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REVIEW ARTICLE

Consideration of host nutritional status as a mitigating factor against current and future pandemics: a review of nutrient studies and experiences with infectious diseases including Covid-19

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ABSTRACT

For over 3 years, the Covid-19 pandemic felt like a world war and has taken close to 7 million lives, disabled many more people, and caused innumerable economic losses around the globe. What can we learn from this tragedy? Are we ready for another Covid-19-like pandemic? Studies show that the majority of people with SARS-Cov-2 infection either show no symptoms or only mild to moderate clinical manifestations; only a small percentage develop severe Covid-19 disease, indicating that the clinical severity of Covid-19 disease is not determined only by the SARS-Cov-2 virus, but more importantly by how the host responds to the viral infection, what is known as natural immunity. Research of what enhances or weakens the natural immunity against viral infections and the practical application thereof is an important lesson one can learn from the pandemic. Research of natural immunity enhancing factors is summarized in this paper. One key characteristic of natural immunity against viral diseases is its non-specificity. The importance of this non-specificity helping to prevent and treat other infections of known or unknown viruses is also discussed. Calls for the clinical application of safe and inexpensive nutrients such as vitamin C in the prevention and treatment of Covid-19 have met significant resistance and objection from the medical authorities and the media since the pandemic outbreak. The main objection is the perceived lack of research and the absence of regulatory approvals. This raises a fundamental philosophical question: what is the primary goal of the medical profession? Facing a new viral pandemic like Covid-19 with no prior research, let alone any approved treatments, why is there opposition to known safe, inexpensive, widely available and often effective nutrients like vitamin C? Why are case reports and case series discounted or ignored rather than explored further to try to help more people? Is such objection protecting consumers or harming the public? Statistics show that viral epidemics and pandemics are occurring more frequently, with a recent review of epidemics and pandemics since 1600 concluding " the yearly probability of occurrence of extreme epidemics can increase up to threefold in the coming decades."1. When the next Covid-19-like pandemic of a new virus hits us, are we going to repeat the Covid-19 tragedy? Can improved emphasis on nutritional interventions to prepare for and respond to disease outbreaks mitigate future pandemics?

Introduction

From late 2019 into 2023, the Covid-19 pandemic, caused by the SARS-Cov2 virus, felt like a world war and has taken close to 7 million lives, disabled many more people, and caused innumerable economic losses around the globe. The World Health Organization has counted 769,806,130 confirmed cases, with just under 1% of those cases resulting in death. Analyzing the data by age shows people 60 years of age and older to be at greater risk of death than younger populations. At all ages, the majority of people infected with the SARS-Cov2 virus are asymptomatic or develop only mild to moderate Covid-19 disease. In a meta-analysis of 40 national studies covering 38 countries, Pezzullo et al found the age-stratified infection fatality rates (IFR) of Covid-19 for people under 50 years of age were less than 0.05%, and went up to 0.12% and 0.5% for age groups 50-59 and 60-69 years[2]. These data are not significantly different from those of influenza[3]. The fact that these patients were infected with the same virus, but they had quite different outcomes, varying from asymptomatic to death, indicate clearly that SARS-Cov2 virus infection *per se* does not determine the clinical outcome. A multitude of host factors, including the host's defense (immunity, redox balance, and genetic susceptibilities) impact whether the infected person is asymptomatic or develops severe disease or even death. The strategy focusing primarily on SARS-Cov2 virus including lockdowns and vaccines reflects a major deficiency in current medical thinking, as one of us (RZC) pointed out early in the pandemic.[4] RZC also pointed out early in the pandemic, R&D of vaccines takes time and does not help in the early stages of a new pandemic; the top priority in early pandemic management should be enhancing the population's disease fighting immunity[5]. Global Covid-19 pandemic management missed a key target: It's the host's defenses, not the SARS-Cov-2 virus that ultimately determines the clinical outcome of Covid-19.

Fighting a disease is like fighting a war, not knowing yourself (immunity), you will lose half the battles against diseases.

"If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. ***If you know neither the enemy nor yourself, you will succumb in every battle****". Sun Tsu*

"Keep righteousness inside, evil must not be done". With a strong and healthy immune system maintaining cellular and cell signaling checks and balances against self-harm, viruses can't wreak havoc.

The traditional Chinese medicine classic, "the Yellow Emperor's Inner Classic (***Huangdi Neijing***, 黃帝內經) also teaches us to **"Keep righteousness inside, evil must not be done"**[6]. The ultimate clinical consequence of a viral infection is the balance between our immunity and the virus, as clearly shown in the Covid-19 pandemic. Abundant studies have shown the effectiveness of micronutrients including vitamins, as well as certain existing prescription drugs, against viral infections including Covid-19.

Abundant studies show many vitamins and micronutrients strengthen our immunity.

Vitamins and minerals play various important roles in maintaining our immunity7,8.	
Immune Function	Key micronutrients
Maintaining physical barrier integrity (skin, gut and respiratory tract)	Vitamins A, B6, B9 (folate), B12, C, D, E; iron, zinc
Oxidative burst (to kill pathogens and for immune cell self-protection)	Vitamin C, E; copper, iron, magnesium, selenium, zinc
Innate immune cell proliferation, differentiation, function, and movement	Vitamins A, B6, B12, C, D, E, folate; copper, iron, magnesium, selenium, zinc
Antimicrobial activity (complement, interferons, cathelicidin)	Vitamins A, C, D; copper, iron, selenium, zinc
Regulation of inflammation (triggered by innate immune cells, pro-inflammatory cytokines):	Vitamins A, B6, C, E; copper, iron, magnesium, selenium, zinc
T cell proliferation, differentiation, and function	Vitamins A, B6, B12, C, D, E; copper, iron, selenium, zinc
T-cell inhibitory actions; including Treg function and reduction of autoimmunity risk	Vitamins B6, D, E
Antibody production and function (TH2, B-cells, antibodies):	Vitamins A, B6, B12, C, D, E, folate; copper, magnesium, selenium, zinc
Cell-mediated immunity (TH1, antigen-presenting cells (dendritic cells, macrophages, B-cells), T-cells)	Vitamins A, B6, B12, C, D, E, folate; copper, iron, selenium, zinc

Nutrition and immune health: "*In essence, good nutrition creates an environment in which the immune system is able to respond appropriately to challenge, irrespective of the nature of the challenge. Conversely poor nutrition creates an environment in which the immune system cannot respond well*"[9]. Poor nutrition compromises immunity and increases the risk of infection. Human trials have shown that intakes of some nutrients required for optimal immune function cannot be achieved through diet alone, and supplementation is needed[10]. The European Food Safety Authority has identified vitamins A, C, D, B6, B12, and folate, as well as, zinc, copper, iron, and selenium, as being essential for healthy immune function[11]. Nutrient deficiencies, whether pre-existing or acquired during infections, impair the production, performance, and maintenance of T and B cells including memory cells, and

impair the self-protecting regulatory T cells and cell-signaling needed to prevent self-harm including cytokine storms.

Poor nutrition is a risk factor in COVID-19

Poor nutritional status can increase the severity of COVID-19 outcomes[12]. Calcium, iron, selenium, and zinc levels were shown to be significantly reduced in COVID-19 patients and associated with increased inflammation, fever, and lung damage[8]. A review of 110,380 patients at the University of California showed a higher risk of COVID-19 breakthrough vitamin D deficiency cases. "Lockdown measures increased individual risk of vitamin D deficiency," the authors noted. The paper was delayed by more than 10 months by peer review. The lead author, Dr. Hogarth, wrote on his twitter account: This is the 175th COVID-19 sufficiency study on vitamin D that collectively showed higher levels of risk reduction, p<0.0000000001[13]. A meta-analysis of 54 studies involving more than 1.4 million people showed: low blood vitamin D levels linked to higher risk of Covid-19 infection, ICU admission and mortality[14]. Magnesium deficiency is common. A recent national survey found magnesium deficiency in ~50% of the US adult population[15].

Supplementation helps

The 2-year survey of 662,835 U.S. military veterans concluded that vitamin D3 and vitamin D2 supplementation reduced the risk associated with COVID-19 infection by 20% and 28%, and the risk associated with death within 30 days of COVID-19 infection by 33% and 25%[16]. 50,000 IU vitamin D per day for 5 days in COVID-19 patients resulted in less inflammation and shorter recovery times compared to patients receiving 1,000 IU/day[17]. In addition to standard care, early high-dose vitamin D therapy reduces the risk of ICU admission in COVID-19 patients.[18]

Vitamin C in infectious diseases

"Fighting an infection without vitamin C is like sending an army into battle without ammunition." ~Irwin Stone[19]

Intramuscular (IM) and intravenous (IV) vitamin C has been used as part of the successful treatment of a broad spectrum of infectious diseases since the 1940s. Case studies and case series involving adenoviruses, influenza, poliomyelitis, tuberculosis, tetanus, mononucleosis (EBV), Lyme's disease, Zika virus, Chikungunya virus, coronaviruses (SARS and SARS2), fevers of unknown origin, and viral and bacterial sepsis treated with high dose IM or IV vitamin C have appeared in the medical literature over the past 80 years[20-33]. A study in 1996 showed that the lower the plasma ascorbic acid level in septic patients, the greater the risk of organ failure and death[34]. A recent meta-analysis showed a 27% reduction in sepsis mortality when high dose IV vitamin C (HDIVC) was part of the treatment plan[35]. The studies reviewed used lower doses and shorter treatment durations compared to original HDIVC treatment recommendations.

While these various infectious diseases have many different clinical manifestations, there are several commonalities. All involve cellular oxidation, depletion of cellular NAD+ and antioxidant networks, and in the most severe cases, acidosis, immune dysfunction, shock, and organ failure. The SARS-CoV2 virus exacerbates cellular oxidation more than some infectious

agents due to its antisense and proteolytic enzyme knockdown of thioredoxin reductase 1, selenoproteins F and P, and glutamate cysteine ligase, which is the rate-limiting enzyme for glutathione synthesis. This results in increased reactive oxygen and nitrogen species, upregulation of NF-*k*B, upregulation of inflammatory cytokines and tissue inflammation, and disruption of host DNA production allowing a favorable environment for viral RNA production[36-51].

The oxidative stress-induced niacin sink (OSINS) model of pathogenesis was first published in 2009 in the context of HIV. However, it illustrates the progressive decay of immune system and cellular biochemistry interactions common to many, if not all, viruses as viral load and oxidative stress increases[52]. Oxidative stress is a significant factor in infectious disease due to lipid peroxidation (LPO) chain reactions, leading to damage of lipids which are critical for cellular structure and function. SARS-Cov2, even more than other viral infections, triggers this LOP chain reaction, leading to many downstream oxidative damages. When sufficient antioxidant defense is available, LPO can be prevented or neutralized without causing significant damages to the cells and tissues, which manifests clinically as mild to moderate diseases. However, when imbalance between toxins/oxidants and antitoxins/ antioxidants exists, LPO is triggered and accumulates, leading to severe clinical diseases[53-60].

Counteracting oxidative stress

Doses up to, and occasionally exceeding, 100 grams per day have been used safely and efficaciously. Dr. Frederick Klenner encouraged doses of 350 – 700 mg/Kg/day, increasing the dose and frequency as necessary until the patient recovered. In 2014, Dr. Alpha A Fowler published a successful phase I trial demonstrating the safety of HDIVC in septic patients[61]. No patient had an adverse reaction. As expected, all of the septic patients had low plasma ascorbic acid levels at the start of the study (17.9 +/- 2.4 μM [reference range = 50 – 70 μM]). The plasma ascorbic acid levels rose to 1592 – 5722 μM at the end of the four days of IVC treatment. In the IVC group, C-reactive protein and procalcitonin levels were lower, organ failure scores were lower, and thrombomodulin levels (a marker of endothelial damage) did not rise while they did rise in the control group not given IVC. The only contraindication to HDIVC treatment is glucose-6-phosphodehydrogenase (G6PD) deficiency, as red blood cell hemolysis may result in the setting of this rare condition. There are no reports of infectious microbes developing resistance to HDIVC therapy.

Mechanistically, vitamin C is capable of entering all cells, and is required for many biological processes, including: neuropeptide and neurotransmitter synthesis, catecholamine biosynthesis, tetrahydrobiopterin recycling, redox regulation, collagen and elastin synthesis, carnitine biosynthesis, breakdown of L-tyrosine, primary antioxidant functions, proteosomal degradation of HIF-1alpha, epigenomic regulation, somatic stem cell reprogramming, and immune functions[62-68]. Researchers from Dr. Lee in the 1950s-1960s through Dr. Catravas in 2017, conclusively demonstrated the importance of vitamin C in the health and repair of the endothelium[69 70].Coadministration of cortisol and IVC has been shown to rapidly repair endothelial damage. Vitamin C has been shown to play an important role in preventing

sepsis-related coagulation abnormalities, and reduce markers of thrombosis in high-risk cardiovascular disease and diabetes patients[71]. Oral and HDIVC administration in the setting of acute infections, including COVID-19, has shown a reduction in oxidative stress and inflammatory cytokine production, along with reduced risks of cytokine storm, organ failure, and death[72-74].

Studies have shown more than half of the US, Dutch, and German populations do not consistently consume the RDA or RDI for vitamin C. Starting with low or depleted biochemical defenses reduces a person's buffer from infection to progressive disease. The vast majority of critically ill patients are vitamin C deficient even when receiving "standard ICU care[75-78]". In the setting of critical illness, increased oxidation and metabolic demands to support a sustained robust immune response and healing requires more vitamin C intake than commonly appreciated. Intravenous vitamin C at 2-3 g/day has been shown to raise plasma vitamin C levels to normal levels in critically ill patients, but higher doses (10-16+ g/day) are required to achieve therapeutic levels. Oral intake of 6-24 grams of vitamin C per day was found to be effective for correcting Vitamin C deficiency caused by COVID-19, while 10-20g IVC per day with additional boluses were required in hospitalized severe cases.[79,80] In an RCT of septic patients with ARDS, intravenous vitamin C (200 mg/kg/day) reduced 28-day mortality and increased ICU-free and hospital-free days[81].

There is a consistent trend of better results with larger doses of IVC given for longer periods. The CITRUS-ALI RCT used a dose of 3g/6 hours/day for 96 hours (4 days) and showed a survival benefit, whereas the VICTAS trials used 1.5g/6 hours/day for 4 days and did not (VICTAS also had delayed intervention start times of up to 18 hours). Trials evaluating doses showed better results with 200mg/kg/day than with 50mg/kg/day. Trials employing IVC for 7 days showed more promising results than trials limiting use to 4 days. No trial has explored the doses recommended by the early pioneers of HDIVC treatment for infectious diseases (350 – 700 mg/kg/day until symptoms resolve). However, case studies using these ranges have shown success from the 1940s through the present.

In addition to satisfying a plethora of patient needs, HDIVC has a wide margin of safety. Studies have shown the vast majority of critically ill patients are vitamin C deficient even when receiving "standard ICU care". In the setting of critical illness, increased oxidation and metabolic demands to support a sustained robust immune response and healing requires more vitamin C intake than commonly appreciated.

Additionally, prior to the COVID-19 pandemic, selenite, selenocysteine and vitamin D had been shown to reduce susceptibility and improve outcomes in the settings of hemorrhagic fever, influenza and sepsis[82-85]. In the 1990s and 2000s, it was demonstrated that several viruses, including enteroviruses, coxsackieviruses, and influenza, mutate from benign strains to pathogenic strains within selenium deficient hosts. The mutated strains were then capable of causing disease in the previously unaffected selenium replete hosts[86-91].

Nutritional therapies to support patients' biochemistry and natural immune responses is a sound approach to known and unknown disease outbreaks. Large doses of key nutrients

including vitamins C, D, and B1 (thiamine) may be needed to counteract overwhelming infections[92,93]. In addition to boosting patients' defenses, these nutrient therapies, especially selenite or selenocysteine, can also reduce pathogenic mutations in some viruses.

Early Pandemic Findings

In 2020, reports of successful outcomes using HDIVC as part of COVID-19 treatment plans appeared from China and various states in the USA, including New York, Michigan, Virginia, Texas[94,95,96,97,98,99]. An RCT providing 50mg/kg/day IVC (a mere 1/6 the minimum dose recommended by Dr. Klenner) showed quicker symptom resolution and fewer hospital days in the 75 patients in the treatment group compared to an equal number of controls receiving standard care[100]. One of these authors (RZC) reported a case series of 50 patients treated with 10-20g HDIVC per day showing real time improvement in oxygenation, and all patients survived[101]. Additional boluses of HDIVC were given to some critically ill patients.. An RCT using 3g every 6 hours for 7 days for patients with severe Covid-19 showed decreased rates of mechanical ventilation and cardiac arrest in the treated group[74]. At the same time, reports also emerged of successful interventions with glutathione, selenite and selenocysteine[102.103.104.105]. Glutathione, selenium containing glutathione peroxidase, and vitamin C are interdependent for recycling one another from their oxidized to reduced forms. Separate studies in Israel, Germany, Spain, and the USA showed vitamin D, selenoprotein P, and Zinc to be useful biomarkers for predicting COVID-19 morbidity and mortality[106-110]. An analysis of 5 RCTs involving vitamin D interventions in COVID-19 patients showed ICU admission and mortality reduction with vitamin D treatment. Pooling the studies provided a large enough sample size and statistical power to consider the results conclusive[111].

Pandemic Preparedness – Host Nutritional Status, the Forgotten Virulence Factor, Revisited

Raising the nutritional status of the population should be a central pillar of public health efforts, including pandemic preparedness. A strong nutritional foundation puts individuals and populations in a healthy position to defend against a broad spectrum of challenges. It is less expensive, more broadly applicable, and more proactive than racing to develop disease specific "silver bullets" after a new threat is detected. It also appears to have greater staying power as a long-term public health strategy since "nutrient resistant pathogens" have not emerged yet, contrary to antibiotic and antiviral medications. Additionally, a strong nutritional foundation puts individuals in position to get the most benefit from vaccinations due to increased development and prolonged survival of memory cells in replete individuals compared to those with insufficient or deficient statuses of key nutrients, while also providing a buffer against vaccine and disease induced autoimmunity. Furthermore, including a strong nutritional foundation as a central pillar of pandemic preparedness is likely to offer the "side effect" of delaying and better managing chronic diseases. In addition to direct benefits to the host's health, a strong nutritional foundation can have a direct impact on the mutagenesis of viruses infecting each host. It has been known for decades that several benign viruses will reliably mutate into pathogenic

strains in the absence of key nutrients (this knowledge is often applied in "gain of function" work with viruses). Establishing and maintaining nutrient replete status throughout the food chain is a promising approach to reduce the likelihood of the emergence of viral pathogens, and of new virulent strains within an existing outbreak.

Synergistic and systemic nutrient teamwork for optimal health

The above analysis just scratched the surface of the vast amounts of studies involving many micronutrients and existing medications that show effectiveness and safety against various viral infections.

There is also growing evidence that the biological effects of many of these micronutrients are synergistic and interdependent. As discussed in more detail previously, these micronutrients often complement each other to amplify their immune boosting and virus fighting effects synergistically[112,113]. Often they work interdependently, such as in the case of vitamins C and E, along with sulfur and selenium dependent glutathione and glutathione peroxidase, in the prevention and breaking of lipid peroxidation chain reaction, central to the pathology of severe Covid-19 disease, as previously discussed.[88] Without vitamin C, vitamin E can't protect the cell membrane bound lipids from oxidant attacks. The concepts of interdependence and synergy require nutrients to be studied as a network of related compounds for best results rather than as monotherapies. It is also important to measure blood and tissue levels of nutrients rather than only assessing intake, as most biological reactions take place in the tissue and at the cellular levels. Nutrient demand and consumption also increase markedly during critical illness.

These synergistic and interdependent relationships among micronutrients and other biomolecules (such as various hormonal systems) are common in biological systems including humans. While more research is clearly indicated, when faced with an emergency as grave and widespread as Covid-19, where time is critical, we believe that an integrative treatment to include as many micronutrients and other available treatments in the fight against a Covid-19-like catastrophe is within the medical professional's natural duty. Facing global catastrophy as grave as Covid-19 and without any proven therapies, the medical authorities, government regulatory agencies, the society at large and the healthcare providers should form a united front to fight against the pandemic; and the frontline healthcare providers should be encouraged to apply their knowledge, wisdom and past experiences to fight against the pandemic.

Conclusion

While "germ theory" is important, host nutritional status remains a critical determinate of disease susceptibility and germ virulence. Early aggressive interventions with key nutrients associated with supporting robust host immune responses is a safe and effective approach to combating many infectious illnesses. Strengthening the nutrient status of the entire food chain, and especially humans, is a helpful cornerstone of pandemic preparedness, prevention, and initial response.

Nutrition is the cornerstone for optimal health including our immunity against viral infections.

Abundant research clearly indicates that the insufficiency and deficiency of multiple micronutrients are at the pandemic level globally, including within the USA and other wealthy nations, which was a major contributing factor to failures in the war against Covid-19. Our analysis shows the safety and effectiveness of many micronutrients in the prevention and treatment of viral infections including Covid-19. These micronutrients play various essential roles in our health and defense against viruses and other pathogens. It takes not just one, but all of them, to form our strong immune defense. Their clinical application, therefore, requires integrative nutritional therapy. Only when all nutrients are replete is biochemical synergy optimized to fight disease safely and effectively. The ultimate goal of the medical profession is to heal, with whatever is safe, available, and potentially effective, particularly when specific established therapies are non-existent, such as at the beginning of the Covid-19 pandemic. Not to promote nutritional immunity against Covid-19, but instead, to censor such promotion as seen globally including in the USA (as one of us, RZC, personally experienced) is against the spirit of the medical profession. The effectiveness of vitamin C and other nutrients against Covid-19 requires rethinking of today's medicine.

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