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Peer Review Report for "Etiologic Features of Respiratory Tract Infections Seen in Children with Primary Nephrotic Syndrome: A Cross-Sectional Retrospective Study"

Author(s): Xi-Lin Xiong, Chun-Yu Yu, Mo Wang

Review Timeline:

Submit Date: 2 Nov 2019
Revised Date: 8 Jul 2020
Accepted Date: 11 Aug 2020

Revision (0)

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

Samuel Nkachukwu Uwaezuoke: Reviewer | Revision (0) 26 Jan 2020

Dear AE,
General comments
The authors of this manuscript conducted a retrospective study of cases of primary nephrotic syndrome (PNS) over a 4- year period. They reviewed the patterns of respiratory tract infection in the cases of PNS with emphasis on the types and etiologic organisms. However, the title was not in keeping with the aim of the study. The title gives the reader the impression that the study was focused on the clinical features of PNS that were secondarily complicated by respiratory tract infection. Rather, the authors conducted their review essentially on respiratory tract infection seen in cases of PNS. Thus, this manuscript has major and minor issues that need to be addressed.
Specific comments
Major issues
1. Under the ABSTRACT, no background or introduction was given. The Method is at variance with the objective. Unfortunately, the findings and conclusions of the study are not novel.
2. The INTRODUCTION of this manuscript was so brief that it failed to clearly spell out

what is already know about the topic. The research question was also not outlined.
3. The METHODS were not clear enough. Being a retrospective study, it was prone to unreliable data especially in a study of this nature.
4. There were no illustrations in the form of tables or figures in the manuscript
5. If this study were to make meaning, I suggest the authors modify the topic to read 'Etiologic patterns and types of respiratory tract infections seen in children with primary nephrotic syndrome: a cross-sectional retrospective study'. The Introduction should be expanded to include what is known about the topic and what is not known. From there the authors can develop a research question and an aim/objective for the study. Furthermore, the methods should be present with enough details to replicate the study
Minor issues
1. Several grammar and syntax errors need to be corrected.
Thanks.

REFEREE: Reviewer | **Revision** (0) 2 Feb 2020

Dear AE,
The study was about patients with primary nephrotic syndrome complicated with respiratory tract infection in childhood. The cases were divided as community-acquired and hospital-acquired as well as upper and lower respiratory tract infections. The microorganisms and their responsivity to medications were reported. The results were not surprising, however the patient number was large (2740 children). The underlying microorganisms in other cases without nephrotic syndrome in the same period was not mentioned in the same period, which would make sense.
Some corrections may be useful:
- The title seems not relevant for your manuscript, since it is not about clinical features. It is about the underlying microorganisms. You should change it.
- The microorganism species should be written with Italic characters.
- Spaces should be left before parentheses all through the text.
- I think the frequency of the underlying microorganisms and their sensitivities were "local" and the authors may not generalize the results of their study to all patients with nephrotic syndrome all over the world, such as amoxicillin clavulanate for all bacteriological pathogens.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 11 Feb 2020

Dear EIC,
The manuscript was reviewed by our reviewers. The reviewers have raised concerns regarding the manuscript, and therefore, the paper is not acceptable for publication in this format. However since the reviewers do find some merit in the paper, I would be willing to reconsider if they wish to undertake major revisions and re-submit, addressing the referees' concerns.
Please note that resubmitting your manuscript does not guarantee acceptance, and that your resubmission will be subject to a re-review before a decision is rendered.
Please consider following comments in new version of this manuscript:
- Discussion needs to improvement. Some parts didn't have relevant references. It is

required that you mention the results of other similar studies which have been conducted in other countries in the world and compare your results with their results. Such an approach is missing in your discussion section.
- The limitations of this study should explain at the end of discussion.
Thanks.

REFEREE: EIC | **Revision (0)** 11 Feb 2020

Dear Author,
Thank you for submitting your manuscript to Iran J Pediatr. Your manuscript has now been reviewed by two reviewers and an Associate Editor. I now have the reports of the Referees, which suggest that your manuscript might be suitable for publication following a number of revisions. I attach some reviewer comments and invite you to submit a revised version of your manuscript addressing the points made.
Thanks.

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 ID: 99276 Reply to Reviewers
March 5, 2020

Thank you to the reviewers for their time and thoughtful comments, many of which have been incorporated into the revised manuscript.

Reviewer 1:

Q1: Under the ABSTRACT, no background or introduction was given. The Method is at variance with the objective.

R1: We added a introduction in abstract and revised the objective and the method. The revised objective was included in the introduction part.

Q2: The INTRODUCTION of this manuscript was so brief that it failed to clearly spell out what is already know about the topic. The research question was also not outlined.

R2: we enriched the introduction by adding some present research status about the topic and expounding the research question.

Q3: The METHODS were not clear enough. Being a retrospective study, it was prone to unreliable data especially in a study of this nature.

R3: We added some diagnostic criteria and detection methods of pathogens in the METHODS.

Q4: There were no illustrations in the form of tables or figures in the manuscript.

R4: We added 4 tables and 1 figure in the RESULT.

Q5: modify the topic to read ‘Etiologic patterns and types of respiratory tract infections seen in children with primary nephrotic syndrome: a cross-sectional retrospective study

R5: The topic was was modified to “etiologic features of respiratory tract infections seen in children with primary nephrotic syndrome: a cross-sectional retrospective study”.

Q6： Several grammar and syntax errors need to be corrected

R6： Done.

Reviewer 2:

Q7: The underlying microorganisms in other cases without nephrotic syndrome in the same period was not mentioned, which would make sense.

R7： We mentioned some pathogens in other cases without nephrotic syndrome in the same period in local areas in the DISCUSSION (P8, para1, 2).

Q8: The title seems not relevant for your manuscript, since it is not about clinical features. It is about the underlying microorgansims.

R8： The title was changed to “etiologic features of respiratory tract infections seen in children with primary nephrotic syndrome: a cross-sectional retrospective study”.

Q9: The microoganism species should be written with Italic characters.

R9: Done.

Q10: Spaces should be left before parentheses all through the text.

R10: Done.

Q11: The frequency of the underlying microorgansims and their sensitivities were

“local” and the authors may not generalize the results of their study to all patients with nephrotic syndrome all over the World.

R11: Yes, this is a limitation of our study, and we added an explanation at the end of DISCUSSION (P9).

Associate Editor 1:

Q12: Discussion needs to improvement. Some parts didn’t have relevant references. It is required that you mention the results of other similar studies which have been conducted in other countries in the world and compare your results with their results. Such an approach is missing in your discussion section.

R12: Done. We added relevant references in two parts (P8, para 2, 4). We mentioned the results of other similar studies in other countries and compared our results with their results in the 1st-4th, 6th paragraph of discussion section.
Q13: The limitations of this study should explain at the end of discussion.

R13: Done.

OPEN PEER REVIEW

Revision (1)

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REFEREE: Reviewer | **Revision** (1) 29 Mar 2020

Dear AE,
The SECOND REVIEW OF THE MANUSCRIPT REVISED BY THE AUTHORS BASED ON MY PREVIOUS COMMENTS
RE- ETIOLOGIC FEATURES OF RESPIRATORY TRACT INFECTIONS SEEN IN CHILDREN WITH PRIMARY NEPHROTIC SYNDROME: A CROSS-SECTIONAL RETROSPECTIVE STUDY
COMMENTS TO THE EDITOR
Although the authors tried to address the major and minor issues which I pointed out in the manuscript, a reappraisal of the paper has brought the following concerns to the fore
1. There appears to be a major methodological flaw in this study. Firstly, the study is based on the assumption that respiratory tract infections are common complications of primary nephrotic syndrome. But this assumption is not correct. Respiratory tract infections can occur in any child irrespective of underlying morbidity. I doubt if the etiologic agents of respiratory tract infections in nephrotics will differ from those in non-nephrotics. Evidence in the literature rather points to pneumococcal peritonitis and cellulitis in anasarca patients as the common infectious complications of nephrotic syndrome. Respiratory tract infections do not necessarily influence the outcomes of the nephrotic syndrome because they commonly complicate the syndrome. Rather, respiratory tract infections are the commonest infectious trigger of relapses in primary nephrotic syndrome. Frequent relapses contribute to the morbidity of nephrotic syndrome and thus influence its outcomes. Secondly, if the authors had intended to prove that respiratory tract infections were common in primary nephrotic syndrome, a prospective cross-sectional comparative study could have been ideal. Patients with primary nephrotic syndrome and matched healthy controls would then form the study population.
2. Being a retrospective study, were the hospital records so accurate that the authors noted all these etiologic agents (both viral and bacterial) in the patients' records they reviewed? They inferred that respiratory specimens were obtained by aspiration. I assume they meant lung aspiration as that is the only means to obtain a reliable microbial yield. Do the authors mean it was routine to carry out such an invasive procedure on all nephrotic syndrome patients just to establish if they had respiratory tract infections? That's why a prospective study would have been more convincing despite the ethical issues involved.
3. The authors claimed under the Results that 'In cases of PNS with CARTI, 579 cases underwent sputum culture, and 208 cases (35.92%) were positive.' Sputum culture is not a reliable method of isolating pathogenic organisms because of the high likelihood of culturing

commensals.
Thanks.

REFEREE: Reviewer | **Revision (1)** 1 Apr 2020

Dear AE,
It was the revised form of a study performed on a total of 2740 patients with nephrotic syndrome who were hospitalized in 4-years' time. 2162 of the patients had respiratory system infection, 928 of them were tested and 525 were positive. The authors grouped the patients with upper and lower respiratory system infection, and as community and hospital-acquired and compared the values between the groups.
- I have marked a few words for letter corrections.
- Table 1 and 2 need a last column for p values. All the p values should be reported in the tables rather than being written in the text.
Thanks.

REFEREE: Associate Editor | **Revision (1)** 1 Apr 2020

Dear EIC,
Thanks for revising some parts of the article, however, there are still further corrections that should be done especially on the tables and the discussion sections. Although at least one reviewer suggested to major change the beginning of the method, it wasn't changed at all.
Thanks.

REFEREE: EIC | **Revision (1)** 1 Apr 2020

Dear Author,
The second round of peer review of your manuscript is completed. I now have the reports of the Referees, which suggest that your manuscript needs more correction.
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 ID: 99276 Reply to Reviewers

Thank you to the reviewers for their time and thoughtful comments, many of which have been incorporated into the revised manuscript.

Reviewer 1:
Q1: Table 1 and 2 need a last column for p values. All the p values should be reported in the tables rather than being written in the text.
R1: Done.
Reviewer 2:
Q2: There appears to be a major methodological flaw in this study. Firstly, the study is based on the assumption that respiratory tract infections are common complications of primary nephrotic syndrome. But this assumption is not correct. Respiratory tract infections can occur in any child irrespective of underlying morbidity. I doubt if the etiologic agents of respiratory tract infections in nephrotics will differ from those in non-nephrotics. Evidence in the literature rather points to pneumococcal peritonitis and cellulitis in anasarca patients as the common infectious complications of nephrotic syndrome. Respiratory tract infections do not necessarily influence the outcomes of the nephrotic syndrome because they commonly complicate the syndrome. Rather, respiratory tract infections are the commonest infectious trigger of relapses in primary nephrotic syndrome. Frequent relapses contribute to the morbidity of nephrotic syndrome and thus influence its outcomes. Secondly, if the authors had intended to prove that respiratory tract infections were common in primary nephrotic syndrome, a prospective cross-sectional comparative study could have been ideal. Patients with primary nephrotic syndrome and matched healthy controls would then form the study population.
R2: This study didn’t intend to prove that respiratory tract infections (RTI) were common in primary nephrotic syndrome (PNS). According to previous study(1-2), we found that RTI are one of the common complications of PNS. We didn’t intend to compare the difference of RTI between nephrotics and non-nephrotics. We mainly want to discuss the aetiology of RTI in children with PNS to improve the curative effect of PNS complicated with RTI.
Q3: Being a retrospective study, were the hospital records so accurate that the authors noted all these etiologic agents (both viral and bacterial) in the patients’ records they reviewed? They inferred that respiratory specimens were obtained by aspiration. I assume they meant lung aspiration as that is the only means to obtain a reliable microbial yield. Do the authors mean it was routine to carry out such an invasive procedure on all nephrotic syndrome patients just to establish if they had respiratory tract infections?
R3: As a Pediatric Medical Center, the records of our hospital is accurate. Nasopharyngeal aspirates (NPAs) and blood samples were collected on hospital admission after obtaining informed consent for the detection of common respiratory viruses, bacteria, and other atypical pathogens. Aspiration was mainly carried out in patients with respiratory symptoms.

Q4: Sputum culture is not a reliable method of isolating pathogenic organisms because of the high likelihood of culturing commensals.
R4: The judgment of pathogenic bacteria depends not only on the bacterial culture results but also on the clinical symptoms and treatment effects. We have ruled out most of the culturing commensals according to the clinical symptoms and treatment effects.
Associate Editor 1:
Q5: Major changes of your method should be done.
R5: Done. We described our methods in as much detail as possible.

References

1. Wei CC, Yu IW, Lin HW, Tsai AC. Occurrence of infection among children with nephrotic syndrome during hospitalizations. Nephrology (Carlton) 2012 Nov;17(8):681-8.
2. Moorani KN, Khan KM, Ramzan A. Infections in children with nephrotic syndrome. J Coll Physicians Surg Pak. 2003. 13(6): 337-9.

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: Associate Editor | **Revision** (2) 11 Aug 2020

Dear EIC,
As the authors improved their manuscript based on the reviewer's recommendations, I think it can be accepted.
Thanks.

REFEREE: EIC | **Revision** (2) 11 Aug 2020

Dear Author,
The third round of peer review of your manuscript has been completed, and I am pleased to inform you that your manuscript has now been accepted for publication in our journal.
Thanks.