Asia-Pacific Chiropractic Journal

Reasoning SARS-CoV-2

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Abstract: *Objective* - To present an overview of the current literature is a form that is easy for chiropractors to use with patients.
Discussion - Some 360 papers were retrieved to address and inform a structure built from Practice Wisdom. A wide gamut of approaches suited to conventional chiropractic are described, each with current evidence.
Conclusion - Chiropractors play a critical role in maintaining the general health of people in their community. While the SARS pandemic has impacted practices in various ways, all chiropractors are able to contribute evidence-based support individualised to their patients.

Indexing Terms: chiropractic; clinical reasoning; immunity.

Introduction

This paper will not be comprehensive; the topic is too big for one paper by one author to capture whole. It will not be exhaustive - there are too many researchers publishing too many papers on each aspect of SARS-CoV-2 to include them all. It will not be altogether authoritative; I am a chiropractic physician in general family practice, not a virologist, epidemiologist, pharmacologist, geneticist, immunologist, or infectious disease specialist.

My intention is to present those studies that capture the essence of each topic as much as possible. Note that much of the research I present is not specific to SARS-CoV-2 though it has application here.

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Origins of SARS-CoV-2

The new/novel virus SARS-CoV-2 (SARS-CoV-2) broke into the human population in Wuhan, China in December 2019. There are two strains - L and S subtypes/strains. The L type was more aggressive and was more prevalent early in the Wuhan outbreak and since January 2020 is less prevalent most likely due to natural selective pressures. The higher mortality rates from this re- gion of China early on may be due to the higher percentages of this strain in SARS-CoV-2 in- fected populations at that time. The S strain of SARS-CoV-2 is '*evolutionarily older and less aggressive, might have increased in relative frequency due to relatively weaker selective pressure.*' (1, 2)

From the journal, Nature Medicine, '*It is improbable that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-like coronavirus*' and was not synthesized from an existing coronavirus template/backbone. (3) The vector may have been a wet market or via an infected worker at *Wuhan Institute of Virology*. It is unlikely the virus would have been leaked in Wuhan intentionally. (4)

The wet markets of China, Laos, Vietnam and Myanmar are prone to developing novel/new viruses due to the close proximity and even crowding of domestic and wild animals. (5, 6)

Transmission and Incubation

Transmission is primarily via respiratory droplets broadcast through sneezing, coughing, or through touching surfaces recently in contact with excretions from the nose or throat. The virus is more communicable than common influenza (SARS-CoV-2 (RO 2-2.5); influenza (RO 1.3)).

The virus does not appear to be communicable via blood, urine, or stool. Incubation appears to be ~5 days from infecting exposure, but can be from 2 to 14 days. (7) People with mild cases of SARS-CoV-2 infections usually test no longer as carriers/transmitters approximately 10 days after onset of infection. (8)

But, SARS-CoV-2 can be transmitted by asymptomatic carriers of the infection. (9) Food does not appear to be a vector for transmission of the virus. (10) Breastfeeding probably does not transmit SARS-CoV-2. (11)

Signs and Symptoms of Infection

SARS-CoV-2 is a mild to severe viral lower respiratory infection. Most people (~80%) will have mild to moderate symptoms. Symptoms include fever, cough, and shortness of breath. Because of the infection being lower respiratory, symptoms are typically felt in the chest and lungs.

Symptoms of SARS-CoV-2 Infection (incidence%) (12)

- Fever (88%)
- Dry cough (68%)
- Fatigue (38%)
- Productive cough (33%)
- Shortness of breath (19%)
- Bone or joint pain (15%)
- Sore throat (14%)
- Headache (14%)
- Chills (11%)
- Stuffy nose (5%)

Nausea or vomiting (5%)Conjunctivitis, hyposmia, hypogeusia, and dermatological signs that can include acro-ischemia (due to clotting imbalances), chilblain-type eruptions on digits, petechiae/pruritic rash, chicken- pox like rash, urticaria, erythema multiform-type rash, maculopapular rash, and alopecia have been reported. (13)

For most people symptoms of the infection will be mild to moderate and selfcare typical of hav- ing the 'flu' will be adequate. It is not unusual for people to be asymptomatic carriers/ transmitters of the virus.

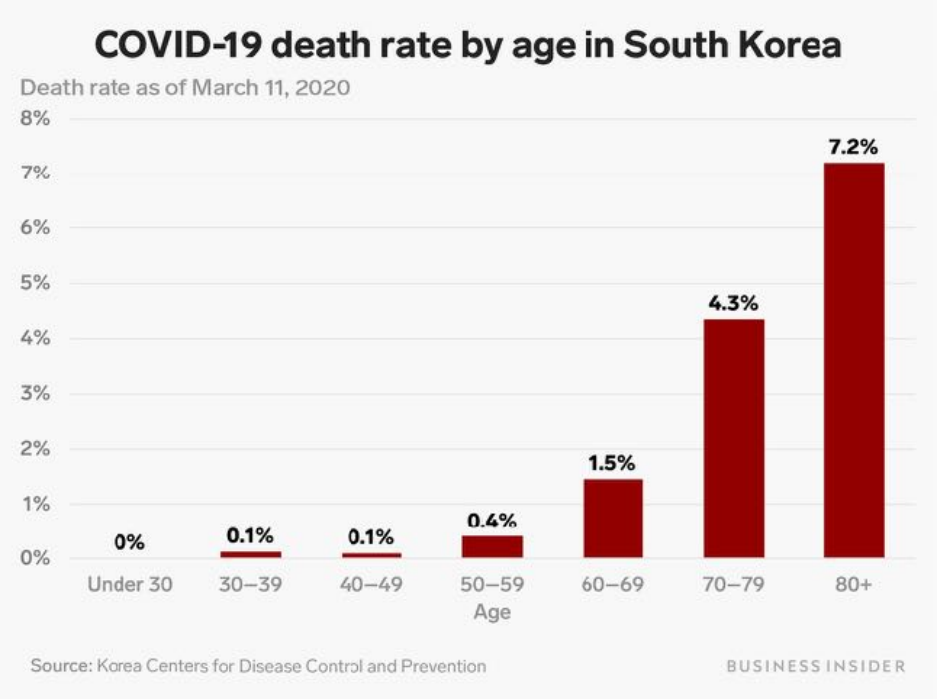
> Important!: Warning signs or symptoms that indicate a need for immediate medical attention include - difficulty breathing or significant shortness of breath, persistent pain or pressure in the chest, new confusion or inability to arouse, bluish lips or face.

Note: It is very useful to have patients at risk and especially with infection to monitor their blood pressure, pulse, temperature, respiratory rate, lung capacity, breath holding time, and oxygen saturation with pulse oximetry. Risk factors for Complications/Mortality

These include advanced age, diabetes, hypertension, heart disease, kidney disease, pregnancy, immunodeficiency, and immunosuppressive drugs. Males 2.4x more likely to die from SARS-CoV-2 compared to women. (14)

Counties with higher disability and poverty rates have a higher mortality rate. African Americans were found to have a mortality rate 2.6x greater than White Americans. Lower wage workers have higher risk for infection and mortality. (15)

Risk for complication and death increases with increased age after 50, markedly after 60, and dramatically after 70. Here is the breakdown from data drawn from South Korea CDC. (16)



Age and SARS-CoV-2 Infection Risk

Age and compromised health are significant risk factors for complications and possible death from SARS-CoV-2 as they are for seasonal flu. CDC mortality rate for seasonal flu is 0.8% for those 65 or older. People with these risk factors need the most support and protection and we all have a responsibility as a community to act in ways that minimize risk for this group. This is one underlying reason that SARS-CoV-2 infection mortality has been high in Italy - an aged population. (17)

Youth dramatically decreases risk statistically. Looking at estimated flu deaths in the US from 2015-2016 to 2019-2020 flu seasons annual death rates ranged from 52,000 to 20,000. In the 2020-2021 annual flu season in the US there were an estimated 20,342 flu-related deaths with 347 deaths from the 0-17 year of age group. (18) According to the CDC, from February 2020 to September 2021, there were 266,597 hospitalizations and 645 deaths estimated attributable to SARS-CoV-2 infection in the US within the 0-17 year of age group. Based on this data, the crude mortality rate from SARS-CoV-2 infection may be equivalent to that of seasonal flu in this age group. (19)

Genetic Effects on Infection and Complication Risk

Over-expressed immune response is at the heart of excessive cytokine levels, high C-reactive protein, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), organ failure, and mortality in Covid-19 infection and genetics drive the cascade. (20)

ACE and TMPRSS

'*ACE2 and TMPRSS2 DNA polymorphisms are strongly associated with the susceptibility, severity of cytokine promotion, and clinical outcomes of COVID-19.*' (21, 22, 23) ACE SNPs rs4341 and rs4343 are predictive markers for complications for COVID-19 infection patients with hypertension, dyslipidemia or diabetes. (24) Interestingly, the TMPRSS2 variant rs12329760 is associated with decreased severity of COVID-19 infection in patients from India. (25)

Vitamin D

T here is a relationship between vitamin D (25 (OH)D) levels and SARS-CoV-2 infection mortality. Research shows vitamin D binding protein (DBP) polymorphisms relate to infection severity, 25 (OH)D serum concentration and survivability. (26) Studies have found '*significant*' associations between genetic variants related to D metabolism, including Vitamin D binding protein, and severity of COVID-19 infection. (27, 28)

D-dimer, Homocysteine, and IFITM3

Various studies have show elevated D-dimer levels increase risk for Covid-19 infection mortality and high D-dimer levels correlate with FGG, FGA, and F5 polymorphisms. Homocysteine levels are adversely influenced by ABO, CBS, CPS1 and MTHFR polymorphisms. The interferon-induced transmembrane 3 (IFITM3) enzyme has been found to block viruses from fusing with cellular membranes - under-expression of the IFITM3 enzyme due to the rs12252-C variant of has been linked to severe influenza. (29)

IL6 and TNF-α

There is evidence that obesity may be a predictor of complications from Covid-19 infection due strong association of TNF-α and IL-6 as inducers of variants of IL-6, TNF-α, VDR (vitamin D receptor) genes are associated with Covid-19 complications and mortality. (31, 32)

'*IL-6 occupies the centre stage in initiating and potentiating the dreaded CS. It also helps in predicting disease severity & mortality in COVID-19*.' (33) Note: Knowing these key genetic variants allows curation of genetic data for Covid-19 infection risk in those patients who have had genetic testing. We can then be proactive in care and recommending self-care. My preferred program for genetic curation is the OPUS23 database.

Incidence of Mortality

Annual flu in the US has a crude mortality rate of ~0.1%. Most complications and death are in the elderly or in those with significantly compromised health. The CDC charts 20,342 flu deaths in the US 2019-2020 flu season making the flu crude mortality rate during that period ~.06%. (34)

Much of the concern regarding SARS-CoV-2 came from early reports of mortality rates as high as 20% of those infected in Wuhan, China to global mortality rates of approximately 5.7%. (35)

There are three methods for contextualizing risks of death from an infection: crude mortality (deaths/population); case fatality (deaths/confirmed cases); and infection fatality rate (deaths/all cases). Crude mortality is an overall estimate of risk of dying from an infection and case fatality is an estimate of risk of dying based on everyone with a serious enough case of the infection to have a confirmed diagnosis. Infection fatality rate is more abstract a figure as it's essentially impossible to come up with the total number of people who have had the infection. (36)

Crude mortality provides the most accurate overall risk of dying from an infection; case fatality provides the most accurate risk of dying from a significant infection.

These rates aren't absolute or constant and change with age, sex, ethnicity, and other demographics of the population tested, median age, overall health, environmental quality (air pollution is a risk factor), and food quality and sufficiency. It is common that arguments arise when the parties involved are using different criteria or calculations for their positions.

A retrospective study of the SARS-CoV-2 infection pattern in China published in *The New England Journal of Medicine* late February 2020 indicated a mortality rate of 1.4% with another article from the same journal projecting a mortality rate of less than 1%. (37, 38)

Some case mortality figures are worldwide ~2%, Germany ~1.8, Italy ~2.7, United Kingdom ~1.5, Egypt ~5.7%, Russia ~2.8%, India ~1.4%, China ~4.7%, Japan ~1%, Australia ~1%, Brazil ~2.8%, Costa Rica ~1.3, Philippines ~1.7, Tanzania ~3.7%, South Korea ~0.8%, and United States ~1.6. 39

Annually, about 3 to 5 million cases of severe illness and 290,000 to 650,000 deaths from seasonal flu occur worldwide. (40) Deaths from SARS-CoV-2 infection worldwide as of 12/4/2021 was ~5.24 million. If we consider that SARS-CoV-2 has been in circulation roughly 2 flu seasons, mortality from SARS-CoV-2 is approximately 10 times that of seasonal flu. (41)

SARS-CoV-2 and Immunity

There is a tendency to ignore or marginalize the value of naturally occurring infection for devel- oping robust, long-term immunity that leads to over-reliance on antibodies as the only measure of immunity to SARS-CoV-2 and ignore those who have survived Covid-19 infection for their contribution to herd immunity.

Clearly, vaccines have led to lower infection rates and less serious 'breakthrough' infections post-vaccine. This is evidenced by hospitalization, intubation, and death rates in the US when comparing vaccinated versus unvaccinated populations. (42, 43)

Yet, there deserves to be a more nuanced conversation about the relative values of natural infection versus vaccination and of a combination of the two. Certain populations deserve extra care and consideration for, in turn, their risks for complication from infection and/or from adverse reactions to vaccines. Medicine and public health is not, in reality, a one size fits all proposition.

General Thoughts on Immunity

The general standard for measuring immunity and resistance to SARS-CoV-2 infection has focused on antibody levels. Yet, antibodies (IgA, IgD, IgE, IgG, or IgM) decline relatively rapidly after infection and has fuelled concern regarding future immunity and resistance whether generated from infection or vaccine. This natural and normal occurrence is seen as a problem that sup- ports the belief that those who have had the infection must still be vaccinated to have immunity and those who have been vaccinated must have regular boosters to support sufficient antibody levels for effective resistance to infection. Yet, a more grounded view of SARS-CoV-2 based upon science and history indicates long term immunity after infection or properly targeted vac- cine should be the norm.

Hellerstein questions use of antibodies as a meaningful measure of long-term immunity and recommends using T-cell responses as a more useful marker for immunity instead. Especially after mild cases of SARS-CoV-2 infection where the antibody response may be weak, yet T-cell immunity is still typically robust. He refers to survivors of SARS-CoV (2003) who still show virus-specific T-cells today and, though antibodies or B-cell responses wane, virus-specific T-cells remain at 6–17 years. Further, while most vaccines target spike protein as an antigen, '*natural*

infection by SARS-CoV-2 induces broad epitope coverage, cross-reactive with other betacoronaviruses.' (44, 45)

The import of immune system function as a whole has been sacrificed for spike protein targeted triggering of antibodies. A more comprehensive and organic approach includes the action of lymphocytes - T cells (thymus originated), B cells (bone marrow originated), and natural killer (NK) cells. T cells are involved in cell-mediated immunity and B cells produce antibodies. CD4 helper T lymphocytes are the source of most interleukins - moderation of CD4 helper response and interleukins is essential to prevent cytokine release syndrome (CRS; cytokine storm) in people infected with SARS-CoV-2.

Tissue resident Memory T cells are essential for effective immune response to reinfection in someone previously infected or breakthrough infection in someone previously vaccinated. They represent the archived protocol for response to re-infection from a specific agent and can even aid in effective crossover response to similar/related agents. (46)

Another immune response archive can be found in the bone marrow in the form of long-lived bone marrow plasma cells (BMPCs) that upon re-exposure to target antigens rapidly differentiate into antibody-secreting plasmablasts. (47) It isn't necessary for the body to maintain high levels of SARS-CoV-2 specific antibodies and measuring for IgG levels as proof of long-term SARS- CoV-2 immunity is a poor metric for continued immunity to infection.

Natural Immunity

'*Few immunologists would consider it likely that infected subjects would develop no immunity after viral clearance.*' (48)

The quotes that follow are from '*Antibody Response to SARS-CoV-2: Let's Stick to Known Knowns*' from T*he Journal of Immunology*, November 1, 2020:

- '*Rigorous studies have shown that seroconversion is almost universal after confirmed infections, even when the disease is mild.*'
- '*All antibody responses, even exceptionally durable ones such as against measles, show an initial decline not inconsistent with what has been observed for SARS-CoV-2 thus far.*'
- '*Studies of adults nearly 90 years after the 1918 influenza virus pandemic demonstrated high titers of serum neutralizing antibodies to the homologous strain.*'
- '*Repeated stimulation of memory B cells is not required for serum antibody maintenance, demonstrating that primary infections and immunizations can confer durable antibody production.*'
- '*Together, these data collectively demonstrate that durable protection against homotypic challenges following acute viral infections is the norm.*'
- '*Though immunity following natural SARS-CoV-2 infection is likely to be durable, this is less clear for immunity to vaccines, especially given the experimental nature of many of these platforms.*'

Reading this particular paper is highly recommended for perspective regarding immunology. There has commonly been assumption by the public and the scientific community that SARS-CoV-2 was somehow different than anything seen before, though the evidence is that this virus operates on the same principles as those that have come before and immunity does come from infection. (49) Particularly in children, a robust immune response is typical even after asymptomatic infections. (50)

Virus-specific B cell response has been proposed as amore reliable marker of long-term humoral immunity than serum antibodies. (51) Duration of B-cell memory is very long after

natural exposures, as seen in responses to viruses such as mumps and measles. (52) Indeed,1918 influenza pandemic survivors show highly functional, virus-neutralizing antibodies to that virus and sustain circulating B memory cells into their 90s. (53) SARS-CoV (2003) infection induces a potent and long-lived T cell response in surviving humans. (54) Along this line, mild SARS-CoV-2 infection results in robust antigen-specific and persistent humoral immune memory associated with long- lived bone marrow plasma cells (BMPCs). (55)

Antiviral antibody responses are stable (1/2 life half-lives ~50 years varicella–zoster to greater than 200 years for measles and mumps. B-cell memory is long-lived without correlation between peripheral memory B-cell numbers and antibody levels for five of the eight antigens tested. (56)

SARS-CoV-2 infection was found to be associated with 84% lower risk of infection 7 months post infection. (57) Even asymptomatic Covid-19 cases showed SARS-CoV-2 spike protein (anti-S) IgG antibodies. (58)

Studies show persistent Memory B and T cells for SARS-CoV-2 even when measured at 15 months post-infection. (59, 60)

While the CDC has focused declining antibodies as proof for declining immunity to SARS-CoV-2, a study published in Science found that although antibodies declined over time, memory B cells increased. (61)

Comparing Natural and Vaccine Immunity

A comprehensive systematic review and meta-analysis (12,011,447 individuals recovered from Covid-19; 54 studies;18 countries) assessed status immunity for 6-8 months and found ~90% of people previously infected with SARS-CoV-2 had evidence of immunological memory to SARS- CoV-2 and low risk of reinfection. (62)

An Israeli study showed natural immunity providing stronger protection against infection and hospitalization from the Delta variant of SARS-CoV-2 when compared to BNT162b2 (Pfizer) two-dose vaccine-induced immunity. The vaccinated and SARS-CoV-2-naïve group was found at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected. (63) (Note: study not peer-reviewed as of 1/2/22.) A study of organ transplant recipients found that a post-infection subjects generated '*robust T cell responses following natural infection*' and that post-vaccine, SARS-CoV-2 infection naive subjects '*generated a comparatively lower T-cell responses following mRNA vaccination.*' (64)

A systematic review and pooled analysis of nine clinical studies showed statistical equivalence between protection of full vaccination and natural immunity with three studies showing natural immunity to be superior. Vaccination after recovery from Covid-19 infection was found to be of marginal benefit. (65)

One study found SARS-CoV-2-specific T cells are detectable in antibody-seronegative asymptomatic/mild Covid-19 infection survivors. In summary, to quote, '*Our collective dataset shows that SARS-CoV-2 elicits robust memory T cell responses akin to those observed in the context of successful vaccines, suggesting that natural exposure or infection may prevent recurrent episodes of severe COVID-19 also in seronegative individuals.*' (66)

Vaccine Immunity

It is all too common that conversations around vaccines tend to extremes, that all vaccines are extremely good or all vaccines are extremely bad. There are pros and cons to vaccines and vaccine immunity. From a pure science based position there can be a nuanced position on vaccine use. Research indicates that there is likely no benefit for populations that have recovered from SARS-CoV-2 infection to be vaccinated, that SARS-CoV-2 infections and mortality have been reduced by

vaccines, and there is a cost/benefit ratio question to consider with regard to mRNA vaccines in the children and teens and risk for myocarditis and pericarditis, especially in males. (67)

Note: Information on vaccines below from CDC data and a report from Yale Medicine.

mRNA Vaccines

Researchers have suggested concern that vaccines focused solely on eliciting antibodies to the S protein might be insufficient for long-term immunity to SARS-CoV-2 variants in that only 3 of the 29 shared epitopes of SARS-CoV-2 are located in the spike protein. (68)

Both Pfizer-BioNTech and Moderna vaccines have been associated with myocarditis and pericarditis (~12.6 cases/million after the second dose).

Pfizer-BioNTech appears to be 91.3% effective in preventing symptomatic Covid-19 infection. It is rated !00% effective in preventing severe disease by the CDC and 95.3% effective in preventing severe disease by the FDA. After 6 months the protection against infection wanes to 84%, though protection against severe disease was 97%. The vaccine appears to be effective against the Alpha, Beta, and Delta variants.

Moderna appears to be 95% effective in preventing symptomatic Covid-19 infection. At six months, Moderna is rated 90% effective for preventing infections and 95% effective for preventing severe disease. There is conflicting evidence as to effectiveness against variants.

Viral Vectored Vaccines

Johnson & Johnson (Janssen) was not measured in trials for effectiveness of preventing infection. It does have 85% effectiveness preventing severe/critical infections 28 days after one dose. A second dose administered 2 months after the initial dose results in 75% protection from symptomatic infection and 100% protection from severe/critical infection. Guillain-Barré syndrome has been reported in a small number of cases (100/12.8 million doses). There have also been cases of cerebral venous sinus thrombosis (CVST) in women aged 18-48 (6/6.8 million doses).

Oxford-AstraZeneca shows a 76% effective at reducing the risk of symptomatic disease after receiving the two doses; 100% efficacy against severe disease. The company also claims the vaccine is 85% effective in preventing infection in people over 65. Oxford-AstraZeneca protection from the Delta variant is 60% effective against symptomatic disease and 93% effective against hospitalization. There is a risk for cerebral venous sinus thrombosis (CVST) in women aged 18-48 (8.1/1 million doses).

Protein Adjuvant Vaccine

Novavax uses a nanoparticle spike protein to stimulate antibody and T-cell immunity. The vaccine is 90% effective for preventing symptomatic infection and 100% effective at preventing moderate to severe disease. Novavax appears to provide very good protection for high-risk populations from severe infection (91%). It showed 93% effective protection from severe infection caused by the Alpha variant.

Note: Among U.S. adults without immunocompromising conditions, vaccine effectiveness against COVID-19 hospitalization during March 11–August 15, 2021, was higher for the Moderna vaccine (93%) than the Pfizer-BioNTech vaccine (88%) and the Janssen vaccine (71%). (69)

Infections, Hospitalization, and Mortality in Vaccinated Populations

Rates of laboratory-confirmed COVID-19 hospitalizations by vaccination status per CDC (70)

- Adults 18+ years: hospitalization rate ~8x greater in unvaccinated persons.
- Adolescents12-17 years: hospitalization rate ~12x greater in unvaccinated persons.

- Adults 18-49 years: hospitalization rate ~13x greater in unvaccinated persons.
- Adults 50-64 years: hospitalization rate ~11x greater in unvaccinated persons.
- Adults 65+ years: hospitalization rate ~6x greater in unvaccinated persons.

Texas Health and Human Services found that in the period from September 4th through October 1st, 2021unvaccinated people were 13 times more likely to become infected with COVID-19 and 20 times to die from COVID-19 infection than fully vaccinated people. (71)

Vaccines do decrease incidence of SARS-CoV-2 infection, hospitalization, and death. There are multiple factors involved in making a decision to vaccinate that, ideally, account for risk/benefit based upon risk factors for infection and adverse reaction based upon health status and genetics, whether or not natural immunity is present, sense of responsibility to community and society, and integrity to principles or faith.

In a referenced letter to *The Lancet,* Gunter Kampf argues that stigmatizing the unvaccinated is not justified based upon evidence that vaccinated individuals continue to have a relevant role in transmission. Dr. Kampf mentions in Germany, over 50% of recent symptomatic COVID-19 cases in patients aged 60 years or older have been in fully vaccinated individuals. Dr. Kampf goes on, '*It is therefore wrong and dangerous to speak of a pandemic of the unvaccinated ... I call on high-level officials and scientists to stop the inappropriate stigmatization of unvaccinated people, who include our patients, colleagues, and other fellow citizens, and to put extra effort into bring- ing society together*.' (72)

Herd Immunity

Both infection and vaccination contribute to herd immunity to SARS-CoV-2. This is evidenced by numerous studies from Qatar, Israel, Britain, and the US, that show equally low infection rates among vaccinated and naturally inoculated populations. (73)

Those with natural immunity from prior Covid-19 infection are more likely to have adverse reactions to vaccine including hospitalization. To quote, '*For the first time, this study demonstrated a significant association between a prior COVID-19 infection and a significantly higher incidence and severity of self-reported side effects after a vaccination for COVID-19*.' (74) This would appear a reasonable argument for forgoing vaccine, especially in those who already have risk factors for over-expressed cytokine system.

Naturally occurring immunity has been too little considered in contributing to overall herd immunity numbers. The Bergamo region of Lombardy, Italy was hit particularly hard in the early months of 2020, yet a second wave of the pandemic in the fall of 2020 had a significantly lower peak of cases in Bergamo province when compared to the rest of Lombardy. Seroprevalence for antibodies was found in a large percentage of the population (37-57%) and that '*cumulative prevalence could have been even higher, considering that a large subset of subjects may have memory B cells, CD4+ T cells and CD8+ T cell memory against SARS-CoV-2, without de- tectable levels of circulating anti-SARS-CoV-2 antibodies. This would suggest that Bergamo province was moving toward natural a degree of natural herd immunity ... '* (75)

As of December 2021 approximately 43% of the US population aged 18-59 had been infected with SARS-CoV-2 per CDC data February 2020 to May 2021. (76)

Covid-19 infection rates during the winter 2020/2021 by region in Massachusetts were found to significantly lower in regions with high concentration of previous infection. (77)

In an Iranian population, Covid-19 re-infection rate was 0.33% after one year of follow-up. All cases symptomatic cases were of moderate severity. (78)

It is a natural progression that SARS-CoV-2 will become endemic globally and represent a beta coronavirus for which the population has essential immunity, either through naturally occurring

or via vaccine. Alexander Beams, an epidemiologist, has been posited that mild or asymptomatic infections by SARS-CoV-2 will become typical seasonal coronavirus in the future. (79) This concept is supported by evidence that reinfection with the Delta variant shows protection from severe disease. (80)

The Omicron variant shows higher infection rates, but lower incidence of hospitalization, intubation, and mortality. (81, 82) The evolutionary biologist, Jesse Bloom, has predicted that SARS-CoV-2 will evolve to become the fifth coronavirus to become endemic in humans. The arc of successful viral evolution accord- ing to evolutionary biology is to greater transmissibility, greater evasion of immunity, and less virulence. Developing variants appear to be following this model. 83

Allopathic Therapeutics

The British Medical Journal (BMJ) maintains a webpage that summarizes recommended protocols for managing the various stages of Covid-19 infection. The graphical decision making algorithm is quite well done. It covers recommended therapies and those that are not recommended and why - *A living WHO guideline* on drugs for covid-19.

On the other end of the spectrum is Front Line COVID-19 Critical Care Alliance (FLCCA). They build much of their protocol around Ivermectin. What is appealing is that they have designed therapeutic protocols that include nutritional therapeutics.

There has also been meta-analysis of randomized controlled trials to establish relative effectiveness of various allopathic therapeutics for the hospitalized Covid-19 patient. This paper has a summary that is remarkably complete and complex. It would be pointless to attempt to summarize it here other than to cut and paste in total in quotes. This author highly recommends its' review. (84)

Thankfully, recognition for the need to support patients with Covid-19 infection early in the course and prior to complication has been recognized. (85)

Hydroxychloroquine (Zinc Ionophore)

Hydroxychloroquine/chloroquine use did not have a significant effect on virological cure, the time of clinical recovery, or improvement in survival in COVID-19 patients. Hydroxychloroquine did show increased adverse effects; there was no significant difference in mortality rate between patients treated with HCQ compared to standard of care or placebo.(86, 87) There was promise for hydroxychloroquine as a zinc ionophore increasing delivery of zinc to the cells; there have been clinical trials terminated due to adverse events, primarily cardiac. (88, 89)

Ivermectin

Besides being a recognized anti-parasitic, Ivermectin has shown utility against many RNA and DNA viruses. Mode of action of Ivermectin with regard to control of viral replication via inhibition of importin α/β-mediated transport. (90) Ivermectin was found to suppress NF-kB expression and significantly decrease production of TNF-α, IL-1ß and IL-6 in vivo and in vitro. (91)

Low to moderate-certainty evidence suggests that prophylactic use of Ivermectin may reduce infection post-exposure, ameliorate infection course, and reduce mortality from SARS-CoV-2. (92)

A meta-analysis of randomized clinical trial studies indicates ivermectin use associated with '*higher rate of negative RT-PCR test results, shorter time to negative RT-PCR test results, higher rate of symptoms alleviations, shorter time to symptoms alleviations, shorter time to hospital discharge, reduction in the severity and mortality rate from Covid - 19.*' (93)

Another meta-analysis of Ivermectin administration for Covid-19 infection determined the drug may improve viral clearance and reduce the need for hospitalization, but that reduction in mortality was uncertain. (94)

Steroids (Dexamethasone / Methylprednisolone)

Multiple meta-analysis of randomized controlled trials showed reduced risk of intubation and mortality in critically ill patients. (95, 96, 97) However, dexamethasone is associated increased risk for secondary respiratory infection. (98)

Anticoagulant (Heparin)

Anticoagulants, mainly heparin, reduced all-cause mortality, but due to bleed risk at therapeutic doses, prophylactic dosages are preferred in non-critically ill COVID-19 patients. (99, 100)

5-Alpha Reductase Inhibitors (Finasteride/Dutasteride)

Male patients aged >55 and medicated with 5ARIs (dutasteride, finasteride) were found 5.57% lower than controls. (101) Acute use of finasteride showed a significant improvement in O2 satura- tion at day 5 for male patients with Covid-19 pneumonia compared to controls, but did not show significant differences in mortality rates. (102)

Sigma-1 Receptor Agonist (Fluvoxamine/Fluoxetine)

The sigma-1 receptor (Sig-1R), found mainly in the mitochondrion-associated endoplasmic reticulum (ER), controls calcium signalling, membrane integrity, and oxidation. The SSRIs, Fluvoxamine and Fluoxetine, are sigma-1 receptor agonist.

One study showed a fourfold odds of survival from fluoxetine therapy when compared to controls. (103) Use of fluoxetine as an antidepressant was also found to be significantly associated with reduced risk of intubation or death. (104)

Study of postmortem Covid-19 patients showed altered T-cell-microglial interactions and '*astrocytosis, axonal damage, and blood-brain-barrier leakage and detected viral antigen in ACE2-re- ceptor-positive cells enriched in the vascular compartment.*' (105) Another study concludes '*Microglia activation is a key component neuropathophysiology associated with Covid-19 infection and control of microglia oxidation is improved by sigma-1 receptor activity*.' (106)

Antiviral (Remdesivir)

Meta-analysis of randomized controlled trials did not show reduced mortality in hospitalized patients with COVID-19 who received remdesivir. (107) A double-blind, randomized, placebo-con- trolled trial found mortality of 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29. (108)

A Korean study found intubation significantly lower in the remdesivir group and intubation was of shorter duration in the remdesivir compared when compared to controls.(109)

Patients who had liver disease or who undergo continuous or intermittent dialysis or those with transient AKI may not be the safe candidates to receive remdesivir. (110)

Monoclonal Antibodies (Casirivimab/Imdevimab)

Casirivimab/Imdevimab administration results in significantly reduced the hospitalization rates for high-risk patients, vaccinated and unvaccinated, with mild to moderate Covid-19. (111, 112)

IL6 receptor inhibitors (Tocilizumab/Sarilumab)

SARS-CoV-2 has a particular talent for up-regulating interleukin 6 (IL-6) expression and promoting a severe cytokine cascade known as cytokine storm. The inflammatory response to Covid-19 infection, as measured via IL-6 can be used as biomarkers for Covid-19 infection severity. IL-6 inhibitors lower cytokines, decrease risk for cytokine storm, and promote antiviral IFN-I responses. (113)

A systematic review and meta-analysis found IL-6 signalling inhibitors reduced mortality rate without increasing secondary infections, but failed to reduce rates of mechanical ventilation, ICU admission, or clinical improvement. (114)

Nutritional Therapeutics

The SARS-CoV-2 pandemic has compelled researchers and clinicians around the world to scramble for answers. There has been a surprisingly robust trend for researching natural therapeutics for prophylactic and therapeutic use in Covid-19 infections. A number of vitamins (A, B6, B12, folate, C, D and E) and trace elements (zinc, copper, selenium, iron) have been demonstrated to have key roles in supporting the human immune system and reducing risk of Covid-19 infections. There is evidence from ARDS in other settings that the cytokine storm can be con- trolled by n-3 fatty acids. (115)

Vitamin A

Vitamin A is essential to normal immunity and health and integrity of the mucous linings of the mouth, throat, sinuses, and lungs. Many people have a genetic variant (BCO1) that inhibits their ability to convert beta-carotene to vitamin A. People in this group need animal-derived sources of vitamin A rich foods butter, cream, eggs, fatty meats, fish liver oil) or to take supplemental vitamin A.

From *Medical Hypothesis* comes an article proposing depletion of retinoic acid reserves results in down-regulation RIG-I (retinoic acid-inducible gene I), impaired type-1 interferon (IFN1) responses to infection, and promotion of TNFα and cytokine discharge. The author calls this process '*retinoic acid depletion syndrome.'* (116)

Serum retinol is found low in patients with severe Covid-19 infection and vitamin A insufficien- cy was was to be a statistically significant risk factor for intubation. (117, 118)

Vitamin A directly enhances white blood cell immune response to viruses and moderates immune response. (119, 120) Vitamin A deficiency results in impaired immune response and impairs regeneration of epithelial cells in the mouth, throat, sinuses and lungs leading to diminished resistance and increased risk of mortality from infection. (121)

Respiratory viral infections are commonly associated with vitamin A deficiency and lower vitamin A levels are associated with more severe cases of infection. (122) Research suggests vitamin A supplementation leads to less complications and mortality from viral and other infections. (123) Retinoic acid supports epithelial and endothelial barrier function. (124)

One study has made a reasoned argument for acute doses therapeutic vitamin A in severe cases of Covid-19 at 300,000-500,000IU a day and in moderate cases at 200,000IU a day. (125)

Bioflavonoids (Quercetin)

Flavonoids, especially quercetin, have been extensively researched for their antiviral activity especially with regard to impairing viral gene transcription. (126) Quercetin is protective of lung epithelial tissues from the inflammatory processes of viral infection. (127)

Quercetin promotes nuclear factor erythroid-derived 2-like 2 (NRF2) which inhibits SARS-CoV-2 replication in lung tissues, antiviral activity against coronaviruses, including SARS-CoV-2, inhibits nuclear factor kappa B (NF-κB) and interleukin-6 (IL-6), modulates coagulation. (128)

One randomized and controlled clinical outcome study found use of quercetin resulted in a short- er time to virus clearance, milder course, and a greater likelihood of benign outcome from infection. (129)

Bromelain

Supplementation of bromelain in hospitalized Covid-19 patients showed significant improvement in SaO2, RR, HR, AST, ALT, BUN, ESR, LDH, and WBC and Lymphocyte count relative to control subjects. (130) Bromelain proteases show anti-thrombus activity in vivo and reduced platelet aggregation in vitro. (131)

Butyric Acid

Butyric acid has been proposed as vector for prevention of cytokine storm and organ failure in Covid-19 patients. (132)

Butyric acid, a histone deacetylase inhibitor, has beneficial effects regulating inflammatory cytokines, especially through inhibition of IL-17 and IL-6 and promotion of anti-inflammatory IL-10. (133, 134, 135, 136) Nuclear Factor Kappa B (NF-κB) has also been implicated as a critical factor in severe Covid infections and is inhibited by butyric acid. (137, 138, 139)

Secretory IgA, an essential actor in barrier defense, is promoted by butyric acid. (140) Long covid has been associated with neuroinflammation mediated by chronically activated microglia cells and butyric acid inhibits microglia inflammation. (141) Butyric acid has even been proposed as a natural alternative to dexamethasone for control of cytokine storm. (142)

Vitamin C

Vitamin C enhances white blood cell production and function. Three controlled studies found high dose vitamin C (>6gm/day) useful in the prevention of pneumonia, a complication associated with SARS-CoV-2 mortality. (143) Vitamin C deficiency is associated with lung pathology com- plications from viral infection. (144)

One study found approximately 82% of critically ill Covid-19 patients with ARDS to be deficient in vitamin C. (145) A retrospective cohort study found use of high dose vitamin C to improve oxygenation and decrease mortality in Covid-19 patients without side effects. (146)

In a study of 54 hospitalized Covid-19 patients, divided equally into a high-dose IV vitamin C group (12 g of vitamin C every 12 hours for 7 days) and placebo, the HDIVC group showed reduction in pro-inflammatory cytokines compared to controls. (147)

Curcumin

A significant decrease in Th17 cells and Th17 cell-related cytokines was found in mild and severe COVID-19 patients treated by curcumin compared to a placebo group. (148) Curcumin also inhibits nuclear factor kappa B (NF-κB) and interleukin-6 (IL-6). (149, 150)

One small clinical outcome study showed restoration of taste and smell with curcumin. (151)

Vitamin D

Interventional and observational epidemiological studies provide evidence that vitamin D deficiency increases risk/incidence for influenza and respiratory tract infection. Additionally, vitamin D appears to decrease inflammatory response in lung tissue during viral infection. (152, 153) Stimulation of the vitamin D receptor protects against respiratory viral infections and increases antiviral responses of epithelial tissues. (154)

Vitamin D promotes production of antiviral proteins that inhibit viral replication increase clearance via autophagy and moderates cytokine responses resulting in decreased risk of cytokine storm. (155)

In 2015, *British Medical Journal Thorax* found '*vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS)*.' In the coronavirus infections associated with SARS-CoV, MERS, and SARS-CoV2 (SARS-CoV-2), acute respiratory distress syndrome is the common serious complication that seems to drive the other complications - lung, cardiac, kidney and liver injuries. This study found 100% of patients with ARDS were vitamin D deficient. (156)

One very intriguing paper proposes that influenza pandemics are triggered by solar cycles and resultant vitamin D deficiency. (157) Vitamin D may also play a role in mitigating the cytokine storm complication associated with SARS-CoV-2. (158)

Vitamin D deficiency has been associated with impaired gap and tight junction barrier defense and TH1 shift promoting increased cytokine expression. (159) Elevated TNF-α, IL-1β, and CRP are found in vitamin D deficient patients. (160)

A systematic review and meta-analysis of 43 observational studies showed low vitamin D levels are associated with increased infections, hospitalizations, and mortality. (161) It's important to note that high dosages of vitamin D at the onset of a viral infection do not appear to provide the same protection as prophylactic use of vitamin D. (162)

Garlic

Garlic inhibits viral proliferation and penetration in cell cultures. (163,164) Garlic is well known to control tissue inflammation by promotion of the antioxidant enzymes glutathione (GSH) and superoxide dismutase (SOD). (165) Garlic is also known to control modulation of cytokines including down-regulation of interleukin-6 (IL-6). (166)

Ginger

Fresh ginger is effective against viral attachment and internalization on airway epithelium. (167) It has also been shown to increase macrophage (white blood cell) activity against viruses. (168) Ginger protects bronchial epithelia from the pro-inflammatory effects of viral infection. (169)

Vitamin K

Vitamin K insufficiency is consistently found in severe Covid-19 patients with thrombosis and this process appears to be due to peripheral depletion of vitamin K and resultant deficiency of endothelial anticoagulant protein S. (170)

Tyro3, Axl, MERTK (TAM) receptor tyrosine kinases are also vitamin K dependent and are implicated in the regulation in clearance of apoptotic cellular debris and modulation of cytokine signaling. Research is looking into vitamin K insufficiency as a promoter of cytokine 'storm' and thrombotic processes. (171)

Manganese

Manganese activates anti-viral innate immunity. Manganese-superoxide dismutase is a manganese dependent antioxidant enzyme that controls tissue inflammation and moderates tissue damage associated with viral induced tissue inflammatory response. (172,173) Low SOD2 (manganese dependent superoxide dismutase) appears to impair T cell development, maturation, and function resulting in impaired immune response to viral challenge. (174)

Melatonin

Melatonin upregulates silent information regulator 1 (Sirt1) and high mobility group box 1 (HMGB1) promotion of interferon, mitochondrial antiviral-signalling protein (mitochondrial antiviral-signalling protein (MAWS), and nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant responses and down-regulates nuclear factor kappa B (NF-κB). (175) Glutathione redox and neutrophil functions are also supported by melatonin. (176) Melatonin inhibits epithelial growth factor receptor (EGFR) signalling which has been shown to inhibit SARS-CoV-2 replication. (177)

Hospitalized Covid-19 patients supplemented with orally with 9mg melatonin a day for 14 days showed improved cytokine status and modulation of Th1/Th2 expression. (178) A randomized, double blind clinical trial of melatonin effectiveness showed greater improvements in CRP, cough, dyspnea, fatigue, pulmonary findings, and shorter mean time to hospital discharge when compared to controls. (179)

NAC (N-Acetylcysteine)

NAC has been found to protect lung tissues from lethal influenza infection in mouse studies. (180) Administration of NAC increases whole blood glutathione levels and lymphocyte count (CD4+ and CD8+), suppresses viral replication, lowers nuclear factor kappa B (NF-κB), TNF-α, and IL- 6 levels. (181, 182)

NAC therapy to hospitalized COVID-19 patients showed significant improvement in arterial oxygen saturation to inspired oxygen fraction ratio (SpO2/FiO2) and NEWS2 scale (respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness) along with reduction in CRP, and length of hospitalization when compared to controls. (183)

Omega-3 Fatty Acids (DHA/EPA)

EPA and DHA decrease secretion of inflammatory cytokines, including Il-6, and lower triglycerides, a risk factor for up-regulated cytokine inflammatory response in Covid-19 infection. (184)

Hospitalized Covid-19 patients supplemented with omega-3 fatty acids showed a significantly higher 1-month survival rate and higher levels of arterial pH, bicarbonate and lower levels of BUN, creatinine, and potassium compared controls. (185)

A 2 week trial of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in hospitalized Covid-19 positive patients resulted in lower CRP and ESR compared to controls. (186)

Probiotics

The biome/flora of the nose, throat, and sinuses play a role in resistance to infection and probiotics designed for the biome of the mouth and throat decrease incidence a severity of upper respiratory infections. (187, 188, 189)

Probiotic use improves balance of interferon, NK cells, and T and B cells, and cytokines. (190) Intestinal biome diversity is inversely related to Covid-19 infection severity. (191)

Selenium

Selenium deficiency is associated with increased viral virulence and has been suggested to play a role in '*the emergence of novel viral diseases*.' (192)

Viral infections leading to lung pathology complications are more common in those who are selenium deficient probably due to impaired glutathione peroxidase production and increased lung tissue inflammatory response to viral infection. (193)

Selenium deficiency appears to increase susceptibility to RNA viral infections and with more complications. Selenium deficiency appears to promote mutations, replication and virulence of RNA viruses. Additionally, selenium may promote a role in host antioxidant capacity with anti-inflammatory and anti-clotting effects. (194)

Strong correlation has been found between low selenium status and complications and mortality from Covid-19 infection. (195, 196) Another study found increased complication and mortality associated with a combined deficiency of selenium and zinc with it being present in 0.15% of healthy subjects, 19.7% of surviving Covid-19 patients, and 50% of non-survivors. (197)

Thymus Gland Extract

Lymphopenia is a characteristic feature of significant COVID-19 infections, along with increased inflammatory cytokines, particularly interleukin-6 (IL-6). The degree of lymphopenia correlates with complications and mortality. (198)

Development and maturation of CD4 and CD8 T cells depends on thymus gland functions. Thymus secretions include the hormones thymosin, thymopoietin and thymulin and the interleukins IL-1, IL-3, IL-4 and IL-6. (199)

Use of calf thymus gland extracts containing thymulin have a long history and result in increased CD4/CD8 ratio, indicating improved immunocompetence. (200, 201) Thymulin therapy also re- duces chemokines and cytokines, including interleukin-6 and TNFα and promotes anti-inflam- matory factors, including interleukin-10. (202, 203, 204) Thymosin therapy has also been shown to promote development and maturation of T cells. (205)

Thymulin is a zinc dependent hormone - make sure patients using thymus gland extracts are zinc sufficient. (206) Thyroid function modulates thymulin levels with lower thyroid function resulting in lower thymulin levels. (207)

Zinc

Covid-19 infected patients with zinc deficiency have been found to have higher incidence of ICU admission, acute respiratory distress syndrome, corticosteroid therapy, prolonged hospital stay, and mortality. (208, 209)

As noted previously, the thymus hormone, thymulin, requires zinc for its' action which results in promotion and maturation of T cells and regulation of cytokines, including the down-regulation of IL-6.

Zinc supplementation decreases the morbidity of lower respiratory tract infection by limiting viral replication and decreased duration and severity of viral infection. (210,211) Zinc inhibits coronavirus (research 2011) RNA polymerase activity. (212) Ionic zinc specifically inhibits SARS-CoV-2 replication in vitro and the effect is potentiated by quercetin which acts as a zinc ionophore. (213)

Zinc supplementation is effective in treatment of acute lower respiratory tract infection and de- creasing incidences of infections in the elderly. (214)

Zinc '*may possess protective effect as preventive and adjuvant therapy of COVID-19 through reducing inflammation, improvement of mucociliary clearance, prevention of ventilator-induced lung injury, modulation of antiviral and antibacterial immunity*.' (215)

Angiotensin-converting enzyme 2 (ACE2) is a zinc dependent enzyme and zinc determined deficiency of ACE2 has been proposed to contribute to Covid-19 infection complications and morbidity. (216, 217)

Secretory IgA, an essential component of barrier defense, is down-regulated by zinc deficiency. (218) Diminished sense of taste (hypogeusia) and smell (hyposmia/anosmia) is commonly associated with zinc deficiency and responsive to zinc supplementation. (219, 220)

Adrenal Glands, Immunocompetence, Inflammation, and Secretory IgA

Selye and Adrenal Function

The Canadian endocrinologist, Hans Selye, MD, developed the models of stress, adaptive responses, and hypothalamic-pituitary-adrenal (HPA) axis that we use today. This author highly recommends reading his seminal book, *The Stress of Life*, which helps to develop a more organic understanding of allostasis, homeostasis, stress, adrenal functions, general adaptive syndrome, autonomic nervous system, hormesis/hormetic stress, and adrenal-immune system interactions.

Study of Selye's work will help the physician better understand what physiological responses a patient will have from Covid-19 infections depending upon whether they are in the Alarm, Resistance, or Exhaustion Stage of the General Adaptive Syndrome per Selye.

Immunocompetence, Inflammation, and Adrenal Function

Adrenal function, largely modulated by the HPA axis and autonomic nervous system, regulates inflammation and immune responses via glucocorticoids, primarily cortisol. There is a feedback loop between interleukin-6 (IL-6), HPA axis, and cortisol function. In healthy subjects, IL-6 sensitizes cortisol response to ACTH stimulation and there is a natural rise in cortisol in a response to control cytokines . (221, 222) By contrast, low glucocorticoids leads to increased production of inflammatory cytokines. (223)

Although there are benefits to high cortisol for controlling inflammation, excessive levels decrease immune response to infection. High cortisol/DHEAS ratio has been associated with lower neutrophil superoxide generation that is mitigated by DHEA-S supplementation. (224)

DHEA-S levels decrease with age to approximately 10-20% of peak levels found in the second decade of life while cortisol remains fairly constant. This results in a typical increase in the cortisol/DHEA-S ratio later in life. Increased cortisol/DHEA ratio has been associated with senescent presentations of aging - atherosclerosis, type 2 diabetes, osteoporosis, cognitive decline, immune dysregulation, sexual decline, depression - and responsive to DHEA-S support. (225)

It is this decline in DHEA-S and increase in cortisol/DHEA-S ratio that is correlative to the lack of robustness and even fragility seen in the elderly in this authors opinion. In traditional Chinese medicine (TCM), this pattern is referred to as depletion of Jing (Primordial Energy) and/or Kidney yin deficiency.

Low DHEA levels have been found associated with severity for subjects hospitalized with Covid-19 infection. (226) Critically ill patients tend to have illness-related corticosteroid insufficiency and that may, in part, be due to a concentration of ACE2 and TMPRSS2 receptors in adrenocortical cells. (227)

An important note is that that zinc acutely lowers cortisol. (228) This effect can be used to optimize cortisol circadian rhythm and anabolic benefit of low cortisol during sleep by dosing zinc after lunch and dinner or only after dinner depending on the degree of elevated cortisol and pattern of alteration in cortisol circadian rhythm.

Secretory IgA

Secretory IgA is significantly controlled by adrenal function and is first defense from viral infection at mucous membranes in the nose, sinus, throat, lungs, and intestinal tract. It is

promoted by parasympathetic tone, zinc, and vitamin A and inhibited by sympathetic tone and cortisol. (229, 230, 231, 232)

Autonomic Tone and Cholinergic Anti-inflammatory Pathway

Low vagal tone as measured by heart rate variability (HRV) has been associated with the severity of Covid-19 infection and use of HRV has proved valuable for prognosis of hospitalized Covid-19 patients. (233) There is direct correlation between heart rate variability and survivability with low HRV values predicting ICU admission and mortality, especially in patients older than 70 years of age. (234)

The parasympathetic nervous system, primarily via vagus tone regulates inflammation through the cholinergic anti-inflammatory pathway (CAP). Activation of the CAP has been proposed as a viable approach for controlling the pro-inflammatory cytokine cascade associated with complications and mortality from Covid-19 infection. (235, 236)

There has been extensive study of the anti-inflammatory and immune-modulating effects of the cholinergic anti-inflammatory pathway and of the benefits of vagus nerve stimulation (VNS). (237, 238) C-Reactive protein and cytokine IL-6 have been shown to be inversely related to heart rate variability. (239) TNF-α is also down-regulated by increased vagal tone. (240)

Somatovisceral Therapeutics

Somatic therapies have somato-autonomic effects that can modulate the autonomic nervous system. (241, 242, 243, 244)

Chiropractic Therapy

Neurosciences have developed to support observations from chiropractic clinicians that dysafferentation can lead to segmentally organized reflex responses of the autonomic nervous system, which in turn may alter visceral function. (245)

Chiropractic adjustment can result in changes in pupillary diameter - both pupillary constriction (parasympathetic) and pupillary dilation (sympathetic) - that indicate systemic autonomic changes from chiropractic care. (246)

Chiropractic care promotes parasympathetic tone when applied to the cervical spine and sympathetic tone when applied to the thoracic spine. (247) Chiropractic adjustment of the lumbar spine has shown upregulation of parasympathetic tone based on heart rate variability. (248)

Chiropractic has effects on the autonomic nervous system that include promotion of white blood cell respiratory burst and CD4 cells. (249, 250, 251)

Craniosacral Therapy

Craniosacral therapy (COT) has been found to be safe and effective for a wide range of symptomatology based on self-reported questionnaires in osteopathic family practice setting. (252)

COT increases parasympathetic tonus as evidenced by heart rate variability (increased HF domain; decreased LF/HF ratio), a measure of vagal tone. (253, 254, 255)

Acupuncture/Meridian Therapy

Acupuncture to the auricular branch of the vagus nerve and shen men - located on upper ear - independently promote vagal tone based on heart rate variability. (256, 257)

Acupuncture to the acupuncture point Stomach 36 showed functional MRI responses in hypothalamus, dorsal raphe nucleus, periaqueductal gray, and rostroventral medulla that

correlated with simultaneous heart rate variability readings of LF/HF ratio (sympathetic/parasympathetic ratio). (258)

Treatment of Heart 7 promotes parasympathetic tone. (259) Acupuncture treatment for hypertension results in long-term promotion of cholinergic tone based on lowered HF/LF ratio on HRV. (260)

Determining Patient Status Via Observation, Vitals, and Lab Findings

This section is intended to cover the practical tests available to the general/family practitioner to monitor a patient's status and progress and to to determine reasonable course of care which may include recommending hospitalization.

Interestingly, one observation that has been found reliable in differentially diagnosing Covid-19 infection from simple upper respiratory infections is significant hyposmia or anosmia. (261)

Patient Vitals

It is reasonable to have patients positive for Covid-19 infection to monitor themselves by keeping a log twice daily at approximately 12 hour intervals for temperature, pulse rate, blood pressure, oxygen saturation, and respiration rate and report daily for review. This provides a trend line of patient status and alerts to change in trend that may require hospitalization.

It is useful to have a patient with Covid-19 infection test their blood pressure sitting, supine, and standing.

A significantly low BP, especially with a low pulse pressure, indicates a patient with low autonomic/adrenal reserves. This can indicate a patient weakening from the infection if it is progressive. If the diastolic increases supine relative to sitting, there is renal stress - monitor this closely for trend.

A pulse pressure significantly greater than 40mmHg indicates adrenergic stress. Normal rise in systolic BP supine to standing is 4-10 mmHg. Significantly higher rise in systolic indicates adrenergic stress; drops in systolic blood pressure indicate adrenal/adrenergic insufficiency - replenishing salt reserves will be helpful (Celtic salt).

Patients, typically, appreciate the extra care and will usually comply until they know they are healing.

Lab Tests

Run an initial CMP, CBC, serum iron, ferritin, vitamin D, CRP, ESR, fibrinogen, prothrombin time, d-dimer, and urinalysis for a baseline on the patient. Retest as indicated from initial test results and trend of patient vitals log reports. From this information you will be able to make appropriate decisions for your patient.

Notes regarding baseline labs concerning risk for complication from Covid19 infection - alkaline phosphatase below 50 (zinc deficiency), (262) low uric acid, (263) high RDW, (264) high LDH, (265) high ALT, AST, and creatinine, BUN, and bilirubin, (266) low albumin (significant risk factor for mortality), (267) low serum iron, (268) ferritin high , RDW high, (269) and ESR high. (270)

D-dimer is useful for the patient you're concerned about and has great prognostic value, but if you're running this from your concern for the patient after the initial baseline, it may be best for them to be hospitalized. (271) CRP and d-dimer have both been useful in combination for monitor- ing patient status and trend. (272)

Thrombocytopenia has been reported as a risk factor, but studies are mixed. Low platelets may be due to consumption from systemic clotting. (273)

Optimal vitamin D to to prevents acute respiratory syndrome (ARDS) is above 60 (note: protection is significantly greater if vitamin D is normalized before infection; it is common to find pa- tients with vitamin D above normal range due to excessive prophylactic supplementation). 274

Long Covid and Persistent SARS-CoV-2 Induced Neuroinflammation

Long Covid, or Post-Acute Sequelae of SARS-CoV-2 infection (PASC) shows an incidence of approximately 30% in symptomatic and 5% in asymptomatic cases and shows a pattern of long-term promotion of inflammatory cytokines. (275) Chronic cytokine elevation has been proposed causative for the PASC pattern. (276)

In a remarkably detailed and comprehensive paper, '*Characterizing long COVID in an international cohort: 7 months of symptoms and their impact,*' the most significant symptoms after six months were fatigue, post-exertional malaise, and cognitive dysfunction. Further this study found '*85.9% of participants (95% CI, 84.8% to 87.0%) experienced relapses, primarily triggered by exercise, physical or mental activity, and stress. 86.7% (85.6% to 92.5%) of unrecovered respondents were experiencing fatigue at the time of survey, compared to 44.7% (38.5% to 50.5%) of recovered respondents.*' (277)

Symptoms of PASC include, but are not limited to fatigue, dyspnea, brain fog, impaired memory and recall, inability to concentrate or focus, anxiety, depression, headache, myalgia, arthralgia, hyposmia/anosmia, hypogeusia/dysgeusia, cough, hair loss, insomnia, wheezing, rhinorrhea, poor exercise tolerance, post-exertion malaise, altered circadian rhythm, arrhythmias, tachycardia, palpitations, chest pain, postural hypotension and tachycardia, indigestion, constipation, diarrhea, and intestinal inflammation.(278)

Brain fog, an essentially universal symptom associated with PASC, appears related to increased microglial activation and interleukin IL-6 and decreased levels of doublecortin, a marker of neu00roblasts and immature neurons within the hippocampus. (279)

Coronaviruses are known for being neuroinvasive, neuroinflammatory, and even neurotropic. (280) The olfactory nerve appears to be a route of Covid-19 infection into the CNS. (281) Neuroinflammation from high pro-inflammatory cytokines is a keynote of Covid-19 infection and commonly results in lasting neuronal damage due to chronic activation of microglia and astrocytes. (282, 283, 284, 285)

SARS-CoV-2 binding of ACE2 receptors of the capillary endothelium of the blood brain barrier results increased pro-inflammatory cytokines, blood brain barrier permeability, monocyte and leukocyte transmigration, and neuroinflammation. (286) There are ACE2 receptors in astrocytes, pericytes, and endothelia of the blood-brain barrier and in the brainstem and limbic system and compromised functions of these systems correlate with neurological manifestations in Covid-19 infection and PASC. (287)

Both microglia and astrocytes comprise the glial lymphatic system (glymphatic) of the CNS and astrocytes surrounding brain capillaries induce endothelial cells to produce tight junctions of the blood brain barrier. Infection with coronavirus (MHV-A59) showed upregulation of IL1 alpha and beta, IL2, IL15, IL13, IL17, all three interferons and TNF in astrocytes consistent with a TH1and TH17 response and upregulation of activated CD8+ T cells, IL6, and TNF in microglia. (288, 289)

The blood brain barrier is compromised along with upregulation of interferon signaling pathways of the region in severe Covid-19 infection. (290)

A post-viral autoimmunity from molecular mimicry between pathogen and host proteins, epitope spreading, production of autoantibodies, and immortalization of effector B-cells has been pro- posed as a mechanism for the persistence of the pathophysiology of PASC. (291, 292)

PASC patients show elevated IFN-γ responses to SARS-CoV-2 N and M proteins, poorly regulated activation of follicular B helper T cells associated with increased anti-Nucleocapsid anti- body production, and impaired CD8 T cell memory when compared to normally recovering Covid-19 convalescents. The PASC group also shows over-amplified response to SARS-CoV-2 vaccination. (293)

Dysautonomia, as evidenced by heart rate variability and postural hypotension, has been proposed as contributory to PASC. (294, 295) Microglia activation cytokine induced injury of the hypothalamus and brainstem can result in dysautonomia and dysregulation of the cholinergic anti- inflammatory pathway and hypothalamic–pituitary–adrenal axis. (296, 297, 298)

Stellate ganglion block of the sympathetic nervous system has shown remarkable resolution in the signs and symptoms of PASC in a case series supporting post-viral dysautonomia of sympatheticotonia as underlying causation. (299)

There are many signs and symptoms that would lead the clinician to suspect that PASC is a form of post-viral chronic fatigue syndrome, yet less than 50% of PASC subjects meet the diagnostic criteria for CFS. (300) PASC is more frequent in women than in men. (301)

Metabolic stress from Covid-19 infection upregulates kynurenine pathway conversion of tryptophan to nicotinamide adenine dinucleotide (NAD+) and results in the decreased serotonin found during and after Covid-19 infection. (302)

Promotion of quinolinic acid, an endogenous neurotoxin, and glutamate and down-regulation of serotonin can result from chronically high NF-κB and cytokines. (303) Chronic upregulation of TNF-α increases CNS glutamate receptors, decreases GABA receptors, and promotes anxiety. (304)

Microglia functions are directly and adversely effected by emotional stress which may play a role in the development and perpetuation of PASC. (305)

Low cortisol may be contributory to PASC and be responsive to glucocorticoid therapy. (306) It is worth noting that hyperammonemia can contribute to compromised astrocyte function complicating the effects of neuroinflammation. (307)

The neuropathobiology of Covid-19 includes compromise of glial cell (microglia, astrocytes, oligodendrocytes) functions and integrity, transneuronal, degeneration, and apoptosis. Aging results in diminished gliotic response to infection, astroglial lymphatic clearance of viral endotoxins, oligodendrial repair and maintenance of myelination, and neurogenesis. This may account for mortality and PASC in the elderly from Covid-19 infection. (308)

Tetracycline has been proposed as a possible therapy for PASC for its' known ability to inhibit microglia reactivity and neuroinflammation. (309)

Hygienics for Mitigating SARS-CoV-2 Infection Risk

Masking and Situational Awareness

Basic cloth masks act as environmental droplet barriers and diminish droplet dispersion. (310) This is their job and they do it well. Cloth masks are not intended to prevent exposure to aerosols in the same fashion as N95 masks or respirators. Cloth masks diminish transmission of droplets and aerosols from speaking, laughing, coughing, and/or sneezing and decrease viral load exposure to prevent overwhelming tolerance. (311, 312)

Wearing masks in open spaces or closed places where there is no concentrated exposure to droplets or aerosols provides no protection. Key to managing viral exposure is to be situationally aware of vectors of exposure - crowded and closed spaces with poor ventilation. Please recommend patients use washable and reusable masks to minimize waste.

Hand Washing

Teach patients to be very clear of viral to hand to mucous membrane vectors of viral transmission. Education in hand washing decreases viral transmission and alcohol-based sanitizers have been found effective. (313, 314) Advocate patients keep their nails short and clean and lotion may be needed to maintain skin integrity with frequent hand washing and alcohol-based sanitizers use.

Hand drying is an essential aspect of effective hand washing. 315

Having patients view hand washing videos can be informative/eye-opening and instructional for patients. Examples are the Purple Paint Demonstration and a John Hopkins Medicine demonstration using WHO protocols.

Glove Use

Regular use of gloves does not result in greater protection and commonly results in greater risk for viral transmission when used by the layperson. (316, 317)

Face Washing

A nicely structured modelling of transfer of virus from facial skin to mucosa of eyes, nose, and mouth makes a case for face washing. To quote, 'Enveloped viruses, such as influenza and coronavirus, may find human facial regions a favorable environment for survival, probably better than on others body parts, including hands, due to more oily, warmer and humid conditions on the face around the nose. At the same time the viral particles in the proximity to nostrils will also experience periodic reciprocal inhale/exhale convective flows generated by the physiological respiration process.' (318)

Oro-Nasal Washing

Use of saline for nasal lavage and gargling has been found 'significantly efficacious' for decreasing viral load from the nasal cavity and pharynx. (319, 320)

Saline Gargling

Gargling with salt water can decreases viral load and risk for infection. Viral replication is inhibited by salt. (321, 322) When gargling relax your throat and gargle as deeply as can comfortably. Aggressively and completely swish the solution around your mouth, teeth, and gums. Avoid drinking or eating for a while when done to optimize the benefit. Ideally, use unrefined sea salt (Celtic salt) for saline solution.

Saline Nasal Lavage

Nasal lavage decreases viral load and risk for infection, especially of the CNS via the olfactory nerve, and maintains mucosal barrier integrity. (323, 324, 325) Nasal lavage is the irrigation of the nasal cavity with saline can combined with other ingredients - iodine, vitamin A, tea tree oil, etc. (educate yourself on forms and dilutions before recommending for patients).

People with sinusitis are more likely to develop pneumonia than those without sinusitis and one of the main pulmonary complications associated with SARS-CoV-2 is pneumonia. (326) Nasal lavage results in improved outcomes for viral respiratory tract infections decreasing severity and shortening duration 'probably in part by removing viruses and inflammatory mediators from and inhibiting viral replication in the nasal cavities.' (327, 328)

Fungal sinusitis is a remarkably common phenomenon, as high as 96% of chronic sinusitis subjects, that impairs mucosal barrier integrity and predisposes to respiratory infection and pneumonia. (329, 330) This author has found that saline nasal lavage with very dilute tea tree oil (1 drop per 12 ounces of water) is reliably effective in resolving fungal sinusitis.

Oropharyngeal Biota

Specific probiotic cultures can be used specifically in and for the upper alimentary tract to inhibit pathogenic bacteria, including Strep, activate immune responses, including secretory IgA, and moderate inflammation. (331, 332, 333)

Diet

Mediterranean pattern diet, a plant-based omnivorous diet with wide variety of fresh and unrefined foods, is proven to moderate inflammation and immune function (334, 335, 336, 337)

A large scale study of 17 regions in Spain and 23 other countries and found that adherence to a Mediterranean pattern was inversely associated with mortality from Covid-19 infection. (338)

Eating organic and preferably grass-fed butter, whole fat dairy, cream, eggs (free-range), salmon, small fish, and whole eggs provide rich sources of vitamins A and D.

Fruits and vegetables provide vitamin C. Nuts, especially Brazil nuts, are good sources of zinc, but meat, seafood, and eggs are more concentrated. Oysters are the highest food source of zinc.

Whole grains, nuts, leafy vegetables, and teas are high in manganese as are bone broths and stocks. Brazil nuts are the champion, by far, for selenium and I recommend eating a few Brazil nuts (~3-4 a day), though selenium is found in meats, seafood, and whole grains.

Broccoli, red and yellow onions, cherries, and grapes are important sources of bioflavonoids. The white pulp of citrus (lemons, limes, grapefruit, oranges, tangerines) and bell peppers. Include some citrus in the diet by peeling and eating the whole fruit to benefit from the white pith high in bioflavonoids.

Tea

Teas and even coffee, in moderation, provide phenolic compounds, including flavonoids that moderate inflammation and immunity. (339)

Fresh Ginger Root Tea (excellent source of phenolic compounds) Make a pot of tea to have available; it keeps remarkably well; use prophylactically or with mild infection:

- Pot of filtered water - from a cup to the whole pot to last the day
- Fresh whole ginger washed well and thinly sliced
- Fresh citrus - lemon, lime, orange
- slice ginger and citrus and put in pot whole (tart and full of bioflavonoids!)
- Boil for 5-20 minutes - the longer you boil it, the stronger it gets
- add a little honey or maple syrup to taste

Sun (Ultraviolet exposure)

Fresh air and sunshine naturally kill off viruses and bacteria. Treating patients with the outdoors and sunshine was a strategy successfully used during the 1918 Influenza Pandemic. The patients got better faster and with less complications and the doctors and nurses were less likely to be- come infected. (340,341)

Breathing

Nasal, rather than mouth breathing, promotes parasympathetic tone. (342) You will be surprised, once you look for it, how many patients compromise their health from mouth breathing.

Teach patients to breathe - most patients breathe to shallowly, too rapidly, and have too much residual volume. Deep, regular (metronomic), and slow diaphragmatic, abdominal, and even pelvic floor breathing promotes parasympathetic/cholinergic tone as evidenced by increased LF/HF ratio on heart rate variability. (343 , 344, 345)

Have patients practice breathing so deeply they can feel their diaphragm move or, better feel the floor of their pelvis move and the ribs expand. Teach them to breathe all the way out. Doing this gets rid of more of their expiratory residual volume.

Alternate nostril breathing further promotes parasympathetic/cholinergic tone. (346, 347, 348)

Exercise

Encourage patients to walk, hike, stretch, yoga, qi gong/tai chi, aerobic exercise, strength train daily. The key is enough, but not too much - to build up, not break down and do something every day.

Moderate aerobic activity moderates immune functions and inflammation. (349, 350, 351, 352)

Have patients exercise below anaerobic threshold. Doing this will insure patients are exercising in the range that will produce results found in research from moderate exercise. Patients can self select their exercise/activity (walking, hiking, swimming, biking, rowing, for example) to stimulate heart rate to a target of 180 minus age for a minimum of 45 minutes to use up muscle glycogen and up-regulate beta-oxidation. Exercise/train aerobic base 2-6 days a week. Over time, improvement in aerobic base will allow more work to be done at the same target heart rate. For more information read Maffetone's seminal paper and/or refer to The 180 Formula. (353)

Sleep

Most patients need to get more sleep than they think and sleep deprivation leads to depressed immune and endocrine functions and increased cytokines. (354, 355, 356, 357) Poor sleep is often a symptom of aerobic exercise deficiency. (358) Make sure to educate patients on sleep hygiene.

Patients commonly have reversal of the normal circadian rhythm of cortisol due to chronic stress. This is evidenced by the patient who wakes up tired and has their highest energy at night (adrenal stress index test can confirm this pattern). Zinc directly lowers cortisol. Dose after lunch and dinner to reinforce normal cortisol circadian rhythm. (359) The effect is enhanced by nutritional lithium. (360)

Isolating

People don't have to self-quarantine unless they have evidence of being exposed in a way that makes them reasonably certain of becoming infected. The standard period for this is 14 days. [Ed: This is subject to political direction by jurisdiction, please check your local expectations].

Those who have contracted the infection need to isolate to minimize exposing others for the du- ration of having symptoms - fever, dry, cough, shortness of breath - usually ~14 days.

Isolation is appropriate for those who have significant risk factors.

Masks are for people with the infection to use so they aren't broadcasting the virus from cough-ing or sneezing, people who work with those infected, or unable to maintain reasonable physical distancing.

Getting outside, taking a walk/walking the dog, answering the door, signing for a delivery ... these are fine. Isolation is avoidance of close proximity or prolonged contact.

It is common for people in isolation to become depressed and not maintain health supporting habits. Encourage patients to stay actively engaged with others via visiting while maintaining reasonable precautions.

The goal is to return to normal life. In the long-term it it is important to consider the emotional and physical benefit of see one another face to face when in conversation and to touch. Reasonable precautions don't exclude handshakes when both parties are in agreement and understand appropriate hand hygiene or hugging or touching (masked as indicated; hugs with faces in oppo- site directions). Touch and connection need to be considered into the big picture of health and wellness as a part of prevention from infection.

SARS-CoV-2 Infection Selfcare: General

The recommendations above for prevention are helpful for those who become infected - adding isolation, more rest and sleep, staying hydrated, monitoring temperature, and following any specific recommendations by your primary doctor.

There are certainly specific treatment and selfcare protocols that go beyond the recommendations herein. However, the specifics will depend on the individual and I have to stop somewhere.

Summary

Much has been learned in the last 2 years about SARS-CoV-2, dynamics of infection and complications, Long Covid/PASC, and prophylactic and therapeutic approaches from conventional and natural medicine. It is hoped this paper will contribute to making sound diagnostic and therapeutic decisions for your patients.

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Cite: Force M. Reasoning SARS-CoV-2. Asia-Pac Chiropr J. 2022;2.5. URL apcj.net/papers-issue-2-5/#ForceReasoningSARS

Patient handout

Write patient name after 'For:'

For:

Patients infected with SARS-CoV-2 need to coordinate care with their primary physician.

For those over 50 or older, the risk for complications increases significantly, and more so with each increasing decade of life.

It is wise for patients to monitor at home their blood pressure (sitting, supine, and standing), pulse, and temperature. For pulmonary function, have patients use a pulse oximeter and check their respiratory rate, and breath holding time.

Patients are to contact their primary physician if:

- Temperature is 103°F, 39.4°C or greater (102°F, 38.9°C degrees or greater with lung/heart disease)
- Breathing rate at rest is 24 or more
- Pulse at rest is consistently 100 or more or constantly increasing
- Blood pressure shows a sudden increase or an increasing trend
- Orthostatic systolic blood pressure change significantly higher or lower than 4-10mmHg
- Pulse pressure of less than 30mmHg or more than 60mmHg
- Oxygen saturation shows a trend of lower and lower numbers
- Oxygen saturation at rest is 92% or less at rest
- Breath holding time keeps decreasing

Note: If patients find their oxygen saturation is 88% or less at rest, I recommend evaluation at a hospital ED.

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