Comment

Why does the sepsis induced by severe COVID-19 have different clinical features from sepsis induced by CrKP?

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I have read the present research report with great interest. This study attempted to explore the differences in sepsis caused by viral and bacterial infections by comparing the clinical features and prognosis of severe COVID-19 and carbapenem-resistant klebsiella pneumonia (CrKP). It is found that respiratory failure and immune suppression are more severe in COVID-19 cases, but systemic inflammatory responses and other systemic organ damages are less severe. Most COVID-19 sepsis is able to achieve a good prognosis. This study provides a rare opportunity for the understanding of sepsis caused by severe COVID-19. In this regard, I would like to offer my views on some of the issues raised in the study.

According to current observations, the clinical manifestations of 2019-nCoV infection and bacterial infection do differ in several points:

1. Bacterial sepsis produces severe systemic inflammation and multiple organ damage, and even septic shock in the early stage, which is the most dangerous stage of such types of sepsis. Due to the improved treatment strategies of fluid resuscitation, infection control, organ support, etc. in the past 20 years, the case fatality rate at this stage has been decreased significantly. However, many patients have not fully recovered, and about half of them enter the chronic phase, i.e. persistent inflammation, immunosuppression, and catabolism syndrome (PICS) or chronic critical illness. In the chronic stage, patients are relatively stable compared with the acute stage and can maintain a longer survival time, but they are often plagued by continuous immunosuppression, repeated infection, low-intensity inflammatory response and severe catabolic metabolism, and the mortality rate increases with the prolonged survival time.

2. In contrast to bacterial infection, 2019-nCoV does not immediately cause obvious immune inflammatory response in the early stage of invasion and can even produce an incubation period of more than 10 days. Even if respiratory impairment has occurred, the general condition of most patients is relatively stable. However, some patients continue to deteriorate, and the most serious threat occurs at the late stage. Sometimes, their condition may worsen suddenly and develop to death. So, the typical symptoms of the acute phase in bacterial sepsis are often significantly delayed in severe COVID-19 cases.

3. For bacterial sepsis, as long as the bacteria are not effectively removed (such as carbapenem-resistant klebsiella), the threat to the survival of patients will persistently exist. While following 2019-nCoV infection, although there is also lack of reliable and effective drugs to clear virus, it is not uncommon for the virus carriers to continue to relieve symptoms. Some of the manifestations of COVID-19 described above also appear in Wu's report. In combination with this report, the questions should to be answered are:

Q1: Why the most serious threats to CrKP and COVID-19 present at different stages of disease course?

I think the main reason is that Klebsiella is more antigenic than 2019-nCoV, and can easily be recognized by the immune system, which quickly makes a severe immune inflammatory response. In addition, bacteria do not need to enter cells — they can continue to proliferate outside the cells and release bacterial internal/external toxins, which act as strong pro-inflammatory substances. Whereas the weak antigenicity of 2019-nCoV arouses insufficient recognition of the immune system. Virus needs and must invade cells and be replicated within cells to cause cell necrosis, releasing large amount of virus to further induce severe immune inflammatory response. Thus,
COVID-19 appears to be different. Although immunosuppression also prevents pathogen clearance and there is no clear and effective antiviral drug for its management, it seems that as long as the patients can survive the deterioration phase, even if the virus cannot be completely cleared, a relatively good prognosis can be obtained. Whether this characteristic of 2019-nCoV infection is related to the so-called “self-limiting” ability as many other viruses is unclear and deserves further exploration. However, research reports have found that in the so-called “cured patients” of COVID-19, about 70% will be left with symptoms of mental disorders, fatigue weakness, etc., which are very similar to the PICS manifestation. The final outcome of these patients is difficult to evaluate right now. So, saying “prognosis of COVID-19 is better than CrKP” seems too early, which may be limited by the short-term observation.

We referred severe COVID-19 as sepsis caused by viral infection because it shares all the pathological and clinical features of sepsis as bacterial infection: systemic inflammatory response, immunosuppression, damage or failure of multiple systems and organs, and chronic damage in some patients. Although there is a national standard for “severe COVID-19”, it should be noted that both the government and hospitals attach great importance to 2019-nCoV infection and COVID-19. These patients are endowed with the most positive attitudes and the most perfect medical conditions that are not available to CrKP patients or other sepsis patients. This difference is bound to have a potential impact on the standard formulation, ICU admission timing, treatment methods, and prognosis between the two groups of patients. I suspect that most of true sepsis induced by COVID-19 is more likely to occur during its sustained progression or sudden deterioration other than in the early phase. Unfortunately, this study did not provide continuous data of these cases or autopsy data on deaths, which should be the most convincing evidence to distinguish the differences of sepsis induced by severe COVID-19 from by CrKP.

References

1. Hawkins RB, Raymond SI, Stortz JA, et al. Chronic critical illness and the persistence of sepsis, immunosuppression, and catabolism syndrome. Front Med. 2018;5:1511. https://doi.org/10.3389/fmed.2018.01512.
2. Mira JC, Gentile LF, Mathias BJ, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45:253–262.
3. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality. J Clin Invest. 2016;126:23–31.
4. Lan L, Xu Y, Ye G, et al. Positive RT-PCR test results in patients recovered from COVID-19. J Am Med Assoc. 2020 Feb 27;323(15):1502–1503.
5. Ling Y, Xu SR, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020;133:1039–1045.
6. Roca-Ho H, Riera M, Palau V, et al. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci. 2017;18:563. https://doi.org/10.3390/ijms18030563.
7. Guo J, Wei X, Li Q, et al. Single-cell RNA analysis on ACE2 expression provides insights into SARS-CoV-2 potential entry into the bloodstream and heart injury. J Cell Physiol. 2020;235:9884–9894. https://doi.org/10.1002/jcp.29802.
8. Jambusaria A, Hong Z, Zhang L, et al. Endothelial heterogeneity across distinct vascular beds during homeostasis and inflammation. Elife. 2020;9, e51413. https://doi.org/10.7554/eLife.51413.
9. Caidavalli A, Profiiska L. In fatal COVID-19, the immune response can control the virus but kill the patient. Proc Natl Acad Sci U S A. 2020;117:30009–30011.
10. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Netw Open. 2021;4, e210830. https://doi.org/10.1001/jamanetworkopen.2021.0830.
11. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397:220–232. https://doi.org/10.1016/S0140-6736(20)32066-4.
12. Bian XW. The COVID-19 pathology team. Autopsy of COVID-19 victims in China. Natl Sci Rev. 2020;7:1414–1418. https://doi.org/10.1093/nsr/nwaa123.
13. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020;395:1517–1520. https://doi.org/10.1016/S0140-6736(20)30920-X.
14. Lin HY. The severe COVID-19; a sepsis induced by viral infection? And its immunomodulatory therapy. Chin J Traumatol. 2020:10.1016/j.cjtte.2020.06.002.