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OPEN PEER REVIEW

Intestinal Carriage of Carbapenemase-Producing *Enterobacteriaceae* Members in Immunocompromised Children During COVID-19 Pandemic

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 28 Jul 2022

Referee 1 Reviewer

MINOR REVISION 28 Jul 2022

Dear author
In cross-sectional observational studies, it is necessary to discuss the obtained results and write the conclusions in the form of hypotheses. In this study, the results are presented in both descriptive and analytical ways, but their use in the discussion and conclusion is unclear. Also, the sentences in the conclusion part do not seem to be inferred from the analysis of the results of the present study.
Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:

Question/ problem: In cross-sectional observational studies, it is necessary to discuss the obtained results and write the conclusions in the form of hypotheses. In this study, the results are presented in both descriptive and analytical ways, but their use in the discussion and conclusion is unclear. Also, the sentences in the conclusion part do not seem to be inferred from the analysis of the results of the present study.

Answer: it is highlighted in the appendix file.

Reviewer 2:

Question/ problem: Where and when the immunocompromised children admitted to the oncology and bone marrow transplantation 11 (BMT) wards. It have to write in the title.

Answer: it is highlighted in the appendix file.

Question/ problem: Which year this study was performed from 21 August to 20 January in Tehran, Iran????

Answer: it is highlighted in the appendix file.

Question/ problem: There aren't provided sample size calculation or justification?

Answer: this study was cross-sectional and we did it in a certain period of time.

Question/ problem: It should be write the brand of antibiotic disks?

Answer: it is highlighted in the appendix file.

Question/ problem: It should be write the name of brand of biochemical tests.

Answer: it is highlighted in the appendix file.

Question/ problem: Some References are not for the last five years.

Answer: most of the references that are not for the last five years are related to the sequence of the carbapenemase genes primers. Some of the references are about the first reports of some carbapenem-resistant genes in Iran, according to that they could be published more than 5 years. But we altered some of them with new latest articles as we could and they are highlighted in the appendix file.

Reviewer 3:

1- CRE must be written as complete form for first time.
   Answer: it is highlighted in the appendix file.
2- words are messy and unclear.
   Answer: we rewrite some parts of the article.

3- In material and methods: line 79 must be rewritten.
   Answer: we rewrite some parts of the article.
4- table 2 is not suitable and some rows and columns must be added.
   Answer: we collected this information due to patients' documentation in the hospital. We don't have extra information at the time.
5- in results: the percentages of frequency of each bacteria must be rechecked.
   Answer: it is highlighted in the appendix file.

Associate Editor's Comments:

1- The introduction is too long and should be shortened appropriately. In the introduction, I expected a statistical comparison and a p-value on the rate of fecal colonization in the COVID-19 positive and COVID-19 negative groups, as well as its relationship with the antibiotic prescription, as well as the clinical outcome. Unfortunately, the reader does not get any useful information from the abstract in this regard.

Answer: we rewrote some parts of the introduction to make it shorter.

We could not speak of such a thing in the introduction, but this data had brought in part 4.4 of the results ``Intestinal CRE carriage in children with Covid-19 and broad-spectrum antibiotic usage``. We compare the rate of fecal colonization in the COVID-19 positive and COVID-19 negative groups and calculate the p-value for them. And there is related information due to the antibiotics and CRE carriers and Covid-19 in table 4. We added this information to the abstract.

2- I am quite surprised by the high tigecycline resistance rate which was detected in this study.

Authors should be more discussed regarding routine prophylaxis regimens which are in use in both wards. The brief discussion which was provided in the discussion section is not helpful.

Answer: the high tigecycline resistance rate was surprising to us too t the first stages, but we doubled check them and reached the same results.

We add some results from approximately similar studies due to prophylaxis may they could be helpful and it is highlighted.

3- again I am just surprised by the prophylaxis regimens which is prescribed in these wards (Line 192). If you use these regimens for prophylaxis how did you treat bacteremia and BSI?

Answer: the data about antibiotic prophylaxis regimens had wrote just as same as the patients documents at the hospital.

4- Lines 187-188: regarding the following statement "The correlation between CRE intestinal carriage, Covid-19 and administrational antibiotics was significant in this study."
First, administrational is not the correct word. Second, no proper statistical test was performed to test this claim, advise your statistical consultant.

Answer: the points had been corrected in the text and highlighted.

5- in Line 206 the authors discussed the co-occurrence of multiple CRE genes; however, no information is provided in the result section?!

Answer: we rewrote the sentence with the proper answer according to the current data.

Other shortcomings

Spell out all abbreviations on the first occasion. Line 61 "patients and samples": spell out all abbreviations in this section on the first occasion.

Answer: it is highlighted in the appendix file.

Lines 37-39: add a reference for this statement.

Answer: it is highlighted in the appendix file.

Line 62: add study conducting year.

Answer: it is highlighted in the appendix file.

Line 84: rewrite this statement with better words, the English language is weak.

Answer: it is highlighted in the appendix file.

Table 2: First, add at least the top five underlying diseases which you find in this study. Second, confirm that "antimicrobial prophylaxis" is correct or "antimicrobial treatment"? It is reasonable that add both of them to the table.

Answer: we added the top five underlying diseases. And yes, those antibiotics are used for prophylaxis as was written in their chart and documents.

Table 4: add all p-values

Answer: it is highlighted in the appendix file.

Discussion should start with overall study findings.

We check them with our high cited references and they were started like this one, but we rewote some sentences.

Add the study limitations at the end of the discussion section.

It was brought up at the end of the discussion, and it is highlighted. Please recheck again.

Several typos:

Line 35: hospital-acquired

Line 36: multiple hospitalization courses

Line 37: the composition ... The richness

Line 41: carbapenem resistant

Line 49: as a human health-threatening

Line 50: long-term

Line 55: in the clinical setting, this study aimed

Line 87: ciprofloxacin is correct

Lines 114 and 116: remove "like" and rewrite the sentences.

line 126: patients (use lesser case)

Line 191: ciprofloxacin is correct

Line 193: a remarkable

All of them are highlighted.

2 Revision 1

1 comment · 23 Sep 2022

Associate Editor

MAJOR REVISION 23 Sep 2022

Editorial comments
Dear authors
The manuscript's overall presentation has improved after the amendments and is now more readable.
Although your replies to the reviewers' concerns are satisfactory, the manuscript still needs to be improved.

First of all, all other unfamiliar styles, such as Covid-19, should be replaced with "COVID-19".
Title: "COVID-19" is correct.

Line 28: "broad-spectrum antibiotics prophylaxis" is correct.
Lines 108-109: replace "We collected total 102 stool samples from 55 boys (54%) and 47 girls (46%), 44 of them (43.13%) were up to 1-5 years old." with "Totally, 102 stool samples were collected. 55 (54%) were boys, with a median age of ... (SD ...) ranged from 1 to 5 years."

Line 110: Which is correct: "broad-spectrum antibiotics" or "broad-spectrum antibiotics prophylaxis"?

Line 111: "ciprofloxacin" is correct.

Line 148: Which is correct: "broad-spectrum antibiotic usage" or "broad-spectrum antibiotic prophylaxis"?

Line 150: "54% (55/102) of the patients have intestinal CRE carriers" is correct.

Line 152: remove these sentences: "after admission to the oncology and BMT wards. Due to the results and statistical analysis, the"

Lines 155-156: Which is correct: "broad-spectrum antibiotics" or "broad-spectrum antibiotic prophylaxis"?

Table 4:
Line 160: Which is correct: "broad-spectrum antibiotic usage" or "broad-spectrum antibiotic prophylaxis"?
- Remove the last two rows, which do not provide helpful information. The title of Table 4 is "The frequency of intestinal CRE carriers", so it is not necessary to report non-carrier status.
- "CRE carriers with a recent history of antibiotic prophylaxis" is a better term. Please replace it.
- "CRE carriers without a history of antibiotic prophylaxis" is a better term. Please replace it.
- Use the correct style: "COVID-19"

Line 162: The discussion should start with the study's overall findings.
My suggestion is: "In this study we investigate ... and we found ..."

Line 217: report the p-value for "CRE intestinal carriage" and "COVID-19", and also for "CRE intestinal carriage" and "history of recent antibiotic therapy/prophylaxis", separately. Note that this statement should be moved to the results section.
Remove the following statement: "Based on our knowledge to date, there is not such a similar study."

Lines 220-221: replace "Previous usage of chemotherapy and antimicrobial prophylaxis could affect the gut microbiota and alter a normal micro-flora with resistant bacteria such as CRE" with "Previous usage of chemotherapy and antimicrobial prophylaxis could affect the gut microbiota and increase CRE colonization"

Lines 223-226: the new sentence is confusing. Rewrite it with clearer words.

Line 225: In the middle sentence, use lowercase for "Fluoroquinolones".

Line 235: study limitations should be mentioned clearly. Start the study limitations with "Our study has some limitations, first ..."

Despite the "first Editor-1 comment" in the previous round, no change has been made to the conclusion. The authors must change the wording of the conclusion. My suggestion: "In this study, we found (high/medium/low) levels of CRE intestinal colonization in studied immunocompromised children. Also, blaOXA-48 and KPC as the two main carbapenemase were detected notably in E. coli isolates. So, based on the obtained results ...."

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear reviewers and editors, we appreciate all your comments to improve the level of our work, we revised the manuscript and answered the questions, and we hope it would satisfy you.

Associate Editor 1:

1. First of all, "COVID-19" should be replaced with all other non-familiar styles such as Covid-19.

Title: "COVID-19" is correct.

Answer: it is highlighted in the appendix file.

2. Line 28: "broad-spectrum antibiotics prophylaxis" is correct.

Answer: it is highlighted in the appendix file.

3. Lines 108-109: replace "We collected total 102 stool samples from 55 boys (54%) and 47 girls (46%), 44 of them (43.13%) were up to 1-5 years old." with "Totally, 102 stool samples were collected. 55 (54%) were boys, with a median age of ... (SD ...) ranged from 1 to 5 years."

Answer: it is highlighted in the appendix file.

4. Line 110: "broad-spectrum antibiotics" or "broad-spectrum antibiotics prophylaxis", which of them is correct.

Answer: broad-spectrum antibiotics prophylaxis is correct and it is highlighted in the appendix file.

5. Line 111: "ciprofloxacin" is correct.

Answer: it is highlighted in the appendix file.

6. Line 148: "broad-spectrum antibiotic usage" or "broad-spectrum antibiotic prophylaxis" which of them is correct?

Answer: it is highlighted in the appendix file.

7. Line 150: "54% (55/102) of the patients have intestinal CRE carriers" is correct.

Answer: it is highlighted in the appendix file.

8. Line 152: remove these sentences: "after admission to the oncology and BMT wards. Due to the results and statistical analysis, the"

Answer: it is highlighted in the appendix file.

9. Lines 155-156: "broad-spectrum antibiotics" or "broad-spectrum antibiotic prophylaxis" which of them is correct?

Answer: broad-spectrum antibiotics prophylaxis is correct and it is highlighted in the appendix file.

10. Table 4:

Line 160: "broad-spectrum antibiotic usage" or "broad-spectrum antibiotic prophylaxis" which of them is correct?

Answer: broad-spectrum antibiotics prophylaxis is correct and it is highlighted in the appendix file.

-Remove the last two rows which are not provided helpful information. Table 4 title is "The frequency of intestinal CRE carriers" so, non-carrier status is not necessary to report.

Answer: it is highlighted in the appendix file.

-"CRE carriers with a recent history of antibiotic prophylaxis" is a better term. Please replace it.

Answer: it is highlighted in the appendix file.

-"CRE carriers without a history of antibiotic prophylaxis" is a better term. Please replace it.

Answer: it is highlighted in the appendix file.

-Use correct style: "COVID-19"

Answer: it is highlighted in the appendix file.

11. Line 162: The discussion should start with the study's overall findings.

My suggestion is: "In this study we investigate ... and we found ..."

Answer: we changed the primary sentences of the discussion and it is highlighted in the appendix file.

12. Line 217: report the p-value for "CRE intestinal carriage" and "COVID-19", and also "CRE intestinal carriage" and "history of recent antibiotic therapy/prophylaxis" separately. Note that this statement should be moved to the result section. Remove the following statement: "Based on our knowledge to date, there is not such a similar study."

Answer: The mentioned changes were done, the sentence is moved to line161, and it is highlighted in the appendix file.

13. Lines 220-221: replace "Previous usage of chemotherapy and antimicrobial prophylaxis could affect the gut microbiota and alter a normal micro-flora with resistant bacteria such as CRE" with "Previous usage of

chemotherapy and antimicrobial prophylaxis could affect the gut microbiota and increase CRE colonization"

Answer: it is highlighted in the appendix file.

14. Lines 223-226. the new sentence is confusing. Rewrite it with clearer words.

Answer: it is highlighted in the appendix file.

15. Line 225: In the middle sentence, use a lesser case for "Fluoroquinolones".

Answer: it is highlighted in the appendix file.

Line 235: study limitations should be mentioned clearly. Start study limitation with "Our study has some limitations, first ..."

Answer: The mentioned changes were done, the sentence is moved to line 235, and it is highlighted in the appendix file.

Despite the "first Editor-1 comment" in the previous round, no change has been applied to the conclusion. The authors must change the manner of speaking in the conclusion. My suggestion: "In this study, we found (high/medium/low) levels of CRE intestinal colonization in studied immunocompromised children. Also, blaOXA-48 and KPC as the two main carbapenemase were detected notably in E. coli isolates. So, based on the obtained results ...."

Answer: it is highlighted in the appendix file.

3 Revision 2

1 comment · 9 Oct 2022

Associate Editor

ACCEPT 9 Oct 2022

I read the revised manuscript.
I have no further comments to add. I thank the authors for their very detailed replies to my comments.