OPEN PEER REVIEW

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https://brief.land/briefland/knowledgebase/category/tree.html#opr.html

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Peer Review Report for "Manifestations and Risk Factors in Children Hospitalized with Respiratory Syncytial Virus Infection"

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Review Timeline:

Submit Date: 22 Aug 2020
Revised Date: 9 Sep 2020
Accepted Date: 26 Sep 2020

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)

26 Aug 2020

Dear AE,
This was an original study evaluating the manifestations of RSV infection in hospitalized children and predictors of severity of the disease.
General
- The manuscript needs linguistic editing.
Title
- The title is not clear.
Abstract
• Since the total number of causes of respiratory tract infections is not determined, the incidence cannot be calculated.
• The conclusion is not completely related to the aim of the study.
MATERIAL AND METHODS
• You mentioned:" The excluded criteria were: 1. primary immunodeficiency; 2. Chronic lung

disease; 3. congenital heart defect; 4. cardiovascular, liver, kidney, endocrine, hematological, neurological, gastroenterological and other diseases that could contribute to immunodeficiency…."

Kindly explain which neurologic diseases were excluded?

• Kindly add the reference for definition of acute bronchitis.

• You mentioned: "…symptoms suggestive of pneumonia were fever above 38°C, tachypnea and intercostal retractions, combined with the crackles as the most indicative respiratory sound."

Kindly add the reference for this definition of pneumonia. Is temperature of >38°C necessary for pneumonia? Pneumonia could occur without fever.

• Kindly define and explain clearly the used terms such as "respiratory failure" in the materials and methods

• You mentioned: "The radiographic features of pneumonia were perihilar peribronchial thickening……" Is perihilar peribronchial thickening necessary for pneumonia? Kindly add the reference for this definition.

• The authors did not explain about the method of RSV isolation in this study.

Results

• Please determine which microorganisms were included in RSV negative group? The results could at least be divided in viral and bacterial subgroups.

• How could the authors confirm that the etiology of otitis media was RSV? was tympanocentesis performed?

• The authors mentioned:" Oxygen therapy, inhaled glucocorticosteroids and beta2-adrenergic agonists were significantly more often used in children with RSV infection (p=0.001)."

Kindly explain why glucocorticosteroids were used for a viral infection in this study?

• It is better to use "manifestation" instead of "complication" in the text. For example, "pneumonia" and "otitis media" are "manifestations" not "complications" of RSV infection.

Conclusion

- The conclusion should be reorganized. The conclusion should be related to the results of this study.

Thanks.

REFEREE: Reviewer | **Revision** (0) 26 Aug 2020

Dear AE,

Thanks for this valuable study. There are some comments for the authors:

-Abstract: Association is better than correlation. Please substitute it instead of correlation in all part of your manuscript.

- Some English revision is needed.

- Introduction: RSV is belonged to Paramixoviridae family not Pneumoviridae and I couldn't see it in references 4 and 5 that you cited.

- References: Following 6 authors et al. should be written not 3 authors.

Thanks.

REFEREE: Reviewer | **Revision** (0) 31 Aug 2020

Dear AE,

1- In the Methods section, please specify which statistical test you performed for which observation and why
2- For what purpose are the laboratory tests mentioned in lines 89 to 91 analyzed?
3- In the method section, the RSV risk factors and how to analyze their relationship to the occurrence of RSV should be specified. As mentioned in the Objectives section, if the purpose of the study is to evaluate the relationship between RSV and its risk factors, the risk factors should be hypothesized before performing statistical analysis. If the purpose is to report the risk factors observed in the study, this is a descriptive and exploratory purpose and should be written differently in the study objectives section.
4- In lines 118 to 131, the side effects, outcomes and risk factors of RSV are indistinguishable from each other.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 31 Aug 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) 31 Aug 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
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.

Reviewer 1

Q1: The manuscript needs linguistic editing.

R1: The manuscript was revised by a native-speaking medical doctor.

Q2: The title is not clear.

R2: The title has been amended.

Q3: Since the total number of causes of respiratory tract infections is not determined, the incidence cannot be calculated.

R3: Since the diagnosis of ALRI does not require the identification of the etiological factor, we based it on the clinical examination combined with the imaging study. The presented results refer to the study group and not to the entire population of our patients. We did not aim to determine the incidence of the diseases.

Q4: The conclusion is not completely related to the aim of the study.

R4: We restructured the conclusion.

Q5: You mentioned:" The excluded criteria were: 1. primary immunodeficiency; 2. Chronic lung disease; 3. congenital heart defect; 4. cardiovascular, liver, kidney, endocrine, hematological, neurological, gastroenterological and other diseases that could contribute to immunodeficiency…."
Kindly explain which neurologic diseases were excluded?

Our aim was to eliminate known conditions that, for various reasons, could predispose the child to more frequent and more severe respiratory tract infections. As for the neurological diseases, we excluded the celebral palsy which may, due to the physical disability, predispose to the acute lower respiratory tract infections.

Q6: Kindly add the reference for definition of acute bronchitis.

R6: The references have been added.

Q7: You mentioned: "…symptoms suggestive of pneumonia were fever above 38°C, tachypnea and intercostal retractions, combined with the crackles as the most indicative respiratory sound."
Kindly add the reference for this definition of pneumonia. Is temperature of >38°C necessary for pneumonia? Pneumonia could occur without fever.

R7: The reference for this definition was added. Yet in the article we did not state that the temperature >38°C is necessary for pneumonia. We stated that when the patient is diagnosed with ALRI (bronchitis/bronchiolitis/pneumonia) the symptoms that may prompt us more to diagnose pneumonia are "fever above 38°C, tachypnea and intercostal retractions, combined with the crackles". But we also added that in any case of suspected pneumonia it should be proved by the imaging study (chest X-ray or lung ultrasound).

Q8: Kindly define and explain clearly the used terms such as “respiratory failure” in the materials and methods.

R8: We have already added the definition to the material and methods.

Q9: You mentioned: “The radiographic features of pneumonia were perihilar peribronchial thickening……” Is perihilar peribronchial thickening necessary for pneumonia? Kindly add the reference for this definition.

R9: The perihilar peribronchial thickening is not necessary for pneumonia but it is one of the radiographic features that may occur in pneumonia (alongside interstitial infiltrates and consolidation). We edited this sentence to make it clear.

Q10: The authors did not explain about the method of RSV isolation in this study.

R10: We added the information about the method of RSV isolation in the part “Material and methods”: “Rapid-VIDITEST RSV, a one-step coloured immunochromatographic test was used for the detection of RSV antigens in nasal discharge of all children qualified for the study. During the test, a sample collected from the nasopharynx with a swab was reacted with anti-RSV antibody-coated particles on the strip test. In case of the positive result, the specific antibodies reacted with the conjugate and form a coloured line. The test sensitivity was 95%, whereas the specificity >99%.”

Q11: Please determine which microorganisms were included in RSV negative group? The results could at least be divided in viral and bacterial subgroups.

R11: Unfortunately, we did not isolate any other microorganisms in RSV negative group. After the diagnosis of ALRI (clinical symptoms + imaging study) we performed the Rapid-VIDITEST RSV in every child who was under 18 months of age. After that we divided the patients into two groups: RSV positive and RSV negative.

Q12: How could the authors confirm that the etiology of otitis media was RSV? was tympanocentesis performed?

R12: Actually, we did not confirm that the etiology of otitis media was RSV and we did not perform tympanocentesis. The diagnosis of RSV infection was performed by the nasal swab, as described in the answer no. 10. We admitted to the hospital children with ALRI and observed their clinical status during hospitalization – if they developed otitis media, conjunctivitis or respiratory failure.

Q13: The authors mentioned:” Oxygen therapy, inhaled glucocorticosteroids and beta2-adrenergic agonists were significantly more often used in children with RSV infection (p=0.001).”
Kindly explain why glucocorticosteroids were used for a viral infection in this study?

R13: We have added an explanation of this issue in the manuscript. The glucocorticosteroids – only in combination with beta2-adrenergic agoints – were used in this group only in the case of accompanying increased airway obstruction. We are aware of the fact that there is inconsistency in the studies regarding the optimal management of bronchiolitis, including

administration of inhaled glucocorticosteroids and beta2-adrenergic agonists. Nevertheless, in the reviews and meta-analysis we could find information that the combination of these medicines may be beneficial in case of the airway obstruction, especially in children with positive family history of allergies. It is also consistent with our clinical observations.

Q14: It is better to use “manifestation” instead of “complication” in the text. For example, “pneumonia” and “otitis media” are “manifestations” not “complications” of RSV infection.

R14: Thank you for this remark. We revised the entire manuscript in order to name and analyze these ailments as “manifestations” not “complications” of RSV infection.

Q15: The conclusion should be reorganized. The conclusion should be related to the results of this study.

R15: We restructured the conclusion.

Reviewer 2

Q1: In the Methods section, please specify which statistical test you performed for which observation and why.

R1: Actually, we put it in the paragraph “statistical analysis”: “Measures of central tendency and their spread as well as statistical distribution were determined for the analyzed variables. The non-parametric Mann-Whitney U test was used to compare variables whose distribution was significantly different from the Gaussian distribution. When comparing qualitative data, the chi-square test was used.”

We were comparing the parameters either between RSV (+) and RSV (-) groups (Tab. 1, 2, 3) or between groups that experienced or not particular manifestation (Tab.4.). For the comparison of the quantitative data (such as WBC, CRP, heart rate or body temperature) we used Mann-Whitney U test, whereas for the comparison of the qualitative data (such as presence of older siblings, positive allergic history) - chi-square test. We clarified it in the Methods section.

Q2: For what purpose are the laboratory tests mentioned in lines 89 to 91 analyzed?

R2: The laboratory tests mentioned in these lines (WBC, CRP, NLR, ESR, level of hemoglobin and capillary blood gases) are mentioned because there were one of the analyzed risk factors for severe course of the infection and its complications. Thanks to this analysis we showed that the lower inflammatory markers on admission to the hospital, the higher the risk of severe course of the disease.

Q3: In the method section, the RSV risk factors and how to analyze their relationship to the occurrence of RSV should be specified. As mentioned in the Objectives section, if the purpose of the study is to evaluate the relationship between RSV and its risk factors, the risk factors should be hypothesized before performing statistical analysis. If the purpose is to report the risk factors observed in the study, this is a descriptive and exploratory purpose and should be written differently in the study objectives section.

R3: In the method section we added a paragraph regarding the RSV risk factors and predictors of the disease severity that we had evaluated.

Q4: In lines 118 to 131, the side effects, outcomes and risk factors of RSV are indistinguishable from each other.

R4: We reorganized this paragraph to make it more transparent.

Reviewer 3

Q1: Abstract: Association is better than correlation. Please substitute it instead of correlation in all part of your manuscript.

R1: Thank you for this remark. I have already replaced the world “correlation” with “association” in all part of the manuscript.

Q2: Some English revision is needed.

R2: The manuscript was revised by a native-speaking medical doctor.

Q3: Introduction: RSV is belonged to Paramixoviridae family not Pneumoviridae and I couldn’t see it in references 4 and 5 that you cited.

R3: We checked it in a taxonomy of viruses, and it is stated (as we wrote in the article) that RSV is belonged to Pneumoviridae. Moreover, it can be found in the reference 4 in the heading “The virus, prone to genetic change” as cited: *Human respiratory syncytial virus* are found within the genus *Orthopneumovirus*, family *Pneumoviridae*, order *Mononegavirales*.”.

Q4: References: Following 6 authors et al. should be written not 3 authors.

R4: Thank you four this remark. We corrected the references.

Associate Editor 1

Q1: Pneumonia, bronchiolitis, otitis media and conjunctivitis are clinical manifestation of RSV virus in ARI tract (not complication), but if you found bacterial etiology for above manifestation you can consider these items as complication of RSV disease.

R1: Thank you for this remark. We revised the entire manuscript in order to name and analyse these ailments as “manifestations” not “complications” of RSV infection. However, it should be noted that in most of the studied that we referred to in the discussion these states are called “complications”. Therefore, comparing the achieved results could be misleading.

Q2: Which percent of your patients had bronchiolitis manifestation as a most manifest ion of RSV virus in respiratory tract.

R1: We added this information to the table 3. We estimated that the percentage of bronchiolitis amounts to 36.92%.

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Revision (1)

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** (1) 25 Sep 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (1) 26 Sep 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.