Reviewer 1 v.1

Comments to the Author:

Abstract: 'tolerates' should be tolerate

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

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

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.

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?

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

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

In the text section on study design, please specify in each study that these were non-CF bronchiectasis patients (except for the last study obviously). It would also be helpful to know average baseline FEV1 for each study. That could be added to 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.

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. 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.

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.

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.

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

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.

Reviewer 2 v.2

Comments to the Author:

Thanks to the authors for their willingness to modify the manuscript based on reviewer comments.

I've noted a minor typo / grammatical error in the added sentence at the end of the HS+HA section as follows:

'...it is likely that older age and worse lung function decrease contribute to decreased tolerability.'

Also, is this the authors hypothesis, or can this statement be linked to existing evidence? If the former, perhaps consider changing the wording from 'likely' to 'possible', if the latter, this should be clearly referenced.

Provided these small amendments are made, i have no further comments.

Reviewer 2 v.1

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.

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.

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

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?

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

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?

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.