A Pragmatic Approach to Immunity & Respiratory Viral Infections

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My paternal grandmother was notorious in our family for having succinct and poignant pearls of wisdom. One that was used a lot under stressful times was, “You play the cards in your dealt in life to the best of your abilities.” During these unprecedented, turbulent times in our modern world, these sagacious words ring even more true.

We are unfortunately living in a time when SARS-CoV-2, more colloquially known as COVID-19 (corona virus disease 2019) is as pervasive on everyone’s mind and in the media, as the necessity it is to drink water in order to survive. Our stressful times are now exacerbated by riots, civil unrest, political and economic uncertainties.

What we’re experiencing as a nation and as a world has not been seen in generations. It seems to affect everyone differently, physical, emotionally, and spiritually. I have family, friends, colleagues, and patients, for whom it’s just another day, and I have ones that are on the complete other side of the spectrum, feeling so distraught, they will descend into madness; and everything in between.

In just the past few months since the pandemic really seemed to grip the world, the research literature has exploded into thousands of articles. I won’t even go into everything else: blogs, tweets, posts, videos, etc., as it’s mindboggling and many times nauseating. Everyone seems to have an opinion, whether based on sound logic and science or not.

At first, I was going to write an article on the history of SARS-CoV-2, as well as pathophysiology, pathogenesis, testing, clinical symptoms, and naturopathic therapeutic interventions.

I have decided not to approach this article via this manner, given that there are so many sources out there that have done an outstanding job. For example, I cannot put into words how the Centers for Disease Control (CDC)’s Focus on COVI-19, Vol 19, No. S1. It is exceptionally thorough and very well done.

So, why should I write what already has been written, albeit some of the following may be a bit redundant of other outstanding articles? Instead, I will write about the most common viruses that cause respiratory disorders, and what naturopathic treatment interventions have been proven in the scientific literature (evidence-based) to be effective in both prevention and treatment of many viruses, regardless of type. There are too many interventions to list, so I will focus on the ones I have utilized in my private practice for the past ten years (clinical-based medicine). I will provide a brief overview of SARS-CoV-2 virology, along with epidemiology. I will also discuss interventions to mitigate cytokine storm and attenuate inflammation, outside the use of acetaminophen and NSAIDS.

Lastly, there is a fact that I feel has been significantly neglected the past few months since the pandemic really gained so much momentum, and that is the emotional impact. I will discuss some “natural” therapies that have proven efficacy in what many are seeing in not only our patients, but friends, families, colleagues and maybe even ourselves—anxiety, depression and even despair.

Coronavirus Context

According to Nature Reviews Microbiology, there are more than $1 \times 10^{13}$ (10 quintillion, or in the US, nonillion) viruses on Earth, but only a bit more than 200 are capable of causing human illness. The human microbiome contains approximately 38 trillion bacteria. Compare this to the human virome, which contains approximately 380 trillion viruses! Viruses are some of the smallest creatures on Earth, between 20-400 nanometers (nm) in diameter. They are essentially packets of nucleic acids (either RNA or DNA), surround by a protein shell and sometimes lipids. They are dormant outside a living cell and they need to hijack a host’s metabolic machinery in order to survive and produce copies of itself.

According to the Centers for Disease Control (CDC), colds and flus occur all year, but the “season” for them is typically December through February. Viral infections most commonly cause upper respiratory tract infections (URTI’s), of which the most common are caused by influenza A and B, H5N1 and H7N9 avian influenza A, parainfluenza 1 through 4, adenoviruses, respiratory syncytial virus A and B and human metapneumovirus, rhinoviruses and yes, coronaviruses.

Given the current times, I would like to focus on coronaviruses. These are zoonotic pathogens of enveloped RNA viruses that cause respiratory illnesses of varying severity from the common cold to fatal pneumonia and only seven are known to cause disease in humans. Four out of the seven most frequently cause symptoms of the common cold; coronaviruses 229E and OC43 are known to cause the common cold. Serotypes NL63 and HUK1 have also been associated with the common cold. Rarely,
severe lower respiratory tract infections, including pneumonia, can occur, primarily in infants, older people, and the immunocompromised.10

Epidemiology, Pathogenesis and Testing

As of August 21, 2020, there have been 22,773,308 confirmed global cases of COVID-19, with 795,196 deaths. In the United States, there have been 5,600,107 cases and 174,647 deaths (case fatality rate of 3.12%).11 I emphasize confirmed because many countries may be underreporting cases and/or deaths.12 Some countries, like North Korea, refuse to even report data to the World Health Organization (WHO).13

Viral shedding and the period of greatest infectiousness seems to be earlier in the stages of illness, when viral RNA levels in respiratory droplets are highest.14 Is this person asymptomatic (does not have symptoms but is infected and will never develop symptoms), or pre-symptomatic (the phase when an individual is infected and may be shedding virus but hasn’t yet developed symptoms), and can one tell the difference? No, since symptoms may show up between 2 to 14 days after exposure, with infectiousness starting about 2 days prior to symptom onset, peaking about 0.7 days before symptom onset, then declines within seven days, but can occur up to 21 days after exposure. This is where nucleic acid amplification (NAAT), most commonly with reverse-transcription polymerase chain reaction (RT-PCR) tests can be valuable, since they can detect the viruses about a week before any symptoms even show up.15,16,17

Serological testing (IgA, IgM and IgG) seem to be a more precise diagnostic tool after day 14 of symptom onset, with IgA and IgM titers tending to dissipate after 3 weeks, while IgG confers long-term immunity, approaching 100% seropositivity by 16 to 20 days.18,19 Recently, The Infectious Diseases Society of America (IDSA) released a statement stating that 3 to 4 weeks after exposure, is optimal.20

It should be noted that these are “general” statistics, in that antibody produced with SARS-CoV-2 are predicated upon how seriously ill the individual (i.e., less severe disease has been shown to lead to smaller antibody production21) became and underlying immune competence. Given this novel virus, we also don’t know how long a person will have protective antibodies. One study showed IgG levels declining by a median of approximately 75 percent from the acute to early convalescent phase of illness, and at eight weeks following infection, 40 percent of asymptomatic patients and 13 percent of symptomatic patients did not have detectable IgG.22

According to a recent CDC report of over 370,000 confirmed COVID-19 cases in the US, the most common symptoms are cough in 50 percent, fever (subjective or >100.4°F/38°C) in 43 percent, myalgia in 36 percent, headache in 34 percent, and dyspnea in 29 percent. Anosmia, ageusia, abdominal pain, and rhinorrhea occur in less than 10% of cases.23 Those infected with SARS-CoV-2 can have absolutely no symptoms, to mild, to severe and even death. Complications can be seen in the form of respiratory failure, arrhythmias, and thromboembolisms.24 Certain lab values have now been associated with worse outcomes: elevations in D-dimer, ferritin, CRP, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), troponin, as well as lymphopenia and thrombocytopenia.25,26,27

Convalescence appears to be around two weeks for mild infections and three to six weeks for severe disease.28 The most common persistent symptoms were fatigue (53 percent), dyspnea (43 percent), joint pain (27 percent), and chest pain (22 percent).29 Recovery course is variable and depends on age and pre-existing comorbidities in addition to illness severity.

The immense details of the various common viral infections are beyond the scope of this article, but in this author’s view, four main points should be considered: infection prevention, specific antiviral interventions, inflammation modulation, and immune balance and enhancement.

Prevention

Benjamin Franklin coined the axiom, “an ounce of prevention is worth a pound of cure.” This is especially apt today, particularly when it comes to infections. General strategies cannot be underscored enough. Diligent hand washing, use of hand sanitizer that contains at least 60% alcohol, respiratory hygiene (e.g., sneezing into elbow crease), avoiding touching the face, avoiding crowds and close contact with ill individuals, cleaning and disinfecting objects (bleach or at least 60% alcohol), surfaces that are frequently touched, wear a mask and stay at least 6 feet from other people who are not from your household in both indoor and outdoor spaces.30,31

Let us not kid ourselves, these are very stressful and trying times for everyone. Now, maybe more than we have ever experienced before in our lifetimes; ourselves and our patients need to be more cognizant of how stress and poor sleep negatively impacts our immune system. Chronic stressors are associated with suppression of both cellular and humoral response2and infection-fighting antibodies and cells are reduced during periods when you don’t get enough sleep.33

Given the aforementioned statements, the diligent use of adaptogens and non-addictive sleep aids may provide tremendous benefits for the immune system, stress, anxiety and depression.34 Botanical adaptogens like Withania somnifera (ashwagandha), Glycyrrhiza glabra (licorice) and Rhodiola rosea (rhodiola), have been used for thousands of years in Ayurvedic and Chinese medicines to help the body cope with stress, increase stamina and vitality, and also support the immune system.35,36,37

One of the added benefits of the use of adaptogens, is also the typical positive effect on the immune system. The withanolides and sitoindosides in ashwagandha
cause a mobilization of macrophages, phagocytosis, and lysosomal enzymes.\textsuperscript{38} The glycyrrhizin triterpene saponin may provide use in viral infections, particularly COVID-19 because it “binds angiotensin-converting enzyme II (ACE2), downregulates proinflammatory cytokines, inhibits the accumulation of intracellular reactive oxygen species (ROS), inhibits thrombin, inhibits the hyperproduction of airway exudates, and induces endogenous interferon.”\textsuperscript{39} Rhodiola contains over 30 compounds\textsuperscript{40} including the most well studied being salidroside, rhodioloside and rosavin (exclusive to the rosea species)\textsuperscript{41}, increases B cells, T cells, NK cells, and cytokine facilitation.\textsuperscript{42}

Melatonin’s most famous use is as a sleep-aid, improving both sleep latency and quality of sleep,\textsuperscript{43} but this revered hormone is also highly anti-inflammatory,\textsuperscript{44} strong antioxidant,\textsuperscript{45} antiviral, showing efficacy in COVID-19 neurological sequelae\textsuperscript{46} and immunomodulating.\textsuperscript{47}

Simple interventions for which we have some of the greatest control over—diet and exercise—are often overlooked. What doesn’t exercise do that is positive? It relieves stress, helps improve sleep quality and improves immune function.\textsuperscript{48,49,50}

A healthy diet is the cornerstone of any aspect of proper immune function. Professor Philip Calder says it better than I: “Practically all forms of immunity are affected by protein-energy malnutrition, but non-specific defenses and cell-mediated immunity are most severely affected. Micronutrient deficiencies impair immune function … the gut-associated lymphoid tissue is especially important in health and well-being because of its close proximity to a large and diverse population of organisms in the gastrointestinal tract and its exposure to food constituents.”\textsuperscript{51}

Speaking of gut health, the human gastrointestinal (GI) microbiome has been well established to play an enormous role in human health, disease, immune function and inflammatory processes.\textsuperscript{52,53,54} Ergo, the prudent use of prebiotics, probiotics, synbiotics and \textit{Saccharomyces boulardii} can’t be understated. Different strains supply different health aspects, but generally speaking all play vital roles in increasing sIgA, have anti-inflammatory properties, inhibit biofilm formation and are competitive inhibitors for opportunistic and yeast and bacteria.\textsuperscript{55,56,57,58,59}

Then there is the world of immunobiotics. These are bacteria that either have been heat-shocked or have had their cell walls lysed and therefore are no longer alive. They promote systemic health through the mucosal immune system.\textsuperscript{60} One strain in particular, \textit{Lactobacillus plantarum} L-137 has a reasonable amount of human data showing that it activates IFN-\gamma and \( \beta \), IL-12 (increasing the Th1 immune response), decreases upper respiratory tract infections, incidences, duration and severity, along with improving lung function.\textsuperscript{61,62,63,64}

**Immune Support Nutrients**

Vitamins A and D are critical for lymphocyte activation and proliferation, Th cell differentiation, tissue-specific lymphocyte homing, production of specific antibody isotypes, regulation of the immune response, increasing sIgA and the production cathelicidins (host defense peptides with antimicrobial and immunomodulatory functions).\textsuperscript{65-69}

The cobalamin family (vitamin B\textsubscript{12}) enhances natural killer (NK) cell activity, increases circulating lymphocytes and is immunomodulatory.\textsuperscript{70,71} Probably the most well covered nutrient during the COVID-19 pandemic is vitamin C and it may well deserve its time in the spotlight. It is an antioxidant, stimulates NK activity and function, stimulates IL-2, stimulates conversion of naïve T helper cells to Th1 cells (required for host defense against intracellular viral and bacterial pathogens), stimulates T-lymphocyte activity, phagocyte function and leukocyte mobility.\textsuperscript{72} Furthermore, it has been demonstrated in humans that during times of infection, ascorbate demands increase and when taken, shortens severity and duration of numerous infections.\textsuperscript{73,74}

Selenium has been well studied and plays an important role in acute cellular immune response, particularly in viral and bacterial infections.\textsuperscript{75} It is also a necessary cofactor of glutathione peroxidase, which is needed to make reduced glutathione.\textsuperscript{76,77}

Speaking of increasing glutathione production and status, two of my clinical and well documented favorites are N-acetyl-L-cysteine (NAC) and acetyl-glutathione. Both are anti-inflammatory, antioxidant, heavy metal protectant, immunomodulatory, antiviral, neuroprotective and NAC acts as a mucolytic.\textsuperscript{78,79,80,81,82}

Zinc, like vitamin C seems to be making headlines. A very important mineral in that it is needed for the normal development of the innate and adaptive immune systems.\textsuperscript{83} It is antiviral via disruption of the viral life cycle and inhibits viral entry.\textsuperscript{84,85} Even moderate deficiencies can increase the risk of opportunistic infections, including pneumonia.\textsuperscript{86}

When most clinicians think of iodine/iodide, they think of thyroid. This mineral is also very important for proper immune function,\textsuperscript{87} along with proper brain development.\textsuperscript{88} The increased use of gourmet salts, guidelines for those with hypertension to limit salt intake, and the American diet tends to be low in sea vegetables, there of iodine induced goiter and hypothyroidism have become more prevalent.\textsuperscript{89,90} The WHO estimates that over 30% of the world’s population (about 2 billion people) have insufficient iodine intake.\textsuperscript{91} It is essential for T4 and T3 production, highly concentrated in the thymus and needed for cell-mediated immunity by leukocyte myeloperoxidase.\textsuperscript{86}

Edible (shiitake, maitake, oyster, lion’s mane etc.) and non-edible medicinal mushrooms (reishi, turkey tail, cordyceps, chaga, etc.) while a staple in most Asian
communities, are not viewed the in the same august manner in the United States. There is a reason why these creatures have their own biological kingdom. These are some of my favorite interventions with patients (and myself). There are dozens that have positive implications in human health and individually they are beyond the scope of this article, but generally their active constituents enhance immunity via increasing phagocytosis, increasing NK cell cytotoxicity, increasing T cell counts, and helping with Th1 phenotype potentiation.111,112

One of the most theorized mechanisms for which patients with severe SARS-CoV-2 decompensate and some unfortunately die, is possibly due to the “cytokine storm.”98,99 This is a process an overreaction to infection, leading to excessive and/or uncontrolled release of proinflammatory cytokines and immune system cells. Acute lung injury is a common consequence where local inflammation spills over into the systemic circulation, producing systemic sepsis.97,98

Given the seriousness of this, in my opinion, any intervention that may help prevent this from occurring, is a worthwhile endeavor, especially if those interventions are safe. Essential fatty acids (omega-3, 6 and 9), astaxanthin, green tea polyphenols, molecular hydrogen (H2) are all well-established immunomodulatory and anti-inflammatory agents, that are also very safe.

Omega-3 (eicosapentaenoic acid, docosahexaenoic acid, Docosapentaenoic Acid), 6 (gamma linolenic acid) and 9 (oleic acid) can suppress NF-kB, COX-2, tumor necrosis factor (TNF)-α and IL-1-beta, modulate signal transduction, cell activation and cytokine production.99,100,101

Camellia sinensis (green tea) is high in polyphenols and catechins, which enhance cellular immune response, are antiviral and anti-inflammatory.102,103,104,105,106,107

Haematococcus pluvialis (astaxanthin) a carotenoid with potent antioxidant capabilities, may enhance antibody-mediated and cell-mediated immune responses.108,109 A fascinating paper by Talukdar and others in April of 2020 provides a thorough discussion of how this molecule may attenuate cytokine storm.110

Molecular hydrogen is a diatomic molecule of hydrogen (H2), the smallest known molecule, that is neutrally-charged, nonreactive, and nonpolar, which allows it to easily pass through cellular membranes and biological barriers. H2 neutralizes hydroxyl radical (•OH)-a strong toxic oxidant-turns on antioxidant/detox enzymes and protein transcription via Nrf2 pathway, has anti-inflammatory effects, reducing pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, and acts as a signaling molecule.111,112

Treatment with Antiviral Compounds

My attempts below are not to recapitulate what has already been written, but rather discuss botanicals that I have successfully used clinically for the past ten years, have strong clinical studies are typically very safe, as well as some that haven’t already been discussed in other publications.

Fucoids are polysaccharide rich compounds (esp. polyphenols) in brown macroalgae. They have strong antioxidant properties, decrease IL-6, COX-1, COX-2 and LOX-15. They have been shown to increase NK cell activity, cytotoxic T cells, phagocyte activity and assist in dendritic cell maturation. These compounds also are antiviral by inhibiting viral entry into cell.113,114,115

Humic acid is an organic compound formed from decomposed plant materials and has been shown to be antiviral via binding to the virus, along with having immunostimulatory capabilities. Most of the data is in the herpes family of viruses, but I have seen it effective in those with other acute and chronic viral infections.116,117,118,119

Two of my favorite botanicals are Astragalus membranaceus (Huang Qi/Astragalus) and Andrographis paniculata (Andrographis), since they are strong antivirals and antimicrobials, they are immunomodulatory, anti-inflammatory and have adaptogenic properties. Andrographis has been shown to decrease inflammatory cytokines, prevent binding of viral hemagglutinin to cells, increase antibody activity and phagocytosis by macrophages.120,121,122 Astragalus, like Andrographis, has been used by Eastern medical traditions (Chinese and Ayurveda) for thousands of years. It has been shown to be antiviral, increase IgG, IgA, IL-2, lymphocyte production and NK activity.123,124,125

The class of berberine alkaloids, which come from plants like Berberis vulgaris, Berberis aristata, Mahonia aquifolium, Hydrastis canadensis and others. They are anti-inflammatory, antioxidant, antimicrobial, antifungal, antiprotozoal, antimycobacterial and antiviral.126,127,128,129,130 Caution at higher doses, since there may be some unwanted GI side effects (diarrhea, cramping, etc.).

Similar to the berberine containing genus of plants, the Artemisia genus has many species with medicinal properties. There are over 500 species in this genus,131 comprising more than 839 chemical compounds.132 The most famous species of the genus include Artemisia annua (Sweet Annie), Artemisia vulgaris (mugwort) and Artemisia absinthium (wormwood), with the most well-known constituents being artemisinin, artesunate, and dihydroartemisinin. These constituents have been well established to be antimicrobial, antimalarial, antifungal, and antiviral.133,134,135,136,137

Since the SARS-CoV-2 pandemic, Sambucus nigra (European elder/Black Elderberry) has become one of the most sought after botanicals and has also been in the press lately that it may elicit and/or exacerbate a “cytokine storm” in COVID-19 infected patients. This disseminated information was based upon one small 2001 in vitro study in which cytokines were released from leukocytes of healthy subjects.138 On the contrary, a 2016 paper in Phytomedicine showed elderberry to have anti-cytokine properties.139
There are three main medicinal parts of the plant: flowers, leaves and the berries. The flowers and leaves have been used as a diaphoretic, diuretic, analgesic and anti-inflammatory. The bark and unripe berries and seeds contain cyanogenic glycosides which are toxic to humans. These parts of the plants must be adequately cooked to breakdown the cyanide.

The berries, which are more medicinally well known, contain many flavonoids, but the most well studied include anthocyanins, quercetin, rutin and isoquercetin. They also contain phytosterols and carotenoids. The polyphenols in the plant lend to its high antioxidant potential.

The plant has anti-inflammatory, immunomodulatory and antiviral properties. It has been shown in human studies to shorten the severity and duration of influenza, and the common cold. Pelargonium sidoides (Umckaloabo) is a highly revered medicinal plant, native to South Africa. In recent years it has become popular here in the US, particularly in viral infections causing the common cold. Medicinal constituents of the plant include coumarins, umckalin, catechin, galloccatechin, gallic acid ellagitanins, polyphenols, and proanthocyanidins. These constituents allow the root of the plant to elicit antibacterial, antiviral and immunomodulatory affects.

Caveats

Some of the aforementioned interventions have a relative contraindication in autoimmune diseases, given that some may potentiate the immune system. Most of these cautions are theoretical but should not be taken without some level of caution. Assess the situation on a patient by patient basis. What I have found to be helpful is to pulse them, if going to be used long term, either few days on, few days off, or few weeks on, few weeks off. In this author's view and experience, short-term (3-10 days) use of these agents has been safe in autoimmune disease patients.

The content discussed in this article includes emerging nutritional science and scientific theories that should not be construed to be conclusive scientific proof of any specific cause, effect, or relationship, particularly when addressing COVID-19, since they have yet to be studied in this illness.

References

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