Translation: Expert consensus on the application of artificial liver blood purification system in the treatment of severe and critical COVID-19

National Clinical Research Center for Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases

Abstract
The prevention and treatment of COVID-19 nationwide has entered a tackling phase. Effective treatment of severe and critically ill patients is the key to reducing the fatality of the disease. The artificial liver blood purification system can remove inflammatory factors, alleviate the damage of the inflammatory response to the body, and has important value for the treatment of severe COVID-19. Led by Academician Lanjuan Li, based on the experience of treating patients across the country, the center summarized and formulated the consensus including the basic principles, treatment indications, relative contraindications, mode selection, monitoring indicators, and efficacy evaluation of artificial liver, which provides reference for the treatment of severe COVID-19 patients.

Keywords: Coronavirus infections; Liver; artificial; COVID-19; Expert consensus

At present, the prevention and treatment of COVID-19 has entered a critical stage. Effective treatment of severe and critical patients is the key to reduce the fatality of this disease. The acute severe respiratory infectious diseases have common clinical characteristics: rapidly progressing inflammation of the lungs, severe hypoxemia and multiple organ failure. The respiratory failure, shock, multiple organ failure and uncontrollable secondary infection are the main causes of death finally. Studies have revealed that severe cases of SARS, avian influenza H5N1 and H7N9 virus infections all present a “cytokine storm”, which is the main factor of disease progression. Therefore, blocking the “cytokine storm” is a key intervention for the treatment of shock, hypoxemia and multiple organ failure. Studies have shown that the artificial liver support system (ALS) can remove inflammatory factors and block the “cytokine storm”, thus reducing damage to the body caused by the inflammatory response, which is of great value for the treatment of severe and critical patients. Clinical practices have shown that Li’s ALS has played an important role in the treatment of patients with severe H7N9 viral infection. After discussions by the expert panel, the consensus has been reached on the principles, indications, contraindications, monitoring indicators and efficacy evaluation of ALS for the treatment of severe and critical COVID-19 patients.

1. Basic principle
ALS integrates plasma replacement, adsorption, perfusion, blood/plasma filtration and other techniques, to remove inflammatory mediators, endotoxins, and small and medium molecules of toxic and harmful substances, to supplement albumin, coagulation factors and other beneficial substances, and to regulate water electrolytes, acids and bases balance. It can block “cytokine storm”, reduce pulmonary inflammation and improve respiratory function. At the same time, it can help to restore immune homeostasis, improve metabolic spectrum disorder in the body, facilitate accurate volume management, improve functions of liver, kidney and other organs, so as to increase the rescue success rate and reduce the fatality rate of severe and critical COVID-19 patients.

2. Indications
Patients should receive ALS treatment if they meet criteria (1) & (2), or only (3).

(1) The inflammatory factors (such as IL-6, etc.) are no less than 5 times the upper limit of the normal value, or the daily increase is greater than 1 times;
(2) Pulmonary imaging shows rapid progression, CT or X-rays indicate that the percentage of lung involvement progresses 10% or more per day;
(3) Patients with basic diseases that require ALS for treatment.

3. Relevant contraindications
There are no absolute contraindications for ALS during the rescue of patients with critical illnesses. But prudent use is necessary in the following situations:

(1) Patients with serious active bleeding or disseminated intravascular coagulation;
(2) Patients who have serious allergies for the blood products or drugs used in the treatment, such as plasma, heparin, protamine, etc.:
Based on the changes of monitoring indicators before and after each treatment, mainly the cytokines (IL-6, etc.) and PSI scores.

6.2 Evaluation of survival rate
Includes 28-day and 12-week survival rate.

7. Criteria for terminating treatment
If criterion (1) in combination with any of the criteria (2) to (5) is met, treatment termination could be considered, except for the condition that patients need continued treatment for basic diseases.

1 Temperature has been normal for 3 days, and respiratory symptoms improve significantly;
2 Inflammatory cytokines (such as IL-6) have dropped below 2 times the normal level for 3 days;
3 Disengaged from respiration supporting therapy;
4 Blood lactate has been below 2.0 mmol/L for 3 days;
5 Pulmonary imaging shows significant improvement for one week, and the pulmonary lesion area is absorbed by more than 30% compared with before.

It should be noted that the current ALSS expert consensus for the treatment of severe and critical COVID-19 patients are based on the empirical data from several centers in Zhejiang, Hubei, Henan and Shaanxi provinces. This consensus can be used as a treatment recommendation for implementation of effective treatment measures during the COVID-19 pandemic. We should make every effort to reduce the fatality rate of COVID-19.

Expert panel

Liang Chen, Yongping Chen, Yruemei Chen, Mingliang Cheng, Xiangchun Ding, Xiaoguang Dou, Weibo Du, Jianhe Gan, Haiyin Gao, Zhiliang Gao, Jiawei Geng, Guozhong Gong, Yuyuan Guan, Peng Hu, Yaoren Hu, Jianrong Huang, Jianming Jiang, Ying’an Jiang, Jun Li, Jiabin Li, Jianguo Li, Lanjuan Li, Yongguo Li, Peng Lin, Shourong Liu, Yingxia Liu, Qinghua Lu, Zhen Ma, Xiaorong Mao, Qinghua Meng, Liang Peng, Huaying Rao, Hong Ren, Jia Shang, Guoping Sheng, Jifang Sheng, Hongli Song, Zhijun Su, Lingling Tang, Hang Tong, Guiqiang Wang, Kai Wang, Xiaoping Wu, Qing Xie, Kaijin Xu, Xiaowei Xu, Dongliang Yang, Zujhen Ye, Liang Yu, Laozhen Zhang, Wenhong Zhang, Yuexin Zhang, Huaifen Zheng, Yimin Zhang, Caiyan Zhao, Yingren Zhao, Xin Zhong, Jiasheng Zhu, Mengfei Zhu.

Secretaries: Jianrong Huang, Mengfei Zhu, Yimin Zhang, Jiajia Chen

Reference

[1] Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China - key questions for impact assessment. N Engl J Med. 2020;382(8):692-694. DOI: 10.1056/NEJMp200929.
[2] Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136(1): 95-103. DOI: 10.1111/j.1365-2249.2004.02415.x.
[3] Hui DSC, Zumla A. Severe acute respiratory syndrome: Historical, epidemiologic, and clinical features. Infect Dis Clin North Am. 2019;33(4): 869-889. DOI: 10.1016/j.idc.2019.07.001.
[4] Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine. 2018;104: 8-13. DOI: 10.1016/j.cyto.2018.01.025.
[5] de Jong MD, Simmons CP, Thanik T, et al. Fatal outcome of
human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med*. 2006;12(10): 1203-1207. DOI: 10.1038/nm1477.

[6] Guo J, Huang F, Liu J, et al. The serum profile of hypercytokinemia factors identified in H7N9-infected patients can predict fatal outcomes. *Sci Rep*. 2015;5:10942. DOI: 10.1038/srep10942.

[7] Sadeghi M, Daniel V, Wang H, Schemmer P, Opelz G. Plasmapheresis adjusts inflammatory responses in potential kidney transplant recipients. *Transplantation*, 2013;95(8): 1021- 1029. DOI: 10.1097/TP.0b013e318286191b.

[8] Liu X, Zhang Y, Xu X, et al. Evaluation of plasma exchange and continuous veno-venous hemofiltration for the treatment of severe avian influenza A (H7N9): A cohort study. *Ther Apher Dial*. 2015;19(2):178-184. DOI: 10.1111/1744-9987.12240.

[9] Gao HN, Lu HZ, Cao B, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. *N Engl J Med*. 2013;368(24): 2277-2285. DOI: 10.1056/NEJMoa1305584.

[10] Li JJ. Artificial liver. Hangzhou: Zhejiang University Press, 2012.

[11] Xu KJ, Cai HL, Shen YH, et al. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. *J Zhejiang Univ (Med Sci)*. 2020; 49(1). DOI:10.3785/j.issn.1008-9292.2020.