OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

International Journal of Infection
Article DOI: 10.5812/iji.108984
Published in: International Journal of Infection: 8(2); e108984

Peer Review Report for "Combination Drug Therapy in COVID-19: Are We Using Sound Science in the Management of These Patients?"

Author(s): Joscilin Mathew, Suresh J. Antony

Review Timeline:

Submit Date: 31 Aug 2020
Revised Date: 29 Dec 2020
Accepted Date: 24 Jan 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 20 Oct 2020

Dear AE,
I have read the manuscript entitled “Combination drug therapy in COVID-19: Are we using sound science in the management of these patients?”. In this retrospective case study, the efficacy of combination therapy for SARS-CoV-2 in decreasing the need for mechanical ventilation was examined.
- This article is a very good topic in the field of COVID-19 infection and provides valuable information on how to treat the infection. This article provides interesting references that provide good tips. Given the importance of this infection in the world, it is necessary to make more effective follow-up on the treatment methods of COVID-19. Although the number of participants in this study was small, its achievements are significant. It is recommended that the article be accepted in the journal after minor changes. The English language of the manuscript is sufficient. But the author needs to make some changes to improve the quality of the article. In my opinion, it is better the authors follow the below points.
1. All abbreviations should be defined when they are used for the first time.
2. Keywords should be selected from MeSH Headings, not MeSH entries. You can find the appropriate keywords on "Mesh Browser" at "https://meshb.nlm.nih.gov/search".
3. Use the same pattern to write the article. The author should pay attention to the main format of the journal.

4. In the abstract, the results and conclusion need more details.
5. The final conclusion still needs correction. The most important details of the study should be mentioned.
Kindest Regards

REFEREE: Associate Editor | **Revision (0)** 30 Nov 2020

Dear EIC,
I have read the manuscript entitled “Combination drug therapy in COVID-19: Are we using sound science in the management of these patients?”. In this retrospective case study, the efficacy of combination therapy for SARS-CoV-2 in decreasing the need for mechanical ventilation was examined.
This article is a very good topic in the field of COVID-19 infection and provides valuable information on how to treat the infection. This article provides interesting references that provide good tips. Given the importance of this infection in the world, it is necessary to make more effective follow-up on the treatment methods of COVID-19. Although the number of participants in this study was small, its achievements are significant. It is recommended that the article be accepted in the journal after minor changes. The English language of the manuscript is sufficient. But the author needs to make some changes to improve the quality of the article. In my opinion, it is better the authors follow the below points.
1. All abbreviations should be defined when they are used for the first time.
2. Keywords should be selected from MeSH Headings, not MeSH entries. You can find the appropriate keywords on "Mesh Browser" at "https://meshb.nlm.nih.gov/search".
3. Use the same pattern to write the article. The author should pay attention to the main format of the journal.
4. In the abstract, the results and conclusion need more details.
5. The final conclusion still needs correction. The most important details of the study should be mentioned.
Kindest Regards

Hamidreza Kouhpayeh: EIC | **Revision (0)** 7 Dec 2020

Dear Authors,
I have read the manuscript entitled “Combination drug therapy in COVID-19: Are we using sound science in the management of these patients?”. In this retrospective case study, the efficacy of combination therapy for SARS-CoV-2 in decreasing the need for mechanical ventilation was examined.
This article is a very good topic in the field of COVID-19 infection and provides valuable information on how to treat the infection. This article provides interesting references that provide good tips. Given the importance of this infection in the world, it is necessary to make more effective follow-up on the treatment methods of COVID-19. Although the number of participants in this study was small, its achievements are significant. It is recommended that the article be accepted in the journal after minor changes. The English language of the manuscript is sufficient. But the author needs to make some changes to improve the quality of the article. In my opinion, it is better the authors follow the below points.
1. All abbreviations should be defined when they are used for the first time.
2. Keywords should be selected from MeSH Headings, not MeSH entries. You can find the

appropriate keywords on "Mesh Browser" at "https://meshb.nlm.nih.gov/search".

3. Use the same pattern to write the article. The author should pay attention to the main format of the journal.

4. In the abstract, the results and conclusion need more details.

5. The final conclusion still needs correction. The most important details of the study should be mentioned.

Kindest Regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Manuscript revisions

Q1. All abbreviations should be defined when they are used for the first time.

R. All abbreviations have been expanded and changes have been highlighted in the manuscript.

Q2. Keywords should be selected from MeSH Headings, not MeSH entries. You can find the appropriate keywords on "Mesh Browser" at "https://meshb.nlm.nih.gov/search".

R. Keywords were selected from "*https://meshb.nlm.nih.gov/search*" database and modified to prompted MeSH headings. New keywords are:

- COVID-19
- Antibodies, Monoclonal, Humanized
- antiviral agents
- adenosine monophosphate
- coronavirus infections
- pandemics
- steroids
- drug therapy, combinations
- drug combinations
- antibodies, viral

Q3. Use the same pattern to write the article. The author should pay attention to the main format of the journal.

R. Rectified

Q4. In abstract, the results and conclusion need more details.

R. The added details have been highlighted below. Currently the word count is 351 (limit is 250-350).

BACKGROUND:
Multiple case reports have shown promising results with Remdesivir, Tocilizumab and convalescent plasma. We evaluated the efficacy and safety of combination therapy with Remdesivir, Tocilizumab, steroids, antibiotics and convalescent plasma in COVID-19 patients.

OBJECTIVE:
To assess whether a multi-pronged approach to tackling SARS-CoV-2 had an impact on our primary end goal of decreasing the need for mechanical ventilation and identify some of the complexities involved with combination treatment regimens.

METHODS:
In this retrospective, single center study, six confirmed SARS-CoV-2 patients with similar demographics and comorbidities treated with a combination of Remdesivir, Tocilizumab, antibiotics, steroids and convalescent plasma were followed.

RESULTS:
At the time of initiation of treatment, all six patients were requiring at least 3 liters of supplemental oxygenation via nasal cannula. All patients received Remdesivir for 5-10 days, Tocilizumab for a total of 4 doses each across 2 days, methylprednisone and antibiotics. Commonly used antibiotics were Cefepime, Azithromycin, Ceftriaxone and Piperacillin/Tazobactam. Convalescent plasma was given to three out of the six patients. Despite combination therapy with Remdesivir, Tocilizumab, steroids, antibiotics and convalescent plasma, four out of the six patients (66.67%) deteriorated and required invasive mechanical ventilation.

CONCLUSIONS:
There are currently no set treatment guidelines for COVID 19. Most institutions appear to be utilizing some form of combination therapy against COVID-19. In this study, invasive mechanical ventilation was avoided in only two of six patients despite robust use of combination therapy in all patients. Our study suggests that multiple medications may not be the answer. Instead, a clearer understanding of the pathophysiology along with timing at which medications are introduced might play a more important role. We propose judicious use of combination therapy in a methodical and sequential use in patients requiring three or more liters of supplemental oxygen. Use of any of these medications, either by itself or in combination, after mechanical ventilation has minimal if any benefits and should be used as a last resort. Currently, a few clinical trials in the recruiting stage are underway that look at various combination therapies that could provide a more comprehensive understanding regarding the efficacy of combination therapy against SARS-CoV-2.

Q5. The final conclusion still needs correction. The most important details of the study should be mentioned.

R. The conclusion has been modified. Changes have been highlighted below.

Conclusion

Treatment modalities for COVID-19 appear to still be in its nascent stage. In our study, despite utilization of multiple drugs that have previously shown favorable results in other reports, invasive mechanical ventilation was thwarted only in 2 out of 6 study subjects. Due to the limited sample size, it is hard to draw any conclusive evidence that using multiple medications (Remdesivir, IL-6 inhibitors, Convalescent plasma, antibiotics and steroids) made any significant difference on stabilizing the patient and decreasing the need for invasive mechanical ventilation,

morbidity and mortality. Combination therapy, however, remains intriguing and controversial. Many centers continue to use a variety of combinations of these medications without supporting data regarding the safety and efficacy profiles. Hopefully, ongoing studies will help further define the use of these medications and improve treatment outcomes. Judicious use of these medications in a methodical sequential use in patients that require three or more liters of supplemental oxygen is proposed. Use of any of these medications, either by itself or in combination, after mechanical ventilation has minimal if any benefits and should be used as a last resort.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 16 Dec 2020

Dear AE,
Please, the authors just correct the reference number and its format in the article text.
Thanks.

REFEREE: Reviewer | **Revision** (1) 19 Dec 2020

Dear AE,
This version of the manuscript is suitable for acceptance.
Regards

Hamidreza Kouhpayeh: Associate Editor | **Revision** (1) 20 Dec 2020

Dear EIC,
The authors should just correct the reference number and its format in the article tex.
Thanks.

Hamidreza Kouhpayeh: EIC | **Revision** (1) 20 Dec 2020

Dear Author,
Just correct the reference number and its format in the article tex.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Manuscript revisions

Q1 Just correct the reference number and its format in the article text.

R1 Reference numbers and it's format have been corrected. All changes have been highlighted in the manuscript.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (2) 12 Jan 2021

Dear AE,
The manuscript has been revised according to the comments.
Thanks.

REFEREE: Reviewer | **Revision** (2) 23 Jan 2021

Dear AE,
Based on the correction in this paper, Now It's suitable for publication.
Regards,

Hamidreza Kouhpayeh: Associate Editor | **Revision** (2) 24 Jan 2021

Dear EIC,
Based on the correction in this paper, Now It's suitable for publication.
Regards,

Hamidreza Kouhpayeh: EIC | **Revision** (2) 24 Jan 2021

Dear authors
Base of correction in this paper, Now It's suitable for publication.
Regards,