PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee
AUTHORS	Fernández-Sarmiento, Jaime De Souza, Daniela Jabornisky, Roberto Gonzalez , Gustavo Ariel Arias López, Maria del Pilar Palacio , Gladys

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Kevin G. Friedman Institution and Country: Boston Childrens Hosp, 300 Longwood Av, United States Competing interests: None
REVIEW RETURNED	22-Oct-2020

GENERAL COMMENTS	The concept of adapting the previously published American College of Rheumatology and UK guidelines for PIMS to low and middle income settings is an important endeavor and should be supported. The manuscript would be strengthened by focusing on specific issues in PIMS diagnosis, treatment and monitoring that are relevant to low and middle-income countries; doing so would distinguish this document from the several previously published more comprehensive reviews of the literature and diagnosis and treatment guidelines. 1). The abstract comment that PIMS is very similar to KD is not entirely accurate. There are key differences from KD (age distribution, ethnicity, lab values, clinical manifestations). It would be more accurate to say that PIMS and KD can overlap in terms of presenting symptoms and in some cases in lab and cardiac findings. 2). the number presented at the end of paragraph 2 in the intro need to be more precise: - 80-90% of cases are asymptomatic - is this in children - if so what age range? - 4-10% may need transfer to PICU.... presumably this is of hospitalized COVid pts - the CAKE study mortalityof 5% and 76% with pneumonia is presumably of patients admitted to PICUs All of these statements need to be made more precise in terms of what population of patients is being referred to, in order to avoid confusion 3). The study inclusion/exclusion criteria are not fully described and seem arbitrary. The largest study to date from the CDC with over 600 pts is not included in this review. There are several

	published reviews on PIMS. What does this review of the literature offer that distinguishes it from the prior publications? My suggestion would be to focus on the issues in diagnosis, treatment, and long-term follow-up that are unique to low and middle income countries in more detail. 4). The discussion of RT-PCR is confusing. Most of the case series published to date have reported that the majority(60-75%) of PIMS pts are PCR negative and that the majority are antibody positive. it would be more useful if the author's described the overall scope of the studies reviewed rather than just the Perez-Toledo study when addressing this topic. 5). It is unclear to why the author's are calling PIMS a SARS-CoV-2 induced sepsis as the majority of the evidence indicates that PIMS is a immune-reponse mediated hyperinflammatory condition and predominantly not a direct viral sepsis... as evidenced by the timing 3-6 weeks post acute COVID and the fact that most PIMS pts are not PCR positive. 6). Although there is overlap between severe acute COVID-19 and PIMS, it is important for the author's to not use these terms interchangably as they are separate conditions. 7). PIMS -TS is NOT viral sepsis -as above.

REVIEWER	Reviewer name: Dr. Suma Balan Institution and Country: Not applicable Competing interests: None
REVIEW RETURNED	06-Nov-2020

GENERAL COMMENTS	While this is a comprehensive review, I sense that the authors have not adequately differentiated Acute COVID 19 infection from MISC/PIMS-TS There is a mention of this being a viral sepsis- the pathophysiology of this condition however is immune dysregulation as a later consequence of COVID 19 infection. Especially since 70-80% of patients across various series are actually negative for COVID antigen/ RTPCR. Similarly the recommendation to cluster patients together to prevent infection is only applicable for the infective patients. A little more detail on type of steroids with doses would be helpful Biologicals in nations who cannot access IL-1 inhibitors A word on followup and long term complications.

VERSION 1 – AUTHOR RESPONSE

Thank you for all the comments. They have been very useful in enriching this paper, especially given its main objective which is to serve as a guide for healthcare personnel working in countries with limited resources. We have engaged in an intense correction job and have made all the adjustments suggested by the reviewers.

Reviewer: 1

Comments to the Author:
The concept of adapting the previously published American College of Rheumatology and UK guidelines for PIMS to low and middle income settings is an important endeavor and should be supported. The manuscript would be strengthened by focusing on specific issues in PIMS diagnosis, treatment and monitoring that are relevant to low and middle-income countries; doing so would distinguish this document from the several previously published more comprehensive reviews of the literature and diagnosis and treatment guidelines.

Answer: Thank you very much for this comment. We also believe that it is valuable to adapt these recommendations to low and middle-income countries. We made revisions throughout the text highlighting the importance of making adjustments for these countries. These are highlighted in red. A subtitle was added following another reviewer's suggestion, addressing PIMS-ST management guidelines for middle and low-income countries.

1). The abstract comment that PIMS is very similar to KD is not entirely accurate. There are key differences from KD (age distribution, ethnicity, lab values, clinical manifestations). It would be more accurate to say that PIMS and KD can overlap in terms of presenting symptoms and in some cases in lab and cardiac findings.

Answer: Thank you very much for the suggestion. We have made these adjustments in the abstract.

2). the number presented at the end of paragraph 2 in the intro need to be more precise:
- 80-90% of cases are asymptomatic - is this in children - if so what age range?
- 4-10% may need transfer to PICU.... presumably this is of hospitalized COVid pts
- the CAKE study mortalityof 5% and 76% with pneumonia is presumably of patients admitted to PICUs
All of these statements need to be made more precise in terms of what population of patients is being referred to, in order to avoid confusion

Answer: Thank you very much for the suggestion. We adjusted the text to make these numbers clearer on page 3 in the manuscript.

3). The study inclusion/exclusion criteria are not fully described and seem arbitrary. The largest study to date from the CDC with over 600 pts is not included in this review. There are several published reviews on PIMS. What does this review of the literature offer that distinguishes it from the prior publications? My suggestion would be to focus on the issues in diagnosis, treatment, and long-term follow-up that are unique to low and middle income countries in more detail.

Answer: The inclusion and exclusion criteria were adjusted. Data from the CDC were included in Table 1 and Table 2, clarifying that they may overlap with those published by Dufort and Feldstein in NEJM. The differential factor in our paper compared to others which have already been published is that we adapted the American College of Rheumatology recommendations and UK guidelines for PIMS for high-income countries. In addition, our aim with this is for the disease to be suspected and diagnosed, and for studies describing its characteristics to be published in countries with limited resources.
Under diagnostic strategies, we highlight the tools available in middle and low-income countries. Also, in the therapeutic focus, we begin by describing early recognition, the bundle and the general approach before suggesting a specific management. We believe that, with this focus, readers in these countries will keep these aspects (which are not always implemented) in mind, and will therefore have a more comprehensive view of this disease.

4). The discussion of RT-PCR is confusing. Most of the case series published to date have reported that the majority(60-75%) of PIMS pts are PCR negative and that the majority are antibody positive. it would be more useful if the author's described the overall scope of the studies reviewed rather than just the Perez-Toledo study when addressing this topic.

Answer: This paragraph was modified to make it a bit clearer. The Pérez-Toledo article is discussed to illustrate the response of other immunoglobulins.

5). It is unclear to why the author's are calling PIMS a SARS-CoV-2 induced sepsis as the majority of the evidence indicates that PIMS is a immune-reponse mediated hyperinflammatory condition and predominantly not a direct viral sepsis... as evidenced by the timing 3-6 weeks post acute COVID and the fact that most PIMS pts are not PCR positive.

Answer: On page 12, a clarification is provided on this topic. Especially in middle and low-income countries, we want to suggest the use of an organized approach strategy like the one used with the bundles for other diseases such as sepsis. The paragraph suggesting that it is a viral sepsis was modified because we agree that it is a hyperinflammatory immune-mediated response. This was clarified in this paragraph.

6). Although there is overlap between severe acute COVID-19 and PIMS, it is important for the author's to not use these terms interchangably as they are separate conditions.

Answer: This suggestion was corrected in the text. Thank you very much.

7). PIMS -TS is NOT viral sepsis -as above.

Answer: We agree. We made the corrections in the manuscript paragraphs that could suggest that it is. Thank you very much.

Reviewer: 2

Comments to the Author
While this is a comprehensive review, I sense that the authors have not adequately differentiated Acute COVID 19 infection from MISC/PIMS-TS. There is a mention of this being a viral sepsis- the pathophysiology of this condition however is immune dysregulation as a later consequence of COVID 19 infection. Especially since 70-80% of patients across various series are actually negative for COVID antigen/ RTPCR.

Answer: This was corrected in the sections of the text where the message was unclear, and acute COVID-19 infection was differentiated from PIMS-TS.

Similarly the recommendation to cluster patients together to prevent infection is only applicable for the infective patients.

Answer: Correct. We made adjustments where the message was unclear.

A little more detail on type of steroids with doses would be helpful

Answer: Adjustments were made on page 14.

Biologicals in nations who cannot access IL-1 inhibitors

Answer: this suggestion was added, clarifying that studies are needed.

A word on followup and long term complications.

Answer: Adjustments were made on page 15.

Editor in Chief
Comments to the Author:
1. Please note the comments of reviewer 1 about providing a perspective for low and middle income countries.

Answer: We made adjustments throughout the paper in this regard, highlighting the importance of identifying the disease in countries with limited resources.

2. Title add "a narrative review and" before "The viewpoint..."

Answer: This was added to the title.

3.What this study adds Delete the first sentence.

Answer: We deleted it.

4.It is not a finding Introduction 1st sentence delete " for the first time in history"

Answer: We deleted it.

5.Methods state your inclusion and exclusion criteria more clearly.

Answer: The inclusion and exclusion criteria were explained more fully.

6. Results needs expansion. You need to describe the key studies and their findings. Some of the text in the discussion should be in Results.

Answer: the results section was modified, describing the most important studies on the topic.

7. Combine Tables 1 and 2 as they describe the same studies (ref 49 missing from Table 2).

Answer: although these tables describe the same articles, please note that they each describe different aspects, and the authors believe these tables can be complementary. Also, due to their length, we left Table 2 as “supplementary material” and the missing Reference 49 was completed. At the discretion of the Editor in Chief, it could be included in the manuscript.

8. Add a new subheading Guidance for low and middle income countries
Answer: This subheading was added.

9. Clarfiy if the guidance is your work or that of the ACCM (page 13)
Answer: we clarify that it is the adaptation of the ACCM guidelines.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Kevin G. Friedman Institution and Country: Boston Childrens Hosp, 300 Longwood Av, United States Competing interests: None
REVIEW RETURNED	02-Dec-2020

GENERAL COMMENTS	The revisions have strengthened the manuscript.