The American Journal of Chinese Medicine, Vol. 48, No. 3, 737–762

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



# 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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Published 13 March 2020

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/arthralgia 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

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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.

*Keywords*: COVID-19; 2019-nCoV; Chinese Medicine; Integrative Medicine; Guideline; Review.



## Introduction

COVID-19 is caused by SARS-CoV-2, a newly identified coronavirus sized 60–140 nm similar to severe acute respiratory syndrome (SARS)-CoV (approximately 80% similar) that fell within the subgenus Sarbecovirus of the Betacoronavirus genus (Chan *et al.*, 2020a,b; Chen *et al.*, 2020a; Heymann and Shindo, 2020; Huang *et al.*, 2020; Lipsitch *et al.*, 2020; Lu *et al.*, 2020b; Wrapp *et al.*, 2020; Xu *et al.*, 2020a; Zhu *et al.*, 2020). SARS-CoV-2 is believed to be introduced from wild animals followed by human-to-human transmission (Chan *et al.*, 2020b; Chen *et al.*, 2020a; Heymann and Shindo, 2020; Huang *et al.*, 2020; Lipsitch *et al.*, 2020; Lu *et al.*, 2020b). Genetic epidemiological analysis showed that the virus may originate from a common ancestor in November–December 2019 from Wuhan, China (GISAID Initiative, 2020). SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor with 10–20 folds higher affinity than SARS-CoV (Wrapp *et al.*, 2020; Xu *et al.*, 2020a) with similarities (40%) in the amino acid identity of Spike's receptor binding domain (RBD) (Chan *et al.*, 2020a).

At present, SARS-CoV-2 is believed to spread through contact, droplet or fomite (Van Cuong *et al.*, 2020; World Health Organization, 2020a). Increasing evidence also points to the faecal-oral route (Guo *et al.*, 2020; Heymann and Shindo, 2020; Holshue *et al.*, 2020; Yeo *et al.*, 2020) and aerosol (National Health Commission and National Administration of Traditional Chinese Medicine, 2020). Latest data showed that viral load from nasal swab peaks at 2 days after symptom onset. Nevertheless, comparable viral load was detected between an asymptomatic patient and other symptomatic patients, and asymptomatic transmission was reported (Chan *et al.*, 2020b; Guan *et al.*, 2020; Hoehl *et al.*, 2020; National Health Commission and National Administration of Traditional Chinese Medicine, 2020; Pan *et al.*, 2020; Rothe *et al.*, 2020; Zou *et al.*, 2020).

As of 22 February 2020, there were 77662 confirmed cases with 2360 deaths, majority from China, of which over 80% were from Hubei province (Dong *et al.*, 2020; GitHub, 2020; Healthmap, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). A longer time between symptom onset and care seeking at hospitals or clinics in Hubei was observed when compared to other provinces in China (Sun *et al.*, 2020a). A sharp increase in confirmed cases was observed on 13 February due to the inclusion of cases with clinical diagnosis (The State Council, The People's Republic of China, 2020b). The current estimated case fatality rate is 1–2% (Guan *et al.*, 2020; Heymann and Shindo, 2020; Lipsitch *et al.*, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Wang *et al.*, 2020c; Xu *et al.*, 2020d) which varied geographically being higher in Wuhan (2.9%) (The Novel Coronavirus

Pneumonia Emergency Response Epidemiology Team, 2020; Wang *et al.*, 2020a). The reproductive number (number of cases that one case can generate) was estimated to be 2.68 (95% CI, 2.47–2.86) and the count is doubling every 6.4 days (95% CI, 5.8–7.1), similar to the early phase of SARS (Wu *et al.*, 2020).

### Clinical Presentation

The median age was 30–69 years old (77.8%) (Huang *et al.*, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Wang *et al.*, 2020a). The infected patients were generally presented with mild upper respiratory infection symptoms similar to the common cold at the early stage and could be afebrile on the first 1–2 days (Chen *et al.*, 2020a; Del Rio and Malani, 2020; Heymann and Shindo, 2020; Holshue *et al.*, 2020; Rothe *et al.*, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Xu *et al.*, 2020e; Yang *et al.*, 2020a,b). Common symptoms included fever (88–98%), fatigue, dry cough, upper airway congestion, sputum production, shortness of breath, myalgia/arthralgia, and gastrointestinal symptoms (Chan *et al.*, 2020b; Chang *et al.*, 2020; Chen *et al.*, 2020a; Del Rio and Malani, 2020; Guan *et al.*, 2020; Holshue *et al.*, 2020; Liu *et al.*, 2020b; Pan *et al.*, 2020; Pongpirul *et al.*, 2020; Wang *et al.*, 2020a; Xu *et al.*, 2020c; Yang *et al.*, 2020b; Yao *et al.*, 2020; Zhang *et al.*, 2020a; Zhu *et al.*, 2020) with lymphopenia, prolonged prothrombin time, elevated C-reactive protein, and elevated lactate dehydrogenase (LDH) (Chan *et al.*, 2020b; Chen *et al.*, 2020a; Guan *et al.*, 2020; Holshue *et al.*, 2020; Liu *et al.*, 2020a; Wang *et al.*, 2020a). Chest computed tomographic showed bilateral patchy shadows or ground glass opacity (Bernheim *et al.*, 2020; Chan *et al.*, 2020b; Chang *et al.*, 2020; Guan *et al.*, 2020; Holshue *et al.*, 2020; Pan *et al.*, 2020; Wang *et al.*, 2020a; Zhu *et al.*, 2020).

Symptoms were estimated to develop 3–6 days after exposure (Chan *et al.*, 2020b; Xu *et al.*, 2020c). The incubation period was reported 3 (median 3, range 0–24) days (Guan *et al.*, 2020) to 5.2 (mean 5.2, 95% CI: 4.1–7.0, 95th percentile at 12.5) days (Li *et al.*, 2020c; Xu *et al.*, 2020c). The estimated time from the first symptom to pneumonia (confirmed by radiology), hospital admission, acute respiratory distress syndrome (ARDS) and intensive care unit (ICU) admission were 5.0, 7.0, 8.0–9.0, and 9.5–10.5 days (Chan *et al.*, 2020b; Huang *et al.*, 2020; Wang *et al.*, 2020a; Xu *et al.*, 2020c; Yang *et al.*, 2020a,b). Median hospital stay was 10 days (Wang *et al.*, 2020a). The rate of severe/critical hospitalized cases were around 7–10% (except Wuhan: 17.7%) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Wang *et al.*, 2020c; Yang *et al.*, 2020a,b). From the 138 hospitalized cases from Wuhan, the non-survivors when compared to the survivors began with reduced lymphocyte count 3 days after onset of disease, followed by increasing leukocyte count, neutrophil count and D-dimer after 5 days before an abrupt rise in creatinine and blood urea after 9 days of disease onset (Wang *et al.*, 2020a). Major complications during hospitalization were ARDS, arrhythmia and shock (Guan *et al.*, 2020; Wang *et al.*, 2020a).

Factors associated with severe presentation included older, underlying comorbidities (hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease) and

presented with dyspnoea, anorexia, and rash (Guan *et al.*, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Wang *et al.*, 2020a; Zhang *et al.*, 2020a). Plasma concentration of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were higher among ICU admitted patients (Huang *et al.*, 2020), possibly caused by a cytokine storm. Higher lung injury Murray Score was associated with lymphopenia and higher levels of C-reactive protein, neutrophil percentage and LDH (Guan *et al.*, 2020; Liu *et al.*, 2020a).

Autopsy histological examination of a COVID-19 ARDS patient showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates and signs of ARDS including pneumocyte desquamation and formation of hyaline membrane. There were also substantial interstitial lymphocyte-dominated mononuclear inflammatory infiltrates. Viral cytopathic-like changes were also observed in the intra-alveolar spaces (Xu *et al.*, 2020e). The clinical presentation of COVID-19 cases is summarized in Table 1.

**Table 1. Latest Demographics and Clinical Presentation of COVID-19**

| **Demographics** | **Range of Best Estimates** |
|---|---|
| Age | 30–69 (77.8%) |
| Incubation period (days) | 3 (range: 0–24.0) to 5.2 (95% CI: 4.1–7.0) |
| Transmission route | Droplet, contact, fomite, aerosol (suspected) |
| Biochemistry | Lymphopenia, prolonged prothrombin time, elevated C-reactive protein and elevated lactate dehydrogenase |
| Radiology | Bilateral patchy shadows or ground glass opacity |
| Symptoms | Fever, fatigue, dry cough, upper airway congestion, sputum production, shortness of breath, myalgia/arthralgia |
| **Median Time from First Symptom to:** | |
| – Hospital admission | 7 (4.0–8.0) |
| – ARDS | 9 (8.0–14.0) |
| – ICU admission | 10.5 (8–17) |
| Severity/critical rate | 7–10% (except Wuhan 17.7%, Hubei 10.4%) |
| Major complications | ARDS, arrhythmia and shock |
| **Risk factor associated with poor prognosis** | |
| – Demographics | Older, with underlying comorbidities (hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease) |
| – Clinical presentation | Presented with dyspnoea, anorexia, rash, greasy fur on tongue |
| – Chronological order for non-survivors | **Since onset of disease:**<br>Day 3: reduced leukocyte, lymphocyte, neutrophil count; increased D-dimer<br>Day 5: increased leukocyte, neutrophil count<br>Day 9 onwards: abrupt rise of creatinine and blood urea |
| – Biochemistry | Increased plasma concentration of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, TNFα, C-reactive protein, neutrophil percentage, lactate dehydrogenase and lymphopenia |
| **Autopsy Histology** | |
| Bilateral diffuse alveolar damage with cellular fibromyxoid exudates; pneumocyte desquamation and formation of hyaline membrane; interstitial lymphocyte-dominated mononuclear inflammatory infiltrates; multi-nucleated syncytial cells with atypically enlarged pneumocytes (large nuclei, amphophilic granular cytoplasm, prominent nucleoli) in intra-alveolar spaces | |

## Theory from Chinese Medicine Perspective

Chinese medicine (CM) formulate treatment based on symptom-based diagnosis, an approach which is increasingly emphasized in other disciplines (Sood *et al.*, 2014; Idborg, 2019). From the existing reports, the COVID-19 patients mainly presented with fever, fatigue, dry cough, upper airway congestion, sputum production, shortness of breath, myalgia/arthralgia (Chan *et al.*, 2020b; Chang *et al.*, 2020; Chen *et al.*, 2020a; Del Rio and Malani, 2020; Holshue *et al.*, 2020; Pongpirul *et al.*, 2020; Wang *et al.*, 2020a; Yang *et al.*, 2020a; Zhang *et al.*, 2020b; Zhu *et al.*, 2020), gastrointestinal symptoms, thick greasy fur on tongue and slippery pulse (Lu *et al.*, 2020c; Wang *et al.*, 2020d; Yang *et al.*, 2020a; Yu *et al.*, 2020b; Zhang *et al.*, 2020b). Poor prognosis was associated with the presence of dyspnoea, anorexia (Wang *et al.*, 2020a) and thick greasy tongue fur (Yu *et al.*, 2020b). While fever, dry cough, upper airway congestion, shortness of breath are respiratory tract infection-associated presentations, patients co-presented with myalgia/arthralgia, anorexia, gastrointestinal symptoms, thick greasy tongue fur, and slippery pulse are further sub-classified into *dampness* subtype according to CM theory (Lu *et al.*, 2020c; Wang *et al.*, 2020d; Yang *et al.*, 2020a).

The pathogenesis of infectious disease is correlated to weather in CM theory. The weather in Wuhan in November was warmer than expected according to historical record, reaching 27°C and staying above 20°C in daytime during 1–16 November 2019. It sharply became humid and cold since 24 November (18°C, 63% humidity) reaching 4°C and 89% humidity in daytime on 25 November until the end of November (Time and Date AS, 2020). The unusually warm temperature caused *endogenous stagnated heat* in the human body, and the abrupt increase in humidity and temperature drop increased the susceptibility to *exogenous cold-dampness* (Ma *et al.*, 2020a; Yang and Yu, 2020). The timeline matched the phylogenetic analysis that the outbreak started in late November to early December (GISAID Initiative, 2020).

Therefore, the core pathogenesis of COVID-19 is a *dampness pestilence* caused by *external cold-dampness distressing lung and spleen, transforming to heat due to dysfunctional qi activity and endogenous stagnated heat* in CM theory. The corresponding treatment at the early stage should target *eliminating dampness* and the strategy should focus on *eliminating dampness, releasing lungs and expelling pathogenic factors* (Fan *et al.*, 2020; Ma *et al.*, 2020a; Miao *et al.*, 2020; Tong *et al.*, 2020; Wang *et al.*, 2020d; Zheng *et al.*, 2020), to shorten fever duration, relieve symptoms, prevent disease progression, reduce mortality, and assist rehabilitation (Miao *et al.*, 2020).

## Management from Conventional Medicine

At present, there is limited evidence from randomized clinical trials to support any vaccines or pharmacological treatments from conventional medicine for COVID-19 (Del Rio and Malani, 2020; Heymann and Shindo, 2020; Jun *et al.*, 2020; National Health Commission and National Administration of Traditional Chinese Medicine, 2020; Wang *et al.*, 2020a). Antiviral treatment and corticosteroids used in SARS and other outbreaks are considered.

Lopinavir/ritonavir, protease inhibitors for human immunodeficiency viruses (HIV) management, were reported to reduce mortality, intubation rate, and use of methylprednisolone when introduced as a treatment among SARS patients of early stage (Chan *et al.*, 2003b; Jin *et al.*, 2020). Ribavirin was also widely used in SARS based on the broad-spectrum antiviral activity. Early SARS case series treated with combined ribavirin and corticosteroids showed clinical improvement (Lee *et al.*, 2003; Tsang *et al.*, 2003) although such efficacy remains controversial (Ho *et al.*, 2003; Sung *et al.*, 2004; Yu *et al.*, 2004; Zhaori, 2003). Commonly documented adverse effects of ribavirin included anaemia and increased alanine transaminase (ALT) (Booth *et al.*, 2003; Chan *et al.*, 2003a; Choi *et al.*, 2003; Knowles *et al.*, 2003; Koren *et al.*, 2003; Stockman *et al.*, 2006; Sung *et al.*, 2004; Yu *et al.*, 2004). Combination of lopinavir/ritonavir and ribavirin showed stronger suppression on viral load and reduced use of steroid (Chu *et al.*, 2004). Interferons have also been shown to suppress the viral replication of SARS *in vitro* and been considered for the current outbreak (Sainz *et al.*, 2004; Scagnolari *et al.*, 2004; Stockman *et al.*, 2006; Jin *et al.*, 2020). These regimens were recommended by the China national clinical practice guideline for the management of COVID-19 associated pneumonia (Jiang *et al.*, 2020).

Corticosteroids were previously used in H1N1 viral pneumonia (Li *et al.*, 2017) and severe community acquired pneumonia (Siemieniuk *et al.*, 2015) with possible reduction of mortality among patients developed ARDS (Siemieniuk *et al.*, 2015; Li *et al.*, 2017). It was used in SARS aiming to suppress cytokine storm to prevent clinical deterioration arise from host immunopathological response in the second phase (Yu *et al.*, 2004; Huang *et al.*, 2005). Corticosteroids use on the current outbreak was widely reported (Stockman *et al.*, 2006; Guan *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020a; Chen *et al.*, 2020a; Xu *et al.*, 2020c). However, the current evidence indicates that the benefit of general use is inconclusive and is likely outweighed by adverse effect (delayed viral clearance, avascular necrosis, osteoporosis, diabetes, psychosis) (Tsui *et al.*, 2003; Arabi *et al.*, 2018; Lansbury *et al.*, 2019; Russell *et al.*, 2020). As of 22 February 2020, the interim guideline of World Health Organisation (WHO) does not support the use of systemic corticosteroids for the treatment of viral pneumonia and ARDS for suspected COVID-19 cases (World Health Organization, 2020b).

Remdesivir, an antiviral agent, has been shown effectively inhibiting the COVID-19 *in vitro* and *in vivo* (Guo, 2020; Wang *et al.*, 2020b), is under clinical trials, and compassionate use was reported on a deteriorating case with good recovery (Holshue *et al.*, 2020). Convalescent plasma/immunoglobulin was used in SARS and Ebola treatment as well with a possible therapeutic effect, but the evidence is inconclusive (Marano *et al.*, 2016; Stockman *et al.*, 2006).

## Major Clinical Practice Guidelines on the Use of Chinese Medicine

The sixth version of China national clinical guideline on COVID-19 associated pneumonia was published on 18 February 2020 (National Health Commission and National Administration of Traditional Chinese Medicine, 2020). Patients presented with 3 out of 4 of: (1) clustering onset, or contact history with confirmed cases/people presented with upper

respiratory infection symptoms from community with confirmed cases within 14 days, or travel history to Wuhan/community with confirmed cases within 14 days, (2) developed fever or upper respiratory tract infection symptoms, (3) chest X-ray showing bilateral patchy shadows or ground glass opacity or (4) normal or reduced leukocyte count, or reduced lymphocyte count, were diagnosed as suspected cases. A further positive reverse transcription polymerase chain reaction (RT-PCR) or sequencing result would confirm the case.

For CM treatment, the national guideline divided COVID-19 into medical observation period and treatment period. The recommended formulation during medical observation period involved huo-xiang-zheng-qi capsule (for patients presented with fatigue and gastrointestinal disorder) and jin-hua-qing-gan granules, lian-hua-qing-wen capsule or shu-feng-jie-du capsule (for patients presented with fatigue and fever). Treatment period is further stratified into four manifestations including mild (*cold-dampness distressing lung* or *dampness-heat accumulation in lung*), intermediate (*endemic toxin distressing lung* or *cold-dampness blocking lung*), severe (*pestilence toxin retention in lung* or *intense heat in qi and ying systems*), and critical (*internal obstruction and external collapse*) followed by a rehabilitation stage (*lung and spleen qi deficiency* or *qi and yin deficiency*). Recommended formulations of corresponding clinical stages and subtypes are summarized in Table 2.

Provincial guidelines were optimized based on the national guideline for local adaptation, including the possible difference in disease clinical presentation. Recent reviews on 26 national/provincial/local guidelines showed that the COVID-19 were generally divided into early, intermediate, severe, and rehabilitation stage and treatment strategy focused on *eliminating (dampness) turbidness and expelling pathogenic factors* (Pang *et al.*, 2020; Zheng *et al.*, 2020).

Most of the provincial guidelines involved CM preventive measures and treatment (Pang *et al.*, 2020; Yu *et al.*, 2020a). For preventive measures, the majority of the guidelines used yu-ping-feng (huang-qi, bai-shu, fang-feng), or huang-qi with *heat clearing* drugs (jin-yin-hua, lian-qiao, guan-zhong) and *turbidness eliminating aromatic* drugs (qing-pi, cao-guo, cang-zhu, huo-xiang, pei-lan) (Pang *et al.*, 2020; Xu *et al.*, 2020b). Most guidelines defined COVID-19 as *endemic, toxic, dampness or warm* infectious disease. The suggested herbal formulations and proprietary CMs for treatment by these national/provincial/local guidelines are summarized in Table 3 (Chen *et al.*, 2020b; Pang *et al.*, 2020; Zheng *et al.*, 2020).

The utilization of CM in managing COVID-19 is substantial in China (Gao *et al.*, 2020). All confirmed COVID-19 cases in Shanghai started integrative Chinese–Western medicine (IM) treatment (Yuan and Qiu, 2020). In Guangdong, Tou-jie-qu-wen granules (formerly known as Pneumonia No.1) were evaluated with a case series and recommended to 30 designated hospitals as the standard treatment of COVID-19 patients (Guangdong Medical Products Administration, 2020). In Beijing, the first recovered patient was treated with IM (National Administration of Traditional Chinese Medicine, 2020a). Overall, over 85% of confirmed cases involved CM use nationally (Wuhan over 67%) (Le and Liang, 2020; The State Council, The People's Republic of China, 2020b) and the first

**Table 2. Summary of Chinese Medicine Treatment for COVID-19 by Chinese National Guideline**

| Stage | Presentation | Recommended Formulation[a] |
|---|---|---|
| Mild case: | | |
| *Cold-dampness distressing lung* | Fever, fatigue, myalgia, cough, expectoration, chest distress, poor appetite, anorexia, vomiting, sticky and greasy stool with unsmooth defecation, pale, swollen and indented tongue or pale red tongue, white greasy tongue fur or thick curdy greasy tongue fur, soft or slippery pulse. | Ma-huang 6 g, shi-gao 15 g, xing-ren 9 g, qiang-huo 15 g, ting-li-zi 15 g, guan-zhong 9 g, di-long 15 g, xu-chang-qing 15 g, huo-xiang 15 g, pei-lan 9 g, cang-zhu 15 g, fu-ling 45 g, bai-zhu 30 g, shan-zha 9 g, shen-qu 9 g, mai-ya 9 g, hou-pu 15 g, bin-lang 9 g, cao-guo 9 g, sheng-jiang 15 g |
| *Dampness-heat accumulation in lung* | Low/no fever, mild chilly, fatigue, malaise, myalgia, dry cough, sore throat, dry mouth but not thirsty, tongue pale-red, white thick greasy tongue fur or yellowish tongue fur, slippery and rapid pulse or soft pulse; may accompany with chest distress, abdominal distension, little/no sweating, anorexia, poor appetite, loose stool or sticky and greasy stool with uncomfortable defecation | Bin-lang 10 g, cao-guo 10 g, hou-pu 10 g, zhi-mu 10 g, huang-qin 10 g, chai-hu 10 g, chi-shao 10 g, lian-qiao 15 g, qing-hao 10 g, cang-zhu 10 g, da-qing-ye 10 g, gan-cao 5 g |
| Intermediate case: | | |
| *Endemic toxin distressing lung* | Fever, dry cough, little/yellowish sputum, chest distress, shortness of breath, abdominal distention, constipation, tongue dull red, tongue swollen, greasy and yellowish tongue fur or dry and yellowish tongue fur, slippery and rapid pulse or slippery and string pulse | Ma-huang 6 g, xing-ren 15 g, shi-gao 30 g, yi-yi-ren 30 g, cang-zhu 10 g, huo-xiang 15 g, qing-hao 12 g, hu-zhang 20 g, ma-bian-cao 30 g, lu-gen 30 g, ting-li-zi 15 g, ju-hong 15 g, gan-cao 10 g |
| *Cold-dampness blocking lung* | Low/no fever, dry cough, little sputum, fatigue, chest distress, abdominal distention, loose stool, pale tongue or pale red tongue, white or white greasy tongue fur, soft pulse; may accompany with anorexia | Cang-zhu 15 g, chen-pi 10 g, hou-pu 10 g, huo-xiang 10 g, cao-guo 6 g, ma-huang 6 g, qiang-huo 10 g, sheng-jiang 10 g, bin-lang 10 g |
| Severe case: | | |
| *Pestilence toxin retention in lung* | Fever, flushing, cough, little yellowish and sticky sputum or hemoptysis, dyspnea, fatigue, dry mouth with bitter taste, anorexia, poor appetite, unsmooth defecation, dark yellowish urine, red tongue, yellowish and greasy tongue fur, slippery and rapid pulse | Ma-huang 6 g, xing-ren 9 g, shi-gao 15 g, gan-cao 3 g, huo-xiang 10 g, hou-pu 10 g, cang-zhu 15 g, cao-guo 10 g, ban-xia 9 g, fu-ling 15 g, da-huang 5 g, huang-qi 10 g, ting-li-zi 10 g, chi-shao 10 g |

**Table 2. (*Continued*)**

| Stage | Presentation | Recommended Formulation[a] |
|---|---|---|
| *Intense heat in qi and ying systems* | High fever, thirsty, dyspnea, confusion, agitation, crimson tongue, little/no tongue fur, deep, thin and rapid pulse or floating, large and rapid pulse; may accompany with purpura/rash/hematemesis/nasal bleeding/limb spasm | Shi-gao 30–60 g, zhi-mu 30 g, di-huang 30–60 g, shui-niu-jiao 30 g, chi-shao 10 g, xuan-shen 30 g, lian-qiao 15 g, mu-dan-pi 15 g, huang-lian 6 g, zhu-ye 12 g, ting-li-zi 10 g, gan-cao 6 g<br>CM proprietary medicine: Xi-yan-ping injection, Re-du-ning injection, Xue-bi-jing injection, Tan-re-qing injection or Xing-nao-jing injection |
| Critical case: | | |
| *Internal obstruction and external collapse* | Dyspnea, confusion, agitation, sweating and cold extremities, dull purple tongue, thick greasy tongue fur or dry tongue fur, floating, large and rootless pulse | Ren-shen 15 g, fu-zi 10 g, shan-zhu-yu 15 g with An-gong-niu-huang pill or Su-he-xiang pill<br>CM proprietary medicine: Xue-bi-jing injection, Re-du-ning injection, Tan-re-qing injection, Xing-nao-jing injection, Shen-fu injection, Sheng-mai injection or Shen-mai injection |
| Rehabilitation stage: | | |
| *Lung and spleen qi deficiency* | Shortness of breath, fatigue, anorexia and poor appetite, abdominal distention, unsmooth defecation and loose stool, tongue pale and swollen, white greasy fur tongue | Ban-xia 9 g, chen-pi 10 g, dang-shen 15 g, huang-qi 30 g, bai-zhu 10 g, fu-ling 15 g, huo-xiang 10 g, sha-ren 6 g, gan-cao 6 g |
| *Qi and yin deficiency* | Shortness of breath, fatigue, dry mouth, thirsty, palpitation, sweating, poor appetite, low/no fever, dry cough, dry tongue, thready pulse or feeble pulse | Nan-sha-shen 10 g, bei-sha-shen 10 g, mai-dong 15 g, xi-yang-shen 6 g, wu-wei-zi 6 g, shi-gao 15 g, zhu-ye 10 g, sang-ye 10 g, lu-gen 15 g, dan-shen 15 g, gan-cao 6 g |

[a]Qing-fei-pai-du decoction (ma-huang 9 g, gan-cao 6 g, xing-ren 9 g, shi-gao 15–30 g, gui-zhi 9 g, ze-xie 9 g, zhu-ling 9 g, bai-zhu 9 g, fu-ling 15 g, chai-hu 16 g, huang-qin 6 g, ban-xia 9 g, sheng-jiang 9 g, zi-wan 9 g, dong-hua 9 g, she-gan 9 g, xi-xin 6 g, shan-yao 12 g, zhi-shi 6 g, chen-pi 6 g, huo-xiang 9 g) can be considered for mild, intermediate and severe cases. Usage in critical cases depends on clinical presentation.

**Table 3. Recommended Chinese Medicine Formulations of Provincial Treatment Guidelines from China**

| Herbal Formulation | Composition |
|---|---|
| Da-yuan decoction | Bin-lang, hou-pu, cao-guo, zhi-mu, bai-shao, huang-qin, gan-cao |
| Sheng-jiang powder | Bai-jiang-can, chan-tui, jiang-huang, da-huang |
| Huo-pu-xia-ling decoction | Huo-xiang, hou-pu, ban-xia, chi-fu-ling, xing-ren, yi-yi-ren, bai-dou-kou, zhu-ling, dan-dou-chi, ze-xie |
| Huo-xiang-zheng-qi powder | Huo-xiang, zi-su-ye, bai-zhi, da-fu-pi, fu-ling, bai-zhu, ban-xia, chen-pi, hou-pu, jie-geng, gan-cao, sheng-jiang, da-zao |
| Ma-xing-yi-gan decoction | Ma-huang, xing-ren, yi-yi-ren, gan-cao |
| Ma-xing-shi-gan decoction | Ma-huang, xing-ren, shi-gao, gan-cao |
| Xuan-bai-cheng-qi decoction | Shi-gao, da-huang, xing-ren, gua-lou-pi |
| Huang-lian-jie-du decoction | Huang-lian, huang-qin, huang-bai, zhi-zi |
| Jie-du-huo-xue decoction | Lian-qiao, ge-gen, chai-hu, dang-gui, di-huang, chi-shao, tao-ren, hong-hua, zhi-ke, gan-cao |
| Yin-qiao powder | Jin-yin-hua, lian-qiao, jing-jie-sui, dan-dou-chi, jie-geng, bao-he, niu-bang-zi, gan-cao, zhu-ye, lu-gen |
| Qing-wen-bai-du decoction | Shi-gao, di-huang, xi-jiao[#], huang-lian, zhi-zi, jie-geng, huang-qin, zhi-mu, chi-shao, xuan-shen, lian-qiao, zhu-ye, mu-dan-pi, gan-cao |
| Bai-hu decoction | Zhi-mu, shi-gao, gan-cao, jing-mi |
| Si-ni-jia-ren-shen decoction | Fu-zi, gan-jiang, gan-cao, ren-shen |
| Su-he-xiang pill | Su-he-xiang, an-xi-xiang, she-xiang, bing-pian, qing-mu-xiang, bai-tan-xiang, chen-xiang[#], ding-xiang, he-zi, xiang-fu, ru-xiang, bi-ba, xi-jiao[#], zhu-sha[#] |
| Zi-xue powder | Xi-jiao[#], ling-yang-jiao[#], shi-gao, han-shui-shi, sheng-ma, yuan-shen |
| **Proprietary Chinese Medicines** | |
| Huo-xiang-zheng-qi formulations | Cang-zhu, chen-pi, hou-pu, bai-zhi, fu-ling, da-fu-pi, ban-xia, gan-cao, huo-xiang, zi-su-ye |
| Jin-hua-qing-gan granules | Jin-yin-hua, shi-gao, ma-huang, xing-ren, huang-qin, lian-qiao, zhe-bei-mu, zhi-mu, niu-bang-zi, qing-hao, bao-he, gan-cao |
| Shu-feng-jie-du capsule | Hu-zhang, lian-qiao, ban-lan-gen, chai-hu, bai-jiang-cao, ma-bian-cao, lu-gen, gan-cao |
| Fang-feng-tong-shen granules | Fang-feng, jing-jie-sui, bao-he, ma-huang, da-huang, mang-xiao, zhi-zi, hua-shi, jie-geng, shi-gao, chuan-xiong, dang-gui, bai-shao, huang-qin, lian-qiao, gan-cao, bai-shu |
| Lian-hua-qing-wen capsule | Lian-qiao, jin-yin-hua, ma-huang, xing-ren, shi-gao, ban-lan-gen, guan-zhong, yuxing-cao, huo-xiang, da-huang, hong-jing-tian, bao-he, gan-cao |
| An-gong-niu-huang pill | Niu-huang, shui-niu-jiao, she-xiang, zhen-zhu, zhu-sha#, xiong-huang, huang-lian, huang-qin, zhi-zi, yu-jin, bing-pian |
| Xue-bi-jing injection | Hong-hua, chi-shao, chuan-xiong, dan-shen, dang-gui |
| Shen-fu injection | Hong-shen, fu-zi |
| Sheng-mai injection | Hong-shen, mai-dong, wu-wei-zi |
| Xi-yan-ping injection | Chuan-xin-lian |

*Note*: [#]Use is prohibited in some countries and should be replaced by other drugs by clinical judgement.

CM-oriented designated Module Hospital in Wuhan operated since 14 February 2020 (Wang and Li, 2020).

## Latest Evidence and Plausible Mechanisms of Chinese Medicine

As of 22 February 2020, there were three retrospective cohorts (Lu *et al.*, 2020a; Xia *et al.*, 2020; Yao *et al.*, 2020), five case series (Cheng and Li, 2020; Dai *et al.*, 2020; Guangdong Medical Products Administration, 2020; National Administration of Traditional Chinese Medicine, 2020b; Yong *et al.*, 2020), and two case studies (Hu *et al.*, 2020; Sun *et al.*, 2020b) on the IM management of COVID-19 arising pneumonia. The involved CM formulations are summarized in Table 4.

**Table 4. Reported use of Chinese Medicine Formulations on COVID-19**

| | |
|---|---|
| 2 Retrospective Cohort (Int vs. Crt: 21 vs. 21; 63 vs. 38) | Lian-hua-qing-wen granules (lian-qiao, jin-yin-hua, ma-huang, xing-ren, shi-gao, ban-lan-gen, guan-zhong, yuxing-cao, huo-xiang, da-huang, hong-jing-tian, bao-he, gan-cao) |
| Retrospective Cohort (Int vs. Crt: 34 vs. 18) | Xing-ren 15 g, hua-shi 30 g, cang-zhu 30 g, bai-zhi 10 g, ban-xia 15 g huo-xiang 15 g, fu-ling 30 g, ma-huang 9 g, da-huang 10 g, chan-tui 10 g, niu-bang-zi 15 g, gan-cao 10 g<br>Xing-ren 10 g, shi-gao 30 g, gua-lou 30 g, da-huang 6 g, ma-huang 6 g, ting-li-zi 10 g, tao-ren 10 g, cao-guo 6 g, bin-lang 10 g, cang-zhu 10 g<br>Hua-shi 20 g, huang-qin 10 g, yin-chen 10 g, huo-xiang 6 g, lian-qiao 10 g, shi-chang-pu 6 g, bai-dou-kou 6 g, bao-he 6 g, tong-cao 6 g, she- gan 10 g, chuan-bei-mu 10 g<br>Xing-ren 10 g, shi-gao 20 g, ma-huang 6 g, gan-cao 6 g<br>Chai-hu 6 g, huang-qin 6 g, cang-zhu 10 g, ban-xia 10 g, gan-cao 6 g, bai-shu 15 g, fu-ling 10 g, chen-pi 10 g, hou-pu 10 g, ren-shen 10 g, zhu-ling 15 g, ze-xie 10 g, gui-zhi 6 g<br>Qing-hao 6 g, zhu-ru 10 g, ban-xia 10 g, chi-fu-ling 10 g, huang-qin 10 g, zhi-ke 6 g, chen-pi 6 g, hua-shi 20 g, qing-dai 10 g, gan-cao 6 g<br>Huo-xiang 6 g, hou-pu 6 g, ban-xia 6 g, fu-ling 10 g, xing-ren 10 g, yi-yi-ren 15 g, bai-dou-kou 6 g, zhu-ling 10 g, dan-dou-chi 10 g, ze-xie 6 g, tong-cao 6 g, chai-hu 6 g, gan-cao 6 g, rou-gui 6 g, ma-huang 6 g, chen-pi 10 g |
| Case Series ($n = 214 + 351 = 565$) | Qing-fei-pai-du decoction (ma-huang 9 g, gan-cao 6 g, xing-ren 9 g, shi-gao 15–30 g, gui-zhi 9 g, ze-xie 9 g, zhu-ling 9 g, bai-zhu 9 g, fu-ling 15 g, chai-hu 16 g, huang-qin 6 g, ban-xia 9 g, sheng-jiang 9 g, zi-wan 9 g, dong-hua 9 g, she-gan 9 g, xi-xin 6 g, shan-yao 12 g, zhi-shi 6 g, chen-pi 6 g, huo-xiang 9 g) |
| Case Series ($n = 54$) | Lian-hua-qing-wen granules (lian-qiao, jin-yin-hua, ma-huang, xing-ren, shi-gao, ban-lan-gen, guan-zhong, yuxing-cao, huo-xiang, da-huang, hong-jing-tian, bao-he, gan-cao) |
| Case Series ($n = 50$) Mild cases | Toujiequwen granules (lian-qiao, sheng-ci-gu, jin-yin-hua, huang-qin, chai-hu, qing-hao, chan-tui, qian-hu, chuan-bei-mu, wu-mei, xuan-shen, tu-bie-chong, cang-zhu, huang-qi, tai-zi-shen, fu-ling) |

**Table 4. (*Continued*)**

| | |
|---|---|
| Case Series ($n = 5$)[a]<br>12 days since symptom onset | Chai-hu 9 g, huang-qin 9 g, ban-xia 9 g, tai-zi-shen 10 g, gan-cao 9 g, cao-dou-kou 6 g, hou-pu 6 g, fu-ling 15 g, huo-xiang 10 g, chen-pi 9 g, zao-jiao-ci 10 g, tao-ren 9 g, ting-li-zi 15 g, ma-huang 9 g, xing-ren 9 g, shi-gao 20 g, tian-hua-fen 15 g |
| Case Series ($n = 5$)<br>8 days since symptom onset | Chai-hu 9 g, huang-qin 9 g, ban-xia 9 g, tai-zi-shen 15 g, gan-cao 9 g, jie-geng 9 g, gan-jiang 6 g, zhi-ke 9 g, ma-huang 9 g, ting-li-zi 15 g, xing ren 10 g, shi-gao 20 g, da-zao 10 g, tian-hua-fen 15 g, zao-jiao-ci 10 g, zhi-zi 10 g, dan-dou-chi 15 g, yi-yi-ren 24 g, jin-yin-hua 15 g, lian-qiao 10 g |
| Case Report ($n = 1$)<br>6 days since symptom onset, $PaO_2/FiO_2 = 195$ mmHg | Qing-hao 12 g, huang-qin 10 g, zhu-ru 10 g, ban-xia 6 g, fu-ling 10 g, chen-pi 12 g, huang-qi 30 g, bai-shu 12 g, fang feng 10 g, sang-ye 12 g, zi-su-ye 12 g, zhi-ke 12 g, jie-geng 12 g, qing-dai 10 g, jin-yin-hua 15 g, lian-qiao 15 g, da-qing-ye 12 g, hua-ju-hong 12 g, guan-zhong 12 g, lu-gen 25 g |
| Case Report ($n = 1$)<br>9 days since symptom onset | Huo-xiang 15 g, hou-pu 10 g, ban-xia 10 g, fu-ling 15 g, zhu-ling 10 g, ze-xie 20 g, tong-cao 10 g, dan-dou-chi 10 g, ma-huang 10 g, gan-cao 10 g, shi-gao 10 g, cang-zhu 20 g, xing-ren 10 g, yi-yi-ren 20 g, sheng-jiang 10 g da-zao 10 g, yuan-zhi 10 g, ge-gen |
| *In silico:* network pharmacology followed by docking | Da-yuan decoction (bin-lang, hou-pu, cao-guo, zhi-mu, bai-shao, huang-qin, gan-cao) |
| *In silico:* docking based on clinical experience | Sang-ye, cang-zhu, zhe-bei-mu, sheng-jiang, jin-yin-hua, lian-qiao, cao-guo |
| *In silico:* docking | Huang-qin, deng-zhan-hua, zhi-shi, chen-pi, fan-hong-hua, gan-cao |

[a]Data of 3 cases in the case series were incomplete for the whole course of management.

### *Retrospective Cohort*

One retrospective cohort with 52 confirmed cases (18 standard care control vs. 34 add-on CM, symptom onset to diagnosis: $7.4 \pm 3.0$ days) used semi-individualized CM treatment based on the China national guideline (Xia *et al.*, 2020). A statistically and clinically significant higher rate of normalizing neutrophil count, C-reactive protein, creatine kinase, LDH, aspartate transaminase (AST), blood urea, D-dimer and radiological changes was reported on discharge. The average duration of fever ($2.6 \pm 1.3$ vs. $4.4 \pm 1.9$ days, $P = 0.001$), days to clinical remission ($5.2 \pm 1.7$ vs. $7.2 \pm 2.1$, $P = 0.002$), and duration of hospital stay ($7.4 \pm 2.1$ vs. $9.6 \pm 3.6$ days, $P = 0.03$) were shorter with add-on CM.

Two retrospective cohorts reported the use of Lian-hua-qing-wen granules (Lu *et al.*, 2020a; Yao *et al.*, 2020). A retrospective cohort with 21 COVID-19 patients (symptom onset to diagnosis: $12.9 \pm 3.3$ days) treated with standard medical care and 21 COVID-19 patients (symptom onset to diagnosis: $12.8 \pm 3.8$ days) treated with add-on Lian-hua-qing-wen granules showed that add-on Lian-hua-qing-wen granules led to better remission rate of fever (85.7% vs. 57.1%, $P = 0.04$), cough (46.7% vs. 5.6%, $P = 0.01$), expectoration (64.3% vs. 9.1%, $P = 0.01$), and shortness of breath (77.8% vs. 0, $P = 0.02$) with slightly shorter duration of fever ($4.6 \pm 3.2$ vs. $6.1 \pm 3.1$ days, $P = 0.22$) (Yao *et al.*, 2020). Another retrospective cohort on 101 suspected COVID-19 cases (38 standard medical care control vs. 63 add-on Lian-hua-qing-wen granules 6 g three times a day) showed that add-on Lian-hua-qing-wen granules led to better remission of fever (86.7% vs. 67.6%,

$P = 0.03$), cough (55.6% vs. 30.6%, $P = 0.02$), fatigue (82.5% vs. 58.6%, $P = 0.03$), and dyspnoea (68.2% vs. 20%, $P = 0.002$) after 10 days with slightly shorter duration of fever (median 6 days vs. median 7 days, $P = 0.17$) (Lu *et al.*, 2020a).

### *Case Series and Case Studies*

Three case series used CM in inpatient management (Dai *et al.*, 2020; Guangdong Medical Products Administration, 2020; National Administration of Traditional Chinese Medicine, 2020b). Qing-fei-pai-du decoction was reported to be effective among 90% cases and 60% patients had improvement in radiology with limited detail ($n = 214$) (National Administration of Traditional Chinese Medicine, 2020b). Further observation of 351 cases showed that 51.8% and 94.6% of confirmed cases had fever subsided 1 and 6 days after taking Qing-fei-pai-du decoction (The State Council, The People's Republic of China, 2020a). Toujiequwen granules was reported to lower fever for all 50 confirmed cases with good remission rates on other symptoms including cough (50%), sore throat (52.4%), and fatigue (69.6%) within 1 week (Guangdong Medical Products Administration, 2020). A case series of 54 confirmed cases showed mean duration of fever was $3.6 \pm 2.1$ days after taking Lian-hua-qing-wen granules (Cheng and Li, 2020). Among the two case studies reported, one was a case of IM treatment for a COVID-19 pneumonia patient with moderate ARDS ($PaO_2/FiO_2 = 195$ mmHg) with good recovery (Hu *et al.*, 2020).

### *Plausible Mechanisms*

A recent network pharmacology and molecular docking analysis of da-yuan decoction, the key CM formulation recommended by the China national guideline demonstrated that the kaempferol and baicalin in da-yuan decoction could bind with ACE2 receptor and regulate T cell receptor signaling pathway through targeting PTGS2, HSP90AA1, ESR1, PIK3CG, and AKT1 genes (Zong *et al.*, 2020). Another molecular docking analysis on 24 CM prescriptions (40 CMs) commonly used during SARS and formulations recommended in the COVID-19 clinical guidelines yielded 46 compounds that could act on the S-protein-binding site of ACE2. The research team proposed a new formulation of seven herbal medicines (sang-ye, cang-zhu, zhe-bei-mu, sheng-jiang, jin-yin-hua, lian-qiao, cao-guo) that these compounds were mainly found (Niu *et al.*, 2020). Similar affinity to ACE2 receptor was also reported on baicalin, scutellarin, hesperetin, nicotianamine, and glycyrrhizin which were mainly found in huang-qin, deng-zhan-hua, zhi-shi, chen-pi, and fan-hong-hua, gan-cao (Chen and Du, 2020).

Ma-huang, chai-hu, huang-qi, sang-ye, jin-yin-hua, lian-qiao, zhe-bei-mu, and gan-cao contain compounds that were commonly identified by multiple *in silico* studies (Chen and Du, 2020; Li *et al.*, 2020b; Ma *et al.*, 2020b; Niu *et al.*, 2020). Network pharmacology analysis also demonstrated that Qing-fei-pai-du decoction can regulate key immunological pathways (Th17 cell differentiation, T cell and B cell signaling) and TNF signaling pathway (Zhao *et al.*, 2020). Xue-bi-jing injection (hong-hua, chi-shao, chuan-xiong, dan-shen, dang-gui) recommended for the management of critical patients could alleviate

pneumonia through regulating TNF-α, IL-1, IL-6, IL-8, IL-17, and TLR4 -NF-κB signaling pathways (Li *et al.*, 2020a).

The current evidence indicated that CM has potential benefit in symptomatic relief, shortening fever duration, reverting radiological changes, and shortening hospital stay (Lu *et al.*, 2020a; Xia *et al.*, 2020; Yao *et al.*, 2020). Nevertheless, these studies were generally of inadequate description and quality in methodology and caution is needed to interpret the clinical significance and internal validity.

## Use of Chinese Medicine in SARS and H1N1 Management

### *Treatment*

During SARS outbreak, CM was introduced as a treatment option since its early stages in China. A report of an international meeting with 68 experts from Hong Kong, Japan, Netherlands, China, Thailand, Vietnam and US on evidence of IM released by WHO indicated that IM has the potential benefits of *"alleviation of fatigue, shortness of breath and other clinical symptoms; facilitation of lung inflammation absorption; reduction of the risk of oxygen desaturation and the stabilization of abnormal fluctuation of oxygen saturation in the blood; reduction in the dosage of glucocorticoid and antiviral agents (and therefore in their associated side-effects) and reduction of cost (treatment with TCM alone costs less than treatment with Western medicine alone)."* Although the therapeutic effect was inconclusive due to limitation in research methodology in an outbreak clinical setting, the panel agreed that IM treatment was safe (World Health Organization, 2004). The presented formulations with controlled comparison are summarized in Table 5. A subsequent meta-analysis on available randomized controlled trials also concluded that add-on CM could potentially improve symptoms (physical inactivity, dyspnoea, depression), shorten fever duration, absorption of pulmonary infiltration, reduce the use of corticosteroid steroid, although the result should be interpreted with caution as the methodological quality was also suboptimal (Liu *et al.*, 2012).

### *Prevention*

CM was also used as a preventive measure among healthcare workers during SARS (World Health Organization, 2004; Leung, 2007). 1063 patients (295 physicians and allied health workers, 485 nurses and 283 supporting staffs) had better quality of life and mental health status with no SARS infection after administrating the preventive CM formulation (sang-ye, ju-hua, xing-ren, lian-qiao, bao-he, jie-geng, gan-cao, lu-gen, huang-qi, fang-feng, da-qing-ye and huang-qin) for 2 weeks when compared to a comparable control group ($n = 36111$) (Lau *et al.*, 2005a,b; World Health Organization, 2004). Increase in CD4/CD8 T-lymphocytes was also noted among the CM users (Lau *et al.*, 2005b).

A recent meta-analysis of CM prevention programmes of H1N1 ($n = 4$) showed that the infection rate of H1N1 were lower with a course of 3–7 days of CM herbal medicine when compared to control (relative risk: 0.36, 95%CI: 0.24 to 0.52) (Luo *et al.*, 2020).

**Table 5. Existing Evidence from Controlled Study Generated from SARS Management**

| Treatment | Source and Study Design | Setting and Demographics | Clinical Implication |
|---|---|---|---|
| Parched Ephedra 5 g, Almond 12 g, Fossilia Chitonis 45 g, Rhizoma Anemarrhenae 10 g, Honeysuckle Flower 15 g, Fructus Forsythiae 12 g, Parched Fructus Gardeniae 12 g, Fructus Scutellariae 12 g, Perilla Leaf 10 g, Herba Artemisiae 15 g, Radices Puerarire 15 g, Pseudostellaria Root 15 g | Report to WHO<br>Randomized or non-randomized case—control studies<br>Sample size: 130 had conventional treatment; 231 had add-on Chinese medicine | SARS patients* with high fever as major symptom | Reduce lung inflammation, especially among severe cases<br>Improve the level of blood oxygen saturation<br>Improve symptoms including tachypnoea, shortness of breath<br>Reduce required dose of glucocorticoid |
| Radix Panacis Quinquefolii 15 g, Lilyturf Root 10 g, Fructus Schizandrae 10 g, and Fructus Corni 12 g, Semen Lepidii 15 g, Radix Asteris 15 g, Folia Eriobotryae 12 g, and Guangdong Earthworm 12 g, Radix Salviae Miltiorrhizae 12 g, Radix Paeoniae Rubra 12 g, Chinese Globeflower 8 g, Fructus Scutellariae 10 g, Trichosanthes Kirilowii Maxim 15 g | | SARS patients* with cough and shortness of breath as major symptoms. | |
| Rhizoma Phragmitis 30 g, Lonicera Japonica 30 g, Periostracum Cicadae (Cicada Slough) 6 G, Bombyx Batryticatus (Stiff Silkworm) 6 g, Almond 10 g, Unprepared Semen Coicis 30 g, and Herba Eupatorii 6 g with IV shuang-huang-lian and Houttuynia injection | Report to WHO<br>Case series<br>Sample size: 60 | Mild SARS patients* presented with fever, cough, headache, muscular stiffness, reddened tongue with white or greasy tongue fur, and slippery pulse | Reduce the cost of hospital treatment and shorten number of days of hospitalization (control group size = 11) |
| Stir-fried Ephedra 6 g, Unprepared Gypsum 30 g, Almond 10 g, Lonicera Japonica 30 g, Rhizoma Phragmitis 30 g, Radices Scutellariae 10 g, Cortex Mori Radicis 30 g and Radices Paeoniae Rubra 30 g with IV qing-kai-ling, Houttuynia and Salvia Miltiorrhiza injection | | Mild SARS patients* presented with high fever, cough, thirst, hyperhidrosis, reddened tongue with thick or greasy and yellowish drug fur, and slippery pulse | |

**Table 5. (*Continued*)**

| Treatment | Source and Study Design | Setting and Demographics | Clinical Implication |
|---|---|---|---|
| Unprepared Gypsum 60 g, Rhizoma Phragmitis 60 g, Radices Scutellariae 15 g, Dried Rehmannia Root 30 g, Buffalo Horn (to be decocted first) 60 g, Unprepared Radices Rhei 6 g, Radices Paeoniae Rubra 30 g and Flores Carthami 10 g with IV xing-nao-jing, Houttuynia and Salvia Miltiorrhiza injection | | Mild SARS patients* presented with persistent high fever, flushed face, cough, shortness of breath, dark reddened or deep red tongue, yellow thick dry or dark tongue fur, with slippery or deep pulse | |
| Unprepared Radices Rehmanniae 30 g, Cortex Phellodendri 15 g, Rhizoma Anemarrhenae 15 g, Unprepared Licorice 10 g, Pberetima 10 g, Radices Paeoniae Rubra 30 g, Herba Lycopi 30 g, and Pseudostellaria Root 15 g with IV Salvia Miltiorrhiza injection | | Mild SARS patients* with dyspnoea, cough, shortness of breath, feverish sensation in the palms and soles, hyperhidrosis, dry mouth and tongue, reddened tongue with little tongue fur, and slippery pulse | |
| Fossilia Chitonis (45 g), Rhizoma Anemarrhenae (15 g), Fructus Scutellariae (15 g), Rhizoma Atractylodis (10 g), Herba Artemisiae Annuae (15 g), Radix Paeoniae Rubra (15 g), Radix Bupleuri (10 g) | Report to WHO<br>Randomized controlled trial<br>Sample size: 32 had conventional treatment; 31 had add-on Chinese medicine | SARS patients* with high fever as major symptom | Reduce lung inflammation<br>Prevent reduction in lymphocyte count<br>Reduce lactate dehydrogenase<br>Symptomatic improvement |
| Fructus Scutellariae (20 g), Diosoreae Gracillimae (10 g), Rhizoma Coptidis (15 g), Faeces Bombycis (10 g), Trichosanthes Kirilowii (30 g), Herba Artemisiae Annuae (15 g), Semen Coicis (30 g), Flos Inulae (10 g), Radix Curcumae (15 g), Radix Salviae Miltiorrhizae (30 g) | | SARS patients* with severe dyspnoea and cough, fever and increasing shadows on lungs | |

*Notes*: *SARS patient clinically diagnosed as having (1) contact history with SARS or travel history to area reported SARS cases, (2) fever with upper respiratory tract infection symptoms, (3) patchy and spot-shaped infiltration in chest X-ray with (4) no obvious effect with antibiotics.

The medicines used included zi-cao, bo-he, gan-cao, guan-zhong, jing-yin-hua, lian-qiao, ban-lan-gen, niu-bang-zi, huo-xiang, zhu-ye, da-qing-ye, Qing-jie-fang-gan granules, Kang-bing-du oral liquid, and Gan-mao-qing-re granules.

## Ongoing Clinical Trials

As of 22 February 2020, 24 and 141 COVID-19 related interventional studies were registered on ClinicalTrials.gov and Chinese Clinical Trial Registry, respectively. The treatment under evaluation included (1) public health intervention: community-based prevention programme, (2) pharmacological therapy: corticosteroid (glucocorticoid, methylprednisolone), antivirals (darunavir, cobicista, lopinavir/ritonavir, azvudine, arbidol, remdesivir, favipiravir, triazavirin, interferon), antimalarials (chloroquine/hydroxychloroquine), antibiotics (carrimycin), immunomodulators (tocilizumab, fingolimod, leflunomide), anti-allergic drug (Tranilast), sodium aescinate and CMs, (3) biologics: mesenchymal stem cell, immunoglobulin/convalescent plasma, microbiota transplantation, PD-1 blocking antibody, recombinant cytokine gene-deprived protein and bevacizumab, (4) supplements: alpha lipoic acid, vitamin C and probiotics, and (5) other therapies: M1 macrophage suppression therapy, hydrogen–oxygen nebulizer, ultra-short wave electrotherapy, and nutrition support.

Of the 53 CM related clinical trials, 27 trials evaluate CM/IM treatment programmes involving CM diagnosis with limited information on the regime involved. Three trials evaluate qi-gon and dao-yin. The remaining trials evaluate Xue-bi-jing injection ($n = 3$), Ba-bao-dan capsule ($n = 2$), Honeysuckle (jin-yin-hua) decoction ($n = 2$), Lian-hua-qing-wen capsule/granule ($n = 2$), Shuang-huang-lian ($n = 2$), Tan-re-qing injection ($n = 2$), Hua-tan-zhi-ke granules ($n = 1$), Kang-bing-du granules ($n = 1$), Ke-su-ting syrup ($n = 1$), Jing-ye-bai-du granules ($n = 1$), qing-yi No. 4 ($n = 1$), Liu-shen capsule ($n = 1$), Re-du-ning injection ($n = 1$), Shen-fu injection ($n = 1$), Shen-qi-fu-zheng injection ($n = 1$), Xiang-xue antiviral oral solution, and Wu-zhi-fang-guan-fan ($n = 1$). Most of these proprietary medicines/preparations are *heat-clearing* agents hypothesized to possess antiviral effect. CM proprietary medicines under major trials included Xue-bi-jing injection (total $n = 860$), Lian-hua-qing-wen granules (total $n = 800$), and Qing-fei-pai-du decoction (total $n = 600$).

Recent press release from the State Council of China indicated that preliminary data showed that chloroquine was effective in preventing the deterioration of COVID-19 related pneumonia (0 case out of 130 trial cases, including 5 severe cases). Preliminary result on the trial of convalescent plasma, favipiravir, and stem cell therapy were also satisfactory and planning for up-scaling (The State Council, The People's Republic of China, 2020b).

## Conclusion and Clinical Implication

The existing epidemiological data indicated that COVID-19 is a highly transmissible outbreak of novel coronavirus that has a moderate to low mortality rate. COVID-19 appears to hit health systems harder than individuals and caused a substantial public health burden. The mortality in Wuhan is exceptionally high, seven folds higher than other provinces in China, likely partly related to the overloading of healthcare facilities and

personnel on screening, diagnosis, and supportive treatment for patients (Lipsitch *et al.*, 2020; Yang *et al.*, 2020b) and therefore a possible delay of care (Sun *et al.*, 2020a).

Given the exceptionally efficient transmission within families, on cruise ships, over dinner parties, religious gatherings, and the alleged asymptomatic infections, the route and vehicle of transmission, such as saliva and faeces via possible inadequate dining table and toilet hygiene, or deficient building services, need urgent clarification for targeted preventive measures. Demographics, transmissibility, and behavioral pattern of these asymptomatic carriers would also be a key determining factor of the control of outbreak that requires further characterization. The battle with COVID-19 is likely to continue for months globally. More strategies on top of containment and mitigation are therefore needed to prepare for hard-landing of COVID-19 on any soil, especially those with underdeveloped healthcare infrastructure (Gilbert *et al.*, 2020), to shorten hospital stay and reduce consumption of healthcare resources (World Health Organization, 2020a).

CM has a good potential to complement the service need as CM treatment relies on symptom-based diagnosis. The clinical evidence of CM on COVID-19 is far from conclusive, similar to other regimens, but may be a good additional candidate at least for trial treatment considering the limited options available for COVID-19. Early reported benefits of CM included symptomatic relief, shortening fever duration, reverting radiological changes, and shortening hospital stay (Lu *et al.*, 2020a; Xia *et al.*, 2020; Yao *et al.*, 2020), similar to the SARS management experience.

To conclude, COVID-19, similar to other outbreaks of any newly identified virus, has limited pharmacological treatment options due to the lack of evidence from well-designed clinical trials. Most clinical decisions are based on the best available evidence including but not limited to retrospective cohorts, *in vivo*, *in vitro*, *in silico* and expert opinion with possible off-label use of existing antiviral drugs as trial or on a compassionate basis. As the methodological quality of the existing studies varies, consideration on a full spectrum of evidence followed by careful interpretation and deduction is needed. Given the paucity of strongly evidence-based regimens, the available data suggest that CM could be considered as an adjunctive therapeutic option in the management of COVID-19.

## Acknowledgments

We thank Ms. Kam Yan Yu for clerical support on the translation of herbs. This work was made possible in part through Health and Medical Research Fund (Ref.: 14151731). The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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