal dysfunction.

The supplemental dose of vitamin D should be within the daily upper range level of 2,000 IU for optimal therapeutic potentials, as reflected by the latest systematic comprehensive review for URTI (Martineau et al., 2017). Dietary zinc supplementation would ideally be at a level of 30 mg daily, the usual therapeutic dose levels reflected by many clinical trials (Wintergerstet al., 2006).

The latter suggested dose levels are well within safety levels for DRI of these nutrients, not exceeding the tolerated upper daily limit, particularly for the short term duration of supplemental intake required for treatment (Health Canada, 2005). To offset the potentials for zinc associated depletions in copper status, DRI levels of supplemental copper will prevent potentials for low copper levels, as provided by the daily DRI for all essential micronutrients.

CONCLUSION

Given the overall safety profile of essential nutrients, the possibility of marginal nutrient deficiencies such as vitamin C, and the evidence showing promise for therapeutic effects, it makes logical sense to consider integrative nutrition therapies to compliment current treatment protocols for COVID-19.

REFERENCES

Anderson, PS (2020) Vitamin C for the Treatment of Coronavirus (COVID-19) – ISOM [Video]. Retrieved May 7, 2020, from https://isom.ca/vitamin-c-coronavirus/

Basu, TK & Dickerson JWT (1996) Vitamins in human health and disease. CAB International. https://www.cabdirect.org/cabdirect/abstract/19961406471

Cahill L, Corey PN, & El-Sohemy A (2009) Vitamin C deficiency in a population of young Canadian adults. *American Journal of Epidemiology*,170(4), 464-471. https://doi.org/10.1093/aje/kwp156

Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, … & the SIDRIA Collaborative Group, Italy (Italian Studies on Respiratory Disorders in Children and the Environment (2000) Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. *Thorax*, 55(4), 283–288. https://doi.org/10.1136/thorax.55.4.283

Gombart AF, Pierre A, Maggini S (2020) A review of micronutrients and the immune system – working in harmony to reduce the risk of infection. *Nutrients*,12(1), 236. https://doi.org/10.3390/nu12010236

Health Canada (2005) Dietary Reference Intakes Tables [Datasets]. https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html

Hemila H & Louhiala P (2007) Vitamin C may affect lung infections. *Journal of the Royal Society of Medicine*, 100(11), 495-498. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2099400/

Hosseini B, Berthon BS, Wark P & Wood LG (2017) Effects of fruit and vegetable consumption on risk of asthma, wheezing and immune responses: A systematic review and meta-analysis. *Nutrients*, 9(4), 341. https://doi.org/10.3390/nu9040341

Jacob RA (1990) Assessment of human vitamin C status. *The Journal of Nutrition*, 120 (Suppl 11), 1480-1485. https://doi.org/10.1093/jn/120.suppl_11.1480

Kim WY, Jo EJ, Eom JS, Mok J, Kim MH, Kim, KU, … & Lee K (2018) Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study. *Journal of Critical Care*, 47, 211–218. https://doi.org/10.1016/j.jcrc.2018.07.004

Laird A & Kenny RA (2020) The Irish longitudinal study on ageing. Trinity College Dublin. https://www.doi.org/10.38018/TildaRe.2020-05

Li L & Werler MM (February 2010) Fruit and vegetable intake and risk of upper respiratory tract infection in pregnant women. *Public Health Nutrition*, 13(2), 276-282. https://doi.org/10.1017/S1368980009990590

Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, … Camargo CA (2017) Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. *BMJ*, 356. https://doi.org/10.1136/bmj.i6583

National Nutrition Survey – U.S.: NHANES – News – Understanding vitamins & more – NUTRI-FACTS. (2016). Retrieved May 7, 2020, from http://www.nutri-facts.org/en_US/news/u-s—nhanes.html

Pauling P (1977) Ascorbic Acid and Cancer [Video]. Retrieved May 7, 2020, from https://www.mediatheque.lindau-nobel.org/videos/31502/ascorbic-acid-and-cancer-1977/meeting-1977

Roll S, Nocon M, Willich SN (January 2011) Reduction of common cold symptoms by encapsulated juice powder concentrate of fruits and vegetables: a randomized, double-blind, placebo-controlled trial. *British Journal of Nutrition*, 105(1), 118-122. https://doi.org/10.1017/S000711451000317X

Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A & Bhan MK (1998) Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: A double-blind, controlled trial. *Pediatrics*,102(1), 1-5. https://doi.org/10.1542/peds.102.1.1

Tanaka K, Hashimoto T, Tokumaru S, Iguchi H & Kojo S (1997) Interactions between vitamin C and vitamin E are observed in tissues of inherently scorbutic rats. *The Journal of Nutrition*,127(10), 2060-4. https://doi.org/10.1093/jn/127.10.2060

Wintergerst ES, Maggini S & Hornig DH (2006) Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Annals of Nutrition and Metabolism, 50, 85-94. https://doi.org/10.1159/000090495

ZhiYong P (2020) Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia. ClinicalTrials.Gov. https://clinicaltrials.g0v/ct2/show/NTC04264533