Peer Review File

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Reviewer A

Comment 1: Line 89 “Therefore, CPGs for the treatment of children with COVID-19 are urgently needed” In my opinion, what it is urgently need are more well designed clinical trials performed in children, as all the clinical guidelines for treating diseases must be based in the evidence provided in clinical trials. I would recommend changing this sentence. In addition, I would recommend to comment the lack of clinical trials performed in children with COVID, as most clinical trials have focused on adult patients. Nowadays only 8% of the available results from completed interventional clinical trials included pediatric populations (you can confirm this in the website https://clinicaltrials.gov/ , searching “Completed, Suspended, Terminated, Withdrawn Studies | Interventional Studies | COVID-19 |” and looking for the search results in pediatric and adult populations). Elaborating a useful therapeutic clinical guide, in the absence of evidence based on clinical trials, is a practically impossible task. This must be highlightened in the introduction and in the discussion section.

Reply 1: Thanks for your suggestion. (1) We agree that the phrase "urgently needed" may be not appropriate, so we replaced "urgently needed" with "required". (2) We also agree that it is necessary to emphasize that the clinical trials for children with COVID-19 are rare. Therefore, we highlighted it in the introduction and discussion section. (3) Reply to the comment “Elaborating a useful therapeutic clinical guide, in the absence of evidence based on clinical trials, is a practically impossible task. This must be highlighted in the introduction and in the discussion section. ”: The quality of a guildeline is not depended on the amount and quality of supporting evidence, but rigorous development process (eg. disclosure of guideline funding sources, conflicts of interest are well declared and managed, use of a systematic review of evidence, etc). If the developing process is rigorous, the guideline can be high-quality and useful even lack high-quality evidence. (Reference: Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. JAMA. 2013;309:139-40.).

Changes in the text: We have modified the sentence as advised (see Page 6, line 106). We have added the sentences as advised (see Page 5, line 100-101; Page 16, line 332-333).

Comment 2: The evidence regarding the use of different drugs have been changing throughout the pandemic, as the results of different clinical trials appeared. Most of the revised guidelines (15/20) were published before May 2020. May be the article could improve if a subanalysis of the last 5 guidelines is offered (the ones published after July), comparing them with the recommendations offered by the guidelines published before May.

Reply 2: Thanks for your suggestion. Initially, we compared quality of the guidelines published before and after May. However, some experts thought it is not appropriate to stratify the guidelines according to this time point if we were unable to provide reason why we choose May instead of other time point as cutoff value. Therefore, we analyzed the impact of time on the guidelines through line graph. We found the quality of the included guidelines increased over time generally (Supplementary appendix 6).

Changes in the text: We have analyzed the impact of time on the guideline quality (see Page 11, line 223-224; see Page 12, line 240-241).

Comment 3: Only one guideline offers moderate quality. Please, specified which this guideline is, and it AGREE score. Only one guideline (5%) was classified as a high reporting rate. Which one? Is it the same one which had a moderate quality?

Reply 3: Thanks for your suggestion. The guideline developed by Children's Hospital of Chongqing Medical University（"Rapid advice guidelines for management of children with COVID-19", View at: http://dx.doi.org/10.21037/atm-20-3754）had the moderate methodological quality (AGREE Ⅱ score: 62%) and the high reporting rate (RIGHT reporting rate: 89%) . Because the working group developed this guideline using the methods and process proposed by the WHO and GRADE working group. All recommendations in this guideline is based on systematic reviews.

Changes in the text: We have specified the guideline in the text as advised (see Page

11, line 213-215, 228-229).

Comment 4: The results' section "Consistency of recommendations" is too long, as many of the interesting data are reported in the attached tables. I suggest reducing this section text.

Reply 4: Thanks for your suggestion. We have revised the section "Consistency of recommendations" to make it more concise.

Changes in the text: We have deleted the following sentences (The following page numbers and line numbers are from original manuscript instead of revised manuscript):

Page 11, line 211-214: As for the dosage of remdesivir, three guidelines recommended 5 mg/kg intravenous (IV) loading dose on day 1, followed by 2.5 mg/kg IV every 24h for children weighing <40 kg; 200 mg IV loading dose on day 1, followed by 100 mg IV every 24h for children weighing >40 kg.

Page 11, line 219: The median number of references cited by these guidelines was 0.5 (range: 0-13).

Page 11, line 226-227: The recommended usage for IFN-α nebulization is 200,000-400,000 IU/kg or 2-4 μg/kg, twice a day.

Page 12, line 230-231: The median number of references cited by these guidelines was 1 (range: 0-21).

Page 12, line 243-244: Among the guidelines recommending glucocorticoid.

Page 12, line 245; Page 13, line 246: One guideline against the use of glucocorticoid cited a systematic review (SR).

Page 13, line 247: The median number of references cited by these guidelines is 1 (range: 0-39).

Page 13, line 262-263: The median number of references cited by these guidelines is 0 (range: 0-9).

Comment 5: Regarding glucocorticoids, I will clarified that the different guidelines proposed different doses and type of corticoids, and that there is now clear the proper regimen (dose/length).

Reply 5: Thanks for your suggestion. We have revised “seven guidelines recommended the use of low-dose glucocorticoid in a short course for severe or critical patients. One guideline recommended high dose glucocorticoids for the critical case with life-threatening complications” as "Doses and types of glucocorticoid varied in different guidelines”.

Changes in the text: We have revised the sentence in the text as advised (see Page 13, line 272-273).

Comment 6: In methods, line 162, the authors said “We compared …..antibiotics, noninvasive ventilation, convalescent plasma therapy, blood purification, extracorporeal membrane oxygenation (ECMO) therapy, and psychotherapy”. Then, in the discussion, the author said “Recommendations were consistent in blood purification therapy, ECMO therapy, and psychotherapy” However, the authors did not mention in the result section their analysis of these therapies. Although data are presented in Figure 5, I would recommend to add a sentence in the result section, guiding the readers to this Figure 5.

Reply 6: Thanks for your suggestion. We have added related content in the result section.

Changes in the text: We have added the sentence in the text as advised (see Page 15-16, line 317-325).

Comment 7: LINE 285 “Recommendations were consistent in blood purification therapy, ECMO therapy, and psychotherapy” …As the authors explained in Figure 5, few guidelines mention convalescents´ plasma (1), blood purification therapy (2), or ECMO (4) for example. I would not conclude that recommendations are consistent. In my opinion, there is a lack of recommendations for many of these therapies in the analyzed guidelines, thus I would not say that recommendations are consistent, and I would highlight the lack of available evidence regarding other type of therapies… although the few available guidelines agree in their indications.

Reply 7: Thanks for your suggestion. We have revised the sentence "Recommendations

were consistent in blood purification therapy, ECMO therapy, and psychotherapy, while varied greatly in the use of antiviral drugs, glucocorticoid, and IVIG" as "Recommendations varied greatly in the use of antiviral drugs, glucocorticoid, and IVIG. There is a lack of recommendations for the use of biologics, antiplatelet and anticoagulation drugs, non-invasive ventilation, psychotherapy, convalescent plasma therapy, blood purification, and ECMO therapy."

Changes in the text: We have revised the sentences in the text as advised (see Page 16, line 329-332).

Comment 8: Regarding Remdesivir, no guidelines reported the timing of initiating remdesivir therapy. I suggest to discuss that remdesivir is an antiviral agent, and it efficacy may depend on the timing of it use, with low efficacy when it is prescribed in advance diseases, with low viral load. Until the date, few clinical trials in adults, and none in children, have administered in the first 5 days of symptoms, when the viral load is high.

Reply 8: Thanks for your suggestion. We have discussed the impact of the timing of initiating remdesivir on its efficacy.

Changes in the text: We have revised the sentences in the text as advised (see Page 17, line 342-347).

Comment 9: Line 293 “The use of remdesivir can cause adverse effects such as transaminase elevations (41)” I would clarify that no data of toxicity is nowadays available in children.

Reply 9: Thanks for your suggestion. We have deleted the sentence.

Changes in the text: We have deleted the sentence in the text as advised.

Comment 10: Line 300 “No clinical studies have demonstrated that interferon is effective in treating children with COVID-19”. But in adults? Please add a summary of adults’ evidence.

Reply 10: Thanks for your suggestion. We have summarized the adults’ evidence.

Changes in the text: We have added the content in the text as advised (see Page 17, line 354-357).

Comment 11: Line 303: The authors said: "SARS-CoV-2 enters into airway epithelial cells by binding angiotensin-converting enzyme 2 (ACE2). Interferon -α drives ACE2 expression. High interferon may promote cellular entry and SARS-CoV-2 infection" This statement is a little bit speculative, not based on clinical trials or solid evidence. In my opinion, it would be better to delete this sentence.

Reply 11: Thanks for your suggestion. We have deleted the sentences.

Changes in the text: We have deleted the sentences in the text as advised.

Comment 12: Line 308 Corticosteroids. In adult populations, it use has clearly demonstrated benefits, especially in late and moderate/severe diseases with high inflammatory parameters. I recommend referring the article Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324:1330-1341.

Reply 12: Thanks for your suggestion. We have added the content and cited the reference.

Changes in the text: We have added the content in the text as advised (see Page 18, line 366-370).

Comment 13: LINE 319 "There was wide variability in recommendations on the use of IVIG". IVIG are not routinely used in children with acute SARS-COV-2 infection. I would recommend the discussion on the utility of IVIG in children with MIS-C, as it is its main indication.

Reply 13: Thanks for your suggestion. We have revised the paragraph and discussed mainly on on the utility of IVIG in children with MIS-C.

Changes in the text: We have revised the content in the text as advised (see Page 18, line 376-385).

Comment 14: In general, as there is lack of evidence for the different drugs in children, I suggest that the authors make a short summary in the discussion section of the most recent quality evidence published in adults for remdesivir, corticosteroids, biological agents and intereferon.

Reply 14: Thanks for your suggestion. We have summarized the evidence published in adults for remdesivir, corticosteroids, biological agents and intereferon, and cited the references as advised.

Changes in the text: We have revised the content in the text as advised (see Page 15-16, line 341-342; Page 17, line 353-357; Page 18, line 366-370; Page 19, line 386-396).

Reviewer B

Comment 1: Please consider adding a brief description about the items included in the treatment recommendations (page 8, line 159).

Reply 1: Thanks for your comments. We have described the items included in the treatment recommendations.

Changes in the text: We have added the content as advised. (see Page 9, line 187-189).

Comment 2: Please include a description of results for respiratory support and others.

Reply 2: Thanks for your suggestions. We have added related content in the result section.

Changes in the text: We have added the sentence in the text as advised (see Page 15-16, line 317-325).

Comment 3: Consider adding discussion about respiratory support and others since there seems to be more consistency in recommendations with regards to respiratory therapy and others.

Reply 3: Thanks for your suggestions. There is a lack of evidence for respiratory support and other therapies. Highlighting the lack of available evidence rather the recommendation consistency may be more appropriate. Therefore, we emphased the

lack of evidence in these fields and the necessity of further researches in the discussion section.

Changes in the text: We have added the contents (Page 16, line 330-332).

Comment 4: Consider including discussion/possible limitation about how this field is evolving and more data may be published by the time the article reaches the readers, since this review included articles only until August 2020.

Reply 4: Thanks for your suggestion. We add the limitation in the text.

Changes in the text: We have added the content in the text as advised. (Page 20, line 410-411).