Expediting COVID-19 Recovery with an Orthomolecular Approach: Two Case Reports

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ABSTRACT

These case reports discuss two middle-aged patients with confirmed symptomatic COVID-19 infection that improved swiftly upon receiving orthomolecular oral and intravenous therapy. The intravenous solution provided minerals like magnesium, as well as vitamin C and B complex vitamins, among others. The patients also started iodine-based nasopharyngeal decontamination spray and oral supplements, including substantial doses of vitamins C, B complex, and D, as well as magnesium, zinc, quercetin, melatonin, and omega-3. In addition, two types of biological response modifiers, palmitoylethanolamide and specialized proresolving factor marine lipid concentrate, were used. As well as reporting on the treatment and evolution of both cases, we review the mechanisms and clinical evidence supporting each element of the treatment protocol.

Keywords: COVID-19; Nasopharyngeal decontamination; Orthomolecular; Metabolic correction

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CASE REPORTS

JL is a 50-year-old female who reported developing continuous fever, body aches, a strong headache, runny nose, acute itch in the throat and ears, upset stomach, diarrhea, metallic taste, loss of smell, fatigue, and respiratory difficulties when lying in bed in the afternoon of December 14, 2021 (day 0). She came to the clinic on December 17 (day 2) with a positive SARS-CoV-2 result (Abbott RealTime SARS-CoV-2 Assay). Lab results from day 0 revealed increased blood lipids and a vitamin D deficiency (25-hydroxycholecalciferol of 17.6 ng/ml). White blood cell count revealed a normal total count with increased lymphocytes (Table 1).

While at the clinic on day 3, JL reported some respiratory difficulty, but the lungs were clear to auscultation and the respiratory rate and oxygen saturation were normal. The patient was given intramuscular injections of vitamin D3 (cholecalciferol 150,000 IU into each gluteus) and intravenous fluids with vitamin B complex, calcium gluconate, magnesium, and vitamin C (Table 2). Since the patient arrived with nausea, she was also given orally dissolving ondansetron tablets (Zofran ODT).

Table 1: JL Complete blood count, December 14, 2021.

- WBC: 6.00 × 10^3/µl
- Neutrophils: 31.6%
- Lymphocytes: 54.6%
- Monocytes: 11.8%

Table 2: Intravenous infusions.

- MgCl: 96.5 mg
- B1: 16.2 mg
- B2: 32.3 mg
- B3: 16.3 mg
- B5: 40.7 mg
- B6: 16.3 mg
- Hydroxy B12: 10 mg
- Ca gluconate: 40.7 mg
- Vitamin C: 644 mg

In addition, she was prescribed a series of oral micronutrients (Table 3), an antiseptic mouthwash to gargle three times a day, and an blend of essential oils (camphor, eucalyptus, and menthol) for inhalation three times a day.

The same day upon arriving home, she started using three pumps of iodine antiseptic oral and nasal sprays every 4 hours. The patient reported rapid and significant improvement after intravenous therapy and oropharyngeal antiseptic spray treatment (Aquara oral and Aquara nasal products). Specifically, she reported improved energy and relief from headache and body aches after the intravenous infusion, and relief from runny nose, sore throat, and metallic taste shortly after the iodine antiseptic oral and nasal sprays. The following day (December 18; day 5) she received an infusion of the monoclonal antibody REGEN-COV (casirivimab and imdevimab). At the follow up, she reported compliance with the prescribed oral supplement regimen. By day 6 (day 4 of therapy), she reported that she was symptom free. No further lab testing was performed for SARS-Cov-2 status due to high demand for lab testing at the time. JL's household members reported conversion to negative status.

JC, a 52-year-old man, developed body aches, a strong headache, runny nose, upset stomach, continuous fever, and fatigue in the morning of

Table 3: Oral supplementation.

- Vitamin C: 3000 mg tid
- Quercetin: 250–500 mg bid
- Zinc: 100 mg qd × 4 weeks, then 30–50 mg qd
- Melatonin: 10 mg hs
- Vitamin D3: 10,000 IU qd × 4 weeks then 5000 IU qd
- Magnesium: 450–500 mg hs
- B complex: 10 ml qd
- Curcumin: 500 mg tid
- Famotidine: 20–40 mg qd
- Omega-3: 1 g qd
- Palmitoylethanolamide (PEA): 1 tab bid
- Specialized proresolving factor (SPF) marine lipid concentrate, 1 cap qd

December 15, 2021 (day 0). Abbott RealTime SARS-CoV-2 Assay came back positive on December 16 (day 1). The next day (day 2), the patient received intravenous fluids with vitamin B complex, magnesium, calcium gluconate, and vitamin C (see Table 2). The following day (day 3), he received an infusion of monoclonal antibody. JC's recovery was much slower than JL's; it took 14 days for him to be almost symptom free. He did not start using iodine antiseptic oral or nasal sprays until day 10 (December 25). A mild cough when talking persisted until the end of January 2022. His SARS-Cov-2 antigen test came back negative on December 29 (day 14). However, on January 4 (day 20), a molecular test returned a positive result.

DISCUSSION

COVID-19 is an infection caused by coronavirus SARS-CoV-2.[1] The original virus was highly contagious, and many deaths were attributed to complications of the infection, mostly related to disseminated and severe inflammation caused by cytokine storm, massive oxidative stress, mitochondrial dysfunction, and coagulopathies. Given the high prevalence of nutritional insufficiencies in the United States, Puerto Rico, and other countries, many infected patients cannot maintain adequate homeostasis and therefore succumb to complications of acute respiratory distress syndrome (ARDS), which can lead to cellular injury, organ failure, and death.[2]

The patients were mainly managed with an orthomolecular regimen including intravenous, intramuscular, and oral micronutrients. Because of their age, they qualified for monoclonal antibody therapy (casirivimab and imdevimab), which neutralizes the SARS-CoV-2 spike protein and has been shown to reduce COVID-19-related hospitalizations and emergency room visits.[3] However, the patients were already recovering at the time of antibody infusion. JL had a faster recovery, possibly due to a high-dose intramuscular vitamin D injection and early use of an iodine-based nasopharyngeal decontamination spray.

Optimal immune system function requires proper amounts of micronutrients. Micronutrients have important cofactor activities in enzymes that regulate inflammation and other immune system processes.[4] In addition, many micronutrients have antioxidant activity that protects cell components (including mitochondria) from damage produce by elevated reactive oxygen species (ROS) in conditions such as COVID-19. A study of COVID-19 patients that evaluated levels of antioxidants and oxidative stress markers concluded that infected patients had significantly lower levels of antioxidants.[5] Furthermore, the study indicated that severe COVID-19 patients are at higher risk of oxidative stress. Although COVID-19 infection is the likely cause of depleted antioxidant cofactors, the study was not designed to determine cause and effect. It has been established that even in rich countries, dietary patterns may not provide adequate micronutrients for optimal immunological function. The National Health and Nutrition Examination Survey (NHANES) is one of a series of health-related programs conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). Data are collected every year from the US population. Recent NHANES data have established that a significant proportion of the US population is deficient in nutrients, including vitamin C (46%), vitamin A (45%), vitamin E (84%), iodine (60%), and vitamin D (95%).[6]

Using nutritional therapies that are based on sound biological mechanisms, clinicians have reported good outcomes for COVID-19 patients.[7] For this reason, the following nutritional supplements were included as part of the treatment protocol for these case reports.

VITAMIN D

Vitamin D is a lipid-soluble vitamin that is ingested as ergocalciferol (plants) or cholecalciferol (animals) and converted in the body to the active metabolite 1,25-dihidroxivitamina D or calcitriol. Vitamin D exerts antibacterial and antiviral effects via multiple mechanisms, including inducing macrophage differentiation and induction of peptides. It also modulates lymphocyte balance by suppressing the release of proinflammatory cytokines.[8] In a study of five patients hospitalized with COVID-19, researchers observed a deficiency of

vitamin D in 76%, and of selenium in 42%, of the patients.[9] Although vitamin D is not considered an antioxidant, it reduces renin-angiotensin-aldosterone system (RAAS) activity and consequently decreases ROS. Vitamin D deficiency is associated with a higher risk of invasive mechanical ventilation and death.[10] Vitamin D deficiency has been found to promote ARDS. Mortality rates from ARDS increase with age and chronic disease comorbidities, both of which are associated with lower 25(OH)D concentrations. To decrease the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 take a loading dose of vitamin D3 to quickly elevate 25(OH)D levels, followed by a maintenance dose of 5000 IU/d.[11]

VITAMIN C

Vitamin C (ascorbic acid) directly and indirectly supports many aspects of the immune system, especially those related to protection from viral infection.[12] Vitamin C is also necessary for skin and mucosal barrier function against pathogens. Vitamin C accumulates in phagocytic cells and enhances chemotaxis, phagocytosis, ROS generation, and eventually microbial killing.[4] Vitamin C has been shown to enhance the differentiation and proliferation of B- and T-cells.[13,14] Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. Infections and inflammation increase the metabolic requirements for vitamin C and can deplete body stores and serum levels. Supplementing with vitamin C was found to improve antimicrobial and natural killer (NK) cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity.[15]

OROPHARYNGEAL ANTISEPTIC DECONTAMINATION WITH IODINE

Iodine is an essential element that must be obtained from the diet or supplementation. It has been shown to increase IgG synthesis.[16] Iodine insufficiency is associated with diminished phagocytic activity of blood neutrophils.[17] Iodine has been shown to kill a wide range of microorganisms. It also inhibits the synthesis and release of bacterial exotoxins, increases the ability of granulocytes to kill infectious organisms,[18] and improves the immune response.[19]

Viral inoculation in the oral and nasal passages triggers an immune response. The initial response is the dispatch of NK and T-cells. If viral replication is interrupted, viral load is minimized, and the patient will likely remain asymptomatic. It has been demonstrated that the lower the viral load, the lower the risk of severe COVID-19 and mortality.[20] Irrigating the oral and nasal passages with an iodine-based rinse deactivates the virus almost on contact, and reduces its ability to replicate and aerosolize into the respiratory tract. The pharmacodynamics of iodine allows for rapid penetration of the microorganism cell wall and disrupts protein nucleic acid structure and synthesis, causing them to become denatured and deactivated.[21] A study of 189 participants compared iodine-based nasal irrigation or spray with a water control. The study reported that approximately 80% of the iodine group achieved negative PCR results versus only 18.5% of the control group over the same time period.[22,23] We recently reported favorable outcomes, with regard to the prevention and treatment of COVID-19, in a study of 175 participants using a proprietary oral and nasal pharyngeal iodine rinsing solution compared with historical controls.[24]

OVERVIEW OF OTHER NUTRIENTS

Quercetin is a flavonoid found in fruits and vegetables that is reported to have many biological effects, such as anticancer, anti-inflammatory, antiviral, and antioxidant activity. It can also inhibit lipid peroxidation, platelet aggregation, and capillary permeability, stimulate mitochondrial biogenesis, and reduce the risk of infection.[25,26] Evidence suggests that simultaneous administration of vitamin C and quercetin exerts a synergistic antiviral action. This is the result of overlapping antiviral and immunomodulatory mechanisms, and the ability of ascorbate to recycle quercetin, thereby increasing its efficacy. Current evidence supports the use of vitamin C and quercetin for prophylaxis in high-risk populations, and for the treatment of patients with COVID-19 as an adjunct to pharmacological agents.[27]

Zinc is an essential micronutrient that functions as a cofactor and signal modulator. The body does not

store excess zinc, so it must be obtained from the diet. Zinc is necessary for human health, growth, and sense of taste. It is involved in carbohydrate and lipid metabolism, as well as in reproductive, cardiovascular, and nervous system function.[28] It also plays a key role in vision maintenance and could have antiviral effects.[29,30] Zinc is commonly used for treating dermatitis, acne, diabetes, anorexia, and burns.[31] Zinc is a key regulator of the proliferation, differentiation, and maturation of white blood cells.[27]

Melatonin is a neurohormone mainly synthesized and secreted by the pineal gland. It has numerous functions including antioxidant, anti-inflammatory, anti-excitatory, sleep-initiating, and immunoregulatory properties.[32] It protects mitochondria from free radical damage and modulates mitochondrial permeability.[33] Given these effects, along with its very good safety profile and positive impact on the RAAS, melatonin may be a beneficial supplement for reducing the risk of COVID-19.[31]

Magnesium serves as a cofactor for over 600 metabolic enzymes. It is required for a wide range of vital functions, such as bone formation; neuromuscular activation; glucose, lipid, and protein metabolism; DNA and RNA stability; and cell proliferation.[34] There is some evidence to suggest that supplementing with magnesium might help protect against SARS-CoV-2 infection, reduce the severity of COVID-19 symptoms, and facilitate recovery after the acute phase of illness.[35]

B complex vitamins modulate the immune response by downregulating proinflammatory cytokines. They may also reduce breathing and gastrointestinal problems, and prevent hypercoagulability, potentially improving outcomes and reducing the length of hospitalization for COVID-19 patients.[36]

Curcumin is well-tolerated even at high concentrations.[37] It shows broad-spectrum antiviral activity against enveloped viruses, and may suppress SARS-CoV-2 infection by directly modifying the spike protein or ACE2 receptors and inducing host antiviral responses by modulating NRF2 and HMGB1. Curcumin exerts immunomodulatory activity by blocking NF-κB-, HMGB1-, and IL-6-driven inflammatory responses. It also dampens ROS production by inhibiting NADPH oxidase, and alleviates oxidative tissue injury by increasing antioxidant defenses via NRF2.[38]

Famotidine is a competitive histamine H2-receptor antagonist commonly used for gastric acid suppression. Early clinical evidence suggests that treatment with famotidine may decrease COVID-19-related morbidity and mortality. The mechanism by which famotidine could improve the outcomes of COVID-19 is currently unknown.[39] It has been suggested that famotidine may reduce COVID-19 severity through antagonism or inverse agonism of histamine signaling.[40] A meta-analysis found no significant association between famotidine use and clinical outcomes.[41]

Omega-3 fatty acids are a diverse group of essential fatty acids with a double bond between the third and fourth carbon atoms from the methyl end. Omega-3 fatty acids are key building blocks of cell membranes and many other compounds, including hormones. They are involved in clotting regulation, arterial contraction and relaxation, and inflammation.[42] They also bind to receptors that regulate genetic expression.[43] Dietary changes over the last 150 years have created an imbalance in the omega-6 to omega-3 fatty acid ratio that is associated with excess prothrombotic, pro-aggregatory, and vasoconstrictive hemostatic effects. This may contribute to the development of chronic illnesses such as cardiovascular diseases, neurological conditions, diabetes type 2, and cancer. Omega-3 fatty acid supplementation may support health.[44] Omega-3 fatty acids exhibit antiviral effects by preventing influenza virus replication. In an expert statement, the European Society for Parenteral and Enteral Nutrition commented that omega-3 fatty acids may improve oxygenation in COVID-19 patients.[45] In a double-blind, randomized clinical trial of 128 critically ill patients infected with COVID-19, those on omega-3 supplementation had a significantly higher 1-month survival rate, as well as higher levels of arterial pH and HCO3, and lower levels of BUN, Cr, and K, compared with the control group.[46]

Palmitoylethanolamide (PEA) is an endogenous lipid believed to be involved in homeostatic mechanisms that are activated as a result of the inflammatory response. The actions of PEA on multiple molecular targets modulate multiple

inflammatory mediators and suggest therapeutic benefits in many domains, including immunity, brain health, allergy, pain modulation, joint health, and sleep and recovery.[47] Although PEA has poor oral bioavailability, advanced delivery systems have been shown to overcome this limitation.[48] A metanalysis found that PEA was associated with significantly greater pain reduction when compared with an inactive control.[49] A small randomized controlled trial found that patients supplemented with PEA had greater improvement in olfactory threshold, discrimination, and identification scores versus controls.[50] PEA was used successfully to treat a 45-year-old COVID-19 patient who developed antiphospholipid syndrome following cytokine storm induced by SARS-CoV-2 infection.[51]

Specialized proresolving mediators (SPMs) are a group of endogenously produced lipid substances that promote the resolution of inflammation. These cell signaling molecules are formed by the metabolism of polyunsaturated fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), along with arachidonic acid (AA) from the diet. The formation of SPMs is dependent on enzymes like lipoxygenase, cyclooxygenase, and cytochrome P450 monooxygenase. SPMs such as resolvins, maresins, and protectins may counteract cytokine storm and reduce inflammation in COVID-19.[52] SPMs hold strong therapeutic potential in the management of COVID-19 as they can regulate macrophage infiltration and cytokine production and also promote a proresolving macrophage phenotype.[53]

PHYSIOLOGIC SYNERGISTIC EFFECT OF SUPPLEMENT COMBINATIONS: THE METABOLIC CORRECTION EFFECT

The most significant complication of SARS-COV-2 infection is ARDS, which occurs as a result of leukocyte infiltration into the alveoli, uncontrolled cytokine storm, coagulopathies, and other severe inflammatory manifestations. Interferons (IFNs) play an important role in immune-related antiviral defenses. Several nutrients, including vitamin D, magnesium, and zinc, are essential for modulating the immune system and IFN signaling pathways. The synergistic action of vitamin D, magnesium, and zinc in IFN signaling may be an important factor in COVID-19 therapy.[54] Micronutrients such as C, D, E, zinc, selenium and omega-3 fatty acids have immunomodulatory properties that are important against infectious diseases including COVID-19.[35] A 20-week study of 50 patients supplemented with zinc, quercetin, vitamins C, D3, E, and lysine found that only 4% had symptoms of influenza compared with 20% of the control group. Additionally, none of the experimental group had positive COVID-19 test results compared with 15% of the control group.[55] Another study found that supplementation with vitamins A, B, C, D, and E could improve the inflammatory response and decrease disease severity in COVID-19 patients.[56] An adequate supply of zinc, selenium, and vitamin D is essential for immune function, resolving inflammation, and resistance to viral infections.[57]

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