Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

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Abstract

This paper presents an evidence-based strategy for improving clinical outcomes in COVID-19. Recommendations are based on the phases of the disease, because optimal interventions for one phase may not be appropriate for a different phase. The four phases addressed are: Prevention, Infection, Inflammation and Recovery.

Underlying this phased approach is recognition of emerging evidence for two different components of pathophysiology, early infection and late stage severe complications. These two aspects of the disease suggest two different patterns of clinical emphasis that seem on the surface to be not entirely concordant. We describe the application of therapeutic strategies and appropriate tactics that address four main stages of disease progression for COVID-19.

Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus may both evade the innate immune response and kill macrophages. Delayed innate immune response and a depleted population of macrophages can theoretically result in a blunted antigen presentation, delaying and diminishing activation of the adaptive immune response. Thus, one clinical strategy involves supporting patient innate and adaptive immune responses early in the time course of illness, with the goal of improving the timeliness, readiness, and robustness of both the innate and adaptive immune responses.

At the other end of the disease pathology spectrum, risk of fatality in COVID-19 is driven by excessive and persistent upregulation of inflammatory mechanisms associated with cytokine storm. Thus, the second clinical strategy is to prevent or mitigate excessive inflammatory response to prevent the cytokine storm associated with high mortality risk.

Clinical support for immune system pathogen clearance mechanisms involves obligate activation of immune response components that are inherently inflammatory. This puts the goals of the first clinical strategy (immune activation) potentially at odds with the goals of the second strategy (mitigation of proinflammatory effects). This creates a need for discernment about the time course of the illness and with that, understanding of which components of an overall strategy to apply at each phase of the time course of the illness.

We review evidence from early observational studies and the existing literature on both outcomes and mechanisms of disease, to inform a phased approach to support the patient at risk for infection, with infection, with escalating inflammation during infection, and at risk of negative sequelae as they move into recovery.

Contents

Summary

Four Phases of COVID-19

Clinicians will encounter patients in one of four phases of COVID-19, each requiring its own focus.

- Prevention - support is focused on immune surveillance efficiency and reduction of baseline levels of inflammation, to improve outcomes if the patient becomes infected,
- Infection - support emphasizes immune activity against infection,
- Escalating Inflammation - support is focused on anti-inflammatory measures, and
- Recovery - support is focused on resolving inflammation, inhibiting fibrosis and other forms of tissue damage, curtailing losses of function, and restoring and reoptimizing function. Because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery Phase.

Determination of the proper clinical targets (the strategy) and assessment of the merits of tools to address those targets (the tactics) are critical for optimizing clinical outcomes. In each of the four phases of COVID-19, knowledge of the underlying immunology should inform the clinician's strategy and tactics. It is therefore essential that the clinician understand the underling immunology that informs clinical decisions in order to react appropriately to the unfolding clinical course.

Five Targets of Support are presented in this paper. The following table summarizes the five Targets of Support (rows) that function across four Phases of COVID-19 (the columns). These Phases and Targets, and the knowledge that undergirds them, can be used to form an optimized clinical approach to patient care. The first table describes the basic structure. The second populates that structure with specific tactics. We encourage the reader to read the paper in full, rather than only using the tables.

The following table summarizes the main features of the clinical strategies and tactics outlined in this paper. Clinicians are cautioned to apply these approaches in the context of ongoing discernment as to the patient's unfolding case and to make course corrections as necessary, as is inherent to the nature of clinical practice. In particular, it is essential for those clinicians who have been accustomed to working with patients whose illnesses are chronic to recognize the inherently different pattern and process of acute illness, and have a low threshold for seeking acute care support.

Figure 1. Five Targets of Support as they apply to the four Phases in the time course of disease. It's essential that if the patient moves from the Infection Phase to the Escalating Inflammation Phase, the emphasis shifts to downregulation of the potentially life-threatening inflammatory process.

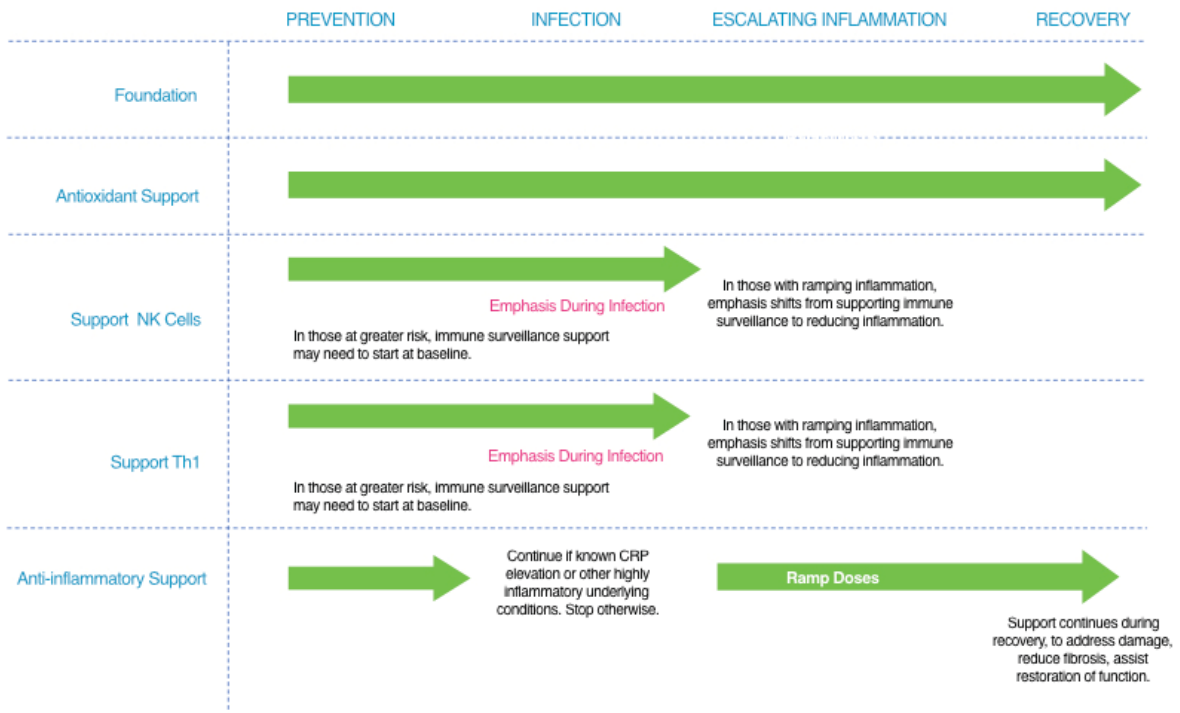
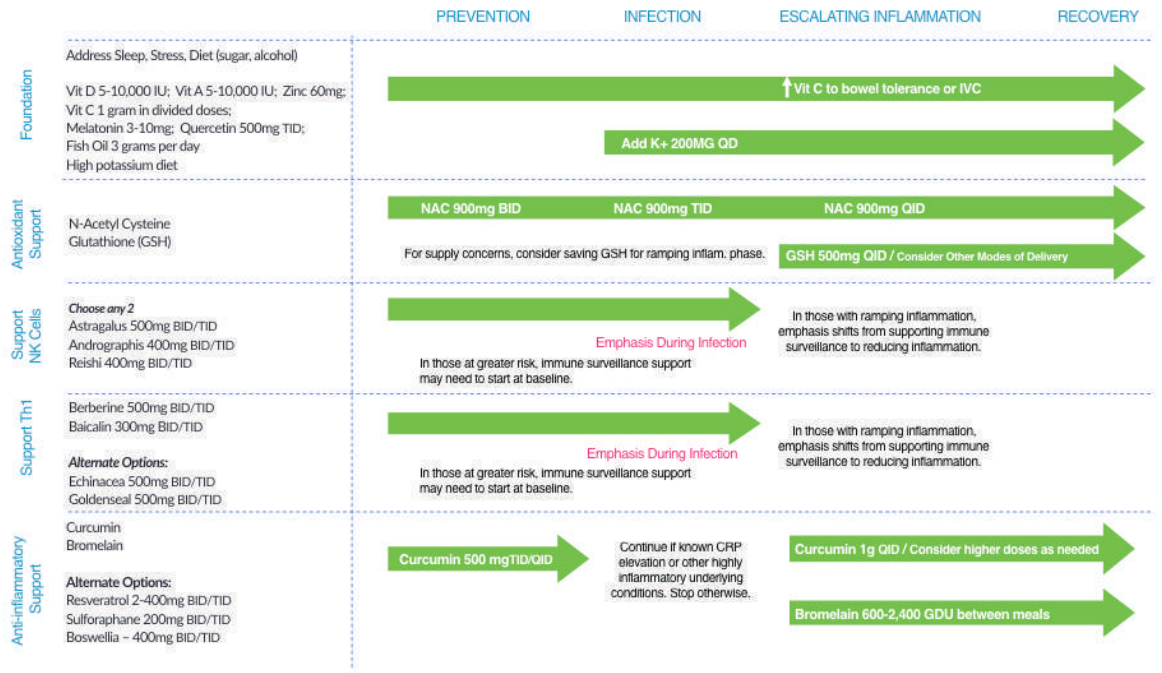


Figure 2. Proposed approach to populating the five Targets of Support, across the four Phases of COVID-19 disease.



Immunological Framework

Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus employs pathogen evasion strategies against macrophages, including delaying macrophage activation and infecting and killing macrophages.[1] The capacity to delay the innate immune response is consistent with the observation that host infection can occur two to fourteen days before the onset of symptoms. In a prospective examination of patients stratified according to percentage of total lymphocytes (without differentiation of constituent cells), those with the most marked lymphopenia (<5%) had significantly higher mortality than those with total lymphocytes <20%, measured at two time points.[2] Lymphopenia linked to mortality implies that macrophages and dendritic cells (DC's) are failing to respond to epithelial cell-derived pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) and hence achieve optimal maturation in order to recognize and ultimately present antigen to naïve T cells, in order to engage the adaptive immune system. Failure of clonal expansion of adaptive immune cells is a driver of lymphopenia. The weakness of the initial round of immune response may also make it more likely that when the clonally expanded populations of T and B cells undergo subsequent timed clonal contraction, there may often still be enough virus left for a surge of disease symptoms in the so-called second wave of illness.

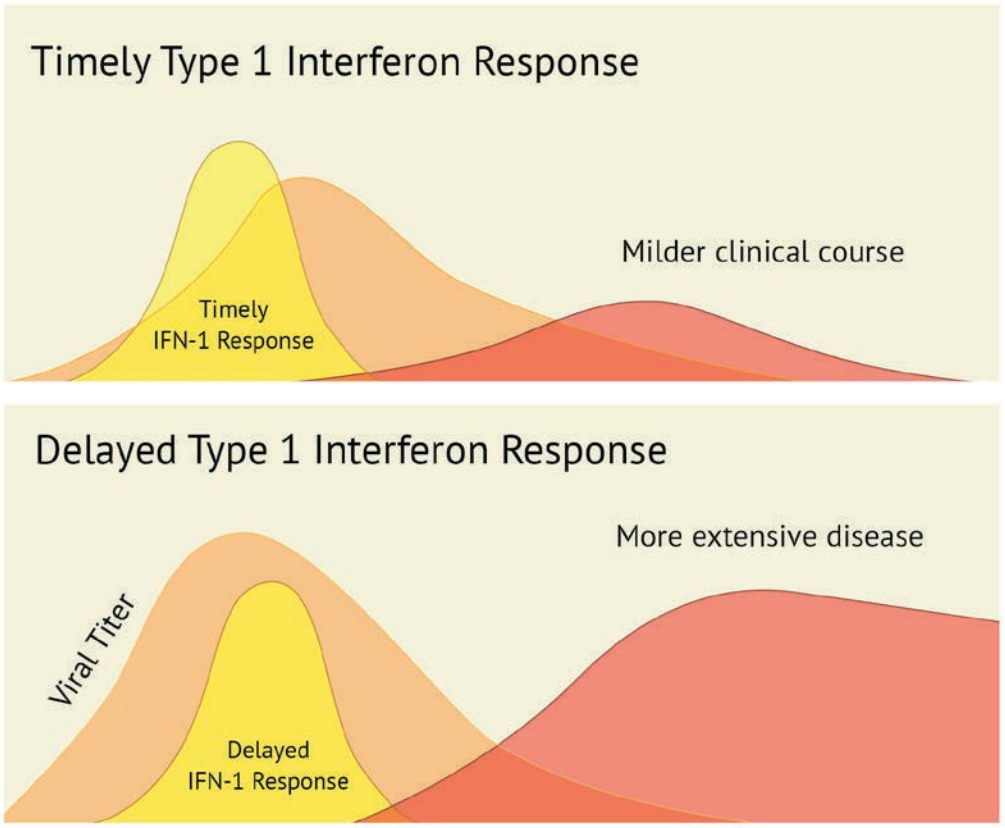
SARS-CoV-2 has also been shown to infect but not replicate in MT-2 experimental T cells in a lab setting.[3] A study of Middle Eastern Respiratory Syndrome (MERS) showed that the MERS coronavirus induced apoptosis (programmed cell death) in the infected T cells.[4] In a SARS-CoV-1 experimental model, robust virus replication was accompanied by delayed type I interferon (IFN-I) signaling, yielding inflammatory responses and lung immunopathology that diminished survival. Early IFN-I administration ameliorated immunopathology, suggesting that supporting efficient immune response early in the infectious process might be useful.[5]

In SARS-CoV-2 infection, if macrophages and DCs are being destroyed by the virus before they can initiate effective antigen presentation to activate the adaptive immune system, those with the highest viral loads might be expected to do most poorly. Higher viral loads would be expected to destroy more macrophages and DCs and to more decisively inhibit the immune activation necessary to get ahead of the virus. This might contribute to understanding of why health care workers, who are potentially exposed to larger volumes of viral load, from repeated exposure to infected patients, would have greater risk of severe disease, as has been observed.[6]

In addition to appropriate measures aimed at social isolation, disinfection, and related approaches, this view suggests the importance of support for efficient activation of the innate immune system both pre-infection in susceptible individuals and as an early phase intervention in infected individuals.

However, every immune response against pathogens carries with it, inherently, an incremental increase in inflammatory cytokine activation.[7] In addition, damage to host tissues drives additional recruitment of neutrophils, macrophages, and other immune elements to the site of

Figure 3. Impact of Timing On Disease Course in COVID-19. Timely type 1 Interferon response yields antiviral response more likely to adequately suppress viral burden, leading to a milder clinical course. Delayed innate immune response, including delayed upregulation of type 1 interferons, may allow greater viral proliferation, leading to more extensive disease and poorer clinical outcomes. Adapted from Channappanavar et al[5] and Klinker et al.[11]



infectious damage.[8] This response can favor pathogen clearance. But, it can also drive more damage, more chemotaxis to recruit immune elements, and creates the potential for an inflammatory loop activation, if signaling chemistry favoring the resolution phase of the inflammatory process fails to turn the tide toward resolution.[9] This upregulatory loop, involving inflammatory cytokine chemistry and its associated sequelae such as ROS generation and oxidative stress, can drive fatality in COVID-19 disease, characterized by cytokine storm, ARDS, septic shock, organ failure and other factors associated with failure to control proinflammatory activation.[10]

It should be noted that field reports raise a question as to whether what's being observed in the lungs of patients with severe forms of COVID-19 should be described as ARDS. Many emergency department and intensive care unit physicians are reporting that the lungs of most of their severely affected patients are not stiff as they would be with ARDS, but virtually all do have extensive microvascular injury on autopsy. These patients also show very high D-dimer levels (personal communication). These observations are consistent with the microvascular thrombotic mechanism described in the NETosis section of this paper. For purposes of this discussion, ARDS will refer to the COVID-19-specific lung pathology, about which understanding is evolving, recognizing that more clarity regarding the details will emerge with time.

When the time course of a patient's infection with SARS-CoV-2 starts to shift toward upregulation of inflammation and damage to lungs, heart, kidneys, or other organs or tissues, the focus of care may need to shift from an emphasis on support for immune system activation to an emphasis on downregulation of excessive inflammatory response. The challenges associated with inadequate anti-pathogen immune response on the one hand, versus anti-inflammatory immune response on the other hand, has been reviewed.[11] Thus, attention must be given to a phased approach to the care and support of patients with SARS-CoV-2 infection, with emphasis on different strategic supports at different phases of the disease process.

The Central Task

Navigating the interplay between early adequate immune activation for antiviral surveillance versus maintaining safe levels of inflammation supporting host survival are key in facilitating a mild disease progression through complete resolution. If the inflammatory process becomes sufficiently

activated, the resulting lung damage can generate more tissue debris that constitutes DAMPs, which will tend to further inflammation.[12] If that reinforcing cycle becomes sufficiently active, the patient can move into cytokine storm, ARDS, septic shock, cardiac or renal damage and other factors associated with fatality risk in COVID-19.[10]

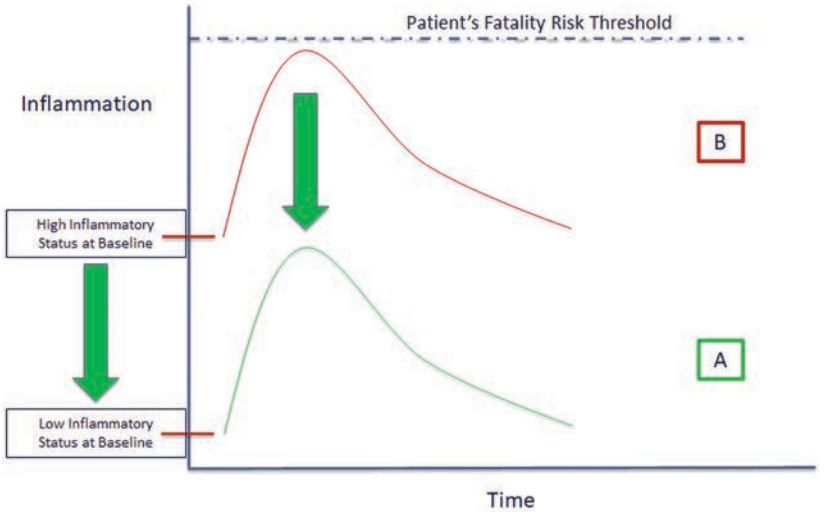
The immune system's process of responding to a pathogen includes effects that are inherently inflammatory. It's important to recognize that "inflammation" is not a single process that simply goes up and down, but an orchestration of interconnected processes with a choreography that normally includes the chemistry of activation—as well as resolution—with many factors involved in regulatory processes that determine to the total outcome. Any and all methods of stimulating, activating and enhancing the immune system's ability to recognize and kill any pathogen, including the SARS-CoV-2 virus, will of necessity involve the immune system generating a cellular and biochemical response, not limited to but including appropriate production of inflammatory cytokines. The immune system is a deeply interconnected system of feedback loops, balances (protease/anti-protease; oxidant/anti-oxidant) and compensatory processes (inflammation/resolution of inflammation). There is no escaping this effect.

Adequate activation > appropriate immune response > > pathogen eradication & triggering of resolution phase chemistry > resolution

Excessive activation > epithelial & endothelial tissue damage > DAMPs/PAMPs > further inflammatory cytokine generation > increased influx of immune elements (neutrophils, macrophages, etc.) > more damage > loop (failure of resolution)

So, any clinical intervention that involves supporting anti-pathogenic immune responses needs to be introduced and sustained with discernment, as excessive inflammatory activation or a skewing toward oxidative stress risks driving the patient to express a potentially excessive inflammatory response. For every patient, there is a moving, multifactorial equation that determines the status of their interconnected systems such as the inflammatory process specifically (itself multifactorial), the effectiveness of resolution chemistry and other modulating mechanisms, and their overall host defense response generally – all against the backdrop of any co-morbidities or pre-existing conditions/disease. This set of variables needs to be addressed with discernment when crafting approaches in the clinical setting. For some patients, concerns about

Figure 4. The patient's baseline level of pulmonary and systemic inflammation may in some cases impact their fatality risk. In **A**, the patient's baseline level of inflammation at onset of infection is modest. As the immune response to the virus evolves, inflammatory cytokines are generated, moving the patient further up the vertical axis. However, the patient's biology can accommodate this increase, as the incremental increase in inflammation is far from that which might risk moving the patient into manifesting ARDS, septic shock, heart or kidney failure, etc. In **B**, the patient's baseline level of inflammation at onset of infection is higher. The same incremental additional inflammation associated with the immune system's choreography of responding to the virus moves the patient correspondingly further up the vertical axis, moving the patient closer to the threshold of manifesting ARDS or other fatality risks. It's noteworthy that, in some cases, inflammation may rapidly escalate from a low baseline to an excessively vigorous inflammatory response that puts the patient in jeopardy, for a host of reasons both known and unknown. So, a low starting inflammatory baseline may not be decisively protective. Nonetheless, moving the patient down the vertical axis, so that the crescendo of the inflammatory process inherent in killing virus doesn't bring them across their threshold of fatality risk, is a worthy clinical goal that may improve the patient's outcome.



specific system processes may be irrelevant. For those for whom SARS-CoV-2 infection may create a substantial morbidity and/or mortality risk due to more aggressive or extensive disease, excessive inflammatory activation is a concern which requires consistent, high level clinical attention. Since there are cases in which young, fit, healthy patients have died of COVID-19,[13] this discernment must be applied in every case.

Clinical Strategy for Patient Support in COVID-19

This section describes strategy. The section that follows populates the strategy with tactics.

Four Phases in the Time Course of COVID-19

We propose four phases in the time course of the disease, requiring different points of emphasis in the clinical support strategy.

Phase 1 - Prevention

In the Prevention Phase, in addition to guidance about social distancing, masks, stress reduction, etc., the task is to support the patient in anticipation of the possibility that they'll contract the virus. This is accomplished by A) identifying and addressing ways to reduce baseline inflammation, and B) identifying and addressing deficiencies in key nutrients that are central to healthy, robust immune system activation.

Part of the clinical task in this Phase is to triage patients as to risk factors for developing severe course of COVID-19. The main non-pulmonary risk factors identified thus far are hypertension (HTN), diabetes, cardiovascular disease[14-16] and malignancy.[16] Pulmonary risk factors include asthma,[12] COPD,[16] and other respiratory diseases that would suggest the patient would be more likely to enter the Escalating Inflammation Phase if they become infected. Environmental inflammatory stressors like air pollution have been shown to increase lung inflammation affect patients with respiratory disorders.[17,18] Two cases of early COVID-19 have been described in patients undergoing lobectomy for adenocarcinoma.[19] Liver and kidney injury are also mentioned.[10] Obesity has also been reported as a risk factor[20] In the H1N1 epidemic, obesity and severe obesity were significant risk factors.[21]

Furman, et al, found that patients over the age of 85 who had greater expression of specific inflammasome gene modules had markedly greater all-cause mortality. The same paper also showed an inflammasome mediated activation of platelet aggregation that may not be age related.[22] That's important, given concerns about thrombotic events in COVID-19. It is useful to notice that biology of inflammasomes, a key intracellular mechanism that drives inflammation, plays a central role in diabetes, CVD, and obesity,[23] in renal disease,[24] in liver disease,[25] and in pulmonary inflammation.[12,26]

For higher risk patients, it may be appropriate to consider early initiation of tactics that appear in the Infection Phase. This lets the high-risk patients get a head start on immune activation.

Phase 2 - Infection

In this Phase, the patient has symptoms that may be presumed to be related to the SARS-CoV-2 virus that causes COVID-19 disease. They may have tested positive for the virus. They may have respiratory or GI symptoms, fever, or other onset of new symptoms. The focus in this Phase is on supporting the components of immune system function that are essential to the patient's ability to fight the infection.

Phase 3 - Escalating inflammation

COVID-19 can enter a dangerous phase in which extreme upregulation of inflammatory cytokines can pose mortal danger.[27] The clinical goal in this Phase is to help the patient stay away from manifesting the excessive inflammatory cytokine production and tissue destruction associated with sepsis,[28] ARDS, and cardiovascular events.[14,29,30] Natural approaches here are supportive, not primary. The unfolding disease process can escalate rapidly.[31]

The current prevailing hypothesis is that a substantial component of the inflammatory process in COVID-19 is driven by activation of the nucleotide binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome.[32,33] Inflammasome-mediated lung inflammation has previously been described as steroid-resistant.[12] Current observations from inpatient settings describe steroids as having equivocal evidence in early acute circumstances, and being ineffective in progressed severe forms of COVID-19.[34]

It's noteworthy that, in addition to asthma[26] and COPD,[16] non-respiratory risk factors like cardiovascular disease, obesity, diabetes, and chronic kidney disease, that present greater mortality risk in COVID-19, share the feature of having NLRP3 inflammasome activation as a key component of their etiologies.[23,35] This connection seems relevant, though whether the greater risk in patients with these diseases is a consequence of greater tendency to vigorous epigenetic expression of NLRP3 or some other mechanism is not clear. Given the speed with which these cases can decline (<24 hrs), it becomes essential to discern the inflection point at which more vigorous measures must be taken to address declining function.

Particular attention may be usefully focused on the relationship between NLRP3, transforming growth factor beta (TGFβ), reactive oxygen species (ROS, and glutathione (GSH). In SARS-CoV-1, the virus upregulated TGFβ via the ROS/p38 MAPK/STAT3 pathway, which correlated with upregulation of profibrotic responses in vitro and in vivo.[36] The role of NLRP3 in inducing TGFβ-mediated activation of fibroblasts has been reviewed,[37] as has the

role of the NLRP3 inflammasome in organ fibrosis and its follow-on consequences for substantial subsequent mortality risk.[37] TGFβ is known to drive fibroblast and fibrocyte transformation into myofibroblasts, the cells responsible for the development of tissue fibrosis.[38] TGFβ and ROS reinforce each other's activation.[38] Production of (ROS) can further drive lung fibrosis[39] and can also promote further NLRP3 inflammasome upregulation,[33,40,41] completing a positive feedback loop.

Inflammasome activation is the driver of autoinflammatory disease.[42] There is a noteworthy association between autoimmune diseases and autoinflammatory disease, with inflammasome activation driving inflammation in many autoimmune diseases.[43,44] This suggests that patients with autoimmune disease in outpatient clinical settings may need to be followed with heightened discernment regarding their risk of shifting into a course of disease process that enters the Escalating Inflammation Phase.

NETs, Thrombosis, Sepsis, and Fibromyxoid Exudates. Increased risk of thrombosis[45] and septic shock[28] have been described in COVID-19. At autopsy, the alveoli are described as containing cellular fibromyxoid exudates.[46] In February, a Chinese respiratory expert described COVID-19 as involving a "large amount of very sticky mucus in their small airways."[47]

Thrombosis, sepsis, and thick mucous secretions share neutrophil extracellular traps as a common causal agent. In addition to phagocytosis and degranulation, neutrophils can kill pathogens by extruding neutrophil extracellular traps (NETs), a process termed NETosis. NETs have been identified in the lungs of cystic fibrosis (CF), acute lung injury (ALI), allergic asthma, and lungs infected with bacteria, virus, or fungi.[48] NETs have been shown to predict adverse outcomes in community acquired infections such as pneumonia.[49] A NET is a chromatin mesh, adorned with anti-microbial peptides and enzymes like neutrophil elastase.[50,51] With increased ROS, a shift toward excessive NETosis drives a significantly exaggerated inflammatory response.[52] Exaggerated NETosis has been described in diabetes and cardiometabolic disease,[53] risk factors that drive greater mortality in COVID-19.

The NETosis response in acute infection can trigger thrombosis. This has been termed immunothrombosis.[54] NETs have been shown to drive death of epithelial cells and endothelial cells, through a histone-dependent mechanism.[55] Extracellular histones, the primary protein of the chromatin mesh of NETs, have been shown to contribute to mortality in sepsis.[56] NETosis contributes to the picture of septic shock.[48,57]

NETosis is involved at the site of lung infection, where it increases mucous viscosity,[58] and in the circulation, where it can promote clot formation.[59,60] NETs appear to provide a third form of clot-forming scaffold, in addition to fibrin and vonWillebrandt Factor (vWF).[60]

Interleukin-6 (IL-6) is a potent inducer of NET formation.[61] This is particularly interesting, in light of the focus on therapeutic downregulation of IL-6 in COVID-19.[62] Of note, CXCR2 antagonism, which inhibits neutrophil migration to sites of infection, plays a down-regulatory role in circulating neutrophil NET formation in COPD.[63] Therefore, therapeutics that can slow/prevent neutrophil migration[64] may be of clinical benefit as another mode of dampening inflammation-based processes that contribute to COVID-19 morbidity.

Phase 4 - Recovery

Disease sequelae, including persistent organ dysfunction, are a significant concern, particularly related to acute lung injury[65] and fibrosis. In SARS-CoV-1, 20% of recovered patients had fibrotic disease nine months post infection.[36] Given the apparent role of the NLRP3 inflammasome in COVID-19, and the role of NLRP3 in driving TGFβ-mediated fibrosis mentioned already, it becomes essential to attend to the patient's potential need for persistent downregulation of inflammasome biology, with the goal of mitigating risk of additional consequences from non-lethal but nonetheless life changing sequelae related to lingering inflammatory and fibrotic effects that occur in the tail of the curve after the crescendo of disease has passed. As mentioned above, because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery phase.

These Phases and their corresponding clinical imperatives are interconnected and bidirectional. There is both a sequencing as the patient transitions between them and an order of importance of tactics to address each of them, addressed in the tables that describe the tactics. If the patient becomes infected, the very same clinical goals that are appropriate to the Prevention Phase (avoiding infection and early virus clearance) will continue to apply as in the Infection Phase. The key tactical transition occurs if the patient enters the Escalating Inflammation Phase.

Five Targets of Support

There are five types of clinical support that target specific patient immune functions. Some forms of support are appropriate to all Phases in the time course of the disease. Others need to be emphasized or deemphasized, depending upon the Phase. Taken together, the five Targets of Support represent a strategy that can be deployed across the four Phases in the time course of the patient's illness.

Target 1 - Foundational Support

In addition to core approaches involving isolation, disinfection, and other such factors, foundational support involves several key components:

a. **Eliminating factors that can drive non-purposeful inflammation and related dysregulatory impacts on immune function.** The patient's inflammatory baseline status is influenced by pre-existing

inflammatory conditions. An opportunity presents itself in the non-infected patient (and potentially in the infected patient early in the course of the disease) to reduce non-purposeful contributions to their level of inflammation, to mitigate the risk of the patient entering the Escalating Inflammation Phase, should they become infected. Several potential areas of interest should be included in the clinical inventory:

i. **Sleep** – Healthy sleep promotes T helper type 1 (Th1) cell response. Th1 cells secrete interferon gamma (IFNγ) that supports anti-viral immune response. Disordered sleep promotes inflammation and Th2 response, at the expense of healthy Th1 response.[66]

ii. **Stress** – Stress chemistry is inherently inflammatory.[67,68] The immune suppressive effects of cortisol are well known. The challenges related to using corticosteroids in the COVID-19 context have recently been reviewed.[69] A recent review examining corticosteroids in COVID-19 suggested possible utility in the early acute phase, but pointed out that conflicting evidence suggests this is not conclusive.[34] As mentioned previously, other research has suggested that lung inflammation driven by the NLRP3 inflammasome mechanism is steroid resistant.[12] Interleukin-1β (IL-1β) production is driven by NLRP3 inflammasome activation, and drives autocrine loop activation in macrophages and other cells in which NLRP3 activation is taking place, reinforcing Signal 1 of the inflammasome assembly sequence.[23] Non-steroidal treatments targeting inflammasome activation, specifically the IL-1R antagonist anakinra, has been shown to block LPS-induced neutrophil influx in healthy subjects.[64]

Cortisol and norepinephrine elevation have also been shown to induce apoptosis of Th1 cells and NK cells in TBI[70] and drive Th2 responses in response to inhaler use in asthma.[71] Though the experience of having COVID-19 would itself be considered a source of acute stress, it should be considered that, in many cases, the acute stress is occurring on top of weeks or months of chronic stress associated with social isolation and related factors.

iii. **Glycemic control** – Insulin resistance, obesity, and impaired glucose tolerance have all been shown to be associated with inflammation.[72-74]

iv. **Dietary factors** – Improvements in diet are strongly associated with reductions in inflammation.[75-78]

v. **Microbiome Balance** – Both the lung and the GI tract have a normal microbiome and the complex relationship between the microbiota of the lung and GI tract, and its bidirectional influence with the immune system, has been reviewed. Dysregulation of the balance of GI microbiome bacteria has been shown to be a source of systemic inflammation.[80-83] Intestinal metabolism of dietary fiber and the resulting increase in short chain fatty acids (SCFAs), specifically propionate, has been shown to enhance hematopoietic generation of macrophages and DC's seeding the lungs. The DC's had increased phagocytic capacity and decreased capacity to induce Th2-bias in lung T cells, an effect that reduced Th2 inflammation.[84] Exacerbations of chronic lung diseases have been proposed to be episodes of lung microbial dysbiosis.[85] The status of the lung microbiome may be especially important in situations requiring the use of ventilators, as depletion of the lung microbiota by broad-spectrum antibiotics prior to high tidal volume ventilation was shown to render mice more susceptible to developing ventilator-induced lung injury.[86]

vi. **Exercise** – Physical activity has long been known to be critical for proper function of virtually all physiological systems. However, to decrease inflammation the right intensity is critical with moderate levels effective at lowering inflammatory markers while intense exercise does not.[87] IL-6 drives significant inflammatory pathology in COVID-19, as discussed here. Skeletal muscle has been shown to produce and releases significant levels of IL-6 after prolonged exercise,[88] so caution should be used when considering the form and duration of exercise.

b. **Supporting levels of vitamins and minerals with known immunological roles.** (see details and references in Tactics section below)

c. **Identification of risk factors that represent increased risk of the patient entering the Escalating Inflammation Phase, if they were to become infected with SARS-CoV-2.** Patients in this category are likely candidates for NK cell and Th1 cell support at baseline. (see details and references in Tactics section below)

Target 2 - Natural Killer (NK) cell support

NK cells drive the core immunological response to viral infection. The diversity of NK cell types and their roles in the healthy and diseased lung have been reviewed.[89] Their overall immunological relevance and coordination with Th1 cells in antiviral immune response are discussed in tandem with the Th1 cell discussion below.

Target 3 - T Helper Type 1 (Th1) cell support

Th1 cells play a key role in antiviral immunity. Th1 cells and NK cells support each other's activation via their loop-reinforcing interactions with macrophages.

This effect is mediated by interleukin 12 (IL-12) made by macrophages that activates the NK and Th1 cells, and by IFNγ made by NK cells and Th1 cells that activates the macrophages and stimulates the macrophages to more rapidly and fully destroy pathogens they have phagocytosed. This is central to the adaptive immune response to viral illness. Th1 response also promotes CD8 cytotoxic T lymphocytes (CTL's) which are essential to antiviral immunity.[90] (CD8 cells are not immune suppressive, despite the lingering terminology).

In a study of COVID-19 patients, the total number of NK cells and CD8 cells has been shown to be markedly decreased, with markers also showing their function to be exhausted. Importantly, NK cell and CD8 cell numbers and function rebound during patient recovery.[91] By contrast, a case report involving a single patient showed significant Th17 cell activation and CD8 cells that were highly cytotoxic and produced copious granzymes and perforin, perhaps associated with the specific treatment strategy employed in the case.[46] This highlights the necessity of attending to each case through the lens of attention to the individual patient's underlying immunology, with crucial attention to the balance of immune surveillance and activation on one side and the need to downregulate excessive inflammatory activation on the other.

Crucially, the IFNγ generated by both NK cells and Th1 cells drives macrophages to execute a more aggressive program of destruction of the pathogens the macrophages have engulfed by phagocytosis.[90] Supporting NK cell and Th1 cell activation drives the production of IFNγ, supporting this function.

There is a prevailing concern in the literature about macrophages and DCs being infected and destroyed by the SARS-CoV-2 virus.[1] It is established in immunology that viruses can escape from phagosomes after engulfment by macrophages and DCs. Normally, the macrophage or DC can handle this event through proteasomal degradation and subsequent presentation of the viral antigen via MHC-1 to naïve T cells that become CD8 cytotoxic T lymphocytes (CTL's) that kill the infected cell, so the virus can't use the cell machinery to replicate. However, given the concern about the SARS-CoV-2 virus engaging pathogen evasion strategies that include delaying macrophage responses and potentially destroying macrophages, a key way to push back against this effect would be to shorten the time course between macrophage/DC phagocytosis of a virion (viral protein/viral particle) or virally infected cell and the time point at which the engulfed material is lysosomally degraded. This is a generally recognized function of IFNγ.[90]

Th2 Dominance Patterns Can Thwart the Attempt to Support Th1 Response

In some patients, there may be a cause for concern regarding a prevailing Th2 dominance. Th2 cells make interleukin-4 (IL-4), inhibits the production of Th1 cell effector cytokines, chiefly IFNγ.[92-94] Factors that diminish the Th1 response raise concerns about blunting overall efficiency of the anti-viral immune response.

It may be crucial in specific patients to downregulate an excessive Th2 dominance, in order to promote an adequate Th1 response. Many factors common in chronic illness can drive the patient into Th2 dominance, including stress chemistry (cortisol and NE),[70,71] sleep disruption,[66] asthma,[95,96] and GI tract inflammation,[96,97] among others. Asthma patients are known to be predominantly Th2 dominant, as are patients with allergic or atopic immune styles.[93]

Diminished reduced glutathione (GSH) status is also associated with loss of IFNγ, increase in IL-4, and a shift away from adequate Th1 response and into Th2 dominance.[98-100] This is especially concerning in light of the mutually reinforcing roles of ROS and TGFβ in inflammation and fibrosis discussed earlier. Depletion of GSH in lung epithelial lining fluid (ELF) carries concerns about loss of anti-inflammatory protection in lung[101] as well as a shift away from anti-viral Th1 response referenced above.

Additional concern regarding excessive Th2 response to the detriment of adequate Th1 comes from evidence that coronaviruses, in this case coronavirus NSP6 protein, interferes with proper formation of autophagosomes in such a way as to prevent merging with lysosomes. The result may be interference with the ability of immune cells to kill virus.[102] It's noteworthy that IFNγ (the primary Th1 cytokine) is required for autophagosome formation and that IL-4 (the primary Th2 cytokine) interferes with this process.[103-105] The machinery of autophagy is known generally to be required for macrophage phagocytosis and autodigestion of phagosome contents. Thus, the emphasis on Th1 may have an added utility if SARS-CoV-2 also targets interference with autophagy as a component of its pathogen evasion strategy.

Lastly, animal coronavirus models[106] have shown that mast cells residing in the respiratory submucosa may play a mixed role, including the generation of Th2 pro-inflammatory cytokines under the influence of viral stimulation and IgE, an antibody type associated with Th2 style immune reaction. Mast cells are stimulated by interleukin-5 (IL-5), a cytokine secreted by Th2 cells. Quercetin has been shown in many human studies to modulate mast cell degranulation.[107]

Target 4 – Anti-Inflammatory Support

The key targets in inhibiting inflammation are the NLRP3 inflammasome, and Nuclear factor kappa B (NFkB).

NLRP3. This is the inflammasome currently hypothesized to drive lung inflammation and some ARDS fatality risk in COVID-19.[32] The role of the NLRP3 inflammasome in sepsis has been reviewed.[108] Inflammasome assembly causes the affected cell to

release IL-1β and IL-18 into the tissue environment,[109] and occurs in response to a wide range of factors, including K+ and/or Cl- efflux from cells, low systemic pH, high glucose, ROS, cholesterol, uric acid, and other factors.[40]

There are two signals that drive classical inflammasome assembly:

Signal-1 - cell membrane receptor stimulation by IL-1β. This induces an increase in cytosolic NFkB, which in turn induces gene expression of pro-IL-1β and pro-IL-18.

Signal-2 - (activation triggered by PAMPS & DAMPS) involves P2X7 receptor stimulation by extracellular ATP from adjacent or nearby cells that are dying, releasing their cytosolic ATP into the extracellular space. It is noteworthy that Ion flux is an important driver of NLRP3 activation, specifically K+ and Cl- efflux out of the cell and elevated intracellular Ca2+, so anything that inhibits K+ and Cl- efflux and lowers cytosolic Ca2+ will contribute to inhibition of NLRP3. Downstream of ion changes is ROS production from stimulated mitochondria that leads to NLRP3 formation, suggesting the utility of anti-oxidants.

There is also a newer alternate/non-classical inflammasome activation of NLRP3 in monocytes (not macrophages) that is K+ independent and requires toll-like receptor 4 (TLR4) ligands, i.e., lipopolysaccharide (LPS), a gram negative bacterial PAMP.[110] This pathway's activation suggests that measures taken to lower baseline LPS levels would have merit. Increased absorption of LPS is found in intestinal dysbiosis, which is associated with chronic upregulation of systemic inflammation that is reversed by restoration of appropriate gut microbial balance.[111]

Given that Signal-2 is stimulation of P2X7 receptors by ATP spilled from the cytosol dying adjacent cells, it may be important to consider avoiding supplements purported to contain ATP or promote ion imbalance per above. Those containing adenosine may also be inappropriate, as adenosine induces T effector cell anergy.[112]

NFkB. NFkB is the key pro-inflammatory protein complex at the center of the NFkB / IL-1β and TNFα activating loop that drives pro-inflammatory cytokine production at the center of the immune response to pathogens and damage.[8] NFkB is produced in response to Signal-1 (priming) of the NLRP3 inflammasome assembly cycle that produces IL-1β and IL-18 and drives pyroptosis (a highly inflammatory form of programmed cell death). Inhibiting NFkB activation or stimulating IkB (inhibitor of KappaB) is therefore anti-inflammatory. In SARS-CoV-1, spike protein activation of IL-6 and TNFα were shown to occur through upregulation of NFkB.[113]

Target 5 – Anti-Oxidant Support

GSH and *N*-acetylcysteine (NAC) play particularly important roles in anti-oxidant support in COVID-19. GSH and NAC are both components of normal human biology. GSH appear to play a key role in supporting both the immune surveillance and anti-oxidant/anti-inflammatory components of the strategy for addressing care for patients with COVID-19. The biological role of GSH in respiratory illnesses including ARDS has been reviewed.[114] The role of GSH in promoting NK cells and inhibiting macrophage infection in TB has been reviewed.[115]

GSH plays a key role in the lung, with the level of GSH in the lung epithelial lining fluid (ELF) strongly influencing the extent of lung inflammation and maintaining oxidant/anti-oxidant homeostasis.[101]

GSH, in addition to its known anti-oxidant function and anti-inflammatory role, is essential for other functions of the immune system, both innate and adaptive: these include T-lymphocyte proliferation[116,117] phagocytic activity of polymorphonuclear neutrophils (PMN)[118] and dendritic cell functions[119] that are crucial to adaptive immune system activation, as DCs function as the professional antigen presenting cell (APC).

N-Acetyl Cysteine. Oral NAC is readily absorbed through the stomach and gut and is converted to cysteine in the liver via first pass metabolism. The majority of cysteine is secondarily incorporated into GSH and released into systemic circulation.[120] Availability of cysteine is the rate limiting factor in GSH synthesis.

The potentially crucial role of neutrophil extracellular traps (NETs) has been discussed above, including promotion of thrombus formation, increased mucous viscosity, epithelial and endothelial cell destruction, and sepsis, and the role of IL-6 as a driver of NETosis. NAC downregulates NET formation through the downregulation of ROS.[58] NAC has been shown to exert an anti-thrombotic effects,[121-123] and increase intraplatelet GSH and reduce platelet ROS.[121] NAC is an accepted treatment for patients with cystic fibrosis. In addition to its directly mucolytic properties, the influence of NAC in reducing ROS and down-regulating NETosis might also be expected to favorably influence these other observed NET-mediated destructive effects in COVID-19 patients.

Inhaled NAC is a well-recognized mucolytic agent and has been a mainstay intervention in cystic fibrosis (CF) patients since the 1960's. In addition to its mucolytic properties, NAC is anti-inflammatory and antioxidant. In one pediatric trial (N = 120 in NAC group), inhaled NAC was well tolerated long-term and attenuated rate of decline in FEV1, outperforming other commonly used mucolytic agents hypertonic saline and inhaled dornase-alfa.[124]

In healthy adults with poor mucociliary escalator function, a 600 mg dose of oral NAC improved mucociliary escalator function by 35%, with washout yielding return to baseline.[125]

Figure 5. The relationships between TGFβ, GSH, ROS, fibrosis, alveolar inflammation, and NETosis in processes occurring at sites of local infection/inflammation. As with all such maps, the reality of the underlying biology is more deeply interconnected.

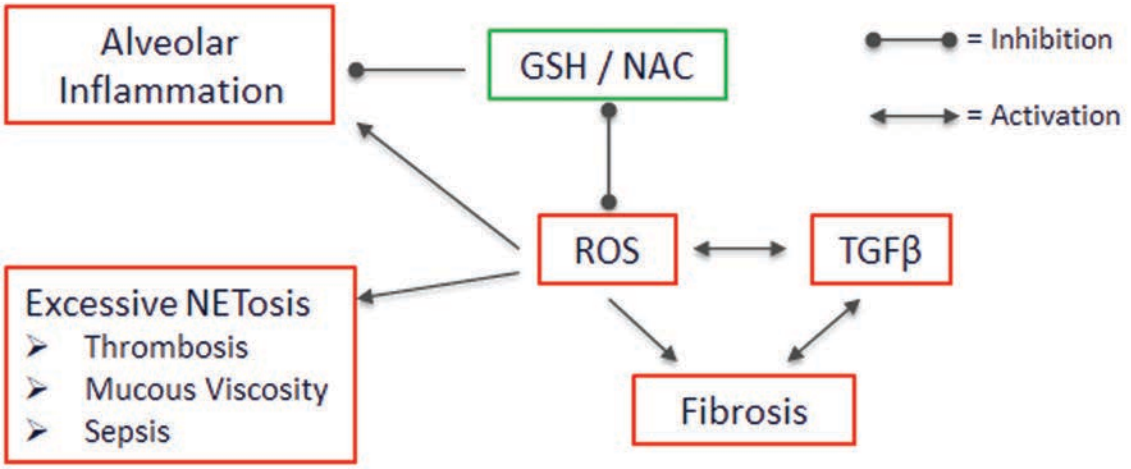
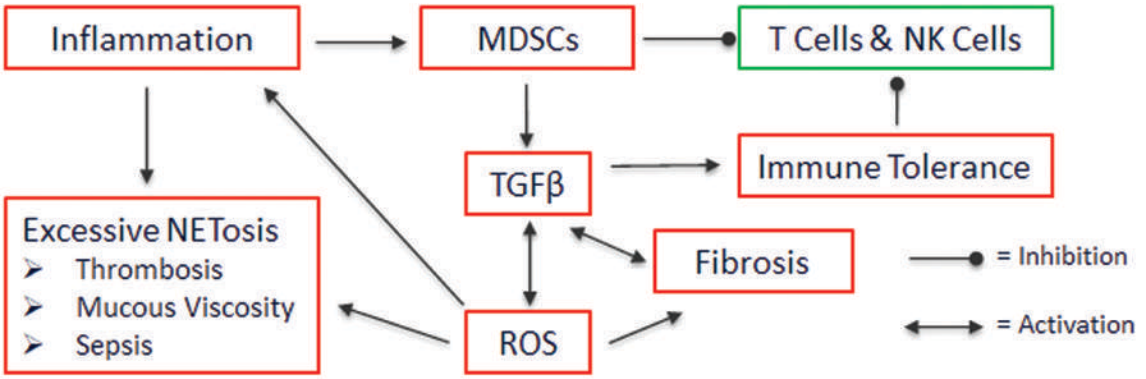


Figure 6. The impact of MDSC / TGFβ / ROS interactions on T Cells and NK Cells.



Glutathione-TGFβ Relationship. The reciprocally inhibitory roles of TGFβ and GSH have been described.[33] GSH plays key roles in the context of respiratory anti-inflammatory support and mitigating the risk of fibrotic damage to lungs and other organs:

- Taken up directly by macrophages through micropinocytosis (anti-inflammatory)[101]
- Necessary for Th1 response[98-100]
- Key inhibitor of TGFβ:[126]
  - TGFβ has been studied in SARS-CoV-1, in relation to lung fibrosis.[36]
  - TGFβ inhibits GSH formation enzymatically, so these are in reciprocal inhibition.[127]
  - TGFβ drives generation of ROS that damage the lung both directly and by inducing NLRP3 inflammasome formation, referenced above.
  - TGFβ promotes fibrosis, referenced above.

The role of ROS in upregulating the NETosis that drives sepsis, destruction of epithelial and endothelial tissue, thickening of mucous secretions, and thrombus formation has already been discussed. Figure 5 describes the relationships between various factors in this process.

MDSCs. In chronic inflammatory states, in the tumor microenvironment, and in infection, immature myeloid cells can be diverted into becoming myeloid derived suppressor cells (MDSC's), instead of maturing to their normal fates as neutrophils, macrophages, and DCs. These MDSCs pour out excessive amounts of TGFβ, driving depletion of GSH and generation of additional ROS. This can become another factor in the further upregulation of inflammation and fibrosis.[128] Added ROS will also drive further expression of NETosis.

Both GSH and NAC have been shown to stimulate effector T cell proliferation.[129] MDSCs take up cysteine as a means of depriving effector T cells of the capacity to activate.[128] Given the preliminary evidence that extent of lymphopenia is related to lethality of COVID-19,[2] adequacy of cysteine in tissues may be an important protective factor.

Tactics to Support the Clinical Strategy

Assessment of Risk Factors

Identifying whether the patient is at increased risk of severe disease course and poorer outcomes with SARS-CoV-2 infection is critical. As an early robust immune response may be predictive of a milder form of disease,[5] patients at greater risk may be candidates for NK cell and Th1 cell support at baseline, rather than waiting until they become infected.

The mechanisms underlying various risk etiologies may give perspective to the individual case and provide clues as to how to treat the patient, with the goal of minimizing these risks.

Health Care Workers

Health care workers, who are potentially exposed to larger volumes of viral load, from repeated exposure to infected patients, have been observed to be at greater risk of developing more severe forms of COVID-19.[6]

Older Individuals

Hospitalization rates for COVID-19 increase with age and are highest among older adults; the majority of hospitalized patients have underlying conditions.[130] Immune function declines with age, particularly T cell-mediated activity, which increases morbidity and mortality from infectious disease. Thymus involution is correlated with aging and loss of T cell activity. Select nutrients recommended in the five Targets of Support and elsewhere including zinc and vitamins A and D have recognized benefit on thymus function and T cell status, and may therefore be especially beneficial for older individuals.[131,132]

Older age carries with it the likelihood of onset of Immunosenescence.[133] Immunosenescence may increase the risk of contracting an infection and may also make it harder to clear infections. In older humans, macrophages become less efficient, phagocytize less, and secrete more inflammatory cytokines. This age-associated low-level inflammatory upregulation is termed "inflammaging." Inflammaging may contribute to poorer immunological outcomes, manifesting as both less efficient macrophage pathogen clearance and greater macrophage production of inflammatory cytokines.[134] Inflammaging is consistent with the description of macrophage activation syndrome (MAS), described as contributing to increased COVID-19 age-related mortality.[135] In MAS, macrophages produce excessive amounts of inflammatory cytokines. This is consistent with the inflammaging model. Inefficient macrophage mediated pathogen clearance would perhaps explain the observation that, early in the disease process, the innate immune system fails to adequately suppress proliferation of the virus, and yet there is copious infiltration of innate immune cells in the lungs of patients with progressed disease. In an autopsy study of six SARS-CoV-1 patients, four were found to have giant cell infiltrates, with increased macrophages in the alveoli and interstitium.[136] Inflammatory cytokine production by macrophages would also induce vigorous neutrophil chemotaxis to sites of inflammation, driving the NETosis referred to elsewhere in this paper. There is significant ongoing discussion of senolytics for the treatment or prevention of COVID-19.[137]

Patients With Known Comorbidities

The risk factors discussed earlier need to be identified, particularly including hypertension, diabetes, cardiovascular disease, malignancy, respiratory problems, and obesity. Underlying upregulation of NLRP3 expression in these diseases suggests that inhibition of the inflammasome, perhaps through greater emphasis on tactics in the Foundational and Anti-inflammatory Targets of Support categories, starting at baseline, may be essential in patients with these risk factors.

Patients With Respiratory Problems

Fibrotic diseases like idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and COPD may confer significantly increased risk. An established fibrotic mechanism involving TGFβ suggests that, in addition to NLRP3 inflammasome inhibition, greater emphasis may need to be placed on GSH[126] and vitamin D,[138] as both can inhibit TGFβ. This may be appropriate early in the clinical course of these cases, and/or as part of an overall prevention strategy in cases with these features.

Patients With Genetic Susceptibilities. As part of the assessment of patient risk factors, genotype testing to assess patient GSH functional capacities may be clinically useful. For example, patients with exaggerated inflammatory neutrophil response to inhaled ozone were 13x more likely to carry the GSTM1null genotype.[139] If infected, these patients might more readily enter the Escalating Inflammation Phase of COVID-19. Higher doses of GSH and NAC may be appropriate in these cases, to compensate for the genotypic disadvantage.

See also the discussion of polymorphisms related to zinc and IL-6 in the discussion of zinc.

Tactics for the Five Targets of Support

This section describes the tactics associated with each of the five Targets of Support. It's important to understand which tactics to apply throughout, and which ones to emphasize during specific Phases of the disease process. Information in the tables and text, along with the clinician's unfolding work with the patient, form the basis for that discernment.

1. Foundational Support

To address foundational support, clinicians can consider addressing factors that impact immunological integrity as well as factors that drive non-purposeful inflammation.

Address factors known to impact immunological integrity

a. **Sleep** - Healthy sleep is anti-inflammatory and promotes appropriate Th1 response. Disordered sleep is characterized by reduced sleep efficiency, less slow wave sleep, and more REM sleep. Disordered sleep yields increased inflammation and increases Th2 response at the expense of Th1 response.[66]

Sound sleep hygiene practices, reviewed elsewhere,[140-143] are fundamental for promoting healthy sleep. In addition, substances such as melatonin may be added to enhance sleep promotion. Not only is melatonin a useful sleep aid, it also inhibits NLRP3 inflammasome activation,[144-146] and reduces airway inflammation.[147] Melatonin has also been identified as a potential therapeutic drug in an in silico model of the human interactome with SARS-C0V-2 (4).

b. **Stress** - As referenced earlier, stress chemistry is inflammatory and has been shown to shift the patient away from effective Th1 response. Many patients will have been enduring significant chronic stress by the time they become infected. Though it is not part of the main protocol, for patients with significantly elevated stress levels, it may be useful to give adaptogens like ginseng or ashwagandha.[148-152]

Stress chemistry can and should also be addressed by a number of other techniques that have proven useful for decreasing the stress response. Patient ability and personal preferences will guide the appropriate choices. Techniques include mindfulness-based stress reduction (MBSR)[153,154] exercise,[155] relaxing music, creative pursuits, biofeedback,[156] and many others, reviewed elsewhere.[157]

Eliminating non-purposeful inflammation

Factors known to drive inflammatory activation, such as dysglycemia, dysbiosis, and/or consumption of inflammatory foods need to be addressed.

Glycemic control, dietary factors, and Lung and GI microbiome balance are all essential components of health and essential areas of focus in the functional approach to patient care. In the Prevention Phase, addressing these systems may present a valuable opportunity to reduce the patient's baseline inflammatory status (Figure 4). In the COVID-19 setting, it's essential to consider whether attention to these factors is a suitable area of focus, with considerations including illness phase, patient capacities to follow multiple instructions, and potential for an intervention to affect short term positive impact on patient outcome.

c. **Glycemic Control** - Addressing glycemic control is a critical part of controlling baseline inflammation. As stated earlier, insulin resistance, and impaired glucose tolerance are associated with inflammation, and may be a contributing factor that puts diabetics at a higher risk for severe COVID-19 outcomes.[158] Most of the work of achieving optimal glycemic control involves subtracting foods from the diet that contribute to an increased post-prandial glycemic response.[159] This avoids adding to the burden of polypharmacy involved in implementing other tactics. While there is individual variation in what food cause a higher glycemic response in specific individuals,[160] the general advice of reducing foods with a high glycemic load is a good place to start.[161] Food combining in order to reduce glycemic burden should also be considered.[162,163] By monitoring blood sugars using a continuous glucose monitor or intermittent glucometers one can get a good sense of what types of foods increase postprandial glycemic response.[164]

d. **Other Dietary Factors** - Dietary factors in addition to those contributing to disrupted glycemic control should also be addressed. A high quality nutrient dense diet that focuses on eating whole plant-based foods that are rich in healthy fats and phytonutrients (multicolored fruits and vegetables) is foundational to decreasing overall inflammation.[165] Reducing or eliminating inflammation promoting foods is also important. Foods that are highly processed and/or contain chemical additives, trans-fats, oxidized fats and added sugars are inherently inflammatory.[166-168]

e. **Lung and GI Microbiome** - The lung microbiome is closely linked to chronic lung diseases and lung inflammation in a bidirectional manner.[169,170] Disruption of gut microbiome can increase sensitivity to viral infections,[171] while treatment with beneficial probiotics can enhance resistance to viral infection.[172] The role of the gut microbiome in overall inflammation has been well established.[173,174] In addition, the lung and gut microbiomes both have an intimate relationship to their respective mucosal membranes, which are critical players in early immune protection.[175] Therefore, maintaining a healthy lung and gut microbiome, and maintaining the integrity of the mucosal linings of both systems is important in decreasing overall inflammatory burden. The use of a high fiber, polyphenol rich diet, prebiotics, and probiotics can be considered to promote a healthy microbial ecosystem.[176-179] Avoiding smoking and air pollution also makes sense.[180,181]

Many of the vitamins, minerals, and botanicals recommended in this paper for their immunological roles also have roles in supporting the microbiome and mucosal membrane integrity and immunity. Vitamin D plays an important role in mucosal immune function[182] and vitamin A is critical in maintaining epithelial barrier integrity.[183] *N*-Acetyl Cysteine protects intestinal health via a number of different mechanisms including tight junction signaling.[184]

Supporting levels of vitamins, minerals, and other substances with known immunological roles.

The role of nutritional agents as immune modulators has recently been reviewed.[185] It's noteworthy that many of these nutrients play dual roles in immunology, supporting immune surveillance while also reducing inflammation.

Vitamin D - The potential utility of vitamin D in COVID-19 has been reviewed, with the authors recommending a multi-day loading of 10 000 iu qd and a steady dose of 5000 iu qd, with the goal of bringing lab ranges above 40-60 ng/ml.[186]

Many studies have shown that vitamin D deficiency not only impairs immune function but also promotes excessive inflammatory reactions. The role of vitamin D in inflammatory and autoimmune disorders has been extensively reviewed, including here.[187] Deficiency has been shown in many inflammatory and autoimmune diseases such as asthma,[188] various types of arthritis,[189] SLE,[190] Type 1 diabetes,[191] Multiple Sclerosis,[192] among others. Supplementation is most likely primarily effective in those deficient in vitamin D or with a VDR polymorphism impairing vitamin D absorption and metabolism.[193]

A meta-analysis of studies on vitamin D and acute lung injury (ALI) found that, in studies that did not use very large, rare bolus dosing, vitamin D was safe and protected against ALI. Patients who were deficient and received non-bolus dosing had the most benefit.[194] Vitamin D has been shown to prevent experimental lung fibrosis and predict survival in patients with idiopathic pulmonary fibrosis, via inhibition of TGFβ.[138] TGFβ is a central player in lung fibrosis and a central generator of the NETosis discussed above, that is associated with sepsis, thickening mucous secretions, and thrombus formation. Vitamin D has also been shown to reduce the risk of acute respiratory infection.[195]

Vitamin D is necessary for the formation of macrophage lysosomal enzymes, a key component of the ability of macrophages to kill pathogens, including viruses, that have been engulfed by phagocytosis.[196] In many experimental models, macrophages are infected with pathogen in vitro, and the cytokine profiles the macrophages generate are measured. As described in the work of Hewison,[196] healthy macrophages with adequate vitamin D status will respond more effectively to infection. This includes greater production of cytokines whose function is to stimulate chemotaxis of neutrophils and other immune elements to the site of infection. Effective neutrophil chemotaxis is induced by inflammatory cytokines, and neutrophil influx into tissue is at the center of normal anti-pathogenic inflammation. These chemical signals are normal in the context of a well-orchestrated inflammatory response, including the resolution phase. Isolating the role of vitamin D in allowing macrophages to respond normally to pathogens does not reflect the total picture of vitamin D's role in the body. Vitamin D plays a key role in both immune system antipathogenic function and anti-inflammatory functions.

ii. **Vitamin A** - Vitamin A was the first fat-soluble vitamin to be identified. Early researchers found that young animals fed a diet deficient in natural fats became very unhealthy and that their eyes became severely inflamed and infected. Vitamin A was once known as the "anti-infective vitamin," and vitamin A status is a major determinant of overall immune status. Those deficient in vitamin A experience impaired antibody response, decreased levels of helper T cells, and impaired integrity of the mucosal linings of the respiratory and gastrointestinal tracts. Vitamin A–deficient individuals are more susceptible to infectious diseases, respiratory conditions like asthma and allergies, and have higher mortality rates.[197]

The prevalence of deficiency is difficult to determine as numbers vary widely worldwide and criteria are inconsistent. Nonetheless, deficiency is common worldwide, with epidemic prevalence in Saharan Arica (48%) and South Asia (44%).[198]

Unfortunately, vitamin A deficiency is also common in the US with 34% of adults consuming less than the EAR.[199] Co-author Pizzorno in an unpublished study of retinol levels in 200 adult oil field workers in Canada found that 40% were deficient.

While beta-carotene is commonly considered synonymous with vitamin A, this an error with significant clinical consequences, especially for vegans. Emerging research has shown multiple, surprisingly common, genomic variations that impair conversion of beta-carotene to vitamin A by 24 to 57%. Single nucleotide polymorphisms have been identified that decrease activity of 15,15'-monoxygenase, the key enzyme converting beta-carotene to retinol. rs12934922) and rs7501331 variants have been found in 42% and 24%, respectively. Those with one copy of the less common allele have shown a 32% drop in activity, while those who are homozygous for the polymorphism experience a 57% reduction in conversion rate.[200]

A controlled animal study in calves found that low dietary vitamin A impaired IgG1 titers against intramuscularly inoculated inactivated bovine coronavirus vaccine.[201]

Vitamin A levels drop during various types of infection and multiple studies have shown that vitamin A supplementation improves resistance and recovery rate.[202] Given the numbers above regarding the high prevalence of vitamin A deficiency, this is cause for concern in the current crisis.

Vitamin A, especially when in balance with vitamin D, has low toxicity except at high dosages. For adults, toxicity is typically seen after 100 000 IU/d for 6 months.[203] A study that looked at the positive effects of multivitamin supplementation in women with HIV showed that Vitamin A was detrimental to outcome.[204] However, in this study, vitamin A was supplemented in the absence of the other fat soluble vitamins notably D and K. Animal studies have demonstrated that vitamin A both decreases the toxicity of and increases the dietary need for vitamin D and vice versa.[205] In addition, concomitant supplementation with vitamin D significantly increased the dose of vitamin A that causes toxicity.[206]

Multiple studies have shown that vitamin A deficiency increases inflammation and more limited research has shown supplementation decreases inflammation. This appears particularly important for the mucosal barriers. However, the research is complex as inflammation itself appears to decrease blood levels of vitamin A.[207]

iii. **Zinc** - Zinc plays a crucial role in the function of essentially all immune cells. Deficiency of this critical element has a profound impact on immune response, increasing susceptibility to a variety of infections.[208-212] One of zinc's critical roles in immune function is its role in thymulin production and activity.[213]

In addition, zinc has specific and well-known antiviral properties.[214] Increasing intracellular zinc concentrations in cell culture impairs the replication of a variety of RNA viruses including SARS-CoV-1. Intracellular zinc has been shown to inhibit RNA synthesis by suppressing the SARS-CoV-1 replication and transcription complex.[215] In vivo evidence for zinc's antiviral role comes from a Cochrane review that found zinc intake was associated with a significant reduction in the duration of the common cold. Many of the studies showing benefit when taken during the course of an infection were in the form of a zinc lozenge.[216] It makes sense to utilize this mode of delivery during the acute infection phase.

Zinc has also been shown to suppress Th17 cell development.[217] Interleukin-17 (IL-17) made by Th17 cells has been shown to drive an inflammatory feedback loop via IL-6 induction.[218] Zinc dependent transcription factors are involved in the regulation of the gene expression of IL-6 and TNFα.[219] The effect of SNPs in genes encoding zinc transporters on blood zinc levels in humans has been examined.[220] Older individuals with gain of function IL-6 SNPs have been shown to have a greater need for zinc.[221] Zinc supplement in older individuals with gain of function IL-6 SNPs and low zinc were shown to have lower IL-6 and MCP-1 levels upon zinc supplementation.[222]

Anosmia (loss of smell) and dysgeusia (distorted sense of taste) are commonly being reported in patients at every phase of COVID-19.[223] These are also classic symptoms of zinc deficiency. It is too early in the discovery process to determine if this is cause or effect, nonetheless zinc deficiency greatly impairs immune function, especially resistance to viral infections. Notably, inadequate dietary consumption of zinc is found in almost half the older population.[224]

iv. **Vitamin C** - Vitamin C is recognized as an essential nutrient in many aspects of the immune system, especially immune cell function of both the innate and adaptive immune responses.[225,226] Microbial killing requires vitamin C for chemotaxis, phagocytosis and generation of ROS.[227,228] Vitamin C deficiency contributes to decreased immune responsiveness and increased susceptibility to infections. Once infected, the enhanced inflammation and metabolic requirements place a further demand for additional vitamin C.[229] Vitamin C supplementation has been shown to both prevent and treat respiratory and systemic infections. The utility of vitamin C and thiamine in sepsis has been reviewed.[230]

Optimal cell and tissue levels of vitamin C in the plasma saturation range are needed for prophylaxis, while treatment of infections requires significantly higher doses.[231,232] In addition, vitamin C's role as an antioxidant is important in protecting the body against the damage from oxidative stress generated during an infection.[233,234] Vitamin C also plays an critical role in endothelial stability, supporting nitric oxide generation and vasodilation. In light of the coagulopathy found in many COVID-19 patients, this role seems highly relevant.[235]

The CITRIS-ALI study, an RCT published in *JAMA* in 2019, showed a possible decrease in mortality in 167 patients with sepsis-related ARDS receiving ~15 grams/day of IV vitamin C for four days.[236] Recruitment is underway at this writing for an RTC IV vitamin C trial (24g/day) in COVID-19 patients hospitalized with severe pneumonia.[237] At Northwell Hospital in New York, there are multiple anecdotal reports of the use of IV vitamin C (1500 mg TID to QID) in COVID-19 patients. Those receiving the IV vitamin C appear to be doing significantly better than those not receiving it.[238]

A meta-analysis of six controlled trials published in March 2019 demonstrated that an average oral delivery of 2 grams of vitamin C per day shortened length of ICU stay by 8.9%. In three trials in which patients required mechanical ventilation for over 24 hours, vitamin C shortened the duration by 18.2%.[239]

v. **Quercetin** - As discussed above, the antiviral roles of zinc are well documented. However, protection of cells against viral appropriation of cellular metabolism to replicate viral RNA requires adequate intracellular zinc. Ionophores play a critical role in facilitating transport of zinc into cells. The commonly available flavonoid quercetin is a zinc ionophore and has been shown to facilitate transport of zinc across lipid membranes. This is particularly relevant as chloroquine is also a zinc ionophore, which has been postulated as a possible mechanism for its apparent efficacy against SARS-CoV-v2.[240,241]

Quercetin is also important as one of multiple flavonoids shown in vitro to block the activity of MERS-CoV 3CLpro, a critical enzyme for coronavirus replication. Animal studies are limited at this time but support efficacy.[242]

In a molecular docking study looking for agents that could bind to the SARS-CoV-2 Viral Spike Protein and thus have potential to inhibit its infectivity, researchers found quercetin to be the fifth most effective.[243] However, quercetin has low bioavailability and therefor requires special formulations to achieve clinically effective blood levels. A trial with a phytosomal quercetin formulation has been started in Italy on 660 hospitalized COVID-19 patients (private communication with study PI).

vi. **Fish Oil** - The role of fish oil in reducing inflammation is long established. However, in an acute care setting, the time scale involved in addressing acute inflammation may preclude the use of fish oil as a strategy for influencing the body's inflammatory equilibrium. Nonetheless, it is worth mentioning the potential role that specialized pro-resolving lipid mediators (SPMs) may play in influencing the biology of risk, in those for whom care is occurring in the Prevention Phase.

SPMs are downstream products of the metabolism of EPA and DHA, the primary active constituents of fish oil. EPA is the precursor for the E series resolvins, and DHA is the precursor for the D series resolvins, neuroprotectins, and maresins.[244,245] These lipid mediators play a key role in the resolution phase of the inflammatory process.[9]

SPMs can inhibit priming and activation of macrophage NLRP3 inflammasome (in vivo and in vitro). SPMs, specifically D2,[246] suppressed IL-1β production and secretion in LPS- and ATP-challenged macrophages, and reduced inflammasome assembly and caspase-1 activity. D2 also deactivated the inflammasome in a mouse peritonitis model, as shown by reduced IL-1β release and increased M2 markers of inflammation resolution.

2. Natural Killer (NK) cell support

a. ***Radix astragali*** **(Astragalus)** - One of the top prescribed botanicals in TCM preparations for SARS-CoV-1 was Radix astragali, with numerous published clinical trials demonstrating significant efficacy for both prevention and treatment. In SARS-CoV-2, astragalus continues to be the most common botanical in TCM prevention formulas prescribed in China.[247]

b. ***Andrographis paniculata*** **(Andrographis)** - The antiviral properties of andrographis have been proposed as leads for pharmaceuticals in the antiviral drug discovery literature.[248-251] Andrographis has been shown in human randomized controlled trials to be effective in upper respiratory tract infection[252,253] and pharyngotonsillitis.[254] Andrographis has been shown to promote natural killer cell activity[255,256] and also reduce the levels of inflammatory cytokines.[257]

c. ***Ganoderma lucidum*** **(Reishi mushroom)** - Ganoderma has been used in traditional Chinese medicine (TCM) for thousands of years. The antiviral properties of ganoderma have been studied in dengue,[258,259] HIV,[260] HPV,[261] enterovirus[71,262] and herpes.[263] Reishi activates NK cells[264-268] and Th1 cells[269,270] and downregulates inflammatory cytokines in human alveolar epithelial cells.[271,272]

3. Th1 cell support

a. **Berberine-containing Botanical Medicines (*Hyrastis canadensis, Coptidis Chinensis*)** - Berberine has been shown to have activity across a broad range of viruses.[273-280] Berberine has activity against RSV via upregulation of type 1 interferons.[281] Type 1 interferons are key activators of NK cells and play a central role in antiviral immunity.[282,283] The anti-inflammatory,[284-286] cardioprotective,[285,287] and antifungal effects of berberine have also been reviewed.[288] One mechanism by which berberine downregulates inflammation is through activation of AMP kinase (AMPK).[289] AMPK is a known activator of SIRT2,[290] a known inhibitor of NLRP3 inflammasome assembly.[23] Other mechanisms of berberine inhibition of NLRP3 have also been described.291-293 Berberine-induced AMPK inhibits IL-6-induced inflammation in human liver cells by inhibiting STAT3, the signal transduction factor required for Th17 cell differentiation.294 Berberine promotes the Th1 cytokines IL-12 and IFNγ and inhibits the Th2 cytokine IL-4.[295-297]

Berberine also has potential advantages in impacting clotting. Hypoxia inducible factor 1 alpha (HIF1α) has been described as a promoter of thrombosis.[298-300] As the name implies, HIF1α is upregulated by tissue hypoxia. With poor oxygenation, higher HIF1α levels will drive more thrombus formation. As described before, neutrophil NETs offer an additional base material for clot formation.[60]

The combination of these factors may be a driving force in the extensive pulmonary microvascular damage seen in severe manifestations of COVID-19. Berberine has been shown to downregulate HIF1α.[301-305]

In a human trial with 130 acute coronary syndrome subjects receiving percutaneous coronary intervention, those receiving 300 mg of berberine TID for 30 days had significant reductions in matrix metalloproteinase (MMP)-9, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, C-reactive protein, IL-6 and monocyte chemoattractant protein-1 (MCP-1), all of which are inflammatory signaling molecules.[306]

Goldenseal is often used because its high concentration of berberine. In a study examining the inhibition of influenza A by berberine, goldenseal at higher dosages was found to be effective at inhibiting both growth of influenza A and production of TNFα and PGE2.[307]

b. Baicalin-containing Botanical Medicines (*Scutellariae baicalensis* (SB) and other Scutellaria spp.) - The high infectivity rate of SARS-CoV-2 separates it from the genetically similar SARS-CoV-1. Preprint research suggests that one difference might lie in a unique furin-like cleavage site on the SARS-CoV-2 Spike protein that is absent in SARS-CoV-1.[308] Dengue virus also infects human cells via furin cleavage, and could be inhibited in vitro and in vivo by application of the flavonoid luteolin.[309]

Evidence for antiviral, antioxidant, and anti-inflammatory effects of SB has been reviewed.[310,311] The ability of SB to downregulate Th17 cell differentiation , the major source of IL-17 that induces macrophage IL-6 production , has been reviewed.[312] Compounds isolated from SB have been shown to have antiviral and Nrf2-promoting antioxidant properties.[313] SB has shown utility in downregulation of NLRP3 inflammasomes,[314,315] antimycobacterial and anti-inflammatory effects in macrophage infection,[316] and anti-H1N1 activity in vitro and in vivo through induction of IFN-γ producing cells.[317] Activity against H1N1 and H3N2 infected cells has been show to be associated with upregulation of type 1 interferons.[318]

In children with acute lymphocytic leukemia, administration of SB extract yielded increased production of IFNγ in peripheral blood lymphocytes (PBLs), and reduced TNFα and IL-10 production in bone marrow cells (BMC), in all patients.[319] The increase in immune surveillance (increased IFNγ) and downregulation of inflammation (reduced TNFα) constitute a potentially useful dual effect. Other phytochemicals similar to SB have been identified that block the entry of SARS-CoV into host cells.[320]

***c. Glycyrrhiza glabra* (Licorice root)** - Glycyrrhiza glabra, common name licorice root, has a long history of use in Western herbal medicine for viral infections and in traditional Chinese medicine (TCM) as a key ingredient for pandemic formulas. It was a component in TCM formulas for SARS-CoV-1 prevention and treatment. Along with astragalus, it is the most frequently used botanical in TCM formulas for SARS-CoV-2 prevention in China.[321] Multiple clinical trials have demonstrated its effectiveness as a part of TCM formulas for CoV-1 and H1N1.[322] Numerous in-vitro studies have shown the major active constituent of licorice, glycyrrhizin, to be effective against SARS-CoV-1.[322] The Th1 promoting properties of licorice may contribute to its antiviral action and have been reviewed.[323]

A 2003 study published in Lancet looking at two clinical isolates of coronavirus from patients with SARS-CoV-1 identified glycyrrhizin to be the most active component of licorice in inhibiting viral replication as compared to ribavirin, 6-azauridine, pyrazofurin, and mycophenolic acid.[324]

A preprint molecular docking study suggests that the major active constituent, glycyrrhizin, can bind the ACE2 receptor, and therefore may have anti-SARS-CoV-2 activity.[325]

Licorice is considered a botanical of low toxic potential and has been safely used in Western and Eastern herbal medicin for millennia. However, excessive use can exert an aldosterone-like affect resulting in potassium wasting. Prescribing glycyrrhizin in individuals on potassium wasting medications may result in hypokalemia.[326] It's also important to note that SARS-CoV-2 itself has been associated with potassium wasting,[327] as is hydroxychloroquine, a drug gaining some renown as a potential COVID19 therapeutic, especially early in the disease process.[328] Clinical considerations for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions or co-morbidities or consequent to inherited syndromes, have been reviewed.[329] Thus, while glycyrrhizin may be a very important COVID19 intervention, serum potassium should be monitored to avoid hypokalemia in vulnerable individuals.

Note that while DGL has substantial clinical research for such conditions as gastric ulcers, this form is not appropriate for COVID-19 as it is deglycyrrhizinated, i.e., the antiviral constituent has been removed.

d. Echinacea spp. - Extracts of various species of echinacea have been used traditionally in North America for many years and are currently popular for the treatment of many types of upper respiratory infections. Recent studies have supported its use by demonstrating that echinacea extracts possess potent

pleomorphic antiviral activities. Direct viricidal activity has been demonstrated particularly against membrane containing viruses including coronaviruses by targeting membrane components, capsid proteins, and virus replication. In addition, reversal of the pro-inflammatory response of epithelial cells to viral infection, and reduction of excessive mucin secretion has also been observed.[330,331]

Of possible particular utility in COVID-19 is a species of echinacea with a long history of use in Western herbal medicine: Echinacea angustifolia. Also known as narrow-leaved purple coneflower, this medicinal herb is native to North America. A particular standardized extract of echinacea was shown to upregulate IL-2 and IL-8 and downregulate TNFα and IL-6 gene expression.[332] An uncontrolled pilot study of this preparation in 36 adults with existing respiratory disorders (chronic bronchitis, respiratory insufficiency, or intrinsic asthma) found improved response to influenza vaccination and a substantial, statistically significant increase in IgG.[333]

Variation in extractions methods, errors in identification, and inconsistent choices in part of plant used present challenges in the clinical choice of echinacea products. Research on a particular extract cannot be reliably extrapolated to other products.

e. Th2 Dominance Inhibition - Understanding the complex dynamics of T cell polarization patterning has gone far beyond Mossman's original Th1/Th2 dichotomy.[334] There are currently seven known maturation fates of naïve T cells, and immunologists no longer think of Th1 as inflammatory and Th2 as anti-inflammatory. In patients whose baseline function likely involves Th2 dominance, indicated by asthma, chronic sinusitis, allergies, or other known Th2-dominant disease processes, or in patients for whom there are other concerns about the prospect of a loss of adequate Th1 response early in the infection phase of illness, it may be useful to consider downregulating an overly exuberant Th2 response.

i. ***Perilla spp***. - Perilla has been shown to downregulate Th2 dominance-based processes like allergic airway inflammation, seasonal allergic rhinoconjunctivitis, and asthma.[335,336] Mechanistic studies suggest this effect is mediated by downregulation of Th2 effector cytokines, including most importantly (IL-4), the cytokine driving Th2-biased autocrine responses. Perilla has also been shown to inhibit platelet aggregation and thrombus formation.[337,338] Dietary supplementation with perilla seed oil in patients with asthma suppressed the generation of leukotriene (LT) C4.[339]

ii. ***Radix astragali*** **(Astragalus)** - Astragalus has substantial Th2 inhibiting properties. As with perilla, astragalus significantly decreased intensity of Th2 dominance-based disease processes like rhinorrhea.[340] Mechanistic studies have shown that astragalus downregulates Th2 cytokines and lowers the ratio of GATA3 (Th2 cell transcription factor) to Tbet (Th1 cell transcription factor).[341-343] Astragalus also upregulates the formation of NK cells in peripheral blood mononuclear cells (PBMCs) from SLE patients.[344]

4. Anti-Inflammatory Support

Inhibition of the NLRP3 inflammasome and NFkB are central to this task.

a. Potassium - Maintaining blood potassium levels is important, to prevent potassium cellular efflux, which upregulates inflammasome assembly.[42]

COVID-19 drug therapy guidance published on April 8, 2020, from the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society states that hypokalemia should be corrected to >4.0 mEq/L and hypomagnesemia corrected to >2.0 mg/dL.[345]

b. Curcuma longa **(Tumeric)** - Curcuminoids are long used turmeric-derived compounds with well-documented pleotropic effects, including antiviral and anti-inflammatory activity.[346,347]

As has been discussed, the aggressive virulence of SARS-CoV-2 may be driven in part by upregulation of NLRP3 leading to production of IL-1β, IL-18 and pyroptotic cell death.[348]

Curcuminoids have been shown to specifically inhibit caspase-1 activation and IL-1β secretion through suppressing LPS priming and NLRP3 activation.[349]

Regarding activity specific to SARS-CoV-2, recent prepublication molecular docking data suggest that the curcuminoids demethyoxycurcumin and curcumin have viral replication inhibition potential against the main protease (Mpro) identified as likely involved in viral maturation and spread. Note that a number of other flavonoids demonstrated inhibition potential in the docking study, with the strongest and best potential SARS-CoV-2 Mpro inhibitors being: kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate.[350]

In another molecular docking study, curcumin showed effective inhibition of SARS-Cov-2 Spike viral glycoprotein binding to ACE2 receptor. While these data are clearly preliminary, the findings suggest the potential of curcumin to halt viral entry into host cells. Other effective flavonoids included hesperidin, with the highest binding affinity.[351]

c. Bromelain - Many studies have documented efficacy of bromelain in reducing inflammation and inflammatory diseases. Clinical benefit has been shown in injuries, infections, respiratory tract diseases, arthritis, inflammatory bowel disease, etc. Of particular importance here is its documented ability to decrease tissue edema and inflammation.

Several studies have shown that bromelain is effective in respiratory conditions such as asthma, bronchitis, and sinusitis that are characterized by increased mucus production and inflammation. Spirometry before and after bromelain treatment demonstrated increased FEV1 and vital capacity, which were suggested by the researchers to be a result of bromelain's mucolytic activity.[352,353]

Of particular interest here is the limited research showing that bromelain decreases cytokines. A placebo-controlled randomized clinical trial found that high-dose oral bromelain showed immunomodulation of both Th1- and Th2- cytokines.[354]

d. Resveratrol - Constituents of resveratrol have been shown to reduce inflammation via several mechanisms including downregulation of IL-6 and TNFα and promotion of Sirtuins.[355-358] Crucial to the utility of resveratrol is its ability to inhibit the accumulation of acetylated α-tubulin caused by mitochondrial damage in macrophages stimulated by NLRP3-inflammasome induction. Inflammasome assembly is strongly induced by acetylated α-tubulin. Resveratrol upregulates SIRT2, a known deacetylator of α-tubulin.[359-361] The utility of resveratrol has been studied in SARS-CoV-1.[362] Resveratrol has been shown to protect lung epithelia against the effects of cigarette smoke by upregulating Nrf2 to promote GSH.[363]

The utility of resveratrol has been studied in a wide range of diseases including cardiovascular[364] and metabolic inflammatory processes.[365]

e. Quercetin - See the quercetin discussion above.

f. Melatonin - See the melatonin discussion above.

***g. Boswellia serrata* (Boswellia)** - Via a variety of mechanisms, boswellic acid (BA), an active constituent in Boswellia serrata, exerts a number of anti-inflammatory effects. BA was shown to potently inhibit TGFβ induced pulmonary fibrosis and 5-lipoxygenase in an animal model.[366] BA has also been shown to significantly inhibit cyclooxygenase, NFKB signaling and TNFα.[367,368]

h. Sulforaphane - Sulforaphane is a well-studied anti-inflammatory phytochemical found in cruciferous vegetables that also inhibits NLRP3 inflammasome biology.[369,370] Sulforaphane activates the antioxidant Nrf2 pathway and drives significant anti-fibrotic activity benefit in both TGFβ treated cell lines, and induced fibrosis in animal models.[371] Sulforaphane also upregulates GSH levels.[372,373]

It is noteworthy that curcumin, resveratrol, quercetin, and berberine have all been shown to promote AMPK.[374] AMPK is a promoter of SIRT2, also known to inhibit NLRP3 inflammasome assembly.[23]

5. Anti-Oxidant Support

Patient GSH status can be supported with oral GSH (liposomal forms appear to offer better absorption), NAC, vitamin E, and selenium. In addition, GSH can be delivered by nebulizer or by IV. It may be appropriate to give both NAC and GSH, in service of supporting GSH status. When available, lab testing can support the clinician's monitoring of GSH levels.

NAC and GSH – Oral and Nebulized Delivery

Nebulized NAC and reduced GSH have a long history of clinical use by natural/ integrative/ functional/ holistic doctors for the treatment of COPD and other chronic inflammatory lung conditions. While there is substantial research support for the value of oral NAC and oral GSH in respiratory illnesses, the research to date on the nebulized delivery is limited but encouraging.

NAC—oral, IV and nebulized—has considerable research support for improving respiratory tract immunity, normalization of inflammation, helping reduce excessive mucous secretion and functioning as a mucolytic. A recent review well summarized its value in respiratory diseases:

> Biological and pharmacological effects of NAC include improvement in rheological properties of mucus, reduction of excess mucin production, restoration of mucociliary clearance and production of sIgA, suppression of excess production of IgE and IgG4, destruction of biofilms and inhibition of their formation, suppression of adhesion of pathogenic bacteria to epithelial cells, antioxidant activity, regulation of the production of pro-inflammatory and profibrotic cytokines.[375]

While nebulized forms are likely more effective, oral NAC at 600 mg bid was shown in in a controlled study of patients with COPD to significantly improved PaO_2, $PaCO_2$, wheezing, and dyspnea and decrease the need for nasal oxygen support.[376]

While most studies support this intervention, a clinical study on mechanically ventilated patients showed that while NAC was more effective than saline in decreasing mean secretion density the results were not statistically significant (P = .087), likely due to a small sample size (20 patients in each arm). However, despite small sample size, NAC was significantly effective at increasing O_2 saturation.[377]

A randomized, controlled study of IV NAC (50 mg/kg/day for three days) for 27 ICU patients with ALI/ARD demonstrated statistically significant improvement in oxygenation and decreased mortality.[378]

Normally, nebulized GSH would be recommended for respiratory inflammation. However, the high level of mucous secretion in COVID-19 could impair its ability to penetrate deeply enough into the lungs. Therefore, the authors recommend IV GSH, to protect both the lungs and also the heart from the damaging inflammation.

While there are a considerable number of controlled clinical studies on the various forms of NAC, there is a surprising dearth of such studies on IV GSH as an independent therapy. Virtually all existing studies examine the use of IV GSH in conjunction with drugs, especially chemotherapy agents. There are several studies showing modest benefit in Parkinson's disease, but virtually no other conditions we could find in PubMed.[379]

The research is clear that inhaled GSH substantially increases blood levels. A few controlled studies have shown modest benefit from inhaled GSH in cystic fibrosis and asthma.[380,381]

Dosage Information

Other than research to date cited here, clinical research on nutritional substances in COVID-19 has not yet been done. All nutritional supports listed here have shown efficacy in human trials in other conditions. Dosages recommended here reflect the well over 100 years of combined clinical experience and judgement of the authors.

Regarding Pregnancy and the five Targets of Support

Safety and dosing recommendations of the compounds listed in the Five Targets of Support have not been established for pregnant women. While some, but not all, of the recommendations in the foundational Target and other Target areas may be safe during pregnancy (e.g. vitamin D, zinc, vitamin C, fish oil), appropriate doses of those nutrients should be determined on an individual basis by the patient's care provider.[382]

Data Collection Resources

As clinical experience and research on COVID-19 continue to emerge, more information will become available to inform clinical decisions about dose and form of vitamins, minerals, botanicals, and other substances. Helpful resources for data collection include the following:

1. The Helfgott Institute IRB-approved online case registry, available to all clinicians: https://redcap.nunm.edu/redcap/surveys/?s=PE3EHAYDT3 Traditional, Complementary and Integrative Health and Medicine COVID-19 Support Registry
2. https://www.millihealth.com/covid-data
3. The COVID-19 Universal Registry, Cure-19, is a public dataset registry. https://www.cure19.org/

Dual Role Substances

In considering potential choices for influencing patient immunological function, it is generally useful to consider favoring strategies that support both the goal of efficient immune surveillance and also the goal of quieting excessive inflammatory activation. These may offer the advantage of efficient anti-pathogenic immunological activity, while also providing anti-inflammatory functions, so that inflammatory cytokine upregulation that comes with immune response to the virus does not move the patient high enough on the vertical axis of Figure 4 to increase their risk of expressing cytokine storm, sepsis, ARDS or other potential morbidity or mortality. For example, vitamin D inhibits activation of the inflammatory protein complex NFkB.[383] Vitamin D is also necessary for the formation of macrophage lysosomal enzymes, without which the macrophages can't kill phagocytized pathogens.[196]

Because many patients with COVID-19 die of complications driven by excessively intense upregulation of inflammatory mechanisms, it is essential to consider that any tactic deployed solely to create an inflammatory adjuvant may carry with it a greater risk than tactics that function in the dual roles of supporting anti-pathogenic efficiency and downregulation of inflammatory response. Further discernment is useful between substances whose anti-pathogenic activation is primarily a consequence of upregulation of inherently inflammatory mechanisms, via upregulation of NFkB and cytokines like TNFα, IL-1β, IL-6, and IL-8, versus substances whose anti-pathogenic activity relies on upregulation of immune-directing cytokines like IL-12 and IFNγ, with the consequences of activation yielding efficiencies reviewed elsewhere in this paper.

Substances Normal to the Body

In the overall clinical endeavor, it is likely useful to consider favoring the clinical application of substances that are normal to the body, such as GSH, NAC, vitamins D, A, and C, and zinc.

Summary

Though much is yet to be understood about the SARS-CoV-2 virus and COVID-19, substantial knowledge of the underlying immunology and clinical tools that apply to therapeutic targets in the underlying immunology provide a basis for clinical application, careful observation, and discernment of the needs of patients who seek support for favorable outcomes in the context of COVID-19. A phased functional approach, based on attention to the time course of the disease process, may provide a useful basis for engaging the clinical process with these patients.

Appendix I. Drug – Nutrient Interactions

Nutraceutical/ Botanical	Significant Concern	Theoretical/Minor Concern
Vitamin D		• Steroids, phenobarbital and dilantin can interfere with vitamin D metabolism • Orlistat and cholestyramine may interfere with vitamin D absorption
Vitamin A	• Warfarin activity may be affected by Vitamin A	• Retinoid medications and other products containing vitamin A may interact with each other • Neomycin, orlistat, and cholestyramine may interfere with vitamin A absorption
Vitamin C	• Warfarin activity may be affected by Vitamin C	• Vitamin C may increase aluminum absorption from antacids • Vitamin C may decrease exogenous estrogen metabolism • Vitamin C may decrease fluphenazine concentrations • Large doses of vitamin C may reduce half-life of HIV protease inhibitors
Zinc		• Zinc may decrease absorption of some antibiotics when taken at same time • Zinc may increase side effects of cisplatin • Zinc may decrease the absorption of penicillamine • Amiloride may increase amount of zinc in body
Melatonin		• Possible interactions with warfarin, nifedipine and immune suppressing drugs.
Quercetin	• Quercetin may affect medications metabolized by CYP2C8, CYP2D6, CYP3A4, and P-glycoprotein substrates	• Quercetin may decrease the effectiveness of some antibiotics • Quercetin may increase concentrations of cyclosporine
Fish Oil		• Fish oil may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
***N*-Acetyl Cysteine**		• Caution in those with a sulfur sensitivity
Glutathione		• Caution in those with a sulfur sensitivity
Astragalus		• Astragalus may decrease the effectiveness of cyclophosphamide and other immune suppressants • Astragalus may decrease the excretion of lithium
Andrographis		• Andrographis may decrease blood pressure, taking with blood pressure medications may cause hypotension • Andrographis may decrease the effectiveness of immune suppressing medications • Andrographis may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Reishi		• Reishi may decrease blood pressure, taking with blood pressure medications may cause hypotension • High doses of reishi may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Berberine	• Berberine may decrease metabolism of cyclosportine	• Berberine may affect medications metabolized by CYP3A4
Baicalin		• Baicalin may decrease the effects of exogenous estrogen • Baicalin may decrease the excretion of lithium
Echinacea		• Echinacea might decrease caffeine metabolism • Echinacea may affect medications metabolized by CYP3A4 and CYP1A2 • Echinacea may decrease the effectiveness of immune suppressing medications
Goldenseal		• Goldenseal may decrease cyclosporine metabolism • Goldenseal may increase digoxin levels • Goldenseal may affect medications metabolized by CYP2D6, CYP3A4, and P-Glycoprotein substrates.
Curcurmin		• Curcumin may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Bromelain		• Bromelain might increase levels of amoxicillin • Bromelain may change levels of tetracyclines • Bromelain may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding.
Resveratrol		• Resveratrol may affect medications metabolized by CYP3A4. • Resveratrol may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding.
Sulforaphane		• Sulforaphane may affect medications metabolized by CYP1A2
Boswellia		• None known

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