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Adjuvant therapy with traditional Chinese medicine in a heart failure patient complicated by hospital-acquired pneumonia: A case report

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ABSTRACT

Objective: We report a case of congestive heart failure complicated by hospital-acquired pneumonia that was successfully treated with traditional Chinese medicine (TCM) and antibiotics.

Clinical features and outcome: A 33-year-old man with a history of heart failure developed pneumonia during hospitalization. After the standard antibiotic therapy for 3 days, he continued to experience persistent fever and progressive cough with purulent sputum. Broad spectrum antibiotics did not relieve the fever or the purulent sputum; therefore, the patient requested TCM for integrated therapy, and was subsequently treated with a regiment of “clearing heat and damp excreting” decoction according to TCM theory. After three days of TCM combination therapy, the pneumonia patches significantly improved on chest X-ray. His sputum was obviously decreased in amount and the fever was complete remission in the 5th day of TCM adjuvant therapy.

Conclusion: Integrated therapy with a “clearing heat and damp excreting” decoction may have improved hospital-acquired pneumonia in a patient comorbid with congestive heart failure. The anti-pyretic, anti-inflammatory, antitussive and diuretic effects of TCM may be responsible for the observed improvement. Further experimental studies are warranted to confirm the efficacy and mechanism of TCM action in the treatment of pneumonia.

1. Introduction

Pneumonia is one of the most common infectious diseases causing significant morbidity and mortality in adults even in the modern medical care system.¹ According to the World Health Organization statistics, pneumonia was the 4th leading cause of death, causing 3.0 million deaths worldwide in 2016.² As the 3rd leading cause of death in 2016,³ the social-economic burden of pneumonia in Taiwan is significant. Pneumonia is classified as community acquired (CAP) or hospital acquired (HAP) according to the acquisition site.⁴ The prognosis of HAP patients is unfavorable, especially for those with comorbidities such as chronic obstructive pulmonary disease, immunocompromised status, and congestive heart failure (CHF).⁵

The standard treatment for HAP includes antimicrobial therapy and supportive care. Antibiotics can attenuate the infectious process. However, with the widespread overuse and misuse of antibiotics, multiple-drug-resistant pathogens give rise to pneumonia that is

difficult to treat.⁶ The mortality rate for HAP (27.7%) is greater than that of CAP and is especially high in those patients with multiple comorbidities.^{7,8}

Xu et al conducted a prospective, multi-center, double-blind, parallel, randomized controlled trial to evaluate integrated therapy consisting of Traditional Chinese Medicine (TCM) and antibiotics in elderly patients with pneumonia.⁹ Their findings indicate that TCM combination therapy is safe and effective in ameliorating expectoration and promoting the absorption of pneumonia lesions.⁹

Here, we report a HAP patient comorbid with CHF who was treated with TCM adjuvant therapy. The patient exhibited rapid, significant improvement in symptoms and image findings.

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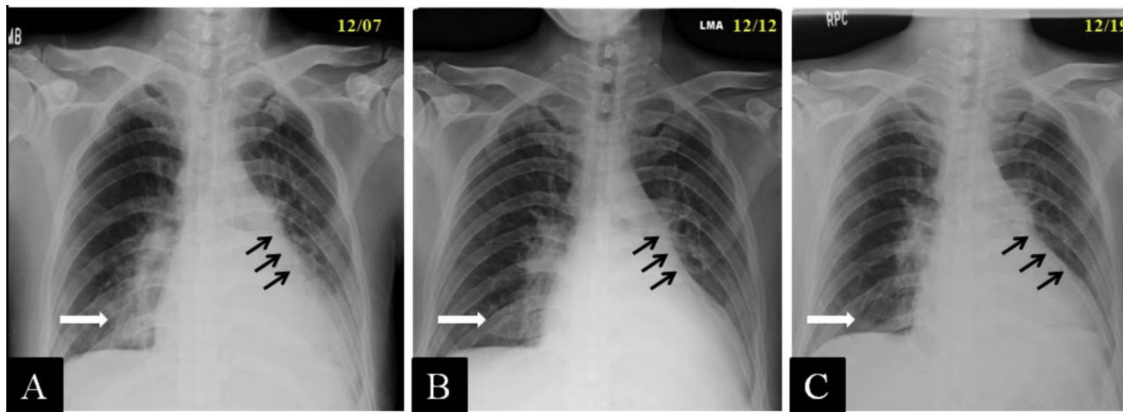


Fig. 1. Chest X-Ray before and after Traditional Chinese Medicine (TCM) treatment. (A) Pre-TCM treatment CXR on December 7: The CXR revealed peribronchial cuffing, dilated azygos vein, diffuse pulmonary consolidations with air bronchograms (white arrow) over right lower lung field accompanied by blurring of the silhouette sign of left heart border (black arrow heads). This findings indicated pneumonia over right lower lung accompanied by pulmonary edema. (B) Post-combination of TCM treatment CXR on December 12: Decreased dilatation of azygos and cardiac silhouette, with significant improvement in consolidation over right lower lung field (white arrow). The blurring of the silhouette sign over left heart border (black arrow heads) was disappeared. This findings suggested the improvement of right lower lung pneumonia patches and pulmonary edema. (C) Post-combination of TCM treatment CXR on December 19: The consolidation over right lower lung field was disappeared and the pulmonary edema was also improved.

Table 1
Ingredients and functions of traditional Chinese herbal formulas.

Chinese and Scientific Name (daily dosage)	TCM Action	Pharmacology Action
Ma Huang (3.75 g) <i>Herba Ephedrae</i>	<ul style="list-style-type: none"> • Release the exterior • Disperse wind-cold 	<ul style="list-style-type: none"> • Anti-pyretic effect • Anti-tussive effect
Shi Gao (3.75 g) <i>Gypsum Fibrosum</i>	<ul style="list-style-type: none"> • Clear excess heat from the lungs 	<ul style="list-style-type: none"> • Anti-pyretic effect
Gan Cao (3.75 g) <i>Radix Glycyrrhizae</i>	<ul style="list-style-type: none"> • Moisten the Lungs and resolves Phlegm 	<ul style="list-style-type: none"> • Anti-inflammatory effects
Huang Qin (11.25 g) <i>Radix Scutellariae</i>	<ul style="list-style-type: none"> • Clear lung-heat and removes toxin 	<ul style="list-style-type: none"> • Anti-inflammatory effects
Yu Xing Cao (18.75 g) <i>Houttuyniacordata</i>	<ul style="list-style-type: none"> • Reduce swellings and abscesses • Expel pus • Clear heat and relieves toxicity 	<ul style="list-style-type: none"> • Anti-inflammatory effects
Lianqiao (11.25 g) <i>Fructus Forsythiae</i>	<ul style="list-style-type: none"> • Clear heat and invigorates the blood 	<ul style="list-style-type: none"> • Anti-inflammatory effects • Antibacterial effects
Mu Dan Pi (11.25 g) <i>Cortex Moutan</i>	<ul style="list-style-type: none"> • Clear heat and invigorates the blood 	<ul style="list-style-type: none"> • Anti-pyretic effect • Anti-inflammatory effect • Expectorant effect
Sang Bai Pi (11.25 g) <i>Cortex Mori</i>	<ul style="list-style-type: none"> • Drain heat from the lungs • Promote urination • Clear Lung Heat and transforms hot Phlegm 	<ul style="list-style-type: none"> • Anti-inflammatory • Expectorant,
Gua Lou Shi (11.25 g) <i>Fructus Trichosanthis</i>	<ul style="list-style-type: none"> • Drain the Lungs and reduces phlegm • Circulate water and reduces edema • Promote urination • Leach out dampness 	<ul style="list-style-type: none"> • Diuretic effect • Anti-inflammatory effect • Diuretic effect
Ting Li Zi (7.5 g) <i>Semen Lepidii</i>	<ul style="list-style-type: none"> • Warm heart, kidney and spleen yang 	<ul style="list-style-type: none"> • Cardiotoxic action
Fu Ling (11.25 g) <i>Poria cocos</i>		
FuZi (3.75 g) <i>Radix Aconiti Lateralis Preparata</i>		

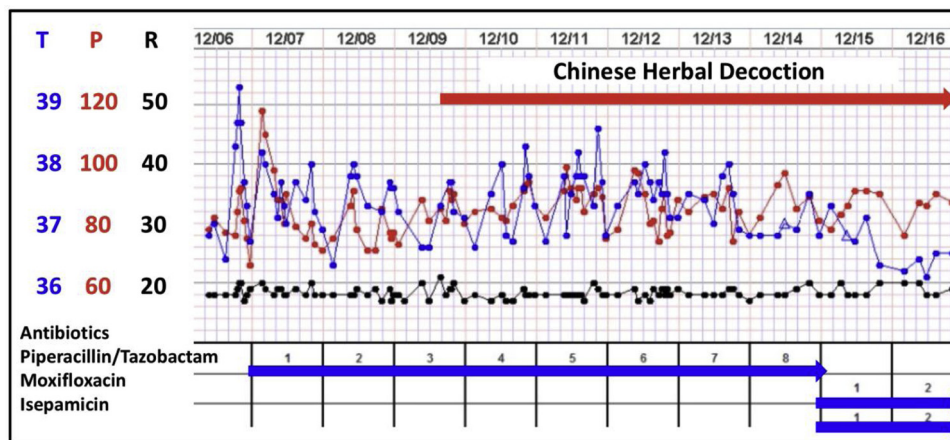


Fig. 2. Medical records of the patients, including vital signs, and the time course of TCM therapy and standard antibiotic treatment. The fever subsided on the 8th day after antibiotic treatment and the 5th day after TCM treatment. T, temperature; P, pulse; R, respiration.

2. Case presentation

2.1. Case

On December 6, 2016, a 33-year-old man presented with fever off-and-on up to 39.6 °C, chills, and cough with purulent sputum. He had been discharged from a rehabilitation ward 1–2 days before this admission. His medical history included acute myocardial infarction complicated by cardiogenic shock over the previous year, and his present left ventricular ejection fraction (LVEF) was reduced to 28%. Serial laboratory examinations showed no leukocytosis but neutrophil dominance (83.1%) and an elevated C-reactive protein (C-RP) level of 7.62 mg/dL. Sputum and blood culture analysis were performed on December 6, yielding negative findings. Thoracic radiography revealed a bilateral perihilar alveolar pattern, a dilated azygos vein, and diffuse pulmonary consolidations with air bronchograms in bilateral lower lung fields (Fig. 1). Accordingly, HAP accompanied by pulmonary edema was diagnosed. Empiric intravenous antibiotic treatment with piperacillin/tazobactam 4.5 g every 8 h was promptly initiated on December 6, 2016. Nevertheless, the patient continued to experience fever and progressive cough with purulent sputum during antibiotic treatment. He asked for TCM combination therapy, which was started on December 9, 2016 (the 3rd hospital day).

2.2. Treatment and intervention

The diagnosis according to the TCM theory was “exterior evil inward invasion” and “accumulation of phlegm and heat in the lung” in a yang-deficiency constitution. The “clearing heat and damp excreting” decoction was prescribed three times a day as shown in Table 1. After a 3-day course of treatment, the pneumonia lesions significantly improved on chest X-ray (Fig. 1). The sputum clearly decreased in volume, and the fever had completely abated by day 5 of TCM adjuvant therapy (Fig. 2). The patient’s report of cough decreased. He also felt much better and more energetic.

3. Discussion

We report a HAP patient comorbid with CHF who experienced rapid and significant improvement in symptoms and image findings following treatment with TCM adjuvant therapy. Because the bacterial cultures from sputum and blood were all negative, we believe that the anti-pyretic, anti-inflammatory, and antitussive effects of the TCM regimen acted against the persistent inflammation in this patient.

The integration of TCM and Western medicine has been shown effective for treating patients with pneumonia in a previous clinical trial and an animal study of the anti-inflammatory effects of TCM.^{9,10} Ma-Xing-Gan-Shi-Tang (MXGST) is an old TCM formula consisting of four ingredients: *HerbaEphedrae* (Ma Huang), *Semen Armeniacae* (Xing Ren), *Gypsum Fibrosum* (Shi Gao), and *Radix Glycyrrhizae* (Gan Cao).¹¹ This formula has been used to treat patient with common-cold-related fever and bronchial asthma for several centuries. In a rat model of bronchial asthma, MZGST was shown to exert anti-tussive and anti-pyretic effects through promoting airway smooth muscle relaxation and inhibiting neutrophil recruitment in the airway.¹¹ In an animal study, treatment of lipopolysaccharide-induced lung injury with MXGST resulted in decreased inflammation and a hyperpermeability reaction in lungs through regulation of the toll-like receptor 4, Src, and NF-κB pathways.¹²

In this case, we chose *HerbaEphedrae* (Ma Huang), *Gypsum Fibrosum* (Shi Gao) and *Radix Glycyrrhizae* (Gan Cao) as the major components of our mixture because of their antipyretic and anti-asthmatic effects.¹³ We added Yu Xing Cao (*Houttuyniacordata*), Huang Qin (*Radix Scutellariae*), Mu Dan Pi (*Cortex Moutan*), Sang Bai Pi (*Cortex Mori*), and Gua Lou Shi (*Fructus Trichosanthis*) to increase the antipyretic and anti-inflammatory effects. We added Ting Li Zi (*Semen Lepidii*) and Fu Ling

(*Poria Cocos*) to improve the edema status of this patient and Huang Qin (*Scutellariae Radix*) and Mu Dan Pi (*Moutan Cortex*) to ameliorate lung inflammation, based on the results of previous investigations.¹⁴ The main component of *Moutan cortex* is Paeonol, which is reported to have anti-inflammatory effect and anti-pyretic effects against lipopolysaccharide-induced acute lung injury.^{15,16} Yu Xing Cao (*Houttuyniacordata*) was chosen as a key herb for the treatment of severe acute respiratory syndrome and exhibits anti-inflammatory effects according to multiple studies.^{17,18,19} Lianqiao (*Fructus Forsythiae*) was confirmed by studies to have antibacterial, antiviral, antioxidant, and anti-inflammatory effects.²⁰ Fu Ling (*PoriaCocos*) has anti-inflammatory and diuretic effects, which are reported to improve cardiac function in CHF rats via the AVP-V2R-AQP2 axis.^{21,22} Fuzi (*Radix Aconiti Lateralis Preparata*) is proven to have cardiogenic action and reverse the dysfunction in CHF processing.^{23,24} Although the pharmacological mechanisms underlying the actions of Gua Lou Shi (*FructusTrichosanthis*), Sang Bai Pi (*Cortex Mori*), and Ting Li Zi (*Semen Lepidii*) remain unclear, their functions in dealing with phlegm retention are abundantly documented in the “Compendium of Materia Medica” (BencaoGangmu), an ancient TCM herbal text book.

The role of TCM in this case was not to act as antibiotics to kill pathogens. In fact, the patient had been treated with antibiotics and all the culture reports showed negative results. Therefore, TCM was prescribed to help patient with “clearing heat and damp excreting” and have some diuretic effects to improve pulmonary congestion. We suggest that TCM was helpful for the edema and sputum in this case for two reasons: First, after the administration of standard antibiotic therapy, the fever and the progressive cough with purulent sputum persisted. TCM was an extra intervention administered during the fever period. Second, because the bacterial cultures of sputum and blood were all negative before and after antibiotic treatment, the intermittent fever due to inflammatory reaction was highly suspicious after exclusion of other comment causes of fever, such as tumor fever and endocrine disorders. The “clearing heat and damp excreting” decoction we use was proven to have anti-inflammatory effects in a previous clinical trial and animal study. We suggest that the decreased time to fever abatement was caused by the improvement of lung inflammation after TCM adjuvant therapy.

4. Conclusion

Adjuvant therapy with a “clearing heat and damp excreting” decoction may improve HAP in a patient comorbid with CHF. These effects may be exerted through the anti-pyretic, anti-inflammatory, antitussive and diuretic effects of TCM. Further investigations are warranted to confirm the efficacy and mechanism of TCM treatments for pneumonia.

Consent

The institutional review board (IRB) of the Taichung Veterans General hospital approved this case report with a reference number CE17307A on December 5, 2017. The organized IRB operates according to the good clinical practice and applicable laws and regulations.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
2. Organization WH. *The top 10 causes of death*. 2018; 2018 [Accessed 18 June 2018]. <http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>.

3. Welfare MoHa. Taiwan's leading causes of death in 2016. 2017; 2017<https://www.mohw.gov.tw/cp-3425-33347-2.html>.
4. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128(6):3854–3862.
5. Napolitano LM. Use of severity scoring and stratification factors in clinical trials of hospital-acquired and ventilator-associated pneumonia. *Clin Infect Dis*. 2010;51(Suppl 1):S67–80.
6. Paterson IK, Hoyle A, Ochoa G, Baker-Austin C, Taylor NG. Optimising antibiotic usage to treat bacterial infections. *Sci Rep*. 2016;6:37853.
7. Efrati S, Deutsch I, Antonelli M, Hockey PM, Rozenblum R, Gurman GM. Ventilator-associated pneumonia: current status and future recommendations. *J Clin Monit Comput*. 2010;24(2):161–168.
8. Sopena N, Heras E, Casas I, et al. Risk factors for hospital-acquired pneumonia outside the intensive care unit: a case-control study. *Am J Infect Control*. 2014;42(1):38–42.
9. Xu H, Li M, Wang C, et al. Evaluation on clinical efficacy of Fuzheng Jiedu Huayu Decoction combined with antibiotics in the treatment of pneumonia in the elderly – a multi-center, double-blind, parallel, randomized controlled trial. *Complement Ther Med*. 2018;37:127–132.
10. Xiao Z, Jiang Y, Gao X, et al. Comparison of the ameliorative effects of Qingfei Tongluo formula and azithromycin on *Mycoplasma pneumoniae* pneumonia. *J Nat Med*. 2017;71(4):685–692.
11. Kao ST, Yeh TJ, Hsieh CC, Shiau HB, Yeh FT, Lin JG. The effects of Ma-Xing-Gan-Shi-Tang on respiratory resistance and airway leukocyte infiltration in asthmatic guinea pigs. *Immunopharmacol Immunotoxicol*. 2001;23(3):445–458.
12. Ma LQ, Pan CS, Yang N, et al. Posttreatment with Ma-Xing-Shi-Gan-Tang, a Chinese medicine formula, ameliorates lipopolysaccharide-induced lung microvessel hyperpermeability and inflammatory reaction in rat. *Microcirculation*. 2014;21(7):649–663.
13. Mei F, Xing XF, Tang QF, et al. Antipyretic and anti-asthmatic activities of traditional Chinese herb-pairs, Ephedra and Gypsum. *Chin J Integr Med*. 2016;22(6):445–450.
14. Shin YO, Park CH, Lee GH, Yokozawa T, Roh SS, Rhee MH. Heat-processed scutellariae radix enhances anti-inflammatory effect against lipopolysaccharide-induced acute lung injury in mice via NF- κ B signaling. *Evid Based Complement Alternat Med*. 2015:456846.
15. Fu PK, Yang CY, Tsai TH, Hsieh CL. Moutan cortex radices improves lipopolysaccharide-induced acute lung injury in rats through anti-inflammation. *Phytomedicine*. 2012;19(13):1206–1215.
16. Fu PK, Yang CY, Huang SC, et al. Evaluation of LPS-Induced acute lung injury attenuation in rats by aminothiazole-paeonol derivatives. *Molecules*. 2017;22(10).
17. Lu HM, Liang YZ, Yi LZ, Wu XJ. Anti-inflammatory effect of *Houttuynia cordata* injection. *J Ethnopharmacol*. 2006;104(1-2):245–249.
18. Lau KM, Lee KM, Koon CM, et al. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *J Ethnopharmacol*. 2008;118(1):79–85.
19. Li W, Zhou P, Zhang Y, He L. *Houttuynia cordata*, a novel and selective COX-2 inhibitor with anti-inflammatory activity. *J Ethnopharmacol*. 2011;133(2):922–927.
20. Zhou W, Qin KM, Shan JJ, et al. Improvement of intestinal absorption of forsythoside A in weeping forsythia extract by various absorption enhancers based on tight junctions. *Phytomedicine*. 2012;20(1):47–58.
21. Lee SR, Lee S, Moon E, Park HJ, Park HB, Kim KH. Bioactivity-guided isolation of anti-inflammatory triterpenoids from the sclerotia of *Poria cocos* using LPS-stimulated Raw264.7 cells. *Bioorg Chem*. 2017;70:94–99.
22. Wu ZL, Ren H, Lai WY, et al. Sclerotia of *Poria cocos* exerts its diuretic effect via suppression of renal aquaporin-2 expression in rats with chronic heart failure. *J Ethnopharmacol*. 2014;155(1):563–571.
23. Zhou G, Tang L, Zhou X, Wang T, Kou Z, Wang Z. A review on phytochemistry and pharmacological activities of the processed lateral root of *Aconitum carmichaelii* Debeaux. *J Ethnopharmacol*. 2015;160:173–193.
24. Wang L, He Y, Zhang Y, et al. Effects of active components of Fuzi and gancao compatibility on Bax, Bcl-2, and Caspase-3 in chronic heart failure rats. *Evid Based Complement Alternat Med*. 2016;2016:7686045.