

Gu Syndrome, Lurking Pathogens, and Long Covid: An Old Take on a New Disease

With Pacific College of Health and Science Expert Heidi Lovie, LAc, DACM

Now that we have been living with SARS-CoV-2 for more than 18 months, we are beginning to see the long-lasting effects the virus has had on survivors. The current statistics paint a harrowing picture. The Centers for Disease Control and Prevention (CDC) estimates that as of May 2021, there have been more than 120 million infections in the United States and 767 000 deaths attributed to Covid-19.¹ Preliminary data suggests that 10% to 30% of individuals infected with Covid-19 are experiencing debilitating symptoms within 6 months after being infected.² These numbers can lead us to reasonably estimate that anywhere between 12 and 36 million individuals in the United States are currently Covid-19 long haulers.

Long Covid is a condition for which the medical community has yet to devise objective diagnostic tests or biomarkers. It often presents as a range of symptoms that can last weeks, months or we may discover even years.³ Formally studied symptoms include fatigue, mood disorders, cognitive impairment, persistent muscle weakness, shortness of breath and debilitating pain or discomfort. All of which are severe enough to have an impact on daily living and occupational activities.⁴ Anecdotal reporting from survivor support groups extends the list to include loss of smell, vertigo, dizziness, migraines, tachycardia, insomnia, neuropathy, hair loss, persistent low-grade fever, sore throat, amenorrhea, dysmenorrhea, swollen lymph nodes and tremors.⁵ To date, there are no proven treatments or rehabilitation guidelines that we can follow as clinicians to help our patients resume a normal life. The effects of Long Covid will have an impact on not only the survivor's ability to function in society but will hinder the US economic recovery efforts and have catastrophic consequences on a healthcare system unequipped to manage long-term care.

Biological reductionism has served us well in this pandemic, providing a deep understanding of spike proteins, angiotensin converting enzyme (ACE) receptors and mRNA viral transcription. However, when integrated methods are employed in immunologic studies of infectious disease, additional information can be extrapolated from the same data that might have otherwise been lost.⁶ In other words, when looking at the data, the more eyes the better. We stand to gain a better understanding of Long Covid by shifting from a virus-

centric to patient-centric school of thought. These views are not mutually exclusive, but rather mutually informative.

We can start by looking for historical examples of contagion that have created post-infection chronic disease disorders, in which patient symptomatology occurs in diverse patterns, diverse demographics, affects multiple organ systems and the effects are long lasting. Modern examples include Lyme disease, syphilis, Epstein Barr, Bartonella, malaria, cytomegalovirus and HIV. If our reductionist focus is solely on viral infections, we miss the lessons presented by spirochetes and bacteria. We need to explore what all these diseases have in common and whether there is historical precedence to treatment.

Epidemiology has occupied an enormous portion of Chinese classical medical literature since the Han Dynasty (206 BCE to 220 CE) and treatises on epidemics have been central to the development of Chinese medical thought.⁷ In addition to the current research on SARS-CoV-2, Chinese medicine practitioners in the field treating Long Covid have been looking to scholars versed in classical Chinese medical texts for additional clues on viable treatment strategies. There are a few schools of thought that have been incredibly helpful.

Gu Syndrome (*Gu Zheng*) historically refers to parasitic infections with references dating back to the 7th century. Although archival sources throughout different Chinese dynasties present varying hypotheses on the provenance of Gu Syndrome, the texts agree that “*by definition [Gu] is not a regular parasitic infection, but a condition that weakens the entire organism by having become systemic in nature.*” Further writings teach us that “*Gu ranks second only to the viciousness of wild beasts when it comes to harmful natural influences; although Gu unfolds its harmful nature only long after the initial encounter, it kills people just the same.*”⁸

The symptoms presented by Gu Syndrome are inclusive but not limited to muscle weakness, fatigue, depression, chaotic thought patterns, low grade chronic fever and a range of digestive symptoms. It refers to diseases that are recalcitrant, debilitating, present disparate symptoms, are resistant to standard forms of treatment and originate from an external infection. However, part of the syndrome definition notes that there is often a preexisting condition that has enabled the infection to take root.⁹ The immune system has been rendered

ineffective in this situation due to either comorbidities or other environmental factors that have taxed the body's defense mechanisms.

Patients are often advised that treatment is not a matter of months but may be a matter of years. Ending therapy too early can result in a resurgence of symptoms that are often more difficult to treat opposed to if therapy had not been interrupted. If symptoms of Gu Syndrome are relatively new and the patient presents as otherwise in good health, treatment duration is often only several months. However, if the patient was in poor health prior to the infection or if treatment was started long after symptoms first occurred, treatment is long term and difficult.

The writings of Wu Youke are another source from which Chinese medicine clinicians working with Long Covid are finding treatment inspiration. As a scholar physician in the late Ming Dynasty, Youke was actively treating patients during a plague epidemic that started in 1633 CE and lasted until 1644 CE with 3 separate distinct waves of infection. He recorded 2 types of observably communicable pathogens that he labeled "passing pathogens" (行邪 / *xíng xié*) vs "lurking pathogens" (伏邪 / *fú xié*).¹⁰

Passing pathogens are diseases that move through the system like a traveler along a road. Modern equivalents would be low grade influenza or rhino viruses. Even if the presenting symptoms are serious, treatment is straight forward, and recovery is the norm rather than the exception. Lurking pathogens are described as being like a wild animal in a cave, or a bird perching in its nest.¹⁰ These are diseases that burrow into various tissues where they can comfortably proliferate and are difficult to reach with medication or other treatment strategies. This observation is in alignment with a current theory that hypothesizes that fragments of the Covid virus can linger in remote pockets of the body, known as reservoirs. Remnants of Sars-CoV-2 have been discovered in almost every tissue of the body including the brain, kidneys and liver.¹¹

Youke recognized that some pathogens are stronger than our body's innate defense systems, regardless of how healthy the individual presents prior to the infection. Therefore, comorbidities will not necessarily determine whether you become infected, but whether you can recover.

Although the current literature on Long Covid is sparse, a similar post-viral syndrome was observed in survivors of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). Survivors reported symptoms of fatigue, myalgia and psychiatric impairments for up to 4 years.¹² Even at 7-year and 15-year follow-up, pulmonary and bone radiologic complications were still evident among a portion of SARS survivors who were younger than 40 years old at the time of the infection.¹³ This implies that Long Covid recovery may take years and is in line with not only Gu Syndrome treatment outcomes, but lurking pathogen theory pointing

to specific tissue degradation that was separate from the pathogen's initial point of entry.

It can be tempting to use Chinese herbs as western drugs, ie, prescribing phytochemicals that are known to be anti-viral, anti-bacterial, or immune enhancing. However, if that strategy is employed in our treatment of Long Covid, it is doomed to fail. That form of biological reductionism is not only virus-centric but divorces itself from historical precedent. By using Gu Syndrome and the concept of lurking pathogens to maintain contextual integrity of Chinese herbal medicine, we are better equipped to find reparative solutions that are integratively patient centric.

Where Chinese medicine clinicians in the field are reporting preliminary success in Long Covid is by looking to specific categories of herbal formulations. However, the prescription is based on an assessment of at least 3 things. The practitioner starts with a differential pattern diagnosis regarding how the patient's health was presenting prior to the infection. Consideration is given to preexisting conditions, comorbidities and constitution (CCC). Next, the practitioner determines where the patient is residing on the disease process continuum by the severity of symptom presentation. Finally, the practitioner is going to inspect the relationship of how the patient's CCCs are interfacing with the infection.

By July 2020, there were 133 registered clinical studies in China being conducted on the integration of Chinese medicine and Western medicine in the treatment of Covid-19. A total of 3 Chinese patent medicines (*Lianhua Qingwen Keli* / *Jiaonang* (Forsythiae and Honeysuckle Flower Pestilence-Clearing Granules/Capsules), *Jinhua Qinggan Keli* (Honeysuckle Flower Cold-Relieving Granules) and *Xuebijing* (Stasis-Resolving & Toxin-Removing) *Injection* were officially approved by the National Medical Products Administration in China as adjunct treatments for treating patients hospitalized with Covid-19.¹⁴

What is interesting to note is that the formulations approved for the initial stages of the infection are heat clearing herbs that have anti-viral effects; however, that was not the sole consideration. There are myriads of phytochemicals that fulfill that qualification. These formulations were chosen because they also have an impact on common CCC's. The decision by the prescribing physician regarding which of the 3 formulas to employ was based on the strategy outlined above. The addition of Chinese medicine shortened the symptom duration by 2 days, improvement rate of CT imaging increased by 22%, severe cases were reduced by 27%, and patients were released on average 2.2 days earlier.¹⁵

Success in our approach to Long Covid will depend on a similar approach. A puzzling feature of Long Covid is that neither severity nor duration of the initial Covid-19 infection can be used as a predictor for who will develop the syndrome. At this time, females afflicted by Long

Covid outnumber males by 4 to 1, with an average age of approximately 40 years.¹⁶ As we investigate pathophysiology, we will of course look at genetics, how endocrine systems play a role, immune system response and inflammatory markers. We need to investigate what is the constitutional pattern among the afflicted vs individuals who recovered unscathed.

As more patients move into the post-infection phase with Long Covid symptoms, we can take a page from the Gu Syndrome and lurking pathogen playbooks. Treatment time will be long. Treatment strategies will need to be individualized. Treatment methods will need to be varied so lurking pathogens are less likely to adapt. We need to review *Materia Medica* categories with a relativist eye and integrative heart. We need to fight the temptation to simply look for solutions that are anti-inflammatory, antiviral, anti-apoptotic and adaptogenic. Such an approach is working with one hand tied behind our backs because we can easily overlook solutions that are hiding in plain sight.

The holistic paradigm from which Chinese medicine was born rejects being reduced because it is expansive rather than contractive. As clinicians, we are in service to our patients and the communities in which they reside. While herbology is often labeled as alternative medicine, a more apt label would be original medicine. Plant medicine is the pharmacology of our ancestors, regardless of where we are from. Someone in our family tree was able to understand what plants on their land held the ability to heal, harm, nourish or kill. The language of this medicine does not always correspond with the language of organic chemistry. As we research solutions to predicaments such as Long Covid, we need to expand our vocabulary and search criteria to include language such as yin tonifying, damp draining, toxic heat clearing, Qi harmonizing and expulsion of parasites. Novel viruses are nothing new and, even if this is the first time we have encountered a specific pathogen, it must abide by certain natural laws to survive. The physicians who came before us left us treatises documenting their understanding of these natural codes and immutable rules of nature, along with instruction manuals regarding what worked. To move forward, it will behoove us to look back.

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