TITLE: Hypertonic Saline Nebules for Patients with Cystic Fibrosis and Bronchioectasis: A Review of the Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Hypertonic saline (HS) is a solution which has a concentration of sodium and chloride ions greater than that found in isotonic saline (IS; 0.9% saline).\(^1\) Nebulized (inhaled) HS has been used as an agent to aid airway clearance and sputum induction in a variety of respiratory disorders, such as cystic fibrosis (CF) and bronchioectasis (BE).\(^2,3\)

CF is a life threatening, recessively inherited disease caused by defects in a gene on chromosome 7.\(^4\) The faulty gene causes increased production of thickened secretions in many organs in the body.\(^4\) In the respiratory tract, these thickened secretions impair the clearance of microorganisms resulting in recurrent infections, inflammation, lung damage, and possibly death from respiratory failure.\(^4\) Although CF is a progressive condition, the prognosis for survival of the CF patient group has been improving, which has led to a rapidly increasing number of adult patients with more severe problems.\(^3\) Current median survival for patients with CF is more than 30 years.\(^3,4\)

Difficulty clearing secretions from airways is a universal complaint of CF patients who have moderate to severe lung disease.\(^3\) HS has been administered by inhalation to hydrate the thick mucus present in the airways of patients with CF.\(^3\) The mechanism of action is not clear, but it is presumed that the high osmolality of the solution draws water from the airway to reestablish the aqueous surface layer that is deficient in CF.\(^3\)

Nebulized HS has also been used in BE to loosen mucus and expel it from the lungs.\(^2\) BE is an irreversible widening of the large airways (bronchi) in the lungs.\(^2\) BE can be present at birth, but the condition usually develops in older children following inhalation of a foreign object or complications of pulmonary infection. When bronchial walls are damaged, the cilia that line the bronchi lose their ability to clear mucus from the lungs. When the cilia cannot remove mucus

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normally, it accumulates and dust and other airborne irritants become trapped. This promotes bacterial growth and infection, which can further damage the bronchi, leading to a cycle of more mucus accumulation, inflammation, and repeat infections. The bronchi may become increasingly dilated and scarred, reducing their capacity to move air in and out of the lungs and sufficiently supply the body with oxygen. BE can lead to other serious conditions, including heart failure.²

This report was requested to review the evidence for the use of HS nebulizers for patients with CF and BE. The information will be used to support a decision about coverage of HS nebulizers in these patient populations.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of hypertonic saline nebulizers for patients with cystic fibrosis or bronchiectasis?

2. What is the cost-effectiveness of hypertonic saline nebulizers for patients with cystic fibrosis or bronchiectasis?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, Embase, The Cochrane Library (Issue 4, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Results include articles published between 2002 and February 2009, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

From the literature search one systematic review and two randomized controlled trials (RCTs) (one of which included an economic evaluation) on the use of HS in patients with CF were identified. For patients with BE, one cross-over design study was identified.

Systematic reviews and meta-analyses

Wark et al. (2005)⁶ conducted a CF study for the Cochrane Database of Systematic Reviews. The objective was to investigate the effects of treatment with nebulized HS on people with CF compared to placebo or to other treatments that enhance mucociliary clearance. The authors searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, comprising references identified from comprehensive electronic database searches, hand searches of relevant journals, and abstract books of conference proceedings. Selected studies were controlled trials assessing the effect of HS compared to placebo or other mucolytic therapy, for any duration or dose regimen in people with cystic fibrosis of any age or severity. Two authors independently reviewed identified trials and all data collected. Trial quality and allocation concealment were assessed. The review was assessed as up-to-date as of May 23 2005.

Nine trials met the inclusion criteria. They involved 235 participants with an age range of 6 years to 46 years. Two short-term trials of immediate effect on mucociliary clearance demonstrated
that HS increased mucociliary clearance (measured by isotope clearance) compared to IS for CF patients. One of the two studies also included inhaled mannitol and found that both HS and mannitol were equally efficacious and well tolerated in improving bronchial mucus clearance in patients with CF. Lung function, measured by forced expiratory volume in one second (FEV$_1$) was observed in four trials comparing HS to IS. When 3% to 7% saline was used in a volume of 10 mL twice per day, HS led to a significant increase in FEV$_1$ (weighted mean difference 12.20; 95% CI, 4.28 to 20.10). Two other trials compared HS to recombinant human deoxyribonuclease (rhDNase). One of these trials found, over a three week period, a non-significant difference in FEV$_1$ (mean difference 1.60; 95% CI, -7.96 to 11.16). However, the other rhDNase trial showed that after 12 weeks treatment in participants with moderate to severe lung disease, rhDNase led to a greater increase in FEV$_1$ than HS treatment at 5 mL twice-daily (mean difference 8.00; 95% CI, 2.00 to 14.00). A final trial compared HS to the mucolytic agent 2-mercaptoethane sulphonate (Mistabron). Forced vital capacity (FVC) was not significantly different in either group. In the review, no serious side effects were noted for HS in patients with CF. The authors concluded that nebulized HS improves mucociliary clearance in short-term clinical trials and appears to increase lung function compared to control. In comparison to rhDNase, HS may be less effective at improving lung function after three months. The authors felt there was insufficient evidence to support the use of HS as routine treatment for people with CF.

Randomized controlled trials

In 2002 the NHS R&D HTA Programme in the UK published an RCT on children with cystic fibrosis. The objective was to compare daily rhDNase, alternate-day rhDNase, and HS. Forty-eight children with a confirmed diagnosis of CF were recruited from two large CF centres in London, England. The children were between 5 to 18 years of age, had the capacity to perform spirometry, and were currently using rhDNase or had a FEV$_1$ of less than 70% of the predicted value (a generally accepted level for the clinical introduction of rhDNase therapy). In random order, each patient was allocated consecutively to 12 weeks of treatment with either once-daily 2.5 mg rhDNase, alternate-day 2.5 mg rhDNase, or twice-daily 5 mL of 7% HS. The children were assessed at the beginning and end of each of the three treatments, and the primary outcome measure was FEV$_1$.

Following 12 weeks of treatment there was a mean increase in FEV$_1$ over baseline of 3% for HS [standard deviation (SD) 21%]), 14% for alternate-day rhDNase (SD 22%), and 16% for daily rhDNase (SD 25%). Daily rhDNase showed a significantly greater increase in FEV$_1$ compared to HS [8%; 95% confidence interval (CI) 2% to 14%; p=0.01). However, there was no significant difference between daily rhDNase and alternate-day rhDNase (2%; 95% CI -4% to +9%; p=0.55). The study concluded that 7% HS was not as effective as daily rhDNase in patients with CF, although there was some variation in individual response. Alternate-day rhDNase appeared to be as effective as daily rhDNase.

This study included a full economic evaluation alongside the crossover trial, which is described in the section on economic evaluations.

Elkins et al. (2006) tested the safety and efficacy of inhaled HS for CF in a long-term trial. In a double-blind, parallel-group trial, 164 patients with stable CF aged six years or more were randomly assigned to inhale 4 mL of either 7% HS or 0.9% (control) saline twice daily for 48 weeks. Quinine sulfate (0.25 mg per mL) was added to each solution to mask the taste. A
bronchodilator was given before each dose, and other standard therapies were continued during the trial.

The measures of lung function, FVC, FEV₁, and forced expiratory flow at 25 to 75 percent of FVC (FEF₂₅-₇₅), did not differ significantly between groups during the 48 weeks of treatment. However, the absolute difference in lung function between groups was significantly higher for HS (p=0.03) when averaged across all post-randomization visits in the 48 weeks. Compared to the control group, the HS group had significantly higher FVC (difference of 82 mL; 95% CI, 12 to 153) and FEV₁ (difference of 68 mL; 95% CI, 3 to 132) values, but similar FEF₂₅-₇₅ values. The HS group also had significantly more patients without exacerbations (76% versus 62% in the control group; p=0.03). HS was not associated with worsening bacterial infection or inflammation. The authors concluded that HS preceded by a bronchodilator is a safe and effective additional therapy for patients with CF.

Kellett *et al.* (2005)⁸ analyzed nebulized HS (7%) as an adjunct to physiotherapy in patients with stable BE. Twenty-four patients with BE received four treatment strategies, over a four week period, in random order in a cross-over design study. The strategies were active cycle breathing technique (ACBT) alone; nebulized terbutaline then ACBT; nebulized terbutaline, nebulized IS (0.9%) then ACBT; and nebulized terbutaline, nebulized HS (7%) then ACBT.

Based on this study, sputum weights were significantly higher after HS than IS (p=0.002). A significant linear trend to reduced sputum viscosity was found with HS (p=0.0002). The score for ease of expectoration was lower (i.e. easier) with HS than IS (p=0.0005). This suggests that despite producing more sputum with HS, patients found it easier to expectorate, probably due to reduced viscosity. There were also small but significant differences in FEV₁ (p=0.043) and FVC (p=0.011). The authors concluded that in stable patients with low sputum yield, 7% HS is a well tolerated, safe, and easily administered adjunct to physiotherapy airway clearance techniques and is more effective than 0.9% IS for patients with BE. They felt nebulized HS can be used safely and effectively as an adjunct to physiotherapy in selected BE patients. The authors recommended that the study be repeated in patients with different disease severities, and that a prospective long-term study is indicated to determine its effectiveness on long-term infection rate, quality of life and lung function.

**Economic evaluations**

The RCT by Suri *et al.* (2002)¹ also included an economic evaluation of HS, alternate-day rhDNase, and daily rhDNase for children age 5 to 18 years with CF. A health care provider perspective was taken. Health resources assessed in the economic evaluation included hospital contacts (inpatient, outpatient, and day case), radiological investigations, blood tests, drug use, and the use of community services, including community nurse, physiotherapist and general practitioner. Drug costs were taken from the British National Formulary. Other unit costs came from the two postgraduate hospitals in London where patients were recruited for the trial, and from a district general hospital to represent care provided by that type of hospital. Community care costs came from the personal Social Services Research Unit, University of Kent. A cost-consequence analysis was done, comparing both the costs and effectiveness of the three comparators. A cost-effectiveness analysis (CEA) was also undertaken, using the primary outcome measure from the trial (FEV₁). The CEA did not calculate an incremental cost-effectiveness ratio (ICER) but instead analyzed the trade-off between costs and consequences using cost-effectiveness acceptability curves (CEACs) and the net benefit statistic. The CEA included a probabilistic sensitivity analysis.
The drug cost per day was £0.38 for HS, £20.39 for daily rhDNase, and £10.20 for alternate-day rhDNase. Based upon the cost-consequence analysis, it was concluded that the difference in total cost over each 12-week treatment period between rhDNase and alternate-day rhDNase was £513 (95% CI, -£546 to £1510) and between daily rhDNase and HS it was £1409 (95% CI, £440 to £2318). It was also concluded that administration of rhDNase on an alternate-day rather than a daily basis appeared to be as effective, and on average reduced health care costs relative to daily rhDNase over a 12-week period. The results of the CEA analysis suggested that if decision makers were prepared to pay £200 for a 1% gain in FEV$_1$ over a 12-week period, then either rhDNase strategy, on average, has positive net benefits compared with HS and could be adopted. In other words, on average, either rhDNase strategy is cost-effective relative to HS. The results also suggested that since alternate-day rhDNase has the lower average costs, this may prove to be the most cost-effective option.

**Limitations**

In the Cochrane Collaboration systematic review of HS in CF, the trials where the interventions were described as “blinded” may have been compromised due to the discernible taste of HS. Also, most of the trials were described as “randomized”, but in most, the methods of randomization and allocation concealment were not discussed. One of the trials in the review was reported as an abstract and no details were given concerning inclusion criteria, withdrawals, randomization method, or statistical analysis.

The RCT by Suri et al. was not blinded due to the taste of HS. The trial did not have a placebo (IS; 0.9% saline) arm. The RCT by Elkins et al. was described as double-blind, however was subject to the same problem as the other studies due to the taste of HS.

There has been limited work on the economic evaluation of HS for CF. Our search returned only one study, and the Suri et al. economic evaluation of CF had several inherent limitations:

- Given the UK setting, it is not clear if the clinical and cost inputs to the model would be generalizable to the Canadian healthcare system.
- A placebo or no-treatment comparator would have been useful to put the cost-effectiveness of HS in context.
- A quality-of-life outcome, rather than the FEV$_1$ effectiveness measure, would have allowed for a cost-utility analysis, facilitating broader comparisons outside this particular disease area.
- The results of the economic evaluation apply only to a 12-week observation period, so the duration of the study was insufficient to assess whether the treatment regimen had an effect on survival.
- The different methods applied in the analysis of outcome measures in the crossover trial and the economic evaluation produced somewhat different estimates of incremental effectiveness.

Our review identified very limited evidence analyzing the use of HS for the treatment of BE. One trial and no economic evaluations were identified. The trial by Kellett et al. was short-term (4 weeks), had a small sample size (24), and was limited to patients with low severity of symptoms (low sputum volume). These factors impact the generalizability of the trial results.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

A systematic review for CF identified in our search concluded that HS improves mucociliary clearance in short-term clinical trials and appears to increase lung function compared to placebo. It also concluded that HS may be less effective than rhDNase at improving lung function after three months, and is equally efficacious and well tolerated compared to mannitol in improving bronchial mucus clearance in patients with CF. A further RCT identified compared HS to placebo (IS; 0.9% saline) for approximately one year and found a moderate yet sustained improvement in the level of lung function for CF patients. It also found significant reductions in the number of exacerbations, antibiotic use for exacerbations, absenteeism from school or work, and increased ability to engage in other usual activities with the use of HS. Another RCT identified compared rhDNase and HS for children with CF, and found HS was not as effective as daily rhDNase, although there was some variation in individual response. A cost-effectiveness study in a UK context concluded that both alternate-day rhDNase and daily rhDNase are cost-effective relative to HS. However, there was no comparison to placebo in this economic evaluation.

With regard to the treatment of BE with HS, the one included trial identified in our review found HS to be a safe, effective, and easily administered adjunct to physiotherapy in select patients (i.e. patients with low sputum volume). However, further generalizability of these results will depend on larger, long term trials in a wider BE patient group. We are unable to make any statements about the cost-effectiveness of HS for BE due to the absence of cost-effectiveness studies in this area.

Overall, and subject to the limitations of the studies, the evidence suggests that for CF treatment, HS is more effective than placebo, with significantly fewer exacerbations. However, the cost-effectiveness of HS versus placebo for CF has not been studied. The limited information for use of HS in patients with BE should be considered when deciding about the use of HS in this patient population.

PREPARED BY:
Allan Brown, BSc MBA MA
Becky Skidmore, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


