

Acupuncture-Immune Modulation and the Gut-Lung Axis

Joseph Audette*

Harvard Medical School, 133 Brookline Avenue, Boston MA 02215, USA

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***Author for Correspondence:** Joseph Audette, Harvard Medical School, 133 Brookline Avenue, Boston MA 02215, USA

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When we view the immune system through the lens of Chinese Medicine, we think of the organ function of Lung. The Lung in Chinese Medicine is much more than just the organ lung and includes complex functional relationships with the upper respiratory system, our skin and is integral in the creation of *wei* (defensive) and *ying* (nutritive) Qi—all of which provides us with adequate defenses against the invasion of external pathogenic factors such as viruses. But even with the enhanced, functional Chinese medical view of the Lung, the story does not end there. With Chinese Medicine, you cannot think about the function of Lung (yin) without immediately bringing in its yang pair Large Intestine. Then, when we energetically connect these two organ systems and meridians of the hand to their corresponding organ systems and meridians of the leg, we have the circuit of Yang Ming (Large Intestine and Stomach) paired with Tai Yin (Lung and Spleen). If we were to translate those energetic relationships into western terms, we cannot consider the immune function of Lung without also considering the gut, namely the Large Intestine, Stomach and Spleen, as part of a comprehensive approach to using acupuncture to modulate the immune system. Interestingly, this holistic view of the function of the Yang Ming/Tai Yin system parallels our growing modern scientific understanding of the importance of the Gut and the microbiome to our immune function.

The human gut microbiota consists of 10^{14} resident microorganisms which include bacteria, archae, viruses and fungi [1]. In a healthy individual, this mix of organisms play a symbiotic role in helping with digestion, the elimination of toxins and importantly, ensuring an effective immune defense against pathogens. The loss of gut bacteria diversity can lead to dysbiosis which has been shown to put individuals at risk for a variety of diseases in addition to lowering their resistance to infection. Conversely, the gut microbiome can also be adversely affected by infections including bacterial, parasitic and importantly viral. The response can vary

depending on an individual's environmental and genetic make-up as well as overall gut health. There is a complex interplay between the gut microbiome and an individual's immune system, as demonstrated by studies showing associations with allergy, inflammatory conditions, and respiratory diseases. A number of viruses that are typically considered respiratory viruses are known to also cause gastrointestinal (GI) symptoms. In particular, influenza and the common cold version of the corona viruses are known to often lead to GI symptoms [2]. The SARS virus (severe acute respiratory syndrome) was also well documented to cause GI symptoms and based on autopsy results was found to cause severe disruption of both the lung and small intestine epithelium leading to increased permeability of the intestinal wall to lipopolysaccharide (LPS) and bacterial toxins. LPS and bacterial toxins have in turn been shown to activate an over-production of tumor necrosis factor, interleukin-1, and interleukin-6, which can worsen the respiratory component of the disease [3]. It is now clear that COVID-19 can lead to GI symptoms but importantly, the state of an individual's microbiome will have a major effect on the response of that individual to a COVID-19 infection [4]. Some of the medical conditions that have been found to be major risk factors for severe COVID-19 infections including age, diabetes, cardiovascular, stroke, respiratory, and obesity are also conditions where there is a significant adverse alteration in the gut microbiome composition [5]. In addition, a recent prospective observational review of risk factors for the development of long COVID symptoms includes factors such as low antibody response to the acute COVID infection but also interesting anosmia and diarrhea [6]. This connects us back to the Lung (anosmia) and Large Intestine (diarrhea) organ functions and suggest that if the pathogenic factor penetrates through our *wei* level defenses and penetrates to the Yang Ming energetic level, we are more at risk for long haul COVID symptoms.

When the gut microbiota are healthy, they provide a regulatory control on the response of our immune system to prevent either an over or an under reaction to pathogens. For example, the inflammatory response is understood to be regulated by the balance of T-cells and excessive TH1 cell activity can lead to an excessive immune response and autoimmune reactions while excessive TH2 cell activity can lead to allergies and asthma. In addition, there is a third subset of T cells, TH17, that is also implicated in the development of autoimmune diseases such as rheumatoid arthritis. The gut microbiota can also regulate innate immunity including macrophages and natural killer cells [7]. There is evidence now that our diet can have profound effects on the microbial balance of the gut which can then lead to changes in the activity of the innate immune cells. Interestingly, the western diet (WD) has been linked to overactive innate immune response.

There is evidence that the gut microbiota also has a direct effect on pulmonary health through a vital crosstalk between the gut microbiota and the lungs which is referred to as the “gut-lung axis.” The gut-lung axis is bidirectional, meaning the endotoxins, microbial metabolites can impact the lung through blood and when inflammation occurs in the lung, it can affect the gut microbiota as well [8]. Without a balanced immune response to a pathogen, an inadequate response can lead to pneumonia a death, but an excessive response can lead to the type of cytokine storm leading to organ failure as seen in many COVID-19 patients who died with acute respiratory distress syndrome.

Acupuncture has been shown to have a regulating effect on inflammation and has even been shown to improve outcomes in the treatment of sepsis when combined with conventional therapies [9]. In a recent review of the multitude of acupuncture effects on the inflammatory processes, there is evidence that acupuncture can regulate the innate immune response through its effect on macrophage activation as well as the adaptive response through regulation of T cell activation. Common acupuncture points used to regulate these changes were ST36 (*Zusanli*), ST25 (*Tianshu*), LI11 (*Quchi*) and SP6 (*Sanyinjiao*), both points in the Yang Ming/ Tai Yin circuit with direct influence on the gut. For example, in animal models of inflammatory joint disease, ST36 can down regulate the activity pro-inflammatory macrophages (M1) and up regulate the anti-inflammatory population of macrophages (M2) which then inhibits the expression of inflammatory cytokines such as Tumor necrosis factor alpha (TNF- α) and interleukin 1 (IL-1) and enhances expression of tissue repair factors such as interleukin 10 (IL-10) and Tissue growth factor beta (TGF- β) [10]. Other key points that are used in Chinese medicine to typically influence and promote

gut health such as ST40 (*Fenglong*), SP9 (*Yinlingquan*) and SP6 have all been found to down regulate nuclear transcription factor kappa beta (NF- κ B), which is a major regulator factor in limiting uncontrolled inflammation. In a study comparing the anti-inflammatory effects of the points ST36, LI11 and ST25, ST36 and LI11 were found to have similar effects working via a vagal pathway while the anti-inflammatory effect of ST25 led to sympathetic activation.

The autonomic nervous system plays a critical role in regulating our immune response [12]. In particular, the cholinergic anti-inflammatory pathway involving activation of the vagus and parasympathetic system ties in well with the Chinese view of the Yang ming/ Tai Yin circuit. There is evidence that many of the immune effects of acupuncture, which are believed to be mediated by the down-regulation of specific cytokines, such as IL-6 and IL1 β , can be regulated through the vagus. One can hypothesize that the effect of acupuncture on the gut microbiome is also connected to vagus nerve modulation. The sympathetic pathway appears to modulate the immune response in a bidirectional manner and can affect the concentration of neurotransmitters and immune cell surface subtypes which can either up regulate or down regulate the system [13]. More research is clearly needed to understand the mechanism by which acupuncture stimulation can influence the gut microbiome. However, a recent study of patients with Crohn’s disease showed that acupuncture was able to cause a significant enrichment of intestinal microorganisms [14].

All of these leads to consideration of treatment options to help strengthen the Gut-Immune access to help reduce inflammation and potential disease in our patients. Classically, the point LI11 is used to expel heat from the lung (reduce inflammation in the body). According to Nagano, a famous Japanese master, the region between LI10-LI11 should be evaluated to find the most active point and combined with KD6, GV14 and TW16 (Master Nagano’s immune points). This approach expands beyond Yang Ming/ Tai Yin considerations and includes treatment of the Kidney which based on its mother (Lung-metal) child (Kidney-child) relationship with the Lung and is essential in any immune treatment. GV14 and TW16 are working at the wei level to try to expel the pathogenic factor before it penetrates to the Yang Ming level.

For example, when treating a COVID infection from a Traditional Chinese Medicine point of view, the symptoms develop due to an invasion of pathological heat. In this phase, the organ pathology is more functional and, although the patient may have many symptoms, the actual lung organ

is not damaged. For example, imaging of the lungs would remain clear. The next phase is when the layer of *wei qi* defense fails and the nutrient or *ying qi* is affected, leading to more overt organ pathology. This is when the pathological heat is no longer kept at the surface of the body but starts to invade more deeply to the organ level. In this phase, pneumonia develops and more serious respiratory issues that may require hospitalization and respiratory support. The third phase, the Yang Ming/Tai Yin energetic layer is affected leading to more GI symptoms and dampness from a Chinese point of view. The fourth phase is when the heat invades the blood. This can be extremely serious and leads to the vascular and cardiac issues seen with COVID. From a TCM point of view, this would be viewed as a Liver disturbance with blood stagnation and blood heat. This is also when severe organ parenchymal damage occurs. In the Wanzhou and Chongqing districts of China, a study analyzed cases of COVID-19. From a TCM point of view, presentations were characterized as an invasion of a damp heat with the development of “heat obstructing lung syndrome” (30%), dampness obstructing syndrome (16%), and cold dampness stagnating lung syndrome (12%). The goal of treatment focused on strengthening the lungs and clearing heat and dampness with additional treatment focused on strengthening Qi and nourishing Yin [15].

Initially, the pathogenic virus penetrates the surface or the Tai Yang Zone and symptoms will typically include fever, headaches and sweating. The key at this early stage is to activate Defensive or *wei qi* [15]. Then, if the defensive qi is not strong enough to expel the pathogenic factor, the qi disturbance penetrates deeper eventually affecting the Yang Ming Zone and causing symptoms to penetrate into the lungs and importantly, the intestines which as we have discussed likely leads to alteration of the gut microbiota. This is the level of pathology that is seen in most patients who present with COVID or long COVID symptoms since typically in the West, we do not see patients in the acute phase.

From an acupuncture point of view, in the acute phase, the goal is to expel the pathological heat and clear dampness, so the lungs and other organs do not get obstructed. Treatment would focus on the Tai Yang using immune points such as Nagano's immune points LI 11, GV 14 and TW 16 to expel heat with KD 6, BL 23 and CV 6 or CV 4 to nourish and mobilize Qi. But as the pathology lingers and certainly in the long haul COVID, treatments should include focus on Yang Ming zone. The goal should be to nourish points for the lungs and digestive system such as LU 5, SP 6, CV 12 (Stomach Mu) and ST 36 together with the Back Shu points for Lung and Spleen (BL 13 and BL 20).

Classically SP6 and ST 36 are used to regulate digestion and help build Qi through the digestive function and can be combined with the Lung and Large Intestine points to enhance the immune modulatory effect with more direct influence on the gut. However, there are other options including SP3 which is the source point, and SP8 which is the Xi cleft point. If patients are struggling with an uncontrolled immune system or cytokine storm and excessive production of phlegm, then Spleen treatments can play an important role. From a TCM point of view, phlegm is a form of dampness and treatment of Spleen is very important to help with this issue. In addition, Spleen function is important to nourish the lungs and acts to prevent the excess release of cytokines, histamine and inflammatory mediators from cells (the holding function of Spleen in TCM).

In Japanese acupuncture, instead of using ST 36 a set of points are used along the lateral aspect of the tibia called the Stomach Qi line.

When treating the Stomach Qi line, you are in effect stimulating the Lower He Sea points of the Large and small intestine. In Chinese Medicine, the points are BL 37 and BL 39 respectively. However, the Japanese approach is to stay closer to the tibia and find fascial holes as you drag your finder down the entheses of the tibialis anterior muscle and place the needles down with the flow of the meridian superficially in these points (Figure 1).

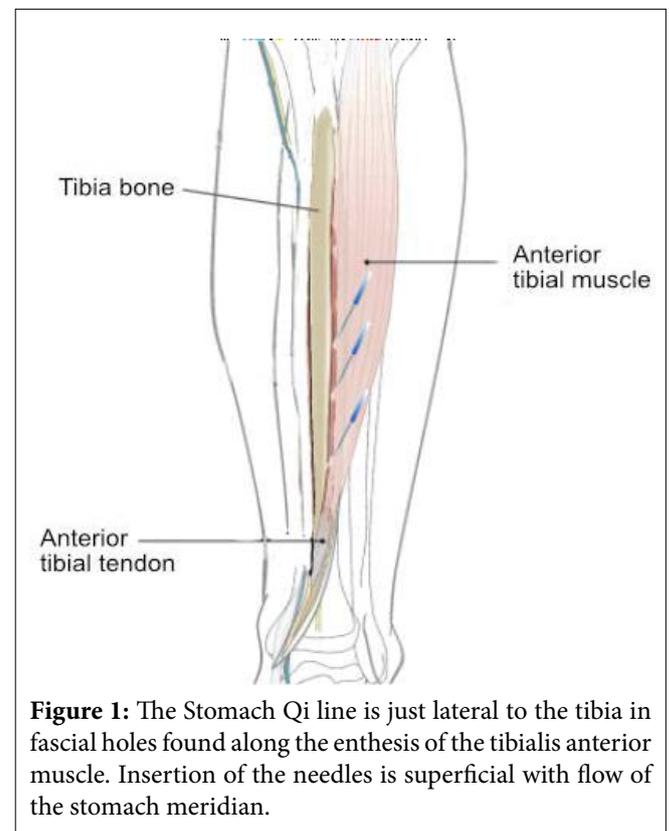


Figure 1: The Stomach Qi line is just lateral to the tibia in fascial holes found along the entheses of the tibialis anterior muscle. Insertion of the needles is superficial with flow of the stomach meridian.

Another approach to regulate the Yang Ming/ Tai Yin circuit is to use an extraordinary vessel (EOV) combination of Chong Mai with Ren Mai. This is regulating to the Gut (Chong Mai) and the Lung (Ren Mai). Based on the Japanese Master Kawai's theory, when combining the command and couple points of two EOVs, it is energetically better to cross the points from, for example, the right foot to the left hand. One approach is to check which side of the body has greater tightness in the region of ST30 and use that side to treat SP4, the command point of Chong Mai. Then the coupled point, PC6 is crossed over to the left arm. That leaves the right arm for the command point of Ren Mai, LU7 and the left foot for the coupled point KD6 (Figure 2).

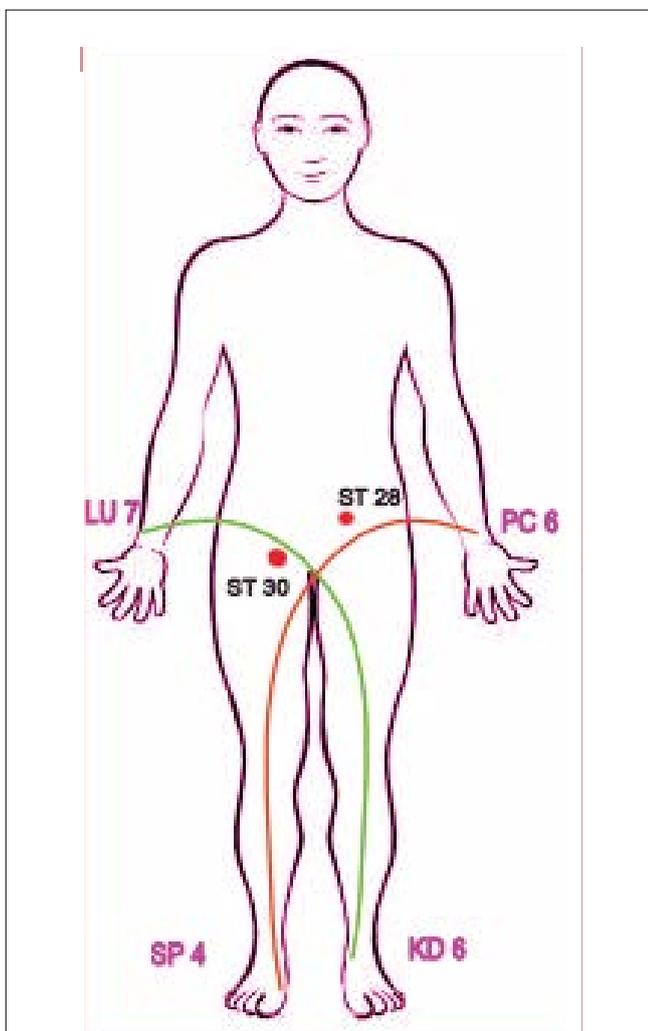


Figure 2: Example of a Chong Mai/Ren Mai treatment crossing over the command and couple point combination. Comparison of the tightness at ST 30 is used to decide which side the command point for Chong Mai (SP4) is inserted. Then the coupled point PC6 is crossed over to the opposite hand. This leaves the opposite foot and hand for the Ren Mai command and couple points.

Often, if there is an associated sense of pressure or constriction in the chest over the Pericardium Mu point, CV17, an important addition to Spleen is to add PC 6. This should relieve the pressure pain at CV 17 and the sense of chest tightness. Relief of this sense of oppression is another natural use of the EOV Chong Mai with the combination of SP4 and PC6. SP4 is particularly useful to reduce excess production of phlegm. Also adding points such as SP9 and ST40 can help with phlegm and dampness.

In the post-COVID state, the goal is to nourish the underlying weakness in Lungs and Kidney Qi and build energy and regulate the gut microbiota by supporting the digestive function. An important consideration is to also help with tissue oxygenation. In the cases of patients with underlying issues of hypertension (HTN) treatment of this constitutional weakness is vital. The renin-angiotensin (RAS) pathways play a critical role in both the acute respiratory distress of patients and potentially in the long-haul symptomatology that many patients feel after clearing the virus. RAS is a known regulator of blood pressure but also plays a role in local tissue homeostasis. Angiotensin-converting enzyme (ACE) and ACE2 act to regulate a homeostatic balance in the system. When ACE predominates, pathological cell proliferation, inflammation, fibrosis and thrombosis predominate. In contrast when ACE2 predominates, there is activation of a protective pathway that stimulates the reduction in inflammation as well as anti-fibrotic and anti-thrombotic effects [16]. The high replication capacity of SAR-CoV-2 is directly related to the coupling to ACE2 and cell infection. With this coupling, there is a concomitant reduction of ACE2 in the infected organs, tipping the balance towards the pathological consequences of ACE being predominant. The resultant hypoxia stimulates angiogenesis further altering the alveolar respiratory function. Hypoxia is also found to stimulate the hypoxia-inducible factor (HIF) that creates a feed forward vicious cycle, causing further shift towards the expression of ACE and inhibiting ACE2. The imbalance of ACE and ACE2 also has a primary role in inducing the uncontrolled inflammatory reaction to SAR-CoV-2 and subsequent cytokine storm seen in the severe cases of COVID-19.

I have had the opportunity to work with Kiiko Matsumoto, a Japanese acupuncture master in the treatment of two severe post-COVID cases. Both had a history of renal hypertension with dysregulation of the renin-angiotensin system.

Both patients' manifest tenderness in the Huato Jiaji area at the L1-2 levels, which from the Japanese point of view is a reflection zone of renal hypertension. From an anatomic standpoint, this is the level that the renal artery enters the Kidneys (Figure 3).

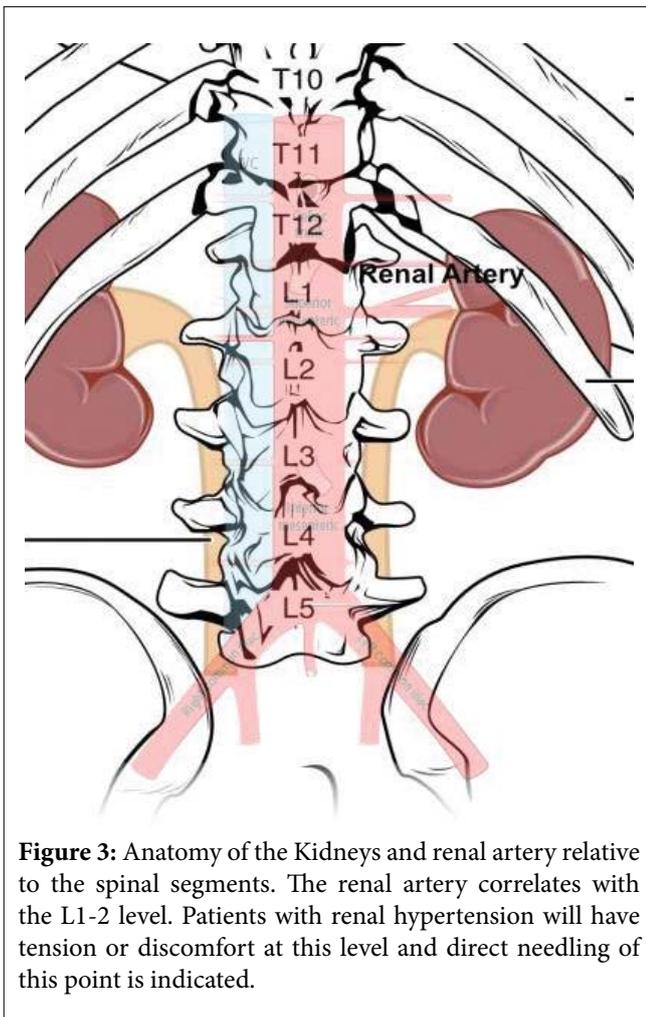


Figure 3: Anatomy of the Kidneys and renal artery relative to the spinal segments. The renal artery correlates with the L1-2 level. Patients with renal hypertension will have tension or discomfort at this level and direct needling of this point is indicated.

In addition, an interesting diagnostic region to determine if tissue level oxygenation is an issue is ST9. This point is at the level of the thyroid cartilage of the neck, medial to the SCM muscle, overlying the carotid artery. This reflex can be considered the carotid body/sinus reflex, which, from a physiological point of view, is involved with blood pressure regulation as well as monitoring blood oxygenation and CO₂ levels. If tender, the treatment would be ipsilateral LI4 and LU8. The point LU8 is particularly important for tissue oxygenation as it is the metal on metal point for Lung.

In conclusion, acupuncture is a powerful tool that can help augment and balance the immune response to infections such as the COVID-19 virus. The growth of scientific knowledge regarding the influence of the state of the gut microbiota on disease and the ability to adequately respond to the invasion of external pathogens converges with the ancient Chinese understanding of the human immune system. As acupuncture becomes more integrated into the health care system in the

West, there is evidence that this approach can provide a safe and potentially helpful tool to use with patients both during the acute phase of the illness as well those suffering from post-COVID symptoms. More research is needed to demonstrate efficacy, but early data from China and personal experience suggests that this can be a powerful tool to help our patients regain quality of life and rid themselves of lingering effects of the COVID-19 infection.

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