

Tratamiento en Medicina Tradicional China de COVID-19

Investigación y Evidencia Científica,
Recopilación de Noticias y Guías

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INTRODUCCIÓN

Los datos epidemiológicos existentes indican que el COVID-19 es un brote altamente transmisible de coronavirus. Es probable que la batalla con COVID-19 continúe durante meses a nivel mundial. Por lo tanto, se necesitan más estrategias además de la contención y la mitigación para su llegada a cualquier zona, especialmente aquellos países con infraestructura de salud poco desarrollada, para acortar la estancia hospitalaria y reducir el consumo de recursos sanitarios (Organización Mundial de la Salud, 2020a).

En la actualidad, el COVID-19, al ser un virus recientemente identificado, tiene opciones de tratamiento farmacológico limitadas. La Medicina Tradicional China tiene un buen potencial para complementar las necesidades existentes, pudiendo ser una buena opción adicional considerando las opciones limitadas disponibles para COVID-19 (Chan et al, 2020). En China, la Medicina China se propone como una opción de tratamiento de alto uso según las directrices nacionales y provinciales. Se revisaron las últimas guías clínicas nacionales y provinciales, estudios de cohorte retrospectivos, series de casos sobre el tratamiento de COVID-19 con la Medicina China como tratamiento complementario, entre otros. Los datos disponibles sugieren que Medicina China podría considerarse como una opción terapéutica complementaria en el tratamiento de COVID-19. La estrategia debe enfocarse en ir al origen del problema para acortar la duración de la fiebre, aliviar los síntomas, prevenir la progresión de la enfermedad, reducir la mortalidad y ayudar a la recuperación. La evidencia actual indica que la MTC tiene un beneficio potencial en el alivio sintomático, acortando la duración de la fiebre, revertiendo los cambios radiológicos y acortando la estancia hospitalaria (Lu et al., 2020a; Xia et al., 2020; Yao et al., 2020).

Para el tratamiento del COVID-19 con MTC, la directriz nacional estableció varios periodos; el periodo de observación médica, el período de tratamiento (leve, intermedio, grave y crítico) y el periodo de recuperación. En cada periodo y fase se recomiendan fórmulas fitoterapéuticas de Medicina china y acupuntura. Las directrices provinciales se optimizaron en función de las directrices nacionales para la adaptación local, la mayoría involucraban medidas preventivas y de tratamiento de Medicina china (Chen et al., 2020b; Pang et al., 2020; Zheng et al., 2020).

La utilización de la Medicina china en la gestión del COVID-19 ha sido muy significativa en China (Gao et al., 2020). Los casos confirmados de COVID-19 en Shanghai comenzaron el tratamiento integral de Medicina China y la Medicina Occidental (Yuan et Qiu, 2020). En Guangdong, los gránulos de *Tou-jie-qu-wen* (neumonía n.º1) se evaluaron con una serie de casos y se recomendaron a 30 hospitales designados como el tratamiento estándar de los pacientes con COVID-19 (Administración de Productos Médicos de Guangdong, 2020). En general, más del 85% de los casos confirmados involucraron el uso de MTC a nivel nacional (Wuhan más del 67%) (Le y Liang, 2020; El Consejo de Estado, la República Popular de China, 2020b) y el primer Hospital Módulo designado orientado a MTC en Wuhan funcionó desde el 14 de febrero de 2020 (Wang y Li, 2020).

Son varios los estudios puestos en marcha, a partir del 22 de febrero de 2020, había tres cohortes retrospectivas (Lu et al., 2020a; Xia et al., 2020; Yao et al., 2020), cinco series de casos (Cheng y Li, 2020; Dai et al., 2020; Administración de Productos Médicos de Guangdong, 2020; Administración Nacional de Medicina Tradicional China, 2020b; Yong et al., 2020), y dos estudios de caso (Hu et al., 2020; Sun et al., 2020b) sobre la gestión integrada con Medicina China y Medicina Occidental del COVID -19.

A partir del 22 de febrero de 2020, se registraron 24 y 141 estudios de intervención relacionados con COVID-19 en ClinicalTrials.gov y Chinese Clinical Trial Registry, respectivamente, incluyendo la Medicina China. De los 53 ensayos clínicos relacionados con Medicina China, 27 ensayos evalúan los programas de Medicina China y tratamiento integrado.

La acupuntura y moxibustión juegan un papel activo en la prevención y el tratamiento de enfermedades infecciosas, habiendo participado activamente frente al COVID-19, en la prevención y el control, logrando buenos resultados, y estableciéndose las Directrices sobre Intervención de Acupuntura y Moxibustión para el COVID-19 (Guidelines on Acupuncture and Moxibustion Intervention for COVID-19 (second edition)).

En la lucha contra la pandemia de neumonía causada por la infección del COVID-19, el Hospital Provincial de Medicina Tradicional China de Hubei utilizó diligentemente las especialidades de la Medicina China, en cooperación con los departamentos pertinentes para estudiar y formular programas de prevención y tratamiento de la neumonía, estableciendo protocolos de acupuntura y moxibustión para la prevención y el tratamiento del coronavirus. Se puso de manifiesto que la fitoterapia china jugó un papel importante en los resultados positivos del tratamiento. Las fórmulas herbales chinas albergan el potencial único de reducir los síntomas de la fiebre y la tos, limitar la progresión de la enfermedad y mejorar la inmunidad general y, por lo tanto, la capacidad de una persona de generar una respuesta inmune esencial al virus, debiéndose integrar en un plan de tratamiento integral que utilice tanto la medicina occidental como la china para garantizar resultados óptimos para el paciente. Los resultados de la colaboración entre la medicina occidental y la china en Wuhan han sido muy prometedores (Chen et al., 2020).

Son varias las Guías publicadas en China sobre la MTC y el COVID19 y varias las noticias que resaltan los buenos resultados gracias a la integración de la Medicina China y la Medicina Occidental para hacer frente al COVID-19. Una de estas noticias más recientes expone las declaraciones de Yu Yanhong, portavoz del Ministerio de Sanidad Chino y también subdirector de la Administración Nacional de Tradicional Medicina china, indicando que el método puede mejorar rápidamente la condición de los pacientes con síntomas leves, como fiebre, tos, dolor de garganta, debilidad y falta de apetito, también puede ayudar a reducir la duración de la estancia en el hospital. Los expertos chinos señalan buenos resultados de la combinación de medicina china y occidental para el coronavirus y encuentran que la combinación puede ayudar a prevenir el desarrollo de síntomas leves en condiciones graves y críticas, lo que reduce la tasa de mortalidad de la enfermedad. Desde el brote de Covid-19, las autoridades centrales chinas han destacado en muchas ocasiones la aplicación de la medicina tradicional china combinada con la medicina occidental en el tratamiento de pacientes. Según la Administración Nacional de TMTC, los equipos de expertos médicos en 31 regiones a nivel provincial incluyen especialistas en MTC, y la mayoría de las regiones han realizado esquemas de tratamiento de TCM localizados para la enfermedad (<https://www.infosalus.com/>).

INVESTIGACIÓN Y EVIDENCIA CIENTÍFICA

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RECOPIACIÓN DE NOTICIAS

Muestra de algunas noticias publicadas en referencia al tratamiento de COVID-19 con medicina china ordenadas cronológicamente.

4/02/20

Coronavirus: Chinese researchers claim TCM herbal remedy could “inhibit” Coronavirus

https://www.bioworld.com/articles/432838-coronavirus-chinese-researchers-claim-tcm-herbal-remedy-could-inhibit-2019-ncov?fbclid=IwAR0IW7q4AFzG_ajK4_ArJ15mc568h8Td4MJXlcGpEfEDytJUNeliXAXwJ8Q

12/02/20

Así se trata en China el coronavirus

<https://www.saludnutricionbienestar.com/desvelado-asi-se-trata-en-china-el-coronavirus/>

14/02/20

Envían 2200 especialistas en medicina tradicional china a Hubei

<https://www.telesurtv.net/news/china-especialistas-medicina-tradicional-hubei-coronavirus-20200214-0027.html>

15/02/20

Wuhan abre primer hospital temporal orientado a medicina tradicional china para combatir coronavirus

http://spanish.xinhuanet.com/2020-02/15/c_138784751.htm

17/02/20

Medicina china podría combatir el coronavirus

<https://clustersalud.americaeconomia.com/insumos-y-servicios-hospitalarios/medicina-china-podria-combatir-el-coronavirus>

18/02/20

Titulares de Xinhua: La medicina tradicional china aporta sabiduría oriental a la lucha contra el coronavirus

http://spanish.xinhuanet.com/2020-02/18/c_138796063.htm?fbclid=IwAR08rgU5SkVg4oDD_u8-2imc0TI8N21K_E3PTiwTdxGO4r-u0FaXBP2ebAM

19/02/20

Expertos chinos señalan buenos resultados de la combinación de medicina china y occidental para el coronavirus

<https://www.infosalus.com/actualidad/noticia-expertos-senalan-buenos-resultados-combinacion-medicina-china-occidental-tratamiento-20200220124232.html>

20/02/20

TCM treatment effective against novel coronavirus, says official

<https://www.chinadaily.com.cn/a/202002/20/WS5e4e7afa31012821727915a.html?fbclid=IwAR2tXV9cfQPyhCav1rw11DddwaHZ9NBjYIjnMjR7UZRCnmDjUEpQls4BwQo>

Expertos chinos señalan buenos resultados de la combinación de medicina china y occidental para el coronavirus

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Integrated treatment of western and traditional Chinese medicine helped most COVID-19 patients recover: Report

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6 medicinas tradicionales chinas efectivas para tratar el COVID-19

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Cómo ha tratado con éxito el coronavirus COVID-19 en China y Wuhan con Medicina Tradicional China

<https://www.proyectomtc.com/tratamiento-coronavirus-covid-19-con-medicina-tradicional-china/?fbclid=IwAR1eGznS2tayW2EtNShZPY6jQM0wgZrH6DYCafxb2IU2pOQDQX6hhuwoEck>

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Expertos chinos señalan buenos resultados de la combinación de medicina china y occidental para el coronavirus

https://www.infosalus.com/actualidad/noticia-expertos-senalan-buenos-resultados-combinacion-medicina-china-occidental-tratamiento-20200220124232.html?fbclid=IwAR0AjbCOKn5TBCPHRKYQwEkiQKDDF0kH_0H7AjpAxwPqe9yX7Ume4mv-t-g

GUÍAS

ESTADOS UNIDOS

- [Cómo se trata actualmente COVID-19 en China con MTC](#) (Lotus Institute of Integrative Medicine)
- [Traditional Chinese Medicine \(TCM\) in the Prevention and Treatment of COVID-19 \(2019-nCoV\) & Integration of TCM into Educational Curriculum](#) (Lotus Institute of Integrative Medicine)

R.P.CHINA

- [Diagnosis y tratamiento de la neumonía por el nuevo coronavirus en medicina china](#) (Universidad de Medicina China de Tianjin)
- [Guía de prevención y tratamiento de Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar](#) (Neumonía por Corona-virus) Universidad de Medicina de Tianjin
- [Guidance for CoronaVirus Disease 2019. Prevention, Control, Diagnosis and Management](#) (People's Medical Publishing House)
- [Guidelines on Acupuncture and Moxibustion Intervention for COVID-19](#) (WFAS)
- [COVID-19 Diagnosis and Treatment Plan - tentative 7th edition. \(Hubei Provincial Hospital of TCM\)](#)
- Manual para la prevención y el control de la infección nosocomial en la neumonía por nuevo coronavirus. Primer Hospital Afiliado de la Universidad de Nanchang y Chemical Industry Press (<https://www.yourtcm.sg/>)

ESPAÑA

- [Comprendiendo la amenaza global del Coronavirus COVID-19](#) (Dr. Nuria Lorite)

Anexo I: ARTÍCULOS INVESTIGACIÓN Y EVIDENCIA CIENTÍFICA (COMPLETOS O ABSTRACTS)

1. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. Am J Chin Med [Internet]. 2020;48(3):1–26. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32164424>

COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease

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The University of Hong Kong, Hong Kong Published 13 March 2020

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Institute for Advanced Research in Asian Science and Medicine DOI: 10.1142/S0192415X20500378

Abstract: As of 22 February 2020, more than 77662 cases of confirmed COVID-19 have been documented globally with over 2360 deaths. Common presentations of confirmed cases include fever, fatigue, dry cough, upper airway congestion, sputum production, shortness of breath, myalgia/arthritis with lymphopenia, prolonged prothrombin time, elevated C-reactive protein, and elevated lactate dehydrogenase. The reported severe/critical case ratio is approximately 7–10% and median time to intensive care admission is 9.5–10.5 days with mortality of around 1–2% varied geographically. Similar to outbreaks of other newly identified virus, there is no proven regimen from conventional medicine and most reports managed the patients with lopinavir/ritonavir, ribavirin, beta-interferon, glucocorticoid and supportive treatment with remdesivir undergoing clinical trial. In China, Chinese medicine is proposed as a treatment option by national and provincial guidelines with substantial utilization. We reviewed the latest national and provincial clinical guidelines, retrospective cohort studies, and case series regarding the treatment of COVID-19 by add-on Chinese medicine. We have also reviewed the clinical evidence generated from SARS and H1N1 management with hypothesized mechanisms and latest in silico findings to identify candidate Chinese medicines for the consideration of possible trials and management. Given the paucity of strongly evidence-based regimens, the available data suggest that Chinese medicine could be considered as an adjunctive therapeutic option in the management of COVID-19.

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3. Chen JK, Pharm D, Hsu L, Norris EM, Ac L, Nash-galpern D, et al. Novel_Corona_Virus_-_Tcm_Treatment_From_the_Pprc. 2020;19.

How COVID-19 (2019-nCoV) is Currently Treated in China with TCM

Compiled, Translated by John Chen, Pharm.D., Ph.D., OMD., L.Ac., Lori Hsu, MTOM, MS

Edited by Michael Norris, L.Ac., C.H., Debra Nash-Galpern, Donna Chow, L.Ac., DiplOM

Published on February 19, 2020

Disclaimer: This article is compiled, translated and edited by John K. Chen and Lori Hsu from three references to inform the readers how COVID-19, the 2019 novel coronavirus, is currently treated in China. For readers who may have such an infection, contact and consult your primary physician, go to the hospital or the CDC immediately. For additional information, please contact the World Health Organization (WHO), the Center of Disease Control (CDC) and the Food and Drug Administration (FDA).

With Wuhan on Lockdown for More Than 10 days, the Chinese Government Announces a Major Change in Strategy: All Patients with Confirmed Infections are to Use Chinese medicine. 2/10/2020

The Medical Treatment Unit of Wuhan's [Novel Coronavirus \(2019-nCoV\)](#), currently named COVID-19, Prevention and Control Headquarters issued a "Notice Regarding the Agreement to Recommend the Use of Chinese Medicine in the Treatment of Pneumonia due to Infection from the Novel Coronavirus". The "Notice" emphasizes that all designated medical institutions in Wuhan will ensure that all infected patients take Chinese medicine (Chinese medicine decoction or granules) before midnight (24:00) on February 3, 2020.

A collaboration between Western and Chinese medicine is undoubtedly welcoming news, especially now as the results from the front lines in Wuhan have been very promising. See below for more.

1/29/20 The second dispatch of support from the central government to the Hubei Chinese Medicine Treatment team took over the newly created isolation ward for pneumonia patients infected by the 2019-nCoV in the Hubei Provincial Hospital of Integrated Traditional Chinese and Western Medicine. It is the only medical facility in the Hubei Province that is managed entirely under the supervision of the China's Traditional Chinese Medicine (TCM), TCM system, providing a central point responsible for determining diagnosis and treatment.

The following is reported in the patient wards under the responsibility of Guandong Provincial TCM Hospital: Patient Rounds: The severity of patient conditions was unexpected, and the entire ward was more or less quiet as these patients were so weak, that it seemed that they did not even have the energy to moan. Most of the patients treated were urgently, critically, or severely ill. Many of them had a high fever, a thick tongue coating, slippery and wiry pulses, bowel incontinence, and little to no expression on their faces (perhaps from extreme fatigue?).

1/30/20 Herbal formulas were administered to patients according to the individual's TCM pattern diagnoses, as prescribed by Guandong's experts.

2/1/20 Patient Rounds: Some patients' fever have been reduced. There were more patients with low-grade fever. By and large, tongue coatings changed from thick and greasy to thin, and patient stools were more formed. Furthermore, these patients now had the energy to speak for up to five sentences before the onset of mild wheezing. Also, in general, coughing was significantly less compared to before. Patients' self-reports of conditions have improved quite a bit. Patients can now sit up and practice the qigong exercise, Eight Brocade in bed and/or meditate.

As of 2/4/20: Nearly fifty patients in the ward have clearly improved. The effectiveness of Chinese herbal treatments are being actively observed and witnessed in this clinical setting.

Caption: For the first time, eight patients treated with traditional Chinese medicine or a combination of traditional Chinese and western medicine were discharged from hospital.

1/28/20, Dr. Huang Luqi, the chair of the Chinese Academy of Chinese Medical Sciences, led the medical team of Guang'anmen Hospital and Beijing Xiyuan Hospital of the Chinese Academy of Chinese Medical Sciences to support Wuhan Jinyintan Hospital. Chinese medicine combined with Western medicine, treatment by syndrome differentiation, greatly improved the patients' breathing issues, fatigue, dry mouth, bitterness, chest tightness, diarrhea and other symptoms.

2/3/20, Eight confirmed patients were discharged from the first ward of the South Building of Wuhan Jinyintan Hospital. This represents the first group of patients who were discharged from a hospital using traditional Chinese medicine or a combination of traditional Chinese medicine and Western medicine. Amongst them, six were female, two were male. Of these, six were severe and two were mild cases. The age range of the patients was from twenty-six to sixty-eight. After treatment with traditional Chinese medicine and herbs, most patients had obviously improved symptoms and an overall improved mental state. At the time of discharge, each patient was sent home with a two-week dose of Chinese herbs along with instructions on appropriate exercise and proper diet in order to gain full recovery.

Please share this article and the herbal prescriptions with everyone.

In the fight against the pandemic of pneumonia from 2019-nCoV Novel Coronavirus infection, Hubei Provincial Hospital of Traditional Chinese Medicine diligently used the specialties of TCM, in cooperation with relevant departments to study and formulate pneumonia prevention and treatment programs revealing that Chinese herbs played a definitive role in positive treatment outcomes. Chinese herbal formulas harbor the unique potential to reduce fever and cough symptoms, limit disease progression, and improve overall immunity, and thus a person's ability to mount an essential immune response to the virus.

The following are the recommended formulas, acupuncture and moxibustion protocols for prevention and treatment of Coronavirus according to TCM experts. Please note, the following formulas are not to be used in place of Western medicine rather they are to be integrated into a comprehensive treatment plan utilizing both Western and Chinese medicine to ensure optimal patient outcomes. Furthermore, patients are advised not to self treat or use the formulas blindly, but rather to consult with licensed medical practitioners to ensure optimal treatment on a case by case basis.

Prevention Phase: 预防期

Formula: Pneumonia Prevention #1肺炎预防1号

- Huang Qi 黄芪 (Radix Astragali) 15g,
- Bai Zhu 炒白术 (Rhizoma Atractylodis Macrocephalae), dry fried 10g
- Fang Feng 防风 (Radix Saposhnikovia) 10g
- Mian Ma Guan Zhong 贯众 (Rhizoma Dryopteridis Crassirhizomatis) 10g
- Jin Yin Hua 金银花 (Flos Lonicerae Japonicae) 10g
- Chen Pi 陈皮 (Pericarpium Citri Reticulatae) 6g
- Pei Lan 佩兰 (Herba
- Cases Eupatorii) 10g

Suitable for: Prevention of pneumonia due to viral infections, and the flu.

Acupuncture Treatment for Suspected:

The purpose is to strengthen the immune system, to help alleviate early symptoms, and to shorten the duration of the virus.

Points: Bilateral Zusanli (ST 36), Qihai (CV 6), Zhongwan (CV 12)

Method and Frequency:

Moxa Zusanli (ST 36) on both sides for 15 minutes. Moxa Qihai (CV 6) or Zhongwan (CV 12) for 10 minutes. (alternating from treatment to treatment).

Twice a day, once in the afternoon and once at night.

Influenza Phase: 流感期

Diagnosis: Wind-Cold Invading the Exterior 风寒袭表证

Clinical Manifestations: Onset of fever (mostly low-grade fever), aversion to cold and fear of cold, chills, headache, ticklish throat, soreness of muscles of limbs, no sweat or night sweats.

Examination: Lung CT negative. Tongue is pale, coating is white and thin. Floating pulse

Treatment Strategy: Expel Wind, Release the Exterior; Clear Heat, Detoxify

Herbal Formula: 葛根汤或柴葛解肌汤 (Ge Gen Tang (Kudzu Decoction) or Chai Ge Jie Ji Tang (Bupleurum and Kudzu Decoction to Release the Muscle Layer))

Flu Formula #1流感1号

- Ge Gen 葛根 (Radix Puerariae Lobatae) 15g
- Ma Huang 麻黄 (Herba Ephedrae) 10g
- Gui Zhi 桂枝 (Ramulus Cinnamomi) 6g
- Bai Shao 白芍 (Radix Paeoniae Alba) 15g
- Sheng Jiang 生姜 (Rhizoma Zingiberis Recens) 10g
- Gan Cao 生甘草 (Radix et Rhizoma Glycyrrhizae) 10g
- Da Zao 大枣 (Fructus Jujubae) 10g
- Jin Yin Hua 金银花 (Flos Lonicerae Japonicae) 20g

with headache, add Bai Zhi 白芷 (Radix Angelicae Dahuricae) 15g

with dry or ticklish throat, add She Gan 射干 (Rhizoma Belamcandae) 15g

Other possible formulas to consider: Huo Xiang Zheng Qi San

Diagnosis: Toxic Heat Attacking the Lung 热毒袭肺证

Clinical Manifestations: Fever, aversion to cold, sore and dry throat, dry cough, scanty sputum, sore and painful muscles in the limbs, weakness, headache

Examination: CT scan reveals both lungs to have scattered ground-glass opacity (GGO). Tip and sides of the tongue are red; thin white or yellow tongue coating. Floating and rapid pulse.

Treatment Strategy: Expel Wind, Release the Exterior; Clear Heat, Detoxify

Herbal Formula: 银翘散加清瘟败毒散加减 (Yin Qiao San (Honeysuckle and Forsythia Powder) and Qing Wen Bai Du San (Clear Epidemics and Overcome Pathogenic Influences Powder), modified)
Flu Formula #2 流感2号

- Jin Yin Hua 金银花 (Flos Lonicerae Japonicae) 10g
- Lian Qiao 连翘 (Fructus Forsythiae) 10g
- Jing Jie 荆芥 (Herba Schizonepetae) 10g
- Niu Bang Zi 牛蒡子 (Fructus Arctii) 10g
- Bo He 薄荷 (Herba Menthae) 10g
- Gan Cao 生甘草 (Radix et Rhizoma Glycyrrhizae) 10g
- Dan Zhu Ye 淡竹叶 (Herba Lophatheri) 10g
- Lu Gen 芦根 (Rhizoma Phragmitis) 15g
- Huang Lian 黄连 (Rhizoma Coptidis) 6g

Diagnosis: Damp Cold in the Lung 湿寒鬱肺

Clinical Manifestations: Aversion to cold, fever or absence of fever, dry cough, dry throat, fatigue, weakness, chest stuffiness, epigastric distention, nausea, diarrhea. Pale tongue, white greasy coating, slippery pulse.

Treatment Strategy: Expel Wind, Release the Exterior; Dispel Damp Cold

Herbal Formula:

Damp Cold Formula #1

- Cang Zhu 苍朮 (Rhizoma Atractylodis) 15g
- Chen Pi 陈皮 (Pericarpium Citri Reticulatae) 10g
- Hou Po 厚朴 (Cortex Magnoliae Officinalis) 10g
- Huo Xiang 藿香 (Herba Pogostemonis seu Agastaches) 10g
- Cao Guo 草果 (Fructus Tsaoko) 6g
- Ma Huang 生麻黄 (Herba Ephedrae) 6g
- Qiang Huo 羌活 (Rhizoma et Radix Notopterygii) 10g
- Sheng Jiang 生薑 (Rhizoma Zingiberis Recens) 10g
- Bing Lang 檳榔 (Semen Arecae) 10g

Acupuncture Treatment for Mild and Moderate Cases:

The purpose is to reduce the severity of symptoms, shorten the duration, and alleviate emotional burden.

Points: Bilateral Hegu (LI 4), Taichong (LR 3), Zusanli (ST 36), Shenque (CV 8)

Method and Frequency:

Moxa Hegu (LI 4) and Taichong (LR 3) bilaterally for 15 minutes. Moxa Zusanli (ST 36) bilaterally for 10 minutes. Moxa Shenque (CV 8) with a moxa box for 15 minutes.

Twice a day, once in the morning and once in the afternoon.

Pneumonia Phase: 肺炎期

Diagnosis: Shaoyang Syndrome with Damp 少阳夹湿证

Clinical Manifestations: Fever, which is more pronounced in the afternoon, alternating chills with fever, cough, absence of wheezing, bitter taste in the mouth, dry mouth, chest stuffiness, stifling sensation, chest and hypochondriac fullness and distention, irritability, nausea or vomiting, no appetite, weakness. Similar to the beginning stage of pneumonia.

Examination: CT scan reveals both lungs to have multiple scattered or large pieces of ground-glass opacity (GGO). Slightly red tongue, thick and greasy, white or yellow coating, slippery, rapid pulse.

Treatment Strategy: Harmonize Shaoyang Syndrome, Clear Damp-Heat

Herbal Formula: 小柴胡汤合三仁汤或甘露消毒丹 (Xiao Chai Hu Tang (Minor Bupleurum Decoction) with San Ren Tang (Three-Nut Decoction) or Gan Lu Xiao Du Dan (Sweet Dew Special Pill to Eliminate Toxins))

Pneumonia Formula #1 肺炎1号

- Chai Hu 柴胡 (Radix Bupleuri) 24g
- Huang Qin 黄芩 (Radix Scutellariae) 9g
- Sheng Jiang 生姜 (Rhizoma Zingiberis Recens) 10g
- Fa Ban Xia 法夏 (Rhizoma Pinelliae) 12g
- Ku Xing Ren 杏仁 (Semen Armeniacae Amarum) 15g
- Bai Dou Kou 白豆蔻 (Fructus Amomi Rotundus) 10g
- Yi Yi Ren 薏苡仁 (Semen Coicis) 30g
- Dan Zhu Ye 竹叶 (Herba Lophatheri) 15g
- Hua Shi 滑石 (Talcum) 15g
- Tu Fu Ling 土茯苓 (Rhizoma Smilacis Glabrae) 30g
- Gan Cao 生甘草 (Radix et Rhizoma Glycyrrhizae) 10g

Diagnosis: Damp Heat Afflicting the Lung 湿热郁肺证

Clinical Manifestations: Low-grade fever or absence of fever, dry cough, scanty sputum, dry and sore throat, fatigue, weakness, poor appetite, chest stuffiness, epigastric distention, nausea or vomiting, loose stool.

Examination: CT scan reveals both lungs to have multiple scattered or large pieces of ground-glass opacity (GGO). Pale or pink, puffy tongue with teeth marks. White or greasy white coating. Soft or slippery pulse.

Treatment Strategy: Transform Dampness, Detoxify; Disperse the Lungs and Expel Pathogens

Herbal Formula: 麻杏薏甘汤、小陷胸汤、草果知母汤 (Ma Xing Yi Gan Tang (Ephedra, Apricot Kernel, Coicis, and Licorice Decoction), Xiao Xian Xiong Tang (Minor Sinking into the Chest Decoction) and Cao Guo Zhi Mu Tang (Tsaoko and Anemarrhena Decoction))

Pneumonia Formula #2 肺炎2号

- Ma Huang 麻黄 (Herba Ephedrae) 10g
- Ku Xing Ren 杏仁 (Semen Armeniacae Amarum) 10g
- Yi Yi Ren 薏苡仁 (Semen Coicis) 30g
- Huang Lian 黄连 (Rhizoma Coptidis) 6g
- Fa Ban Xia 法夏 (Rhizoma Pinelliae) 10g
- Gua Lou Pi 瓜蒌皮 (Pericarpium Trichosanthis) 10g
- Cao Guo 草果 (Fructus Tsaoko) 10g
- Zhi Mu 知母 (Rhizoma Anemarrhenae) 10g
- Yu Xing Cao 鱼腥草 (Herba Houttuyniae) 15g
- Gan Cao 生甘草 (Radix et Rhizoma Glycyrrhizae) 10g
- Bai Dou Kou 白豆蔻 (Fructus Amomi Rotundus) 9g

Diagnosis: Toxic Stagnation Obstructing the Lung 毒瘀壅肺证

Clinical Manifestations: Cough, stifling sensation, stuffiness and distention in the chest, asthma and wheezing that worsens with exertion, accelerated respiration, thirst, irritability, reddish yellow urine.

Examination: CT scan reveals both lungs to have multiple scattered or large pieces of ground-glass opacity (GGO). Fibrotic changes of the lung are also visible. Dark purplish tongue, yellow dry tongue coating or thick and greasy yellow coating, rapid, slippery pulse.

Treatment Strategy: Detoxify, Arrest Wheezing; Transform Blood Stasis and Open Collaterals

Herbal Formula: 白虎汤加入参汤合四土汤 (Bai Hu Jia Ren Shen Tang (White Tiger plus Ginseng Decoction) with Si Tu Tang (Four Wild Decoction))

Pneumonia Formula #3 肺炎3号

- Shi Gao 石膏 (Gypsum Fibrosum) 30g
- Zhi Mu 知母 (Rhizoma Anemarrhenae) 10g
- Shan Yao 山药 (Rhizoma Dioscoreae) 15g
- Xi Yang Shen 西洋参 (Radix Panacis Quinquefolii) 5g
- Tu Fu Ling 土茯苓 (Rhizoma Smilacis Glabrae) 30g
- Tu Da Huang 土大黄 (Radix Rumicis Obtusifolii) 10g
- Tu Bei Mu 土贝母 (Rhizoma Bolbostemmatis) 10g
- Tu Niu Xi 土牛膝 (Rhizoma Achyranthes Sylvestris) 10g
- Su Mu 苏木 (Lignum Sappan) 10g
- Tu Bie Chong 土鳖 (Eupolyphaga seu Steleophaga) 10g
- Ju Luo 橘络 (Vascular Citri Reticulatae) 15g
- Lai Fu Zi 莱菔子 (Semen Raphani) 20g
- Ting Li Zi 葶苈子 (Semen Descurainiae seu Lepidii) 15g
- Si Gua Luo 丝瓜络 (Retinervus Luffae Fructus) 30g

Diagnosis: Closed Interior and Abandoned Exterior Syndrome 内闭外脱证

Clinical Manifestations: Mental incoherence, irritability, burning or heat sensation in the chest and abdomen, cold extremities, accelerated respiration and need for assisted breathing, scarlet purple tongue, dry yellow or yellowish brown coating, floating, forceful pulse that is empty in the deep level, or rootless.

Treatment Strategy: Open the Closed, Consolidate the Abandoned, Detoxify, Rescue Reversal

Herbal Formula: 四逆加入参汤、送服 安宫牛黄丸、紫雪散 (Si Ni Jia Ren Shen Tang (Frigid Extremities Decoction plus Ginseng), taken with An Gong Niu Huang Wan (Calm the Palace Pill with Cattle Gallstone) and Zi Xue San (Purple Snow Powder))

Pneumonia Formula #4 肺炎4号

- Ren Shen 人参 (Radix et Rhizoma Ginseng) 10g
- Fu Zi 制附子 (Radix Aconiti Lateralis Praeparata) 10g
- Serve with An Gong Niu Huang Wan (Calm the Palace Pill with Cattle Gallstone) and Zi Xue San (Purple Snow Powder).

Recovery Phase: 恢复期

Clinical Manifestations: Absence of fever, dry cough, chest stuffiness, shortness of breath, shortness of breath upon exertion, dry mouth, weakness.

Examination: CT reveals inflammation begins to subside as well as pulmonary interstitial changes. Pale red tongue, thick or greasy coating, thread, rapid pulse.

Treatment Strategy: Tonify Qi, Nourish Yin, Tonify Lung and Open the Collaterals

Herbal Formula: 沙参麦冬汤 (Sha Shen Mai Dong Tang (Glehnia and Ophiopogonis Decoction))

Pneumonia Formula #5 肺炎5号

- Sha Shen 沙参 (Radix Glehniae seu Adenophorae) 15g
- Mai Dong 麦冬 (Radix Ophiopogonis) 15g
- Wu Wei Zi 五味子 (Fructus Schisandrae Chinensis) 15g
- Ren Shen 人参 (Radix et Rhizoma Ginseng) 12g
- Lai Fu Zi 莱菔子 (Semen Raphani) 15g
- Si Gua Luo 丝瓜络 (Retinervus Luffae Fructus) 15g
- Ju Luo 橘络 (Vascular Citri Reticulatae) 15g
- Zi Su Zi 苏子 (Fructus Perillae) 12g
- Zhe Bei Mu 浙贝 (Bulbus Fritillariae Thunbergii) 12g
- Ku Xing Ren 杏仁 (Semen Armeniacae Amarum) 12g
- Huang Qin 黄芩 (Radix Scutellariae) 15g
- Gan Cao 生甘草 (Radix et Rhizoma Glycyrrhizae) 10g

Acupuncture Treatment for The Recovery Phase:

The Purpose is restore Lung and Spleen functions and the body's zheng (upright) qi.

Points: Bilateral Dazhui (GV 14), Geshu (BL 17), Feishu (BL 13), Zusanli (ST 36) or Kongzui (LU 6).

Method and Frequency:

Moxa all points for 15 minutes.

Once a day.

History and experience prove that Traditional Chinese Medicine is effective against epidemic diseases.

From the Western Han Dynasty to the end of the Qing Dynasty, at least 321 large-scale plagues occurred in China. Chinese medicine has served to wage life-and-death battles against various plague consistently through time and has successfully contained the spread of epidemics in a limited area and time. There has never been a similar tragedy in China's history, such as the Spanish flu or the Black Death in Europe. These are examples of global plagues that killed tens of millions of people.

In the Chinese history, whenever a plague is rampant, Chinese medicine practitioners are always on the front lines to battle the disease. Many survived with the help of Chinese Medicine; so in this fight with the insidious and novel Coronavirus, Chinese Medicine once again should take a primary role in effective treatment and must not be absent in action!

Reference 1: <https://mp.weixin.qq.com/s/qzSecLwVXQIfBTQyHQxHQ>

Reference 2: https://mp.weixin.qq.com/s/YaiZ_fycSKEoTBvzhOv5Wg

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[ABSTRACT] The novel coronavirus pneumonia broke out in 2019 and spread rapidly. In 30 different countries, there are over seventy thousand patients have been diagnosed in total. Therefore, it is urgent to develop the

effective program to prevent and treat for the novel coronavirus pneumonia. In view of Traditional Chinese Medicine has accumulated a solid theoretical foundation of plague in ancient and recent decades. Meanwhile, Traditional Chinese Medicine can provide the more effective and personalized treatment via adjusting the specific medicine for each patient based on the different syndromes. In addition, TCM often has different effect on the distinct stages of diseases, contributing to the prevention, treatment and rehabilitation. Nowadays, TCM has exhibited decent effect in the in the fight against NCP. Therefore, it is convinced that Traditional Chinese Medicine is an effective treatment for 2019 novel coronavirus pneumonia.

Introduction

In December 2019, an unknown virus pneumonia broke out in Wuhan China. Later the unknown virus was identified as a novel coronavirus (2019-nCoV) and the unknown pneumonia named as novel coronavirus pneumonia (NCP) by Chinese government and scientists [1]. In early February 2020, over sixty thousand patients have been diagnosed with NCP in 30 different countries all over the world only after 1 month. And 99% of the cases have occurred in China. On account of the NCP reported worldwide for the first time, there is no specific vaccine and drug. Unfortunately, the development of novel vaccine or specific drug will take a few months, cannot keeping up with the development of NCP. Therefore, it is urgent to develop the effective treatment for NCP. Though it is no time to discovery effective drugs, the therapeutic effect of NCP is still remarkable in hospitals. Partly, this is owing to that Traditional Chinese Medicine (TCM) is applied in clinic timely as shown in Fig. 1 [2]. After National Health Commission (NHC) of China announcing the emergency situation in 20 January 2020, the National Administration of Traditional Chinese Medicine (NATCM) rapidly deployed the work, and the first batch of Chinese medicine experts arrived in Wuhan city on the day. In 29 January, National TCM Rescue Team took over Wuhan Jinyintan Hospital. Five days later, eight patients were discharged after treatment with Chinese medicine, of which six were critically ill. Similarly, the first patient diagnosed with NCP in Beijing was discharged after a combination of Chinese and Western treatment. According to the NATCM, the total effective rate of certain TCM prescription for NCP is over 90% [3]. Obviously, TCM have been playing a significant role in the combat with NCP.

In fact, TCM played a unique role in the prevention and treatment of emerging infectious diseases since ancient time. For instance, TCM obtained decent clinical effect on SARS (severe acute respiratory syndrome), H7N9 (H7N9 avian influenza) and EVD (Ebola Virus Disease) at one time [4-6]. In these two thousand years, TCM has laid a solid theoretical foundation in the prevention and treatment of infectious diseases via the fight against diseases. Furthermore, doctors often adjust the specific treatment for each patient or integrate with western medicine scheme after diagnosing the syndrome through comprehensive analysis of symptoms and signs. Up to now, TCM has made a big difference in fight against NCP.

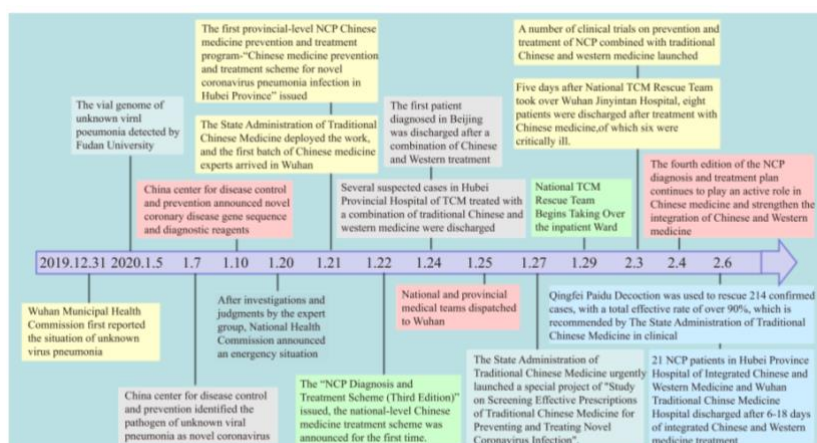


Fig. 1 The actions and treatment of TCM on NCP in China

The theoretical foundation of TCM for NCP Though NCP is a novel infectious disease, the similar syndrome infected by coronavirus are not unfamiliar. Firstly, the history of TCM applied for plague has lasted for over two thousand years [7](Table. 1). And abundant theories of TCM for explosive infectious disease have formed, which have survived as treatises up to now. Meanwhile, TCM also play a significant role in the treatment of these coronavirus pneumonias broke out in the last two decades, such as SARS, MERS and H7N9 avian influenza [4-6]. Obviously, TCM has accumulated a solid theoretical foundation of plague and will be an effective treatment for NCP.

Table 1 The representative theories of TCM for infectious diseases

No.	Date	Book Name	Related theories of TCM for infectious diseases
1	BC 1046 Zhou Dynasty	<i>Zhou Yi</i>	The concept of "Yi Bing" was proposed. It thought that "Yi Bing" was different from common cold. "Yi Bing" was the disease which has infectivity and easily led to epidemic.
2	AD 219 Han Dynasty	<i>Shang Han Lun</i>	The dialectical relationship and treatment theory of exopathogenic disease ("Shang Han") were elaborated. Especially, decades of specific Chinese herbal formulae were specifically treated different phenotypes of Shang Han.
3	AD 341 Tsin Dynasty	<i>Zhou Hou Bei Ji Fang</i>	<i>Zhou Hou Bei Ji Fang</i> was the first literature of emergency treatment. There were plentiful well proved clinical recipes for emergency including Wen Yi, Shang Han, pestilence and so on.
4	AD 652 Tang Dynasty	<i>Qian Jin Yao Fang</i>	In <i>Qian Jin Yao Fang</i> , there were many discussions on the theory and methods of prevention and treatment of infectious diseases. It also described the prescription drugs in detail.
5	AD 1642 Ming Dynasty	<i>Wen Yi Lun</i>	<i>Wen Yi Lun</i> was the first medical book about systematic study of acute infectious disease in the world. It described the etiology, pathogenesis, syndrome and treatment of plague. "Da Yuan Yin" was the classical prescription for plague.
6	AD 1794 Qing Dynasty	<i>Yi Zhen Yi De</i>	This book dealt with the causes of the plague, the main points of diagnosis and treatment, and the discrimination of common symptoms. The representative prescription "Qin Wen Bai Du Yin" was well recognized.

The theories of TCM for infectious diseases NCP is infected by the novel coronavirus, but similar infectious diseases are not unacquainted for doctors of TCM. TCM has accumulated a wealth of experience and a lot of prescriptions, laying a solid theoretical foundation (Table 1). Two thousand years ago (BC 1046), the concept of "Yi Bing" was proposed. It pointed out that "Yi Bing" was different from common cold. "Yi Bing" was the disease which has in western medicine among of 112 cases, not including 7 deaths from severe heart and brain and other basic diseases [9]. In 2013, H7N9 avian influenza also broke out in China. Then NHC of PRC issued the diagnosis and treatment scheme. In Beijing, the first case was also cured additionally by TCM [10].

Similarly, the Chinese Government also issued the diagnosis and treatment scheme of TCM for MERS in 2015 [11]. Thus it can be seen that TCM have long history of treatments for coronavirus pneumonia. It is believed that TCM also can be treated for NCP effectively.

The effect of TCM on NCP In the early stages of the outbreak, there is neither standard of western medicine treatment nor targeted drugs owing to the unknown of NCP. However, in these TCM hospital or Integrated Chinese and Western Medicine Hospital, TCM has been widely used for the treatment of NCP (Fig. 1). Importantly, the effect of TCM on NCP is prominent. As shown in Fig. 2, "Qing Fei Pai Du Tang" (QFPDT) is screened out by the National Administration of Traditional Chinese Medicine (NATCM) and widely recommended nationwide [3].

turning negative. In the recovery, continued TCM treatments will reinforce the healthy qi and eliminate the pathogenic factors. Obviously, TCM improves the patient's symptoms and promotes the complete repair of damaged organs and tissues. Therefore, convalescent patients often continue to take TCM after the nucleic acid detection turning negative.

Table 2 The representative clinical trials of TCM for NCP

No	Registration number	Scientific title	Date of Registration
1	ChiCTR2000029637	An observational study for Xin-Guan-1 formula in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-08
2	ChiCTR2000029628	Observational study of Xin-Guan-2 formula in the treatment of suspected 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-07
3	ChiCTR2000029605	A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-07
4	ChiCTR2000029589	An open, prospective, multicenter clinical study for the efficacy and safety of Reduning injection in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-05
5	ChiCTR2000029487	Clinical Study for Gu-Biao Jie-Du-Ling in Preventing of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in Children	2020-02-02
6	ChiCTR2000029434	A randomized, open-label, blank controlled trial for Lian-Hua Qing-Wen Capsule/Granule in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-01
7	ChiCTR2000029432	A Real World Study For the Efficacy and Safety of Large Dose Tanreqing Injection in the Treatment of Patients with 2019nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP)	2020-02-01

Conclusion

The cure rate of NCP is increasing from 2% in the early days to over 20% in these days. And in partial provinces, the cure rate has exceeded 40% [18]. The application of TCM timely and widely is one of these positive actions in the fight against this outbreak. In view of the excellent performance of TCM at present, increasing number of patients are being treated with TCM additionally. As reported [19], about 88% patients with NCP have been receiving the treatment integrated with TCM. Firstly, TCM has accumulated a wealth of experience of prevention and treatment of emerging infectious diseases in ancient time and recent decades. Then TCM still will adjust the specific medicine for each patient after diagnosing the syndrome, providing the more effective and personalized treatment. In addition, TCM will reduce adverse reactions of western medicine (such as antiviral, anti-bacterial drugs and hormones.) via avoiding or decreasing the use of these drugs in clinic. Therefore, TCM has special advantage in the combat with NCP. However, there are several deficiencies in the development of TCM. As shown in Fig. 1, the national medical team of TCM dispatched to Wuhan timely, but they began to take over the inpatient ward several days later. Because there are no TCM related departments or sufficient Chinese medicine in infectious hospital and western medicine hospital. Obviously, the participation rate of TCM in these hospitals is very low. Secondly, the total number of medical staff of TCM is seriously inadequate in China. Such as this rescue, the medical staff of TCM accounted for less than 20% in the whole dispatched medical staffs from state and province. Moreover, the effect of TCM is not accepted constantly, owing to lack of modern scientific support. Nevertheless, there dozens of TCM for NCP are conducting clinical trials at present, certain specific Chinese medicines are also incorporated (Tabel. 2). As reported [20-22], several Chinese medicines have exhibited favourable effect. In a word, the development of TCM still has long way to go. On all accounts, TCM has accumulated a solid theoretical foundation of plague. In the fight against infectious diseases broke in recent decades, TCM has played an important role in the prevention and treatment. At present, TCM also has been effectively salvaging the patient with NCP. Therefore, TCM is and will be an effective treatment for NCP.

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Traditional Chinese medicine for treatment of coronavirus disease 2019: a review

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Highlights

Coronavirus disease 2019 (COVID-19) has recently become a public health concern worldwide. The use of traditional Chinese medicine (TCM) may have substantial impact on COVID-19. In this review, we summarize the disease pathogenesis, clinical outcomes, and current applications of TCM for the treatment of COVID-19.

Traditionality

The pathogenesis and clinical symptoms related to severe respiratory disease were described many years ago in TCM texts. The ancient book of TCM *Huang Di Nei Jing (Inner Canon of Huangdi)* was written during the Western Han Dynasty of China (dated approximately 99 B.C.E.-26 B.C.E.); the text recorded a plague that could transmit disease from human-to-human with symptoms that were similar to those described for COVID-19. Three additional texts, notably *Shang Han Za Bing Lun (Treatise on Cold Damage Diseases)* written by Zhang Zhongjing (200 C.E.-210 C.E.), *Wen Yi Lun (Theory of Plague)* and *Wen Re Lun (Translated Theory of Warm)* written by Wu Youke (1642 C.E.), recorded therapies and formulas that were effective at treating infectious diseases; among them, the classical prescription Da Yuan Yin and the use of human variolation were considered as means to prevent smallpox. Currently, the use of TCM has resulted in remarkable improvement and alleviation of symptoms in COVID-19 patients.

Abstract

Since late December in 2019, the coronavirus disease 2019 has received extensive attention for its widespread prevalence. A number of clinical workers and researchers have made great efforts to understand the pathogenesis and clinical characteristics and develop effective drugs for treatment. However, no effective drugs with antiviral effects on severe acute respiratory syndrome coronavirus 2 have been discovered currently. Traditional Chinese medicine (TCM) has gained abundant experience in the treatment of infectious diseases for thousands of years. In this review, the authors summarized the clinical outcome, pathogenesis and current application of TCM on coronavirus disease 2019. Further, we discussed the potential mechanisms and the future research directions of TCM against severe acute respiratory syndrome coronavirus 2.

Key words: Severe acute respiratory syndrome coronavirus 2 ; Coronavirus disease 2019 ; Clinical outcome ; Angiotensin-converting enzyme 2 ; Traditional Chinese medicine

Background

Coronavirus disease 2019 (COVID-19) has received extensive attention for its increasing incidence and widespread prevalence [1, 2]. On January 31, 2020, World Health Organization declared that the outbreak of COVID-19 had become public health emergency of international concern. According to statistics from National Health Commission of the People's Republic of China, by February 16, 2020, a total of 70,548 confirmed cases and 1,770 fatal cases of COVID-19 had been reported in China. At this writing, cases of COVID-19 infection have been reported in more than 20 countries and in regions worldwide [3].

Given the recent advances in research and biotechnology, a virus believed to be the etiologic agent of COVID-19 was isolated and the sequence of virus genome was revealed using high-throughput sequencing [4]. Currently, this virus is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5] and the disease resulting SARS-CoV-2 was officially named COVID-19 by World Health Organization [6]. Bats have been identified as the possible animal host of SARS-CoV-2 [7] and a mechanism for SARS-CoV-2 infection has been postulated. The timeline of important events marking the SARS-CoV-2 outbreak since the report of the first case on December 26, 2019 is shown in Figure 1. Traditional Chinese medicine (TCM) has a thousand-year history of experience with all types of infectious diseases and has been employed previously as effective treatments for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [8]. We report here that TCM is currently in wide use for the treatment of COVID-19. In this review, we summarize the clinical outcome, pathogenesis and current application of TCM for the treatment of COVID-19.



Figure 1

Timeline of important events during SARS-CoV-2 outbreak. COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; ICTV, International Committee on Taxonomy of Viruses; NEJM, New England Journal of Medicine; 2019-nCoV, 2019 novel coronavirus; ①, <https://www.ncbi.nlm.nih.gov/nuccore/MN908947>.

Epidemiology of COVID-19

Zhou et al. found that the genome sequence of a coronavirus isolated from a bat showed 96% similarity with the sequence of SARS-CoV-2; these results suggested that bat species might be a host of SARS-CoV-2. In addition, the earliest cases of COVID-19 were all individuals who reported direct contact with the Huanan Seafood Market in Wuhan, China [9]. Many wild animals such as hedgehog, badger, snake and birds are sold for human consumption at this market, although bats are not typically included in this group. Researchers from South China Agricultural University declared the intermediate host of SARS-CoV-2 could be the Chinese pangolin (*Manis pentadactyla*) although this has not been confirmed at this date.

An article published on *New England Journal of Medicine* on January 29, 2020, reported human-to-human transmission of SARS-CoV-2 [10]. Recent epidemiology studies by Guan et al. [11] documented that only a few COVID-19 patients (1.18%) were in contact with wildlife, while 31.8% of COVID-19 patients traveled to Wuhan recently and 71.80% of COVID-19 patients had recent contact with people from Wuhan.

Respiratory and contact transmission are the main transmission routes of SARS-CoV-2. SARS-CoV-2 RNA is also detected in feces of COVID-19 patients, suggesting the possibility of fecal-oral transmission as another potential transmission route [12-14]. Aerosol and transplacental transmission routes are also regarded as among important possibilities to consider, although there is no substantial research supporting this hypothesis at this time.

Clinical symptoms of COVID-19

The asymptomatic incubation period of SARS-CoV-2 is 0 to 24 days, with a median incubation period of 3 days [11]. Once the disease has taken hold, most of the patients report symptoms including fever, cough, dyspnea, muscle soreness and/or fatigue. Some patients also reported sputum production, headache, hemoptysis and/or diarrhea. Patients with mild symptoms develop low-grade fevers and mild fatigue but no symptoms suggestive of pneumonia. By contrast, patients with severe disease experience dyspnea and hypoxemia which can develop into acute respiratory distress syndrome (ARDS), septic shock, severe metabolic acidosis and coagulation disorders [9-11, 15]. The epidemiology of severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 and clinical features of three different coronavirus syndromes (SARS, MERS and COVID-19) are listed in Table 1 and Table 2, respectively.

Table 1 Epidemiology of SARS-CoV, MERS-CoV and SARS-CoV-2

	SARS-CoV [16, 17]	MERS-CoV [17-19]	SARS-CoV-2 [3, 11, 20]
Date of first detection	November, 2002	June, 2012	December, 2019
Location of first detection	Guangdong province, China	Jeddah, Saudi Arabia	Wuhan city, Hubei province, China
Epidemiological distribution	Large outbreaks of imported cases in South China, Canada and Asia	27 countries and regions in the Middle East, Europe, Africa, Asia and North America	Outbreak in China, imported cases in more than 20 countries and regions such as Japan, Singapore, Thailand and others.
Onset season	Winter	Breeding season of camels	Winter
Natural host	<i>Rhinolophus sinicus</i>	Bat (?) ^a	Bat (?) ^a
Intermediate host	Wild mammals (civet in South China)	Camels (Middle East and Africa)	<i>Manis pentadactyla</i> (?) ^a
Route of transmission	Droplets, contact	Droplets, contact, airborne (?) ^a	Droplet, contact, fecal-oral (?) ^a , aerosol (?) ^a , transplacental (?) ^a
Main form of transmission	Human-to-human, animal-to-human	Animal-to-human, human-to-human	Human-to-human, animal-to-human
Incubation period (days)	1.9-14.7	2-14, occasionally up to 21 days	0-24
Age, years (range)	39.9 (1-91)	56 (14-94)	47 (35-48)
Male : female sex ratio	1 : 1.25	3.3 : 1	1.39 : 1
Confirmed cases	8,096	2,494	70,548
Fatal cases	774	858	1,770
Basic reproductive number (R ₀)	0.3-4.1	0.3-1.3	2.68

The statistical characteristics associated with SARS-CoV-2 were derived from the 1099 patients (as of January 29, 2020) reported by the team of Zhong Nanshan. The number of confirmed cases and deaths was determined by the National Health Commission of the People's Republic of China (information presented as reported through February 16, 2020).

(?)^a, presents the result of current hypotheses but without strong evidence at this time; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 Clinical characteristics of SARS, MERS and COVID-19

	SARS [17]	MERS [18]	COVID-19 [11]
Common symptoms	Hyperpyrexia (more than 38 °C)	Fever, cough, polydipsia	Fever, cough, fatigue
Common extrapulmonary symptoms	Diarrhea	Acute renal failure, diarrhea	Diarrhea, emesis
Imaging features	Interstitial ground-glass changes in lung, peribronchovascular lesions in mediastinum	Interstitial ground-glass changes in lung, peribronchovascular lesions in lung	Ground-glass opacity in lung, bilateral patchy opacity in lung
Common complications	ARDS	ARDS, renal failure, disseminated intravascular coagulation and pericarditis	Pneumonia, ARDS, shock
Blood routine and serological tests	Decrease of white blood cells, lymphocytes and blood platelets, increase of ALT and AST	Decrease of white blood cells, lymphocytes and blood platelets in early stage and increase of white blood cells and neutrophils during disease progression, increase of ALT and AST and renal dysfunction	Normal or decrease of white cells, decrease in lymphocytes in mild cases, persistent decrease of lymphocytes in severe cases, increase of ALT, AST, LDH, CK-MB, CRP and ESR in mild cases, increase of cTn in severe cases

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19: corona virus disease 2019; ARDS, acute respiratory distress syndrome; CK-MB, creatine kinase (isoenzyme-MB); ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; cTn, cardiac troponin.

Angiotensin-converting enzyme 2: the receptor for SARS-CoV-2 on target cells

During the pandemic phases of SARS-CoV in 2003, angiotensin-converting enzyme 2 (ACE2) was identified as the SARS-CoV receptor on target host cells [21]. DNA sequencing revealed that SARS-CoV-2 genome shares

89% similarity with that of SARS-CoV, suggesting that the mechanisms for SARS-CoV-2 infection of target cells may be similar to that already identified for SARS-CoV [9, 22, 23]. Zhou et al. [9] demonstrated that ACE2 was the cell entry receptor for SARS-CoV-2 in in vitro infectivity studies. Specifically, Hela cells that were genetically modified to express ACE2 from different species including human, Chinese horseshoe bats, civets, pigs and mice were infected with SARS-CoV-2 in vitro. The results demonstrated that ACE2 proteins from all species tested except mice could serve as entry receptors for SARS-CoV-2. Results from experiments using Hela cells expressing human ACE2, or other known coronavirus receptors, including aminopeptidase N and dipeptidyl peptidase 4, revealed that only ACE2 was effective as an entry receptor for SARS-CoV-2 in vitro.

ACE2 is a type I transmembrane protein composed of 805 amino acids and is primarily expressed in the gastrointestinal tract, heart, kidney and lung. As a negative regulator of the renin-angiotensin system, ACE2 plays an important role in maintaining homeostasis of cardiovascular system and regulating absorption of amino acids in kidney and gastrointestinal tract [24]. Genetic studies also reveal the role of ACE2 in preventing stroke [25].

Coronavirus invasion of host cells depends on the actions of the spike protein (S protein) on virus surface. The SARS-CoV S protein includes 2 subunits [26]. The receptor binding domain (RBD) on the S1 subunit interacts with ACE2 to form a virion-ACE2 complex. The virion-ACE2 complex is then transported and enters the endosome of target cells. Subsequently, the structure domain of heptad repeats (HR)1 and HR2 in S proteins interact with one another to form a six-helix bundle core. This core promotes fusion of the viral envelope with cellular membrane. The RNAs of virus are then released into the cytoplasm of target cells (Figure 2) [27, 28]. SARS-CoV virions may also enter the target cell via plasma membrane fusion, via a means similar to that used by human immunodeficiency virus [29].



Figure 2

SARS-CoV binds to ACE2 and enters target cell through endosomal membrane fusion. ① The receptor binding domain (RBD) on S1 protein may bind with ACE2 on cell membrane to form virion-ACE2 complex. ② The virion-ACE2 complex is transported and enters the endosome of target cells. ③ The structure domain of heptad repeat (HR) 1 and HR2 in S protein interact with one another to form a six-helix bundle core, which promotes fusion between the viral envelope and the cellular membrane. The virus RNAs are then released into the cytoplasm of target cells. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; RBD, receptor binding domain; SARS-CoV, severe acute respiratory syndrome coronavirus; HR, heptad repeat; 6-HB, six-helix bundle.

After entering the target cells, the SARS-CoV RNA genome interacts in a complex with the viral RNA replicase and transcription enzymes. The minus strands of viral RNA are transcribed and are ultimately translated into structural proteins [30]. The cytoplasmic viral RNAs and structural proteins are packaged to form new viruses which are released from infected cells and go on to infect other available target cells in the immediate environment.

In vivo studies were also carried out to investigate the role of ACE2 in a respiratory disease model. ACE2 gene-deleted mice exhibited severe lung injury and dysfunction of renin-angiotensin system in a model of lung injury induced by cationic polyamidoamine dendrimer nanoparticles; likewise, treatment with an angiotensin II type I receptor antagonist suppressed the sequelae of nanoparticle-induced lung injury in wild-type mice [31]. Creation of an in vivo infection model for SARS-CoV and SARS-CoV-2 was not straightforward, as neither interacts with mouse ACE2. Perlman and colleagues

established a human ACE2 transgenic mice model. With this transgenic mouse model, SARS-CoV could be detected in the pulmonary alveoli. It is conceivable that the human ACE2 transgenic mouse model can be an important tool for conducting SARS-CoV-2 infection experiments and for identifying new drugs that would be effective for the treatment of COVID-19 [32, 33].

Role of TCM on treating COVID-19

In TCM, the term “plague” is used to denote infectious disease. From the earliest times, the Chinese people have understood the severity underlying this disease process and have searched for improved understanding. The ancient book of TCM *Huang Di Nei Jing (Inner Canon of Huangdi)* was written during Western Han Dynasty in China (approximately 99 B.C.E.-26 B.C.E.) and recorded that plague, with symptoms familiar to modern times, could be transmitted from human-to-human. *Shang Han Za Bing Lun (Treatise on Cold Damage Diseases)* written by Zhang Zhongjing (200 C.E.-210 C.E.), *Wen Yi Lun (Theory of Plague)* and *Wen Re Lun (Theory of Warm)* written by Wu Youke (1642 C.E.) recorded therapies and formulae used to treat plague, including Da Yuan Yin and the use of human variolation to prevent smallpox [34, 35]. Dr. Tu Yoyo credited the discovery of artemisinin for the treatment of malaria according to the early records of *Zhou Hou Fang (Handbook of Prescriptions for Emergencies)* written by Ge Hong (284 C.E.-364 C.E.) [36]. TCM has provided significant and important therapies for SARS-CoV, influenza A H1N1, influenza A H7N9 and Ebola virus [37-40]. Consequently, TCM is becoming an important means for developing therapies to treat COVID-19.

Pathogenesis of COVID-19 in TCM theory

Ancient Chinese people believed that man is an integral part of nature. According to this theory, environmental factors are critical elements in the pathogenesis of plague. For example, TCM considers that the characteristics of COVID-19 may largely depend on the environment in Wuhan. During the winter of 2019, a large amount of precipitation fell in Wuhan, which resulted in a moist environment and increased the risk of virus infection. This observation implies that a Chinese herb that promotes the elimination of dampness (a kind of pathological product of disease in TCM theory) can be used in the treatment of COVID-19.

TCM treatments for COVID-19

Classical prescription. The fifth edition of “Standard Therapy of COVID-19” (abbreviated Standard Therapy) published on February 9, 2020, recommended that a modification of the integrated Ma Xin Gan Shi decoction with Da Yuan Yin could be used to improve the chest distress, cough and asthmatic symptoms that develop in COVID-19 [12]. The Ma Xin Gan Shi decoction that includes Mahuang (*Ephedrae herba*), Xingren (*Armeniacae semen amarum*), Gancao (*Glycyrrhizae radix et rhizoma*), Shigao (*Gypsum fibrosum*) together with Da Yuan Yin had significant impact on SARS in 2003 [41, 42]. The use of Da Yuan Yin, composed of Binlang (*Arecae semen*), Houpo (*Magnoliae officinalis cortex*), Caoguo (*Tsaoko fructus*), Zhimu (*Anemarrhenae rhizoma*), Shaoyao (*Dioscoreae rhizoma*), Huangqin (*Scutellariae radix*), Gancao (*Glycyrrhizae radix et rhizoma*), was first recorded in *Wen Yi Lun (Theory of Plague)* (1642 C.E.); this decoction has been used to treat plague for thousands of years. The effectiveness of this decoction for the treatment of SARS was evaluated using a molecular docking method; quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin and baicalein were identified as the five compounds with highest connectivity to the SARS-CoV 3CL protease [43]. A report dated February 6, 2020 from the State Administration of Traditional Chinese Medicine recommended the use of Qing Fei Pai Du decoction that includes Mahuang (*Ephedrae herba*), Shigao (*Gypsum fibrosum*), Banxia (*Pinelliae rhizoma*), Zhishi (*Aurantii fructus immaturus*), Shengjiang (*Zingiberis rhizoma recens*), that was derived from a modification of the integration of Ma Xin Gan Shi, She Gan Ma Huang, Xiao Chai Hu, and Wu Ling San decoctions in *Shang Han Za Bing Lun (Treatise on Cold Damage Diseases)* (200 C.E.-210 C.E.); this

recommendation was based on previous experience with SARS and the cold and wet weather in Wuhan. The Qing Fei Pai Du decoction has been demonstrated to be 90% effective in treating COVID-19 [44].

Chinese patent medicine. According to the standard therapy, the patent medicine of Huo Xiang Zheng Qi capsule can be used to treat the gastrointestinal symptoms of COVID-19. Huo Xiang Zheng Qi capsule, derived from *Tai Ping Hui Min He Ji Ju Fang (Prescriptions People's Welfare Pharmacy)* written by Chen Shiwen and others (1151 C.E.), has the effects of resolving dampness and is used to treat diarrhea associated with virus infection [45]. The usage of Huo Xiang Zheng Qi capsule for COVID-19 was closely related to the cold and wet weather in Wuhan. Likewise, Lian Hua Qing Wen capsules and Fang Feng Tong Sheng pills can be used to treat fever, fatigue and cough associated with COVID-19 [12]. Lian Hua Qing Wen capsule has broad-spectrum antiviral and antibacterial effects, most notably used for respiratory virus infections including influenza, SARS and MERS [46]. According to a recent retrospective analysis, use of Lian Hua Qing Wen capsule might reduce fever, cough, expectoration, fatigue and difficulty with breathing in COVID-19 patients. Among the findings, the fraction of severe cases was decreased after the treatment of Lian Hua Qing Wen capsule [47, 48].

Other treatments. Other therapies associated with TCM such as acupuncture, moxibustion, and Tai Chi promote health by enhancing the immune system and improving pulmonary function. Although there is no current evidence relating any of these therapies with COVID-19, they may have crucial roles in disease prevention and likewise in promoting recovery of pulmonary function during recuperation from COVID-19. Acupuncture has been shown to relieve the side-effects of hormonal therapy and to alleviate pulmonary injury [49]. *Ben Cao Gang Mu (Materia Medica with Commentaries)* written by Li Shizhen (1578 C.E.) recorded that moxibustion could improve digestion, relieve asthma and prevent plague; modern studies reveal that moxibustion can limit the acute inflammatory response in respiratory tract [50]. Tai Chi is a traditional sport in TCM and can enhance recovery of pulmonary function through respiratory training [51]. In addition, Jin Zhi (Gold Juice), first recorded in *Ben Cao Qiu Zhen (Truth-Seeking Herbal Foundation)* written by Huang Gongxiu (1769 C.E.), was made from the fermentation of feces from young men. During the Qing dynasty, Jin Zhi was used to reduce fever in patients with plague [52].

Summary and future perspectives

Since the emergence of COVID-19, clinicians and researchers have made great efforts to understand the pathogenesis and clinical characteristics of this infection and to develop effective drugs for its treatment. Currently, there are no effective antiviral available to treat SARS-CoV-2. On February 6, 2020, a clinical trial of remdesivir, a newly-discovered antiviral drug with potential impact on SARS-CoV-2, was initiated in Wuhan. However, given issues related to both safety and efficacy, it will take some time to develop both antiviral drugs and a vaccine to prevent SARS-CoV-2 infection. Western-type antiviral therapies including α -interferon and lopinavir, treatment with antibiotics, and support therapies including oxygen and mechanical ventilation have been used as the treatment of COVID-19. Therapies based on principles of TCM have improved symptoms and enhanced immunity against virus in COVID-19 patients. Positive responses from patients have been noted when efforts are made to combine approaches from TCM and Western medicine on COVID-19. In the future, TCM may also have a role in decreasing the some of the side-effects of Western medicine, notably with respect to recovery of pulmonary function. Finally, we would like to note that many herbs used in these decoctions, including Mahuang (*Ephedrae herba*), Xingren (*Armeniacae semen amarum*), and Chaihu (*Bupleuri radix*) have a bitter taste. Many of the bitter contents of these herbs such as ephedrine and amygdalin are aromatic substances; the hydrophobic properties of these aromatic substances may inhibit the interaction of the virus S protein with ACE2. However, due to the complex targets and multiple contents that are characteristics of TCM decoctions, further studies would be needed to elucidate the detailed mechanisms involved in their impact on COVID-19 using network pharmacology analysis, experimental validation and multi-omics.

The authors declare that they have no conflict of interest.

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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 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 chemotactic 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 needled (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. 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 α_7 nAChRs on macrophages and suppresses pro-inflammatory cytokine release and inflammation. The anti-inflammatory effect of EA at Hegu (LI4) is through this way.

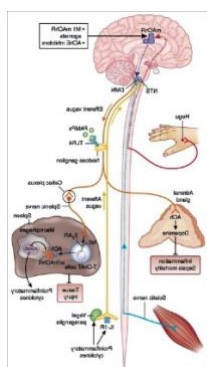


Figure 1: Two vagus-cholinergic anti-inflammatory pathways stimulated by acupuncture at Hegu LI4 or Zusanli ST36 (Illustrated by Debbie Maizels, Springer Nature, for Pavlov and Tracey[11])

The 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 adrenocorticotrophic 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, Addoriso Met *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 to a 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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Report from the Front Line in Wuhan by liu lihong translated by heiner fruehauf at Hankou Hospital No. 8.

On the evening of February 21, carrying the mandate of my teachers Lu Chonghan, Yang Haiying and Yang Zhenhai as well as the expectations of the Tongyou Sanhe community of Chinese medicine practitioners, I arrived in Hankou together with Dr. Lei Ming. The 3rd member of our coronavirus treatment team, Dr. Zhao Jiangbin, arrived the next day.

During the first three days, we underwent intensive training about hospital rules and protective gear. In the afternoon of February 24, we entered into the clinical section of the hospital. The inviting unit, the Hemorrhoid Department No. 3 at Hankou Hospital No. 8, had so far received 20+ patients in all stages of COVID-19 pneumonia. Some of them had been there for almost 2 months, while on the shorter end some had been in inpatient care for about 3 weeks. Quite a few of them never tested positive for the virus, but all CT images revealed typical signs of coronavirus-based pneumonia.

Altogether, we have so far diagnosed and treated more than 10 patients with obvious signs of discomfort. The others either didn't exhibit any symptoms, or they did not wish to be treated with Chinese medicine modalities. According to our own observations and those of other practitioners reporting from the front lines of the outbreak, it has become clear that the initial stage of the infection is not at all characterized by typical pneumonia symptoms such as fever and coughing. Many coronavirus patients cough only little or not at all, while their X-ray images show clear evidence of pathological changes due to COVID-19 pneumonia.

- Dampness (shi): Almost everyone agrees that dampness is at the core of this disease. All of the cases we have encountered so far display a thick, white, sticky tongue coating. Since our arrival in Wuhan, every one of us has observed an increase in sticky coating on our own tongues, as well as the onset of incomplete bowel movements.
- Pulse (mai): The biggest common denominator among patients has been the fact that virtually everyone exhibits a slippery pulse in the cun position of the right hand. This phenomenon signifies that turbid damp obstructing the Lung is the main characteristic of this epidemic.
- Absence of Phlegm (wutan) or Low Phlegm Production (shaotan): Typical symptomology includes either a dry cough or no cough. Because on one hand the normal way of phlegm expulsion by coughing is missing and on the other turbid damp pathogens are obstructing the middle burner, the resultant blockage of normal transformative pathways causes turbid phlegm to congeal into a rubbery and glue-like material that severely interferes with proper airway function and has no way out. This is the most important reason for the lingering "stalemate" quality of the disease, as well as the tendency to take a sudden turn for the worse.
- Complexity Syndrome (hebing) and Dual Affliction (lianggan): According to my own observations, from the very beginning of the epidemic all the way until now at the front line, as well as the opinions shared by my Chinese medicine colleagues working in Wuhan, the etiology of COVID-19 pneumonia is very much a manifestation of Zhang Zhongjing's classical theory of syndrome complexity and dual pathogenesis. In other words, one can confidently say that this particular epidemic from beginning to end bears the characteristics of what is called Complexity Syndrome and Dual Affliction in the Shanghan zabing lun (Treatise on Disorders Caused by Cold and Miscellaneous Disorders). None of the cases we encountered manifested with simple Taiyang Syndrome in the initial stages of the disease, but they all came down right away with Taiyang Yangming Combination Syndrome, or even a situation where all three yang channel systems (taiyang, yangming, shaoyang) were involved. Many patients exhibit signs of dual pathogenesis right from the get-go, by coming down with a rapidly progressing respiratory infection with signs of both taiyang and shaoyang disease. In some instances, the disease lingers at the yangming taiyin dual affliction stage, while others suffer from taiyang shaoyang dual affliction that is further complicated by yangming taiyin issues. Comparatively speaking, shaoyang jueyin dual afflictions are rare. As for the Complexity Syndrome (hebing) variant, which specifically refers to a situation where both the surface and the interior and zang and fu organ systems are involved at the same time, an example would be the simultaneous affliction of the Lung and the Large Intestine. An appropriate prescription needs to take all of these aspects into consideration. Many of the recently publicized

anti-COVID-19 formulas display this characteristic of complexity. The Cinnamon Method (Guizhi Fa) approach suggested by my Fire Spirit School mentor Dr. Lu Chonghan, furthermore, represents a typical approach to Taiyang Yangming Complexity Syndrome. Other suggestions, such as Ma Xing Shi Gan Tang (Ephedra, Apricot Seed, Gypsum, and Licorice Decoction) and similar remedies, or Mahuang Tang (Ephedra Decoction) plus Weijing Tang (Phragmites Decoction) are all examples for approaches to more complex syndromes. For dual affliction (lianggan) conditions, moreover, the Aconite Method (Sini Fa) of the Fire Spirit School is also an important method to consider. Especially in situations where “dampness is pronounced and yang is feeble” (shisheng yangwei) the inclusion of aconite containing formulas is particularly appropriate. Aconite, of course, should always be used cautiously—proper differential diagnostics is always the most important prerequisite for any prescription!

- **Moisten Dryness and Transform Phlegm, Remove Zang Disease via the Corresponding Fu Organ** How is it possible to liberate the airways by expelling the sticky, rubbery, glue-like phlegm that is obstructing the lungs all the way into the alveoli? This question is most relevant for the eventual outcome of the disease process! Why is the typical COVID-19 patient hardly coughing or not coughing at all? I believe that this specific characteristic of the disease is mostly due to the presence of sticky phlegm, which occupies the available airway space, normally required for the generation of a productive cough. From the perspective of Chinese medicine, this phenomenon belongs to the category of dry phlegm (zaotan). This kind of issue requires an approach that involves moisturizing dryness and transforming phlegm (runzao huatan). The herb Dongguairen (Benincasa), for instance, from the afore-mentioned remedy Weijing Tang is a representative herb in this category. Many other seeds possess this type of therapeutic function, i.e. Gualouren (Trichosanthes seed), Laifuzi (Radish seed), Baijiezi (Mustard seed), etc. However, this type of super-sticky phlegm cannot necessarily be completely expelled via the prescription of moisturizing and phlegm transforming herbs. This is where the maneuver of utilizing the zang-fu relationship of Lung and Large Intestine comes into play, by removing zang disease by way of the associated fu organ; by addressing yin disease via its yang counterpart. This approach has often been used within the versatile arsenal of Chinese medicine modalities. Examples can be found in historical case studies. Specifically, this means that the seed varieties of phlegm transforming herbs, if used in sufficient amounts, can expel residual glue-phlegm from the Lung via the Large Intestine. In the arena of acupuncture, the corresponding method would be to needle Taiyuan (LU9) all the way connecting to Yangxi (LI5), or Yangxi all the way to Taiyuan.

II. The Importance of Acupuncture Therapy

Our team began treating every single patient with acupuncture starting on our first day in the coronavirus section. Because of the logistics associated with buying and preparing herbs, our patients started imbibing herbal decoctions only 3 days later. I remember how I felt slightly awkward when approaching my first patient with a needle. For one, the protective gear with its plastic eye goggles blurs the vision. Secondly, three layers of gloves greatly dull sensitivity in the needling hand. And thirdly, I was worried that the patient would trust me, a doctor who had never treated this kind of disease before. I was therefore completely taken by surprise when the patient exclaimed: “This works like a miracle! The stuffy feeling in my chest is completely gone!” And another patient said shortly thereafter: “My throat and chest area used to feel as blocked as a road during rush hour—now it has become like an open road without a single soul on it.”

This sort of feedback was a pleasant and unexpected surprise for us, providing us with hope and strength at the same time. Most of the accompanying symptoms, such as stuffiness in the chest, shortness of breath, abdominal discomfort, itchy throat with the urge to cough, dizziness, cold sensation in the upper back, connective tissue pain, sweating, etc, did either decrease with the acupuncture treatments or resolve entirely.

This experience proved that my earlier suggestion to “use acupuncture and herbal medicine together” in the treatment of this epidemic was realistic. Perhaps the greatest benefit of acupuncture is the immediate improvement in the emotional outlook of patients, since they get to experience a noticeable improvement in a short period of time. This aspect cannot be underestimated in the process of curing this disease. Overall,

however, the term “cure” needs to be used with extreme caution in the context of this pneumonia epidemic. This is definitely not the kind of situation where one is all better once the fever has broken, or one is OK once the coughing spells come to an end, or when the virus test turns from positive to negative. There are at least 3 additional elements that are prerequisites for a complete cure of COVID-19 related issues: 1) The complete remission of pneumonia signs on CT images; 2) The normalization of all Lung channel abnormalities; 3) The disappearance of sticky tongue coating. Otherwise, the disease may come roaring back for another round!

14. Ling C quan. Traditional Chinese medicine is a resource for drug discovery against 2019 novel coronavirus (SARS-CoV-2). J Integr Med [Internet]. 2020;18(2):87–8. Available from: <https://doi.org/10.1016/j.joim.2020.02.004>

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Traditional Chinese medicine is a resource for drug discovery against 2019 novel coronavirus (SARS-CoV-2)

Novel coronavirus pneumonia, named as COVID-19 by the World Health Organization, has spread widely since December 2019 [1–3], with more than 40,000 confirmed cases in China and exportations to over 20 countries [4]. On January 30, 2020, the World Health Organization declared the epidemic to be a public health emergency of international concern in the second meeting of the Emergency Committee [5]. It was recommended that potential vaccines and antiviral medicines should be developed. However, the development of these therapeutics will take months, even years. For this specific indication, rapid performance of traditional Chinese medicine (TCM) can contribute as an alternative measure.

In 2003, patients with severe acute respiratory syndrome (SARS) who were treated with TCM benefited from shorter hospitalization, decrease in steroid-related side effects, and improvement of symptoms [6]. Notably, genomic and in silico structural characterization of novel coronavirus revealed that it is closely related to the SARS coronavirus, further suggesting that TCM may have potential use in the current outbreak [7]. Indeed, the China government is advising doctors to consider combining Western antiviral drugs with TCM remedies in combating novel coronavirus pneumonia. However, there were few studies to help select suitable herbal drugs before costly biological experiments and clinical trials.

Classically, whether a TCM remedy can be clinically used for viral infections depends on two aspects: 1) clinical symptoms and signs of the patient, and 2) the type of TCM remedy and its traditional indications. TCM formulas have been used in China over 2000 years. According to their effectiveness, TCM remedies are divided into various types, each corresponding to a group of diseases. On the other hand, research has shown that many TCM remedies have antiviral ingredients. Selecting specific TCM formula through integrative methods based on both disease symptom and pathogen-directed cause will greatly increase the clinical potential. However, it is still a challenge to experimentally screen many TCM remedies for the treatment of novel coronavirus pneumonia in a short time.

In this issue of the Journal of Integrative Medicine, Zhang et al. [8] provided in silico methods to narrow down TCM remedies that may directly inhibit the coronaviral reproduction. Two principals for selection were proposed: oral effectiveness to inhibit viral infection and compatibility of patient manifestation. The identified TCM remedies should contain anti-novel coronavirus chemicals that meet the requirement for orally administered medical drugs. Meanwhile, the identified TCM remedies should be of the types of TCM remedy that have activity against virus-caused pneumonia. To this end, the authors conducted a series of in silico analyses. A number of natural compounds were selected, which were experimentally validated for their potential activity against SARS or Middle East respiratory syndrome coronavirus. These chemicals were then evaluated for their suitability for oral administration. Most importantly, the molecular structures of these natural compounds were evaluated for their ability to interact, or dock, with the main proteins of the novel coronavirus. Positive docking suggested their ability to inhibit the novel coronavirus infection. In order to com-

ply with patient manifestation, the authors conducted another three rounds of screening. First, TCM herbs that contained at least two of the above natural compounds were selected from the Traditional Chinese Medicine Systems Pharmacology (TCMSPT) database [9]. These medicinal plants were classified by the types of diseases they are used to treat. Only those belonging to the types that have been classically used to treat viral pneumonia were selected for further studies. Next, comprehensive evaluation of the effectiveness of these TCM herbs was performed. The authors downloaded its documented chemical constituents of each herb and analyzed their cellular protein targets for network pharmacological analysis. All these processes found that at least 26 TCM herbs have potential in vivo anti-novel coronavirus effects and can simultaneously regulate host inflammation responses.

This work highlights the prospect of computer-aided, structure-based TCM drug discovery for the novel coronavirus pneumonia. These approaches helped to narrow down the large libraries of compounds into a subset in a relatively short time with limited resources; they also provided guidance for the future clinical use of TCM formulas. Although the potential is great, at the same time, we need to be fully aware of challenges and limitations faced by these tools. Computational prediction is a bridge between theory and experiment, and further research is needed. Inhibitory assays and crystallography should be performed to confirm the interaction of the herbal compounds with viral proteins and structures. It is worth noting that in a recent study to identify potent ebola-virus inhibitors, only two of the eight compounds selected by in silico screening showed inhibitory properties, reflecting the limited reliability of the computational scoring functions [10]. The decoction of the selected 26 TCM herbs should be tested for their effectiveness and safety in both cell cultures and animal models. Eventually, TCM remedies should be evaluated in carefully tal research and clinical use of these remedies, especially in those countries, territories or areas with reported and confirmed cases of COVID-19. Although the difficulties and challenges are fully recognized, we are looking forward to increasing the contribution and benefits from TCM professionals that will provide treatment to many patients with pneumonia caused by 2019 novel coronavirus (2019-nCoV), a new virus also named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

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Understanding of Guidance for acupuncture and moxibustion interventions on COVID-19 (Second edition) issued by China Association of Acupuncture-Moxibustion

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ABSTRACT At present, the situation of global fight against COVID-19 is serious. WHO (World Health Organization)-China Joint Mission fully confirms the success of “China’s model” against COVID-19 in the report. In fact, one particular power in “China’s model” is acupuncture and moxibustion of traditional Chinese medicine. To better apply “non-pharmaceutic measures”—the external technique of traditional Chinese medicine, in the article, the main content of Guidance for acupuncture and moxibustion interventions on COVID-19 (Second edition) issued by China Association of Acupuncture-Moxibustion is introduced and the discussion is stressed on the selection of moxibustion device and the duration of its exertion. Keywords COVID-19, Non-pharmaceutic measures, External therapy, Acupuncture, Moxibustion.

Background Novel coronavirus pneumonia was renamed by World Health Organization (WHO) to be “2019 coronavirus disease” (COVID-19) recently. It is the infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it is a kind of atypical pneumonia. On 1 December 2019, the first case of COVID-19 was confirmed in the city of Wuhan, Hubei province, China and the virus that started the pneumonia outbreak spreads in the country. The major source of infection is the patients with COVID-19 and asymptomatic SARS-CoV-2 carriers seem also a potential source of infection. It is mainly transmitted by respiratory droplets, contact, digestive tract and aerosol transmission. This disease is characterized as highly contagious and is susceptible to humans of all ages. On 8 January, 2020, the first case of COVID-19 was confirmed in Thailand, which is the earliest confirmed case outside China [1]. On 20 January, the first confirmed case was identified in the Republic of Korea [2]. Since then, a number of cases were confirmed in Singapore, Italy, Iran, the United States, Russia, etc.. Thus far, this disease has spreaded globally.

On 31 January 2020, WHO declared this epidemic outbreak a public health emergency of international concern (PHEIC) [3]. On 2 March 2020, Tedros Adhanom Ghebreyesus, the Director-General of WHO, pointed in the opening remarks at the media that outside China, a total of 8739 cases of COVID-19 have been reported to WHO from 61 countries, with 127 deaths [4]. The epidemics in the Republic of Korea, Italy, Iran and Japan are of greatest concerns. The fight against COVID-19 gets more serious globally. From 16 to 24, February 2020, 25 international and Chinese experts of the WHO-China Joint Mission traveled to Beijing, Hubei, Guangdong and Sichuan, China to investigate the fight against the epidemic. On the second day after the end of investigation, Dr. Bruce Aylward, the head of the international expert panel of the WHO-China Joint Mission, the senior adviser to the WHO's Director-General, stated at the press briefing at WHO Headquarters in Geneva, that faced with the unknown pathogen, China has taken ambitious, flexible and aggressive efforts in responding to the epidemic. In the report, WHO-China Joint Mission has confirmed that China has played a crucial role in protecting the international society, buying precious time for countries to adopt active prevention and control measures and providing them with worthwhile experiences. The report also points out specifically the high effective role of non-pharmaceutic measures [5]. The report said that China, as the country with the greatest knowledge on COVID-19, should further enhance the systematic and real-time sharing of epidemiologic data, clinical results and experience to inform the global response.

With regard to “non-pharmaceutic measures” proposed in the report of WHO-China Joint Mission, besides active surveillance, timely detection, voluntary quarantine and rigorous tracing, actually, there is still a mysterious power, that is various kinds of external therapeutic approaches of traditional Chinese medicine (TCM). By the time for the authors submitting the manuscript, it is known that many therapeutic methods of TCM, e.g. Chinese herbal decoction, acupuncture, moxibustion, acupoint plaster, auricular acupuncture and cupping have adopted in the treatment of COVID-19. In the regions where TCM therapeutic methods were highly utilized, the curative rate was increased, the number of severe case decreased and the hospital discharge rate improved remarkably [6]. The utilization of TCM therapeutic interventions block effectively the continuous spreading of COVID-19 in China. Note:



Picture from www.chinanews.com

In application of TCM techniques, e.g. acupuncture and moxibustion in treatment of COVID-19. Main content of Guidance Three sections are included in Guidance, named the principle of acupuncture-moxibustion interventions, the methods of acupuncture-moxibustion interventions, and the self-interventions of acupuncture and moxibustion at home under the instruction of physician. Regarding the principle of acupuncture-moxibustion interventions, Guidance emphasizes: The rigorous quarantine and disinfection are

required. No matter for the confirmed cases or the convalescent cases, they can be treated in the same room respectively and every suspected one should be isolated in a single room for treatment. During the clinical treatment stage, acupuncture can be combined with western medications and Chinese herbal decoction to achieve the collaborative effect. For the cases at the recovery stage, the core role of acupuncture-moxibustion should be played in the rehabilitation. It is recommended to set up acupuncture-moxibustion based COVID-19 rehabilitation clinic. In reference to the clinical stage identification of TCM suggested in Diagnosis and treatment plan of corona virus disease 2019 (tentative seventh edition) issued by National Health Commission (NHC) of the PRC and State Administration of Traditional Chinese Medicine (SATCM) of the PRC, three stages are included in the treatment with acupuncture and moxibustion, e.g. medical observation stage, medical treatment stage and recovery stage. The therapeutic regimens of each stage are introduced as follows.

Acupuncture-moxibustion interventions at the medical observation stage (suspected cases)

Objective: To motivate the antipathogenic qi of human body and the functions of lung and spleen and scatter epidemic pathogens so as to strengthen the defensive capacity of internal organs.

Main acupoints: Group 1: Fēngmén (风门 BL12), Fèishū (肺俞 BL13), and Píshū (脾俞 BL20). Group 2: Héǔ (合谷 LI4), Qūchí (曲池 LI11), Chǐzé (尺泽 LU5) and Yújì (鱼际 LU10). Group 3: Qìhǎi (气海 CV6), Zúsānlǐ (足三里 ST36) and Sānyīnjiāo (三阴交 SP6). One or two acupoints are selected from each group in one treatment. **Symptomatic acupoints:** For fever, dry throat and dry cough, Dàzhū (大椎 GV14), Tiāntū (天突 CV22) and Kǒngzuì (孔最 LU6) are added. For nausea, vomiting, loose stool, swollen tongue with sticky coating and soggy pulse, Zhōngwǎn (中脘 CV12), Tiānshū (天枢 ST25) and Fēnglóng (丰隆 ST40) are added. For fatigue and anorexia, CV12 and the four points around the umbilicus (1 cun bilateral, directly above and below the center of the umbilicus), BL20 are added. For clear nasal discharge, soreness of the shoulders and the back, pale tongue with white coating and slow pulse, Tiānzhu (天柱 BL10), BL12 and GV14 are added.

Acupuncture-moxibustion interventions at the clinical treatment stage (confirmed cases)

Objective: To propel the antipathogenic qi of lung and spleen, protect internal

organs, reduce damage, eliminate the epidemic pathogens, cultivate the earth to generate the metal, block the development of illness, ease the emotions and strengthen the confidence on conquer the pathogens.

Main acupoints: Group 1: LI4, Tàichōng (太冲 LR3), CV22, LU5, LU6, ST36 and SP6 Group 2: Dàzhū (大杼 BL11), BL12, BL13, Xīnshū (心俞 BL15) and Géshū (膈俞 BL17). Group 3: Zhōngfǔ (中府 LU1), Dànzhōng (膻中 CV17), CV6, Guānyuán (关元 CV4) and CV12. For the mild case or the ordinary case, 2 or 3 acupoints are selected from group 1 and group 2 in each treatment. For the severe case, 2 or 3 acupoints are selected from group 3. **Symptomatic acupoints:** For consistent fever, GV14 and LI11 are added, or bloodletting at Shíxuān (十宣 EX-UE11) and Ěrjiān (耳尖 HX6). For chest oppression and shortness of breath, Nèiguān (内关 PC6) and Lièquē (列缺 LU7), or Jùquē (巨阙 CV14), Qīmén (期门 LR14) and Zhàohǎi (照海 KI6) are added. For cough with expectoration, LU7, ST40 and Dìngchuǎn (定喘 EX-B1) are added. For diarrhea and loose stool: ST25 and Shàngjùxū (上巨虚 ST37) are added. For cough with yellow and sticky sputum and constipation: CV22, Zhīgōu (支沟 TE6), ST25 and ST40 are added. For low fever or feverish sensation and discomforts in the body, or fever absence, nausea, vomiting, loose stool, pale or slightly red tongue with white or white sticky coating: BL13, ST25, Fùjié (腹结 SP14) and PC6 are added.

Acupuncture and moxibustion interventions at the recovery stage **Objective:** To clear away residual toxins, restore the primary qi, promote the repair of internal organs and recover the functions of lung and spleen. **Main acupoints:** PC6, ST36, CV12, ST25 and CV6.

(1) Qi deficiency of lung and spleen The main symptoms are shortness of breath, fatigue, anorexia, nausea, vomiting, fullness in the epigastric region, weakness in defecation, loose stool, incomplete bowel movement, pale and swollen tongue with white and sticky coating. For the cases with marked symptoms of lung system, e.g. chest oppression and shortness of breath, CV17, BL13, LU1 are added. For the cases with marked symptoms of spleen and stomach dysfunction, e.g. poor appetite and diarrhea, Shàngwǎn (上脘 CV13) and Yīnlíngquán (阴陵泉 SP9) are added. (2) Qi and yin deficiency.

The main symptoms are fatigue, dry mouth, thirst, palpitation, profuse sweating, poor appetite, low fever or fever absence, dry cough with little sputum, dry tongue and lack of moisture, thready or weak pulse of deficiency type. For the cases with marked fatigue and shortness of breath, CV17 and Shénquè (神阙 CV8) are added. For the cases with marked dry mouth and thirst, Tàixī (太溪 KI3) and Yángchí (阳池 TE4) are added. For the cases with marked palpitation, BL15 and Juéyīnshū (厥阴俞 BL14) are added. For the cases with profuse sweating, LI4, Fùliū (复溜 KI7) and ST36 are added. For the cases with insomnia, Shénmén (神门 HT7), Yìntáng (印堂 EX-HN3), Ānmíán (安眠 EX-HN22) and Yǒngquán (涌泉 KI1) are added. (3) Insufficiency of lung and spleen, phlegm stagnation and collateral blockage The main symptoms are chest oppression, shortness of breath, dislike to speak, lassitude, sweating on exertion, cough with sputum, difficulty in expectoration, coarse skin, mental fatigue, loss of appetite, etc. BL13, BL20, BL15, BL17, Shènsū (肾俞 BL23), LU1 and CV17 are added. For difficulty in expectoration, ST40 and EX-B1 are added.

Guidance points out specifically that either acupuncture or moxibustion is optioned corresponding to the individual conditions at each stage of COVID-19. Additionally, the combination of these two interventions or the combination with acupoint application, auricular therapy, acupoint injection, scraping therapy, infantile tuina or acupoint massage is adopted accordingly. The even needling technique of acupuncture is used and the needle is retained for 20 to 30 min at each acupoint. Moxibustion is exerted for 10 to 15 min at each acupoint. The treatment is given once daily. The manipulation is implemented in reference to the national standard, GB/T21709 Standardized manipulations of acupuncture and moxibustion and clinical experiences. The third section of Guidance is the most characteristic: the self-interventions of acupuncture and moxibustion at home under the instruction of physician.

Moxibustion therapy: Moxibustion is applied by the patient him/herself at ST36, PC6, LI4, CV6, CV4, SP6, etc., about 10 min at each acupoint.

Acupoint application therapy: The plaster, e.g. moxibustion-thermal plaster or moxibustion-like plaster, is used at ST36, PC6, CV6, CV4, BL13, BL12, BL20, GV14, etc.. Tuina therapy at meridian and acupoints: The different tuina methods are exerted at the acupoints on the lung meridian and the heart meridian, the acupoints located below the knee on the spleen meridian and the acupoints on the stomach meridians, such as finger-pressing method, kneading method, palm pressing method, kneading-pressing method, tapping method or knocking method. Each manipulation is exerted for 15 to 20 min till the patient feels soreness and distention in the local area. Traditional physical exercise: The traditional physical exercise is optional according to the individual recovery conditions, including Yijinjing (Exercise for muscle and tendon strengthening), Taijiquan (Taiji boxing), Baduanjin (Eight-section exercise), Wuqinxi (Five-animal exercise), etc.. Each physical exercise is applied once daily, 15 to 30 min each time. Emotional counseling: The attention is paid to emotional regulation. Auricular points, moxibustion, tuina, herbal diet, herbal tea, medicated bath and music are applicable in combination for physical and mental relaxation, anxiety relief and sleep assistance.

Foot bath and fumigation-washing therapy: the herbs for expelling wind, clearing heat and eliminating pathogen are selected, i.e. Jīngjiè (荆芥 Herba Schizonepetae), Àiyè (艾叶 Folium Artemisiae Argyi), Bòhe (薄荷 Herba Menthae), Yúxīngcǎo (鱼腥草 Herba Houttuyniae), Dàqīngyè (大青叶 Folium Isatidis), Pèilán (佩兰 Herba Eupatorii), Shíchāngpú (石菖蒲 Rhizoma Acori Tatarinowii), Làiliǎocǎo (辣蓼草 Polygonum lapathifolium

L.), Yùjīn (郁金 Radix Curcumae) and Dīngxiāng (丁香 Flos Caryophylli), 15 g for each, as well as Bīngpiàn (冰片 Borneolum Syntheticum) 3g. The decocted Chinese herbal liquid is poured into a foot tub and an appropriate amount of warm water is added. When the water is ready at 38 to 45°C, foot bath is exerted for around 30 min. All of the interventions above are the dominant techniques of health care in TCM. Their utilization fully embodies the idea of “disease prevention” in TCM, meaning, preventing from illness before suffering, preventing from the progress of illness after suffering and preventing from recurrence after cured. They play the crucial role in reducing the incidence of COVID-19 and preventing from its recurrence. Suggestions It is observed that the regimens in Guidance recommended are on the base of the ancient literature research, modern clinical research and experimental research of acupuncture and moxibustion and in reference to a series of achievements obtained in the effect mechanism research of acupuncture and moxibustion in recent years. Firstly, the regimens recommended in Guidance are in agreement to the staging of TCM treatment in Diagnosis and treatment plan of corona virus disease 2019 (tentative seventh edition) issued by NHC and they focus specially on the characteristics of acupuncture-moxibustion therapies. Secondly, the implementation of various therapeutic methods is in compliance with “being convenient, safe and effective”. Thirdly, Guidance determines its efforts for the contribution of acupuncture-moxibustion therapies to each stage of the diseases, points out the combination of acupuncture with western medication and Chinese herbal decoction, plays the coordination effect of acupuncture and moxibustion and believes the crucial effect of acupuncture and moxibustion at the recovery stage of COVID-19.

COVID-19 is the seriously epidemic disease. TCM and acupuncture-moxibustion have not been adopted as the first option in treatment. Besides the limited understanding in the effectiveness of them, the other key reason is for TCM therapy, especially acupuncture-moxibustion, the physician has to very closely contact with patient during treatment, which highly increases the infectious incidence of medical staffs. Therefore, the protection to medical staffs must be in the top priority when exerting acupuncture, moxibustion, seed-pressure of auricular acupuncture, cupping, scraping, etc.. The acupuncture physicians who had participated in the treatment of COVID-19 responded that it is very inconvenient to operate acupuncture with three-layer protective gloves. In case the gloves are broken, infection may occur. The authors believe that for moxibustion interventions, the mild moxibustion with hand-holding moxa stick is not suggested. The moxibustion device with the function of smoke abatement or smoke discharge should be optioned to avoid the stimulation of moxa smoke to the respiratory tract of patient. But, such mild moxibustion with hand-holding moxa stick can be applicable for the home nursing care. Regarding the effectiveness of moxa smoke, the consensus has not been met yet in academic field. But, in reference to the records of ancient medical works and the nowadays popular method of moxibustion in the folk, moxa smoke is applicable for the prevention of infectious diseases.

For example, it is recorded in Zhǒuhòu Bèijífāng 《肘后备急方》 (Emergency Formulas to Keep Up One's Sleeve), written by Hong GE, in the Jin Dynasty(317年—420AD) that smoking with moxa around the patient's bed, one moxa cone on each side of the bed is optimal to prevent from epidemic infection. The medical masters in the later generations had inherited this idea. The same prevention method is also recorded in Tàipíng Shèngguāifāng (《太平圣惠方》 Formulas from Benevolent Sages Compiled during the Taiping Era) and Pǔjīfāng (《普济方》 Formulas for Universal Relief). This moxibustion intervention is the earliest-recorded measure of air disinfection in history. The modern research discovers that moxa smoke acts on anti-bacteria, anti-fungus, anti-virus and anti-pathogen [8]. Therefore, on the base of individual tolerance, the appropriate use of moxa smoke in room brings a certain effect of disinfection. In Guidance, the duration of moxibustion at each acupoint is 10 to 15 min. But, in clinical practice, the moxibustion is seldom exerted on acupoints one by one. Instead, the special device, moxa box or moxa holder is used to cover several acupoints simultaneously in one moxibustion intervention. The duration of treatment is over 30 min generally and it will be even longer if the heat-sensitive moxibustion is exerted. Therefore, the authors believe that the duration of moxibustion intervention should be longer to achieve a better effect if the patient is in a comfortable posture and has strong endurance.



Note: Picture from CCTV Compared

Compared with Guidance of the first edition, the content of Guidance of the second edition is much richer and more practical and instructive. With the development of COVID-19, the people are getting deep understanding of the disease and more and more experiences in treatment will be accumulated gradually. It also reflects that the nature of medical development is the process of constant understanding, rectification and conquering disease. At present, COVID-19 is spreading in many countries of the world. China's experiences in fight against COVID-19 have been recognized and advocated by WHO. Of them, the application of Chinese herbal medication, acupuncture and moxibustion have their unique characteristics. Undoubtedly, the modern medicine measures give priority to treatment and salvage of COVID-19. But, no matter which medical theoretic system is adopted, faced with the epidemic, every measure should aim to treating disease and saving lives. More weapons available in the fight against the disease do bring more benefits to patients.

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Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs LUO Hui, TANG Qiao-ling, SHANG Ya-xi, LIANG Shi-bing, YANG Ming, Nicola Robinson, and LIU Jian-ping

Results: The use of CM to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in Huangdi's Internal Classic (Huang Di Nei Jing) where preventive effects were recorded. There were 3 studies using CM for prevention of SARS and 4 studies for H1N1 influenza. None of the participants who took CM contracted SARS in the 3 studies. The infection rate of H1N1 influenza in the CM group was significantly lower than contracted SARS in the 3 studies. The infection rate of H1N1 influenza in the CM group was significantly lower than the non-CM group (relative risk 0.36, 95% confidence interval 0.24–0.52; n=4). For prevention of COVID-19, 23 provinces in China issued CM programs. The main principles of CM use were to tonify qi to protect from external pathogens, disperse wind and discharge heat, and resolve dampness. The most frequently used herbs included Radix astragali (Huangqi), Radix glycyrrhizae (Gancao), Radix saposhnikoviae (Fangfeng), Rhizoma Atractylodis (Baizhu), Lonicerae Japonicae Flos (Jinyinhua), and Fructus forsythiae (Lianqiao). **Conclusions:** Based on historical records and human evidence of SARS and H1N1 influenza prevention, Chinese herbal formula could be an alternative approach for prevention of COVID-19 in high-risk population. Prospective, rigorous population studies are warranted to confirm the potential preventive effect of CM. **KEYWORDS:** Chinese medicine, corona virus disease 2019 (COVID-19), prevention program, clinical evidence, review

In December 2019, a pneumonia associated with the corona virus disease 2019 (COVID-19) emerged in Wuhan, Hubei Province, China.(1)

It is highly contagious and has quickly spread to many other parts of China and some other countries within 1 month since the first report emerged. As of February 11, 2020, 44,653 cases of confirmed infections and 1,113 deaths have been reported in Chinese mainland.(2) Outside of China, there had been 395 confirmed cases and 1 death from 24 countries were reported as of February 11, 2020.(3) The outbreak of COVID-19 raised intense attention not only within China but internationally.(4) On 20 January 2020, the Chinese government added it to the Notifiable Communicable Disease List and gave the highest priority to its prevention and treatment.(5) On 30 January 2020, the World Health Organization (WHO) declared a public health emergency of international concern for China's COVID-19.

Although the WHO said: "To date, there is no specific medicine recommended to prevent or treat the novel coronavirus", (6) in China, historically, when the outbreak started, Chinese medicine (CM) approaches including oral administration of preventive herbal formulae, wearing CM sachets, indoor herbal medicine fumigation, etc. were recommended for prevention and treatment.(7,8). For example, in 2003, CM approaches were used to prevent and treat severe acute respiratory syndrome (SARS),(9,10) which was the most serious infectious disease outbreak in China prior to the COVID-19. In 2009, during the pandemic of H1N1 influenza around the world, the National Administration of Traditional Chinese Medicine of China issued a CM

prevention program, which included 4 Chinese herbal medicine (CHM) formulae for adults of different CM body constitutions and one for children.(11)

The current outbreak of COVID-19 resulted in many provinces in China issuing CM prevention and control programs, among which the prevention programs are mainly oral CHM formulae. This study has reviewed the historical and human research evidence on CM in preventing and control of infections in order to provide guidance for the prevention of COVID-19.

METHODS

Data Sources

Three types of data were searched, including historical classics records, human research evidence and current prevention programs. (I) Historical classics records: records on the prevention of epidemic diseases in ancient CM books were searched, including history, treatment principles, medicines and application of CM to prevent epidemic disease. (II) Human research studies: studies to evaluate the preventive effects of CM on contagious respiratory virus diseases were included. The inclusion criteria were as follows. (1) Study design: clinical trials, cohort studies, and other population studies without control. (2) Population: high-risk populations exposed to SARS or H1N1 influenza. (3) Intervention: oral CHM formulae, including decoction, granules, or patent medicine. (4) Control: placebo, blank or without control group. (5) Outcome: infection rate defined as laboratory-confirmed incidence of disease. (III) Current prevention programs: CM prevention programs for COVID-19 issued by the state or provincial health authorities in China. Considering that some provinces had regularly updated the programs according to the local prevalence and clinical practice, the most recent versions of the programs were included for analyses in this study.

Literature Search

Retrieval strategy differed among the above three types of data. The first type of data was based on mainly manual retrieval of ancient books of CM on epidemic diseases, supplemented by electronic database retrieval. The list of literature retrieved was determined by discussion among all authors. Secondly, 6 databases were searched including PubMed, Google Scholar, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and CQVIP database, with the key words of "severe acute respiratory syndrome" (or "SARS"), "influenza", "H1N1", "prevent*" and "Chinese medicine" (pinyin: zhongyi or zhongyao). Thirdly, government websites or official media websites were searched for prevention programs on COVID-19. Two authors (Luo H and Tang QL) conducted the literature search independently. The search date was up to February 10, 2020.

Data Extraction and Analysis

The following data were extracted and analyzed: source of evidence, time of publication or release, author, setting, basis for formulation of CM prevention strategy, composition of CM prescription, target disease, course of prevention, effect, and adverse reaction. The data was qualitatively described and presented, and if possible, quantitative or descriptive statistics were conducted. When the data were available for pooling, meta-analysis would be conducted by RevMan 5.3 software (<https://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download>).

RESULTS

CHM Formula for Preventing "Pestilence" in Ancient CM Classics

The theory of prevention and treatment of "pestilence" (refers to fatal epidemic disease, pinyin: wenyi) in CM originated from Huangdi's Internal Classic (Huang Di Nei Jing), which was written about 2000 years ago.(12)

It suggested two aspects which should be employed to prevent the spread of epidemics. One was to maintain and improve the healthy qi in the body by taking preventive medicine [Xiaojin Dan (小金丹) in Huangdi's

Internal Classic, the first recommended formula of CM to prevent pestilence], healthy diet care, exercise and so on, so as to resist the invasion of external pathogen, and the other was to avoid the source of infection.(13)

These two principles of epidemic disease prevention have been followed by CM practitioners till now.(12,14)

Since Huangdi's Internal Classic, a large number of formulae for preventing epidemic diseases have been recorded in other ancient CM classics, such as, the Handbook of Prescriptions for Emergencies (Zhou Hou Bei Ji Fang), Essential Prescriptions Worth a Thousand Gold for Emergencies (Bei Ji Qian Jin Yao Fang), Medical Secrets of an Official (Wai Tai Mi Yao), Compendium of Materia Medica (Ben Cao Gang Mu), etc.(15)

The famous doctor SUN Si-miao (541–682 AD) expounded the basis of medicines to prevent "pestilence" in his book Essential Prescriptions Worth a Thousand Gold for Emergencies: "pestilence comes from nature, so to prevent it, we need to find medicinal herbs that also come from nature. People would not be infected if they know and take preventive medicine."(16)

A literature study compared the characteristics of medicinal formulae for preventing pestilence in different periods of ancient China, found that during the Jin and Tang Dynasties (3rd–10th century AD), medicinal formulae were mainly used to eliminate the pathogenic factors, while Ming and Qing dynasties (14–20th century AD) focused on fortifying Spleen (Pi), resolving dampness, clearing heat, and detoxifying.(17)

Although many formulae for pestilence prevention were recorded in ancient CM books, the case description of prevention was relatively rare. Through limited literature searches, we found an interesting case report: SU Shi (1037-1101 AD), a famous poet in the Northern Song Dynasty, accidentally found a formula for preventing pestilence named Sheng San Zi (圣散子), a powder consisting of 22 herbs.(18)

Later, when he was demoted to Huangzhou, Hubei Province, the pestilence had been outbreak for several years. He disclosed the prescription to the local people. After taking this formula, the number of patients with the disease was significantly reduced, and many lives were saved. This story was recorded by SU Shi himself, when he wrote a preface to his doctor friend PANG An-shi's book General Treatise on Febrile Diseases (Shang Han Zong Bing Lun).(18)

Evidence of CHM Formula for Preventing SARS Three studies were identified including 1 controlled study (19) and 2 single cohort studies (20,21) conducted during the epidemic of SARS. Lau, et al (19) designed a controlled study to evaluate a herbal formula for prevention of SARS (no herbal intervention in the control group) and conducted it in Hong Kong SAR, China. The sample size was 16,437 (1,063 in the herbal group and 15,374 in the non-herbal group), and all participants were hospital care workers including doctors, nurses, and other staff. The result showed that none of the participants who took modified formula of Yupingfeng Powder (玉屏风散) plus Sangju Decoction (桑菊饮) contracted SARS, while 64 out of 15,347 (0.4%) in the non-herbal group were infected with SARS ($P=0.035$). Nineteen cases (1.8%) appeared minor adverse effects after 14 days taking herbal medicine, including diarrhea, sore throat, dizziness, and nausea.

Both single cohort studies were conducted in Beijing, China with sample sizes of 3,561(21) and 163, respectively. All participants were medical staff from two hospitals, where SARS patients were recruited and treated during the study period. Among them, Xu, et al's study (20) only included first-line medical staff in treating SARS. The courses of taking herbal formulae for prevention were 6 days (20) and 12–25 days,(21) respectively. The formulae used in these studies were both classical formula Yupingfeng Powder plus some heat-clearing and detoxifying herbs. The results showed that none of the participants who took the preventive herbal medicine had contracted SARS in the two studies. Information on the safety of the herbal medicines was not reported.

The details of the preventive herbal formulae of the three studies are presented in Table 1.

Evidence of CHM Formula for Preventing H1N1 Influenza

Four studies were identified, including 3(22-24) randomized controlled trials (RCTs) and 1(25) non-randomized controlled clinical study. All the studies were conducted during the prevalence of H1N1 influenza in Chinese mainland and published in Chinese. In these studies, participants were exposed to high-risk environments, such as hospitals and schools where H1N1 influenza occurred. The total sample size was 25,636 with the largest one of 25,329.(25)

The testedherbal interventions included self-made herbal formulae and Chinese patent medicines [Qingjie Fanggan Granule (清解防感颗粒), Kangbingdu Oral Liquid (抗病毒口服液); Ganmao Qingre Granule (感冒清热胶囊)]; while in the control group, 1 study used placebo and 3 used blank control. The course of herbal formulae ranged from 3 to 7 days, while the follow-up ranged from 5 to 30 days. The outcome measure was infection rate of H1N1 infl uenza tested by laboratory serological diagnosis. One study reported that no adverse events occurred,(22) while the others did not report. The details of the characteristics of included trials are presented in Table 2.

The data on infection rate of H1N1 influenza from 4 studies were pooled in meta-analysis. The results showed that the infection rate in the herbal formulae group was significantly lower than that in the control group [relative risk (RR) 0.36, 95% confidence Interval (CI) 0.24–0.52, $P<0.01$]. A sensitivity analysis was conducted to exclude non-RCT and the results showed similar effect (RR 0.36, 95% CI 0.21–0.62, $P<0.01$, Figure 1).

Summary of Officially Issued CM Prevention Recommendations for COVID-19

Up to February 12, 2020, the National Health Commission of China has issued 5 versions of diagnosis and treatment programs for COVID-19, but none have included any content on CM prevention and control, but on treatment since the 3rd versions.(26)

Table 1. Ingredients of Herbal Formulae for Preventing SARS

Study	Latin name	Phylin	Chinese name
Liu JY 2005 ⁽²⁴⁾	Folium mori	Sargol	桑叶
	Flos chrysanthemi	Juhua	菊花
	Semen artemisiae annuum	Xingren	苈子
	Fructus forsythiae	Lianqiao	连翘
	Herba menthae	Bohe	薄荷
	Radix platycodonis	Jiegeng	板蓝根
	Radix glycyrrhizae	Gancao	甘草
	Rhizoma phragmitis	Lugen	芦根
	Radix astragal	Huangqi	黄芪
	Radix saposhnikoviae	Fangfeng	防风
	Folium isatidis	Banlangen	板蓝根
	Radix scutellariae	Huangqin	黄芩
	Lonicerae Japonicae Flos	Jinyinhua	金银花
	Radix astragal	Huangqi	黄芪
Xu ZY 2005 ⁽²²⁾	Rhizoma Alcyonidis	Beishu	白术
	Radix saposhnikoviae	Fangfeng	防风
	Ginseng Radix	Shenren	人参
	Crystal sugar	Bingtang	冰糖
Zhang L 2005 ⁽²⁵⁾	Radix astragal	Huangqi	黄芪
	Rhizoma Alcyonidis	Beishu	白术
	Radix saposhnikoviae	Fangfeng	防风
	Cyrtosium fortunei J. Sm.	Guanghong	广红
	Isatidis Folium	Dangqin	板蓝根
	Radix Scutellariae	Huangqin	黄芩
	Talcum	Huashi	石膏
	Radix glycyrrhizae	Gancao	甘草

Table 2. Characteristics of Included Trials of Herbal Formulae for H1N1 Influenza

Study	Design type	Population	Average age (Year)	Sample size (Case, P/C)	Herbal intervention	Control	Course (d)	Follow up (d)	Outcome
Song YP 2019 ⁽²¹⁾	RCT	Population in close contact with H1N1 influenza patients; high-risk population	P: 25.6 ± 14.2 C: 27.1 ± 14.5	200 (100/100)	Qingjie Fanggan Granule	Placebo	3	30	Infection rate; adverse event
Liu L 2013 ⁽²³⁾	RCT	Medical staff	P: 30.5 ± 5.3 C: 31.4 ± 4.7	3 (28/25)	Decoction of self-made formula ^a	Blank	7	10	Infection rate
Xia BL 2010 ⁽²²⁾	RCT	Population in close contact with H1N1 influenza patients	23.5 (18–26)	54 (27/27)	Kangbingdu Oral Liquid; Ganmao Qingre Granule	Blank	3	14	Infection rate
Liu BL 2010 ⁽²⁴⁾	CCT	Student	Not report	25329 (23947/1382)	Decoction of self-made formula ^b	Blank	5	5	Infection rate

Notes: RCT: randomized controlled trial; CCT: controlled clinical trial; C: control group; P: prevention group. Ingredients of formulae: ^a Arnebiae Radix (Zicao), Herba Menthae (Bohe), and Radix Glycyrrhizae (Gancao). ^b Cyrtosium Fortunei J. Sm (Guanghong), Lonicerae Japonicae Flos (Jinyinhua), Fructus Forsythiae (Lianqiao), Folium Isatidis (Banlangen), Fructus Arctii (Niubangzi), Herba Agastache (Huoxiang), Lophatheri Herba (Zhuyue), Radix Glycyrrhizae (Gancao), and Isatidis Folium (Dangqin).

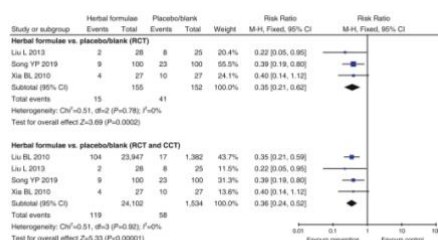


Figure 1. Meta-Analysis of Comparison between Chinese Medicine Prevention and Control (Blank or Placebo) on Infection Rate of H1N1 Influenza

Of the 31 provinces (including autonomous regions, and municipalities) in Chinese mainland, health authorities in 23 provinces had officially issued programs recommending herbal formulae to preventing COVID-19. These 23 provinces cover 7 regions of mainland: Northeast, North, Central (including Wuhan, Hubei Province, the original outbreak of COVID-19), South, East, Northwest, and Southwest China. All programs were formulated by clinical experts organized by local health authorities according to local geographic and climate

characteristics and COVID-19 prevalent conditions. The earliest program recommending CM for prevention was issued by Sichuan Province on January 21, 2020. Ten provinces have updated their programs since the first announcement, 7 of them have issued the 2nd edition and 3 issued the third edition. The applicable population of preventive programs included general and special population (such as the elderly, children, pregnant women, patients with chronic comorbidity diseases). Different groups of populations had specified preventive CM formulae. The programs issued by the 23 provinces included CM formulae ranging from 1 up to 10, with an average of 3.4 per program. With regard to the course of CM formulae for prevention, 11 provinces recommended from 3 to 14 days, while 12 provinces did not mention. In addition, Tibet Autonomous Region recommended Tibetan medicine and Guizhou province recommended Miao medicine formulae (one of the minority folk medicines). The basic characteristics of 23 provincial programs are shown in Appendix 1.

We counted the frequency of the herbs used in CM formulae for prevention of general population issued by the 23 provinces. The results showed that these formulae contained 54 different herbs, of which 19 herbs with a frequency of use for 3 or more times in preventive formulae for general population (Figure 2). The top two were Radix astragali (Huangqi) and Glycyrrhizae Radix Et Rhizoma (Gancao).

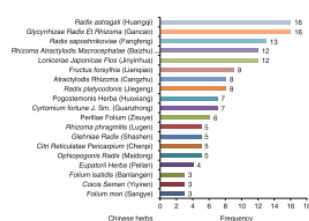


Figure 2. Frequency of Commonly Used Herbs in Preventive Formulae for COVID-19

DISCUSSION

As a new emerging acute respiratory infectious disease, COVID-19 lacks effective methods to control and treat the infection. It is urgent and reasonable to explore effective intervention strategies from traditional medicine for its prevention. This study examines the historical records for infection prevention in CM, as well as previous clinical evidence on CM prevention for similar public health emergencies such as SARS and H1N1 influenza. Recorded literature showed that the use of CM to prevent epidemics of infectious diseases can be traced back to ancient CM practice over thousands of years, and its successful effects were preliminarily substantiated by modern human clinical researches when applied to SARS and H1N1 influenza epidemics suggesting that historical CM experience is a worthwhile approach.

Based on the comprehensive analyses of the prevention programs issued by 23 provinces since the COVID-19 outbreak, we found that the main CM principles in preventing COVID-19 were to tonify qi to protect and provide defense from external pathogens, disperse wind and discharge heat, and resolve dampness with aroma. It was also similar to the characteristics of CHM formulae for preventing "pestilence" in ancient times and SARS in 2003.(17,19)

The 6 most commonly used herbs were Astragali Radix (Huangqi), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikovia Radix (Fangfeng), Atractylodis Macrocephalae Rhizoma (Baizhu), Lonicerae Japonicae Flos (Jinyinhua), and Forsythiae Fructus (Lianqiao). Astragali Radix (Huangqi), Saposhnikovia Radix (Fangfeng), and Atractylodis Macrocephalae Rhizoma (Baizhu) are all ingredients of a classical herbal formula Yupingfeng Powder, for tonifying qi to protect from external pathogens. In Lao, et al's controlled study (19) of CM formula for preventing SARS, Yupingfeng Powder was also the main ingredients. Some studies have confirmed that Yupingfeng Powder has antiviral, anti-inflammatory and immunoregulatory effects.(27,28)

Japonicae Flos (Jinyinhua) and Forsythiae Fructus (Lianqiao) are the core components of Yinqiao Powder, which is a classical formula used to prevent and treat respiratory infectious diseases in ancient.(29)

An experimental study found that the effect of Yinqiao Powder (银翘散) in preventing and treating upper respiratory tract infection could be explained by its antibacterial and antiviral properties and improvement of the function of upper respiratory mucosal immune system.(30)

A multicenter, large-scale, randomized trial found that Yinqiao Powder plus another heat-clearing formula could reduce time to fever resolution in patients with the influenza virus infection.(29)

At present, the National Health Commission of China has not issued a CM prevention program for COVID-19. The reasons may be, first, according to the CM theory of three-factors concerned treatment (Sanyin Zhiyi, 三因制宜), due to the differences of individual, regional, and seasonal factors in the occurrence and distribution of diseases, these factors should be considered in prevention and treatment,(31,32) and second, lack of solid evidence of CM formula for COVID-19. By comparing and analyzing the prevention programs issued by provincial levels, we also found that there was slight regional difference in the recommended herbal formulae and prescription principles. For example, due to the dry climate in northern China, there are additional one or two herbs for nourishing yin in the formula, like Glehniae Radix (Shashen) and Ophiopogonis Radix (Maidong), while in the south, due to the humid climate, aromatic herbs with the function of resolving dampness and turbidity are used in the formulae, like Pogostemonis Herba (Huoxiang) and Eupatorii Herba (Peilan).

Individual difference was also considered in the prevention programs in some provinces. There were two or more formulae recommended in 18 provinces' programs, which were applicable for different populations, such as the elderly, children, pregnant women, or patients with chronic comorbidity diseases, population in close contact with COVID-19 patients, etc. In addition, 7 provinces or province-level municipality (Beijing, Tianjin, Shanxi, Henan, Hunan, Shandong, Yunnan) recommended formulae according to the types of CM body constitutions of the population. This tailored prevention strategy might help to improve the preventive effect.

We suggest that the safety should also be paid attention to when taking CHM formula to prevent COVID-19, especially when they are used for long period. The public should choose the prescriptions under the guidance of CM doctors according to the program issued by provincial health authorities, and avoid taking the prescriptions or herbs with unknown origin and without official approval. It should also be noted that the prevention advice for taking decoction were not reported in the 12 provinces' program. According to the programs of other provinces, it is appropriate to take the decoction for 1 week.

Based on the consideration of health economics and balance of risks and benefits, we do not recommend that all people should take CHM to prevent COVID-19. Due to the highly contagion,(33,34) high-risk populations exposed to COVID-19 patients, including medical personnel, family members, and other people who are in close contact with COVID-19 patients, as well as residents living in COVID-19 outbreak areas, would probably benefit from taking CHM formulae for prevention. These formulae recommended in the prevention programs are easily available in pharmacies and hospitals across the country.

As there is no direct clinical evidence for the prevention of the new emerging COVID-19, currently reported researches were from previous literature on the prevention of SARS and H1N1 influenza by CM which can only be considered as indirect evidence to refer to the current outbreak. Thirdly, the prevention programs for preventing COVID-19 were issued shortly after the outbreak, which were formulated by CM experts based on their previous experience in the prevention and treatment of similar diseases and their initial understanding of the disease; therefore, the actual effect of these programs needs to be verified in clinical application, and updated and improved according to the evidence of new researches on COVID-19.

For future studies, we recommend prospective cohort studies, RCTs or registry studies to evaluate the effect of CHM formulae in prevention of COVID-19. At present, as the COVID-19 has not yet been controlled, we expect that a series of prospective population studies with rigorous design and large sample should commence with protocol registration, ethical approval, and implementation in a timely manner, to produce reliable evidence for CM prevention of COVID-19 or similar emerging respiratory infectious diseases in the future.

In conclusion, based on historical records and clinical evidence of SARS and H1N1 influenza prevention, CHM formula could be an alternative approach for the prevention of COVID-19 in high-risk population while waiting for the development of a successful vaccine. Prospective well design population studies are needed to evaluate the preventive effect of CM.

Conflicts of Interest

The authors declare that they have no competing interest.

Author Contributions

Luo H, Tang QL, and Liu JP conceived of the design and carried out the study. Tang QL undertook the literature review of historical evidence and assisted in writing the manuscript. Shang YX and Liang SB translated and assisted in analyzing Chinese data. Yang M provided suggestions for the design of study. Luo H undertook the literature review of prevention programs and wrote the manuscript. Liu JP supervised the study and revised the manuscript. Robinson N revised the manuscript and provided important perspectives. All authors read and approved the final manuscript. Luo H and Tang QL contributed equally to this work.

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Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)

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Since December 2019, multiple cases of novel coronavirus pneumonia (NCP) have been identified in Wuhan, Hubei. With the spread of the epidemic, such cases have also been found in other parts of China and other countries. As an acute respiratory infectious disease, NCP has been included in Class B infectious diseases prescribed in the Law of the People's Republic of China on Prevention and Treatment of Infectious Diseases, and managed as an infectious disease of Class A. By taking a series of preventive control and medical treatment measures, the rise of the epidemic situation in China has been contained to a certain extent, and the epidemic situation has eased in most provinces, but the incidence abroad is on the rise. With increased understanding of the clinical manifestations and pathology of the disease, and the accumulation of experience in diagnosis and treatment, in order to further strengthen the early diagnosis and early treatment of the disease, improve the cure rate, reduce the mortality rate, avoid nosocomial infection as much as possible and pay attention to the spread caused by the imported cases from overseas, we revised the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6) to Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7).

I. Etiological Characteristics

The novel coronaviruses belong to the β genus. They have envelopes, and the particles are round or oval, often polymorphic, with diameter being 60 to 140 nm. Their genetic characteristics are significantly different from

SARS-CoV and MERS-CoV. Current research shows that they share more than 85% homology with bat SARS-like coronaviruses (bat-SL-CoVZC45). When isolated and cultured in vitro, the 2019-nCoV can be found in human respiratory epithelial cells in about 96 hours, however it takes about 6 days for the virus to be found if isolated and cultured in Vero E6 and Huh-7 cell lines. Most of the know-how about the physical and chemical properties of coronavirus comes from the research on SARS-CoV and MERS-CoV. The virus is sensitive to ultraviolet and heat. Exposure to 56°C for 30 minutes and lipid solvents such as ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, and chloroform can effectively inactivate the virus. Chlorhexidine has not been effective in inactivating the virus.

II. Epidemiological Characteristics

1. Source of infection Now, the patients infected by the novel coronavirus are the main source of infection; asymptomatic infected people can also be an infectious source. 2. Route of transmission Transmission of the virus happens mainly through respiratory droplets and close contact. There is the possibility of aerosol transmission in a relatively closed environment for a long-time exposure to high concentrations of aerosol. As the novel coronavirus can be isolated in feces and urine, attention should be paid to feces or urine contaminated environmental that leads to aerosol or contact transmission. 3. Susceptible groups People are generally susceptible.

III. Pathological changes

Pathological findings from limited autopsies and biopsy studies are summarized below: 1. Lungs Solid changes of varying degrees are present in the lungs. Alveolar damage involves fibromyxoid exudation and hyaline membrane formation. The exudates are composed of monocytes and macrophages, with plenty of multinucleated syncytial cells. Type II alveolar epithelial cells are markedly hyperplastic, some of which are desquamated. Viral inclusions are observed in type II alveolar epithelial cells and macrophages. Alveolar interstitium is marked with vascular congestion and edema, infiltration of monocytes and lymphocytes, and vascular hyaline thrombi. The lungs are laden with hemorrhagic and necrotic foci, along with evidence of hemorrhagic infarction. Organization of alveolar exudates and interstitial fibrosis are partly present. The bronchi are filled with desquamated epithelial cells, mucus and mucus plugs. Hyperventilated alveoli, interrupted alveolar interstitium and cystic formation are occasionally seen. On electron microscopy, cytoplasmic NCP virions are observed in the bronchial epithelium and type II alveolar epithelium. NCP virus antigen positivity in some alveolar epithelia and macrophages are revealed through immunohistochemistry staining, which are positive for NCP virus nucleic acid via RT-PCR. 2. Spleen, hilar lymph nodes and bone marrow The spleen is evidently shrunk. Lymphocytopenia and focal hemorrhage and necrosis are present. Macrophagocyte proliferation and phagocytosis are noted in the spleen. Lymph nodes are found with sparse lymphocytes and occasional necrosis. CD4+ and CD8+ T cells are present in reduced quantity in the spleen and lymph nodes, revealed by immunohistochemistry staining. Pancytopenia is identified in bone marrow. 3. Heart and blood vessels Degenerated or necrosed myocardial cells are present, along with mild infiltration of monocytes, lymphocytes and/or neutrophils in the cardiac interstitium. Endothelial desquamation, endovasculitis and thrombi are seen in some blood vessels. 4. Liver and gall bladder Appearing enlarged and dark-red, the liver is found degenerated with focal necrosis infiltrated with neutrophils. The liver sinusoids are found hyperemic. The portal areas are infiltrated with lymphocytes and monocytes and dotted with microthrombi. The gall bladder is prominently filled. 5. Kidneys The kidneys are noted with protein exudation in the Bowman's capsule around glomeruli, degeneration and desquamation of the epithelial cells of renal tubules, and hyaline casts. Microthrombi and fibrotic foci are found in the kidney interstitium. 6. Other organs Cerebral hyperemia and edema are present, with degeneration of some neurons. Necrosis foci are noted in the adrenal glands. Degeneration, necrosis and desquamation of epithelium mucosae at varying degrees are present in the esophageal, stomach and intestine.

IV. Clinical Characteristics 1. Clinical manifestations Based on the current epidemiological investigation, the incubation period is one to 14 days, mostly three to seven days. Main manifestations include fever, fatigue

and dry cough. Nasal congestion, runny nose, sore throat, myalgia and diarrhea are found in a few cases. Severe cases mostly developed dyspnea and/or hypoxemia after one week. In severe cases, patients progress rapidly to acute respiratory distress syndrome, septic shock, metabolic acidosis that is difficult to correct, coagulopathy, multiple organ failure and others. It is worth noting that for severe and critically ill patients, their fever could be moderate to low, or even barely noticeable. Some children and neonatal cases may have atypical symptoms, manifested as gastrointestinal symptoms such as vomiting and diarrhea, or only manifested as low spirits and shortness of breath. The patients with mild symptoms did not develop pneumonia but only low fever and mild fatigue. From current situations, most patients have good prognosis and a small number of patients are critically ill. The prognosis for the elderly and patients with chronic underlying diseases is poor. The clinical course of pregnant women with NCP is similar to that of patients of the same age. Symptoms in children are relatively mild.

2. Laboratory tests General findings In the early stages of the disease, peripheral WBC count is normal or decreased and the lymphocyte count decreases. Some patients see an increase in liver enzymes, lactate dehydrogenase (LDH), muscle enzymes and myoglobin. Elevated troponin is seen in some critically ill patients while most patients have elevated C-reactive protein and erythrocyte sedimentation rate and normal procalcitonin. In severe cases, D-dimer increases and peripheral blood lymphocytes progressively decrease. Severe and critically ill patients often have elevated inflammatory factors. Pathogenic and serological findings (1) Pathogenic findings: Novel coronavirus nucleic acid can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces and other specimens using RT-PCR and/or NGS methods. It is more accurate if specimens from lower respiratory tract (sputum or air tract extraction) are tested. The specimens should be submitted for testing as soon as possible after collection. (2) Serological findings: NCP virus specific IgM becomes detectable around 3-5 days after onset; IgG reaches a titration of at least 4-fold increase during convalescence compared with the acute phase.

3. Chest imaging In the early stage, imaging shows multiple small patchy shadows and interstitial changes, apparent in the outer lateral zone of lungs. As the disease progresses, imaging then shows multiple ground glass opacities and infiltration in both lungs. In severe cases, pulmonary consolidation may occur while pleural effusion is rare.

V. Case Definitions 1. Suspect cases Considering both the following epidemiological history and clinical manifestations: 1.1 Epidemiological history 1.1.1 History of travel to or residence in Wuhan and its surrounding areas, or in other communities where cases have been reported within 14 days prior to the onset of the disease; 1.1.2 In contact with novel coronavirus infected people (with positive results for the nucleic acid test) within 14 days prior to the onset of the disease; 1.1.3 In contact with patients who have fever or respiratory symptoms from Wuhan and its surrounding area, or from communities where confirmed cases have been reported within 14 days before the onset of the disease; or 1.1.4 Clustered cases (2 or more cases with fever and/or respiratory symptoms in a small area such families, offices, schools etc within 2 weeks).

1.2 Clinical manifestations 1.2.1 Fever and/or respiratory symptoms; 1.2.2 The aforementioned imaging characteristics of NCP; 1.2.3 Normal or decreased WBC count, normal or decreased lymphocyte count in the early stage of onset. A suspect case has any of the epidemiological history plus any two clinical manifestations or or all three clinical manifestations if there is no clear epidemiological history.

2. Confirmed cases Suspect cases with one of the following etiological or serological evidences: 2.1 Real-time fluorescent RT-PCR indicates positive for new coronavirus nucleic acid; 2.2 Viral gene sequence is highly homologous to known new coronaviruses. 2.3 NCP virus specific Ig M and IgG are detectable in serum; NCP virus specific IgG is detectable or reaches a titration of at least 4-fold increase during convalescence compared with the acute phase.

VI. Clinical Classification

1. Mild cases The clinical symptoms were mild, and there was no sign of pneumonia on imaging.

2. 2. Moderate cases Showing fever and respiratory symptoms with radiological findings of pneumonia.
3. 3. Severe cases

Adult cases meeting any of the following criteria

- (1) Respiratory distress (≥ 30 breaths/ min);
- (2) Oxygen saturation $\leq 93\%$ at rest;
- (3) Arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) $\leq 300\text{mmHg}$ ($1\text{mmHg}=0.133\text{kPa}$).

In high-altitude areas (at an altitude of over 1,000 meters above the sea level), $\text{PaO}_2/\text{FiO}_2$ shall be corrected by the following formula: $\text{PaO}_2/\text{FiO}_2 \times [\text{Atmospheric pressure (mmHg)}/760]$ Cases with chest imaging that showed obvious lesion progression within 24-48 hours $>50\%$ shall be managed as severe cases.

Child cases meeting any of the following criteria:

- (1) Tachypnea ($\text{RR} \geq 60$ breaths/min for infants aged below 2 months; $\text{RR} \geq 50$ BPM for infants aged 2-12 months; $\text{RR} \geq 40$ BPM for children aged 1-5 years, and $\text{RR} \geq 30$ BPM for children above 5 years old) independent of fever and crying;
- (2) Oxygen saturation $\leq 92\%$ on finger pulse oximeter taken at rest;
- (3) Labored breathing (moaning, nasal fluttering, and infrasternal, supraclavicular and intercostal retraction), cyanosis, and intermittent apnea;
- (4) Lethargy and convulsion;
- (5) Difficulty feeding and signs of dehydration.

4. Critical cases

Cases meeting any of the following criteria: 4.1 Respiratory failure and requiring mechanical ventilation; 4.2 Shock; 4.3 With other organ failure that requires ICU care.

VII. Clinical early warning indicators of severe and critical cases

1. Adults

1.1 The peripheral blood lymphocytes decrease progressively; 1.2 Peripheral blood inflammatory factors, such as IL-6 and C-reactive proteins, increase progressively; 1.3 Lactate increases progressively; 1.4 Lung lesions develop rapidly in a short period of time.

2. Children.

2.1 Respiratory rate increased; 2.2 Poor mental reaction and drowsiness; 2.3 Lactate increases progressively; 2.4 Imaging shows infiltration on both sides or multiple lobes, pleural effusion or rapid progress of lesions in a short period of time; 2.5 Infants under the age of 3 months who have either underlying diseases (congenital heart disease, bronchopulmonary dysplasia, respiratory tract deformity, abnormal hemoglobin, and severe malnutrition, etc.) or immune deficiency or hypofunction (long-term use of immunosuppressants).

VIII. Differential Diagnosis

1. The mild manifestations of NCP need to be distinguished from upper respiratory tract infections caused by other viruses. 2. NCP is mainly distinguished from other known viral pneumonia and mycoplasma pneumoniae infections such as influenza virus, adenovirus and respiratory syncytial virus. Especially for suspect cases, methods such as rapid antigen detection and multiplex PCR nucleic acid detection should be adopted as much

as possible for detection of common respiratory pathogens. 3. It should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis and organizing pneumonia.

IX. Case Finding and Reporting Health professionals in medical institutions of all types and at all levels, upon discovering suspect cases that meet the definition, should immediately put them in single room for isolation and treatment. If the cases are still considered as suspected after consultation made by hospital experts or attending physicians, it should be reported directly online within 2 hours; samples should be collected for new coronavirus nucleic acid testing and suspect cases should be safely transferred to the designated hospitals immediately. People who have been in close contact with patients who have been confirmed of new coronavirus infection are advised to perform new coronavirus pathogenic testing in a timely manner, even though common respiratory pathogens are tested positive. If two nucleic acid tests, taken at least 24-hour apart, of a NCP suspect case are negative, and the NCP virus specific IgM and IgG are negative after 7 days from onset, the suspect diagnosis can be ruled out.

X. Treatment 1. Treatment venue determined by the severity of the disease 1.1 Suspected and confirmed cases should be isolated and treated at designated hospitals with effective isolation, protection and prevention conditions in place. A suspect case should be treated in isolation in a single room. Confirmed cases can be treated in the same room. 1.2 Critical cases should be admitted to ICU as soon as possible.

2. General treatment 2.1 Letting patients rest in bed and strengthening support therapy; ensuring sufficient caloric intake for patients; monitoring their water and electrolyte balance to maintain internal environment stability; closely monitoring vital signs and oxygen saturation. 2.2 According to patients' conditions, monitoring blood routine result, urine routine result, c-reactive protein (CRP), biochemical indicators (liver enzyme, myocardial enzyme, renal function etc.), coagulation function, arterial blood gas analysis, chest imaging and cytokines detection if necessary. 2.3 Timely providing effective oxygen therapy, including nasal catheter and mask oxygenation and nasal high-flow oxygen therapy. If possible, inhalation of mixed hydrogen and oxygen (H₂/O₂: 66.6%/33.3%) can be applied. 2.4 Antiviral therapy: Hospitals can try Alpha-interferon (5 million U or equivalent dose each time for adults, adding 2ml of sterilized water, atomization inhalation twice daily), lopinavir/ritonavir (200 mg/50mg per pill for adults, two pills each time, twice daily, no longer than 10 days), Ribavirin (suggested to be used jointly with interferon or lopinavir/ritonavir, 500 mg each time for adults, twice or three times of intravenous injection daily, no longer than 10 days), chloroquine phosphate (500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1&2 and 500 mg qd for Days 3-7 for adults with body weight below 50 kg), Arbidol (200 mg tid for adults, no longer than 10 days). Be aware of the adverse reactions, contraindications (for example, chloroquine cannot be used for patients with heart diseases) and interactions of the above- mentioned drugs. Further evaluate the efficacy of those drugs currently being used. Using three or more antiviral drugs at the same time is not recommend; if an intolerable toxic side effect occurs, the respective drug should be discontinued. For the treatment of pregnant women, issues such as the number of gestational weeks, choice of drugs having the least impact on the fetus, as well as whether pregnancy being terminated before treatment should be considered with patients being informed of these considerations. 2.5 Antibiotic drug treatment: Blind or inappropriate use of antibiotic drugs should be avoided, especially in combination with broad-spectrum antibiotics.

3. Treatment of severe and critical cases

3.1 Treatment principle: On the basis of symptomatic treatment, complications should be proactively prevented, underlying diseases should be treated, secondary infections also be prevented, and organ function support should be provided timely. 3.2 Respiratory support: 3.2.1 Oxygen therapy: Patients with severe symptoms should receive nasal cannulas or masks for oxygen inhalation and timely assessment of respiratory distress and/or hypoxemia should be performed. 3.2.2 High-flow nasal-catheter oxygenation or noninvasive mechanical ventilation: When respiratory distress and/or hypoxemia of the patient cannot be alleviated after receiving standard oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive ventilation can be considered. If conditions do not improve or even get worse within a short time (1-2 hours), tracheal intubation

and invasive mechanical ventilation should be used in a timely manner. 3.2.3 Invasive mechanical ventilation: Lung protective ventilation strategy, namely low tidal volume (6-8ml/kg of ideal body weight) and low level of airway platform pressure ($<30\text{cmH}_2\text{O}$) should be used to perform mechanical ventilation to reduce ventilator-related lung injury. While the airway platform pressure maintained $\leq 30\text{cmH}_2\text{O}$, high PEEP can be used to keep the airway warm and moist; avoid long sedation and wake the patient early for lung rehabilitation. There are many cases of human-machine asynchronization, therefore sedation and muscle relaxants should be used in a timely manner. Use closed sputum suction according to the airway secretion, if necessary, administer appropriate treatment based on bronchoscopy findings. 3.2.4 Rescue therapy: Pulmonary re-tensioning is recommended for patients with severe ARDS. With sufficient human resources, prone position ventilation should be performed for more than 12 hours per day. If the outcome of prone position ventilation is poor, extracorporeal membrane oxygenation (ECMO) should be considered as soon as possible. Indications include: ① When $\text{FiO}_2 > 90\%$, the oxygenation index is less than 80mmHg for more than 3-4 hours; ② For patients with only respiratory failure when the airway platform pressure $\geq 35\text{cmH}_2\text{O}$, VV-ECMO mode is preferred; if circulatory support is needed, VA-ECMO mode should be used. When underlying diseases are under control and the cardiopulmonary function shows signs of recovery, withdrawal of ECMO can be tried. 3.3 Circulatory support: On the basis of adequate fluid resuscitation, efforts should be made to improve microcirculation, use vasoactive drugs, closely monitor changes in blood pressure, heart rate and urine volume as well as lactate and base excess in arterial blood gas analysis. If necessary, use non-invasive or invasive hemodynamic monitor such as Doppler ultrasound, echocardiography, invasive blood pressure or continuous cardiac output (PiCCO) monitoring. In the process of treatment, pay attention to the liquid balance strategy to avoid excessive or insufficient fluid intake. If the heart rate suddenly increases more than 20% of the basic value or the decrease of blood pressure is more than 20% of the basic value with manifestations of poor skin perfusion and decreased urine volume, make sure to closely observe whether the patient has septic shock, gastrointestinal hemorrhage or heart failure.

3.4 Renal failure and renal replacement therapy: Active efforts should be made to look for causes for renal function damage in critical cases such as low perfusion and drugs. For the treatment of patients with renal failure, focus should be on the balance of body fluid, acid and base and electrolyte balance, as well as on nutrition support including nitrogen balance and the supplementation of energies and trace elements. For critical cases, continuous renal replacement therapy (CRRT) can be used. The indications include: ① hyperkalemia; ② acidosis; ③ pulmonary edema or water overload; ④ fluid management in multiple organ dysfunction. 3.5 Convalescent plasma treatment: It is suitable for patients with rapid disease progression, severe and critically ill patients. Usage and dosage should refer to Protocol of Clinical Treatment with Convalescent Plasma for NCP Patients (2nd trial version). 3.6 Blood purification treatment: Blood purification system including plasma exchange, absorption, perfusion and blood/plasma filtration can remove inflammatory factors and block "cytokine storm", so as to reduce the damage of inflammatory reactions to the body. It can be used for the treatment of severe and critical cases in the early and middle stages of cytokine storm. 3.7 Immunotherapy: For patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing, Tocilizumab can be used for treatment. The initial dose is 4-8mg/kg with the recommended dose of 400mg diluted with 0.9% normal saline to 100ml. The infusion time should be more than 1 hour. If the initial medication is not effective, one extra administration can be given after 12 hours (same dose as before). No more than two administrations should be given with the maximum single dose no more than 800mg. Watch out for allergic reactions. Administration is forbidden for people with active infections such as tuberculosis.

3.8 Other therapeutic measures For patients with progressive deterioration of oxygenation indicators, rapid progress in imaging and excessive activation of the body's inflammatory response, glucocorticoids can be used in a short period of time (three to five days). It is recommended that dose should not exceed the equivalent of methylprednisolone 1-2 mg/kg/day. Note that a larger dose of glucocorticoid will delay the removal of coronavirus due to immunosuppressive effects. Xuebijing 100ml/time can be administered intravenously

twice a day. Intestinal microecological regulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections. Child severe and critical cases can be given intravenous infusion of γ -globulin. For pregnant severe and critical cases, pregnancy should be terminated preferably with c-section. Patients often suffer from anxiety and fear and they should be supported by psychological counseling.

4. Traditional Chinese Medicine treatment

This disease belongs to the category of plague in traditional Chinese medicine (TCM), caused by the epidemic pathogenic factors. According to the different local climate characteristic and individual state of illness and physical conditions, the following treatment Protocol may vary. The use of over-pharmacopoeia doses should be directed by a physician.

4.1 During medical observation

Clinical manifestation 1: fatigue and gastrointestinal discomfort Recommended Chinese patent medicine: Huoxiang Zhengqi capsules (pills, liquid, or oral solution) Clinical manifestation 2: fatigue and fever Recommended Chinese patent medicine: Jinhua Qinggan granules, Lianhua Qingwen capsules (granules), Shufeng Jiedu capsules (granules), Fangfeng Tongsheng pills (granules)

4.2 During clinical treatment (confirmed cases)

4.2.1 Lung cleansing & detoxifying decoction

Scope of application: It is suitable for light, moderate and severe patients, and can be used reasonably in combination with the actual situation of patients in the treatment of critically ill patients. Recommended prescription: Ephedra 9g, Zhigancao 6g, Almond 9g, Gypsum 15-30g (fried first), Guizhi 9g, Zixie 9g, Zhuling 9g, Baizhu 9g, Zhiling 15g, Bupleurum 16g, Scutellaria baicalensis 6g, and Pinellia 9g, Ginger 9g, aster 9g, winter flower 9g, shoot dry 9g, asarum 6g, yam 12g, coriander fruit 6g, tangerine peel 6g, aquilegia 9g. Suggested use: Traditional Chinese medicine decoction pieces for decocting in water. One dose per day, twice in the morning and evening (forty minutes after a meal), take with warm water, and three doses a course.

If conditions permit, the patient can take half a bowl of rice soup each time after taking the medicine, and can take up to one bowl if the patient has a dry tongue and is deficient in bodily fluids. (Note: If the patient does not have a fever, the amount of gypsum should be little. If having a fever or strong heat, the amount of gypsum can be increased). If the symptoms improve but do not fully recover, then take the second course of treatment. If the patient has special conditions or other underlying diseases, the prescription of the second course of treatment can be modified based on the actual situation and the medicine should be discontinued when the symptoms disappear. Source of prescription: Notice on Recommending the Use of 'Lung cleansing & detoxifying decoction' in Treatment of NCP by Integrated Traditional Chinese and Western Medicine by the Office of the State Administration of Traditional Chinese Medicine & the General Office of the National Health Commission. (2022 No.22)

4.2.2 Mild cases

4.2.2.1 Cold dampness and stagnation lung syndrome

Clinical manifestations: fever, fatigue, sore body, cough, expectoration, chest tightness, suffocation, loss of appetite, nausea, vomiting, sticky stools. Tongue has thin fat tooth mark or is faint red, and the coating is white thick rot or white greasy and the pulse is moisten or slippery. Recommended prescription: Raw ephedra 6g, raw gypsum 15g, almond 9g, loquat 15g, gardenia 15g, Guanzhong 9g, Dilong 15g, Xu Changqing 15g, Huoxiang 15g, Peilan 9g, Cangzhu 15g, Yunling 45g, Atractylodes 30g, Jiao Sanxian 9g each, Magnolia officinalis 15g, betel coconut 9g, yarrow fruit 9g, ginger 15g. Suggested use: one dose daily, boiled with 600ml water, take it three times at morning, noon and evening before meal.

4.2.2.2 Dampness and heat-accumulation lung syndrome

Clinical manifestations: low or no fever, slight chills, fatigue, heavy head and body, muscle soreness, dry cough, low phlegm, sore throat, dry mouth, do not want to drink more, or accompanied by chest tightness, no sweat or sweating, Or vomiting and loss of appetite, diarrhea or sticky stool. The tongue is reddish, and the coating is white, thick and greasy or thin yellow, and the pulse is slippery or sloppy. Recommended prescription: Betel nut 10g, apple 10g, Magnolia 10g, Zhimu 10g, scutellaria baicalensis 10g, Bupleurum 10g, red peony 10g, forsythia 15g, artemisia annua 10g (decocted

later), 10g of green leaves, 10g of green leaves, 5g of raw licorice. Suggested use: one dose daily, boiled with 400ml water, take it twice at morning and evening.

4.2.3 Moderate cases 4.2.3.1 Dampness and stagnation lung syndrome Clinical manifestations: fever, low cough and sputum, or yellow sputum, suffocation, shortness of breath, bloating, and constipation. The tongue is dark red and fat; the coating is greasy or yellow and the pulse is slippery or stringy. Recommended prescription: raw ephedra 6g, bitter almond 15g, raw gypsum 30g, raw coix seed 30g, grass root 10g, patchouli 15g, artemisia annua 12g, Polygonum cuspidatum 20g, verbena 30g, dried reed root 30g, gardenia 15g 15g of orange red, 10g of raw licorice. Suggested use: one dose daily, boiled with 400ml water, take it twice at morning and evening.

4.2.3.2 Cold dampness lung syndrome

Clinical manifestations: low fever, low body temperature, or no heat, dry cough, low sputum, fatigue, chest tightness, nausea, or nausea. The tongue is pale or red, and the coating is white or greasy, and the veins are pulsating. Recommended prescription: Atractylodes lancea 15g, Chenpi 10g, Magnolia 10g, Aquilegia 10g, grass fruit 6g, raw ephedra 6g, Zhihuo 10g, ginger 10g, betel nut 10g. Suggested use: one dose daily, boiled with 400ml water, take it twice at morning and evening.

4.2.4 Severe cases 4.2.4.1 Plague poison and lung-closing syndrome Clinical manifestations: fever, flushing, cough, yellowish phlegm, or blood in sputum, wheezing, shortness of breath, tiredness, fatigue, dryness and stickiness, nausea, food loss, poor stool, and short urination. Red tongue, yellow greasy coating, slippery pulses. Recommended prescription: Raw ephedra 6g, almond 9g, raw gypsum 15g, licorice 3g, fragrant fragrant 10g (back), Magnolia 10g, atractylodes 15g, grass fruit 10g, pinellia 9g, Poria 15g, raw rhubarb 5g (back) 10g, gardenia 10g, red peony 10g. Suggested use: one or two doses daily, boiled with 100-200ml water, take it 2-4 times, oral or nasal feeding.

4.2.4.2 Syndrome of flaring heat in qifen and yingfen Clinical manifestations: Hot fever, thirst, shortness of breath, shortness of breath, blurred vision, or spotted rash, or vomiting blood, bleeding, or convulsions in the limbs. Tongue ridges have few or no moss, and the pulse sinks finely, or floats large and counts. Recommended prescription: 30-60g gypsum (fried first), 30g of Zhimu, 30-60g of raw land, 30g of buffalo horn (fried first), 30g of red sage, 30g of black ginseng, 15g of forsythia, 15g of paeonia, 6g of peony 12g, gardenia 15g, raw licorice 6g. Suggested use: 1 dose per day, decoction, first decoct gypsum and buffalo horn, then apply other pieces, 100ml-200ml each time, 2-4 times a day, orally or nasally. Recommended Chinese patent medicines: Xiyanping injection, Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection. Drugs with similar efficacy can be selected according to individual conditions, or can be used in combination according to clinical symptoms. Traditional Chinese medicine injection can be used in combination with traditional Chinese medicine decoction.

4.2.5 Critical cases (syndrome of inner blocking causing collapse) Clinical manifestations: dyspnea, dyspnea, asthma or need mechanical ventilation, fainting, irritability, cold sweating, dark purple tongue, thick or dry moss, large floating roots. Recommended prescription: 15g of ginseng, 10g of Heishun tablets (decoct first), 15g of dogwood, delivered with Suhexiang Pill or Angong Niu Huang Pill. For patients on mechanical ventilation with abdominal distention or constipation: 5-10g of Dahuang. For patients with human-machine asynchronization: 5-10g of Dahuang and 5- 10g of Mangxiao while administering sedatives and muscle relaxants. Recommended Chinese patent medicines: Xuebijing injection, Reduning injection, Tanreqing injection, Xingnaojing injection, Shenfu injection, Shengmai injection, Shenmai injection. Drugs with similar efficacy can be selected according to individual conditions, or can be used in combination according to clinical symptoms. Traditional Chinese medicine injection can be used in combination with traditional Chinese medicine decoction

Note: Recommended usage of Chinese medicine injections for severe and critical cases The use of traditional Chinese medicine injections follows the principle of starting from a small dose and gradually adjusting the

dosage according to the instructions of the drug. The recommended usage is as follows: Viral infection or combined mild bacterial infection: 0.9% sodium chloride injection 250ml plus Xiyanping injection 100mg bid, or 0.9% sodium chloride injection 250ml heated Duning injection 20ml, or 0.9% sodium chloride injection 250ml plus Tanreqing injection 40ml bid. High fever with disturbance of consciousness: 250ml of 0.9% sodium chloride injection and 20ml bid of Xingnaojing injection. Systemic inflammatory response syndrome or/and multiple organ failure: 250ml of 0.9% sodium chloride injection and 100ml of Xuebijing injection. Immunosuppression: 250ml of 0.9% sodium chloride injection and 100ml bid of Shenmai injection. Shock: 250ml of 0.9% sodium chloride injection plus 100ml bid of Shenfu injection.

4.2.6 Convalescent period 4.2.6.1 Lung and spleen qi deficiency syndrome

Clinical manifestations: shortness of breath, fatigue, anorexia, nausea, fullness, weak stool, and uneasiness. The tongue is pale and greasy. Recommended prescription: French Pinellia 9g, Chenpi 10g, Codonopsis 15g, Sunburn Astragalus 30g, Stir-fried Atractylodes 10g, Poria 15g, Huoxiang 10g, Amomum villosum 6g (later), and Licorice 6g Suggested use: 1 dose per day, boiled with 400ml of water, twice a day at morning and evening.

4.2.6.2 Qi and Yin deficiency syndrome Clinical manifestations: Fatigue, shortness of breath, dry mouth, thirst, palpitations, sweating, poor appetite, low or no lever, dry cough and little sputum; dry tongue, fine or weak pulses. Recommended prescription: North and south radix salviae 10g, 15g ophiopogonis, 6g American ginseng, 6g schisandra, 6g gypsum 15g, 10g light bamboo leaves, 10g mulberry leaves, 15g reed root, 15g salviae miltiorrhiza, 6g raw liquorice. Suggested use: 1 dose per day, boiled with 400ml of water, twice a day at morning and evening.

XI. Discharge criteria and after-discharge considerations 1. Discharge criteria 1) Body temperature is back to normal for more than three days; 2) Respiratory symptoms improve obviously; 3) Pulmonary imaging shows obvious absorption of inflammation, 4) Nuclei acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs (sampling interval being at least 24 hours). Those who meet the above criteria can be discharged.

2. After-discharge considerations 2.1 The designated hospitals should contact the primary healthcare facilities where the patients live and share patients' medical record, to send the information of the discharged patients to the community committee and primary healthcare facility where the patients reside. 2.2. After discharge, it is recommended for patients to monitor their own health status in isolation for 14 days, wear a mask, live in well-ventilated single room if possible, reduce close contact with family members, separate dinning, practice hand hygiene and avoid going out. 2.3 It is recommended for the patients to return to the hospitals for follow-up and re-visit in two and four weeks after discharge.

XII. Patients Transportation Principles Patients should be transported in accordance with the Work Protocol for Transfer of the Novel Coronavirus Pneumonia Patients (Trial Version) issued by the National Health Commission.

XIII. Nosocomial Infection Prevention and Control Measures to prevent and control nosocomial infection should be implemented in accordance with the requirements of the Technical Guidelines for the Prevention and Control of Infection by the Novel Coronavirus in Medical Institutions (First Edition) and the Guidelines on the Usage of Common Medical Protective Equipment against Novel Coronavirus Infection (Trial Version) formulated by the National Health Commission.

The General Office of National Health Commission Office of State TCM Administration

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Combination of western medicine and Chinese traditional patent medicine in treating a family case of COVID-19 in Wuhan

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Abstract In December 2019, an outbreak of novel coronavirus (2019-nCoV) occurred in Wuhan, Hubei Province, China. By February 14, 2020, it has led to 66 492 confirmed patients in China and high mortality up to ~2.96% (1123/37 914) in Wuhan. Here we report the first family case of coronavirus disease 2019 (COVID-19) confirmed in Wuhan and treated using the combination of western medicine and Chinese traditional patent medicine Shuanghuanglian oral liquid (SHL). This report describes the identification, diagnosis, clinical course, and management of three cases from a family, suggests the expected therapeutic effects of SHL on COVID-19, and warrants further clinical trials.

Keywords novel coronavirus (2019-nCoV); COVID-19; Chinese traditional patent medicine; Shuanghuanglian oral liquid

Introduction

Since December 31, 2019, a cluster of patients with pneumonia of unknown cause has been reported in Wuhan, China. This special pneumonia was associated with a novel coronavirus, 2019-nCoV, named initially by the World Health Organization (WHO) in January 2020 [1]. An outbreak of 2019-nCoV pneumonia (officially and internationally named as COVID-19 on February 11, 2020 by the WHO) occurred and spread to the entire China and multiple countries worldwide [2]. By February 14, the number of patients confirmed with COVID-19 reached 66 492, 8969 suspected patients, and 1523 deaths were identified in China [3]. By February 14, the number of confirmed patients and deaths were 37 914 and 1123, respectively, and the mortality of COVID-19 was 2.96% in Wuhan City, Hubei Province, which is considered as the origin of first cluster of patients [3]. The confusing and difficult thing for physicians is that they do not have specific drugs to either treat or prevent the aggravation and serious complications of COVID-19 for such patients [4]. Thus, Chinese herbs attract our attention, and investigations for different clinical trials are in progress. The present report described a family case, including three cases who received western medicine and Chinese traditional patent medicine Shuanghuanglian oral liquid (SHL) treatments and achieved rapid recovery.

Case report

The family case includes parents and a daughter. The family lives in an apartment 3 km from the Huanan Seafood Wholesale Market in Wuhan, Hubei Province. These cases are a typical familial cluster where all of them had COVID-19 [5]. All the patients were informed about the clinical trial (ChiCTR2000029605) and signed informed consent. Case 1 is a 51-year-old female. On January 17, 2020, the patient presented a feeling of general malaise and coldness. On January 19, she had fever with body temperature of 37.3 °C and experienced diarrhea and vomiting. She started to receive intravenous injection of cefotaxime in community clinic and took oral Jinyebaidu granules (another Chinese traditional patent medicine) and oseltamivir (75 mg, twice a day) for 4 days. She had persistent severe fever with body temperature from 37.6 °C to 38.3 °C for four days. On January 23, her chest computed tomography (CT) scan showed multiple patchy ground glass opacity and consolidation shadow in bilateral lung and subpleural regions (Fig. 1A). She was highly suspected with COVID-19. Oral moxifloxacin and arbidol were prescribed, and she continued to take Jinyebaidu granules and oseltamivir. On January 24, her body temperature reached 39.9 °C and experienced severe fatigue, diarrhea, and breathlessness despite continuous treatments of the above drugs. She felt better after intravenous injection of immunoglobulin (IVIG, 5 g per day) and dexamethasone (5 mg, once to twice a day). However, the patient experienced recurrent fever (body temperature of 39 °C) and breathlessness, and her blood oxygen saturation fluctuated from 90% to 95% at the night of January 27. On January 28, the second chest CT scan indicated that her pneumonia aggravated for the past 5 days (Fig. 1B). A nasopharyngeal swab specimen was obtained and sent for detection of 2019-nCoV. Although the patient's 2019-nCoV test was negative (Table 1), she was diagnosed of COVID-19 in accordance with her symptoms and chest CT display. On the same day, she was confined into an isolation ward and started to take oral SHL (twice a day, 20 mL once). On the next day, SHL administration increased to three times a day (20 mL once) without using any other drugs. From January 29 to 31, the patient's symptoms resolved with body temperature decreasing from 37.3 °C to 36.5 °C and without vomiting and diarrhea. The patient gradually felt strong except for slight cough. After February 6, the patient's symptoms disappeared, and her third chest CT scan (Fig. 1C) showed significant absorption of bilateral ground glass opacity compared with the previous ones. The association of her symptoms with treatments is shown in Fig. 2, and the clinical laboratory results are shown in Table 2. Cases 2 and 3 became simultaneously ill 9 days after they had close contacts with case 1 [5]

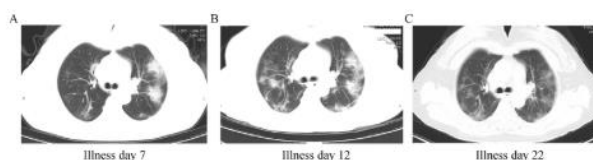


Fig. 1 Chest CT images of case 1. (A) CT imaging on January 23, 2020 shows ground glass opacity in both lungs on illness day 7. (B) Image taken on January 28, 2020, shows aggravation of pneumonia on illness day 12. (C) Image taken on February 6, 2020 shows the absorption of bilateral ground glass opacity after SHL treatment from January 28.

Table 1 Testing results of 2019-nCoV

Specimen	Case 1				Case 2			Case 3	
	Illness day 12	Illness day 20	Illness day 23	Illness day 3	Illness day 11	Illness day 14	Illness day 3	Illness day 11	
Nasopharyngeal swab	Negative	Negative	NT	Negative	Negative	NT	Positive	Negative	
Anal swab	NT	NT	Negative	NT	NT	Negative	NT	NT	

NT, not tested.

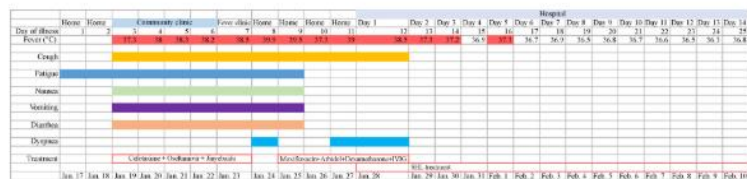


Fig. 2 Symptoms, maximum body temperatures, and treatment timeline in accordance with day of illness and day of hospitalization (January 17 to February 10).

Table 2 Clinical laboratory results of case 1

Measure	Reference range	Illness day 13 Hospital day 2	Illness day 24 Hospital day 13
White cell count ($\times 10^9/L$)	3.50–9.50	5.93	5.46
Red cell count ($\times 10^{12}/L$)	3.80–5.10	4.13	4.06
Neutrophil count ($\times 10^9/L$)	1.90–6.30	3.04	3.27
Lymphocyte count ($\times 10^9/L$)	1.10–3.20	2.11	1.5
Eosinophil count ($\times 10^9/L$)	0.02–0.52	0.12	0.15
Platelet count ($\times 10^9/L$)	125.0–350.0	361	323
Hemoglobin (g/L)	115.0–150.0	113	111
Hematocrit (%)	35.0–45.0	35	35
Sodium (mmol/L)	136–214	140	140.4
Potassium (mmol/L)	3.50–5.10	4.22	4.8
Chloride (mmol/L)	99–110	104.6	102.4
Calcium (mmol/L)	2.15–2.50	2.06 ↓	2.19
Carbon dioxide (mmol/L)	22.0–29.0	21 ↓	25.1
Glucose (mmol/L)	4.11–6.05	–	5.01
Blood urea nitrogen ($\mu\text{mol/L}$)	2.6–7.5	3.1	3.6
Creatinine ($\mu\text{mol/L}$)	45–84	53	60
Total protein (g/L)	64–83	68.4	68.6
Albumin (g/L)	35–52	29.6 ↓	33.2 ↓
Total bilirubin ($\mu\text{mol/L}$)	≤ 21	6.4	4.5
Procalcitonin (ng/mL)	≤ 0.05	0.03	0.03
Alanine aminotransferase (U/L)	≤ 33	17	20
Aspartate aminotransferase (U/L)	≤ 32	16	19
Alkaline phosphatase (U/L)	35–105	59	83
Fibrinogen (g/L)	2.00–4.00	5.31 ↑	–
Lactate dehydrogenase (U/L)	135–214	248 ↑	–
Prothrombin time (s)	11.5–14.5	13.6	–
International normalized ratio	0.80–1.20	1.03	–
Creatine kinase (U/L)	≤ 170	35	27
C-reactive protein (mg/L)	≤ 3	57.8 ↑	–

Case 2 is a 27-year-old female nurse at the clinical trial center of Division of Cardiology of Tongji Hospital, Wuhan, daughter of case 1, who took care of her mother. On January 26, the patient presented mild weakness, diarrhea, and low fever, and she started to take oral Jinyebaidu granules, oseltamivir, moxifloxacin, and arbidol. On the next day, all her symptoms aggravated with body temperature reaching to 38.3 °C, frequent vomiting, and diarrhea for 5 times a day. At the night of January 27, her body temperature reached 39.5 °C with chest tightness and shortness of breath. Although she took nonsteroidal anti-inflammatory drug (loxoprofen), her fever remained high (39 °C). On January 28, her chest CT scan showed consolidation shadow in the left lung, and her 2019-nCoV test showed negative using nasopharyngeal swab specimen. Considering her contact history with her mother, she was also confined into an isolation ward and started to take SHL 20 mL once for three times a day without taking other drugs. Her body temperature ranged from 37.5 °C to 38.5 °C during January 29 to 31 and decreased from 37.5 °C to 36.5 °C on February 1. All other symptoms resolved on February 2 with recovered appetite and spirit. Two repeated 2019-nCoV tests were negative (Table 1). On February 6, her second chest CT scan showed the absorption of the left lung shadow (Fig. 3). After her disease symptoms disappeared, the oral dose of SHL reduced to 10 mL once for three times a day. The patient's clinical laboratory results are shown in Table 3. Case 3 is a 53-year-old male, husband of case 1 and father of case 2, who presented mild diarrhea, vomiting, and fever on January 26. On January 28, the patient was diagnosed of COVID-19 with positive 2019-nCoV test using nasopharyngeal swab specimen (Table 1) and chest CT scan showing patchy ground glass opacity in the right lower lung subpleural fields (Fig. 4). He had no fever, cough, and breathlessness. Thus, the patient started to isolate himself at home and took SHL (20 mL once, three times a day), moxifloxacin, and arbidol on January 28.

Since February 2, all his symptoms resolved with exception of light nausea, and he continued taking SHL with other drugs. On February 4, he felt slightly weak. On February 7, the patient fully recovered, and the repeated 2019-nCoV RNA test was negative (Table 1). Niu, M., R. Wang, Z. Wang, P. Zhang, Z. Bai, J. Jing, Y. Guo, X. Zhao, X. Zhan, Z. Zhang, X. Song, E. Qin, J. Wang and X. Xiao. Rapid establishment of traditional Chinese medicine prevention and treatment for the novel coronavirus pneumonia based on clinical experience and molecular docking. China J. Chin. Mater. Med., 2020, doi:10.19540/j.cnki.cjcmm.20200206.501.

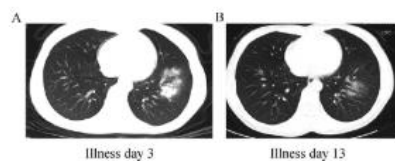


Fig. 3 Chest CT images of case 2. (A) CT imaging obtained from case 2 on January 28, 2020 shows consolidation shadow in the left lung on illness day 3. (B) Image taken on February 6, 2020 shows the absorption of consolidation shadow after SHL treatment from January 28.

Measure	Reference range	Illness day 4 Hospital day 2	Illness day 13 Hospital day 13
White cell count ($\times 10^9/L$)	3.50-9.50	3.63	5.79
Red cell count ($\times 10^{12}/L$)	3.80-5.10	4.5	4.28
Neutrophil count ($\times 10^9/L$)	1.90-6.30	2.12	3.2
Lymphocyte count ($\times 10^9/L$)	1.10-3.20	1.25	1.98
Eosinophil count ($\times 10^9/L$)	0.02-0.52	0.01	0.17
Platelet count ($\times 10^9/L$)	125.0-350.0	139	308
Hemoglobin (g/L)	115.0-150.0	125	117
Hematocrit (%)	35.0-47.0	37.9	36.2
Sodium (mmol/L)	130-144	135.3	143.5
Potassium (mmol/L)	3.50-5.10	3.69	4.27
Chloride (mmol/L)	99-110	97.1	106.3
Calcium (mmol/L)	2.15-2.50	2.25	2.27
Carbon dioxide (mmol/L)	22.0-29.0	22.3	25.2
Glucose (mmol/L)	4.11-6.05	4.31	4.82
Blood urea nitrogen (mmol/L)	2.6-7.5	2.7	3.4
Creatinine (mmol/L)	45-84	59	52
Total protein (g/L)	64-85	77.2	65.6
Albumin (g/L)	35-52	41.5	37.5
Total bilirubin (mmol/L)	<0.21	6.6	4
Procalcitonin (ng/mL)	<0.05	0.04	—
Alanine aminotransferase (U/L)	<33	8	30.1
Aspartate aminotransferase (U/L)	<32	21	27
Alkaline phosphatase (U/L)	35-105	52	22.1
Fibrinogen (g/L)	2.00-4.00	3.42	—
Lactate dehydrogenase (U/L)	135-214	170	186
Prothrombin time (s)	11.5-14.5	13.6	—
International normalized ratio	0.80-1.20	1.03	—
Creatine kinase (U/L)	<170	52	27
C-reactive protein (mg/L)	<3	9.4.1	—

1. The patient's value was below normal. 2. The patient's value was above normal.

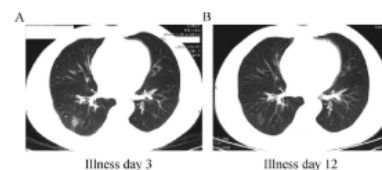


Fig. 4 Chest CT images of case 3. (A) CT imaging obtained from case 3 on January 28, 2020 shows ground glass opacity in the left lung on illness day 3. (B) Image taken on February 7, 2020 shows the absorption of ground glass opacity after SHL treatment from January 28.

Discussion

This report described the first typical family case of COVID-19 treated using the Chinese traditional patent medicine SHL because of poor response to other treatments. The three patients were a close family, and the mother was the first victim with typical symptoms of severe viral pneumonia and confirmed as COVID-19 in accordance with the symptoms and chest CT scan. Cases 2 and 3 had close contact history with case 1, and 9 days later they became ill with positive diagnosis of COVID-19. All their symptoms resolved after using the Chinese traditional patent medicine SHL and rapidly recovered without obvious adverse effects when the patients showed no response and their symptoms continued to aggravate after other treatments, including IVIG (5 g per day) and dexamethasone, antibiotics, and antiviral compounds. SHL, a Chinese traditional patent medicine containing extracts of three Chinese herbs, namely, honeysuckle, forsythia, and Scutellaria baicalensis, is usually used to treat cold, sore throat, and cough with fever. SHL has been used in clinical practice for a long time because of its affordable cost and no serious adverse reaction. Recent news from preliminary study findings indicated that SHL can inhibit 2019-nCoV (http://www.cas.cn/yw/202001/t20200131_4733137.shtml, accessed on January 31, 2020). Considering that no specific drugs are recommended to treat COVID-19, we started our clinical trial (ChiCTR2000029605) to investigate whether SHL can treat this disease and the family case is a part of the clinical trial. These cases suggest that SHL might be effective for COVID-19 although subsequent clinical trials are needed. In this family case report, we described two patients who had poor response to other treatments but responded well to SHL therapy. Case 3 showed positive therapeutic effect although he simultaneously received arbidol. Early treatments may contribute to patients' outcome and several errors, including taking antibiotics, and combination of two antiviral drugs should be avoided. This report suggests that SHL treatment might be effective for COVID-19 and warrants subsequent clinical trials to obtain sufficient evidence for clinical recommendation.

Acknowledgements

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Li Ni, Ling Zhou, Min Zhou, Jianping Zhao, and Dao Wen Wang declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained from all

the patients in which their identifying information are included in this article. Other ethical board approval is not applicable in this case report.

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Traditional Chinese medicine for COVID-19 treatment 1. Summary The current 2019-nCoV outbreak is moving rapidly [1], the cumulative number of confirmed cases in mainland China has reached 80151, with 47,204 (58.89 %) cured cases and 2943 (3.67 %) deaths as of 2-Mar-2020, and no specific drug has been discovered for Coronavirus Disease 2019 (COVID-19). However, a number of clinical practice results showed that traditional Chinese medicine (TCM) plays significant role in the treatment of COVID-19, bringing new hope for the prevention and control of COVID-19. TCM has a long history and played an indispensable role in the

prevention and treatment of several epidemic diseases. During the SARS epidemic in 2003, the intervention of TCM has also achieved remarkable therapeutic effect. During the treatment period of COVID-19, more than 3100 medical staff of TCM were dispatched to Hubei province, and TCM scheme was included in the guideline on diagnosis and treatment of COVID-19 [2], and TCM experts fully participate in the whole rescue process. The decoction, Chinese patent medicine, acupuncture and other characteristic therapy of TCM was comprehensively employed, mainly treated based on syndrome differentiation. Specific TCM wards were set up, and established the designated hospital, moreover, TCM team participates in treatment collectively. Currently, the total number of confirmed cases treated by TCM has reached 60,107 [3]. In 102 cases of mild symptoms treated with TCM, the clinical symptom disappearance time was shortened by 2 days, the recovery time of body temperature was shortened by 1.7 days, the average length of stay in hospital was shortened by 2.2 days, the improvement rate of CT image was increased by 22 %, the clinical cure rate was increased by 33 %, 27.4 % reduction in the rate of common to severe cases and 70 % increase in lymphocyte. In addition, in the treatment of severe patients with TCM, the average length of stay in hospital and the time of nucleic acid turning negative has been shortened by more than 2 days. From current treatment results, TCM based on an over-all symptoms of 2019-nCoV pneumonia patients, has suggested to prescribe prescription that are likely to be effective, such as qingfei paidu decoction (QPD), gancaoganjiang decoction, shenganmahuang decoction, qingfei touxie fuzheng recipe, etc. QPD which consisted of Ephedrae Herba, Glycyrrhizae Radix et Rhizoma Praeparata cum Melle, Armeniacae Semen Amarum, Gypsum Fibrosum, Cinnamomi Ramulus, Alismatis Rhizoma, Polyporus, Atractylodis Macrocephalae Rhizoma, Poria, Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma Praeparatum cum Zingibere et Alumine, Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Farfarae Flos, Belamcandae Rhizoma, Asari Radix et Rhizoma, Dioscoreae Rhizoma, Aurantii Fructus Immaturus, Citri Reticulatae Pericarpium, and Pogostemonis Herba, has been promoted as a general prescription in the diagnosis and treatment plan of COVID-19 in China [2]. Among the 701 confirmed cases treated by QPD, 130 cases were cured and discharge clinical symptoms of 51 cases disappeared, 268 cases of symptoms improved, and 212 cases of stable symptoms without aggravation [3]. The effective cure rate of QPD against COVID-19 is over 90 %. According to the theory of TCM, the target organ location of COVID-19 is the lung, and the etiology attribute is "damp and toxin plague". The network pharmacology analysis showed that QPD has an overall regulatory effect via multi-component and multi-target. The primary site of pharmacological action is the lung, as 16 herbs to lung meridian, which indicated that the decoction is mainly specific for lung diseases. In addition, it can play the role of dehumidification through the rise and fall of the spleen and stomach, and exhibited the protection for heart, kidney and other organs. Among the potential targets screen, most of them co-expressed with ACE-2, the receptor of COVID-19, indicating the potential improvement of COVID-19. It can inhibit the replication of COVID-19 by acting on multiple ribosomal proteins. COVID-19 can lead to strong immune response and inflammatory storm [4]. Functional enrichment analysis showed that QPD could inhibit and alleviate excessive immune response and eliminate inflammation by regulating immune related pathway and cytokine action related pathway [5]. Furthermore, through the prediction of molecular docking, it was found that patchouli alcohol, ergosterol and shionone in the formula had better anti-COVID-19 effect, which provided new molecule structures for new drug development [6]. Here, we take one highly suspected COVID-19 patient treated with TCM as a case example to show its effectiveness [7]. The male patient was on a business trip in Wuhan for several days before the onset of the disease. During the admission period, fever and cough were repeated, and respiratory rales of both lungs were not obvious. Western medicine was used firstly, including orally take oseltamivir phosphate capsule, intravenous infusion of ganciclovir, aerosol inhalation of recombinant human interferon α 1b, etc. Although the nucleic acid test was negative, the results of chest CT showed that the fusion of two lung ground glass shadows was enlarged and the density was increased, which was more advanced than that of admission (Fig. 1a-1c). As the serious illness, combined with the patient's performance of damp-heat syndrome, and the heat is more serious than damp, QPD was added for treatment. On the night of administration, the body temperature dropped to 36.2 °C, and then tended to be normal. After 6 days of treatment, chest CT was better than before, tracheobronchial shadow was normal, and inflammation was obviously absorbed (Fig. 1d). The patient had no fever or asthenia, coughing

occasionally, and the rales of two lungs were weaker than before. After discharge, continue to take 7 doses of the prescription, occasionally cough, no special discomfort was found. The clinical symptoms and imaging examination of the patients improved significantly after the treatment, reflecting the advantages of TCM. TCM has own characteristics such as holistic concept, balance of Yin and Yang, syndrome differentiation and treatment, strengthening the body resistance to eliminate pathogenic factors. TCM has thousands of years of experience in regulating the body and enhancing the resistance to epidemic diseases, with unique insights and prevention and control experience. For mild and common patients, the early intervention of TCM can effectively prevent the disease from transforming into severe and critical disease. In the severe cases, TCM has won time for rescuing them by improving symptoms (<http://www.scio.gov.cn/xwfbh/xwfbh/wqfbh/42311/42560/index.htm>).

Treatment practice of COVID-19 showed that early intervention of TCM is important way to improve cure rate, shorten the course of disease, delay disease progression and reduce mortality rate. Furthermore, the reason why TCM works is not only to inhibit the virus, but might block the infection, regulate the immune response, cut off the inflammatory storm, and promote the repair of the body. Moreover, the prevention and control measures of COVID-19 fully reflect the ideology of “preventive treatment of disease”. Apart from the epidemic diseases recorded in the Han Dynasty should be isolated, the preventive measures of TCM also include psychology, sports, diet, medication, etc. In the next prevention and control work of COVID-19, it should give full play to the advantages of TCM in syndrome differentiation and the whole therapeutic effect, reduce the complications as well as death rate. Besides, the scientific research should also be carried out on the TCM with definite curative effective of COVID-19, to comprehensively evaluating its action mechanism and in-depth understanding COVID-19.

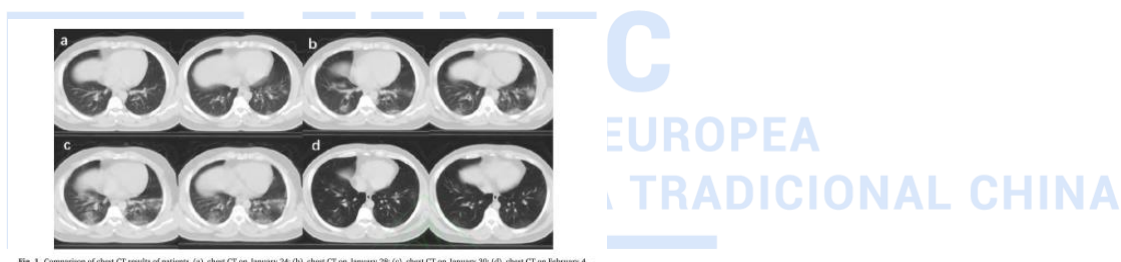


Fig. 1. Comparison of chest CT results of patients: (a), chest CT on January 24; (b), chest CT on January 28; (c), chest CT on January 30; (d), chest CT on February 4.

Declaration of Competing Interest There are no conflicts to declare.

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Appendix A. Supplementary data Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.phrs.2020.104743>.

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Natural Methods to Protect Your Respiratory System from Infection During the Current Flu and Coronavirus Season. Heiner Fruehauf, phd, lac March 7, 2020

1. Reduce sugar intake. White and brown sugar causes our bodies to become more acidic, which benefits the growth of bacteria. Synthetic sugar alternatives such as Splenda are harmful to the nervous system and should also be avoided. Use maple syrup, local honey, or coconut sugar for sweetening.

2. Increase your intake of naturally occurring trace minerals, which make the body more alkaline and have the potential to prevent infection. For instance, use Bio Nativus' Ionic Trace Minerals (a trace mineral extract made from concentrated water from the Great Salt Lake). Add 5-15 drops to every glass of water or liquid you drink, up to 5x/day.

3. Gargle with saltwater after brushing your teeth, preferably with a full-spectrum natural salt such as Real Salt.

4. Get a skin brush and start brushing your skin after showering in the morning, especially the head, neck and chest areas. This will stimulate lymphatic circulation and increase your general feeling of vitality and well-being.

5. Apply essential oils before going out in public, either in the form of an anti-viral massage oil (applied to the chest, neck and lower arm areas) or an anti-viral "perfume" (applied to the area below the nostrils). During the bubonic plague in the middle ages, essential oils prevented the professions of perfumers (who exclusively worked with oils on a daily basis) and thieves (who fortified themselves with oils before burglarizing abandoned houses) to become ravaged by the pandemic. Since different viruses thrive in the environment every year, the types of appropriate oils also vary from year to year. Of the many types of essential oils available on the market, I have found that the following oils have proven to be most effective for the prevention and treatment of upper respiratory infections in early 2020:

- Eucalyptus • Tea Tree • Niaouli • Lemon • Cinnamon leaf • Clove • Rosemary • Thyme
- Frankincense • Myrtle

Any or all of the oils described above can be mixed together to produce an essential oil blend. Massage oils should incorporate 30 drops of essential oils per ounce (blended into a base of high-quality olive oil or apricot seed oil). “Perfumes” should be mixed 50/50 with a base oil like jojoba oil or apricot seed oil, and used by applying 1-2 drops of the blend to the area below the nostrils. Alternatively, according to a recent report I received, Chinese medicine practitioners during the 1938 epidemic in China successfully swabbed their nostrils with vinegar before seeing afflicted patients.

6. Additionally, the internal application of Chinese herbs has been proven effective in the prevention and treatment of both the COVID-19 and SARS strains during the 21st century coronavirus epidemics in mainland China. For my recent suggestions to natural medicine practitioners flooded by the question of how to best protect oneself during the current season of respiratory vulnerability see my separate article, “Initial Thoughts on Coronavirus Prevention and Treatment with Chinese Medicine”.

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REVIEW ARTICLE

Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts’ consensus statement

Abstract

Since the outbreak of 2019 novel coronavirus infection (2019-nCoV) in Wuhan City, China, by January 30, 2020, a total of 9692 confirmed cases and 15,238 suspected cases have been reported around 31 provinces or cities in China. Among the confirmed cases, 1527 were severe cases, 171 had recovered and been discharged at home, and 213 died. And among these cases, a total of 28 children aged from 1 month to 17 years have been reported in China. For standardizing prevention and management of 2019-nCoV infections in children, we called up an experts’ committee to formulate this experts’ consensus statement. This statement is based on the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition) (National Health Committee) and other previous diagnosis and treatment strategies for pediatric virus infections. The present consensus statement summarizes current strategies on diagnosis, treatment, and prevention of 2019-nCoV infection in children.

Background

In December, 2019, a cluster of pneumonia cases, who were later proven to be caused by a novel coronavirus (named as “2019-nCoV”), emerged in Wuhan City, Hubei Province,

China. By January 30, 2020, 9692 confirmed cases and 15,238 suspected cases have been reported around 31 provinces and cities in China. Among the confirmed cases, 1527 were severe cases, 171 had recovered and been discharged at home, and 213 died. Twenty-eight confirmed cases aged from 1 month to 17 years had been reported in China [1]. Coronavirus (CoV) belongs to the Coronaviridae family, Nidovirales order. CoVs are divided into four genera: α -, β -, γ -, and δ -coronavirus. α - and β -coronaviruses only infect mammals, whereas γ - and δ -coronaviruses mainly infect birds, with a few infecting mammals. Human CoVs include α -coronaviruses (229E and NL63), β -coronaviruses (OC43 and HKU1), the Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), and 2019-nCoV. The 2019-nCoV belongs to the β -coronavirus genus [2], which includes bat-SARS-like (SL)-CoVZC45, bat-SL-CoVZXC21, SARS-CoV, MERS-CoV, and 2019-nCoV. Current studies have revealed that 2019-

nCoV may originate from wild animals, but the exact origin remains unclear. 2019-nCoV infected patients are the main infection sources. However, we also should attach importance to asymptomatic cases which may play a critical role in the transmission process. Respiratory droplets and contact are the main transmission routes [3]. Close contact with symptomatic cases and asymptomatic cases with silent infection are the main transmission routes of 2019-nCoV infection in children. People of all ages are susceptible to 2019-nCoV. The elderly and those with underlying chronic diseases are more likely to become severe cases. Thus far, all pediatric cases with laboratory-confirmed 2019-nCoV infection were mild cases, and no deaths had been reported. For standardizing the prevention and treatment of 2019-nCoV infections in children, we called up an experts' committee to formulate this consensus statement. This statement is based on the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition) (National Health Committee) and other previous diagnosis and treatment strategies for pediatric virus infections.

Clinical manifestations

Based on the current epidemiological data, the incubation period of 2019-nCoV infections ranges from 1 to 14 days, mostly ranging from 3 to 7 days. Current reported data of pediatric cases revealed that the age of disease onset ranged from 1.5 months to 17 years, most of whom had a close contact with infected cases or were family cluster cases [4]. Infected children might appear asymptomatic [5] or present with fever, dry cough, and fatigue, and few have upper respiratory symptoms including nasal congestion and running nose; some patients presented with gastrointestinal symptoms including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea. Most infected children have mild clinical manifestations.

They have no fever or symptoms of pneumonia with a good prognosis. Most of them recover within 1–2 weeks after disease onset. Few may progress to lower respiratory infections. No newborns delivered by 2019-nCoV infected mothers have been detected positive; and no newborn cases have been reported yet. It should be noted that clinical manifestations in pediatric patients should be further defined after collecting more pediatric case data. Furthermore, the number of confirmed infected cases will increase after a wide use of pathogen analysis. Data from adults reveal that severe cases often develop dyspnea one week after disease onset. Severe cases may rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, and coagulation dysfunction [6, 7]. Although no deaths in children have been reported up to now, the potential risk of death should be highlighted. Though clinical symptoms in pediatric patients are relatively milder compared with those in adult patients, ARDS and death cases also occurred in infected children during the SARS and MERS epidemics [8–11].

Auxiliary examinations Laboratory examination [3]

1. In the early phase of the disease, white blood cell count is normal or decreased, with decreased lymphocyte count; liver enzymes, muscle enzymes, and myohemoglobin levels are increased in some patients.
2. Most patients display elevated C-reactive protein level and erythrocyte sedimentation rates, and normal prolactin levels.
3. Severe cases show high D-dimer levels and progressively decreased blood lymphocytes counts.
4. Samples from throat swabs (better using nasopharyngeal swab in children), sputum, lower respiratory tract secretions, stool and blood, etc. are tested positive for 2019-nCoV nucleic acids.

Chest imaging examination [3]

Suspected cases or confirmed cases should undertake chest X-ray examination as soon as possible. Chest CT scan is required when necessary. In the early stage of disease, chest images show multiple small plaques and interstitial changes, which are obvious in the lung periphery, further deteriorate to bilateral multiple ground-glass opacity and/or infiltrating shadows. Lung consolidation may occur in severe cases. Pleural effusion is rarely seen.

Diagnosis

Suspected cases

2019-nCoV should be suspected in patients who meet any one of the criteria in the epidemiological history and any two of the criteria in clinical manifestations.

Epidemiological history

1. Children with a travel or residence history in Wuhan city and neighboring areas, or other areas with persistent local transmission within 14 days prior to disease onset;
2. Children with a history of contacting patients with fever or respiratory symptoms who have a history of contact with patients from Wuhan city and neighboring areas, or other areas with persistent local transmission within 14 days prior to disease onset;
3. Children who are related with a cluster outbreak or close contact with 2019-nCoV infected cases;
4. Newborns delivered by confirmed 2019-nCoV-infected mothers.

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3. Children who are related with a cluster outbreak or close contact with 2019-nCoV infected cases;
4. Newborns delivered by confirmed 2019-nCoV-infected mothers.

Clinical manifestations

1. Fever, fatigue, dry cough; some pediatric patients may have low-grade fever or no fever;
2. With above-mentioned chest imaging findings (refer to the section of Chest imaging examination);
3. In the early phase of the disease, white blood cell count is normal or decreased, or with decreased lymphocyte count;
4. No other pathogens are detected which can fully explain the clinical manifestations.

Confirmed cases Suspected cases who meet any one of the following criteria [3]:

1. Respiratory tract or blood samples tested positive for 2019-nCoV nucleic acid using RT-PCR;
2. Genetic sequencing of respiratory tract or blood samples is highly homologous with the known 2019-nCoV.

Clinical classifications

1. Asymptomatic infection (silent infection) Children tested positive for 2019-nCoV, but without manifestations of clinical symptoms or abnormal chest imaging findings.

2. Acute upper respiratory tract infection Children with only fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia or discomfort, etc., and without signs of pneumonia by chest imaging or sepsis.

3. Mild pneumonia Children with or without fever, respiratory symptoms such as cough; and chest imaging indicating pneumonia, but not reaching the criteria of severe pneumonia.

4. Severe pneumonia Meeting any of the following criteria [3, 12–15]:

(1) Increased respiratory rate: ≥ 70 times/min (< 1 year), ≥ 50 times/min (≥ 1 year) (after ruling out the effects of fever and crying);

(2) Oxygen saturation $< 92\%$; (3) Hypoxia: assisted breathing (moans, nasal flaring, and three concave sign), cyanosis, intermittent apnea;

(4) Disturbance of consciousness: somnolence, coma, or convulsion;

(5) Food refusal or feeding difficulty, with signs of dehydration.

5. Critical cases Those who meet any of the following criteria and require ICU care:

(1) Respiratory failure requiring mechanical ventilation; (2) Shock; (3) Combined with other organs failure.

Early identification of critical cases

According to the experiences in diagnosis and treatment of community-acquired pneumonia in children, children with a history of contact with severe 2019-nCoV infected cases, or with underlying conditions (such as congenital heart disease, bronchial pulmonary hypoplasia, respiratory tract anomaly, with abnormal hemoglobin level, severe malnutrition), or with immune deficiency or immunocompromised status (under long-term use of immunosuppressants) who meet any one of the following criteria may become severe cases:

1. Dyspnea: respiratory rate > 50 times/min for 2–12 months old; > 40 times/min for 1–5 years old; > 30 times/min in patients over 5 years old (after ruling out the effects of fever and crying);

2. Persistent high fever for 3–5 days; 3. Poor mental response, lethargy, disturbance of consciousness, and other changes of consciousness;

4. Abnormally increased enzymatic indexes, such as myocardial enzymes, liver enzymes, lactate dehydrogenase;

5. Unexplainable metabolic acidosis; 6. Chest imaging findings indicating bilateral or multi-lobe infiltration, pleural effusion, or rapid progression of conditions during a very short period;

7. Infants younger than 3 months; 8. Extrapulmonary complications; 9. Coinfection with other viruses and/or bacteria.

Differential diagnosis [3]

Differential diagnosis should be made to distinguish from influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS coronavirus, and other known viral infections, as well as mycoplasma pneumoniae and chlamydia pneumonia and bacterial pneumonia. The coinfection of 2019-nCoV with other viruses and/or bacteria should be considered in diagnosis.

General treatment

The general treatment strategies include bed rest and supportive treatment; ensuring sufficient calory and water intake; maintaining water electrolyte balance and homeostasis; monitoring vital signs and oxygen saturation; keeping respiratory tract unobstructed and inhaling oxygen when necessary; measuring blood routine, urine routine, C-reactive protein, and other blood biochemical indexes including liver and kidney

function, myocardial enzyme spectrum, and coagulation function according to patients' conditions. Blood gas analysis and timely re-examination of chest imaging should be performed when necessary.

Symptomatic treatment

The patients with high fever should be actively controlled. If patients' body temperature exceeds 38.5 °C with obvious discomfort, physical cooling (warm water bath, use of antipyretic patch, etc.) or antipyretic drug treatment should be performed. Common drugs include: ibuprofen orally, 5–10 mg/kg every time; acetaminophen orally, 10–15 mg/kg every time. Keep children quiet and administer sedatives immediately when convulsions or seizure occur.

Oxygen therapy

When hypoxia appears, effective oxygen therapy should be given immediately including nasal catheter, mask oxygen. Nasal high-flow oxygen therapy, and non-invasive or invasive mechanical ventilation should be undertaken when necessary.

Antiviral therapy Interferon-α [3, 16–28]

Interferon-α can reduce viral load in the early stage of infection which can help to alleviate symptoms and shorten the course of disease. Based on our clinical research and World Journal of Pediatrics experiences of using interferon-α in treating bronchiolitis, viral pneumonia, acute upper respiratory tract infection, hand foot mouth disease, SARS, and other viral infections in children, the recommended usage is as follows:

1. Interferon-α nebulization: interferon-α 200,000– 400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water, nebulization two times per day for 5–7 days;
2. Interferon-α2b spray: applied for high-risk populations with a close contact with suspected 2019-nCoV infected patients or those in the early phase with only upper respiratory tract symptoms. Patients should use 1–2 sprays on each side of the nasal cavity, 8–10 sprays on the oropharynx, the dose of interferon-α2b per injection is 8000 IU, once every 1–2 hours, 8–10 sprays/day for a course of 5–7 days.

Lopinavir/litonavir [3, 29, 30]

Lopinavir/litonavir has been tried to apply to the treatment of adult patients with 2019-nCoV pneumonia, but its efficacy and safety remain to be determined.

Usage of other agents Antibiotics [3, 12]

Avoiding irrational use of antibiotics, especially in combination with broad-spectrum antibiotics. Paying close attention to the changes of conditions in children with coinfection of bacterial or fungal infection; actively collecting samples for pathogen analysis and timely or rational use of antibiotics or anti-fungal drugs.

Arbidol [31], oseltamivir [32] and other anti-influenza drugs

Arbidol is administered for adults infected with 2019-nCoV; however, its efficacy and safety remain unclear. Oseltamivir and other anti-influenza agents can be applied for patients coinfecting with other influenza virus.

Other drugs [3, 12] Glucocorticoids

The use of glucocorticoids should be based on the severity of systemic inflammatory response, degree of dyspnea, with or without ARDS, and the progress status of chest imaging results. Glucocorticoids can be used in a short period (3–5 days). The recommended dose of methylprednisolone should not exceed 1–2 mg/kg/day.

Immunoglobulin

Immunoglobulin can be used in severe cases when indicated, but its efficacy needs further evaluation. Treatment of severe and critically ill cases [3, 12]

On the basis of symptomatic treatment, we should actively prevent and treat complications, underlying diseases, secondary infection, and provide organ function support as indicated.

Respiratory support

Children who undergo non-invasive mechanical ventilation for 2 hours without improvements in conditions, or cannot tolerate non-invasive ventilation, with increased airway secretions, severe cough, or hemodynamic instability, should be subjected to invasive mechanical ventilation promptly. The invasive mechanical ventilation should adopt low tidal volume “lung protective ventilation strategy” to reduce ventilator related lung injury. If necessary, prone position ventilation, lung recruitment, or extracorporeal membrane oxygenation (ECMO) can be applied.

Circulation support

On the basis of full fluid resuscitation, improve microcirculation, use vasoactive drugs, and monitor hemodynamics if necessary.

Traditional Chinese medicine

This disease belongs to the epidemic disease category of Traditional Chinese Medicine and results from contracting epidemic pathogens. Different regions can refer to the following plans for dialectical treatment according to the patient's conditions, local climate features, and physical characteristics of children.

Clinical treatment period 1. Asymptomatic infection:

(1) Therapeutic methods: strengthening the healthy and dispelling pathogenic factors;

(2) Recommended prescription and drugs: modified Yupingfeng powder in combination with Buhuanjin Zhengqi powder composed of 9–12 g of Zhihuangqi (Prepared Astragalus), 6–9 g of Chaobaizhu (Roasted Rhizoma Atractylodis Macrocephalae), 3–9 g of Houpo (Officinal Magnolia Bark), 6–9 g of Cangzhu (Atractylodes lancea), 6–9 g of Chenpi (Pericarpium citri reticulatae), 3–6 g of Jiangbanxia (Ginger processed pinellia), 6–9 g of Huoxiang (Agastache rugosus), 6 to 9 g of Fuling (Poria cocos), and 3–6 g of Zhigancao (Prepared Liquorice Root).

2. Old and damp tightening the lung

(1) Clinical manifestations: aversion to cold, fever or no fever, dry cough, sore throat, nasal congestion, tiredness and fatigue, nausea and retching, loose stool, pale tongue or reddish tongue with whitish-greasy fur, floating, and soft pulse;

(2) Therapeutic methods: dispersing lung to promote pathogenic factors, detoxify, and dispel dampness;

(3) Prescription and drugs: modified Qingqi decoction composed of 6–9 g of Cangzhu, 3–9 g of Houpo, 6–9 g of Chenpi, 6–12 g of Huoxiang, 3–9 g of Banxia, 3–9 g of Xingren, 9–15 g of Suye, 6–9 g of Jiegeng, 6–9 g of Guanzhong, 6–9 g of Fuling, 3–6 g of Shengjiang, and 3–6 g of Gancao.

3. Plague poison obstructing lungs:

(1) Clinical manifestation: fever persists or chill and fever alternate; cough with little or yellow phlegm; shortness of breath holds back; abdominal distension constipation. The tongue is red, while the moss is yellow and greasy or yellow and dry. Slide number of arteries and veins;

(2) Therapeutic methods: detoxification, opening and closing, clearing the lungs, and dampness;

(3) Prescription and drugs: modified Xuanbai Chengqi decoction composed of 6–9 g of Huoxi-ang, 10 g of Cangzhu, 3–6 g of Zhimahuang, 3–9 g of Chaoxingren, 15–30 g of Shengshigao, 10 g of Gualou, 3–6 g of Jiujuun (to be added later in preparation), 6–9 g of Huangqin, 6–9 g of Ful-ing, 6–9 g of Danpi, 6–9 g of Shichangpu, and 3–6 g of Chuanbei.

4. Inner blocking causing unconsciousness and collapse:

(1) Clinical manifestation: dyspnea, lethargy, restlessness, cold and sweat in limb, dark purplish tongue, thick and slimy fur or dry fur, big floating and unstable pulse, cyanosis in fingerprints, and reaching for the Mingguan point (distal phalanx)

(2) Therapeutic methods: opening the blocking and solidification dysfunction, detoxifying, and reviving the unconscious;

(3) Prescriptions and drugs: modified Shenfu decoction plus Shengmai drink composed of 3–6 g of Renshen (radix ginseng), 6–12 g of fuzi (radix aconiti Praepareta) (to be decocted one hour first), 6–12 g of Shanzhuyu (Fructus Corni), 10 g of Maimendong (Radix ophiopogonis), and 3–6 g of Rougui (Cinnamomum cassia), to be taken with Angong Niu Huang Pill.

5. Qi deficiency of both the lung and spleen.

(1) Clinical manifestation: feeble cough, lassitude and asthenia, spontaneous sweating, poor appetite, loose stool, pale tongue with whitish and slippery fur, thready, and weak pulse;

(2) Therapeutic methods: nourishing the lungs and strengthening the spleen, nourishing qi, and dehumidifying;

(3) Prescription and drugs: modified LiuJunZi decoction composed of 15 g of Zhihuangqi (Prepared Astragalus), 10 g of Xiyangshen (American Ginseng), 10 g of Chaobaizhu (Roasted Rhizoma Atractylodis Macrocephalae), 6 g of Fabanxia (Rhizoma Pinelliae preparatum), 6 g of Chenpi (Pericarpium citri reticulatae), 3 g of Chuanbei (Tendril-leaved fritillary bulb), 15 g of Ful-ing (Poria cocos), 6 g of Huoxiang (Agastache rugosus), and 3 g of Sharen (Fructus amomi) (to be added in later).

Psychotherapy

Psychological counseling plays an important role in disease recovery. If patients (especially older children) show mood swing, fear, or psychological disorders, active psychological intervention and treatment are needed.

Release and discharge criteria [3]

Confirmed patients can be discharged from isolation or transferred to the corresponding departments for treatment of other diseases if all the following criteria are met:

1. The body temperature returns to normal longer than 3 days;
2. The respiratory symptoms improve obviously;
3. The detection of respiratory pathogenic nucleic acid is negative for two consecutive times (the sampling interval is at least 1 day).

Suspected patients can be discharged from isolation when the detection of respiratory pathogenic nucleic acid is negative for two consecutive times (the sampling interval is at least 1 day).

Prevention [33–35]

Novel coronavirus infection is a new communicable disease with an emergent outbreak that affects all populations. 2019-nCoV infection has been classified as category B infectious disease legally but managed as

category A infectious disease. It is paramount to implement infection control practices by infection source controlling, transmission route blocking, and susceptible population protection.

Controlling infection sources

Patients infected with 2019-nCoV are the main infection sources. Children infected by novel coronavirus should be isolated at home or admitted to designated hospitals under the guidance of healthcare workers depending on the severity of their medical conditions. Try to provide single rooms for isolated children, and reduce the chance of contact with the co-residents. There are enormous demands for room ventilation, necessary cleaning, and disinfection work for the articles used by children. Equally crucial is the need of equipment with disposable masks and properly disposal after use when taking care of the sick.

Blocking transmission routes

1. Preventing transmission by respiratory droplets and contact: Cover mouth and nose with napkin or towel when coughing or sneezing. Wash hands for children frequently, or teach children seven-step washing technique. Try not to touch mouth, nose, or eyes before cleaning hands thoroughly after returning from public places, after covering the mouth when coughing, before eating or after using toilet; regularly disinfecting toys by heating at 56 °C for 30 min, 75% alcohol or chlorine-containing disinfectants, and ultraviolet rays.
2. Reduce exposure to infection: Avoid public transport at epidemic areas, and wear masks when going to crowded or poorly ventilated public places; avoid touching or eating wild animals, and going to markets selling with live animals.
3. Children's health monitoring: Children with a history of close contacts of infected patients need to be monitored for body temperature and clinical features routinely. When presenting with suspicious symptoms, children should be taken to a designated hospital for screening. Newborns delivered by infected mothers must complete a pathogen test and be isolated in a single ward or at home according to their medical conditions.

Boosting immunity

Balanced diet, oral health, adequate exercise, regular rest, avoiding excessive fatigue, and boosting immunity are the powerful measures to preventing infection, as well as maintaining emotional stability and mental health. Vaccination is an effective way to prevent virus infection. The research and development of anti-virus vaccines has been carried out in China at present.

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Journal of Chinese Medicine | Issue123 | June 2020 Acupuncture in the Treatment of COVID-19: An Exploratory Study. Peilin Sun & Wen Sheng Zhou

Abstract

The coronavirus COVID-19 has presented a serious new threat to humans since the first case was reported in Wuhan, China on 31 December 2019. By the end of February 2020 the virus has spread to 57 countries with nearly 86,000 cases, and there is currently no effective vaccination available. Chinese herbal medicine has been used in this epidemic with encouraging results, but with concerns regarding disturbance of patients' digestive function. This study aims to explore the role of acupuncture in treating COVID-19 by investigating relevant current literature along with classical Chinese medicine texts on epidemics. Based on this analysis, acupuncture points and strategies are suggested for practitioners to use as a guide to treatment.

Keywords Coronavirus, COVID-19, acupuncture, Chinese medicine, ghost points, infection, epidemic, pandemic.

Introduction

Coronaviruses (CoV) can cause severe diseases like severe acute respiratory syndrome (SARS-CoV) or Middle East respiratory syndrome (MERS-CoV). The first case of a novel zoonotic coronavirus (nCoV) was reported in Wuhan, China on 31 December 2019 and it now presents a serious threat to humans. One month later, nCoV became a global emergent health issue and was renamed COVID-19 by the World Health Organization (WHO). By 29 February (the time of writing), 38 days after the lockdown in Wuhan, China has 79,394 reported cases and 2,838 deaths, while 85,641 cases have been reported globally across 57 countries with 2,933 deaths.¹ Among those infected, 20 per cent are in intensive care. The WHO has already released 675 million dollars to help combat this global emergency, to cover the period from February to April, and has also gathered 300 top health professionals internationally to develop a vaccine before COVID-19 becomes pandemic. Despite Chinese medicine experts apparently not being included in these efforts, in reality many studies from affected hospitals in China have reported that Chinese medicine has been playing an important role in the battle against COVID-19.^{5,6}

Disappointingly, according to some Chinese medical academics, in some locations acupuncture has not featured as a treatment throughout the course of patients' infection, but only during the recovery period.⁷ Chinese medicine has a recorded history of over two thousand years of combating epidemics, with acupuncture playing a vital role alongside herbal medicine. For instance, Wu Youke (1580-1660) in his text *Zhen Jing* (Acupuncture Canons) pointed out how infectious qi attacks the human body via the mouth and nose and then penetrates inwards, as well as noting which acupoints should be employed in treatment.⁸ This study provides acupuncture strategies to treat COVID-19 and is based on both classical Chinese medicine theory and current literature. The aim of this article is to shed new light on this urgent health struggle, and to help acupuncture practitioners contribute to their local communities. Clinical manifestations of COVID-19 Chen et al.⁹ and Wang et al.¹⁰ each reported a case series based in two separate hospitals 10 miles apart in Wuhan during January 2020, which included a total of 237 subjects presenting with COVID-19. Chen et al.'s study documented infected patients as presenting with signs of fever (83 per cent) and cough (82 per cent), followed by dyspnoea (31 per cent), confusion (11 per cent) and headache (8 per cent), while 1 to 5 per cent of patients exhibited sore throat, rhinorrhoea, chest pain, diarrhoea, nausea and vomiting; 68 per cent of

patients were male, 51 per cent experienced chronic illness and 75 per cent developed bilateral pneumonia. Wang et al.'s study reported the main symptoms as being fever (98.6 per cent), fatigue (69.6 per cent), dry cough (59.4 per cent), myalgia (34.8 per cent) and dyspnoea (31.2 per cent), with 54.3 per cent of the patients being male. Most of the patients in the two studies received antibiotic and antiviral treatments. The authors concluded that hypertension, diabetes, cardiovascular illness and malignancy are common comorbidities of COVID-19. Wang et al. point out that the best approach to COVID-19 is to avoid becoming infected in the first place, as the medication currently available is ineffective. A few points are worth drawing out from these two reports:

- There are big differences in the major clinical manifestations of the illness as outlined in the two studies.
- A fair number of patients showed atypical symptoms, such as diarrhoea and nausea.
- Major complications appeared during hospitalisation, such as acute respiratory distress syndrome, arrhythmia and shock (Wang et al.).
- Traditional Chinese medicine texts that describe how epidemics have been fought through Chinese history can be used to address these points.

The Chinese medicine understanding of epidemic disease. The original Chinese term for epidemic, li yi (戾疫, literally 'ferocious epidemic'), has a recorded history of over two thousand years. In 524 BCE, the Zhou dynasty king Jing was admonished for his luxurious lifestyle, which he was advised put him at risk of contracting li (戾, ferocious qi).¹¹ Mozi (4th Century BCE) also mentions li yi, which was interpreted by Johnston (2010) as 'pestilence and plague'.¹² Large-scale epidemics have emerged in China dozens of times since the beginning of the first millennium, often occurring in cold and damp years as defined by five-phase philosophy.¹³ A large number of Chinese medicine scholars produced doctrines during or after such disasters that in time became famous. Zhang Zhong jing (150-129), who suffered the loss of many family members, composed the Shang han lun (Treatise on Cold Damage) in which he expounded that cold, wind or damp can invade the human body, penetrating from the yang channels of the outer body inwards the yin channels or organs. He stated that li yi is acute and infectious, its symptoms develop much swifter than typical shang han (cold damage), and can easily progress to a critical - even fatal - stage. It is important for physicians to intervene accurately and rapidly in such diseases to reverse the patient's situation. Prior to the Ming dynasty, most Chinese medicine scholars believed li yi to be caused by cold, but this idea was challenged by Ming scholars such as Wu Youke after experiencing several epidemics that swept China, such as in 1641. Wu argued that cold only presents in winter, whereas warm epidemics (wen yi 温疫) can present in all seasons, and that li yi represents an extremely merciless exogenous qi that differs from the usual six exogenous forms of qi. Wu thought any acute epidemic disease related to unseasonable warmth, and should be treated with herbal medicine. He condemned some medical professionals for mistaking epidemic yi qi for shang han and therefore failing in their duty to adequately treat patients.

Warm disease theory was to cause many controversies; for instance, Qing dynasty scholars Ye Lin and Li Guanxian thought Wu may have confused his idea of warm disease with epidemic disease due to the phonetic similarity of their characters (温 warm and 瘟 epidemic – a character that did not exist in ancient Chinese).^{15,16} However, 瘟 was not only shown as an entry in the Chinese rhyme dictionary Jiyun (1037)¹⁷ but was also actually specifically identified and annotated by Wu in the chapter on Miscellaneous Qi in his text Wen yi lun (Treatise on Warm Epidemics).¹⁸ This warm versus cold controversy has still not been resolved, including Wu's conclusion that herbal medicine is the only cure for epidemic disease. Regardless of whether or not Wu was correct on this point, the influence of the climate in Wuhan on the recent spread of COVID-19 can be understood using his theory. The Chinese medicine academic Tong¹⁹ as well as many other Chinese medicine scholars believe that the climate in Wuhan in December 2019, with its continuous rain and abnormal warmth, led to the epidemic by fostering cold and damp qi that impairs human yang qi, particularly in the Lung and Spleen. The facts on which this understanding is based are: 1. Patients mostly complain of fatigue, poor appetite, nausea, vomiting, fullness, diarrhoea or constipation, which points to damp-cold affecting the Spleen

and Lung. 2. Patients' tongue coatings are very thick and greasy (described as fu tai 腐苔, a tongue coating that looks like rotten bean curd), indicating heavy dampness and turbidity. Tong and his team have drafted a four-stage differentiation and a treatment protocol, as follows: 1. Damp-cold stagnating the Lung; 2. Epidemic toxicity blocking the Lung; 3. Visceral obstruction causing collapse; 4. Lung and Spleen deficiency. Subsequently, Wang et al.,²⁰ Ma et al.²¹ and Chen et al.^{22,23} have expanded on this general outline with detailed herbal prescriptions to be tailored to individual patients' conditions. The primary principles of treatment are to warm yang, disperse cold and eliminate damp. Hubei medical experts characterised the COVID-19 virus as 'loving cold and being afraid of warmth'.

The role of acupuncture in treating COVID-19 Somewhat dispiritingly, while scholars have delivered strategies for herbal medicine, acupuncture treatment has received little attention. This article aims to explore the feasibility of acupuncture treatment for COVID-19-infected patients, and is based on published herbal strategies for this disease as well as Chinese medicine theory. Professor Sun, co-author of this article, has been practising Chinese herbal medicine and acupuncture in Europe for over 40 years. This analysis is based on his empirical observations of what is more likely to suit European patients. All Chinese medicine academics emphasise that this epidemic is characterised by damp, cold and toxicity, which easily lead to heat and stasis. Professor Sun underlines that the key to treatment is to identify whether the pattern is one of damp-cold toxin causing heat or heat-toxin mixing with damp. In patients with constitutional yang excess, damp-cold accumulation can quickly turn to damp-heat. In such cases, the treatment principle should be to eliminate damp-cold whilst simultaneously clearing heat. Heat toxin mixed with damp represents a different scenario; even though damp is also present, the root treatment is to clear heat and remove toxin, whilst additionally eliminating damp. If the former pattern is mistaken for the latter when treating with herbal medicine, then damp toxin could be aggravated further. In general, the primary treatment principles should be to boost Stomach and Spleen qi while at the same time 1) dispersing cold and scattering damp, 2) eliminating inner toxic qi by venting the exterior, and 3) increasing qi to eliminate turbidity. Epidemic qi attacks the body rapidly and violently, therefore clinical features can change dramatically and vary significantly between cases. Severe symptoms can develop within just a few days. The following clinical possibilities should be borne in mind: • Once damp-cold becomes significant, it can: a) block the Lungs causing dyspnoea; b) attack the Pericardium causing chest tension, nausea, cold sweat and shock; c) cause Kidney yang failure, inducing haematuria, dehydration, abnormal urination and weight loss; and d) damage the Stomach and Spleen, leading to vomiting and diarrhoea. • Once damp-cold turns to heat, it will occlude the Lungs and yangming (Stomach and Large Intestine) resulting in fever, coughing, chest tension and shortness of breath, fatigue, poor appetite, nausea, vomiting, bloating, diarrhoea or constipation, eventually destroying the body's yin and evolving into endogenous wind syndrome. How can one avoid contracting such a ferocious epidemic virus? The Nei jing (Inner Classic) provides the answer: people with strong zheng (upright) qi will avoid the worst effects of epidemic infection despite the fact that everybody, no matter their age or gender, may be affected.²⁴ Because each individual has a different physical constitution, the manifestations of the disease will vary, and so a single herbal prescription cannot be universally effective for every patient. Acupuncture is conducted with patients on a one-to-one basis, and is oriented more to provide symptomatic relief than the generic herbal decoctions applied during epidemic periods. The relevant acupuncture protocols, based on the Chinese government four-stage differentiation scheme for treating COVID-19, are outlined below. Suspected infection period Invasion of the Lung by damp-cold: beginning of infection with fever, chills, joint and muscle pain, fatigue, sore throat, bitter taste in the mouth, dry throat, a pale tongue with thin white coating and a slightly rapid floating pulse. Acupuncture prescription:

- Lieque LU-7 + Zhaohai KID-6, Waiguan SJ-5 + Zulinqi GB-41 with even method.
- Hegu LI-4, Fengchi GB-20, Zhigou SJ-6, Neiguan P-6, Feishu BL-13, Yanglingquan GB-34, Zhongwan REN-12, Fenglong ST-40 and Zusanli ST-36 with reducing method.

Damp-cold obstructing the Spleen: gastrointestinal discomfort, possibly fever, muscle pain, nausea, vomiting, diarrhoea, abdominal distension, fatigue, a pale tongue with a white greasy coating and a deep-slow or deep-delayed (chen-chi) pulse. Acupuncture prescription:

- Waiguan SJ-5 + Zulinqi GB-41, Neiguan P-6 + Gongsun SP-4 with even method.
- Zhigou SJ-6, Neiguan P-6, Feishu BL-13, Yanglingquan GB-34, Zhongwan REN-12, Fenglong ST-40, Tianshu ST-25, Yinlingquan SP-9, Zusanli ST-36 with even method.

Clinical treatment period Initial stage: Damp-cold occluding the Lung: possible fever, dry cough, bitter taste in mouth, dry throat, fatigue, chest tightness, nausea and/or vomiting, loose stools, pale or reddish tongue with white greasy coat, and a floating-soft pulse. Acupuncture prescription:

- Lieque LU-7 + Zhaohai KID-6, Neiguan P-6 + Gongsun SP-4, Waiguan SJ-5 + Zulinqi GB-41 with even method.
- Hegu LI-4, Chize LU-5, Zhongwan REN-12, Yanglingquan GB-34, Zusanli ST-36 and Qiuxu GB-40 with reducing method.

Intermediate stage: Damp obstructing the middle and upper burner: Cough, white or yellowish sputum, rough expectorate, chest tightness, shortness of breath, stomach distension, nausea, abdominal bloating, poor appetite, loose stools, pale or reddish tongue with a white greasy coat and a floating-soft or weak pulse. Acupuncture prescription:

- Lieque LU-7 + Zhaohai KID-6, Neiguan P-6 + Gongsun SP-4, Waiguan SJ-5 + Zulinqi GB-41 with even method.
- Chize LU-5, Feishu BL-13, Yuji LU-10, Zhongwan CV-12, Fenglong ST-40, Yanglingquan GB-34, Zusanli ST-36, Tianshu ST-25 and Qiuxu GB-40 with reducing method.

Epidemic toxin obstructing the Lung, heat dropping into yangming: High fever, cough with yellow sputum, chest tightness, shortness of breath, panting, wheezing on exertion, bloated lower abdomen, constipation, red tongue with yellow greasy or dry coat and a slippery and rapid pulse. Acupuncture prescription:

- Lieque LU-7 + Zhaohai KID-6, Neiguan P-6 + Gongsun SP-4 with even method.
- Chize LU-5, Feishu BL-13, Shanzhong REN-17, Yuji LU-10, Hegu LI-4, Quchi LI-11, Tianshu ST-25, Fenglong ST-40 and Neiting ST-44 with reducing method.

Severe stage: Internal obstruction causing collapse, yin and yang separating: Severe breathing difficulty, asphyxia (mechanical ventilation may be needed), unconsciousness, restlessness, sweaty and cold extremities, a dark purple tongue with thick or dry coat, and a large floating rootless pulse. Acupuncture prescription:

- Baihui DU-20, Guanyuan REN-4, Qihai REN-6, Zusanli ST-36, Feishu BL-13, Shanzhong REN-17 and Sanyinjiao SP-6 with reinforcing method, and moxibustion on Guanyuan CV-4 and Qihai CV-6.
- Tianshu ST-25 and Fenglong ST-40 with reducing method.

Recovery stage: Lung and Spleen qi deficiency, deficiency of yuan (original) qi: Shortness of breath, fatigue, poor appetite, nausea, abdominal distension and fullness, asthenic-type constipation, sticky loose stools, a pale swollen tongue with a greasy white coat and a deep, slow pulse. Acupuncture prescription:

- Guanyuan REN-4, Qihai REN-6, Zusanli ST-36 and Taixi KID-3 with reinforcing method and moxibustion at Guanyuan REN-4 and Qihai REN-6.
- Feishu BL-13, Pishu BL-20 and Shenshu BL-23 with reinforcing method.

Qi and blood deficiency, Liver and Kidney yin deficiency: Shortness of breath, fatigue, poor appetite, insomnia, asthenic-type constipation, flushing, night sweats, dry mouth, restless, dizziness, weak knees, scanty urine, a pale red tongue with scanty or flaking coat, thin and weak pulses. Acupuncture prescription:

- Guanyuan REN-4, Qihai REN-6, Zusanli ST-36, Sanyinjiao SP-6, Taixi KID-3, Yingu KID-10 and Ququan LIV-8 with reinforcing method.
- Taichong LIV-3 and Neiguan P-6 with even method.

Acupuncture point categories

The acupuncture prescriptions in this article are based on published papers on the Chinese medicine treatment of COVID-19, Chinese state-broadcast information combined with the classical Chinese medicine theory that has been used to deal with numerous epidemics over thousands of years. However, acupuncture is by its very nature an individualised therapy. Practitioners must take into consideration each patient's individual condition and constitution, and tailor the above prescriptions accordingly. It is recommended that practitioners bear in mind the following point categories during treatment. Ghost points There are many methods of acupuncture practised globally, each of which has its main focus area, such as musculoskeletal issues or emotional problems.¹³ Ghost point needling is one method that is relevant in the treatment of epidemics. Before the

1st century CE, the term yi (疫) was associated with ghosts or demons (gui 鬼), as in the term yi gui which appears in Lunyu (Analects of Confucius) by Confucius (551–479 BCE), where it is often rendered ‘hungry ghost’ in the English translations of the text.²⁵ Uncontrollable infectious diseases - li yi - were at this time regarded as evil qi and associated with ghosts.²⁶ Shaman doctors commonly used the term gui (ghost) as a term for unexplained illness and disease. Of course, symptoms of mental illness can be part of the clinical presentation during acute infectious disease. Ghost points initially appeared in the Shang dynasty (1520-1030 BCE) and were used for fighting epidemics in the Zhou dynasty (1030-727 BCE), for example for treating coma during the Warring States Period (475-221 BCE). These points were later recommended by Sun Simiao (581- 682) for treating mental-emotional illness such as madness.²⁷ The concept gui (ghost) should be seen within its historical context. Throughout most of the Han-Tang period, frequent wars and epidemics resulted in great social and economic stress.²⁸ Cao Zhi (192-232 CE), the prince of the state of Wei expressed his grief for friends who died during an epidemic in 217 CE in Shuo yi qi (Speaking Epidemic Qi), and also described people’s devastation and hopelessness during that disaster.⁸ The ‘ghost qi’ from unseasonable weather thus not only caused deadly epidemics but also consequent fear. That is, people have more anxiety during epidemic periods whether they become infected or not - which the needling of the ghost points can effectively counter. Unfortunately, since the systematic development of Chinese medicine in the Han dynasty and the cultural revolutions in the 20th century, medical scholars began to avoid use of practices involving the term ‘ghost’ in order to distant themselves from shamanism.¹⁵ Some modern authors believe that ghost points are actually related to the treatment of yin fire.²⁹

Obviously, when yin and yang separate, yang floats upwards and outwards; this creates a volatile, unbalanced state, which ferocious epidemic qi can easily take advantage of (and might explain why certain body types are infected more easily than others). However, it is the opinion of the authors of this article that these points can still be valid in the fight against today’s epidemic threat, especially Shaoshang LU-11 and Yinbai SP-1, which can be applied throughout the whole treatment period of COVID19. They are both jing-well points and are located at the end of the Lung and the beginning of the Spleen channels (the major organs primarily attacked by COVID-19). Their functions are as follows:

- Shaoshang (Lesser Shang, also known as Gui Xin, Ghost Trust) LU-11: Clears the Lung and purges fire, expels evil, treats cough and dyspnoea due to exogenous pathogenic qi occluding the Lung, as well as sore and swollen throat, nasal congestion and epistaxis.
- Yinbai (Hidden White, also known as Gui Lei or Ghost Fortress) SP-1: The Zhenjiu Jiayi jing (Systematic Classic of Acupuncture & Moxibustion) recommends this point for treating dyspnoea, asthma, abdominal distension, heat and fullness in the chest, violent diarrhoea, dyspnoea when lying supine, cold feet, epigastric glomus, nausea and vomiting, and poor appetite. Confluent points The confluent points of the Extraordinary Vessels are located in the limbs and can be exceptionally effective for opening the channels and easing body tension. However, they should be treated in a strict order.³⁰ The upper burner organs are the first targeted and obstructed by epidemic qi, followed by the middle burner and finally the lower burner. Therefore for acute infection by COVID-19, opening up the blockage in the upper burner should be the first priority. The actions of these points can be summarised as follows:
 - Lieque LU-7 and Zhaohai KID-6: regulate qi and blood in the chest, thorax and upper abdomen, and balance the Ren Mai (Conception Vessel) and Yin Qiao Mai (Yin Motility Vessel)
 - Neiguan P-6 and Gongsun SP-4: regulate abdominal qi and blood, and balance the Chong Mai (Penetrating Vessel) and the Yin Wei Mai (Yin Linking Vessel)
 - Waiguan SJ-5 and Zulinqi GB-41: Release exterior tension and clear heat from the Liver and Gall Bladder, harmonise Yang wei mai (Yang Linking Vessel) the Dai Mai (Girdle Vessel) and Shao Yang channel collaterals.

Conclusion

This is a public domain data-based exploratory study which has limitations in terms of having no empirical evidence. Despite this, it is based on review and analysis of extensive documentation. As currently there is no cure for or vaccination to prevent COVID-19, exploring possible therapies to contribute to this recent global

health crisis could prove vital. While results from Chinese herbal treatment in this area have been encouraging, they have involved unintended consequences, such as disturbing patients' Stomach and Spleen function. Historically, acupuncture has been used effectively to treat epidemic infectious diseases, and despite historical neglect, it could become a crucial weapon in the battle against COVID-19 and other future epidemics. Of course, practitioners should ensure that they are properly protected when working with infected patients, which means wearing a protective suit and administering acupuncture in a hospital environment (which brings its own challenges). Inspiring evidence of the role of acupuncture has been appearing since the beginning of March 2020. Professor Zou Xu is a critical care medical expert from Guangdong TCM hospital. As one of the supporting medical staff in Wuhan Leishenshan hospital, he always takes acupuncture needles during his ward inspections to help COVID-19 infected patients, especially those with acute symptoms such as shortness of breath, coughing, dizziness, insomnia, restlessness, palpitations, diarrhoea or vomiting. The effect of his acupuncture was often instantaneous. A 72 year old female patient with high blood pressure and diabetic chronic illness complained of a lower back ache, whereupon Zou needled the point Taixi KID-3 and the patient was able to stand upright immediately. Zou explains that acupuncture can improve the patients' oxygen supply and consumption, helping them regain yuan-original qi while blocking the toxicity attacking the Lung. Most importantly, acupuncture is not aiming to destroy the epidemic qi, but instead it can influence the conditions of its survival in the body.³¹ Zou's team was in charge of 16 patients, of which six patients volunteered for Chinese medicine treatment alone; as of 1st March 2020, all six have fully recovered and have been discharged from hospital.³² In another 'Report from the Front Line in Wuhan', Professor Liu Li Hong has also documented the work of his team treating patients with COVID-19 in Wuhan, emphasising the importance of acupuncture in helping patients immediately with symptoms such as stuffiness in the chest, shortness of breath, abdominal discomfort, itchy throat, cough, dizziness, pain and sweating.³³

Acknowledgements Wen Sheng Zhou gives thanks to M. J. Fleming for his editorial help. Authors sincerely thank Daniel Maxwell and the Journal of Chinese Medicine for their tremendous effort in publishing this article. Peilin Sun has been engaged in clinical practice and teaching of traditional Chinese medicine for more than 40 years and has written and published many articles and textbooks on the subject. He is a professor at the Instituut voor Complementaire Zorg Opleidingen in Belgium (www.ICZO.be), visiting professor and PhD supervisor at Nanjing University of Chinese Medicine and maintains a private clinical practice in Belgium. Wen Sheng Zhou, has a BA in Chinese language and literature in China and an MSc in acupuncture from the University of Westminster (UK). She is currently studying for her PhD with Nanjing University of Chinese Medicine and practises acupuncture in London (UK).

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Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment

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SUMMARY

Pneumonia associated with the 2019 novel coronavirus (2019-nCoV) is continuously and rapidly circulating at present. No effective antiviral treatment has been verified thus far. We report here the clinical characteristics and therapeutic procedure for four patients with mild or severe 2019-nCoV pneumonia admitted to Shanghai Public Health Clinical Center. All the patients were given antiviral treatment including lopinavir/ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) and other necessary support care. After treatment, three patients gained significant improvement in pneumonia associated symptoms, two of whom were confirmed 2019-nCoV negative and discharged, and one of whom was virus negative at the first test. The remaining patient with severe pneumonia had shown signs of improvement by the cutoff date for data collection. Results obtained in the current study may provide clues for treatment of 2019-nCoV pneumonia. The efficacy of antiviral treatment including lopinavir/ritonavir, arbidol, and SFJDC warrants further verification in future study.

Keywords 2019-nCoV, lopinavir, ritonavir, arbidol, Shufeng Jiedu Capsule

1. Introduction

Coronaviruses mainly cause respiratory tract infections and some strains have high infectivity and mortality as well as heavy damage on public health, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (1). A pneumonia associated with the 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China in December, 2019 and has spread rapidly, with 24,324 confirmed cases in mainland China as of February 4, 2020 (2,3). The most common clinical presentation is fever, fatigue, and dry cough and some patients present with nasal congestion, runny nose, and diarrhea (4). In severe cases, dyspnea usually occurs one week after the disease onset and some patients can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, and coagulation disorders (4). Thus far, there is no approved or verified effective drugs specific to the virus (5). We report here that four patients with mild or severe 2019-nCoV pneumonia have been cured or have significant improvement in their respiratory symptoms after treatment with combined lopinavir/ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) on the base of supportive care.

2. Methods

2.1. Patients

For this retrospective study, four patients were recruited from January 21 to January 24, 2020 at Shanghai Public Health Clinical Center, Shanghai, China, which is a designated hospital for 2019-nCoV pneumonia. All patients were diagnosed as having 2019-nCoV pneumonia according to WHO interim guidance. Informed consent to therapeutic regimen was obtained from each patient prior to treatment.

2.2. Data collection

Epidemiological, demographic, clinical, laboratory, management, and outcome data were collected through a review of medical records. Clinical outcomes were followed up until February 4, 2020. Laboratory confirmation of 2019-CoV was done in Shanghai Municipal Center for Disease Control and Prevention. Throat-swab specimens from the upper respiratory tract that were obtained from all patients at admission were maintained in viral-transport medium. 2019-nCoV was confirmed by real-time RT-PCR using the same protocol described previously (6). All patients were given chest computed tomography (CT) or chest radiography.

3. Results and Discussion 3.1. Demographics and baseline characteristics

Four patients with 2019-nCoV are included in this study, two of whom are under the age of 35 and the other two are over the age of 60 (Table 1). All the patients had epidemiologic linkage to areas with community transmission of 2019-nCoV. Among them, two patients (Case 1 and 4) had recent travel history to Wuhan, one patient (case 2) is a student who was ordinarily a resident in Wuhan and went back to

Shanghai for winter holiday, and one patient (Case 3) is the husband of a confirmed 2019-nCoV case. It took 11 and 6 days from disease onset to confirmed diagnosis for case 1 and case 2, while 1 and 2 days for case 3 and case 4. Fatty liver was reported in the case 1. No underlying medical conditions were reported in the other three cases.

3.2. Clinical characteristics and laboratory assessment

On admission, the most common symptoms were fever or history of fever, followed by cough, fatigue, dizziness, nasal congestion, and rhinorrhea (Table 2). Diarrhea was not observed in all patients, on the contrary, two of them were reported to have constipation. Physical examination revealed increased respiratory rate in three patients, one of whom had tachypnea (26/min). Lung auscultation revealed rhonchi in left or right lower lobe in three patients. In all patients, there were marked abnormalities on chest radiography; involvement of both lungs was found by chest computerized tomography (CT) in 2 patients at presentation. Ground-glass opacities and consolidation were the most common radiologic findings. On admission, leucocytes were in the normal range in all the patients (Table 3). One patient (case 4) had neutrophils above the normal range, indicating the existence of concurrent bacterial infection. Lymphocytes were below the normal range in one patient (case 4) and within the normal range in other three patients. Blood gas analysis revealed that oxygen pressure was below the normal range in two patients (7.60 kPa in case 3 and 5.45 kPa in case 4) (Table 3). On the basis of the above results, two patients (case 1 and 2) were diagnosed with mild pneumonia and the other two patients (case 3 and 4) with severe pneumonia

Table 1. Demographics, baseline characteristics, and clinical outcomes of 4 patients admitted to Shanghai Public Health Clinical Center

Items	Case 1	Case 2	Case 3	Case 4
Age	32	19	63	63
Sex	Male	Male	Male	Female
Exposure history	Recent travel to Wuhan	Resident of Wuhan	Close contact with 2019-nCoV patient	Recent travel to Wuhan
Chronic medical illness	Fatty liver	None	None	None
Days from illness onset to diagnosis confirmation	11	6	1	2
Clinical outcome	Discharged	Discharged	Remained in hospital	Remained in hospital

Table 3. Clinical laboratory results of patients with 2019-nCoV pneumonia

Variable	Case 1		Case 2		Case 3		Case 4	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Blood routine								
Leucocytes ($\times 10^9$ per L; normal range 3.5-9.5)	4.23	4.68	6.48	6.58	4.40	5.31	6.84	10.84
Neutrophils (%; normal range 50-70)	57.2	49.1	57.0	47.6	50.0	55.4	93	94
Lymphocytes (%; normal range 20-40)	30.3	37.1	30.6	39.4	24.5	25.0	6.10	3.2
Blood gas analysis								
pH (normal range 7.35-7.45)	7.33	7.33	7.43	7.33	7.40	7.36	7.44	7.33
PCO ₂ (kPa; normal range 4.65-6.0)	3.42	6.05	4.55	5.96	5.45	5.59	4.23	5.52
PO ₂ (kPa; normal range 10.6-13.3)	22.00	11.90	16.6	13.4	7.60	12.0	5.45	21.9

Table 2. Clinical characteristics at presentation and treatment of patients with 2019-nCoV pneumonia

Items	Case 1	Case 2	Case 3	Case 4
Signs and symptoms				
Fever	Yes	Yes	Yes	Yes
Cough	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes	Yes
Diarrhea	Yes	Yes	Yes	Yes
Nasal congestion	Yes	Yes	Yes	Yes
Rhinorrhea	Yes	Yes	Yes	Yes
Constipation	Yes	Yes	Yes	Yes
Respiratory rate	22/min	19/min	26/min	22/min
Lung auscultation	Rhonchi (left lower lobe)	No rhonchi	Rhonchi (right lower lobe)	Rhonchi (left lower lobe)
Chest CT findings				
Unilateral pneumonia	Yes	Yes	Yes	Yes
Bilateral pneumonia	Yes	Yes	Yes	Yes
Treatment				
Oxygen therapy	Yes	Yes	Yes	Yes
Mechanical ventilation	Yes	Yes	Yes	Yes
Antibiotic treatment	Yes	Yes	Yes	Yes
Low-molecular-weight heparin/SFEDC	Yes	Yes	Yes	Yes
Intravenous immunoglobulin therapy	Yes	Yes	Yes	Yes

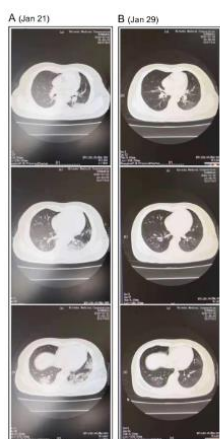


Figure 1. Chest CTs of patient 1 obtained on January 21 (A) and January 29 (B), 2020.

Figure 1. Chest CTs of patient 1 obtained on January 21 (A) and January 29 (B), 2020

3.3. Treatment and clinical outcomes

All patients received antiviral treatment, including lopinavir/ritonavir (Kaletra®, lopinavir 400 mg/ritonavir 100 mg, q12h, po), arbidol (0.2 g, tid, po), and SFJDC (2.08 g, tid, po). The duration of antiviral treatment was 6-15 days. In addition, all patients were all given antibiotic treatment and started on supplemental oxygen, delivered by nasal cannula after admission to hospital (Table 2).

Patient 1 was admitted to hospital on January 21, 2020 and thereafter received the above treatment. On January 27, routine blood analysis revealed that leucocytes and lymphocytes were increased, indicating recovery and restoration of immune function (Table 3). On January 29, chest CT demonstrated bilateral pneumonia with scattered multiple nodules, which was obviously improved compared with that obtained on January 21 (Figure 1). 2019-nCoV was twice negative in throat-swab specimens from the upper respiratory tract. The patient was free of fever, productive cough, dyspnea, short breath, abdominal pain, and diarrhea, and thus discharged on January 29, 2020. Patient 2 was admitted to hospital on January 24, 2020 and then received the above mentioned treatment. On January 28, routine blood analysis showed increased count of leucocytes and lymphocytes (Table 3). Blood gas analysis revealed no obvious abnormality. On January 29, chest CT revealed unilateral pneumonia in the left lobe, which was mildly improved compared with the images obtained on January 24 (Figure 2). Results of two continuous 2019-nCoV tests were negative for throat-swab specimens. Symptoms associated with pneumonia had improved and the patient was discharged on January 30, 2020.

Patient 3 was admitted to hospital on January 24, 2020 and thereafter received the above mentioned treatment. The fever disappeared after one day of treatment. On January 29, chest CT showed progressed pneumonia in the right lobe (Figure 3). The treatment was continuous and the pneumonia appearance improved on February 1 as reflected by the CTimage (Figure 3). On February 3, blood gas analysis demonstrated obviously increased oxygen pressure compared with that at admission. The patient had mild cough with white phlegm, and was free of fever, dyspnea, short breath, abdominal pain, and diarrhea. 2019-nCoV test result was negative for the first time on February 4, 2020. The patient remained in hospital for the second virus test.

Patient 4 was admitted to hospital on January 22, 2020. In addition to the above mentioned treatments, the patient was also given human seroalbumin and γ -immunoglobulin. On January 31, the patient was given an intubated ventilator-assisted breathing therapy because of refractory low blood oxygen pressure. Routine blood analysis on February 1 demonstrated the percentages of neutrophils and lymphocytes were 94% and 3.2%, respectively, which were comparable with those at admission (Table 3).

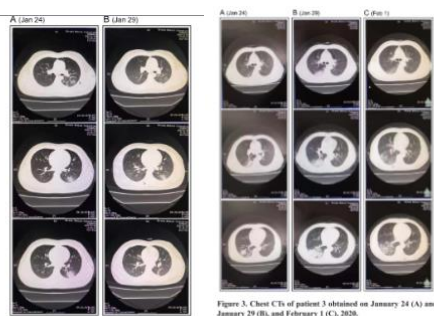


Figure 3. Chest CTs of patient 3 obtained on January 24 (A) and January 29 (B), and February 1 (C), 2020.

Figure 2. Chest CTs of patient 2 obtained on January 24 (A) and January 29 (B), 2020.

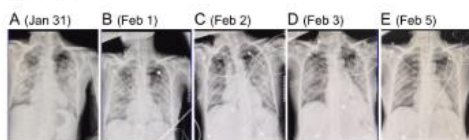


Figure 4. Posteroanterior chest radiographs of patient 4 obtained on January 31 (A), February 1 (B), February 2 (C), February 3 (D), and February 5 (E), 2020.

Chest radiography demonstrated bilateral pneumonia, which improved compared to the image obtained on January 31 (Figure 4). Chest radiograph on February 2 revealed further mild improvement. On February 3, bilateral pneumonia remained but the appearances of left lobe improved and right lobe mildly worsened. On February 5, the appearance of pneumonia improved compared with the last image (Figure 4). The patient was still using ventilators at data cutoff.

We report here the clinical characteristics and therapeutic procedure for four patients with 2019- CoV pneumonia receiving comprehensive therapy. The antiviral treatment regimen includes lopinavir/ritonavir (Kaletra®), arbidol, and SFJDC. By February 4, 2020, two patients were confirmed 2019-nCoV negative and one patient was virus-negative at the first test. Lopinavir/ ritonavir (Kaletra®) is a human immunodeficiency virus (HIV) medicine used in combination with other medicines to treat adults and children over 14 days of age who are infected with HIV-1 (7). It was revealed that lopinavir/ritonavir among SARS-CoV patients was associated with substantial clinical benefit (fewer adverse clinical outcomes) (8). The combination of lopinavir and ritonavir is currently a recommended antiviral regimen in the latest version of Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (version 5) issued by National Health Commission of the People's Republic of China (4). Arbidol is an antiviral treatment for influenza infection used in Russia and China (9). It was claimed that arbidol was effective against 2019-nCoV at a concentration range of 10-30 μ M in vitro (10). A randomized multicenter controlled clinical trial of arbidol in patients with 2019-nCoV (ChiCTR2000029573) has been initiated in China (11). SFJDC is a traditional Chinese medicine for treatment of influenza in China. This drug is also recommended for treating 2019-nCoV infection in the latest version of Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (version 5) (4).

In conclusion, two mild and two severe 2019- nCoV pneumonia patients were given combined Chinese and Western medicine treatment, three of whom gained significant improvement in pneumonia associated associated symptoms. The remaining patient with severe pneumonia has shown signs of improvement by the cutoff date for data collection. The efficacy of antiviral treatment including lopinavir/ritonavir, arbidol, and SFJDC warrants further verification in future study.

Acknowledgements

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Guía de prevención y tratamiento de Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar (Neumonía por Corona- virus)

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Resumen: La Enfermedad Febril por Calor incluye enfermedad Wén Bing (溫病), Wen Bing (瘟病), Yi Bing (疫病) y Li Bing (痢病) en la Medicina Tradicional China (MTC). El Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar (incluye los Yi Bing y Li Bing) abarca múltiples tipos de enfermedades infecciosas pulmonares, tales como: Leptospirosis Hemorrágica Pulmonar, Peste Neumónica, Neumonía por Coronavirus, etc. Existen cuatro fases en el desarrollo de la Neumonía por Coronavirus: fase temprana (grado leve, preponderancia de la Humedad sobre el Calor), fase intermedia (grado moderado, igual gravedad de Humedad y Calor), fase crítica (grado severo) y fase secuelar. Este artículo tiene como objetivo brindar herramientas de manejo clínico en el diagnóstico, tratamiento, pronóstico, prevención y cuidados posteriores a la Neumonía por Coronavirus. Palabras claves: Humedad-Calor, Wen Bing, Coronavirus, Neumonía.

Declaración de intereses: El autor declara no poseer ningún conflicto de interés. Cita bibliográfica: Xiong-Zhi, Wu. Guía de prevención y tratamiento de Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar (Neumonía por Coronavirus). Classical Chinese Medicine Research.

<https://www.tmrjournals.com/ccmr/CN/10.12032/CCMR2020004>. Editor Ejecutivo: Yang-Tao Li, Ying-Chun Sun. Enviado: 23 de febrero de 2020, Aceptado: 23 de febrero de 2020, En línea: 23 de febrero de 2020

Introducción

Wén Bing (溫病) es la Enfermedad Febril por Calor. Tiene como eje la respuesta inflamatoria que es causada en la mayoría de las veces por enfermedades infecto-contagiosas de la Medicina Moderna. Wen Bing (瘟病) es un subtipo de la enfermedad anteriormente mencionada. Posee capacidad infecto-contagiosa, y puede dar muerte a grupos de personas con disminución de la inmunidad tales como ancianos, lactantes e infantes. Yi Bing (疫病) se refiere a Wen Bing pero con marcada letalidad y puede provocar la muerte incluso adultos jóvenes sanos. Li Bing (疔病) se refiere a Yi Bing con mayor infectividad y letalidad aún.

Sin importar si el estado inmune de los contactos cercanos sea alto o bajo, son propensos de contraer la enfermedad. Los que debutan en la fase crítica, tiene alta mortalidad a corto plazo, en cuestión de minutos, horas o días. Por estas razones, esto ha causado la extinción de familias completas y hasta pueblos enteros en la antigüedad. El Wen Bing que trata esta guía engloba al Wen Bing, Yi Bing y Li Bing.

Sugiero al Estado que publique documentos relacionados al mismo, así como elaborar un nomenclador de guía de conceptos de Wen Bing, Yi Bing y Li Bing desde MTC. (Consultar el nomenclador de las enfermedades infecto-contagiosas, categoría A, B y C de la medicina moderna). Wén Bing se divide en dos categorías: Enfermedad por Calor intenso y Enfermedad por Humedad-Calor. La Enfermedad por Calor intenso se caracteriza anatómo-patológicamente por una inflamación de tipo alterativa, donde predomina el daño tisular y la necrosis celular. En cambio, la inflamación en la Enfermedad por Humedad-Calor es de índole exudativa donde prevalece el edema y la exudación tisular que evoluciona en la mayoría de los casos hacia la fibrosis. La Enfermedad Taiyin incluye a las enfermedades del Taiyin Bazo (tracto digestivo) y del Taiyin Pulmón (vías respiratorias). El Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar (incluye los Yi Bing y Li Bing) abarca múltiples tipos de enfermedades infecciosas pulmonares, tales como: Leptospirosis Hemorrágica Pulmonar, Peste Neumónica y Neumonía por Coronavirus, etc. Esta guía trata principalmente la Neumonía por Coronavirus, explicando y debatiendo detalladamente acerca de la prevención y el tratamiento del Wen Bing del Síndrome de Humedad-Calor de Taiyin Pulmonar.

En esta enfermedad es necesario tomar en cuenta las características de la localización de la afección por la Humedad patógena: ① Si la Humedad-Calor no reside en el Bazo-Estómago, reside en Hígado-Vesícula Biliar. Esto se debe a que el Bazo es el origen de la Humedad. Los que sufren de Insuficiencia de Bazo, les es más fácil sufrir la Humedad por afección interna y externa. Shaoyang-Sanjiao es la ruta de humores que participa en el metabolismo del agua y de los humores, a su vez, “El Qi del Fuego trata las enfermedades en Shaoyang”, esto facilita la génesis de Calor por Represión de Humedad o la afección directa del Calor Patógeno. Por estas razones, en el tratamiento de dicha enfermedad hace hincapié en el Taiyin y Shaoyang. Clínicamente, es frecuente la lesión hepática; la fiebre se acompaña de astenia (el Hígado es la base de la resistencia a la fatiga) y, el rechazo a las grasas, síntomas característicos de la lesión en Shaoyang. Otros síntomas a tomar en cuenta son: sensación de gusto amargo en la boca, molestias en la garganta, ojo rojo, pulso de cuerda e hinchazón de los bordes de la lengua. ② La Humedad Patógena impregna Sanjiao, difundiéndose hacia arriba y hacia abajo; hacia arriba se presenta con tos; hacia el medio con diarrea, náuseas, vómitos y distensión abdominal; hacia abajo, dificultad para orinar e injuria renal. ③ La Humedad-Calor puede presentar tanto manifestaciones externas como internas. Por afuera, es frecuente el rush cutáneo y por adentro, daño miocárdico que en casos severos lleva al shock y al coma. ④ Si hay Exceso, es Yangming; si hay Insuficiencia, es Taiyin. Por ende, Yangming predomina Calor sobre Humedad, y Taiyin viceversa.

Claves en las indicaciones médicas: ① El calor no se libera mediante diaforesis. Luego de que el paciente transpira, baja la fiebre y sienta mejoría clínica, con o sin tratamiento, no significa que la enfermedad se haya aliviado. Sin embargo, muchos pacientes presentan fiebre alternante con intervalos de mejoría que se caracterizan por la incapacidad de recuperar la normalidad del pulso (pulso tranquilo), de la temperatura corporal (frialidad) y de la saburra lingual. ② Los que sufren Calor Ondulante en horario fijo (Ej: muchos lo hacen por la tarde), pueden recibir una dosis de medicación treinta minutos a una hora previo al próximo evento (Ej: Los que sufren de Calor intenso luego de las 13:00 horas, adicionar una dosis extra de Yin Chai Xiao Du Dan, ya que el Calor se encuentra en Yangming; por otro lado, los que lo hacen antes de las 13:00 horas o

inclusivo antes de las 11:00 horas, hay más posibilidad de recibir Chai Ling Tang, puesto que el Calor se encuentra casi siempre en Taiyang. ③ A los más graves se les puede indicar una dosis cada 4 horas, mientras que a los críticos, cada 3 horas. Tener especial cuidado con el Bazo y el Estómago. ④ El curso de la enfermedad en los pacientes leves es aproximadamente de 14 días. No obstante, pese a la mejoría clínica íntegra luego de unos días de tratamiento, se recomienda completar los 14 días de tratamiento.

1. Fase temprana

1.1 Clasificación de fases y tipos

Esta fase se encuentra más frecuente en:

① Fase temprana de la enfermedad: Tener en cuenta que la fase temprana y la fase intermedia no dependen de manera determinante al tiempo de evolución de la enfermedad. Muchos pacientes permanecen en esta fase (los leves), otros debutan en fase intermedia (los moderados), y algunos fallecen de manera rápida (los críticos).

② Paciente con marcada Insuficiencia del Bazo, que presenta mayor Humedad que Calor: Al momento de la examinación, se debe prestar mucha atención en la parte media y basal de la lengua ya que si se encuentra pálida, indica Insuficiencia del Bazo o del Yang. Cuando la fiebre no es muy alta o después del descenso de la temperatura con medicación, se puede explorar los dedos de los pies para valorar si hay Insuficiencia del Yang, debido a que los que sufren Insuficiencia del Yang severo, los dedos de sus pies permanecen fríos aun cuando estén cursando una fiebre. Las improntas dentales en los bordes de la lengua indican también Insuficiencia del Bazo, y hay que diferenciarlo de la hinchazón lingual lateral (fenómeno de represión de Qi del hígado). Cuando ésta última es difícil de apreciar, inspeccionar las improntas dentales en la cara interna de las mejillas.

③ Pacientes leves: Hay que prestar especial atención porque a veces existe una disociación de la clínica con el curso de la enfermedad. Es decir, que sea leve o no, no depende meramente de la presentación clínica, sino que es necesario una evaluación completa semiológica de lengua y pulso, con o sin métodos diagnósticos complementarios contemporáneos como radiografía de tórax o tomografía computada.

La fase temprana muchas veces es diagnosticada de manera errónea como Síndrome Frío-Humedad debido a las siguientes causas:

① La Insuficiencia del Bazo produce Humedad interna, y por afección interna externa, se torna más fácil contraer Patógeno Externo. Estos pacientes presentan a menudo lengua pálida con improntas dentales.

② Mientras más Humedad haya, más saburra blanca se produce, y a veces oculta toda la lengua roja; otras veces se ignora el enrojecimiento del dorso lingual generado por represión del Calor. ③ En el comienzo de la transformación en Calor, se puede observar una capa fina de saburra amarilla por encima de la blanca muchas veces desaparecida. Es imprescindible interrogar sobre la materia fecal. La saburra amarilla de los estreñidos desaparecerá una vez que se evacúe; por otro lado, la saburra amarilla es producida por la respuesta inflamatoria y confirma la transformación en Calor.

④ La saburra de los inmunosuprimidos no se convertirá en amarilla a pesar de la transformación en Calor.

⑤ La respuesta inflamatoria necesita entre horas a uno o dos días para que los leucocitos se conviertan en piocitos. Por eso, los pacientes con Enfermedad Calor intenso muestran saburra blanca y seca en la fase temprana. Se puede precisar la saburra granulada en la inspección detallada pese a que la Humedad pueda encubrir la Sequedad.

⑥ Otro punto para recalcar del Síndrome Frío-Húmedad es la presencia del pulso moderado en ausencia de fiebre, a diferencia de un pulso basal levemente más rápido en el Síndrome Humedad-Calor. Por estas razones, no se debe diagnosticar como Frío-Húmedad.

⑦ Algunos pacientes aparentan lengua pálida con saburra blanca y grasienta. Empero, una vez que reciben medicación del Calor, se vuelven con el pulso taquisfígmico y saburra amarillenta, coincidente con el mecanismo de expansión de Humedad-Calor del Wen Bing de Humedad-Calor. En cambio, esta transformación no ocurre en el Síndrome Frío-Humedad, un ejemplo de lo último es Li Zhong Tang para el Síndrome Frío-Humedad por Cólera

⑧ Debido a la presencia de una noxa clara y determinada en Wen Bing, no se sostiene la hipótesis de que una parte de esta enfermedad sea producida por Humedad-Calor y otra por Frío-Humedad. La Humedad es un patógeno Yin y el Calor, un patógeno Yang. Contemplando la variabilidad de la constitución física, sea más frío o más calor, se produce diferentes tipos de manifestaciones clínicas. Sin embargo, esto no influye en el diagnóstico del Síndrome Humedad-Calor de esta enfermedad. Por lo tanto, solo hay que ajustar las fórmulas según la variabilidad de la constitución física y el nivel de Humedad o Calor.

Otros tantos presentan tos seca o con escasa flema, que pueden llevar a un error diagnóstico de Insuficiencia del Yin. La escasa flema se debe a difícil expectoración por su localización en el intersticio alvéolo pulmonar, diferente de la bronquitis y de la bronquiolitis. Por este motivo, no se puede diagnosticar como Insuficiencia del Yin o ausencia de la Humedad por la escasa flema.

1.2 Tratamiento

1.2.1 Elaboración de la fórmula

Fórmula de Wu Men, Chai Ling Tang modificada. Ingredientes: Chai Hu 24g, Huang Qin 9g, Gui Zhi 6-9g, Bai Zhu 9g, Fu Ling 10g, Zhu Ling 10g, Ze Xie 9g, Sheng Gan Cao 6g, Shi Shang Bo 30g, Lian Qiao 30g.

1.2.2 Explicación de la fórmula

En el "Shang Han Lun" está documentado el uso de la fórmula Wu Ling San para el tratamiento de vómito, diarrea, tos y fiebre por afección externa; y Xiao Chai Hu Tang para el Calor por afección externa. Sanjiao es la ruta de los humores, Xiao Chai Hu Tang también se indica para la tonificación de los movimientos de los líquidos corporales, así como se dice: "Si el Jiao superior (Shangjiao) se desbloquea, los líquidos y los humores bajan, entonces, el Qi del estómago se armoniza y el Calor se libera por sudoración lluviosa." [3] Shi Shang Bo se usa para la infección pulmonar y Sheng Gan Cao para la desintoxicación ya que el ácido glicirretínico (ácido de Gan Cao) tiene propiedades antiinflamatorias similares a los glucocorticoides. En "Jing Yue Quan Shu" (Obras completas de Jing Yue) está registrado que al Wu Ling San hay que agregarle Qiang Huo para la afección externa por Frío-Humedad; mientras que en mi experiencia es adicionar Lian Qiao cuando la afección externa fuera por Humedad-Calor. Lian Qiao tiene funciones antieméticas (como Gan Lu Xiao Du Dan), refresca la sangre (como Qing Ying Tang), depura el corazón (como Qing Gong Tang), depura el hígado (como Ma Huang Lian Qiao Chi Xiao Dou Tang) además de liberar la superficie. Puesto que la fisiopatología de Shaoyang es lucha entre lo recto y lo perverso, los que sufren de modo crítico el Síndrome Humedad-Calor evoluciona casi siempre con falla hepática fulminante. Asimismo, es frecuente que Wen Bing afecta directamente a la capa nutricia (營) y a la capa sanguínea (血) por lo que se ve en la fase temprana una lengua espiculada. Contemplando todos los factores mencionados anteriormente, hay que dar más dosis de Lian Qiao. Hay que tener mucho cuidado con el uso de medicamentos que refuerzan la Energía Recta, como Huan Qi o Ren Shen, ya que éstos pueden exacerbar la respuesta inflamatoria. Por esta razón, se quita Ren Shen del Xiao Chai Hu Tang. Para los individuos con complejión débil, se puede aumentar la dosis de Sheng Gan Cao hasta 9-15g e incluso añadir Tai Zhi Shen 15-50g. Cabe destacar, hay que controlar la tensión de lucha entre el Qi recto y el Qi perverso. Se necesita Ren Shen y Huan Qi para eliminar definitivamente la causa patogénica de la infección citolítica en individuos con Insuficiencia del Bazo. Sin embargo, no es ésta la fisiopatología de esta enfermedad. Cuando existe una alteración inmunológica, el tratamiento alopático son los antiinflamatorios anticitoquinas. Empero, el uso de Ren Shen y Huan Qi en MTC refuerza la respuesta inmune, por lo cual se debe indicar con mucha precaución. No se recomienda su uso si no fueran expertos tanto en Wén Bing Xue de MTC como en Infectología de medicina alopática. Se recomienda sumar Zhi Ban Xia 9g y una cucharada de jugo de Jengibre

para enfermos con marcada hiperemesis y diarrea. El jugo de Jengibre facilita la transformación de la Humedad y no genera Calor, por lo que su uso es relativamente mayor que Sheng Jiang en Wén Bing. Por este motivo, el Jugo de Jengibre sustituye a Sheng Jiang en Xiao Chai Hu Tang. Se recomienda incorporar Dang Gui 9g en pacientes con evidente Insuficiencia de sangre o en las mujeres durante el período menstrual. En los pacientes con Humedad intensa, se descarta Da Zhao de Xiao Chai Hu Tang por su nutrición grasienta, y se prefiere al Dang Gui que tiene acción antiinflamatoria específica en capa sanguínea (血分) además de vigorizar y nutrir la sangre.

Se recomienda asociar Ge Gen 30g (método Ge Gen Qin Lian Tang) a los pacientes con diarrea abundante o presentan tez colorada destacable. Se recomienda agregar Cao Guo 3-6g (método Da Yuan Yin) si presenta saburra blanca, gruesa y símil polvo. Cao Guo es medicamento especial para saburra blanca y gruesa (engrosamiento de papilas filiformes). Agregar Hou Pu en caso de distensión abdominal o Bing Lang (debe tener materia fecal sólida) para los más severos.

1.3 Evolución La evolución clínica habitual es la transformación en Calor por Represión de la Humedad, que se asemeja al concepto del síndrome de respuesta inflamatoria sistémica (SIRS) o de sobreinfección bacteriana en la medicina occidental moderna. A continuación se detallan algunos métodos para determinar si la Humedad Patógena se ha transformado en Calor: El primero es ver si sobre la saburra blanca existe otra capa amarilla. El segundo es examinar la presencia o no de enrojecimiento lingual o gloquidios en el dorso de la lengua. El tercero es palpar el pulso. El pulso impetuoso (躁脈 Zao Mai) indica transformación en Calor, pero éste no solo se limita a la frecuencia de pulsos por minuto. Los principiantes pueden contar la frecuencia teniendo en cuenta lo siguiente: la frecuencia basal del pulso moderado de Insuficiencia del Bazo es de 70 por minuto, mientras que la basal de pulso lento de Insuficiencia del Yang es de 60 por minuto. Entonces, palpar el pulso es una manera de evaluar la temperatura corporal ya que por cada aumento de 1°C, la frecuencia de pulso aumenta 10 por minuto. De esta manera, se puede estimar el nivel de transformación en Calor o si existe Calor interno según la relación entre la temperatura corporal y la frecuencia de pulso. El cuarto es verificar si hay sobreinfección bacteriana. Clínicamente es común encontrar dolor de garganta, inflamación o supuración amigdalina o aumento de leucocitos a predominio de neutrófilos absolutos en el análisis de sangre. Como esta enfermedad genera linfopenia, el aumento porcentual relativo de neutrófilos no implica infección bacteriana. Se recomienda quitar Gui Zhi o bajar su dosis a 3-6g o reemplazarla por Rou Gui cuando es difícil determinar si hay transformación en Calor o no. La fórmula de la fase intermedia es más segura mientras que la de fase temprana libera más rápido el Calor. Es decir, al no poder discernir claramente la presencia de transformación en Calor, indicar directamente la fórmula de fase intermedia, especialmente para los principiantes de la MTC. Al indicar fórmula de fase intermedia en pacientes de fase temprana, que muchas veces sufren de Insuficiencia del Bazo constitucional, es importante adicionar Chen Pi y/o Cang Zhu para cuidado del Bazo y Estómago. Hay dos formas de manejo en los pacientes que predomina el Calor: el primero es indicar directamente la fórmula de la fase intermedia y; el segundo es incorporar Shi Gao, Hua Shi y Han Shui Shi (Método Gan Lu Yin) sobre la fórmula de la fase temprana así como sustituir Rou Gui 3g por Gui Zhi en la decocción o Rou Gui 1g vía oral.

2. Fase intermedia

2.1 Clasificación de fases y tipos

Existen tres tipos:

- ① Los individuos con Calor Interno constitucional, debutan directamente en fase intermedia cuando contraen esta enfermedad.
- ② Los pacientes con predominio de Humedad en síndrome Humedad-Calor son más propensos a desarrollar la Transformación en Calor por Represión de Humedad.

③ Pacientes tipo moderado. Hay que prestar especial atención porque amenudo existe una disociación de la mejoría clínica con la progresión de la enfermedad. Es decir, que sea moderado o no, no depende meramente de la presentación clínica, sino que es necesario una evaluación semiológica completa de lengua y pulso, con o sin métodos diagnósticos complementarios con- temporáneos como radiografía de tórax o tomografía computada.

Se debe prestar atención al pulso en casos de Wen Bin sin Calor:

① La presencia de Calor. Se revela con el pulso impetuoso. En caso de no dominar la semiología de pulso, contar la frecuencia diariamente. Ante la ausencia de Calor con aumento de pulsos por minuto, se debe prestar atención a la aparición de fiebre alta súbita, semejando al estado previo del SIRS. En el texto original de "Shang Han Lun" menciona el término fiebre alta súbita y se diagnostica con el pulso.

② El nivel de Humedad. Se revela de 3 formas: Primero, si el pulso es fino. Segundo, si el pulso es moderado. Prestar atención a Yi Bing del Taiyin Bazo, por ejemplo la fiebre tifoidea intestinal, que se ve poco en Yi Bing del Taiyin Pulmón Tercero, si el pulso es áspero y débil. Una manera para los principiantes de MTC es ver si pueden sentir claramente bajo sus dedos cada pulsación. De lo contrario puede estar relacionado con la Humedad. (El pulso áspero y débil no solo aparece en enfermedades de Humedad).

Fíjese que la Humedad es un patógeno Yin perverso mientras que el Calor, un patógeno Yang perverso. La mayoría de las manifestaciones clínicas de la Humedad y del Calor son contrapuestas:

① El pulso del Calor es rebosante, grande y rápido; mientras que el de la Humedad es fino, débil y moderado (rebosante-débil, grande-fino, moderado-rápido), totalmente opuestos. A pesar de que los pulsos se enmascaran entre sí, la presencia de saburra gruesa grasienta y amarilla o el dorso de la lengua enrojecida indican gravedad igual de Humedad y Calor.

② Los aspectos de la lengua también se enmascaran entre sí. Cuando hay Humedad intensa, se ve lengua pálida e Insuficiencia del Bazo, mientras que en el Calor intenso, lengua roja vinosa. La clave para diferenciar del Calor está en la punta de la lengua y en la saburra. Si hay Calor oculto, ver dorso de la lengua.

③ La insuficiencia del Yin también se enmascara con la Humedad. El pulso de Humedad-Calor es fino pero no hueco (芤 Kou), ya que la presencia de éste indica Insuficiencia del Yin o de sangre. Cuando sufren de síndrome Humedad-Calor, en los individuos con insuficiencia de sangre constitucional, se produce una disminución rápida de glóbulos rojos, como ocurre en los casos de glomerulonefritis crónica. Tener en cuenta la observación de las grietas finas linguales.

④ Los gloquidios también pueden ser enmascarados por la Insuficiencia del Bazo, particularmente en la punta de la lengua. Hay que prestar atención que los abundantes gloquidios no enrojecidos indican déficit de Qi Recto, grupo de pacientes que fallecen fácilmente ante infección citotóxica por disminución de su inmunidad. Sin embargo, ante una infección viral no citotóxica (sí citolítica) se desencadena un daño inmunitario inflamatorio, que por la respuesta inmune deficiente, raras veces genera muerte súbita. Empero, facilita la persistencia de la enfermedad, que puede llevar a la muerte por sobreinfección bacteriana o al desarrollo de la fibrosis una vez superada la fase aguda. Otros pueden cronificarse dependiendo de la naturaleza propia de la enfermedad.

2.2 Tratamiento

2.2.1 Elaboración de la fórmula

Fórmula Yin Chai Xiao Du Dan modificado. Ingredientes: Chai Hu 24g, Huang Qin 9g, Jin Yin Hua 30g, Lian Qiao 30g, Chang Pu 9g, Yu Jin 9g, Huo Xiang (agregar tarde) 9g, Pei Lan 9g, Yin Chen 30g, Bai Dou Kou (agregar tarde) 6g, Dang Gui 9g, Dan Pi 9g, Yi Yi Ren 60g, Shi Shang Bo 30g, Shen Gan Cao 6g.

2.2.2 Explicación de la fórmula Chai Hu más Huang Qin se usa en el Calor por afección externa. Como Sanjiao es la ruta de los humores, Xiao Chai Hu Tang también se indica para la tonificación de los movimientos de los líquidos corporales, así como dice: “Si el Jiao superior se desbloquea, los líquidos y los humores bajan y entonces, el Qi del estómago se armoniza y el Calor se libera por sudoración lluviosa”. Se combina Jin Yin Hua con Lian Quio para liberar el patógeno externo. La asociación de Chang Pu con Yu Jin previene el deterioro hacia la fase crítica como la aparición de coma y convulsiones, conceptualmente entendido por la MTC de la siguiente manera: “Una vez que el Calor superficial se interioriza, los meridianos colaterales profundos se bloquean”. La suma de Huo Xiang y Pei Lan transforman la Humedad por sus propiedades aromáticas. Cabe destacar que Pei Lan es un medicamento específico para la inhibición de secreción de mucoproteínas, que tradicionalmente se indica para tratar boca pastosa y boca dulce en la MTC. Se puede usar hasta 20-30g de Pei Lan para disminuir la secreción de grandes cantidades de mucoproteínas en el pulmón, evitando las obstrucciones por flema. Yin Chen más Bai Dou Kou liberan la Humedad-Calor de Sanjiao. Dang Gui más Dan Pi protege la capa sanguínea. En caso de constipación, agregar Zi Cao. Yi Yi Ren elimina la Humedad-Calor externa y es antiviral. Shi Shang Bo es específico para la infección pulmonar. Sheng Gan Cao se usa para la desintoxicación ya que el ácido glicirretínico posee propiedades antiinflamatorias similares a los glucocorticoides. Chai Hu es bueno para eliminar el Calor. Jin Yin Hua tiene buen efecto contra el dolor de garganta. Se recomienda añadir Pei Lan si hay síntomas gastrointestinales marcadas. Las propiedades específicas del Yin Chai Xiao Du Dan consiste en lo siguiente: Chai Hu más Huan Qin elimina Calor; Jin Yin Hua más Lian Qiao expulsa el patógeno a través de la superficie y Pei Lan más Huo Xiang tonifica el estómago. Se puede sustituir Jin Yin Hua por su rocío puesto que posee mejor propiedad para liberar calor y evitar el bloqueo interno.

2.2.3 Modificaciones

Debe prestarse especial atención en pacientes con Insuficiencia del Yin, y evaluar la eliminación de Chai Hu o en el peor de los casos sustituirlo por Sheng Di Huang 15g en pacientes que cursan con fiebre persistente por varios días, ya que éste puede secuestrar Yin de Hígado. La Insuficiencia del Yin aparece a menudo en pacientes con fiebre, vómito o diarrea persistente. Para el diagnóstico precoz de la Insuficiencia del Yin por Síndrome Humedad-Calor hay que precisar si en la lengua existe pequeñas grietas no constitucionales (explicado en la clase de inspección de lengua las grietas constitucionales), que confirma la Insuficiencia.

Hay 4 formas de abordaje para estos casos. Primero, se aconseja quitar Chai Hu y agregar Sheng Di Huang para alimentar el Yin, de lo contrario, la Humedad-Calor difícilmente reduce. Segundo, agregar Xuan Shen que potencia el cultivo del Yin. Se recomienda asociar Xuan Shen con Dang Gui 30g como antiinflamatorio (Método Si Miao Yong An Tang). Esto está contraindicado en pacientes en shock porque Xuan Shen y Dang Gui son vasodilatadores y bajan la presión arterial. Se excepcionan su uso en casos con soporte vasopresor y monitoreo estricto continuo, por lo que se desaconseja su empleo en principiantes. Tercero, sumar Lu Gen 30-50g. Este medicamento contiene coixenolida que facilita la eliminación de Humedad y actúa como antiviral; también contiene asparagina que potencia el cultivo del Yin y es antitusígena; y vitamina B que regenera la saburra; y antipirética. Por último, agregar Zhi Mu cuando el Síndrome Humedad-Calor deteriora el Yin y se acompaña de Calor. La fiebre persistente agota la corteza adrenal o altera el ritmo circadiano de la secreción corticoidea. Zhi Mu protege la corteza adrenal (Métodos Bai Hu Tang y Da Yuan Yin) previniendo el deterioro del Yin por el Síndrome Humedad-Calor. Por lo que se recomienda su uso en estos pacientes. Se recomienda incorporar Dan Zhu Ye 30g más Lu Gen 30g cuando la Humedad es más intensa.

Se recomienda incorporar Da Qing Ye 30g cuando el Calor es más intenso y Chen Pi 6-9g como protector gástrico. Si a esta fórmula se le añade Da Qing Ye, puede aparecer dolor abdominal, diarrea, falta de apetito en pacientes con Insuficiencia del Bazo, por lo que no se recomienda dosis altas. Solo Da Qing Ye 15g combinando con Chen Pi 9g o Cang Zhu 9g. Aunque altas dosis de Yi Yi Ren posee efectos antivirales marcados, pero enfría el estómago, entonces, se recomienda agregar Chen Pi.

2.3 Evolución

La primera evolución es hacia la fase crítica de tipo severo. La segunda es la mejoría post tratamiento. La tercera es la aparición de Insuficiencia del Bazo más Humedad intensa luego de la mejoría posterior a la transformación en Calor por Represión de Humedad. Clínicamente se manifiesta el cambio de saburra a blanca, y la lengua a pálida. En este momento de desaparición de calor, hay que indicar la fórmula de fase temprana, sustituyendo Gui Zhi por Rou Gui 3g en decocciones o Rou Gui 1g vía oral y agregar hierbas que dispersan calor tales como Hua Shi, Han Shui Shi, etc. Si vuelve el Calor, reiniciar la fórmula de fase intermedia, y así viceversa. Ante la inexistencia de Insuficiencia del Bazo y de lengua pálida, no se recomienda abordar de esta manera. La cuarta evolución consiste en la persistencia de Humedad-Calor. Debido a que la Humedad es un patógeno Yin perverso, no se disuelve si no es con Calor. Pacientes con marcada Insuficiencia del Bazo que no muestra clara respuesta de transformación de Humedad luego de recibir esta fórmula, se recomienda rotar a fórmula de fase temprana, sustituyendo Gui Zhi por Rou Gui 3g en decocciones o Rou Gui 1g vía oral y agregar hierbas que dispersan calor tales como Hua Shi, Han Shui Shi, etc y monitorizar estrictamente la respuesta inflamatoria.

3.Fase Huai Bing Huai

Huai Bing se asemeja a la fase crítica de la medicina contemporánea. Esta enfermedad tiene dos tipos de presentaciones: el primero, de tipo fulminante, donde el paciente debuta en fase crítica y se observa principalmente cuando existe el Calor Tóxico Candente. Este grupo de paciente evoluciona de manera rápida y tórpida hacia la muerte en poco tiempo, inclusive en minutos cuando haya bloqueo interno del pericardio; el segundo es de tipo común, donde las fases iniciales tienen un período prolongado hasta que el paciente alcance el punto crítico y desarrolle velozmente la transformación en Calor con pronto deterioro de la enfermedad. Este estado crítico requiere una atención urgente y aparece muchas veces por haber ignorado las fases iniciales demasiado estables. Clínicamente en Huai Bing (fase crítica) se observan insuficiencia cardíaca, insuficiencia respiratoria e insuficiencia renal, con disfunción hepática, gastrointestinal y trastorno de la coagulación que requiere reanimación urgente. Frecuentemente se encuentra una disociación entre el alivio sintomático y el curso de la enfermedad en Yi Bing. Para determinar el punto crítico, hay que examinar si la saburra lingual pertenece al Calor intenso de Yangming. En casos no fulminantes el punto crítico generalmente está alrededor del décimo día, mientras que si no hubo deterioro luego de 14 días, comparativamente están fuera de peligro.

Las formas de diagnosticar Huai Bing son: Primero, examinar si existe gran cantidad de gloquidios en la lengua ya que esto indica la profundización de la enfermedad a la capa sanguínea y ha generado cierto grado de hemorragia. Segundo, examinar la presencia o no de pulso cuerda filosa, que indica convulsión debido a la Agitación Interna del Viento. La saburra lingual también aporta en el diagnóstico: es blanca, de capa gruesa y símil polvo en Humedad intensa, mientras que es amarilla, de capa gruesa y seca, o exfoliada en Calor intenso. Ambos indican la persistencia de la enfermedad con probabilidad de deterioro hacia la fase crítica. La textura oscura y púrpura de la lengua señala hipercoagulabilidad causada por la infección si no fuese por éstasis sanguínea constitucional. En este caso, la progresión de la enfermedad suele ser más lenta. En la aparición rápida de lengua oscura y púrpura en Wen Bing de Taiyin Pulmonar se debe descartar la baja saturación de oxígeno, indicador de gravedad en enfermedades pulmonares, del éstasis sanguínea causada por Calor ferviente. Este último puede generar hemorragias por lo que se recomienda agregar Qian Cao 30g, Zi Cao 9g, Guan Zhong 15g, o directamente la fórmula Shen Xi Dan de "Wen Re Jing Wei." En comparación, la dificultad respiratoria más la semiología de lengua y pulso son determinantes más específicos que los síntomas gastrointestinales, la tos, el esputo y la fiebre para definir el avance de la enfermedad. Ante la aparición de dificultad respiratoria, en medios accesibles, hay que monitorear la saturación de oxígeno y efectuar rápidamente radiografía de tórax o tomografía computada para esclarecer el estado pulmonar. En caso de falla respiratoria derivar de modo urgente al servicio de emergencias. Se recomienda agregar Ma Huang 9g con acción anti-choque, y la dosis puede alcanzar hasta 30-40g según la tensión arterial; así como las fórmulas Ma Xing Shi Gan Tang, Ma Xing Yi Gan Tang y Ma Huang Lian Qiao Chi Xiao Dou Tang, éste último con buen efecto protector de daño hepático post infección viral. La efedrina tiene acción símil adrenalina. Ma Huang

Sheng Ma Tang es una fórmula estándar de MTC para tratar infecciones graves. Dicha fórmula trata las infecciones severas y a los 6 meridianos en simultáneo. Para su indicación hay que modificarla según signo sintomatología. Se recomienda la posibilidad de aplicación de inyectables anti insuficiencia cardíaca como Ren Shen, Fu Zi, Yu Zhu, Shen Fu o Sheng Ma Por otro lado, pese a que Ban Bian Lian tiene efecto específico contra la falla respiratoria de origen central, no se recomienda su uso en esta enfermedad por sus resultados desalentadores especialmente en pacientes con alteración del sensorio y convulsiones. El ácido glicirretínico es un símil glucocorticoides. En caso de no contar con otra medicación antiinflamatoria, sustituir los glucocorticoides por altas dosis de Gan Cao 30g que tiene efecto antiinflamatorio potente. No obstante, añadir medicación evacuadora de agua como Chen Pi y Fu Ling para antagonizar los efectos adversos de Gan Cao. Chang Pu y Yu Jin son buenas opciones para prevenir la fase crítica ya que evita el coma y las convulsiones, precedidas por la opresión precordial de la fase temprana así como lo explica “Una vez que el Calor superficial se interioriza, los meridianos colaterales profundos se bloquean.” Una vez instalado el coma y las convulsiones, el tratamiento urgente tradicional de MTC son los “Tres Tesoros.” El los pacientes que sufren daño del Yin por el síndrome Humedad-Calor se recomienda indicar fórmula Jia Wei Bai He Di Huang Tang (Bai He, Sheng Di, Zhu Ye, Shi Gao y Dan Pi) más Hua Shi y Gan Cao con efecto analéptico marcado. Se recomienda agregar Jiang Nan Quan Bo 30g de inmediato sin otras evaluaciones en el marco de derrame pericárdico o derrame pleural secundario a la extravasación de líquido. Chan Tui es un estimulante de la síntesis de IFN y posee efecto antiviral potente como por ejemplo en la fórmula Sheng Jiang San. Se puede usar altas dosis de 30-40g, pero hay que tener extrema precaución en casos severos. No se recomienda indicarlo en contexto de respuesta inflamatoria exagerada ni tampoco se recomienda su uso si no fueran expertos tanto en Wén Bing Xue de MTC como en Infectología de medicina alopática.

4. Fase secuelar

La secuela principal de esta enfermedad es el desarrollo de la fibrosis pulmonar. En este contexto se indica Yu Ke Tang (Xiang Fu, Xuan Fu Hua, Yi Yi Ren, Tao Ren, Dang Gui, Wu Gong, San Qi, Bai Jie Zi) de la fórmula de Wu Men. Contemplando los efectos adversos de cada medicina, se puede adicionar Shan Ci Gu, Shang Lu, Zao Jiao Ci según signo-sintomatología. Los que sufren de enfisema pulmonar deben tomar Tai Yi Xi Sui Gao durante 3 años sucesivos. Para conocer su uso específico, consulte el libro Wu Men Yan Fang (Fórmulas eficaces de la familia Wu).

5. Prevención y medidas higiénico-dietéticas

5.1 Prevención Optimizar la ventilación ambiental; evitar la concurrencia a lugares de concentración multitudinaria; prevenir el contacto con pacientes infectados; y aún más importante, evitar el cansancio y el estrés. Es fundamental el lavado de manos con frecuencia y el uso de barbijos. Es necesario considerar la alta infectividad de Yi Bing y Li Bing, así como los antiguos chinos lo denominaban “enfermedades de fácil contagio”. Bajo estas condiciones, la inmunocompetencia de los individuos sanos es insuficiente para no contraer esta enfermedad. Entonces, tampoco encuadra el concepto de “Si conserva Qi Recto en el interior, el Qi Patógeno perverso no puede invadir” en esta patología de alta infectividad, por ende, es sustancial evitar el contacto cercano. La MTC sugiere alimentar la energía en postura sentada (Qigong y meditación sīmā-bandha), prender incienso (incluye el uso de sachet aromática) y evitar el miasma, medicamentos como Xiao Jin Dan de Neijing. Según este mismo protocolo, se puede alternar la indicación de fórmulas de fase temprana e intermedia según la constitución física de cada paciente y el nivel de exposición. También se puede digitopuntar la planta del pie (centro del acupunto Yon Quan, K1, 81 veces) y el arco del pie (en el centro acupunto de Ran Gu, K2, 81 veces, o simplemente de 5 a 10 minutos). Además, hay que tener mucha cautela el contacto con pacientes convalecientes hasta los 14 días posteriores ya que permanecen con infectividad activa. Por el momento, tampoco se puede descartar la posibilidad de convertirse en portadores crónicos en algunos casos esporádicos. La clave reside en el pulso: a los que aún conservan el pulso impetuoso a la palpación media y profunda, pese a la mejoría clínica e imagenológica, llámese curado, tienen mayor probabilidad de transformarse en portador crónico.

5.2 Medidas higiénico-dietéticas

- ① Dieta: caldo de arroz y gran cantidad de verduras. Evitar comidas grasientas, dulzonas y bebidas frías. Es importante mantener un buen ritmo eva- cuatorio.
- ② Evitar agotamiento físico, mental y sexual. Se recomienda abstinencia sexual hasta 14 días posteriores a la convalecencia.

6. Instructivo de la guía

6.1 Puntos claves para el diagnóstico y tratamiento:

El punto clave para diferenciar y tratar las enfermedades Wen Bing reside en dilucidar el mecanismo fisiopatológico principal. Cuantos más tipos de sín- dromes se describa por esta enfermedad más lejos estamos de la esencia de Wen Bing. Con respecto a esto, lo mejor es lograr una hierba por enfermedad, o si no fuera posible, una fórmula. Aún no poder conseguirlo, hay que definir por lo menos el síndrome central según el mecanismo fisiopatológico princi- pal.

Aunque clínicamente diferentes factores originarán múltiples tipos de síndromes paralelos o transformantes capaces de influir en el pronóstico, no obstante, no reflejan la esencia propia de la enfermedad. Es considerable mejorar el síndrome, compuesto por signos y síntomas, mientras que es im- prescindible el tratamiento dirigido desde la MTC a la noxa causante de Wen Bing y Li Bing y al mecanismo fisiopatológico principal. Debido a que la noxa de cada enfermedad infecto-contagiosa es única, su mecanismo fisiopatológico central es relativamente homogénea, por lo que miles de variaciones no se alejan del eje.

6.2 Pronóstico Es frecuente la disociación entre la mejoría clínica sintomatológica y el avance de la enfermedad en Wen Bing e Yi Bing severos. Esto quiere decir que la evolución sindromática y el curso de la enfermedad son disicrónicos. Con- cretamente, el cambio de la semiología lingual y del pulso es crucial y, a veces superiores, que los síntomas para la determinación del pronóstico.

6.3 Integración Medicina Tradicional China - Medicina Alopática Se recomienda la integración de la Medicina Tradicional China con la Medicina Alopática para la prevención y el tratamiento de Wen Bing e Yi Bing. Es necesario que la MTC se fusione con la Infectología y la Terapia Intensiva y además, con las áreas de vacunación, aislamiento, desifección, prevención, tratamiento de soporte y Emergentología de la medicina contemporánea.

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Abstract

Currently, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV, the causative pathogen of Coronavirus Disease 2019 (COVID-19)) has rapidly spread across China and around the world, causing an outbreak of acute infectious pneumonia. No specific anti-virus drugs or vaccines are available for the treatment of this sudden and lethal disease. The supportive care and non-specific treatment to ameliorate the symptoms of the patient are the only options currently. At the top of these conventional therapies, greater than 85% of SARS-CoV-2 infected patients in China are receiving Traditional Chinese Medicine (TCM) treatment. In this article, relevant published literatures are thoroughly reviewed and current applications of TCM in the treatment of COVID-19 patients are analyzed. Due to the homology in epidemiology, genomics, and pathogenesis of the SARS-CoV-2 and SARS-CoV, and the widely use of TCM in the treatment of SARS-CoV, the clinical evidence showing the beneficial effect of TCM in the treatment of patients with SARS coronavirus infections are discussed. Current experiment studies that provide an insight into the mechanism underlying the therapeutic effect of TCM, and those studies identified novel naturally occurring compounds with anti-coronaviral activity are also introduced.

Key words: SARS-CoV-2, Traditional Chinese Medicine (TCM), coronavirus pneumonia

Introduction

In December 2019, there was an outbreak of unexplainable pneumonia in Wuhan city, Hubei province, China [1]. By Jan 7, 2020, it was confirmed that a new type of coronavirus named SARS-CoV-2 (formerly named as 2019-nCoV) had emerged [2]. The World Health Organization (WHO) named the Wuhan pneumonia as Coronavirus Disease-2019 (COVID-19) on Feb 11, 2020 [3]. The COVID-19 patients showed typical respiratory symptom (such as cough, fever, and lung damage) and some other symptoms such as fatigue, myalgia, and diarrhea [4, 5]. As of February 17, 2020, a total of 73,332 cases of the SARS-CoV-2 infected pneumonia has been reported in China and 25 other countries, of which 72,528 cases was found in China [6]. Due to the rapid spread of SARS-CoV-2 through human-to-human transmission, the cases currently continue to rise.

SARS-CoV-2 extracted from patients with pneumonia in Wuhan is an enveloped single stranded RNA-type beta-coronavirus [7]. The genome sequences of SARS-CoV-2 shared 79.5% sequence identity to severe acute respiratory syndrome-related coronaviruses (SARS-CoV) [8, 9]. In addition, the spike (S) protein of SARS-CoV-2 and SARS-CoV enters human alveolar epithelial cells through binding angiotensin-converting enzyme 2 (ACE2) receptor [8]. COVID-19 can be diagnosed by either chest CT radiography or a laboratory testing. Unfortunately, specific antiviral drugs or vaccines currently have not been available for the treatment [10, 11]. According to

coronaviral will be summarized and analyzed, including the laboratory studies that provide an insight into molecular basis of therapeutic benefits.

Conventional treatment of SARS-CoV-2: is there a room for Chinese medicine? Due to the absence of a specific antiviral therapeutics and vaccine, main treatment strategy for COVID-19 is supportive care, which is supplemented by the combination of broad-spectrum antibiotics, antivirals, corticosteroids and convalescent plasma [16] (Table 1). HIV protease inhibitors ritonavir and lopinavir have been used, typically in combination with appropriate antibiotics or with IFN α -2b, in the treatment of SARS-CoV-2 infected patients [7, 17]. Nucleoside analogs such as ribavirin [12] may be potentially beneficial for the treatment of COVID-19, since ribavirin was approved for treating respiratory syncytial virus (RSV) infection [18] and used extensively during the SARS and MERS outbreak [10]. However, ribavirin had severe side effects such as anemia [18] and whether it had sufficient antiviral activity against SARS-CoV-2 is unclear. Nucleoside analogs favipiravir (T-705) can effectively inhibit the activity of RNA polymerase of RNA viruses such as influenza [19]. A recent in vitro study found that it had the anti-SARS-CoV-2 activity [20], but the in vivo effect remains elusive. Remdesivir may be the most promising antiviral drug for treating COVID-19. It has in vitro and in vivo antiviral activity against a wide array of RNA viruses including SARS and MERS [21], and could decrease viral loads and pathology of lungs in animal models [22]. A study showed remdesivir markedly inhibited the infection of SARS-CoV-2 in Vero E6 cells [20], and most symptoms of the first US patient infected with SARS-CoV-2 had resolved swiftly after intravenous administration with remdesivir [23]. Currently, it is under clinical trial to evaluate the safety and efficacy of intravenous remdesivir for patients with SARS-CoV-2 infection [24]. Oral oseltamivir has been used for the treatment of the cases with SARS-CoV-2 [7], while its efficacy currently remains uncertain.

Host-targeted small molecules approved for other human diseases may modulate the virus-host interactions of SARS-CoV-2. Chloroquine, a potential broad-spectrum antiviral drug [25, 26], was shown by a recent study had anti-SARS-CoV-2 activity [20]. Its clinical efficacy is under study in an open-label trial (ChiCTR2000029609) [12]. IFN α (5 million U) atomization inhalation was recommended as antiviral therapy to treat SARS-CoV-2 [16]. A trial testing IFN α -2b combination of the approved anti-HCV inhibitors has been initiated [17], however, whether it could act synergistically against SARS-CoV-2 is unclear. Corticosteroids were frequently used to suppress the elevated cytokine levels in patients with SARS-CoV [27, 28] and MERS-CoV [29, 30]. However, there are no evidence showing that the mortality of SARS and MERS patients was reduced by the treatment with corticosteroids, while the clearance of viral was delayed by such treatment [31-33]. Consequently, corticosteroids are not suggested to systemically use in SARS-CoV-2 infected patients [34, 35].

Previously, it was shown that, either in severe influenza or SARS-CoV infection, convalescent plasma treatment could significantly decrease viral load and reduce the mortality [31, 36]. Convalescent plasma has been used for severe SARS-CoV-2 infection in China [22], although promising, the efficacy and safety need to be carefully further evaluated. Consistent with previous analysis, WHO also concluded "to date, there is no specific medicine recommended to prevent or treat SARS-CoV-2" [37]. TCM has been used in control of infectious diseases for thousands of years. There is a clear room for the intervention of TCM as a complementary therapy for COVID-19 patients. It is reported that the patients with SARS-CoV infection have benefited from TCM treatment [38], including amelioration of side effect of conventional therapeutics [39, 40]. Based on these factors, there is a general expectation that TCM would be a valuable weapon in the armory against SARS-CoV-2.

Traditional Chinese Medicine in the treatment of patients infected with SARS-CoV: clinical evidence

Application of TCM in the treatment of SARS-CoV-2 is largely inspired by the treatment of SARS caused by outbreak of SARS coronavirus (SARS-CoV) in the late of 2002 in the Guangdong Province of China which spread rapidly during the 2003, with the cumulative number worldwide of over 8,000 [41-43]. Ranging from case reports, case series, controlled observational studies and randomized clinical trials, clinical studies aiming to examine the effect of TCM on SARS have been carried out and reported. There are quite compelling evidences support the notion that TCM has beneficial effect in the treatment or prevention of SARS. For example, the

rate of fatality in Hong Kong and Singapore was approximately 18%, while the rate for Beijing was initially more than 52% until the 5th of May and decreased gradually to 4%-1% after the 20th of May in 2003. The dramatic reduced fatality from late May in Beijing was believed to be associated with the use of TCM as a supplement to the conventional therapy [44]. Lau and colleagues reported that, during SARS outbreak, 1063 volunteers including 926 hospital workers and 37 laboratory technicians working in high-risk virus laboratories used a TCM herbal extract, namely Sang Ju Yin plus Yu Ping Feng San. Compared with the 0.4% of infection in the control group, none of TCM users infected. Furthermore, there was some evidence that Sang Ju Yin plus Yu Ping Feng San could modulate T cells in a manner to enhance host defense capacity [45, 46]. In a controlled clinical study, the supplementary treatment with TCM resulted in marked improvement of symptoms and shortened the disease course [47]. The clinical beneficial effect of TCM appears to be supported by laboratory studies. For example, a high-profile research published in the Lancet reported that glycyrrhizin, a major active constituent liquorice root which is the most frequently used Chinese herb, potentially inhibited the replication of clinical isolates of SARS virus [48]. Another independent study confirmed the antiviral activity of glycyrrhizin by plaque reduction assays and this study found that another Chinese herbal compound baicalin also had the anti-SARS activity [49]. Furthermore, Wang et al. found MOL376, a compound derived from TCM, may become a lead compound for SARS therapy by inhibition of cathepsin L, a target for the treatment of SARS [50]. There is a myriad of literature on TCM treatments for SARS published after the SARS epidemic in China. A critical analysis of these publications would be useful to confirm the beneficial effect of TCM. Liu et al. systematically reviewed eight randomized controlled trials, and concluded that, by combination with conventional medicine, TCM showed the beneficial effects such as decrease of mortality and relief of symptom, as well as control of fungal infections in patients with SARS. However, the evidence is not sufficient enough due to the poor quality of methodology used in the trials [13]. Leung analyzed 90 peer-reviewed papers with reasonable quality from 130 publications and concluded that TCM used together with conventional treatment had some positive effects, including better control of fever, quicker clearance of chest infection and other symptoms. However, such beneficial effect of TCM is not conclusive and more high-quality clinical studies are required [15].

In another thorough literature analysis, Liu and colleagues concluded that there was no benefit of adjuvant treatment with TCM in terms of mortality [39]. Due to the lack of high quality TCM trials and biases that influenced the validity of results, Wu and colleagues suggested to re-run clinical trials of TCM for the treatment of acute respiratory tract infections (ARTIs) [51].

Identification of anti-novel coronaviral compound from Traditional Chinese Medicine Natural products used in TCM remains to be a wealthy source for the identification of novel therapeutic agents for the treatment of human diseases [52]. In the past decade, scientists have made a considerable effort to identify multiple component herbal formulae in TCM with anti-SARS-CoV activity (Table 2). Further identification of chemical entities contained in TCM herbs responsible for the anti-SARS-CoV effect was also pursued (Table 3). Due to the homology of SARS-CoV and SARS-CoV-2, these previous studies may shed light on the naturally occurring compounds with the capacity to inhibit SARS-CoV-2. 3-chymotrypsin-like protease (3CLpro) is vital for replication of virus, and thus represents a promising drug target for the development of therapeutic agents for SARS-CoV as well as other human coronaviruses including SARS-CoV-2. It was reported that following TCM herbal extracts had the capacity to inhibit the enzymatic activity of SARS 3CLpro: Chinese Rhubarb extracts (IC₅₀: 13.76 ± 0.03 µg/mL) [53], water extract of *Houttuynia cordata* [54, 55], flavonoid extracted from litchi seeds [56] and beta-sitosterol (IC₅₀: 1210 µM) extracted from the root extract of *Isatis indigotica* [57]. Further, following herb-derived naturally occurring compounds including sinigrin (IC₅₀: 217 µM), indigo (IC₅₀: 752 µM), aloe-emodin (IC₅₀: 366 µM), hesperetin (IC₅₀: 8.3 µM) [57], quercetin (IC₅₀: 73 µM), epigallocatechin gallate (IC₅₀: 73 µM), gallic acid (IC₅₀: 47 µM) [58], herbacetin, rhoifolin and pectolinarin [59] were able to inhibit the SARS 3CLpro activity. Moreover, the flavonoids namely herbacetin, isobavachalcone, quercetin 3-β-D-glucoside, and helichrysetin had the potential to block the enzymatic activity of MERS-CoV 3CL protease [60].

[illegible]

TCN Compound	Mode of action	Reference
Fluorinated derivatives of compounds and first series of G-protein coupled receptors	Inhibit the cleavage activity of SARS-CoV protease	[24]
Water extract of <i>Hydrocotyle</i> species	Inhibit the SARS-CoV RNA polymerase (RNA pol) and RNA helicase (RH) immunohistochemically	[25, 26]
Acetylenes and acetylenes	Inhibit the viral RNA polymerase	[27]
Naphthalene from <i>Scirpus</i> sp.	Inhibit viral replication by blocking the RNA polymerase	[28]
Hydroquinone, quercetin, naphthalene, 5,8-difluoronaphthalene and chalcones	Inhibit viral replication and proliferation	[29, 30]
Quercetin, flavonoids, and chalcones	Inhibition of SARS-CoV RNA polymerase	[31]
Chalcone Riboflavin esters	Inhibit the expression of SARS-CoV ORF3 and nonstructural proteins, immunohistochemically	[32, 33]
Flavonoids (for example coumarin from <i>Scirpus</i> sp.)	Inhibit SARS-CoV RNA polymerase	[34]
Flavonoids, quercetin, genistein, genistein, genistein, genistein, and genistein	Inhibit the cellular entry of SARS-CoV	[35, 36, 38]
Quercetin and 3,6,7-trimethylflavone	Inhibition of SARS-CoV RNA polymerase	[37]
Enols derived from green <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[38]
Resorcinol derivatives	Inhibition of SARS-CoV RNA polymerase	[39]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[40]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[41]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[42]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[43]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[44]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[45]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[46]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[47]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[48]
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Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[60]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[61]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[62]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[63]
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Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[67]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[68]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[69]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[70]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[71]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[72]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[73]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[74]
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Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[77]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[78]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[79]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[80]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[81]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[82]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[83]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[84]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[85]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[86]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[87]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[88]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[89]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[90]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[91]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[92]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[93]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[94]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[95]
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Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[98]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[99]
Enols from <i>Hydrocotyle</i> species	Inhibition of SARS-CoV RNA polymerase	[100]

Same as SARS-CoV and HCoV-NL63, SARS-CoV-2 uses host receptor ACE2 for the cellular entrance [63-66]. Therefore, TCM with the capacity to target ACE2 holds the promise to prevent the infection of SARS-CoV-2. Emodin from genus *Rheum* and *Polygonum* [67], baicalin from *Scutellaria baicalensis* [44,68], nicotianamine from foodstuff (especially “soybean ACE2 inhibitor (ACE2iSB)”) [69], scutellarin [70], tetra-O-galloyl- β -D-glucose (TGG) from *Galla chinensis* and luteolin from *Veronica linaria* [71] markedly inhibited the interaction of SARS-CoV S-protein

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Yu Ping Feng San) may have beneficial immunomodulatory effects for the prevention of viral infections including SARS-CoV [46].

Moreover, a number of anti-coronaviral agents have been identified from TCM herbs, although the mechanisms of action have not yet been elucidated. For example, extracts from *Lycoris radiata*, *Artemisia annua*, *Pyrrosia lingua*, and *Lindera aggregata* possessed the anti-SARS-CoV activity [84], 3 β -Friedelanol isolated from *Euphorbia neriifolia* [85], Blaucoxanthone isolated from the roots of *Calophyllum blancoi* [86] exhibited anti-HCoV-229E activity.

Traditional Chinese Medicine used in the treatment of SARS-CoV-2-infected patients: the current situations TCM is highly valued by the government of China in their campaign to contain and eradicate SARS-CoV-2. For example, Health Commission in 26 provinces have officially declared that TCM should be used in combination with conventional medicine in the treatment of COVID-19 patients. On 17, February, National Health Commission (NHC) of the People's Republic of China reported that 60,107 confirmed COVID-19 patients (85.20% of total confirmed cases) had been treated with TCM [87]. As for March 1, 2020, a total of 303 ongoing clinical trials aiming to evaluate the efficacy and safety of treatments for CoV-19 patients have been launched in China. Among them, 50 trials (16.5%) are about the use of TCM, including 14 cases (4.6%) to examine the effect of combined treatment with TCM and Western medicine. In 22 TCM trials (7.3%), the effect of self-made herbal preparations such as Xin Guan-1 Formula, Xin Guan-2 Formula and Qing Yi-4 are examined. In another 14 TCM trials (4.6%), commercially available TCM products such as Tan Re Qing Injection and Lian Hua Qing Wen Capsule are studied (Table 4). To date, NHC has published 6 editions Guidelines of Diagnosis and Treatment for COVID-19 [88]. Since the fourth versions, different herbal medicines used in TCM system has been recommended for the treatment of COVID-19, based on the stage of disease and symptom differentiation [89]. According to the latest edition of Guideline [88], following multiple component Chinese herbal products are recommended for the patients in the medical observation period, presumably as a preventive measure: Huo Xiang Zheng Qi Shui, Lian Hua Qing Wen Capsule, Shu Feng Jie Du Capsule and Jin Hua Qing Gan Granule. In the clinical treatment period, Qing Fei Pai Du Tang, Xi Yan Ping Injection, Xue Bi Jing injection, Re Du Ning Injection, Tan Re Qing Injection Xing Nao.

Jing Injection and some other Chinese medicine formulae should be selected [90]. In addition, for the patients in critical condition, Shen Fu Injection, Sheng Mai Injection, Shen Mai Injection, Su He Xiang Pill and An Gong Niu Huang Pill should be administered (Table 5). Through analysis of the frequency of TCM used in 23 provinces, Luo, et al. [37] concluded that *Astragalus membranaceus*, *Glycyrrhizae uralensis*, *Saposhnikovia divaricata*, *Rhizoma Atractylodis Macrocephalae*, *Lonicerae Japonicae* Flos, *Fructus forsythiae*, *Atractylodis Rhizoma*, *Radix platycodonis*, *Agastache rugosa*, and *Cyrtomium fortunei* J. Sm were 10 most commonly used Chinese herbs in the treatment of COVID-19. Xu, et al. [91] reported that *Astragalus membranaceus* and Yu Ping Feng were used in the 13 prevention programs (in Beijing, Tianjin, et al.) for “reinforcing vital qi”, a terminology used in TCM that is similar to boosting host defense capacity.

Ophiopogon japonicus and *Scrophularia ningpoensis* are TCM herbs which were most frequently used for “nourishing yin” in northern China, while *Atractylodis Rhizoma*, *Agastache rugosa* and other Chinese medicinal herbs with the property of “aromatic dehumidification” were commonly used in southern China (Table 6).

Table 4. Ongoing TCM Clinical Trials for the treatment of SARS-CoV-2 infection

Registration number	Design type	Time	TCM herbal medicine	Sample size	Phase
ChiCTR1800029432	CCT	Real world study for the efficacy and safety of large dose Tansheng Injection in the treatment of patients with novel coronavirus pneumonia (COVID-19)	Tan Fei Qing Injection	72	4
ChiCTR1800029434	RCT	A randomized, open-label, blank-controlled trial for Lian Hua Qing Wen Capsule/Capsules in the treatment of novel coronavirus pneumonia (COVID-19)	Lian Hua Qing Wen Capsule/Capsules	400	4
ChiCTR1800029487	CCT	Clinical study for Gu-Biao-Jie-Du-Ling in preventing of novel coronavirus pneumonia (COVID-19) in children	Gu-Biao-Jie-Du-Ling	200	0
ChiCTR1800029598	CCT	An open, prospective, multicenter clinical study for the efficacy and safety of Reaching Injection in the treatment of novel coronavirus pneumonia (COVID-19)	Re Du Ning Injection	40	0
ChiCTR1800029605	RCT	A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of novel coronavirus pneumonia (COVID-19)	Shuang-Huang-Lian Oral Liquid	400	4
ChiCTR1800029706	RCT	A multicenter, randomized, open, controlled trial for the efficacy and safety of Shen-Fu-Pu-Zhong Injection in the treatment of novel coronavirus pneumonia (COVID-19)	Shen-Fu-Pu-Zhong Injection	140	4
ChiCTR1800029781	RCT	A multicenter, randomized, open and controlled trial for the efficacy and safety of Kang-Bing-Du granules in the treatment of novel coronavirus pneumonia (COVID-19)	Kang-Bing-Du Granules	140	4
ChiCTR1800029822	RCT	A randomized-controlled trial for honeyuckle decoction in the treatment of patients with novel coronavirus (COVID-19) infection	Jin-Yin-Hua-Tang	130	0
ChiCTR1800029891	RCT	A randomized, open-label, controlled trial for the safety and efficacy of Reaching syringe and Reaching capsule in the treatment of mild and moderate novel coronavirus pneumonia (COVID-19)	Re Du Ning Syringe and Reaching Capsule	72	4
ChiCTR1800030043	RCT	Shen-Fu Injection in the treatment of severe novel coronavirus pneumonia (COVID-19): a multicenter, randomized, open-label, controlled trial	Shen-Fu Injection	300	4
ChiCTR1800030117	RCT	A multicenter, randomized, open, parallel controlled trial for the evaluation of the effectiveness and safety of Shengying Injection in the treatment of common type novel coronavirus pneumonia (COVID-19)	Sheng Ying Injection	340	4
ChiCTR1800030229	RCT	Efficacy and safety of Jing-Yin-Guan-Zhi in the treatment of novel coronavirus pneumonia (COVID-19) with heat syndrome	Jing-Yin-Guan-Zhi	300	4
ChiCTR1800030268	RCT	Efficacy and safety of Shao-Bing Injection in the treatment of severe cases of novel coronavirus pneumonia (COVID-19)	Shao-Bing Injection	40	0
ChiCTR1800030313	RCT	Clinical Trial for Tansheng Capsules in the Treatment of Novel Coronavirus Pneumonia (COVID-19)	Tan Fei Qing Capsules	72	0

Notes: RCT: randomized controlled trial; CCT: controlled clinical trial.

Table 5. TCM recommended by 6th editions Guidelines of Diagnosis and Treatment for COVID-19 [88]

Stage of disease	Symptom	Recommended Chinese patent medicine
Medical observation period	Fatigue with gastrointestinal discomfort	Tian Xiang Zheng Qi Shui
Clinical treatment period (confirmed patients)	Fatigue with fever	Lian Hua Qing Wen Capsule, the Jing Fei Du Capsule, Jin Hua Qing Gan Capsule
	Mild cases	Qing Fei Pai Du Tang
	General cases	Qing Fei Pai Du Tang
Critical cases	Severe cases	30 Yau Ping Injection, Xue Bi Jing Injection, Re Du Ning Injection, Re Du Qing Injection, Sheng Ying Injection, Qing Fei Pai Du Tang
	Critical cases	Xue Bi Jing Injection, Re Du Ning Injection, Tan Fei Qing Injection, Shen Fu Injection, Hong Xie Injection, Shen Mai Injection, Su Shi Xiang Pin, Su Gong Xie Xiang Pin

Table 6. Frequently used TCM herbs for the Prevention of COVID-19 infection

Reported by	Herbs (Latin name)	Herbs (Chinese Pinyin)	Applicable regions
Luo, et al. [91]	Astragalus membranaceus	Huangqi	25 provinces covered: Northeast, North, Central (including Yunnan, South, East, Southeast, and Southwest China).
	Cypripedium calceolus	Genma	
	Saposhnikovia divaricata	Fangfang	
	Batrachium septentrionale	Baizhu	
	Lonchocarpus japonicus	Jingzhu	
	Fraxinus chinensis	Lingmu	
	Albizia julibrissin	Cangchun	
	Bala stipularis	Jingmu	
	Agave americana	Huanyang	
	Cynodon dactylon	Guanghuang	
Xu, et al. [92]	Atractylodes chinensis	Huangqi	Beijing, Tianjin, Shandong, Shaanxi, Gansu, Hebei, Shanxi, Henan, Fujian, Jiangxi, Hunan, and Yunnan
	Camptotheca chinensis	Cangchun	Five regions in southern China (Hubei, Jiangxi, Hunan, Yunnan, and Sichuan)
	Epimedium japonicum	Fangfang	
	Agave americana	Huanyang	
	Chrysanthemum indicum	Maifeng	
	Saposhnikovia divaricata	Yunnan	
	Batrachium septentrionale	Yunnan	
	Batrachium septentrionale	Yunnan	
	Adiantum species	Shaochen	
	Adiantum species	Shaochen	

According to the report of National

Administration of Traditional Chinese Medicine, up to February 5th, 2020, 214 COVID-19 patients were treated with Qing Fei Pai Du Tang in Shanxi, Hebei, Heilongjiang and Shaanxi Provinces with overall effective rate $\geq 90\%$. Among them, the symptoms of majority of patients ($\geq 60\%$) were markedly improved, while illness of others (30%) was stabilized [92]. After that, 701 COVID-19 patients were treated with Qing Fei Pai Du Tang in 10 provinces in China. The result showed that 130 patients (18.5%) were completely cured after treatment. The treatment also resulted in the disappearance of characteristic symptoms of COVID-19 such as fever and cough in 51 patients (7.27%). In addition, symptom improvement or stabilization were observed in 268 patients (38.2%), and in 212 patients (30.2%), respectively [87]. Yao, et al. and Lu, et al. [93, 94] retrospectively analyzed the clinical efficacy of Lian Hua Qing Wen Capsule in treatment of confirmed and suspected COVID-19 patients. The results indicated that this herbal product could markedly relieve major symptoms such as fever and cough and had the capacity to promote the recovery. Some patients with mild illness in the early stage could suddenly progress to severe disease, and eventually died due to septic shock with multiple organ dysfunction syndrome (MODS), which was associated with cytokine storm [95]. There is compelling evidence that some TCM herbal products or its components have potent immunosuppressive effects, as shown by our own and other's studies [79, 96-103]. For example, Wang, et al. [104] reported that Shen Fu Injection could inhibit the lung inflammation and decrease the levels of IL-1 β , IL-6 and other cytokines. Chang, et al. [105] reported that Re Du Ning Injection could markedly reduce the levels of IL-1 β , TNF- α , IL-8, IL-10, and some other cytokines of LPS-induced model of acute lung injury in rats. We recently reported that tetrandrine, a compound isolated from an anti-rheumatic Chinese herb, could potentially inhibit proinflammatory Th1, Th2 and Th17 responses in LPS-challenged mice [106]. Therefore, TCM with the capacity to inhibit cytokine storm and its devastating consequences may be harnessed in the treatment of severe COVID-19 patients. Currently, the laboratory study on the effect of TCM is apparently lagging behind the clinical application of TCM in the treatment of COVID-19 patients. Nevertheless, some scientists have started to examine the effect of TCM products or its components on SARS-CoV-2 in their laboratories. For example, an in vitro study showed that Shuang Huang Lian Oral Liquid had the inhibitory effect on SARS-CoV-2 [78]. However, its clinical efficacy and safety for the treatment of COVID-19 patients has not been evaluated. We noticed that this TCM product was not recommended by HNC's Guideline [89]. Same as SARS-CoV, SARS-CoV-2 uses receptor ACE2 for the cellular entrance [8]. Theoretically, blockade of ACE2 can prevent the infection of SARS-CoV-2. Chen and Du thus performed the molecular docking study and they found that TCM-derived compounds, including as baicalin, scutellarin, hesperetin, glycyrrhizin and nicotianamine could interact with ACE2 [107]. Therefore, these compounds as well as herbs containing these ingredients may have the capacity to inhibit the infection of SARS-CoV-2. We anticipate more experiment studies showing anti-SARS-CoV-2 activity of TCM or its components will be published in the near future. Closing remarks TCM has accumulated thousand-of-year's experiences in the treatment of pandemic and endemic diseases. Providing complementary and alternative treatments are still urgently needed for the management of patients with SARS-CoV-2 infection, experiences in TCM is certainly worth learning.

Fighting against current epidemics also provide an opportunity to test the true value of TCM in treating emerging contagious diseases. Randomized, double-blind and placebo-controlled studies is the best way to provide the most reliable evidence for a therapy, including TCM. It is encouraging that the controlled clinical studies to evaluate the efficacy of TCM in the treatment of SARS-CoV were conducted and reported. However, the most of these studies were found to be poorly designed and the results could lead to potential biases in evaluating the effectiveness of TCM treatment [13]. Hopefully, current clinical study to evaluate the effect of TCM on COVID-19 will use more strict protocols, concealment of allocation, and double-blinding, in order to ensure the compliance of international acceptable standards. Furthermore, standardized products of TCM, rather than self-prepared formulations, should be used in clinical study. Experiment study may be able to elucidate the mechanism underlying the therapeutic effect of TCM in the treatment of COVID-19. The further study of TCM may lead to the identification of novel anti human coronavirus compounds that may eventually prove to be useful in the treatment of SARS-CoV-2 or other emerging fatal viral diseases as conventional therapeutic agents. The safety of TCM in the treatment of emerging coronavirus diseases was not included in the observation on SARS patients [13]. It was reported that some herbs used in TCM contain nephrotoxins and mutagens [108], while the toxicological features of the most of Chinese herbal medicines remain to be fully understood [109]. Furthermore, herbs used in TCM can mimic, or magnify, or oppose the effect of conventional medicines [110]. Thus, the safety of TCM used in treatment of emerging coronavirus infections should be carefully evaluated. It is particularly important to avoid toxicity or interfere with the efficacy of conventional treatment caused by herb-drug interaction.

Supplementary Material Supplementary figures and tables.

<http://www.ijbs.com/v16p1708s1.pdf>

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Competing Interests

The authors have declared that no competing interest exists.

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JIM-02-2020-OA-ER-0077 In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus

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ABSTRACT

Objective: In this study we execute a rational screen to identify Chinese medical herbs that are commonly used in treating viral respiratory infections and also contain compounds that might directly inhibit 2019 novel coronavirus (2019-nCoV), an ongoing novel coronavirus that causes pneumonia. **Methods:** There were two main steps in the screening process. In the first step we conducted a literature search for natural compounds that had been biologically confirmed as against severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus. Resulting compounds were cross-checked for listing in the Traditional Chinese Medicine Systems Pharmacology Database. Compounds meeting both requirements were subjected to absorption, distribution, metabolism and excretion (ADME) evaluation to verify that oral administration would be effective. Next, a docking analysis was used to test whether the compound had the potential for direct 2019-nCoV interaction. In the second step we searched Chinese herbal databases to identify treatments containing the selected compounds. Plants containing 2 or more of the compounds identified in our screen were then checked against the catalogue for classic herbal usage. Finally, network pharmacology analysis was used to predict the general in vivo effects of each selected herb. **Results:** Of the natural compounds screened, 13 that exist in traditional Chinese medicines were also found to have potential anti-2019-nCoV activity. Further, 125 Chinese herbs were found to contain 2 or more of these 13 compounds. Of these 125 herbs, 26 are classically catalogued as treating viral respiratory infections. Network pharmacology analysis predicted that the general in vivo roles of these 26 treatments were related to regulating viral infection,

immune/inflammation reactions and hypoxia response. Conclusion: Chinese herbal treatments classically used for treating viral respiratory infection might contain direct anti-2019-nCoV compounds.

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Correspondence: Prof. Deng-hai Zhang; E-mail address: shanghai_zhang@hotmail.com 1. Introduction

Toward the end of December 2019, a novel coronavirus (2019-nCoV) with human-to-human transmission and severe human infection, originating in Wuhan, China, was identified [1]. This virus has affected many persons in China and spread to other countries in a very short time. On January 30, 2020, the Director-General of the World Health Organization declared that the outbreak of 2019-nCoV constitutes a public health emergency of international concern and issued temporary recommendations under the International Health Regulations [2]. According to the Daily Report of China National Health Commission, as of this writing on February 2, 2020, 14,488 cases, including 304 deaths, have been confirmed in China; 146 cases, including 1 death, have also been reported among 23 other countries. This pandemic is still ongoing, so it is urgent to find new preventive and therapeutic agents as soon as possible. In addition, commensurate with the risk, strong measures for early detection, isolation and treatment of cases, as well as minimization of transmission through social interaction must be implemented.

While specific vaccines and antiviral agents are the most effective methods to prevent and treat viral infection, there are not yet effective treatments that target the 2019-nCoV. Development of this treatment may require months or years, meaning that a more immediate treatment or control mechanism should be found if possible. Herbs used in traditional Chinese medicine present a potentially valuable resource to this end. The effectiveness of herbal treatment to control contagious disease was demonstrated during the 2003 severe acute respiratory syndrome (SARS) outbreak [3]. As such, the Chinese government is encouraging the use of herbal plants in fighting this new viral pneumonia. However, the application of herbal treatment is mainly guided by the type of herb (based on the catalogue of classic literature on herbs) and the patient's symptoms or signs. There is often not enough information to predetermine whether the herbs in question can directly target the viral cause, in other words, herbal usage is generally not guided by viral pathology. We think more detailed knowledge about the direct antiviral effects of different plants would be greatly helpful to the doctors selecting them. In fact, after the outbreak of SARS, many groups dedicated themselves to finding anti-coronavirus agents, including some natural compounds that exist in traditional Chinese herbal medicines [4–12]. The coronavirus encodes more than one dozen proteins, some of which are essential to viral entry and replication. Among these proteins, the most well-studied are papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein. Coronavirus PLpro not only processes the viral polypeptide onto functional proteins but is also a deubiquitinating enzyme that can dampen host anti-viral response by hijacking the ubiquitin (Ub) system. For example, SARS PLpro cleaves ISG15, a two-domain Ub-like protein, and Lys48-linked polyUb chains, releasing diUbLys48 products [13,14]. SARS-3CLpro is a cysteine protease indispensable to the viral life cycle [15]. Coronavirus spike protein uses angiotensin-converting enzyme 2 as a receptor to help the virus enter cells [16]. These three proteins make attractive targets for drug development. Through in silico and biological processing, a series of small molecules, including those from natural compounds, have been screened and confirmed to directly inhibit these important proteins in SARS or Middle East respiratory syndrome (MERS) coronavirus [17–23]. The gene sequence of 2019-nCoV has been released, which suggests high similarities between the main proteins in this virus and those previously identified in SARS-Cov or MERS-Cov [24,25]. In this sense, previously reported anti-SARS-Cov or anti-MERS-Cov natural compounds may become a valuable guide to finding anti-coronavirus (2019-nCoV) herbal plants among the traditional Chinese herbs used to treat viral pneumonia. It is a challenge to screen out the herbs containing anti-coronavirus (2019-

nCoV) compounds from the large number of those possibly being used for patients infected with this pathogen, especially in very short time. Here, we propose two principles to guide such work: oral effectiveness and compatibility. The first principle refers to the fact that most Chinese herbal plants are orally ingested after boiling with water, meaning that the anti-coronavirus (2019-nCoV) ingredients in selected plants should be absorbable via oral preparation. The second principle recognizes that candidate plants should be consistent with the type classifications for traditional herbal usage, since type-guided applications are integral to herbal use, as mentioned above. Following these two principles, we used a 6-step selection process (3 for each principle), including drug-likeness, evaluation of oral bioavailability, molecular docking, network pharmacology analysis and other methods to identify herbs that have both a high possibility of containing effective anti-coronavirus (2019-nCoV) compounds and are classified as treating virus-caused respiratory infection.

2. Materials and methods

2.1. Literature search and compound selection PubMed literature concerning natural compounds against SARS or MERS coronavirus activity was selected using the query “coronavirus AND inhibitor AND (SARS OR MERS OR SARS-CoV OR MERS-CoV).” After careful reading of the studies returned by this search, the natural compounds that had biologically confirmed antiviral activities were compared with the Traditional Chinese Medicine Systems Pharmacology database (TCMSP, <http://www.tcmspw.com/browse.php?qc=herbs>), the Encyclopedia of Traditional Chinese Medicine (ETCM, <http://www.nrc.ac.cn:9090/ETCM/>) and SymMap (<https://www.symmap.org/>). Natural compounds both associated with antiviral activity and contained in herbs were examined in the next step of our study.

2.2. ADME screening of natural compounds Since Chinese herbal treatments are always taken orally after boiling with water, an *in silico* integrative model of absorption, distribution, metabolism and excretion (ADME) was used to screen for natural compounds that may be bioactive via oral administration. The indices used for the screening include evaluation of oral bioavailability, Caco-2 permeability, drug-like value, and drug half-life. The threshold values indicating effectiveness for these four indices were > 30%, > -0.4, > 0.18 and > 3 h, respectively, as recommended by Hu et al [26]. The values of these four indices can be obtained from the TCMSP database.

2.3. Protein-molecular docking We used molecular docking software AutoDock 4 to perform protein compound docking analysis, according to the following procedure: (1) We built three-dimensional (3D) structure files of the proteins. We used the online server SWISS-MODEL (<https://swissmodel.expasy.org/>) to build the 3D structures of the proteins of interest by template-based modeling, these template structures being the reported 3D structures of the corresponding proteins from SARS-CoV. The models built were of Protein Data Bank (PDB) format. (2) To retrieve the required 3D structure files of compounds, the structure data file (SDF) format of compounds were retrieved from the PubChem website and then converted to PDB format by Discovery Studio. (3) AutoDock 4.2 was used to prepare PDBQT format files for target and ligand screening (Target.pdbqt and Ligand.pdbqt) and grid and docking parameter files (a.gpf and a.dpf). (4) Molecular docking was performed using AutoDock in Cygwin and finally the results were analyzed. The process and parameters used were detailed by Rizvi et al [27].

2.4. Plant selection Herbs were selected through three steps. (1) Primary selection: molecules chosen from the above steps were used as input for the TCMSP, ETCM and SymMap to search for plants containing that input and the plants were filtered by the numbers of antiviral compounds they contain. Those containing 2 or more antiviral compounds were selected for the next step. (2) Classic usage catalogue cross-reference: only herbs traditionally used to treat viral respiratory infection were retained for further study. (3) Predication of general effects *in vivo* with network pharmacology analysis, which is detailed as follows.

2.5. Network pharmacology analysis The TCMSP provided the main components of each herb and the protein targets for each. We identified the reported chemical constituents for each plant in the final analysis and used the ADME indices listed above to find the orally absorbable and drug-like compounds for the plant. The protein targets of these compounds were downloaded from the TCMSP database. All protein targets for each individual plant were used as input for the String online server (<https://string-db.org/>) to perform protein-protein interaction

analysis and pathway enrichment. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enriched (with $P < 0.01$) by the input were downloaded.

All data were processed using the statistical language R (3.6.2), unless otherwise specified.

3. Results

3.1. Overlapping of natural compounds biologically confirmed to be anti-SARS or anti-MERS coronavirus in literature and in Chinese herbal database We received 261 hits from conducting our search in the PubMed database. After careful evaluation of the abstracts from these citations we downloaded and carefully analyzed the full text of 23 highly relevant papers. The natural compounds reported to have biologically confirmed anti-coronavirus activity were identified and then compared to the ingredients listed in TCMSP. The result was 115 overlapping ingredients, which we used for further testing (Fig. 1).

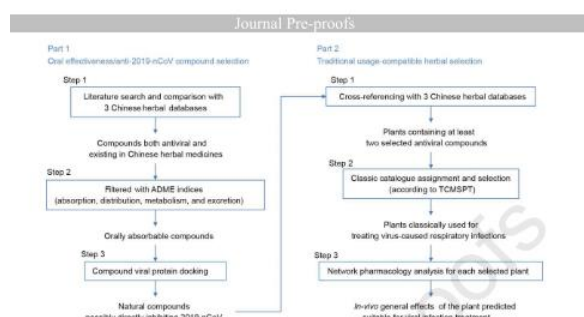


Fig. 1. Workflow scheme. The work is divided into two main parts, natural compound selection and herbal plant selection. Each part consists of three steps. As detailed in the text, oral effectiveness is important in compound selection, while in the plant selection portion, the selected herbs should be compatible with the classic usages of herbal treatment in traditional Chinese medicine. TCMSP: Traditional Chinese Medicine Systems Pharmacology.

3.2. Filtration of compounds selected by ADME The antiviral activities of the 115 natural compounds were reportedly confirmed with enzyme-based (cell-free) or cell-based experimental systems. To be utilized as a Chinese herbal medicine, they must be absorbable via oral prescription. Therefore, we performed ADME screening for the 115 natural compounds, reducing the number of candidates to 13. **3.3. Docking between selected compounds and their reported targets** To perform the docking analysis, the 3D structure files of 2019-nCoV PLpro, 3CLpro and spike proteins were built based on the corresponding SARS-CoV templates, i.e., PDB 5e6j, 1uj1 and 6cad, respectively. Then, molecule-protein docking was carried out between the molecules and their reported targets. If the molecules were reported to inhibit viral entry, they were docked with spike proteins (Table 1). Each separate analysis returned positive results (Table 1, Fig. 2 and online supplementary Fig. S1), indicating the natural compounds we selected might directly inhibit 2019-nCoV. The molecules selected to target PLpro (M2, M3, M7, M9, M10, M11 and M13) mainly bound in the region between the thumb and palm domains, which might interfere with substrate entering this enzyme's active sites, located at the bottom of the two domains [29]. The molecules reported to inhibit 3CLpro (M1, M2, M3, M4, M5, M7, M8, M10, M11, M12 and M13) mainly entered the region between domains 2 and 3, and this region is important for 3CLpro to form a dimer [30]. M6 was reported to inhibit viral entry, accordingly it bound the fusion cone of spike protein; this cone structure is important for viral membrane fusion [31] (Fig. 2 and online supplementary Fig. S1).

Table

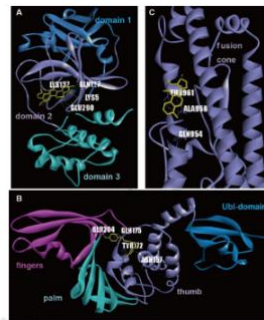
No.	Molecular name	Targets or inhibition	Reference	PL-pro	3C-like protease	Uti domain
M1	Berberine acid	Replication, 3C-like protease	[16]	Undo	-4.23	Undo

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Natural Products

M2	Camphor	PL-pro and 3C-like protease	[11,20]	-3.22	-4.18	Undo
M3	Cryptotanshinone	PL-pro and 3C-like protease	[19]	-5.25	-4.23	Undo
M4	Diosmetin	Replication, 3C-like protease, and entry	[6]	Undo	-3.52	Undo
M5	Dihydrochalcone	3C-like protease	[7]	Undo	-3.88	Undo
M6	Dihydrochalcone 1	Entry, and spike protein	[26]	Undo	Undo	-5.16
M7	Geniposide	PL-pro and 3C-like protease	[11]	-2.15	-4.08	Undo
M8	Lignan	Replication, 3C-like protease	[16]	Undo	-4.27	Undo
M9	Mangiferin	PL-pro	[26]	-3.65	Undo	Undo
M10	Nicotinamide	PL-pro and 3C-like protease	[11,20]	-3.11	-4.31	Undo
M11	Quercetin	PL-pro and 3C-like protease	[20]	-4.62	-4.28	Undo
M12	Sagittarin	Replication, 3C-like protease	[16]	Undo	-6.04	Undo
M13	Tanshinone IIa	PL-pro and 3C-like protease	[19]	-8.02	-3.17	Undo

3C-like protease; PL-pro: papain-like protease.



3.4. Selection of antiviral herbal plants The 13 molecules passing the three-round selection process were then compared to the three Chinese herbal databases, and we found 230 herbs containing these molecules (online supplementary file Table S1). We then evaluated these herbs for those containing 2 or more of the 13 natural compounds, leaving 125 results. We cross-referenced the 125 results with the classic categorizations for herbal usage in the TCMSP database, finally choosing 11 types that are traditionally used to treat viral respiratory infections. There are 26 herbal plants within the 11 types. The timeframe during the course of a viral infection that each of these 26 herbal plants (Table 2) should be used was also documented by seeking advice from senior practitioners of traditional Chinese medicine. For example, plants catalogued as antipyretic detoxifying drugs, qi-reinforcing drugs, antitussive antiasthmatics, pungent cool diaphoretics and phlegm-resolving medicines may all be used throughout the course of infection, whereas drugs belonging to the interior warming group may be best utilized in prevention.

Table 2. The 26 Chinese herbs screened and the possible time for usage.

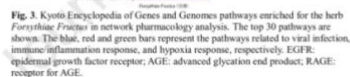
No.	Herbal name	Chinese name	Number of compounds	Chinese category	Time to use
1	<i>Pericaria frutes</i>	羌活	3	Antipyretic detoxifying	清解表药
2	Lonicera	金银花	3	Qi-reinforcing	补气药
3	<i>Mori cortex</i>	桑白皮	3	Antitussive antiasthmatics	止咳平喘药
4	<i>Cheilanthes flus</i>	菟丝子	2	Pungent cool diaphoretics	辛凉解表药
5	<i>Pericaria frutes</i>	羌活	2	Antitussive antiasthmatics	止咳平喘药
6	<i>Lonicera japonica</i>	金银花	2	Antipyretic detoxifying	清解表药
7	<i>Mori cortex</i>	桑白皮	2	Pungent cool diaphoretics	辛凉解表药
8	<i>Pericaria frutes</i>	羌活	2	Phlegm-resolving medicine	化痰药
9	<i>Rhizoma Japagici</i>	金沸草	2	Antipyretic detoxifying	清解表药
10	<i>Tangeris coccum</i>	西河柳	3	Pungent-warm, crumple relaxing medicine	辛温解表药
11	<i>Eriogon</i>	红景天	3	Pungent-warm, crumple relaxing medicine	辛温解表药
12	<i>Radix buplei</i>	半枝莲	2	Pungent cool diaphoretics	辛凉解表药
13	<i>Capitula rhizoma</i>	黄芩	2	Heat-clearing and dampness drying medicine	清热燥湿药
14	<i>Houttuernia herba</i>	热藜藜	2	Antipyretic detoxifying	清解表药
15	<i>Houttuernia herba</i>	热藜藜	2	Antipyretic detoxifying	清解表药
16	<i>Radix flus</i>	菟丝子	2	Phlegm-resolving medicine	化痰药
17	<i>Eriogon frutes</i>	红景天	3	Antitussive antiasthmatics	止咳平喘药
18	<i>Houttuernia herba</i>	热藜藜	3	Qi-reinforcing	补气药
19	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
20	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
21	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
22	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
23	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
24	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
25	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药
26	<i>Lonicera frutes</i>	金银花	3	Antitussive antiasthmatics	止咳平喘药

*: the number of antiviral natural compounds contained in the plant.

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3. 5. Network analysis of possible effects or mechanisms Each of the potentially effective herbal remedies contains many ingredients in addition to the antiviral ones found here. To evaluate the possible general in vivo effects of each of our identified herbs, we used the ADME indices listed above to examine each of the orally absorbable and drug-like ingredients recorded in the TCMSP database for each plant. We then extracted the target proteins for each ingredient which had passed the screening process. All proteins belonging to a single plant were combined as input on the online protein-protein interaction analysis server, String, to find the pathway enrichment. For the 26 herbs, about 1/3 of the top 30 KEGG-enriched pathways (mean = 11) were related to regulating viral infection, immune/inflammatory reactions and hypoxia response, indicating that they are potentially effective treatments for viral respiratory infection (Fig. 3 and online supplementary Fig. S2). Note that some of the herbal plants selected here had been reported to be effective for SARS-CoV infection in 2003 (online supplementary Table S2).

Thus, the general effects of each plant should be examined by combining the effects of all of the orally absorbable and biologically active ingredients in it.



multiple absorbable ingredients might exert their effects on the body, the general effects of herbs may be dictated by all of the absorbable ingredients they contain. With this consideration in mind, we extracted the recorded ingredients of each of the plants selected from the Chinese medicine database and screened these ingredients for drug-likeness and oral availability (via ADME filter) [26,32]. The target proteins of all ingredients passing ADME selection were used for network enrichment to predict the general effects of the herbal plants. For all the plants analyzed, nearly half of the top 30 pathways enriched in KEGG are related to antiviral, immune/inflammatory responses and hypoxia response indicating that these herbs are suitable for anti-viral usage. In fact, some of the herbal plants selected here had been reported effective in against SARS-CoV infection in 2003 (online supplementary Table S2). We thought that the general antiviral and immune/inflammation effects predicted for the 26 plants are correlated with the fact that these plants were selected according to Chinese herbal type classifications. Of course, it should be pointed out that Chinese herbs that have not been identified through this screening process may still have beneficial effects. Further, considering that the biologically validated natural compounds reported in the literature cannot cover all antiviral natural compounds, and the natural compounds included in the Chinese medicine database are not complete, the process that we have followed may have excluded herbs that would be well suited to this treatment. Nevertheless, the purpose of this screening was to provide a rational approach for selecting Chinese herbal medicines with a high potential efficacy in treating 2019-nCoV and related viruses. The specific dosage and usage of each herb should be determined based on patients' manifestations. Finally, the key step in this screening was molecular docking. The 3D structures of the proteins used here are based on reported gene sequences. If the virus mutates during transmission, a new screening is recommended. In conclusion, this work has identified several Chinese medicinal plants classified as antiviral/pneumonia-effective that might directly inhibit the novel coronavirus, 2019-nCoV. Additionally, we propose screening principles and methods which may provide guidance in screening antiviral drugs from other natural drug databases.

Authors' contributions

DZ conceived the study, participated in its design, coordination, and all the work processes. KW participated in herbal selection. XZ participated in data collection and network pharmacology analysis. SD helped to collect data. BP helped to draft the manuscript.

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