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# The Efficacy and Tolerability of the Combination of Inhaled Hypertonic Saline and Hyaluronic Acid versus Inhaled Hypertonic Saline in Patients with Cystic Fibrosis

Kelsie Look

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## **Abstract**

**Background:** Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease found among Caucasians. It is known to target many organs systems such as the lungs, liver, and intestines but the most affected organ is the respiratory tract. Patients with CF usually develop some type of pulmonary dysfunction resulting in frequent asthma-type exacerbations and chronic bacterial infections due to excessive mucus adhesion. Maintenance therapy with hypertonic saline (HS) has shown to be beneficial in helping with mucociliary clearance but compliance is low due to a high profile of side effects. Recent studies have shown that hyaluronic acid (HA) in addition to HS helps improve the tolerability of HS. The purpose of this review is to further evaluate the benefits of combination therapy on tolerability and efficacy in patients with CF.

**Methods:** A comprehensive search of the medical literature was conducted using various search modalities including Medline/OVID, EBSCOhost/CINAHL, Web of Science, and Google scholar. Keywords used included: cystic fibrosis, hypertonic saline, and hyaluronic acid.

**Results:** Three articles met the inclusion and exclusion criteria for this systematic review. All three articles were randomized control trials which showed a statistically significant improvement regarding tolerability with the addition of HA to HS.

**Conclusion:** This systematic review provides evidence that supports the indication for combination therapy with HA to improve tolerability and efficacy of HS therapy alone in patients with CF. However, these results would be strengthened with larger and longer randomized controlled studies.

**Keywords:** cystic fibrosis, hypertonic saline, hyaluronic acid

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## **Degree Name**

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## **Keywords**

cystic fibrosis, hypertonic saline, hyaluronic acid

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**The Efficacy and Tolerability of the Combination of  
Inhaled Hypertonic Saline and Hyaluronic Acid versus  
Inhaled Hypertonic Saline in Patients with Cystic  
Fibrosis**

**Kelsie Look**



*A Clinical Graduate Project Submitted to the Faculty of the*

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*Faculty Advisor: Mary E. Von, DHEd, PA-C, DFAAPA*

*Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS*

## **Biography**

Kelsie Look is a native of Honolulu, Hawai'i and graduated with a Bachelor of Science degree in Biology from the University of Hawai'i Manoa in 2009. After completion of her undergraduate studies, she worked as a lab assistant at Queen's Medical Center in the pathology department. She also volunteered at Shriners Hospital for Children and at an internal medicine practice in Kuakini Hospital. Kelsie will be moving back to Hawai'i to practice medicine upon completion of her degree at Pacific University of Oregon's Physician Assistant program in October 2014.

## **Abstract**

**Background:** Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease found among Caucasians. It is known to target many organs systems such as the lungs, liver, and intestines but the most affected organ is the respiratory tract. Patients with CF usually develop some type of pulmonary dysfunction resulting in frequent asthma-type exacerbations and chronic bacterial infections due to excessive mucus adhesion. Maintenance therapy with hypertonic saline (HS) has shown to be beneficial in helping with mucociliary clearance but compliance is low due to a high profile of side effects. Recent studies have shown that hyaluronic acid (HA) in addition to HS helps improve the tolerability of HS. The purpose of this review is to further evaluate the benefits of combination therapy on tolerability and efficacy in patients with CF.

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Table I: Characteristics of Reviewed Studies

Table II: Summary of Findings

**List of Abbreviations**

CF.....Cystic Fibrosis  
CTFR.....CF Transmembrane Conductance Regulator  
HS.....Hypertonic Saline  
HA.....Hyaluronic Acid

# **The Efficacy and Tolerability of the Combination of Inhaled Hypertonic Saline and Hyaluronic Acid versus Inhaled Hypertonic Saline in Patients with Cystic Fibrosis**

## **BACKGROUND**

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive genetic disorder found among caucasians.<sup>1</sup> The disease involves various organ systems such as the lungs, liver, and intestines.<sup>2</sup> The most affected organ system is the respiratory tract and lung disease which causes a 95% morbidity and mortality in patients with CF.<sup>3</sup>

CF is caused by a defect in the chloride-ion transport protein, CFTR, which functions as an apical epithelial chloride channel. Absence of CFTR results in failure to secrete Cl<sup>-</sup> and unrestrained Na<sup>+</sup> absorption leading to the depletion of the airway surface fluid that covers airway epithelial cells.<sup>4</sup> The depletion of airway surface liquid as well as consecutive breakdown of mucociliary transport ultimately causes excessive adhesion of mucus to airway surfaces.<sup>5</sup> This retention of mucus is believed to favor bacterial overgrowth which triggers chronic infections and airway inflammation.<sup>4</sup> There is some controversy about how the loss of CFTR function contributes to the pathogenesis of CF but several mechanisms have been proposed.<sup>3</sup> However, it is known that patients with CF often acquire *Pseudomonas aeruginosa* infections that are frequently refractory to antimicrobial therapy. Therefore, regardless of antimicrobial therapy, CF airway infections are suppressed for short periods before reoccurring.<sup>6</sup>

The management of CF is based around chest physiotherapy to loosen and break up mucus, antibiotics to treat infections, pancreatic enzyme replacement, and careful monitoring of nutritional status.<sup>7</sup> However, it is understood through previous studies that the inhalation of hypertonic saline (HS) increases mucociliary transport and improves

lung function.<sup>8</sup> HS increases the NaCl concentration on airway surfaces resulting in increased absorption of Cl<sup>-</sup> in the paracellular path due to the absence of CFTR.<sup>9</sup> This path has a slower rate of NaCl absorption compared to the normal Cl<sup>-</sup> channel used when the CFTR is functioning. The result is an increased retention of NaCl on airway surfaces and an osmotic gradient which favors water flow from the HS that persists for longer periods of time. In simpler terms, HS helps increase hydration of airway surface liquid by improving mucociliary clearance. The overall outcome is less mucus adhesion.<sup>10</sup>

However, a main issue with HS treatment is compliance due to the side effects patients with CF experience. Common complaints include increased cough, chest tightness, and throat irritation.<sup>11</sup> Particularly in children, the salty taste of HS contributes to the lack of long term compliance and use.<sup>10</sup>

Hyaluronic acid (HA) has been used in lung disease to help prevent bronchoconstriction due to its hydration properties.<sup>12</sup> A case study done in 2013 involving a 13 year old Caucasian boy with CF who was experiencing recurrent wheezing and consistent asthma-type exacerbations despite treatment with maintenance therapy with HS. The patient was observed over a period of seven years while on treatment with HS+HA. The overall results with combination therapy showed a significant decrease of oral antibiotic administration, an elimination of the need for oral steroids, and an improvement in the frequency of pulmonary exacerbations this patient experienced.<sup>13</sup> This study showed that the addition of HA to HS may improve tolerance to HS as well as results in stability of pulmonary function.

HA is a glycosaminoglycan whose function is to balance water homeostasis in the extracellular matrix. Many studies have been done *in vitro* and *in vivo* demonstrating the

potential benefits of HA by inhalation. One unique property of HA which is particularly useful is its water-retaining properties and the fact that the water content of a tissue depends on the amount of HA it contains.<sup>12</sup> For these reasons, it is believed that the use of HA in lung disease such as CF will be beneficial in reducing the adverse effects of HS as well as decreasing poor compliance with therapy.

The goal of this study is to conduct a systematic review of the literature on patients with CF and to further evaluate the benefits of using combination therapy versus HS alone.

## **METHODS**

A comprehensive search of the medical literature was conducted using various search modalities including Medline/OVID, EBSCOhost/CINAHL, Web of Science, and Google scholar using the keywords “cystic fibrosis,” “hypertonic saline,” and “hyaluronic acid” individually or in combination. Inclusion criteria for this systematic review were publication dates from 2000-2014, English language studies on humans, and randomized controlled trials. Excluded from this review were case reports. The reviewed studies were critically appraised and assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).<sup>14</sup>

## **RESULTS**

A total of three articles which met the inclusion and exclusion criteria were examined in this review (see Table I). The average sample size was approximately 29,

with the largest group studied consisting of 40 patients with CF, and the smallest group consisting of 20. The shortest study lasted 2 days and the longest study lasted 28 days. All three articles<sup>2,15,16</sup> included in this review were randomized, controlled studies. Of those three articles, two were double-blinded while the other used computer randomization. All studies looked at the benefit of using combined HA+HS versus HS in patients with CF.

### **Ros et al**

Ros et al,<sup>15</sup> conducted in 2014, was a double-blinded, randomized controlled study that looked at the effects of using HS+HA versus HA alone during a four week treatment period. Participants were recruited from four Italian CF centers and were required to be at least 8 years old with a confirmed diagnosis of CF. Other inclusion criteria were the presence of clinically and therapeutically stable disease during the previous 30 days, a FEV<sub>1</sub> ≥ 50% of predicted value, and intolerance (cough, throat irritation, saltiness) to HS solution. Exclusion criteria included a decrease in FEV<sub>1</sub> > 15% after HS, an infection with *Burkholderia cepacia*, infective exacerbation requiring antibiotics in previous 15 days, non compliance to standard therapy, a history of lung transplant, the inability to perform reproducible spirometry, intolerability to beta 2 bronchodilators, current enrollment in other clinical trials, or having circulating plasmatic creatinine or transaminase levels higher than twice normal values.<sup>15</sup>

A total of 40 patients of both sexes, 10 participants per center were enrolled in the study and randomized to one of two treatment groups. The treatment groups consisted of 20 patients to standard therapy with HS and 20 patients to HS+HA therapy. Before

starting treatment, qualified participants were given 200 µg of salbutamol. The test product (HA+HS or HS) was then administered with a nebulizer over approximately 15 minutes. Spirometry was done three times: at time 0, then 15 minutes after salbutamol, and lastly 30 minutes after the test product. All participants were given 60 visually identical vials to be used twice a day for 28 days. They were required to use salbutamol 15 minutes prior to each treatment and to complete self-assessment cards every week. The last dose of treatment was given in hospital and spirometry was again performed three times as before. There were no significant differences in baseline characteristics and spirometric evaluation of patients between groups. There were five patients who did not complete the study, two from the HS+HA group and three from the HS group. Reasons for incompleteness of the study included cough or throat irritation, and respiratory exacerbation.<sup>15</sup>

The primary outcome was to assess whether the combination product of HS+HA was better tolerated than HS alone in patients who had shown little tolerance to HS. Effects were evaluated based on cough, throat irritation, salty taste and overall acceptability using a semiquantitative scale on a diary card weekly. The secondary outcome evaluated the change in FEV<sub>1</sub> at the end of treatment.<sup>15</sup>

The severity of cough, throat irritation, and saltiness decreased in patients treated with HS+HA compared to HS alone. In the group of patients who received HS+HA, symptoms of cough, throat irritation, and saltiness was milder (10%, 15%, and 10%) compared to HA alone (60%, 40%, and 60%). In addition to these values, the RRR for each symptom was 83%, 62%, and 83% respectively which shows a significant reduction when using combination therapy of HS+HA.<sup>15</sup>

Although there was an increase in FEV<sub>1</sub> in both groups after inhalation with salbutamol, there was no significant reduction in FEV<sub>1</sub> with both treatments (HS+HA and HS alone). Furthermore, there was no significant difference of FEV<sub>1</sub> between the two groups after 28 days treatment.<sup>15</sup>

### **Funari et al**

Funari et al,<sup>2</sup> conducted in 2012, was a double-blinded, randomized controlled study that assessed the tolerability of HS when used in combination with HA over a period of 28 days. The study took place at the Regional Reference Centre for Cystic Fibrosis in Italy. The inclusion criteria were male and female patients at least 10 years old, a clinical diagnosis of CF, a FEV<sub>1</sub> at least 40% of predicted value, current stable antibiotic, mucolytic, or anti-inflammatory treatment in 3 months prior to the study, and provided informed consent. Exclusion criteria included any *Burkholderia cepacia* infection, HS therapy in the 15 days preceding enrollment, an exacerbation of infection in the 15 days before inclusion which required antibiotic therapy, or changes in chronic therapy in the 28 days before the enrollment period. Those who qualified for the study were immediately assessed after receiving treatment at their baseline visit. If treatment was not tolerated even after use of a beta 2 bronchodilator, they were dismissed from the study.<sup>2</sup>

A total of 30 patients of both sexes were enrolled in the study and randomized to one of two treatment groups: 15 patients to therapy with 7% HS and 15 patients to Hyaneb (HS+HA) therapy. Treatment consisted of one inhalation of the assigned product twice a day for 28 days to be done at home. A short-acting B2 bronchodilator was given



to the selected patients in case of bronchospasm which was recorded in patient diaries if used. They were allowed to continue with their usual treatment for lung disease or concomitant diseases as long as they were under such treatment during the time of the study inclusion. FEV<sub>1</sub> was measured twice; before and one hour after inhalation of the assigned product. All patients were required to complete an evaluation questionnaire on tolerability and pleasantness of their assigned treatment weekly and log their results in a patient diary. There were no significant differences in demographic characteristics and spirometric evaluation between the two groups in this study. There was a total of one dropout which was from the baseline visit while two others did not complete their diaries and were omitted from the final results of the study (two participants from the HS group and one from the combination therapy group).<sup>2</sup>

The primary outcome was to assess whether the addition of HA improved the tolerability of HS in patients with CF. Effects were evaluated based on bronchospasm which was measured based on the amount of beta 2 agonists used and FEV<sub>1</sub> before and after treatment. The secondary outcomes evaluated cough, irritation, thoracic constriction, saltiness, and efficacy of the combination product on pulmonary function.<sup>2</sup>

The use of beta 2 agonists was statistically significantly lower in the Hyaneb group versus the HS group (RRR= 60%, P<0.0001, 95% CI of -1.3 to -1.1). At the end of the study, two patients (14.3%) in the Hyaneb group required beta 2 agonists compared to the five (35.7%) in the HS group.<sup>2</sup> There was a greater change in FEV<sub>1</sub> at baseline before and after treatment in the HS group compared to the Hyaneb group (4.3 versus 2.2 respectively). However, there was no significant difference in FEV<sub>1</sub> before and after treatment at the end of 4 weeks.<sup>2</sup> Analyzing the evaluation questionnaire confirmed the

positive benefits of HA on tolerability with statistically significant lower cough and throat irritation in the Hyaneb group ( $p=0.0010$ ). At baseline, 14 patients (100%) in the Hyaneb group had no or light throat irritation compared to the 11 (73.3%) in the HS group. By week 4, there was 10 patients (71.4%) with no irritation, four (28.6%) with light irritation, and none with moderate throat irritation in the Hyaneb group compared to eight (61.5%) with no irritation, three (23.1%) with light irritation, and two (15.4%) with moderate irritation in the HS group.<sup>2</sup> Overall pleasantness of treatment was significantly different ( $p<0.0001$ ) in favour of the Hyaneb group. Most patients in the Hyaneb group (92.8-100%) reported an absence of taste or saltiness compared to 46.7%-69.3% of patients in the HS group reported absence of taste or a light salty taste.<sup>2</sup>

### **Buonpensiero et al**

Buonpensiero et al,<sup>16</sup> conducted in 2010, was an open, randomized crossover trial which compared a single treatment of HS and a single treatment of HS+HA over a period of three days. Each treatment lasted one day with a washout period of one day inbetween. Allocation was concealed using an off-site investigator. Participants were recruited for one month from a regional pediatric CF center based on the following inclusion criteria of an established diagnosis of CF, an age of at least 6 years, a FEV<sub>1</sub> of 50% or more of the predicted value, and a clinically stable lung disease. Exclusion criteria were evidence of reactive airway or a clinical diagnosis of asthma.<sup>16</sup>

A total of 20 patients of both sexes who routinely received HS were placed into treatment groups through computer randomization, ten received treatment with HS and

ten received treatment with HS+HA. A dose of salbutamol was administered 30 minutes before each assigned treatment.<sup>16</sup>

The primary outcome of this study was to the tolerability of HS and HS+HA due to cough. Effects were evaluated based on cough, throat irritation, and salty taste using a four-point ordinal scale after each treatment. Results were recorded on a diary card. The secondary outcomes evaluated lung function testing and overall pleasantness. FEV<sub>1</sub> was measured using spirometry before and after each treatment while overall pleasantness was assessed using a Likert-type scale.<sup>16</sup>

There was a statistically significant difference between treatment groups regarding the measurement of cough, throat irritation, and saltiness ( $P < 0.05$ ).<sup>16</sup> The treatment group who received HS+HA rated the severity of cough 0 (absent) while the group receiving HS rated the severity 2 (moderate). Cough immediately after inhalation of HS occurred in 18 of 20 participants (90%) while after inhalation with HS+HA, cough occurred in only 7 of 20 participants (35%). There was a statistically significant reduction of cough with the addition of HA demonstrated by a RRR of 61% and an ARR of 55% (95% CI: 25%, 73%).<sup>16</sup> There was a significant reduction in prevalence of throat irritation with the combination treatment shown by ratings of 0 (absent) compared with ratings of 1 (mild) in patients treated with HS alone. Throat irritation immediately after inhalation of HS occurred in 14 of 20 participants (70%) while after inhalation with HS+HA, throat irritation occurred in only 1 of 20 participants (5%). Statistically, the RRR for throat irritation was 93% and the ARR was 65% (95% CI: 36%, 81%).<sup>16</sup> The ratings for severity of salty taste was 0 (absent) in the combination treatment group and 2 (moderate) in the HS group. A salty taste immediately after inhalation of HS occurred in all participants

(100%) while after inhalation with HS+HA, a salty taste occurred in only 2 of 20 participants (10%). The RRR for the prevalence of salty taste was 90% and the ARR was 90% (95% CI: 64%, 97%), which once again shows a significant reduction when using combination therapy of HS+HA.<sup>16</sup> For overall pleasantness, the ratings for the combination treatment group was 0 (absent) and 2 (moderate) for treatment with HS. There was a statistically significant reduction in unpleasant taste with the addition of HA shown by a p value < 0.05.<sup>16</sup>

The values of FEV<sub>1</sub> were identical in both treatment groups of HS or HS+HA preinhalation and postinhalation. There were no statistically significant differences or changes regarding lung function based on spirometry.<sup>16</sup>

## **DISCUSSION**

Pulmonary complications are highly probable in patients with CF since the respiratory tract is the most affected organ.<sup>3</sup> The main purpose of using inhaled HS in patients with CF is to improve mucociliary clearance and overall lung function. The benefit of HS is that it increases hydration of airway surfaces but at the same time, it is difficult to tolerate due to side effects such as unpleasant taste, increased cough, and airway irritation.<sup>10</sup> Some research has shown that with the addition of HA to HS, tolerability and efficacy has improved.

This systematic review evaluated three studies<sup>2,15,16</sup> which assessed the benefit of using combination therapy (HS+HA) versus HA alone and how this change affected tolerability and efficacy. All three studies demonstrated positive effects in regards to tolerability when using combination therapy in patients with CF (See Table II).

Specifically, Ros et al<sup>15</sup> demonstrated a statistically significant overall improvement in severity of cough, throat irritation, and saltiness with combination therapy with RRR values of 83%, 62%, and 83% respectively. Furthermore these findings were consistent with the Funari et al<sup>2</sup> study which showed a statistically significant improvement of saltiness with combination therapy versus HS alone ( $p < 0.0001$ ). Moreover, there was a statistically significant decrease in cough and thoracic constriction with combination therapy which was evaluated by usage of a beta 2 bronchodilator (RRR=60%) and spirometry. There was improvement of airway irritation in the HS+HA group versus HS group. The combination therapy group showed an increased tolerability with use of a five-point scale by scoring the study as acceptable whereas the HS group scored the study as disgusting and unpleasant.<sup>2</sup> The last study by Buonpensiero et al<sup>16</sup> also evaluated for cough, throat irritation, and salty taste. The addition of HA showed a statistically significant reduction in all outcomes (RRR of 61%, 93%, 90% respectively) and statistically significant improvement in pleasantness ( $p < 0.05$ ). However, there was no significant improvement in pulmonary function measured by FEV<sub>1</sub> in any of the studies with the two different treatments. This lack of significance is mostly due to the duration of the studies being less than several months.

There was little risk of bias in these three studies since two were double-blinded randomized controlled studies while the third was a randomized crossover trial which used computerized randomization and allocation was concealed using an off site investigator. The major limitations of these studies included cohort size and length of study. The small sample size of the three studies ( $\leq 40$  subjects) limits the precision of estimating the benefit of combination therapy in patients with CF ultimately

compromising validity. The short duration of exposure ( $\leq 28$  days) for the three studies limits the boundaries of safety regarding long term treatment with combination therapy. Assessment for quality of each study were done using the GRADE assessment tool which is shown in Table I.<sup>14</sup>

Based on the results of the most current studies presented here, further studies are warranted. Future studies should follow the format of the literature presented here with randomized, controlled, blinded studies. There should be an improvement in validity by recruiting a larger cohort of participants and holding the clinical trial for longer durations of time. The benefit of increasing the length of time for follow-up of patients will give insight into whether or not lung function would respond to this therapeutic response. Future studies should consider evaluating the effects of HS+HA on mucus production since the literature so far assesses only tolerability and pleasantness. Furthermore, studies involving a younger set of patients in order to evaluate whether or not HS+HA combination therapy can protect lung function would be worthwhile. It would also be a good idea to consider addressing the cost-effectiveness of HS+HA as an alternative to other mucolytic therapies.<sup>16</sup>

## **CONCLUSION**

Pulmonary dysfunction continues to be one of the most troublesome problems that patients with CF have to endure. Chronic bacterial infections and recurrent asthma-type exacerbations contribute to lung disease which can lead to death if not treated. Maintenance therapy with inhaled HS has been used but due to its high profile of side effects, compliance with treatment is low.<sup>4</sup> The results from this systematic review

provides evidence that HA significantly improves the tolerability and efficacy of HS. This combination therapy has shown to reduce salty taste, cough, airway irritation, and bronchoconstriction; all common side effects of treatment with HS alone in patients with CF.<sup>2,15,16</sup> There has been sufficient evidence to support the indication for combination therapy of HS+HA as an alternative mucolytic agent in patients with CF not only to reduce the amount of side effects from HS alone, but to improve quality of life.

## REFERENCES

1. Katkin, Julie P., MD. "Cystic Fibrosis: Clinical Manifestations and Diagnosis." *Uptodate*. N.p., Updated 25 June 2014. Web. Accessed 20 Aug. 2014.
2. Furnari ML, Termini L, Traverso G, et al. Nebulized hypertonic saline containing hyaluronic acid improves tolerability in patients with cystic fibrosis and lung disease compared with nebulized hypertonic saline alone: a prospective, randomized, double-blind, controlled study. *Therap adv respir dis*. 2012;6:315-322.
3. Voynow JA, Fischer BM, Zheng S. Proteases and cystic fibrosis. *Int J Biochem Cell Biol*. 2008;40:1238-1245.
4. Ratjen F. Restoring airway surface liquid in cystic fibrosis. *N Engl J Med*. 2006;354:291-293.
5. Boucher RC. Airway surface dehydration in cystic fibrosis: pathogenesis and therapy. *Annu Rev Med*. 2007;58:157-170.
6. Boucher RC. Evidence for airway surface dehydration as the initiating event in CF airway disease. *J Intern Med*. 2007;261:5-16.



7. Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. *Science*. 1992;256:774-779.
8. Elkins MR. Robinson M. Rose BR. Harbour C. Moriarty CP. Marks GB. Belousova EG. Xuan W. Bye PT. National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med*. 2006;354:229-240.
9. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell*. 1993;73:1251-1254.
10. Tarran R, Donaldson S, Boucher RC. Rationale for hypertonic saline therapy for cystic fibrosis lung disease. *Semin Respir Crit Care Med*. 2007;28:295-302.
11. Rosenfeld M, Davis S, Brumback L, et al. Inhaled hypertonic saline in infants and toddlers with cystic fibrosis: short-term tolerability, adherence, and safety. *Pediatr Pulmonol*. 2011;46:666-671.
12. Turino GM, Cantor JO. Hyaluronan in respiratory injury and repair. *Am J Respir Crit Care Med*. 2003;167:1169-1175.
13. Ros M, Casciaro R, Lucca F, et al. Hyaluronic acid improves the tolerability of hypertonic saline in the chronic treatment of cystic fibrosis patients: a multicenter, randomized, controlled clinical trial. *J Aerosol Med Pulm Drug Deliv*. 2014;27:133-137.

14. GRADE working group. GRADE website. <http://gradeworkinggroup.org/>.

Accessed August 17, 2014.

15. Ros M, Casciaro R, Lucca F, et al. Hyaluronic acid improves the tolerability of hypertonic saline in the chronic treatment of cystic fibrosis patients: a multicenter, randomized, controlled clinical trial. *J Aerosol Med Pulm Drug Deliv.* 2014;27:133-137.

16. Buonpensiero P, De Gregorio F, Sepe A, et al. Hyaluronic acid improves "pleasantness" and tolerability of nebulized hypertonic saline in a cohort of patients with cystic fibrosis. *Adv Ther.* 2010;27:870-878.

17. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med.* 2006;354:241-250.

18. Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol.* 1996;21:77-83.

19. Subbarao P, Balkovec S, Solomon M, Ratjen F. Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis. *Pediatr Pulmonol.* 2007;42:471-476.

20. Tam J, Nash EF, Ratjen F, Tullis E, Stephenson A. Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. *Cochrane Database of Systematic Reviews*. 2013;7:007168.

**TABLE I: Characteristics of Reviewed Studies**

<b>Quality Assessment</b>						
	<i>Downgrade Criteria</i>					<i>Quality</i>
<i>Design</i>	<i>Limitations</i>	<i>Indirectness</i>	<i>Imprecision</i>	<i>Inconsistency</i>	<i>Publication bias likely</i>	
<b>Ros et al<sup>15</sup></b>						
RCT	Not serious	Not serious	Serious <sup>a</sup>	Not serious	No bias likely	Moderate
<b>Funari et al<sup>2</sup></b>						
RCT	Not serious	Not serious	Serious <sup>a</sup>	Not serious	No bias likely	Moderate
<b>Buonpensiero et al<sup>16</sup></b>						
RCT	Serious <sup>b</sup>	Not serious	Serious <sup>a</sup>	Not serious	No bias likely	Low

<sup>a</sup> Small sample size<sup>b</sup> Short study duration of 3 days

**TABLE II: Summary of Findings**

<i>Study</i>	<i>Number of Patients</i>		<i>Outcomes</i>				
	<i>Treatment (total)</i>	<i>Placebo or no treatment (total)</i>	<i>Improved overall tolerability/pleasantness (P value)</i>	<i>Cough (RRR/ARR)</i>	<i>Throat irritation (RRR/ARR)</i>	<i>Saltiness (RRR/ARR)</i>	<i>FEV1</i>
Ros et al <sup>15</sup>	20	20	<0.0001	83%/---	62%/---	83%/---	No significant improvement
Funari et al <sup>2</sup>	27	14		60%			No significant improvement
Buonpensiero et al <sup>16</sup>	20	20	<0.05	61%/55%	93%/65%	90%/90%	No significant improvement