Author’s response to reviews

Title: Bacterial Contamination of Home Nebulizers in Children with Cystic Fibrosis and Clinical Implication on the Number of Pulmonary Exacerbations

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Author’s response to reviews:

Dear editor in chief and the reviewers

We are so grateful for your valuable comments on the manuscript entitled “Microbial Contamination of Home Nebulizers in Children with Cystic Fibrosis and Clinical Implication on the Number of Pulmonary Exacerbations”. All the comments and recommendations were reviewed by all co-authors, and the changes were made. The manuscript was sent for English edit. Finally, the revised and edited manuscript was read by all co-authors. Below you can find each reviewer’s comment and the answers (blue highlights). We are kindly asking you to let us know if we should provide more changes.
John David Aubert, MD (Reviewer 1):

Overall the authors have nicely answered the comments and queries from the reviewers, both on methodology and results. The addition of antibiotic testing for Ps aeruginosa in nebulizer and sputum samples is definite plus of the study.

I have three minor remarks:

I do not understand the use and significance of Odds Ratio applied to the Chi-square analysis for bacterial culture: in my opinion the p value is enough: “The overall correlation of sputum and nebulizer cultures was 93% (P &lt;0.001, OR=20.95)."

The OR has been removed from the manuscript

The new paragraph and table 4 on hygiene protocol and maintenance is confusing: it is said that only ~50% of the patients washed their nebulizers but in the next sentence that all the patients did the cleaning procedure properly. Obviously one of the affirmation is incorrect, unless the second one applies only to the 50% who did the procedure? Please clarify

Thank you for your comment, we have evaluated nebulizers’ hygiene in 4 separated aspects (cleaning step, disinfection, drying step and the frequency these steps) so it is possible that someone does the cleaning, drying and disinfection correctly but instead of doing it after each use (which is considered the ideal frequency by CF foundation), he/she does it every week. In our study all patients did the cleaning step correct (as it was obvious and easy to wash the nebulizer with water) but the problem was they did not know that nebulizers’ hygiene and maintenance was not only washing with water….they had to the disinfection step too and also they should have let the device dry on air (the only acceptable way of drying by CF foundation). And also apart from doing all these 3 steps correctly the had to do it with correct frequency (after each use).

I have changed the text in a way to clarify these steps and decreasing the misunderstanding.

Table 1: keep the same number of decimals between the results (nb of daily inhalation) and the SD

Correction was done
Reviewer 2

The entire manuscript needs to be reviewed closely for language use. Grammatical and syntactical problems are obscuring in many places the meaning of the sentence the authors wanted to convey.

English editing has been done to the best of our knowledge and changes have been highlighted in green.

Abstract Results: last line: These numbers are not making sense as currently written. Generally in the whole manuscript, numbers written in the text are often unclear, and without units.

The requested correction was done.

Background: penultimate paragraph: "Several cohort studies" is mentioned. Please provide references for these studies to support this. (Currently, only one reference is noted.)

2 more references were added.

Methods: The statement of No Placebo in current study is superfluous, since by design, this is not a placebo controlled study.

The mentioned sentences was deleted from the text.

Methods: CLSI publication needs a proper citation.

The reference number 18 was added in the manuscript.

Methods: There is a serious mistake in the Statistical Analysis as currently written. If results were expressed as means with Standard deviations, this assumes that the distribution of data points was Gaussian/normal. Therefore, parametric measurements such as T-tests and ANOVA would be appropriate. Mann-Whitney U test (non-parametric) is appropriate when the data is NOT normally distributed. Please correct this error, and correct your calculations if necessary.
Respected sir we first assessed the data for distribution and with normal distribution we have used student T test and we have made changes in the manuscript. The continuous variable which were not distributed normally Mann-Whitney U test have been used that too give mean and SD but definitely different value when compared to Student T test. We have rewritten the statistical analysis part.

We hope that this clarifies all the queries raised

Description of Figure 1 in text. Please correct the spelling of 'Swab'.

The correction was done.

Results: Nebulizer, sputum culture and Candida -- this relationship is marked as significant, but the P is above 0.05.

There was writing mistake and we apologies for the same. We have made all the corrections and now the statement hold right

Discussion: Where is the antibiogram data?

As I have mentioned in the cover letter of the first revision, we could not perform antibiogram for all microorganisms as it was our study limitation despite we had planned to do it. So in the manuscript we had submitted initially we did not reveal mention anything about antibiogram results. Since it was mentioned and suggested by reviewer 1 in the first revision that the antibiogram data would strengthen the relevance of the correlation, we decided to add the only antibiogram result we had which was for pseudomonas spp, we know the data on antibiograms was not completed but we thought it would be interesting for readers and it would be a suggestion and guide for future studies. But if you find this data confusing we can omit it from the manuscript. We have written this in the limitation of the study.

Device contamination impact on clinical outcomes: If this is considered important to be discussed, there needs to be actual descriptive data showing what kind of 'exacerbations' the authors are referring to.

We have written this in method that we sought last 12 months data of all patient and analysed the number of exacerbations ended in hospital admission and IV antibiotics per year in study group. We again compared these finding in the patient who had and who didn’t have any pathogenic bacterial growth from the nebulizer. The result showed significant increase in the observed parameters.
Last paragraph of discussion: ""Older patients"" is an unclear term. Since it refers to older children, it should be clarified, if necessary by indicating the age range.

Older patients refer to older children. We have already mentioned the age range in the result session “the mean age of the subjects not properly observing the hygiene of nebulizers was significantly higher than the ones doing the whole process correctly (8.4±4.1 years vs 5.3±3.5 years; P <0.001).” but in order to make this part more clear as you have suggested we replaced this statement with “older children”.

Conclusion: poor nebulizer hygiene linked to treatment non-adherence seems to be all speculative. This needs to be clarified in the text of Conclusions. The unnecessary verbiage should be cut down by combining sentences.

Requested changes was done.

Limitations: It is not at all clear how the stated factors can confound the observation of presence or absence of bacteria on home nebulizers. If these are indeed important, this needs to be discussed at the end of the discussion (or under the limitation section).

Requested changes was done.

Figures 1 & 2: For Enterobacter and other organisms, the error bars seem to have gone into the negative axis. This does not make numerical or scientific sense. It is also completely unclear from the text what the percentage values in the Y-axis represent."

We have made figures again and have labelled both X axis and Y axis again

Reviewer 3

Francesca Bai (Reviewer 3): The authors have tried to modify the text accordingly to reviewers' comments.

I only suggest a further revision of the statistical analyses by a statistician

We have made changes in the statistical analysis of the study