

Considerations for the Cytokine Storm

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In severe, acute infectious respiratory disease, especially epidemic pathogens such as influenza and the SARS viruses, one of the leading causes of death is the cytokine stormⁱ: an excessive response of our innate immune system. This article will discuss some considerations for the practitioner of Chinese medicine to help identify risk factors for this problem and provide interventions.

INNATE IMMUNE SYSTEM VS ACQUIRED IMMUNE SYSTEM

In modern medicine the innate immune system is our body's automatic and undifferentiated response to pathogenic factors. In contrast, "acquired" immune response happens at the blood level and includes T-cells and antibodies, each of which recognize specific proteins on invading pathogens that the body had already been exposed to. (All vaccines are designed to generate immunity by causing the acquired immune system to produce cells that recognize and attack specific invaders by their proteinaceous identifiers.)



Modern medicine actually offers no positive definition of health, only the negative definition that "health is the absence of disease."ⁱⁱ It is important to bear in mind that health is not defined by the number and variety of the antibodies we produce. Antibodies do not make us healthy; they merely help prevent us from developing illness when exposed to this or that pathogen. But what about all those countless times in our life when we are exposed to a pathogen for the first time, before we have developed an antibody to it?

Consider that the human body is thought to contain approximately 10^{10} (10 billion) antibodies,ⁱⁱⁱ yet our oceans, air, and soil contain about 10^{31} viruses^{iv}—more than the estimated number of stars in the universe – and these are constantly mutating! The math here strongly suggests that the key to good health can never come from simply adding more and more antibodies to our arsenal. Good health does not come from our acquired immune system but is expressed in

the strength and responsiveness of our innate immune system. If our innate immune system is in good working order, properly regulated, and with good support, we should fare well when exposed to new pathogens. This notion is reflected in the ancient Chinese assertion that if one's *zheng qi* (antipathogenic qi) is sufficient, an external pathogen cannot cause disease in that person.^v Because the innate immune system is a first line of defense, the acquired immune system is dependent upon it, not the other way around. (In fact, T-cells cannot respond to an invasion without the innate immune system "presenting" the antigen to the T-cell.^{vi})

A major player in the automatic response of the innate immune system is the production of chemical mediators of inflammation, called cytokines. Cytokines are chemical mediators that recruit immune cells to infection sites and are responsible for our inflammatory response. Under certain conditions, not always understood, a person's cytokine response can become hyperactive during an acute infection. It can become locked in a cycle of over-expression to the point of death. The cytokine storm is now suspected to be the most important

factor that pushes a mild or moderate case of respiratory infection into a severe or fatal condition.^{vii, viii}

In Chinese medicine, the innate immune system is closely identified with our *zheng qi*. *Zheng qi* consists of 3 components and one function. The three components are *yang*, *wei qi*, and *jin*/thin fluids. As "commander of the qi" the lung function needs to be in good working order as well. If the lungs are unable to descend or diffuse/disperse, the *zheng qi* will not have its full antipathogenic force.

YANG QI AND INFLAMMATION

Yang provides some of our "innate" immune response on its own. It is pre-intelligence and generalized, like a fever. Yang qi is characterized as the most basic and undifferentiated form of qi. The qualities of yang involved in innate immune responses are rising, expansion, and warming. The warming action of a generalized fever is an obvious example of a yang response. Sneezing is another way that our yang responds to

pathogens. When we need to sneeze, our yang rises and expands in order to discharge pathogenic cold and particulates through the yang orifice of the nose. Coughing is another yang qi surge the body will use to expel a pathogen.

Wei qi, though warming, is primarily about movement and reaction. When the body senses a pathogen, the *wei qi* will react by immediately moving to and accumulating at the affected site. The accumulation of *wei qi* then becomes the conduit for the inflammation that originates from the heat provided by the yang qi. In this way the *wei qi* can be seen as the conductor of the cytokine response.

WEI QI

The normal operation of *wei qi* does not involve intelligence; it is a reflex action, constantly adjusting our bodies to our immediate surroundings. Yang is the basis of and raw material for *wei qi*. *Wei qi* draws from the reservoir of yang to convert it into quick responses to external influences. A steady allowance of yang is converted into *wei qi* continuously for normal, ongoing adaptation to our environment, but this rate can increase when adaptation involves a defensive action. For example, exercise requires a more rapid conversion of yang into *wei qi* than sitting at a computer. In a similar manner, when we need to cough or sneeze (each recruiting apparatuses of movement), the burst of yang behind this action is mediated by the *wei qi*: always involved in movement and in reaction to the external environment.

Wei qi moves muscles and fluids but cannot move on its own without a medium. Just like the blood carries the *ying qi*, the *jin*/thin fluids are the mediumship and conveyance of the *wei qi*. In an inflammatory response the *jin* fluids not only allow for smooth movement of the *wei qi* to the site, they also provide the mediumship for the *wei qi* to carry off the casualties of the battle (dead cells, chemical byproducts, and viral material). Insufficient *jin* fluid can therefore be a complicating factor for managing the inflammation.

TIGHT JUNCTIONS

Tight junctions are the intercellular matrix in epithelial tissue that provide a barrier between what is internal and what is external. They are a branching network of proteins that join together the cytoskeletons of adjacent epithelial cells and fill in the spaces between the cells to form a barrier. Breaches in the tight junctions are responsible for the spread of inflammation. In the gut, the tight junctions regulate the passage of nutrients to the interior and prevent the passage

of dangerous microbiota. They are thus an essential partner of the microbiome: that part of our innate immune system that originates in the gut is also the most important part of our innate immune system. In the lungs, tight junctions are found on the surface of the alveoli; in the kidneys, they line the tubules. They even play an important role in the barrier function of the skin and line the nasal passages and throat. In short, tight junctions are found everywhere in the body that have interactions with substances originating from the external environment: air and airborne particles, food, water, sunlight. They provide the physical barrier that separates the internal from the external terrains and regulate what is allowed to enter as nourishment and what is denied entry. They are the yin infrastructure the body provides for defense against invasion from the exterior. In the nose, intestines, and elsewhere the tight junctions are positioned underneath a layer of mucosal lining; the two networks work together as a layered defense system.^{ix} Without good tight junctions we would be in a more or less constant state of reactivity and inflammation because there would be insufficient yin to balance the body's yang response.

Yin and Immune Response

Yin is not a component of *zheng qi*, but it plays a vital role in managing the amplitude of our inflammatory response by balancing and restraining the yang component. If the tight junctions are damaged, the inflammation spreads in direct proportion to the size of the gaps. Many pathogens, such as influenza, are successful in causing a cytokine storm precisely because they damage the tight junctions.^{x, xi} SARS-CoV-2 similarly erodes the tight junctions.^{xii}

If the surrounding tissue at an infection site is yin deficient or the *jin*/thin fluids cannot carry away the byproduct of the inflammatory process, the inflammation can spread into the healthy cells. When the yang that is being converted by the *wei qi* overwhelms the body's yin, this will cause a cytokine storm.ⁱ

PREVENTION OF THE CYTOKINE STORM

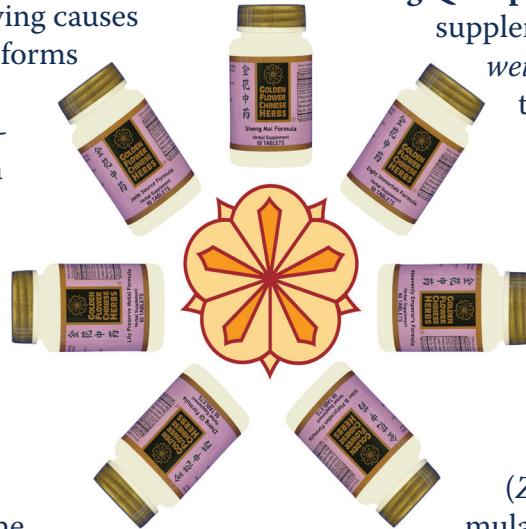
A cytokine storm is a complicating factor that can lead to respiratory collapse, organ failure, even death. It is a major deciding factor in a case turning from severe to critical. In Chinese medicine terms, a cytokine storm is a persistent surge of yang with unrestrained *wei qi*. If we look back to our discussion on *zheng qi* we notice something missing here: the fluids. The *jin*/thin fluids not only carry the *wei qi*, they also help to contain it. But that is not all that is going on here. Yang is restrained by yin. So, a cytokine storm is more likely

to be avoided in those patients who have sufficient yin and fluids. The yin restrains the yang inflammation and the *jin*-fluids provide mediumship for the *wei* qi to move yang qi in, and inflammatory byproducts out of the area. If we look at the populations that are most at risk of a cytokine storm, we find diabetics, the elderly, people with chronic kidney disease and/or serious heart conditions, individuals with hypertension, and those with blood clots. Old age and chronic organic disease are almost invariably associated with (among other individual factors) yin deficiency. Diabetes is strongly associated with the *jin*/thin fluids in type II, and with yin deficiency and *jin*/fluid deficiency in type I. Hypertension seems an interesting outlier here, but not after one considers the underlying causes of high blood pressure. The excess forms of HTN originate in the liver, with liver fire or liver wind. But the deficiency patterns are associated with kidney yin. One thing you can do to help your patients and loved ones who are at risk is to encourage them to eat quality foods and take herbs that nourish the yin and fluids. [See below.]

But having sufficient fluids is not the only precaution. The routes of elimination must be open or else the pathogens cannot be expelled, and the body will have difficulty cooling down. The chief routes of normal elimination are through the bladder and colon, but also important is venting through the pores of the skin and sweating. For blockage in the lungs due to sticky phlegm or heat, the most important route to have open is the bowels because of the yin-yang relationship between the lungs and large intestine. If the surface is closed, then at least part of the acute illness is still external and one should include a percentage of herbs that release the exterior, such as bupleurum (*chai hu*). If someone has their routes of elimination open and their yin and fluids in sufficient supply, it will be nearly impossible for a cytokine storm to develop. Note that prevention of a cytokine storm is best addressed well before exposure. During an acute infection, your strategies should be focused on the particular presentation at the time of illness, but these factors concerning the cytokine storm should be kept in mind for formulations.

FORMULAS TO SUPPORT ZHENG QI AND PROTECT AGAINST A CYTOKINE STORM

In terms of having a strong immune response at initial exposure, the key is to support your *zheng* qi: make sure that you have sufficient *wei* qi, yang, and *jin*-fluids. Strong *zheng* qi is your first line of defense. If the disease is inflammatory in nature (warm disease/*wen bing*), and if the first line fails to repel the attack, you need to be sure that your body can manage being sick without developing a hyperimmune response. Prevention of a cytokine storm must begin a long time prior to exposure. Having sufficient *jin*-fluids is necessary for the *wei* qi to perform optimally, but to prevent a cytokine storm, you need to have the routes of elimination open and you need sufficient yin.^{xiii}



Zheng Qi Support Formula (*Zheng Qi Fang*)

supplements all the components of *zheng* qi: *wei* qi, yang, and *jin*-fluids. It supports the qi of the lung and spleen, astringes leakage of qi, and frees the chest/ regulates qi in the chest. It can be used by most anyone to prepare for seasonal viruses. It works best if started 4-8 weeks before it is needed and should be taken throughout the infectious season. If an infection manages to get past the initial line of defense, cease **Zheng Qi Support (*Zheng Qi Fang*)** and start taking a formula for an acute infection that matches the pattern presentation.

Lily Preserve Metal Formula (*Bai He Gu Jin Tang*) is best taken if an earlier infection left the individual with deficient yin in the lungs and there is some cough lingering. **Lily Preserve Metal Formula (*Bai He Gu Jin Tang*)** can nourish the lung yin and resolve the remaining phlegm to stop the cough. This is an especially important strategy since many times a person will become severely ill because they contract another virus before fully recovering from a previous one. The actions of **Lily Preserve Metal Formula (*Bai He Gu Jin Tang*)** are strong to support kidney and lung yin while also resolving phlegm and stopping cough.

Jade Source Formula (*Jia Jian Yu Quan Wan*) is one of the best formulas to generate fluids. Its origins lie in the treatment of *xiao ke*/wasting and thirsting syndrome. It supports lung yin, cools the lungs and stomach, and supports the spleen qi. It should be the first formula to consider for generating fluids if the patient is diabetic.

Heavenly Emperor's Formula (*Tian Wang Bu Xin Dan*) is another superior formula for generating fluids. The emphasis of **Heavenly Emperor's Formula** (*Tian Wang Bu Xin Dan*) is much more on the lower burner and less on the lungs. It will be the formula of choice for yin deficiency due to aging (when hormone levels are dropping) or when dryness and yin deficiency are causing insomnia.

Eight Immortals Formula (*Ba Xian Chang Shou Wan*) is best employed when the patient has an underlying chronic kidney yin deficiency that affects the lungs. It treats chronic dry weak cough (from yin deficiency) and asthmatic conditions due to constitutional yin deficiency.

Sheng Mai Formula (*Sheng Mai San*) was developed in the 13th Century to treat qi and yin deficiency that was caused by a severe or long-endured disease, leaving the pulse typically some combination of weak, thin, and rapid. In terms of a cytokine storm, the most dangerous combination of these pulse qualities is when all three present at once. This would indicate a qi and yin deficiency with some smoldering deficiency fire. Note that the yin deficiency in this pattern is not as deep as is found in other yin supplementing formulas discussed above because it has no substances that nourish the yin of the kidneys. This pattern is qi and yin deficiency of the lung with stomach fluid deficiency and possible leakage of qi, generally due to a previous disease that consumed them.

Siler & Platycodon Formula (*Fang Feng Tong Sheng San*) is the only formula in this list that can be used during an acute cytokine storm or when one seems imminent. **Siler & Platycodon Formula** (*Fang Feng Tong Sheng San*) excels at clearing heat by opening up all the routes of elimination. It opens the chest, vents the skin, drains the bladder, promotes urination, and unblocks the bowels. This strategy is very efficient to clear heat, lower fever, and ameliorate a cytokine storm. But it has no action to generate fluids or support the yin. It is important to remember that during an acute febrile condition nourishing strategies need to take a back seat to clearing strategies or you run the risk of a) trapping the pathogen (with yin) or b) strengthening the pathogen (with qi). If the lung yin is insufficient and a cytokine storm is a strong possibility in an acute situation, you can combine **Siler & Platycodon Formula** (*Fang Feng Tong Sheng San*) with **Reed & Seed Formula** (*San Ren Wei Jing Tang*).

ENDNOTES

ⁱ There are several early studies in the COVID-19 pandemic that indicate that cytokine storms play a major role in morbidity with this infection. A Google Scholar search using the terms “cytokine” “storm” and “COVID-19” yields over 25,000 hits! But more recent studies are looking at bradykinin storms as playing a more important role in the pathomechanisms of SARS-CoV-2. [For a synopsis of the bradykinin storm issue with COVID-19 see the Fall 2020 issue of this Newsletter.]

ⁱⁱ Even though modern medicine does not have a working definition of health, in recent years there has been a lot of energy devoted to quantifying fitness. Health and fitness are often confused.

ⁱⁱⁱ Fanning LJ, Connor AM, Wu GE, "Development of the immunoglobulin repertoire". *Clinical Immunology and Immunopathology*. 79 (1): 1–14.

^{iv} <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6924909/>

^v It is precisely this idea of strong *zheng* qi that led some Chinese physicians to shift their focus away from the study of external pathogens toward nourishing and supplementing strategies, such as Zhu Dan-Xi's Yin Nourishing School and Li Dong-Yuan's Earth School.

^{vi} This innate immune process is known as “antigen presentation” and is considered an essential part T-cell response, which is part of the acquired immune system.

^{vii} Hojyo S, Uchida M, Tanaka K, Hirano T, et al, “How COVID-19 produced cytokine storm with high mortality,” *Inflammation and Regeneration*. 2020;40:37.

^{viii} Tisoncik J, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG, “Into the eye of the cytokine storm,” *Microbiology and Molecular Biology Reviews*. 2012;76(1)16-32.

^{ix} Capaldo CT, Powel DN, Kalman D, “Layered defense: how mucus and tight junctions seal the intestinal barrier,” *Journal of Molecular Medicine*. 2017;95(9)927-934.

^x Short KR, Kasper J, Van der Ana, S, Kuiken T, et al, “Influenza damages the alveolar barrier by disrupting epithelial cell tight junctions,” *Mechanisms of Lung Disease*. Jan, 2016.

^{xi} Wang S, Le TQ, Kurihara N, Chida JJ, Cisse Y, Yano M, Kido H, “Influenza virus—cytokine protease cycle in the pathogenesis of vascular hyperpermeability in severe influenza,” *The Journal of Infectious Diseases*. 2010(202);7:991-1001.

^{xii} One of many supporting studies is Teoh KT, Siu YL, Chan WL, Nal B, et al, “The SARS coronavirus E Protein interacts with PALS1 and alters tight junction formation and epithelial morphogenesis,” *Molecular Biology of the Cell*. 2010;21(22):3838–3852.

^{xiii} With COVID-19 it is also important to invigorate blood, since there is a very high incidence of clot formation with this disease.

