Research Article

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COVID-19 and Acupuncture: is there a new line of therapeutic research?

Abstract

The pandemic produced by COVID-19 has surprised almost all health and socio-economic systems worldwide with its high degree of infectivity and mortality. In short time we have learned many aspects of the epidemiology, pathophysiology and clinic of the virus responsible, SARS-Cov-2, and the disease it induces. COVID-19 is known to produce in some patients the development of an excessive immune response and hyper inflammation, damaging various organs and sometimes causing death. There is no effective treatment available at the moment, other than life support, and for this reason different revealing therapeutic options are being tested but pending confirmation of their effectiveness and safety in well-designed clinical trials. We describe the anti-inflammatory and immunomodulatory effects of Acupuncture, as well as its preclinical and clinical effectiveness in different conditions that have similar COVID-19 immunological disorders. The proven biological plausibility of Acupuncture, together with its acceptable level of clinical effectiveness and safety, make this medical technical procedure an option to try in this health emergency situation. We propose an adjusted classification of the clinical presentation of COVID-19 and an appropriate adjuvant Acupuncture protocol for each phase of the disease.

Keywords: acupuncture, COVID-19, SARS-CoV-2, immunomodulation, hyper inflammation, sepsis, treatment protocol

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Introduction

Coronaviruses (CoV) are viruses that can cause pathology in mammals, birds, and humans. They are large RNA viruses, with the largest genome among known RNA viruses and they owe their name to their spherical shape from which spicule in the shape of a crown protrude. Human coronaviruses were first isolates in the 1960s. Seven types of human coronaviruses are known, four of them (HCoV-229E, HCoV- OC43, HCoV-NL63, HCoV-HKU1) are the causative agent of common cold along with rhinoviruses. Three other new coronaviruses have emerged in the 21st century, having caused serious outbreaks with acute respiratory distress syndrome (ARDS): SARS-CoV (China, 2002), MERS-COV (Middle East, 2012)[1] and the current SARS-CoV-2.[2]

IN December 2019 in Wuhan, Hubei Province (China) an outbreak of pneumonia cases caused by a new β-coronavirus, SARS-CoV-2, was first detected.[3] From China it quickly disseminates around the world, putting health, economic and political systems to the limit. A pandemic that is generating a situation of unknown global crisis and has more than 375,000 confirmed cases in 196 countries and more than 16,000 deaths.[4] On February 11, 2020, the world Health Organization (WHO) gave the official name of the infection. The name was coronavirus disease 2019, and it was abbreviated COVID-19**.** In the abbreviated name, "CO" stands for "corona", "VI" for "virus" and "D" for "disease". Previously, the way to refer to this disease was "new coronavirus 2019" or "2019-nCoV".[5]

The natural reservoir of all coronaviruses are bats and through an intermediate mammal they can infect humans. Transmission between persons was observed from the first reported cases of COVID-19[6] taking measures of early confinement and exhaustive general hygiene to limit contagiousness within the population. Other possible risk factors are being studied such as age, s ex, underlying disease, viral inoculation dose, genetic susceptibility,[7] environmental factors such as smoking.[8]

SARS-CoV-2 data confirm that it is a highly infectious virus with a high transmission capacity. It is transmitted primary through *Flügge* droplets from the respiratory secretions of infected persons when they exhale. In addition, when these *Flügge* droplets fall, they deposit on surfaces, where other people can contract the infection if they touch those objects or surfaces with their hands and take them to eyes, nose of mouth.[9]

This high infectivity rate is enhanced by its high incubation time (between 1 and 14 days), which provides it with a great pre-symptomatic transmissibility. After the disease is cured transmission is also possible. There are also cases of fecal-oral transmission due to the digestive symptoms that may happen during the disease. No cases of perinatal or breast milk transmission have been reported to date.[10]

Pathophysiology of COVID-19

The SARS-CoV-2 infection induces an immune response in two phases,[11] the first phase the viral pathogenicity predominates and, the second, in which the pathology is mainly due to the excessive immune response of the host. Being the transition from one phase to another, both from a clinical and analytical point of view, progressive. During incubation and in the non-severe phase of the disease, a specific adaptive immune response is required to try to eliminate the virus and limit progression to more advanced stages of infection. The second phase begins when the protective immune response is altered.[12] As a sign of the dysfunction of the immune system we can observe the decrease in CD3+ and CD+ T cells. The dysregulation of the immune system will trigger a series of disproportionate and negative immune responses for different affected tissues. Starting through the complex signaling recruitment adapters that develop a molecular cascade that activates nuclear transcription factor $\kappa\beta$ (NF-$\kappa\beta$) and the production of type I interferons (IFN-α/β) and a series of pro-inflammatory cytokines (IL-1β, IL-6, macrophage colony stimulating factor (MCSF), IP-10, MCP-1, hepatocyte growth factor (HGF), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α). The cytokine profile associates with severe COVID-19 resembles that seen in secondary hemophagocytic lymphohistiocytosis (sHLH): increased IL-2, IL-7, granulocyte colony-stimulation factor, interferon-γ, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and TNF-α.[13] Not much is known about sHLH a hyperinflammatory syndrome characterized by fulminant hypercytokinemia and fatal multiorgan failure, which can occur in 3.7 – 4.3% of cases of viral sepsis in adults. sHLH presents with sustained fever, cytopenias and hyperferritinemia, and lung involvement in 50% of the patients (SDRA).[14]

According to a multicenter retrospective study of 150 cases of COVID-19 in Wuhan, it suggests that mortality could be due to viral hyperinflammation and increases ferritin and IL-6 would act as markers of severity.[15] Other predictors of severe SARS-CoV-2 disease are elevated D-dimer on admission, lymphopenia, and increase high-sensitivity troponin 1.[16]

The current treatment of COVID-19 is supportive, and respiratory failure due to ARDS is the leading cause of mortality. Accumulated evidence suggests that a subgroup of patients with severe COVID-19 may have a cytokine release syndrome (CRS).[17] Early identification and treatment of hyperinflammation, using all existing therapies with acceptable safety profiles is important to address the immediate need to reduce mortality.[18]

Clinical classification

SARS-Cov-2 infection does not progress similarly in everyone who comes in contact with it. The interest in the clinical classification lies in being able propose the most appropriate therapeutic approach for each patient according to the phase in which they are. According to the classification proposed by Shi et al.,[19] there is an initial asymptomatic incubation period (PHASE I),[20] similar to the incubation periods of SARS and MERS,[21] although there is evidence that this period can have a highly variable period depending on the inoculation dose.[22] Of the infected and confirmed cases, between 60-80% have a mild to moderate symptomatology (PHASE II), characterized by fever, dry cough, asthenia and myalgias, which is adequately managed on an outpatient basis with symptomatic treatment. The remaining 20-40% have a serious clinical course with multiple organ involvement (PHASE III), predominantly at the respiratory level, needing between 5-8% critical care for respiratory failure and sepsis. With a mortality rate of 3.6% (95% CI: 3.5 to 3.7) although these mortality rates are based on the number of confirmed cases of infection, which does not represent the current mortality rate.[23] The WHO has recently reported that the time between the onset of symptoms and death varies from 2 to 8 weeks.[24]

The classification proposed by Siddiqi & Mehra[25] also distinguishes 3 periods. Period I (mild or early infection) ranging from inoculation to the establishment of the disease characterized by nonspecific symptoms such as malaise, fever, dry cough, headache, anosmia or ageusia. At the analytical level, the blood count can reveal lymphopenia and neutrophilia without other significant abnormalities. Period II (moderate or with respiratory involvement without hypoxemia (IIA) or with hypoxemia (IIb)) with establishment of respiratory disease with worsening of symptoms and appearance of radiological signs of viral pneumonia (infiltrates or opacities in characteristically bilateral ground glass) and analytical abnormalities (exacerbation of lymphocytopenia, moderate elevation of D-dimer and transaminitis), as well as the onset of elevation of systematic markers of inflammation, but not in a extreme way, highlighting a normal to low procalcitonin. At this stage, most patients with COVID-19 would need to be hospitalized for observation and treatment. A relevant clinical aspect in this period is the appearance of hypoxemia as a marker of the progression of the infection and the possible need for mechanical ventilation resulting from the pulmonary inflammation hyperresponse that, if not interrupted, will lead to Period III (severe or systematic hyperinflammation). Clinically, in this stage, multiorgan involvement is observed in many patients with a progressive evolution towards worsening and hemodynamic instability and sepsis. This period is characterized by a significant elevation of systemic inflammation markers (IL-2, IL-6, IL-7 granulocyte colony stimulating factor, macrophage inflammatory protein 1α, TNF-α, C-reactive protein (PCR), ferritin and D-dimer). Ferritin is the key indicator of macrophage activation. D-dimer rises similarly to antiphospholipid syndrome along with thrombocytopenia and coagulation disturbances.

Current therapeutic approach

To date, there is no effective antiviral treatment against SARS-CoV-2. Antiviral drugs and systemic corticosteroids useful in other viral infections have not been shown to be valid for COVID-19. Recent studies have revealed attractive therapeutic options, although they have yet to be confirmed in studies in rigorous preclinical and clinical models.[26] Some authors highlight the use of corticosteroids at the beginning of the hyperinflammatory response and not in the early stages, where their early use could provoke viral replication.[27] Remdesivir, a RNA antiviral, has been used to successfully treat the first case of COVID-19 in the USA.[28] Even though it is the most promising antiviral currently being investigated, its efficacy and safety are not yet established. The viral load in COVID-19 has been shown to decrease significantly, in one case, after administration of Lopinavir/Ritonavir,[29] although the efficacy of this drug mixture is nor definitively established. Several studies have found that Hydroxychloroquine can inhibit some steps in the replication of various viruses, with a potent effect on the infection and spread of other viruses of the coronavirus family.[30] Hydrochloroquine also has immunomodulatory effects, suppressing the production and release of TNF-α and IL-6.[31] Currently, the efficacy, dose and safety of Hydroxychloroquine for the treatment and prevention of COVID-19 are not established, and more data is needed on whether its in-vitro activity against SARS-CoV-2 corresponds to clinical efficacy. Recent publications show that the combined use of Hydroxychloroquine and Azithromycin are more effective in eliminating the virus.[32]

In the line of suppressing different proinflammatory cytokines, various quasi-experimental protocols are been initiated at hospital level to modulate the excessive immune response and thus avoid the damage produced by the CRS, this phenomenon been responsible for the fatal outcome in some cases of infection by SARS-CoV-2.

Proposal of clinical classification for the approach with Acupuncture

Inspired by Siddiqi & Mehra, we propose a 5-stage classification (Figure 1) to try to identify the different clinical characteristics and enhance the most appropriate therapeutic approach for each phase. Acupuncture can be potentially useful in all phases as a complementary and synergic treatment to try to improve the patient's global condition, prevent progression and help during convalescence.

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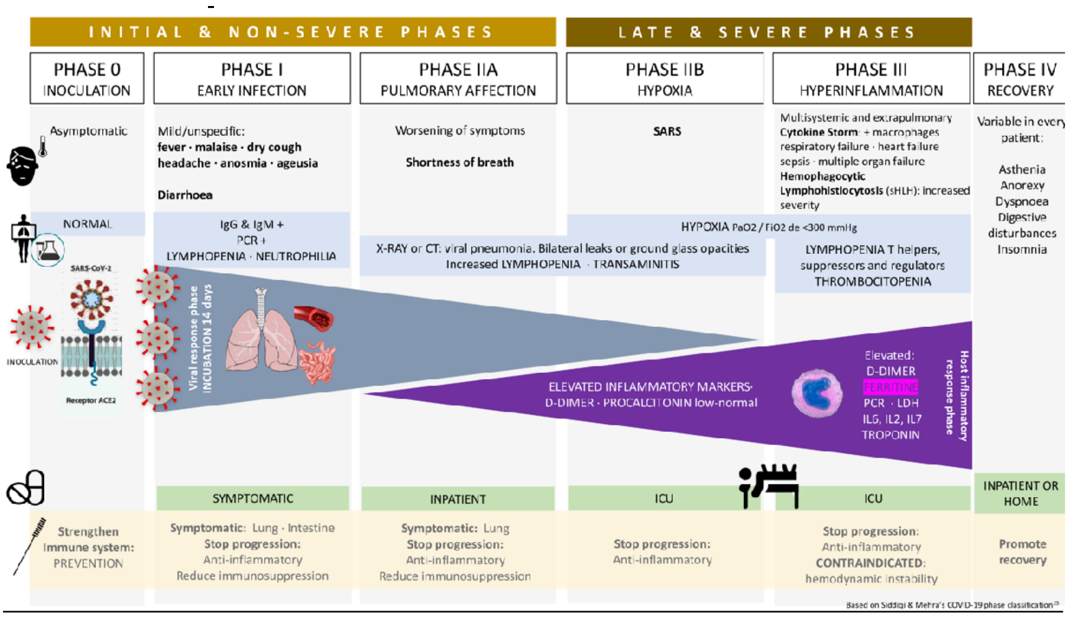

Figure 1 Adaptation Siddiqi & Mehra.[25]

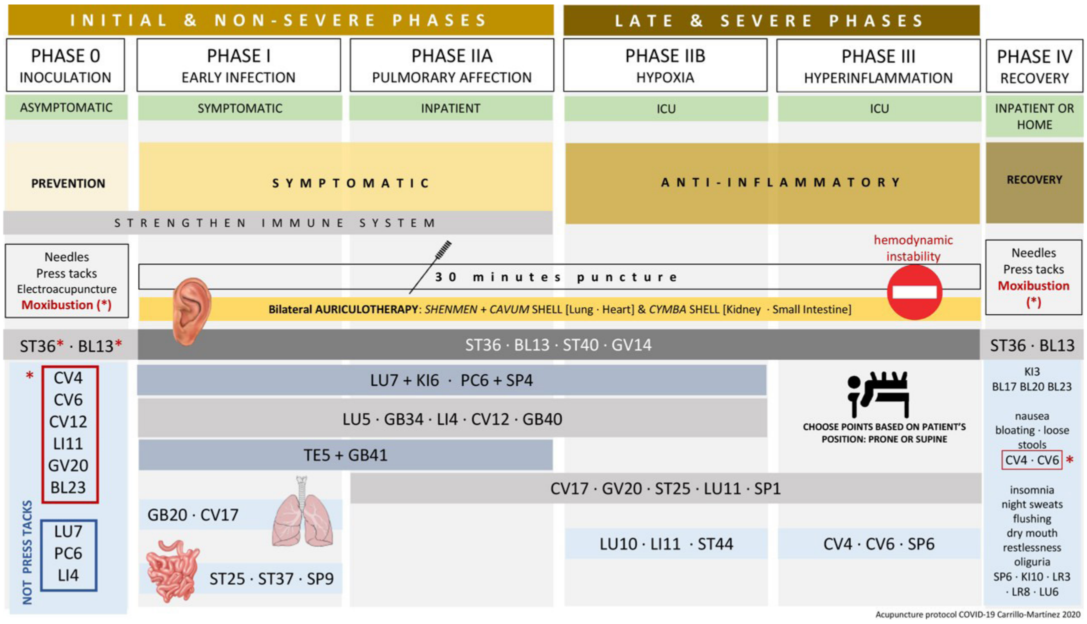

Figure 2 Acupuncture protocol COVID-19 Carrillo-Martínez.

a. **Phase 0:** period from inoculation to the development of first symptoms of disease. There are no symptoms and no viral detection (negative PCR).

b. **Phase I:** period of early infection asymptomatic or with mild symptoms (fever, cough, headache…). Positive viral detection (positive PCR). With few analytical alterations and no radiological signs.

c. **Phase II:** period that begins with lung involvement (viral pneumonia), with clinical and radiological worsening.

IIa: analytical, clinical and radiological alterations without hypoxemia.

IIb: clinical worsening, severe analytical and radiological changes, appearance of hypoxemia.

Phase III: period characterized by an excessive immune response (cytokine storm) with multi- system involvement in different degrees, including septic shock.

Phase IV: recovery. As of today, the long-term evolution of people affected by COVID-19 is still an enigma. Given the predominantly pulmonary involvement of the acute phase, we can suspect that most of the sequelae will be at this level. Radiological studies of patients in remission phase show gradual reabsorption of acute phase lesions on computed tomography, but cord-like high density shadows indicative of fibrosis.[33] Based on epidemiological, immunological and clinical evidence, it is expected that patients who survive SARS-CoV-2 infection may suffer, as the most serious complication, pulmonary fibrosis.[34] There is preclinical evidence that moxibustion has a positive effect on pulmonary fibrosis comparable to prednisone, attributed to the inhibition of transforming growth factor-β (TGF-β) and IFN-γ, measured both at mRNA and protein level.[35]

Therapeutic approach with acupuncture

The therapeutic approach at the present time is being developed as the pathophysiology, and clinical characteristics of COVID-19 are been discovered. It seems reasonable to guide investigation to the acute phase (non-severe and severe phases) and to the recovery phase. In these phases it is proposed that the synergistic technical medical procedure of Acupuncture can add a beneficial effect to conventional treatment:

The initial / non-severe phases, where viral pathogenicity predominates (phases 0, I and IIa). Looking for measures that improve the host's immune response in order to limit the progress of the disease to more severe phases.

The late/severe phases, where the immune response and hyperinflammation (cytokine storm) to limit multi-organ damage.[36]

The recovery phase, the sequelae of the inflammation will favour the appearance and progression of pulmonary fibrosis that can condition the lung capacity and quality of life. The objective is to limit the extension and progression of fibrosis and promote recovery of lung function.

Why acupuncture may be of interest as an adjunctive treatment in COVID-19

Acupuncture is a medical therapeutic procedure widely used both in the east and western countries for different conditions, mainly in pain, but also in other non-pain conditions. The mechanisms of action of Acupuncture have been extensively studied, and it has been seen that it has a modulating effect at different levels. One of the most recognized is the immunomodulatory and anti-inflammatory effect.[37,38,39,40] There are recent reviews on how Acupuncture attenuates the immune response to various conditions, such a surgical stress on cognitive function,[41] postsurgical ileus,[42] inflammatory bowel disease,[43] allergic rhinitis,[44] depression,[45] anxiety,[46] migraine,[47] spinal cord injury,[48] knee surgery in the elderly,[49] sepsis,[50] lung injury secondary to limb reperfusion ischemia,[51] arthritis,[52] rheumatoid arthritis,[53] cerebrovascular disease,[54,55] cognitive decline,[56] myocardial ischemia[57] and obesity.[58,59]

Basis for the application of acupuncture in the initial phase of COVID-19: boosting host immunity Acupuncture has been extensively studied to understand its mechanisms of action. Far from traditional concepts, Acupuncture is now known to allow the restoration of homeostasis by the regulation it exerts between the autonomic nervous system, innate immunity and other systems.[60] The autonomic nervous system is considered one of the most important mediators of acupuncture stimulation, since it can interconnect peripheral somatosensory stimulus with responses of different organs through networks of the central nervous system. The vagus nerve, which regulates the function of different organs, has been the most studied target of the possible effects of Acupuncture.[61] Vagus nerve stimulation by Acupuncture is known to have three major pathways with strong anti-inflammatory effects: the hypothalamic-pituitary-adrenal axis, the cholinergic anti-inflammatory pathway, and the sympathetic-splenic-anti-inflammatory pathway.[62]

Reviewing the literature, we can find many articles that show the action of Acupuncture and the modulation of the immune system. The abbreviation of each Acupuncture point is broken down in the final annex:

a. In 31 patients with Takayasu Arteritis, the abnormally low levels of CD3+, Cd4+ and CD8+ T cells found in some of the patients was significantly normalized after a treatment with Acupuncture stimulating the following points: ST9, HT1, LU5, GB1 y 20, BL13, 15 y 17, with moxibustion on LU9, BL13, 15 y 17.[63]

b. IN an animal model of asthma, it is observed that a Acupuncture treatment every other 48 hours (GV14, BL12 and BL13) increases the number of CD4+INF-γ y CD4+ Foxp3+ T cells in lung tissue, while reducing the number of CD4+ Il-17a+ T cells. In this study it is suggested that the effect of Acupuncture in the animal model of asthma is based on the regulation of the balance of CD4 T cell subtypes.[64]

c. In a preclinical study on the regulation of lymphocytes during the postoperative period with electroacupuncture (EA) session before and after surgery at acupoint ST36, an earlier recovery of CD3+ and CD4+ T cells levels is achieved. Concluding that EA relieves immune suppression and promotes recovery of cellular immunity function.[65]

d. In a group of male patients with COPD, a disease that is immunologically characterized by a decrease in the number of CD4+ T cells and a decrease in the CD4+/CD8+ ratio, the effect of laser Acupuncture compared to stimulation with respiratory physiotherapy was analysed. Stimulation of the following points, LI4, LI11, KI27, LU7 three times a week for two months, showed a significant increase in CD4+ T cells and CD4+/CD8+ ratios in both groups, but higher in the laser Acupuncture group.[66]

e. In an animal model of bone cancer, EA at ST36 and BL60 every 48 hours for a total of 8 sessions manages to relieve pain, although to a lesser degree than morphine, but manages to increase CD3+, CD4+ and CD8+ T cells subtypes. This response being blocked by naloxone, suggesting that the mechanism is related to the endogenous opioid mediated pathway.[67]

f. IN a group of healthy rats, applying daily EA for 14 days the number of CD4+ T cells increased significantly compared to sham and control groups. Indicating that EA at ST36 enhances immune function via the differentiation and activation of splanchnic T cells.[68]

g. Although this is an old study (1994), it is interesting because it shows that Acupuncture treatment at ST36, LI11 and CV6 for 10 days in cancer patients manages to significantly increase the activity of NK T cells and IL-2. Suggesting that Acupuncture may enhance the function of cellular immunity in cancer patients.[69]

h. In a randomized group of children with cerebral palsy, moxibustion is performed at acupoints CV4, BL23 and ST36 daily for 1 month, resulting in an increase in CD3+, CD4+ T cells, CD4+/CD8+ ratio and serum immunoglobulin levels (IgG, IgA) ($p<0.01$, $p<0.05$). With a significantly lower disease index at follow up at 6 and 12 months ($p<0.05$).[70]

We can summarize the action of the most frequently studied acupoints in the modulation of the immune system to justify their use in the initial phase or COVID-19 (Table 1).

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Table 1 Acupuncture and immunity

Acupuncture and Immunity	ST36	LI11	CV6	CV4	BL23	BL60	KI27	LU7	LI4	BL12 BL13 GV14	Other: ST9, HT1, LU5, GB1, GB20, BL15, BL17 Moxibustion: LU9, BL13, BL15 and BL17	Study Model
↑ IL-2												Human[69]
↑ IFN-γ												Animal[64]
↑ NK												Human[69]
↑ T cell CD3+												Human[63,70] Animal[65,67]
↑ T cell CD4+												Human[63,66,70] Animal[64, 65,67,68]
↑ CD4+/CD8+												Human[66,70]
↑ IgG, IgM, and IgA												Human[70]

Bases for the application of acupuncture in the late phases of COVID-19: anti-inflammatory action to control the "cytokine storm"

Sepsis is a clinical syndrome characterized by a generalized inflammatory response similar to what occurs in COVID-19. The etiology is multiple, although the course of all patients and the systemic pathophysiological changes are similar among them. In this sense, we find multiple studies that evaluate the effects of Acupuncture in animal models of sepsis. These studies induce sepsis by injection of lipopolysaccharide (LPS) or D-galactosamine, or by ligation and posterior cecum perforation (CLP). A systematic review of these pooled studies on the effect of Acupuncture on ST36 has recently been published (Lai, F et al[71]). They find and analyse 54 studies publishes between 2006 and 2018 (31% in the last 5years). Most of these studies use EA, although also Manual Acupuncture (MA), at different points: ST36, PC6, BL13 and LI4. The results show that Acupuncture has a beneficial effect in the evolution of sepsis and manages to reduce the degree of injury on different target organs, such as lung,[72,73] kidney[74,75] brain[76,77,78] digestive tract,[79,80] liver,[81] cardiovascular system[82] and with positive data o survival.[83]

These effects are justified by modulating the immune response, reducing proinflammatory cytokine levels (TNF-α, IL-6, IL-1β),[84] increased anti-inflammatory cytokines (IL-10),[85] decreased oxidation,[86,87] microcirculation improvement.[88]

The most likely mechanisms to achieve these effects are through the cholinergic anti-inflammatory pathway,[89,90] with its effect on macrophages, inhibiting the release of pro-inflammatory cytokines, without ruling out other routes such as dopaminergic,[91,92] Nrf2/ACE,[93] ERK1/2, heme-oxygenase-1 (HO-1) pathway,[94,95] stimulation of the mitogen-activated protein kinase p38 (p38MAPK),[96,97] inhibition of the expression of group of high mobility proteins B1 (HMGB1) that promotes the expression of ghrelin.[98]

Many of these results are observed in studies that initiate Acupuncture before the onset of septic symptoms. Some authors consider that once the excessive immune response in initiated, it may be more difficult to control the immunological alterations and clinical presentation. Having therefore relevance when considering the application of Acupuncture in the initial phase of the disease to limit the progression of COVID-19 to severe stages.

Some of the studies in animal models published in the medical literature are:

a. One of the first references we found regarding the effectiveness of Acupuncture in sepsis is a study in an animal model of sepsis induced by CLP. Noting that the Acupuncture protocol increased survival and reversed defective migration of neutrophils into the peritoneal cavity.[99]

b. In another animal model of pharmacological (LPS) sepsis, it was observed how EA at PC6 manages to reduce plasma levels of nitrous oxide and TNF-α, in addition to stabilizing blood pressure.[100]

c. In two studies carried out in the same LPS sepsis model, it was observed how Acupuncture stimulation of ST36 significantly mitigated the degree of acute lung injury, iNOS lung expression and pulmonary nitric oxide biosynthesis. The same group carried out a similar study determining that Acupuncture pre-treatment at ST36 protected the kidneys in the same way, but did not benefit the liver.[101]

d. IN a complex preclinical study with CLP induced sepsis, it was observed how ES at ST36 significantly alleviates edema and insult to the intestinal mucosa, with significantly higher activity of jejunal blood flow and diamine oxidase, with lower levels of xanthine oxidase, malondialdehyde (MDA) and water content. It is suggested that the cholinergic anti- inflammatory pathway is one of the main mechanisms of this protective intestinal effect of EA on ST36.[102]

e. In a study carried out by the same group, using the same sepsis model and EA at ST36, it was observed that the hepatic blood flow was significantly higher compared to all controls (sham EA, vagotomy and vagotomy + ES). Liver levels of MDA, xanthine oxidase, ALT and water content were significantly better than controls. The authors conclude that EA at ST36 promotes blood flow, inhibits lipid peroxidation and relieves edema at liver level in animal model of sepsis.[103] In other words, they found the same results that they saw in the jejunum, but also in the liver, that were not seen previously (Huang CL et al, 2007).

f. In an animal model study or LPS induced sepsis, it was observed that auricular- EA managed to significantly reduce levels of TNF-α and IL-6, and the pulmonary expression of p65 NF-$\kappa\beta$ by cholinergic anti-inflammatory mechanisms.[104]

g. It is found in the same sepsis model, but using EA at PC6, an attenuation of the elevation of hepatic biochemical parameters and the infiltration of neutrophils, but without seeing changes in blood pressure nor tachycardia nor plasma levels of nitric oxide.[105]

h. In a treatment with EA at ST36 and PC6 prior to the induction of sepsis by LPS compared to sham EA, significant differences were observed in favour of real EA with decreased TNF-α, IL-1β, increase levels of IL-10 and decreased iNOS and NF-$\kappa\beta$; as well as a significant decrease in BUN, Cr and renal histopathological score. The authors conclude that pre-treatment with EA at ST36 and PC6 attenuate the inflammatory response induced by LPS and mitigate kidney injury.[106]

i. The detailed study on the same model observed that pre-treatment with EA at LI4 significantly improves survival and attenuates pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), the effect is more powerful than PC6 stimulation, and that electrostimulation on non-acupoints is not effective at all. This effect is considered to be produced by the cholinergic anti-inflammatory pathway that activates macrophage nicotinic receptors by inhibiting the release of pro- inflammatory.[107]

j. Other studies have shown mechanisms of action of the positive effect of EA in sepsis, this the study in rabbits shows that EA (ST36 and BL13) during 5 days prior to the induction of sepsis attenuate lung injury due to increase HO-1 expression.[108]

k. In a model of CLP sepsis in rats, it is observed that EA at ST36 manages to significantly reduce pro-inflammatory cytokines in brain tissue.[109]

l. In Torres-Rosas[110] study in mice, it also demonstrated how EA at ST36 manages to reduce, in a model of LPS induced sepsis, all levels of cytokine analysed, including TNF-α, IL-6, IFN-γ and chemotactic protein of monocytes-1, proposing that the pathway is mediates by dopamine. Similar results were published by Chavan, SS.[111]

m. An increase in oxidative stress is also observed in sepsis, partly being responsible for the damage at different tissue levels, specially the lungs. The study in rabbits by Yu, JB et al[112] demonstrated how EA (ST36 and BL13) significantly mitigates LPS induced septic shock, increasing the activity of antioxidant enzymes and reducing the level of pro-inflammatory cytokines by activating the Nrf2/ACE pathway.

n. Similarly, the same group published similar results in the following study by Zhang Y et al,[113] but studying other probable routes of action of EA (E36 and BL13). Aiming for the role of extracellular signal regulation kinases 1/2 (ERK1/2) That potentiates HO-1. Achieving that treatment with EA showed only a sight degree of lung injury compared to the groups without EA or with sham EA, and decreasing TNF-α, MDA and increasing SOD.

o. The study by Wu, J et al.[114] concludes that EA at ST36 can inhibit the expression of HMGB1 in the jejunum and promote the expression of ghrelin that would justify its anti-inflammatory action.

p. The digestive tract plays a major role in the development of multiorgan failure in sepsis, which is why Zhu, MF et al.[115] carried out a study in an animal model of sepsis induced by CLP. They observed that EA pre-treatment at ST36 reduces intestinal injury and increased permeability and has a protective effect on the immunological barrier of the intestinal mucosa. Significantly increasing the percentages of CD3+, γ/δ, y CD4+T cells and the ratios of CD4+/CD8+ T cells.

q. AA pre-treatment of EA (ST36 and GV20) in an animal model of sepsis shows an improvement in survival, attenuates edema and brain injury, neuronal apoptosis and cognitive dysfunction. It decreases TNF-α, IL-6, MDA and increases the activity of SOD and catalase in serum and hippocampus. Inhibiting the expression of TLR-4, NF-κB.[116]

Human studies have also shown the effectiveness of Acupuncture in the management of sepsis:

r. The randomized study of 50 patients with sepsis (26 EA and 24 controls), to whom EA was applied for 3 days, shows a significant reduction in the EA (ST36, ST25, ST37, and ST39) groups of the ratio of lactulose/mannitol excretion in urine and D-lactic acid in serum. The time to restart feeding was also significantly reduced, with a total effectiveness rate of 80.8% in the intervention group compared to 54.2% in the control group ($p<0.05$). Conventional treatment combined with EA can improve intestinal permeability in patients with sepsis.[117]

s. In a group of 90 septic patients, they were divided into 3 groups (control, Subcutaneous thymosin and Acupuncture at ST36, GB34, PC6 and CV4 in 6 sessions in 6 days). CD3+, CD4+, CD8+, IgG, IgA and IgM were significantly increased in the thymosin and Acupuncture groups versus control ($p<0.01$). ICU stay, hospital readmission rate, and 28-day mortality were significantly lower in these same groups.[118]

t. In the prospective randomized study by Yang G et al[119] a total of 58 septic patients using EA (ST36 and CV4). No significant differences in mortality were observed between both groups (17.2% in EA vs. 31% in control). However, a significant difference ($p<0.01$) in APACHE-II score in favor of EA is observed after treatment. Levels of CD3+, CD4+, CD8+ T cells and CD4+/CD8+ ratio were significantly higher in the EA group. Human leukocyte antigen (HLA)-DR monocyte expression was significantly increased in the EA group, suggesting that the positive effect on sepsis is mediated by regulation of the immune system.

u. To evaluate the effect on inflammatory rates of gastrointestinal septic dysfunction of EA (ExB2) in total 10 sessions in 10 days. A comparative study was conducted in 118 septic patients, showing from the 6th day a significant reduction in gastrointestinal dysfunction score and inflammation indices (hs-PCR, procalcitonin) in the EA group, in addition to a total effectiveness index of 91.5% (EA) vs. 76.3% (control) ($p<0.05$).[120]

v. IN a study of 82 septic patients undergoing EA (two daily sessions) treatment for 5 days, significant lower levels of TNF-α, IL-1β in the group that received EA were observed compared to controls that only received conventional intensive treatment.[121]

w. In a prospective study of 44 patients who underwent craniotomy for different reasons, they were assigned either to 6 Acupuncture sessions in the 8 days after surgery or a control group without EA. Significantly lower levels of IL-1β and TNF-α, were observed, with no episodes of fever of unknown origin being observed in the Acupuncture group, while it was present in 27% of controls.[122]

We can summarize the action of the most studied acupoints in sepsis that would justify their use in late stages of COVID-19 in Table 2.

Table 2 Acupuncture and sepsis

Acupuncture and Sepsis	PC6	ST36	LI11	LI4	BL13	GV20	ST25 ST37 ST39	GB34	CV4	*Jiaji EXB2*	Auricular Acupuncture a	Study model
↓ plasmatic nitrous oxide												Animal[100, 107,]
↓ TNF-α												Animal[100, 105, 107, 108, 110,111,112, 114,117] Human[122,123]
↓ NF-$\kappa\beta$												Animal[105,117]
↓ IL-6												Animal[105,107,108, 110,111,112,117]
↓ IL-1β												Animal[107,108,] Human[122,123]
↓IFN-γ												Animal[111,112]
↑ IL-10												Animal[107]
HMGB1 inhibition												Animal[109,115]
Antioxidant effect												Animal[114,117]
↑ CD3+ T cell												Animal[116] Human[119,120]
↑ CD4+ T cell												Animal[116] Human[119,120]
↑ CD4+/CD8+												Animal[116] Human[119,120]
↑ IgG, IgM and IgA												Human[119]
Blood pressure												Animal[100,]
Decrease Acute Lung Injury												Animal[72, 73, 102, 105, 113]
Nephroprotection												Animal[74, 75, 102, 107,]
Hepatoprotection												Animal[81,104, 106]
Brain protection												Animal[76, 77, 78, 110, 117]
Intestinal edema improvement												Animal[79, 80, 103, 115, 116] Human[118, 121]
Survival Increase												Animal[83, 99, 108,] Human[119]
Cholinergic pathway												Animal[99, 106]
↓ proinflammatory cytokines in CNS												Animal[110]
Dopaminergic pathway												Animal[91, 92, 109, 110]
↓ lactulose / mannitol excretion												Human[118]
↓ refeeding time												Human[118]
↓ ICU stay												Human[119]

a: pinna Shell points that stimulate the vagus nerve and the cholinergic anti-inflammatory pathway

Bases for the application of acupuncture in the recovery phase: effect on the formation of fibrosis: There are different studies at different tissue levels that show how Acupuncture prevents the formation of fibrotic tissue:

IN a spontaneous hypertension model in rats comparing EA with losartan, it is observed that EA at BL17 and/or BL23 manages to control blood pressure, expression levels of tissue inhibitory metalloproteinases (TIMP-1), plasminogen activated inhibitor-1 (PAI-1) and muscle actinlysa-α (α-SMA), as well as the histopathological changes observed at kidney level after staining with hematoxylin/eosin in a similar way as losartan.[123]

The therapeutic effect of EA on bruised skeletal muscle has been confirmed in various clinical studies. In this publication, it is observed how EA at ST36 helps the regeneration of bruised skeletal muscle, relieving fibrosis and increasing the size of the regenerated myofibrils. EA increased the number of M2 macrophages and decreased those of M1, as well as decreases the levels of IFN-γ and increases levels of IFN-α, IL-4, IL-13 that contribute to the regeneration of injured tissue and the less formation of fibrosis.[124]

The effects of Acupuncture on renal interstitial fibrosis were studied in an animal model of chronic renal failure. The results show that, Acupuncture stimulation on BL23, BL20 and GV4, reduces levels of TNF-α, ILK, TGF-β, IL-8, IL-1β, Smad and iNOS expression, acting on the TGF-β/Smad pathway.[125]

In an animal model of muscle injury, it is observed how EA at BL40 reduces the degree of muscle fibrosis and promotes tissue regeneration in the initial phase, this effect being associated with the regulation of the expression of collagen I proteins and metalloproteins matrix 2.[126]

The anti-inflammatory effects of EA at ST36 allows, in addition to reducing the local post-surgical inflammatory response (decreases TNF-α), attenuate angiogenesis (decreases vascular endothelial growth factor (VEGF)) and alleviates the formation of adhesions in part by cholinergic anti-inflammatory mechanisms.[127]

Creating a cervical intervertebral disc lesion in rats, it was seen that EA at BV14 inhibits cellular apoptosis of fibrous ring by suppression of TNF-α, TNF receptor 1 and caspase-8 positive cells and the expression of integrin β1 and Akt mRNA.[128]

In an animal model of muscular injury, EA at ST36 and trigger points, achieves significantly higher levels of serum activity of total SOD and total antioxidant capacity, and lower levels of MDA. In the EA group, the diameter of the myofibrils was uniform with a regular arrangement. EA significantly decreased fibrosis formation. The mechanisms are attributed to the improvement of blood flow and antioxidant capacity.[129]

These studies show how Acupuncture reduces fibrosis formation in different organs that are undergoing a period of high inflammation and oxidation. Modulation of the immune system has been considered the key step in the therapeutic effect of Acupuncture and Moxibustion.[130] EA can inhibit the induction and transmission of pain signals and consequently, through its antinociceptive and anti-inflammatory effects, rebalance neuro-immune-endocrine interactions.[131]

The studies previously analysed show the beneficial effect of Acupuncture on the immune system. In the health of non-serious disease situations, it boosts immunity, while in chronic and acute disease, when there is a situation of hyperinflammation, it manages to ”appease” this excessive and negative immune response in different organs and for the whole individual. We therefore have studies on the biological plausibility of Acupuncture in inflammation.

Proposed protocol of intervention with Acupuncture for COVID-19

The studies analysed show the beneficial effect of Acupuncture on the immune system. In light of the data, it would be interesting to assess and include Acupuncture as a complementary treatment for the management of patients with COVID-19 to try to prevent or contain the poor evolution related to an uncontrolled immune response and a state of hyperinflammation. These are the fields in which most preclinical and clinical research has been carried out in the last 20 years in the field of Acupuncture.

There is not yet any study that analyses the effect of Acupuncture in patients with COVID-19, nor do they exist for almost all treatments that are been empirically used at the moment. They are underway, according to clinical evidence and from the urgency that these pandemic warrants. From China, favourable data on the use of traditional Chines medicine, mainly phytotherapy, has been published, although data on the use of Acupuncture is still lacking, some recommended protocols for different stages of the disease have transcended,[132] that more or less coincide with the acupoints used in the studies analysed above.

Following the guidelines proposed by the paper of Sun y Zhou,[133] the experience of the Chinese health authorities and, taking into account the published medical literature, we propose the following Acupuncture protocol as a synergistic and complementary treatment in COIVD-19. We would like to include, in Phase 0, a simple protocol for the prevention or strengthening of the immune system that could also be applied to health care professionals who are in the front line of servingCOVID- 19 patients with a high risk of becoming infected. We propose daily puncture with needle insertion time of 30 minutes.

Phase 0: period from inoculation to the development of first symptoms of disease. Everyone with potential, recognized and non-symptomatic epidemiological contact could be included. In this phase we could include uninfected health professionals, to strengthen their immune response globally.

Suggested acupoints: acupoints can be needled, leave continuous stimulation with press tack needles and/or use moxibustion. EA can also be used at low frequency (2-3Hz) if there is no medical contraindication:

I. ST36, CV4, CV6, CV12, LI11, GB20, BL13 y BL23: moxibustion can apply.

II. LU7, PC6, LI4: not recommended press tack needles on healthcare personnel, due to their need to continuously wash hands with soap and water or hydroalcoholic solution.

Phase I: period of early infection, asymptomatic or with mild symptoms: fever, cough, headache, myalgia and arthralgia.

Suggested acupoints: acupoints can be needled, continuous stimulation with press tacks, moxibustion is not recommended:

III. ST36, BL13, ST40 and GV14

IV. LU7+ KI6, TE5 + GB41, PC6 + SP4

V. LU5, GB34, LI4, CV12 and GB40

Prevalence of respiratory symptoms: cough and / or odynophagia.

VI. VB20 y VC17

Prevalence of digestive symptoms: abdominal pain, bloating, nauseas, vomiting, or diarrhoea.

VII. ST25, ST37 y SP9

Phase II: period with lung involvement (viral pneumonia), with clinical and radiological worsening.

Suggested acupoints: acupoints can be needled, continuous stimulation with presstack, moxibustion is not recommended.

VIII. ST36, BL13, ST40 y GV14

IX. LU7+ KI6, PC6 + SP4

X. LU5, LU11, SP1, GB34, LI4, CV12 and GB40

XI. CV17, GV20, ST25, LU11 and SP1

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IIa (without hypoxemia) add: TE5 + GB41

IIb (hypoxemia) add: LU10, LI11 y ST44

Phase III: period characterized by an excessive immune response, hyperinflammation (cytokine storm), with multi-system involvement including septic shock. Only recommended stimulation with needle. Do not use moxibustion. Acupuncture is contraindicated in hemodynamic instability.

Suggested acupoints: in this phase, some patients may be placed in a prone position to promote ventilation. The appropriate acupoints should be chosen depending on the position of the patient.

XII. ST36, BL13, ST40 and GV14

XIII. CV17, GV20 and ST25

XIV. CV4, CV6 and SP6

Phase IV: recovery.

Suggested acupoints: aimed at promoting the recovery of the patient during convalescence ST36 and BL13.

ST36 and BL13

KI3, BL17, BL20 and BL23

If the patient presents: nausea, bloating and loose stools**.**

CV4 and CV6: moxibustion can apply

If the patient presents: insomnia, night sweats, flushing, dry mouth, restlessness, dizziness, muscle weakness or oliguria.

SP6, KI10, LI3, LI8 y LU6

In all phases of active infection, it is recommended to add bilateral auriculotherapy by puncturing, with continuous stimulation (press tack needles), sedation and analgesic points such as *shenmen*, and points in the shell area related to vagus nerve stimulation. In the area of the *cymba* shell, the kidney and small intestine points, and in the area of the shell cavum, the lung and heart points.

Continuous stimulation points (press tack needles) should always be changed no later than 72 hours after puncturing under strict aseptic conditions, like all Acupuncture needles.

Acupuncture in children with COVID-19

In children, the infection is usually milder, but in some cases, it can be complicated and require hospital admission or even intensive care. In children under 7years of age, it is recommended to use press tack needles to stimulate the proposed acupoints described above, leaving them inserted up to 72hours, and following replacement. To improve tolerance to treatment, points can be placed unilaterally to try to reduce the number of points and increase tolerance to Acupuncture. IN collaborative children over 7 years old, it can be considered to use acupuncture needles and / or press tack needles.

Conclusions

The data and therapeutic protocols of COVID-19 are constantly evolving. The severity of the disease requires rapid interventions. It is a highly transmissible pandemic with a considerable mortality rate in some age groups, and its fatal evolution is related to an excessive immune response and a state of hyperinflammation. Acupuncture has known mechanisms of action extensively studies in the field of immunomodulation and anti-inflammatory effect in various clinical presentations, including sepsis.

The COVID-19 health emergency has put our health systems, our economy and our lifestyle in check. It has forced us to react urgently, applying empiricism of known drugs (such as hydroxychloroquine and azithromycin), of off-label drug trials or other non-patentable substances, such as vitamin C or B3. We are doomed to put aside strict clinical trials to try to save lives, with all the knowledge we have, within acceptable margin of safety and efficacy and a low risk/benefit ratio, in this scenario ofuncertainty.

Acupuncture is an old acquaintance, non-patentable, cheap medical procedure, very safe in expert hands and that in light of the reviewed publications, can offer a potential benefit that deserves to be evaluated in patients, designing a single center or multicenter study that combines efforts, from all possible medical approaches, to deal with COVID-19.

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Conflicts of interest

The authors are professionally engaged in Medical Acupuncture.

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Endnotes

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