Author Response 1

Reviewer: 1

Comments to the Author

Abstract: 'tolerates' should be tolerate

Corrected, thank you.

Page 6, line 24: Should be 'enhancing' instead of enhance

Corrected, thank you.

Page 6, line 57: Is there evidence that higher salt concentrations increase nebulization time? Please cite.

Thank you for highlighting this erroneous statement. There is no evidence for it, and therefore we have deleted it.

In the mechanisms of action section, it is worth mentioning that the airway actively transport salt from the airways through ENaC. It would be useful to discuss whether there is anything special about salt in this role or whether anything that generates an osmotic gradient might work just as well.

We have modified the paragraph to include the effects of ENaC:

In addition to improvement of mucociliary clearance, some studies have shown that HS decreases mucus viscosity33,34, stimulates cough9,35, enhances the effectiveness of respiratory physiotherapy in both CF27 and bronchiectasis patients14,15, accelerates mucociliary clearance via electrostatic interactions with mucins36, or inhibit epithelial sodium channels (ENaC).31 Goralsi et al, using human bronchial epithelial cells speculated that sodium transport would modify the magnitude of HS-induced airway surface liquid volume expansion immediately after initiation of HS administration. As compared to HS alone, co-administration of a selective ENaC blocker produced a more rapid and sustained ASL response during nebulisation.31

We have introduced references:

Goralski JL, Wu D, Thelin WR, et al. The in vitro effect of nebulised hypertonic saline on human bronchial epithelium. Eur Respir J 2018; 51: 1702652.

Tang XX, Ostedgaard LS, Hoegger MJ, et al. Acidic pH increases airway surface liquid viscosity in cystic fibrosis. J Clin Invest. 2016 ; 126: 879-891.

In the mechanisms of action section, a discussion of what is known about mucus in bronchiectasis would be helpful. There isn't a mechanism for dehydration like there is in CF and there isn't a mechanism for mucus hypersecretion like there is in chronic bronchitis. Why would a hydrating agent line HS help?

We have introduced the following paragraph on this topic:

Although the mechanism of HS in bronchiectasis patients is not well known, in these patients the sodium and chloride concentrations are below the optimum for mucociliary transport, as suggested by Wills33. Retained mucus favors infection, which ultimately causes the vicious cycle of events leading to chronic lung inflammation. HS could possibly increase the salinity of the retained secretions, particularly the gel surface, where improved effectiveness of interactions with cilia could result in increased mucociliary clearance33.

Reference 33:

Wills PJ, Hall RL, Chan W, et al. Sodium chloride increases the ciliary transportability of cystic fibrosis and bronchiectasis sputum on the mucus-depleted bovine trachea. J Clin Invest 1997; 99: 9-13.

Page 9: 'FEV1 and FVC percentages' should be described as percentages of predicted values

Thank you, change made

Please refer readers to Table 2 at the beginning of the study design section in the text.

Thank you, change made

In the text section on study design, please specify in each study that these were nonCF bronchiectasis patients (except for the last study obviously).

Please note that, as stated in the beginning of the review, when we discuss about nonCF bronchiectasis, we just write 'bronchiectasis'. However, when we refer to bronchiectasis secondary to CF, we refer to it as 'CF'.

It would also be helpful to know average baseline FEV1 for each study. That could be added to table 2.

Included in Table 2.

In the study design section, I have trouble understanding why the authors have included a study about HS in ciliary dyskinesia. This should be justified in the study design section or this study should be removed. This is a very different disease.

We have deleted the reference to ciliary dyskinesia. The reviewer is correct in that patients with bronchiectasis secondary to ciliary dyskinesia have a different prognosis than patients with bronchiectasis of other etiologies. Even so, there are no clinical trials that assess the efficacy of the treatments that are commonly used in ciliary dyskinesia, so the recommendations on patients with this condition are based on the guidelines of CF and are included in the guidelines for bronchiectasis.

In the section on lung function it would be useful to present the extent of the changes in FEV1 from the studies where a significant difference was found. This is helpful in determining whether the result is clinically significant.

Added: "(FEV1 improved 15.1 with HS versus 1.8 with IS)".

Similarly, the point made at the end about differences in baseline pulmonary function between studies should include numbers as well. This information could be put on table 2 with the results along with p-values for significant results.

We have now included the baseline values for the studies by Kellet, Nicolson and Paff in the text and in Table 2.

Under adverse events for HS: It would be useful to know how many subjects were excluded for initial intolerance of hypertonic saline if that was reported in any of the studies. Presumably some did screening treatments with the drug prior to randomization. Something similar to the presentation for HS + HA would be helpful.
We have now included details of patients that had to be excluded during initial screening due to HS intolerance.

In HS + HA section, '...observed in the lungs of people and animals, facilitating ventilation and gas exchange." Please be more specific. What exactly was reported in these studies.
We have added the following text clarifying the role of HA:
HA participates in many biological processes such as homeostasis, angiogenesis, and cell migration and proliferation. Some studies suggest that HA and its degradation products can play an important role in the pathobiology of the respiratory tract.50
We have removed reference by Schdmidt and inserted reference 50 and:
Lauer ME, Dweik RA, Garantziotis S, et al. The rise and fall of hyaluronan in respiratory diseases. Int J Cell Biol 2015; 2015: 712507.

Conclusions: Add references to first line which describes CF outcomes. In general all of the specific statements in the conclusions require references.
We have added references to the conclusions

The conclusions section is very sparse and should be expanded to include general conclusions on the use of HS and HS+HA in bronchiectasis based on reported data on safety and efficacy.
We have included the following referenced paragraph in the conclusions:
In bronchiectasis there is less evidence for the use of HS or HS+HA than in CF. However, some studies suggest that HS can facilitate expectoration,15,16,65 decrease the sputum viscosity,15,16 increase lung function16 and decrease the frequency of exacerbations.16 Due to this and its excellent clinical response to it in clinical practice, most guidelines on bronchiectasis recommend its use.20,21,24

Reviewer: 2

Comments to the Author

Thank you for the opportunity to review this paper, which comprehensively reviews the current state of literature regarding hypertonic saline use in non-CF bronchiectasis. Although the manuscript includes RCTs previously reviewed, discussed and included in international guidelines, the novel summary of up to date trials incorporating the use of hyaluronic acid makes this a useful addition to the literature base.

Hence my comments and suggestions are minor in nature.

The overall paper is well written and composed. The 'comprehensive review' nature allows for a more in-depth investigation of the 3 RCTs included in other, similar review pieces.

We thank the anonymous reviewer for the comments.

Abstract: Depending on journal guidelines, i feel a more conventionally structured abstract would allow the time-restricted reader to appraise the article more easily. ie: results, discussion, conclusion.

Following journal guidelines, the abstract was left unstructured.

I found all the tables to be informative and warranted. For me, Figure 1 seems unnecessary.

We have removed Figure 1 from the manuscript.

Page 5, line 47 - the reference to Elkins et al discusses proinflammatory markers, labelling IL-6 to 10 as 'drugs', would cytokines be more appropriate?

Changed, thank you.

Page 6, line 57-59, it is stated that higher salt concentrations lead to longer neb times. Is there referenced works for this?

Thank you for highlighting this erroneous statement. There is no evidence for it, and therefore we have deleted it.

Page 7, line 55, one of the kellett papers is discussed, stating the use of 2ml HS and IS. I have previously reviewed this paper, and couldn't locate the reference to the 2ml quantity. Could you comment as to whether this was information gathered from the author?

The reviewer is correct. We now substituted '2 ml' for 'one dose'.

HS and hyaluronic acid

I note that the premise of these trials was to make HS more tolerable. In reflection from the first 3 HS trials discussed, adverse events and withdrawal seemed low, making tolerability seemingly not a large hurdle. I feel this section would be improved by the incorporation of a discussion section prior to conclusions as per a classic systematic review in order to elaborate on the impact of these most recent papers on current practice.

The following text has been added:

Although few of patients in the earlier studies using HS had to leave the studies because of intolerance,14,15,16 in the study by Maiz et al, more than a third of the patients were intolerant to HS in the first week of the study.66 Although more studies are needed to know the factors determining tolerance in these patients, it is likely that older age and worse lung function decrease its tolerability.

Author Response 2:

Thank you for the comments from a reviewer. We have now corrected the typo and referenced the statement as requested. The final sentence of the HS+HA section follows:

"Although more studies are needed to know the factors determining tolerance in these patients, it is likely that older age and worse lung function contribute to decreased tolerability.65,66"