Peer Review File

Article information: http://dx.doi.org/10.21037/atm-21-1783

Reviewer A

This is a review article on the rational use of glucocorticoids in patients with severe COVID-19 infection, in addition to reviewing the evidence so far about the time of initiation, dosage and duration of treatment with GC. The article presents content of undeniable value in the current scenario and is well written.

General Reply: We would like to send our appreciations to the reviewer for the efforts to review our manuscript. The reviewer offered valuable feedback and constructive suggestions to improve our manuscript. Responses to the comments have been made point-by-point and relevant changes have been highlighted in italic.

Some suggestions for improving the content of the article are described below:

1. Abstract: The authors believe that "early GC initiation, with a tailored dosage and appropriate tapering may be of particular importance". However, the content of the manuscript leads us to affirm that the ideal moment for starting corticosteroids and the potential benefit of tapering has not yet well established. Considering that the abstract is the "gateway" to the article, I suggest softening this statement and highlighting that there is still a lack of evidence so that precise conclusions about the benefit of these strategies may be affirmed.

Reply: Thanks for the suggestion. We recognized this particular statement took a hard stance and wasn't in the best position to reflect the content in the review. We have softened the statement.

Changes in the text: In the abstract, now the statement reads: *Early initiation of treatment, a tailored dosage with appropriate tapering may be of particular importance, but evidence is inconclusive and more investigations are needed.*

2. Methods: The authors describe general characteristics of the search strategy in the introduction. However, I suggest adding a session of methods, as recommended in the "narrative review reporting checklist", describing aspects such as: which search databases were used? Which publishing languages were included? Which publications up to what date were included? Were pre-published works included?

Reply: Thanks for the suggestion. We have added the session to the manuscript.

Changes in the text: Methods: PubMed and Web of Science were searched using the

terms “glucocorticoid”, “corticosteriod”, “steriod” and “COVID-19” in English through March 2021. Articles in English and in Chinese were included. We also included results from cited references in published articles searched by using the method described above.

3. The pathophysiological description is very well described, congratulations to the authors.
Reply: Thanks for the positive comment. We appreciate it.

4. "GCs have long been considered potent immunomodulators in many diseases, including sepsis (52)." This statement is partially correct. . The Surviving Sepsis Campaign 3 guideline suggests against the use of corticosteroids to treat septic shock in patients with adequate resuscitation with fluids and vasopressors. The use of hydrocortisone at a dose of 200 mg per day would be indicated only for refractory cases, but with a weak recommendation. I suggest rewriting that sentence to make it more suitable. See doi: 10.1097 / CCM.0000000000002255.
Reply: Thanks for the comment. Indeed, in sepsis, recommendations for systemic use of GC are not well supported. We inaccurately described GCs as potent immunomodulators when treating sepsis, which may cause confusions. We would like to emphasize the potential benefits of GC while providing a more neutral image of its effectiveness. Changes have been made in the text.
Changes in the text: Now the sentence reads: *GCs have long been considered potential immunomodulators in many inflammatory diseases. But recommendations for systemic use of GC when treating severe infections, such as sepsis, are weak and are not well supported.(56)*

5. "Physiologically, early GC administration is critical for both short and long-term morbidity and mortality in critically ill patients, as homeostatic correction could quickly turn into exhaustion (31, 72)." In reviewing the cited references, none of the studies shows that the early onset of the GC is effective in improving mortality (only associated with faster disease resolution and ICU discharge). It is not possible to make this statement about mortality in critically ill patients with COVID-19 infection according to the references cited. In addition, it is an extrapolation based on pathophysiological mechanisms. I suggest rewriting this sentence in a more appropriate way according to the references mentioned.
Reply: Thanks for the suggestion. We apologize for the inappropriate description about GC’s impacts on morbidity and mortality in the manuscript. Bases on the references, we have revised this sentence.
Changes in the text: Now the sentence reads: *Physiologically, early GC*

administration may be critical to decrease the acute and long-term negative impact on critically ill patients, as homeostatic correction could quickly turn into exhaustion.(31.73)

6. Statements throughout the manuscript differ from those in the conclusion and abstract: "For the moment, clinicians should decide on a case-by-case basis as in clear evidence has indicated the best possible initiation time for treatment". I suggest reviewing the conclusions of the manuscript.

Reply: Thanks for the advice. We believe this statement is consistent with what has been discussed in this review. Although we do have mentioned an early initiation time is particularly worth being investigated based on previous trials related to ARDS, the best initiation time for treatment in patients with severe COVID-19 is still unclear. The reason why we put this statement is that we would like to emphasize that as no clear evidence has indicated the best possible initiation time for treatment, it's more appropriate for clinicians to realize the importance of individualized decisions and seek for best outcomes as more trials are being done.

7. "Another regimen comprised the administration of pulse dosages for a short time period; an MP pulse (intravenous injection, 250 mg/day for 3 days) generated a significantly increased survival time in patients with severe COVID-19 (65)." Be careful with that statement. The authors should argue that this study included a very small number of participants (34 patients in each group) and that ARDS was considered an exclusion criterion!!!! The conclusions of this work do not apply to the vast majority of patients seen in clinical practice with COVID-19 infection, and should not be erroneously extrapolated, creating risks with treatments that have not been widely tested.

Reply: Thanks for the suggestion. We agree that the conclusions of the study focusing on pulse dosages do not apply to the vast majority of patients seen in clinical practice with severe COVID-19 infection, as ARDS was excluded, and should not be erroneously extrapolated. We have added statements to better interpret the study result.

Changes in the text: Now the sentences reads: *Another regimen comprised the administration of pulse dosages for a short time period; an MP pulse (intravenous injection, 250 mg/day for 3 days) generated a significantly increased survival time in patients with severe COVID-19. But the impact of this study is limited as a very small number of participants (34 patients in each group) were included and that ARDS was considered an exclusion criterion, thus offering poor values when treating patients with severe COVID-19 infections. (66)*

8. A recently published study performing a direct comparison between two GCs (dexamethasone vs methylprednisolone) was not included in the study. I suggest discussing (Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, Erfani A, Khodamoradi Z, Gholampoor Saadi MH. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis. 2021 Apr 10; 21 (1): 337. doi: 10.1186 / s12879-021-06045-3)
Reply: Thanks for the suggestion. This review focuses on the timing, duration and dosage of GCs when treating patients with severe COVID-19. Therefore, the type of GC is not included in the scope of discussion. We do recognize that the type of GC may affect the outcome, and more investigations are necessary. However, when we were drafting the manuscript, we believed that as medications could be limited in many places during the pandemic, compared with the timing, duration and dosage, the type of GC was not as important as it would usually be.
The article suggested here (doi: 10.1186 / s12879-021-06045-3) offers great insight into the type of GC. The author concluded that in hospitalized hypoxic COVID-19 patients, MP(2 mg/kg/day) demonstrated better results compared to DX(6mg/day). However, the stidy only included patients with SpO2<92% on room air, somehow inconsistent with the population we intend to draw attention to. (P/F ratio wasn't reported and according to the updated WHO guildline, severe cases are defined by SpO2<90% on room air). More importantly, after further reference search, a recent systemic review concluded that the use of corticosteroids probably reduces mortality in patients with ARDS and this effect was consistent between corticosteroid types. (*Chaudhuri, D., Sasaki, K., Karkar, A. et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med 47, 521–537 (2021). https://doi.org/10.1007/s00134-021-06394-2*).

9. Throughout the text, the authors explored the positive aspects of using GC. However, we should also paid attention to the adverse effects of acute and prolonged use of GC. I suggest adding a session with the potential risks involved in the administration of these drugs, considering the different treatment choices mentioned (pulse dosages, prolonged use with risk of suppression of the adrenal pituitary axis, hyperglycemia, hypertension, etc.). See https://doi.org/10.1186/s13098-020-00583-7
Reply: Thanks for your advice. We have added a session discussing potential risks.
Changes in the text: We have added a paragraph: *At the same time, potential severe adverse effects associated with GCs need to be considered and cost-benefit analysis should be made when substantial uncertainty occurs. Traditionally, long-term use of GC is associated with various complications, such as infections, diabetes and osteoporosis, psychiatric disorders, and adrenal crisis(85, 86). High-dose GCs is*

related to many metabolic disorders, such as hypokalemia and intravenous pulse GCs have been associated with hypotension, electrolyte disorders, anaphylactic shock, and abnormal behavior.(87) For patients with severe COVID-19, one systemic review including 6 trials concluded that there was no suggestion that the risk of serious adverse events was higher in patients treated with GCs except for the 2 smallest trials(69). A further systemic review published recently draw the conclusion that there were unclear differences in rates of neuromuscular weakness and gastrointestinal bleeding with GCs. Increase in superinfection was not observed. But there was probably an increase in hyperglycemia(88).

Congratulations to the authors, excellent work.

Reviewer B

Your team carried out a clinical practice revision of the use of glucocorticoids in severe COVID-19. I find the review contains rather interesting issues about the immune mechanism of using this drug in COVID-19. The authors also try to focus their manuscript to reach a broader audience of physicians.

I would recommend including a brief, but not minor issue: Why dexamethasone might be superior to other glucocorticoids in COVID-19? DXT has been the only glucocorticoid with consistent results in RCTs – other types have failed, such as methyl-prednisolone or hydrocortisone.

Reply: Thanks for the suggestion. This review focuses on the timing, duration and dosage of GCs when treating patients with severe COVID-19 infection. Therefore, the type of GC is not included in the scope of discussion. We do recognize that the type of GC may affect the outcome, and more investigations are necessary. However, when we were drafting the manuscript, we believed that as medications could be limited in many places during the pandemic, compared with the timing, duration and dosage, the type of GC was not as important as it would usually be. More importantly, after further reference search, a recent systemic review concluded that the use of corticosteroids probably reduces mortality in patients with ARDS and this effect was consistent between corticosteroid types. (*Chaudhuri, D., Sasaki, K., Karkar, A. et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med 47, 521–537 (2021). https://doi.org/10.1007/s00134-021-06394-2*).