

Advantages of Anti-Inflammatory Acupuncture in Treating Sepsis of Novel Coronavirus Pneumonia

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Abstract

Background: Sepsis is one of the most serious complications and a leading cause of death in patients with novel coronavirus pneumonia (NCP; severe acute respiratory syndrome coronavirus 2). In general, it is the result of an unregulated inflammatory cascade such as a postinfection “cytokine storm.” The conventional treatment mainly relies on glucocorticoids, of which curative effects are not ideal, as they come with significant side effects. It is critical to seek or develop other effective therapeutics in dealing cytokine storm to fight NCP with sepsis. **Aims and Objectives:** Raise awareness of the significance applying anti-inflammatory acupuncture in dealing NCP patients with sepsis and provide an appropriate acupuncture protocol that can be easily integrated into existing medical guideline. **Materials and Methods:** Current evidences from animal experiments and clinical trials about acupuncture in treating infectious sepsis are reviewed, and a detailed discussion on advantages of anti-inflammatory acupuncture is followed, then the rationality on the point selection and stimulation parameters of acupuncture is analyzed to propose an appropriate acupuncture protocol. **Results:** Current experiments have shown that acupuncture can play a significant role to improve inflammation reaction and reduce mortality in infectious animal and patients with sepsis and its mechanisms are mainly achieved by stimulating the vagus-cholinergic anti-inflammatory pathways. Applying acupuncture in treating NCP patients with sepsis has four aspects of advantages. Moreover, a simple and convenient clinical acupuncture protocol including point selection and appropriate stimulation parameters is proposed. **Conclusion:** Acupuncture, especially electroacupuncture, has shown potentials in effectively treating infectious sepsis of animal models and critically ill patients in small sample studies by stimulating the nervous system, but has been largely overlooked in the clinic so far. It is advised that acupuncture should be integrated into the existing medical guidelines in dealing with NCP complicated with sepsis.

Keywords: Acupuncture, anti-inflammation, coronavirus disease-19, electroacupuncture, novel coronavirus pneumonia, sepsis, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

As we know, sepsis is defined as a life-threatening organ dysfunction caused by an unregulated host response to infection. To date, it affects more than 30 million people annually worldwide and is one of the major causes of death for terminally ill patients. Any infected person can potentially develop sepsis, and the incidence rate is as high as 1%–2% of all hospitalized patients.^[1] Sepsis is also one of the main complications and causes of death in patients with novel coronavirus pneumonia (NCP; severe acute respiratory syndrome coronavirus 2),^[2] which is also referred as coronavirus disease 2019. A cytokine storm or unregulated inflammatory cascade following a viral infection is the main cause of sepsis. When it occurs, it is of the utmost importance

for the NCP patient to control the spread of inflammation and prevent the development of cytokine storm as soon as possible.

In the treatment of sepsis due to cytokine storm, the conventional therapeutics mainly rely on corticosteroids (glucocorticoids). In most animal studies, corticosteroid administration consistently protected against lethal sepsis. In contrast, however, clinical trials in sepsis found much less consistency in survival benefits

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from corticosteroids, though most trials demonstrated faster resolution in shock and organ dysfunction.^[3] On the other hand, the side effects of excessive use of glucocorticoids are significant. Therefore, for sepsis, other reasonable therapies have been looking for or combining with. In fact, there is also a promising, simple, and no side effect treatment method, that is, anti-inflammatory acupuncture mediated by reflective central inhibition of the innate immune system,^[4] which has been overlooked in the existing medical guidelines so far.^[2,5]

Following a review of recent experimental and clinical evidence and the mechanisms of anti-inflammatory acupuncture in treating sepsis, the authors will delve into the advantages of applying acupuncture in treating the sepsis of NCP patients. A set of acupuncture protocols including point selection and proper stimulation parameters based on previous methods applying in animal studies and clinical trials, combining with the authors' expertise, is proposed herewith. It is advised that acupuncture should be integrated with the existing therapeutics of both conventional medicine and traditional Chinese medicine (TCM), in order to help reduce the incidence of NCP or sepsis, reduce the mortality rate, and speed up the healing process.

Scientific evidences of anti-inflammatory acupuncture for sepsis

Most researchers agree that the degree of inflammatory response heavily impacts the outcome of sepsis, and the elevated level of serum tumor necrosis factor (TNF)- α or interleukin (IL)-6 level is related to the rise of mortality in sepsis patients. A decreased 28-day mortality rate could be found following with decreased concentrations of TNF- α and IL-6 in blood after treatment. So far, there are many laboratory and clinical evidences that show acupuncture or electroacupuncture (EA) may inhibit macrophage activation and the production of TNF, IL-1 beta, IL-6, IL-18, and other pro-inflammatory cytokines via the stimulation of the vagus nerve.^[4]

In 2014, Torres-Rosas *et al.* reported that when EA was applied to mice with sepsis, cytokines that help limit inflammation were stimulated as predicted. The results found that half of those mice survived for at least a week, whereas none of those mice that did not receive acupuncture survived. That discovery presented a potential novel approach to use acupuncture for sepsis in humans. They observed that EA at the Zusanli (ST36) of the mice reduced the lipopolysaccharide-induced serum levels of all cytokines analyzed, including TNF, monocyte chemoattractant protein-1 (MCP1), IL-6, and interferon- γ (IFN- γ). These results indicated that EA had an inhibition effect and not just merely delayed the production of cytokines. It is also found that the surgical removal of the sciatic nerve (not the common peroneal or tibial nerve) can reduce the anti-inflammatory potential of EA. This suggested that both the common peroneal and the tibial nerves contribute to the anti-inflammatory potential of EA by activating the sciatic nerve and demonstrated for the first time ever the ability of the sciatic nerve to control systemic inflammation in sepsis.^[6]

Other researchers have also observed that EA at Zusanli (ST36) and Guanyuan (CV4) of mice (5–8 mm and 3–5 mm depth respectively, then retain the needle for 30 min with continuous wave of 3 Hz, once every 12 h for a total of 3 times) could increase the synthesis and release of vasoactive intestinal peptide in hypophysis and peripheral blood of sepsis rats, and inhibit thymocyte apoptosis through neuro-immune regulation.^[7] Furthermore, EA at Zusanli (ST36), Tianshu (ST25), Shangjuxu (ST37), and Xiajuxu (ST39) could significantly improve the level of CD₁₄⁺/HLA-DR (human leukocyte antigen DR) and immunosuppression in patients with sepsis by EA (continuous wave, frequency 4 Hz, 60 min/time, 2 times/day for 3 days).^[8] CD₁₄⁺/HLA-DR is the antigen expression on the surface of monocyte/macrophage and its decrease is closely related to the degree of immunosuppression in sepsis.

In 2015, there were also small sample clinical trials of acupuncture for sepsis in China. A total of ninety patients with sepsis were randomly divided into a control group, thymosin α 1 group, and acupuncture treatment group, thirty cases in each group. The control group received routine treatment according to the guiding principle of survival activities of sepsis. Thymosin α 1 group was injected subcutaneously once a day for 6 days. In the acupuncture treatment group, Zusanli (ST36), Yanglingquan (GB34), Neiguan (PC6), Guanyuan (CV4), and other associated acupoints were needed (e.g., needling in the morning, twirling and toning for about 20–30 s, keeping the needle for 30 min, during which three times of needling were conducted, each time for about 20 s), once a day for 6 days. T cell subsets (CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺) and immunoglobulins (IgG, IgA, and IgM) were detected. The hospitalization time, readmission rate, and 28-day mortality rate of the three groups were compared. The results showed that after 6 days of treatment, the T cell subsets and Igs were significantly increased in the three groups ($P < 0.01$). The levels of CD3⁺, CD4⁺, CD8⁺, IgG, IgA, and IgM in thymosin α 1 group and acupuncture group were significantly higher ($P < 0.01$). Compared with the control group, the length of stay in intensive care unit (ICU) of thymosin α 1 group and acupuncture treatment group was significantly shorter, and the readmission rate and 28-day mortality rate were lower ($P < 0.05$, $P < 0.01$). There was no significant difference between thymosin α 1 group and acupuncture group.^[9] In addition, other researchers observed that EA at Zusanli (ST36) and Guanyuan (CV4) of sepsis patients, with the vertical depth of 5–10 mm and 5–7 mm inserted, respectively, could not only reduce the inflammatory reaction of sepsis, but also shorten the length of stay in the ICU when reducing the level of blood lactate.^[10]

As for the main mechanism of acupuncture or EA in the treatment of sepsis, it has been almost clear that it is achieved by strengthening the vagus-cholinergic anti-inflammatory pathways to weaken the cytokine storm. Figure 1 shows two anti-inflammatory pathways^[11] activated by acupuncture (EA) in Hegu (LI4) or Zusanli (ST36) in the treatment of sepsis.

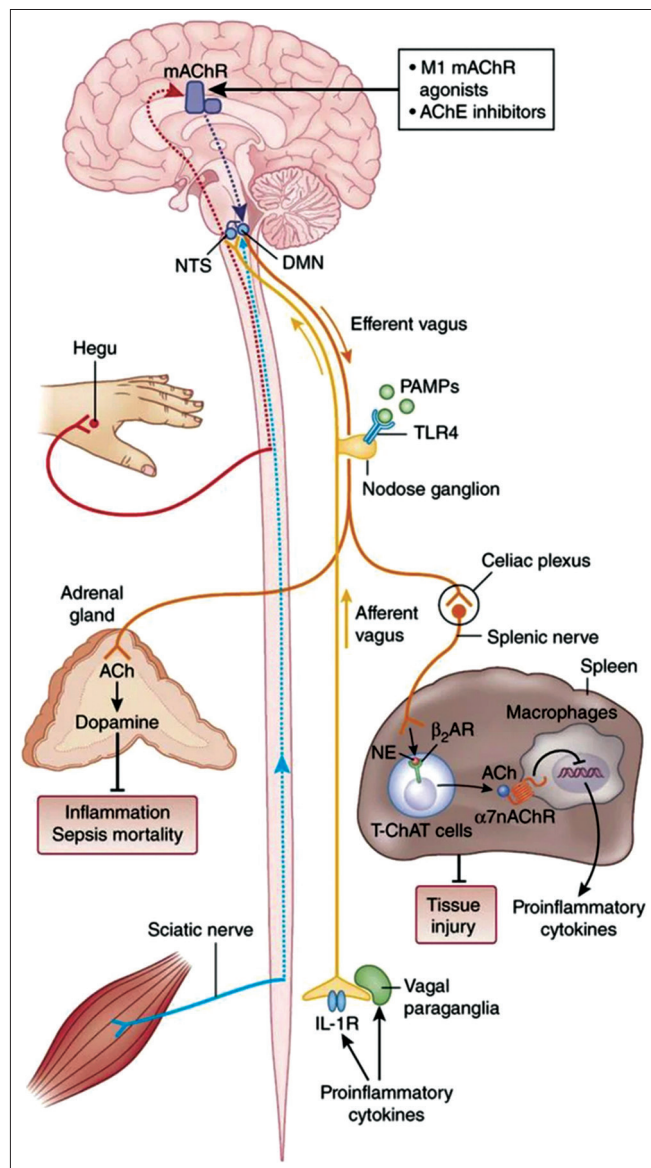


Figure 1: Two vagus-cholinergic anti-inflammatory pathways stimulated by acupuncture at Hegu LI4 or Zusanli ST36 (Illustrated by Debbie Maizels, Springer Nature, for Pavlov and Tracey^[11])

The first pathway is the vagus-spleen-cholinergic pathway, in which the efferent signal of vagus nerve is propagated to the celiac ganglia and the superior mesenteric ganglion in the celiac plexus, where the splenic nerve originates. Norepinephrine (NE) released from the splenic nerve interacts with β_2 -adrenergic receptors (β_2) and causes the release of acetylcholine (ACh) from T cells containing functional choline acetyltransferase (T cells). ACh interacts with $\alpha_7nAChRs$ on macrophages and suppresses pro-inflammatory cytokine release and inflammation. The anti-inflammatory effect of EA at Hegu (LI4) is through this way.

The second pathway is vagus-adrenal medulla-dopamine pathway, that is, EA at Zusanli (ST36) activates sciatic nerve signals, which by unknown mechanisms convert to efferent vagus nerve signaling to the adrenal medulla (which is usually

dominated by sympathetic nerve, now known to also have the distribution of the vagus nerve), resulting in dopamine release. Dopamine suppresses inflammation and improves survival in a model of sepsis.^[6]

In addition to the effects on the sympathetic and parasympathetic pathways, acupuncture can activate the hypothalamic–pituitary–adrenal (HPA) axis governing the systemic release of glucocorticoids from the adrenal glands that has an anti-inflammatory role. A typical example of its role is that acupuncture on Huantiao (GB30) inhibits complete Freund’s adjuvant-induced paw edema in mice through a mechanism that is prevented by adrenalectomy and glucocorticoid inhibitors. HPA axis stimulation can be a successful strategy to induce the production and systemic distribution of glucocorticoids to modulate metabolic and immune responses.^[12]

Analyzing benefits of using acupuncture to treat sepsis of novel coronavirus pneumonia

According to the preliminary clinical observation, most of the terminally ill patients with NCP showed significant increase of pro-inflammatory cytokines, such as IL-6, TNF- α , and IFN- γ , with the characteristics of cytokine storm.^[13] Integrating acupuncture to treat NCP complicated with sepsis has the following four advantages.

First, acupuncture therapy is suitable for all stages of the NCP patients. For mild cases, it can strengthen the immunity of the body and reduce the risk of deterioration. For severe cases, it can also alleviate the disease as much as possible through the rapid neural and bidirectional regulation of the immune function.

The early stage of sepsis is generally thought to be caused by an unregulated production of pro-inflammatory mediators forming a cytokine storm, that numerous cytokines such as TNF- α , IL-1, IL-6, IL-12, IFN- α , IFN- β , IFN- γ , MCP-1, and IL-8 are rapidly produced in body fluids after the body is infected. This stage is characterized by a hyperactivity of the immune system. With the progress of the pathological course, the body exhibits a process of compensatory anti-inflammatory response by releasing a large amount of inflammatory suppressing cytokines. In this stage, immunosuppression is being dominated, which is often the key to determine the prognosis of sepsis patients.^[14] Therefore, the production or release of pro-inflammatory cytokines should be controlled or limited as soon as possible in the early stage of sepsis, and the immunosuppression should be relieved or reduced as soon as possible in the later stage of sepsis.

Acupuncture therapy has the characteristics of bidirectional regulation of immune function. No matter to control the cytokine storm in the early stage of sepsis or to improve the immunosuppression in the late stage of sepsis, acupuncture shall play an important regulatory role. Moreover, the regulatory direction of acupuncture depends on the functional state before acupuncture, that is, if the production or release of cytokines is excessive, the acupuncture stimulation may

weaken the cytokine storm, and if the immunosuppression has occurred, the acupuncture stimulation may decrease the immunosuppression. When applying acupuncture in the treatment of sepsis, those side effects of glucocorticoids would not occur.

Animal studies have shown that acupuncture can regulate the secretion of adrenocorticotropic hormone (ACTH) and corticosteroids bidirectionally: increase when it was originally low and decrease when it was originally high. Other studies have observed that ACTH level in the blood of healthy people increased rapidly after acupuncture, reaching 1.5–2 times of that before the treatment, and peaking at 2–5 min. The concentration of cortisol in the blood increased to 1.5–2 times (15%) of that before the treatment.^[15]

After 20 min of acupuncture at Hegu (LI4) and Zusanli (ST36), the level of corticosteroids in the blood of healthy people increased significantly and had a longer lasting effect. In patients with appendicitis receiving acupuncture, 17-ketosterol and corticosterone (CORT) were increased in 24-h urine, which indicates the increase of ACTH after acupuncture. In animal experiments, after EA, the content of ACTH in the blood was measured directly, and there was also a significant increase. If the levels of ACTH and corticosteroids had increased before acupuncture, acupuncture could reduce them.

In 2017, when studying the effects of acupoint association on the related hormones of HPA axis in insomnia rats, Wu *et al.* observed that the levels of corticotropin-releasing hormone (CRH) in hypothalamus and ACTH and CORT in serum were significantly higher in the insomnia group. After acupuncture with three different acupoint associations (Baihui + Shenmen, Baihui + Sanyinjiao, and Baihui (GV20) + nonacupoint group), the levels of CRH, ACTH, and CORT of them decreased to some extent, compared with the model group.^[16]

In several of these animal studies, sepsis was associated with a significant early increase in ACTH levels, which returned to baseline around 72 h. The clinical studies have found that the ACTH level of critical patients was significantly lower than that of the control group, especially in septic shock.^[3] From this, the effect of acupuncture on sepsis seemed related to the bidirectional regulation of ACTH.

Second, the anti-inflammatory or the regulating immunity actions of acupuncture are achieved by stimulating the nervous system. The neural regulation by acupuncture has a rapid and accurate feature, although not lasts long, which has great potential significance in preventing and treating NCP patients, especially in rescuing severe cases complicated with sepsis.

Let us take the acute stress reaction (e.g., fight or flight) as an example to follow the timeline: in response to acute stress, the body's sympathetic nervous system is activated. The sympathetic excitation stimulates the adrenal glands triggering the release of catecholamines, which include adrenaline and noradrenalin (NE). This results in an increase in heart rate (HR), blood pressure, and

breathing rate. After the threat is over, it takes between 20 and 60 min for the body to return to its prearousal levels. If the threat is real and the "fight" is unavoidable, the HPA axis is activated after the first surge of adrenaline subsides. The release of cortisol by the adrenal cortex starts later takes place within 20–30 s and thus last longer. Once the danger has passed, the production of cortisol will cease too and consequently the balance between the sympathetic and parasympathetic nervous systems is attained.^[17] The elevated endogenous cortisol secretion is generally more suitable for the sake of activating body's anti-inflammation action, as it does not have potential side effects brought on by supplementing exogenous glucocorticoids.

Although it is known that stress can suppress the immune system through the action of adrenaline and cortisol, researches have shown that the HPA axis can actually have a positive effect on the immune system, reversing the effects of cortisol and increasing the killing ability of natural killer cells. ACTH, part of the HPA axis response, has an opposite effect to that of cortisol. These results may be of great significance in the treatment of diseases related to excessive or persistent inflammation, such as autoimmune diseases, as well as in treating NCP.

Time is of the essence for terminally ill patients with sepsis. Once acupuncture effectively stimulates sympathetic nervous system (especially postganglionic fiber), or vagal cholinergic anti-inflammatory pathways, it is possible to quickly calm the cytokine storm and rescue some patients from deathbeds. As for the short duration of action from each acupuncture session, it can be improved by shortening the treatment interval by increasing treatment frequency from daily to even several sessions per day.

Third, acupuncture therapy not only has the effect of regulating immune function or anti-inflammatory role, but also has a beneficial effect on other system functions of the body.^[18] For example, the lung is the first target organ damaged by sepsis, which is often manifested as acute lung injury or acute respiratory distress syndrome. Needling the bilateral Zusanli (ST36) of rats (directly inserted the needle at the depth of 7 mm), followed by a pulse current of (3 V, 2 m, 3 Hz) for 12 min, 8 h for 1 time, for 2 days, reduced the inflammatory reaction and the acute lung injury of rats with sepsis after being scalded.^[19] In another study, acupuncture reduced the acute lung injury of sepsis patients by regulating the balance of pro-inflammatory and anti-inflammatory cytokines, inhibiting the inflammatory reaction: Needling Zusanli (ST36) and Cheze (LU5), following Deqi (acquire Qi with movement of needle), EA was added with disperse and dense wave, continuously stimulating for 30 min, 1 time a day for 5 days, which improved the oxygenation index of sepsis patients, reduced the APACHE II score and TNF- α in patients' serum and alveolar lavage fluid, and increased the concentration of IL-12.^[20]

Another example is that the gastrointestinal tract is often the initial organ of sepsis. In the process of sepsis onset, the

free radicals released by inflammatory cytokines first destroy the gastrointestinal function, and then the gastrointestinal mucosa is swollen and eroded, the permeability is increased, and the intestinal bacteria are displaced, thus inducing systemic inflammatory response syndrome and multiple organ dysfunction syndrome. Therefore, regulating gastrointestinal function should be the focus of early treatment of sepsis. Reported by Yu *et al.*, needling bilateral Zusanli (ST36), Zhongwan (CV12), Tianshu (ST25), Neiguan (PC6), Shangjuxu (ST37), and Qihai (CV6) at (30 min/time, once a day for 5 days) could effectively improve gastrointestinal symptoms, reduce gastric retention and intra-abdominal pressure, improve serum motilin level, and reduce gastrin level in elderly patients with severe sepsis.^[21]

Reported by Wu *et al.*, on the basis of routine treatment, acupuncture was used to stimulate Zusanli (ST36), Tianshu (ST25), Shangjuxu (ST37), and Xiajuxu (ST39) in patients with sepsis. After Deqi, EA was applied (continuous wave, 4 Hz, 60 min each time, twice a day for 3 days). It improved the intestinal permeability of patients with sepsis, restored the intestinal function as soon as possible, and achieved the target 20–25 Kcal/kg per day feeding in the early stage of the patients with critical illness.^[22] In 2009, Hu *et al.* observed that EA (a constant voltage, 2–100 Hz, 2 mA for 0.5 h) at Zusanli (ST36) significantly lowered the elevated levels of pro-inflammatory factors in the small intestine and alleviate tissue edema and mucosal dysfunction in rats of sepsis caused by cecal ligation and puncture. It was apparent that these were resulted from the activation of vagus-cholinergic anti-inflammatory pathways.^[23]

Acupuncture treatment can alleviate some serious life-threatening symptoms, such as for patients in shock, low blood pressure can be improved by enhancing microcirculation; for bleeding coagulation imbalance, acupuncture can also play a regulatory role. As for the treatment of mild cases of NCP, it is more effective. Therefore, when NCP patients are treated with various conventional or TCM therapeutics, the authors highly recommend that acupuncture should be utilized first and foremost.

Fourth, acupuncture seemed to have a faster stimulation effect on the autonomic nervous system (ANS) than moxibustion. Although moxibustion also has the effect of regulating immune function,^[24] its effects are not the same as that of acupuncture. In a pilot controlled clinical trial,^[25] it was observed that acupuncture and moxibustion at bilateral Zusanli (ST36) and Guanyuan (CV4) had different effects on fatigue by regulating ANS. Acupuncture was more effective in instantaneous changes of HR variability that reflects the activity of vagus nerve and moxibustion in long-term aspects. Both acupuncture and moxibustion improved fatigue in chronic fatigue syndrome (CFS) patients, but moxibustion was more effective. The possible mechanism of the intervention may be through the activation of the vagus nerve and the conclusion drawn was that moxibustion was

deemed more effective than acupuncture in the long-term treatment of CFS.

From the view of needling sensations, the pain stemmed from a stronger needle stimulation can be easily recognized as a kind of stressor by the body, thus stimulating the sympathetic nerve and the HPA axis. Previously, we have discussed the characteristics of quick stress response. In addition, the local microtrauma via needling can also induce the anti-inflammatory effect of the body, which cannot be achieved by general moxibustion (unless blistering moxibustion or purulent moxibustion is applied). Therefore, in authors' opinion, moxibustion is more suitable for the treatment of chronic inflammatory diseases or to prevent NCP. However, for severe cases, such as concurrent sepsis, acupuncture intervention may generate faster results than moxibustion, which, of course, needs to be evaluated further to reach a proper conclusion.

Of course, as acupuncture is a procedure involving sharp needles penetrating the skin, worries in its usage for such highly contagious and infectious disease such as NCP are reasonable indeed. However, be rest assured that this can be resolved as long as the cleaning needling technique is strictly adhered by the practitioner during the needle operation, while also being trained in self-protection techniques, such as manipulating the needles with gloves. Wearing gloves to perform acupuncture may be a bit inconvenient to the practitioner, especially when begin to manipulate the needles. but it is worth in the long-run when compared with the possible therapeutic effects from acupuncture. As for whether other external treatments (such as massage, cupping, or scraping) can be alternatives of acupuncture in the treatment of sepsis, more comparative studies are needed. At the moment, the anti-inflammatory role of acupuncture is achieved by manual needling or EA at acupoints. Similar effects may also be achieved by transcutaneous electrical stimulation or implantation of electrodes near the vagus nerve trunk *in vivo*. Although the vagus-stimulating action of acupuncture is not as precise and repeatable as implantable electrode stimulation, it is still more simple and feasible, with no need to worry about excessive stimulation.

Anti-inflammatory acupoint selection and appropriate stimulation parameters

Based on the prior clinical studies for sepsis when combining our own expertise, we hereby propose a set of acupuncture protocols (selection of acupoints and stimulation parameters) for preventing and treating NCP patients complicated with sepsis. These protocols are easy to operate and convenient for clinical application. It is suggested to use them in conjunction with existing integrative therapeutics.

Point selection and needling methods

Any single one or combinations of the following three groups of main acupoints can be selected to treat NCP with sepsis:

1. Bilateral Zusanli (ST36), Shangjuxu (ST37) (or nearby tender/reflex points)

2. Bilateral Hegu (LI4), Shousanli (LI10) (or nearby tender/reflex points).
For the above acupoints, the filiform needle should be directly inserted into the muscle beneath the acupoints, and it is optimal to *Deqi* (attaining the feeling of soreness, distension, heaviness, numbness, or the sensation of “like fish swallowing bait” beneath the needle).
In case that it is difficult to *Deqi*, simply retain the needle for 30 min. Every 5 min, perform “needle-awakening manipulation” (slightly twist the needle) to enhance the stimulation for up to a 1 min.
3. Bilateral ear reflex points/tender points inside the concha (such as the lung/heart points in the cavum concha and the kidney/small intestine points in the cymba concha).

First, detect the tender points either by simple pressure or measurement of low electrical conductance. Use a slightly thick filiform needle (0.25–0.3 mm in diameter) to penetrate the ear point (such as lung point to heart point) to the subcutaneous area of the reflex area. It is optimal to have sharp pain immediately (such as no pain, the needle should be pulled out and pricked again). Retain the needle for 30 min. After the removal of needle, the needling spot can slightly bleed (about 10 drops is proper) or without bleeding.

Other associate points: add Tianshu (ST25), Qihai (CV6) for symptoms of the intestines; add ChiZe (LU5), Neiguan (PC6) for symptoms of the lung, etc.

Electrical stimulation parameters

For patients without contraindications of electrical stimulation, EA should be used as much as possible to ensure sustained stimulation for a certain period with sufficient stimulation input. Low frequency (3–4 Hz), continuous wave or disperse-dense wave, suitable (medium) intensity, at least 30 min each time is recommended.

When applying the above acupuncture protocol, sufficient treatment frequency should be ensured, preferably 2–4 times per day, which can be adjusted according to the patient’s condition and sensitivity as well as response to acupuncture. Although needling sensations are not necessary for acupuncture efficacy, it is more appropriate for critical or acute patients to perceive needling sense as a sign of therapeutic information of acupuncture being inputted into the body.

Supporting evidence for the protocol

In the treatment of NCP with sepsis, because the local anti-inflammatory effect of acupuncture is not required, distal acupoints can be chosen. The above-mentioned three sets of main points in the protocol are located in the upper limbs, lower limbs, and auricle, respectively. When those points are stimulated simultaneously, that is referred as a type of point-association method through different afferent pathways:^[26] The point association of ear reflex points innervated by cranial nerves with the limb acupoints innervated by spinal nerves, or the point association of Hegu (LI4),

Sousanli (LI10) on the upper limb with Zusanli (ST36), Shangjuxu (ST37) on the lower limbs innervated by different spinal nerves.

Although the stimulation of vagus nerve used in previous experiments is often realized by stimulating vagus efferent nerve or certain limb acupoints innervated by spinal nerve, in fact, the auricular branch of the vagus nerve distributed on the auricle (concha area) as the afferent nerve can also be another target of vagus stimulation. It has been confirmed that stimulation of the concha area can activate the vagus nerve. In 2019, Addorisio M *et al.* observed that the use of vibration to stimulate the external ear could inhibit the production of TNF, IL-1 β , and IL-6 in healthy people and improve the symptoms of rheumatoid arthritis patients.^[27] Therefore, acupuncture at the ear reflex points found at the concha area is deemed a simple and easy method to stimulate cholinergic anti-inflammatory pathways.^[28]

There are also evidences that acupuncture at Hegu (LI4) or Sousanli (LI10) of the hand can stimulate the excitation of vagus nerve.^[11,29] The effect of EA at Zusanli (ST36) on sepsis by stimulating cholinergic anti-inflammatory pathways through sciatic nerve has also been confirmed in animal experiments.^[6] Combined use of Shangjuxu (ST37) with Zusanli (ST36) has showed an improvement of immunosuppression and gastrointestinal function in severe cases.^[8,21,22]

As for the relationship between the degree of needling sensations and perceived acupuncture effects, the experience of classical acupuncture for thousands of years is that “The arrival of Qi (referred as *Deqi*) equates to be effective.” It has been thought that intense acupuncture can raise sympathetic tone, whereas weak acupuncture can cause parasympathetic excitation. Accordingly, from the view of stimulating sympathetic nerve and activating the HPA axis, it should be that the stronger the acupuncture stimulation is, the better the effects. However, from the anti-inflammatory view of stimulating vagus nerve, the requirements for acupuncture sensations or *Deqi* are not quite that high. In a recent study, Uchida *et al.* studied the effect of needling sensations on transient HR slowing and ANS function during needling. It was observed that in 32 healthy men with deep acupuncture, needling on their hands at Sousanli (LI10) (15–20 mm), even without needling sensations, could significantly reduce their HR. Moreover, regardless of the level of *Deqi* or perceived pain during needling, their autonomic nerves are still transferred o parasympathetic advantage.^[29] This study provides further support for the selection of limb acupoints and stimulation parameters in the above acupuncture protocol that can stimulate cholinergic anti-inflammatory pathways.

As for the benefits of combined electrical stimulation in support of anti-inflammation, some studies have shown that both manual acupuncture and EA can have a significant impact on leukocytes and their related cytokines. However, in subjects with collagen-induced arthritis and inflammation, EA was more effective than manual acupuncture in reducing

pro-inflammatory cytokines such as IL-6, IFN- γ , and TNF- α .^[30]

The reason why low-frequency electrical stimulation should be selected is that its anti-inflammatory action is different from that of high-frequency electrical stimulation. It was found that the sympathetic nerve stimulation induces both local and systemic catecholamine secretion, depending on the selected frequency of electrical stimulation. A high-frequency EA can activate the preganglionic nerve that innervates the adrenal medulla to induce systemic catecholamine secretion, whereas a low-frequency EA seemed to activate the postganglionic sympathetic nerve to induce local release of NE,^[31] so it can achieve a better inflammatory inhibition action.

As a clinical reference, the above acupuncture protocol is designed to enhance the vagus-cholinergic anti-inflammatory pathways when dealing with NCP complicated with sepsis. Actually, aiming at different purpose of prevention and treatments (prevention-based or life-saving centric), there are myriad types of acupuncture or moxibustion protocols. For example, for patients with mild-to-moderate symptoms and/or in recovery period, moxibustion could be selected. For severe patients with sepsis or in shock, acupuncture with an intense stimulation at the extremities or the governor/DU meridian (central reflex area) may be critical to stimulate the sympathetic-adrenal system and HPA axis to save life. Although the effectiveness of these protocols remains to be verified via large sample and high-quality clinical trials, it is clear that acupuncture and moxibustion can bidirectionally regulate the immune system with little or no side effects. This is especially true when applying acupuncture including EA to treat infectious sepsis by an enhanced stimulation to the nervous system.

Finally, we would like to emphasize that even though it is common knowledge that the body's inflammatory response to the invasion of pathogenic microorganisms is one of the wisdoms of the body, many people are probably not familiar with another related wisdom of the body, that is, neuronal networks to control excessive inflammation and infectious disorders.^[6] Both laboratory and clinical evidence have recently shown that there is a negative feedback loop between the ANS and the innate immunity. Electrical stimulation of the vagus nerve inhibits the activation of macrophages and the production of various pro-inflammatory cytokines.^[4] Acupuncture, as one of the most convenient and effective natural protocols of TCM, is the best choice to stimulate the neural networks, with little or no side effects. As NCP is now running rampant around the globe, why not give anti-inflammatory acupuncture a chance?

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Conflicts of interest

There are no conflicts of interest.

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