Herbal Medicines and Cytokine Storm in respiratory infection.

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The “cytokine” storm emerged into scientific literature and into popular consciousness between 1997 and 2003 when the Bird Flu (H5N1) (1997) and SARS Coronavirus (2003) infections killed a number of people in Asia. The cytokine storm is a phenomenon is an excessive immune response which may occur in late stage severe illness, as a drug side effect, or several other causes, typically occurring in conditions of a critical care unit. Subsequently it was speculated that the severity of the 1918 influenza pandemic in young adults was due to an excessive cytokine response. As with the H5N1 and SARS epidemics, young urban adults were dying, and it was proposed that because they were young and healthy, that the inflammatory response they produced was excessive. In 2009, The H5N1 flu pandemic emerged in North America, and the question arose among herbalists about whether the herb *Echinacea* should be used for this flu or if it presented a problem of stimulating a cytokine storm. Now in 2020, a similar question has arisen about the herb *Sambucus*, and if it has the potential to stimulate or aggravate cytokine storm in COVID-19 infections. (See Review: Sino Biological)

Unfortunately, both medical professionals and herbalists after 2003 have taken a two-dimensional view of the cytokine storm phenomenon. Originally among professionals treating H5N1 in 1997, the heightened pro-inflammatory cytokines led clinicians to prescribe steroids to reduce the inflammation. All patients treated with this strategy died, until the WHO issued guidelines that steroids should not be used to treat these virally-induced storms. Today's understanding of the cytokine storm is more nuanced, that it is not a simple on-off, inflammatory switch, but a complex orchestrated response of many cytokines. While some induce pathologies related to inflammation, others are not pathological but positive. Non-inflammatory portions of the cytokine storm facilitate viral clearance and promote tissue repair, and regulate the severity of the inflammatory cytokines (Guo XJ). This may explain why steroids, resulted in death in all the N5N1 patients they were given to. The beneficial and regulatory cytokines were suppressed along with the inflammatory, and anti-viral immunity was suppressed.

This is also why herbalists cannot take an isolated experiment showing the effect of an herb or its constituents on a single cytokine, and extrapolate that to the net effect of the plant on the whole spectrum of cytokines. In fact both Echinacea and Sambucus have been shown to stimulate immuno-regulatory cytokines, with a net non-inflammatory effect. Elderberry extracts were shown to enhance both inflammatory and anti-inflammatory cytokines in human cells in lab experiments (Barak et al.). In another lab study, an extract of Sambucus flowers *inhibited* all pro-inflammatory cytokines measured (Harokopakis et al.) Another yet another showed regulation through partial inhibition of inflammatory cytokines (Yesilada et al). One trial of the use of a combination of *Echinacea* and *Eupatorium perfoliatum* found no net inflammatory effect produced by cytokines in humans at the dose tested (Elsasser-Beile et al.) Researchers at University of British Columbia who have studied Echinacea extensively concluded that the plant has a net *anti-inflammatory* effect, while maintaining “direct and selective” antiviral and antibacterial activity. In infected cell media, genes that code for pro-inflammatory cytokines, were stimulated by the pathogens, but Echinacea *reversed* the effects. A study showed that infection with virus or bacteria in cell arrays induced secretion of pro-inflammatory cytokines, but that this was also reversed by Echinacea (Hudson et al).

The timing of the development of cytokine storm is also important to understand the potential role of the herbalist in aggravating it. Cytokine storms are a phenomenon of the critical care unit or the ICU. Here patients with advanced respiratory disease are losing the battle against the viral infection, and have acquired pneumonia, or other complications such as multi-organ involvement or sepsis during the late stage of the disease. The intense cytokine reaction might be seen as a last-gasp desperate attempt by the body, in a apparently losing battle the equivalent of a military unit whose position has

been overrun calling in an airstrike on its own position. This happens late in the disease process, in hospitalized patients. At this point, the herbalist will not be likely given access to the patient anyway, so what to give or not give them will not be an issue. This is also consistent in the COVID epidemic in China. In one of the first studies of COVID-19 patients, appearing in the *Lancet* on January 2, 2020, 41 hospitalized patients with confirmed infection were assessed. Of the 41 patients, 22 developed shortness of breath. This occurred after a median time of six days from the first appearance of symptoms. Thirteen were admitted to the ICU, and half of these died. The ICU patients had elevated plasma levels of cytokines relative to those not in the ICU (Huang et al). So the cytokine storm is not an issue for the medical herbalist working for prevention or for treatment of early symptomatic disease.

For many, the COVID-19 virus infection causes mild to moderate illness. But about 14% may require hospitalization, and about 7% require intensive care. A question for the herbalist is what we might offer to prevent the progression from moderate to severe disease, or to support survival in the hospitalized patient. Our normal methods may prevent progression, but we have little to offer once a patient is hospitalized or in the ICU. The answer is probably not herbal for the patient headed to the ICU, but vitamin D status may be important for enhanced immunity at first infection, reduced inflammation in critical care, and reduced complications and death in the ICU. Optimal status can be obtained as prevention, or at any time during the progression of disease.

In a review article of 14 previous studies looking at consequences of vitamin D deficiency in critically ill hospitalized patients, levels of 25(OH)D3 of less than 20 ng/mL were associated with a 57% increased rate of infection, 46% increase in sepsis, in-hospital mortality was increased by 79% and 30-day mortality was increased by 76%, compared to those with level above that (de Haan et al). For reference, the average vitamin D level in North American middle-aged individuals is about 28 ng/mL at the end of summer, and then plummets to about 16 ng/mL at the end of February, because of reduced wintertime sun exposure in northern temperate latitudes. This puts more than half the population at higher risk for severe complications of critical illness. These were not specifically patients with COVID-19 or influenza infection but epidemiological evidence suggests the importance of the seasonal vitamin D winter and its effect on respiratory immunity and systemic inflammation. Seasonal influenza, the SARS epidemic of 2003, and the current COVID-19 epidemic have all followed the pattern of emergence during the vitamin D winter, and improvement as sun exposure increases. (this is not to downplay the heroic efforts in China and by various other governments to contain these epidemics) In one retrospective analysis of the 1918 influenza epidemic, the authors examined case fatality rates and the number of cases progressing to pneumonia in twelve locations in North America where the data was available. Then then assessed the average exposure in those areas to ultraviolet light radiation in both summer and winter, in order to estimate likely vitamin D status of the population there. The authors found a very strong correlation between solar radiation and the likelihood that the influenza would not progress to pneumonia, and also that the patient would survive. The authors point out that correcting vitamin D deficiency up-regulates the antimicrobial immunity, at the same time reducing production of pro-inflammatory cytokines.

A final demonstration of the possible contribution of vitamin D deficiency to the excess mortality of the 1918 epidemic is the fact that the vitamin D deficiency disease Rickets was endemic in the United State in that era. Rates were much lower in 1890, but with the mass migration of a large part of the US population from the countryside to the cities over the next thirty years, Rickets became endemic in the U.S. Medical Historian Mary Weick described the statistics from the 1920's as “almost unbelievable.” (Weick) Nearly 100% of babies born in Boston, New York, Washington DC, Cincinnati, and New Orleans developed Rickets by the age of one year old in 1920. One aspect of Rickets, and of vitamin D deficiency, is increased respiratory infection. These were the conditions that the influenza pandemic encountered: near-universal vitamin D deficiency with accompanying respiratory immuno-deficiency, and the heightened likelihood of progression to pneumonia, and reduced likelihood of recovering from severe disease.

For normal prevention of the wintertime drop in vitamin D levels, and individual needs to take between 4000 IU and 7000 IU of vitamin D3 a day. It is best taken daily, and make up missed doses the next day. If an individual has not been taking vitamin D through the winter, they may assume that they are deficient. This is a very big issue to people of color. When exposed to full body sunlight, a light skinned white person will make 20,000 IU of Vitamin D in 20 minutes. A very dark-skinned person will take 3 hours to make the same amount of vitamin D. People of other skin tones will fall somewhere in between. The reason is that the melanin in the skin acts as a sun block and greatly reduces exposure to the ultraviolet B rays necessary to make vitamin D. Vitamin D deficiency is much more common in dark skinned individuals. Following the above dosing takes weeks to months to restore normal levels. In the midst of a pandemic with cases increasing exponentially day by day, it may be beneficial to follow the advice of a group of vitamin D experts writing on the role of vitamin D in influenza epidemics.

> *"If the ability of vitamin D to stimulate the production of virucidal antimicrobial peptides and to suppress cytokine and chemokine production is clinically significant, then pharmacological doses (1000–2000 IU/kg per day for several days) may be useful in the treatment of those viral respiratory infections that peak in wintertime."*
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> Cannell et al.

The authors suggest this as acute treatment for symptomatic illness in patients suspected of deficiency. This translates into doses of 75,000 to 150,000 IU per day in a 165 lb individual for several days. This level is non-toxic, and for reference, throughout most of the 20th century, after the discovery of vitamin D, doses of 300,000 IU were routinely given to infants and toddlers showing signs of Rickets. Restoration of normal levels may prevent progression to more complicated illness, and may moderate any tendency to cytokine storm or morbidity if the patient ends up in the hospital.

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