THE LANCET

Supplementary appendix

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Supplement to: Carlet J, Payen D, Opal SM. Steroids for sepsis and ARDS: this eternal controversy remains with COVID-19. *Lancet* 2020; published online Oct 9. http://dx.doi.org/10.1016/S0140-6736(20)32132-2.

Appendix: additional comments and references

1) Covid-19 cases have a very complex presentation. They can mimic sepsis and septic shock, with moderate lung abnormalities. Others mimic ARDS, with various abnormalities in gas exchange, and with a large scale of severity. Many patients have both severe infections symptoms with organ failure and ARDS. Of note, those two syndromes are not the same. A particularity is that the symptoms of severity of or ARDS usually appear around one week after the onset of the disease, which is rather unusual in other severe infections (2)). The term “cytokines storm”, which is a naïve concept, is often used in the literature, and by the public. In the last decades, many double blind RCTs with various anti-cytokines failed to decrease mortality of those two syndromes (anti-IL6, anti-TNF alpha, IL1 RA). Therefore, we do not think that it would be wise to try again those drugs in Covid-19
2) We used in the above paragraph the term “sepsis”, just because it is a well-, known severe syndrome due to infectious agents. Many “sepsologists” push very hard and without any doubt to include Covid-19 severe cases in the sepsis syndrome. We disagree with this position. Covid-19 induces an acute activation of inflammatory mediated, but with some differences with other types of severe infections. For example, the activation of the coagulation system is very important, with arterial and venous thrombosis body-wide, and not only in the lung. Moreover, cytokines levels are far lower than in “sepsis”, for the same level of severity. The long delay between the onset of the disease and occurrence of acute symptoms of severity is another particularity.
3) Some authors pointed out that the past negative RCTs might be due, in most part, to their huge heterogeneity and the lack of inflammatory or anti-inflammatory markers allowing to select appropriate and “a la carte” drugs. However, although COVID -19 is due to a single viral pathogen, the methodology of the various studies is still very heterogenous, mixing, particularly in the Recovery trial, and the WHO meta-analysis, very different patterns and patients. In addition, secondary infections with nosocomial pathogens are very frequent in severe COVID-19 disease, making the prognosis even more complex to evaluate.
4) A large (416 patients), recent, phase II B double-blind RCT, showed no effect of CS in severe COVID-19 patients. Although this study was not a phase III one, it’s double blind design and the relatively high number of patients makes it a key information
5) We are surprised to read that on September 25th, the guidelines of the Infectious Diseases Society of America (IDSA) recommend the use of CS in severe COVID-19 cases, without any doubt or comments on the methodology of the various studies (3). The IDSA and WHO recommendation will certainly not help to convince ethical committees that additional new RCTs are needed. This kind of behavior would be very unfortunate.

Additional references

1) 6, 7, 8 references in the letter

2) Steroid controversy in sepsis and septic shock: a meta-analysis R Lefering and EA Neugebauer. Review published: 1995. No difference between treated and placebo groups

3) Adarsh Bhimraj Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19
Last updated September 25, 2020 and posted online at www.idsociety.org/COVID19guidelines.