Author's response to reviews

Title: Altered cardiac rhythm in infants with bronchiolitis and respiratory syncytial virus infection

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Editor
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Dear Editor,

Please Thank you for giving us the opportunity to consider our manuscript # 1133081597437819 “Altered cardiac rhythm in infants with bronchiolitis and respiratory syncytial virus infection” adequate for publication as Research Article in BMC Infectious Diseases.

Please find attached the revised manuscript and our replies to questions and recommendations.

On behalf of all coauthors, I declare that the text has been reviewed by a native English speaker with appropriate knowledge of the subject matter. We hope that you will now find the paper suitable for publication in BMC Infectious Diseases.

Yours faithfully,

Susanna Esposito
Replies to reviewer 1 (Giuseppe Gerna)

Thank you for your comments. We have modified the paper according to your recommendations.

1. On the basis of our previous experience in children with bronchiolitis in which we showed that RSV was the main cause of acute episodes in hospitalized children [22], in this study only RSV was searched on nasopharyngeal secretions. (p. 6, lines 110-113). We have clarified that this represents a limitation of our study (p. 12, line 276). Despite RSV represents the absolute main cause of bronchiolitis in infants and in various studies it has been detected as single pathogen in more than 60% of the cases, it could be interesting to understand whether other viruses may cause a similar cardiac involvement as well as sinoatrial blocks could be more severe and persistent when RSV acts as a co-pathogen with another virus (p. 13, lines 277-281).

2. We have highlighted that the association between high viral load in respiratory secretions and prevalence of sinoatrial blocks is intriguing because since the role of viral load in respiratory secretions is controversial several recent studies have highlighted its importance in conditioning respiratory symptoms and disease’s severity (p. 13, lines 293-297; p. 20, lines 437-459).

3. It has been clarified that in our population all the three cases of severe bronchiolitis showed a sinoatrial block. The very low number of subjects with severe infection could have limited the statistical power to detect between group differences according to disease severity (p. 12, lines 269-272).

Replies to reviewer 2 (Massimiliano Fabbiani)

Thank you for your carefulness and competence. We have modified the paper according to your recommendations.

1. Statistical analysis for continuous data were better described. For the comparison between groups (i.e., RSV-positive vs RSV-negative), the continuous data were analysed using a two-sided Student’s test if they were normally distributed (on the basis of the Shapiro-Wilk statistic) or a two-sided Wilcoxon rank-sum test if they were not. For the comparison within group (i.e., admission vs 28 ± 3 days after admission in the RSV-positive and RSV-negative groups, separately), the continuous data were analysed using a paired two-sided Student’s test or signed-rank test, as appropriate (p. 9, lines 194-200).
2. A column with p values has been added in Table 1 (p. 22).

3. Sorry for the confusion. The Table has been modified (p. 22). We considered the number and percentage of patients and the comparison is related with the proportion of patients. We have also evaluated the mean number of respiratory infections or antibiotic courses, but considering the age of the patients these numbers were around one per patient with respiratory infection or treated with antibiotics. For this reason, we prefer to show the number and proportion of those with respiratory infection or treated with antibiotics.

4. A column with p value has been added in Table 2 (p. 23).

5. A row with mean temperature ± SD has been added as suggested (p. 23).

6. It has been clarified in the text and in the Table that all the patients were treated only with inhalatory bronchodilators (p. 6, line 118; p. 10, lines 213 and 215; p. 23). Considering patients’ age, it is not possible to administer oral bronchodilators because these drugs are not available in soluble form. Moreover, it is not common practice to administer iv bronchodilator even in respiratory failure during bronchiolitis because of the potential adverse events of these drugs in the first months of life and the absence of evidence of their effect in bronchiolitis.

7. Symbols and notes in Table 3 have been clarified (p. 24).

8. As suggested, it has been underlined that in our population all the three cases of severe bronchiolitis showed a sinoatrial block. The very low number of subjects with severe infection could have limited the statistical power to detect between group differences according to disease severity (p. 12, lines 269-272).

9. It has been clarified that the association of sinoatrial block and RSV viral load remains significant even after excluding patients with severe disease (p. 11, lines 235-236).

10. All the patients received inhalatory bronchodilators (p. 6, line 118).

11. The hypothesis on the association with sudden infant death has been deleted as suggested (p.12, lines 272-275; p. 21, lines 459-460).

12. The sentence has been modified as suggested (p. 13, line 293).

13. The word “oximetry” has been corrected (p. 6, line 103).

14. From the beginning of the study, it was decided to estimate pulmonary pressure as well as signs of pulmonary hypertension only in presence of pathologic findings at echocardiography (p. 6, lines 114-116).

15. Previous reference # 28 has been deleted (p. 19, lines 426-437).

Replies to reviewer 3 (Luis Garcia-Guereta)

Thank you for your comments. We have modified the paper according to your suggestions.

1. It has been added that current arrhythmia guidelines do not recommend any kind of intervention in transient sinoatrial block (p. 12, lines 259-262; p. 19, lines
430-436). However, it is reported that the aim of the study was to verify the real frequency of heart involvement in patients with bronchiolitis associated with RSV infection, and whether infants with mild or moderate disease also risk heart malfunction (p. 5, lines 78-80). Our findings highlight the need of further studies on the impact of sinoatrial blocks in patients with chronic underlying disease at risk of complications during RSV infection (p. 12, lines 262-264).

2. It is difficult to create a clear figure with EKG findings, especially clear for the potential reader of our paper. In our opinion, Table 3 represents clearly these data (p. 24). Also on the basis of comments of another reviewer, some clarifications have been done in Table 3.

3. It has been underlined that to the best of our knowledge this is the first report that associates sinoatrial blocks and RSV bronchiolitis (p.11, lines 248-250).

4. Also in agreement with another reviewer, the hypothesis on the association with sudden infant death has been deleted as suggested (p.12, lines 272-275).

5. It has been clarified that on the basis of our findings we do not recommend routine cardiac monitoring of infants with bronchiolitis in general wards (p. 12, lines 259-262).

6. The reference you suggested has been added (p. 4, line 59; p. 16, lines 362-363).