*Inhaled medication other than antibiotics*

# Chronic use of inhaled hypertonic saline

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## Background

Defects in CFTR protein function affect both cAMP-dependent chloride secretion and epithelial sodium channel (ENaC)-mediated ion absorption in the superficial airway epithelium. Increased sodium and water reabsorption across airway epithelial cells leads to dehydration of the airway surface liquid layer, mucus stasis, and airway obstruction. Dehydration of the airway surface liquid layer has been identified as the primary initiating event in CF-related lung disease, making therapeutic interventions to enhance mucus clearance a cornerstone of CF treatment.

Hypertonic saline (HS) represents a potential alternative or supplementary therapy for improving mucociliary clearance (Trimble AT, 2018). Over the long term, enhanced mucociliary function may reduce bacterial load and chronic airway inflammation, thereby slowing the decline in lung function. HS offers the additional advantages of ease of administration and low cost.

HS is defined as a solution with an osmotic pressure greater than that of physiologic isotonic saline (0.9% NaCl). Several mechanisms have been proposed to explain its effectiveness, including alterations in airway mucus rheology, increased airway surface liquid hydration, ENaC inhibition, and immunomodulatory effects. Comprehensive reviews on HS mechanisms and clinical applications are available (Reeves EP, 2015, Southern KW, 2019 and Terlizzi V, 2021.)

Based on available evidence, HS has been recommended as a standard treatment for children aged six years and older in the Cystic Fibrosis Foundation Guidelines (Mogayzel Jr. PJ, 2013) and in the European Cystic Fibrosis Society standards of care (Burgel PR, 2024 ).

Despite these recommendations, HS utilization varies considerably across countries. In the United States, the Cystic Fibrosis Foundation Patient Registry reported that 74.6% of patients aged six years and older used HS in 2019. In Europe, usage rates demonstrate substantial variation, ranging from 34% in the United Kingdom to 80% in Germany and 44% in Italy. In recent years, these proportions have shifted following the introduction of CFTR modulators. By 2023, the percentage of patients aged six and older using HS had declined to 64.2% in the United States, 30.7% in the United Kingdom, and 93.1% and 72.4% in German children and adults, respectively.

A comparative study utilizing national registry data examined longitudinal lung function in children with CF in the United States and the United Kingdom. The analysis revealed that US children homozygous for F508del demonstrated superior lung function compared to their UK counterparts, with this difference primarily attributed to earlier implementation of treatments such as dornase alfa and HS ( Schluter DK, 2022).

A systematic review and meta-analysis by Ullah SE et al. (Ullah SE, 2023), examining seven studies encompassing 390 subjects, concluded that HS treatment in younger children with CF improves lung clearance, symptoms, and quality of life. The authors noted that FEF??–?? may serve as a more sensitive measure for assessing intervention-related improvements in pediatric CF trials.

## Issues

1. To determine whether there is evidence of benefit in using HS in people with CF in terms of a reduction in morbidity or mortality and in terms of improvement of lung function
2. To identify any adverse event associated with the use of HS
3. To evaluate the cost of use of HS
4. To compare the efficacy of HS with other mucolytics
5. To determine the effect of timing of HS inhalation on measures of clinical efficacy in people with cystic fibrosis (in relation to airway clearance techniques or time of the day)
6. To determine the effect of HS on CF sinonasal disease
7. To compare the aerosol characteristics of HS delivered by nebulizers of different operating principles.
8. To evaluate the effect of withdrawing HS or other mucolytics

## What is known

### *Regarding issue 1*

HS was shown to reduce the frequency of pulmonary exacerbations, to have a small effect on improvement in quality of life in adults and, in concentrations of 5% to 7%, to improve mucociliary clearance (MCC), although not in all the patients. Age of patients could be a relevant factor varying the clinical response: a large RCT (48-week study of inhaled hypertonic saline in children with CF under six years of age) failed to demonstrate a treatment-related reduction in the rate of pulmonary exacerbation in this cohort of patients (Rosenfeld M, 2012). A substudy derived from this trial showed that Lung Clearance Index (a noninvasive measure of ventilation inhomogeneity that holds promise as an objective physiologic endpoint for clinical trials in infants and preschool children with CF) improved in the HS group

and remained stable in the isotonic saline group (Subbarao P, 2013).

A recent RCT (Dentice RL, 2016) showed that addition of HS to the management of a CF exacerbation did not reduce the length of hospital stay, although HS speeded the resolution of exacerbation symptoms and allowed patients to leave hospital with greater symptom resolution.

A crossover, randomized clinical (Nenna R, 2017) trial evaluated the effects of inhaled hypertonic (7%) saline on lung function test in preschool children with cystic fibrosis. After a 16-weeks treatment with HS an improvement of FVC (p=0.02) and a favorable trend of FEV1 were registered. A worsening of FEV1 (p<0.0001) and of FEF25-75 (p=0.019) were found in NS group. No differences were found in expiratory and inspiratory Rint in both groups. No serious adverse events occurred. This RCT had, however, some methodological problem.

Little evidence is available that HS leads to an improvement in lung function in the long term. Recently an observational study with a mean follow up of 39.7 months (Ellemunter H, 2016) showed a significant improvement of ventilation inhomogeneity after the start of HS therapy.

Evidence that inhaled HS enhances mucociliary clearance, improves lung function, and reduces pulmonary exacerbations are available especially in people with CF older than age 6 years. German researchers studied feasibility, safety and efficacy of preventive inhalation with HS compared to isotonic saline (IS) in infants with CF including LCI and MRI as outcome measures (Stahl M, 2019). In this RCT 42 infants with CF less than 4 months of age were randomized to twice daily inhalation of 6% HS or 0.9% IS for 52 weeks. Inhalation with HS was safe and well tolerated, and resulted in improvements in LCI and weight gain in infants with CF.

Canadian and US researchers assessed the effect of inhaled HS on the lung clearance index ($LCI_{2·5}$)-a measure of ventilation inhomogeneity-in children aged 3-6 years with CF, using IS as a comparator (SHIP study, Saline Hypertonic in Preschoolers) (Ratjen F, 2019). At 48 weeks, treatment with HS was associated with a significant decrease (ie, improvement) in $LCI_{2·5}$ compared with IS (mean treatment effect -0·63 $LCI_{2·5}$ units [95% CI -1·10 to -0·15]; p=0·010). In conclusion, inhaled HS improved the $LCI_{2·5}$ in children aged 3-6 years, and could be a suitable early intervention in cystic fibrosis. This study was followed by a further evaluation (SHIP-CT study), aiming to assess the effect of inhaled HS on chest CT imaging in children aged 3–6 years with CF. Inhaled HS for 48 weeks had a positive effect also on structural lung changes in children aged 3–6 years with CF relative to IS (Tiddens HAWM, 2022). On this basis, an algorithm was developed and validated to automatically measure bronchus and artery (BA) dimensions of BA-pairs on chest CT. Aim of the study was to assess the effect of HS on bronchial wall thickening and bronchial widening using the BA-analysis. The automatic BA-analysis showed a positive impact of inhaled HS on bronchial lumen and wall thickness, but no treatment effect on progression of bronchial widening over 48 weeks (Chen Y, 2023).

In 2020, US researchers (Donaldson SH, 2020) performed a randomized, placebo controlled, double blind study of 6% versus 0.12% sodium chloride, delivered three-times daily with an eFlow nebulizer for 4 weeks. MCC was measured using gamma scintigraphy at baseline, 2-hours after the first study treatment, and ~12-hours after the final dose (at day 28). Spirometry, respiratory symptoms (CFQ-R), and safety were also assessed. Study treatments were generally well tolerated and safe. HS (6% sodium chloride) resulted in a significant, sustained improvement from baseline in whole lung clearance after 4 weeks of therapy ($p$ = 0.014).Improvements in spirometry with HS did not reach statistical significance but correlated with MCC changes.

In 2023, literature was reviewed by a CDSR (Wark P, 2023). The authors conclude that they are very uncertain if regular use of nebulised hypertonic saline by adults and children over the age of 12 years with CF results in an improvement in lung function after four weeks (three trials; very low-certainty evidence); there was no difference seen at 48 weeks (one trial; low-certainty evidence). Hypertonic saline improved LCI modestly in children under the age of six years. Evidence from one small cross-over trial in children indicates that rhDNase may lead to better lung function than hypertonic saline at three months; qualifying this, the authors highlight that while the study did demonstrate that the improvement in $FEV_1$ was greater with daily rhDNase, there were no differences seen in any of the secondary outcomes. Hypertonic saline does appear to be an effective adjunct to physiotherapy during acute exacerbations of lung disease in adults. However, for the outcomes assessed, the certainty of the evidence ranged from very low to low at best, according to the GRADE criteria. Finally, the role of hypertonic saline in conjunction with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy now needs to be considered, and future research needs to focus on this aspect.

***Regarding issues 2-3***

When delivered following a bronchodilator it appears to be an inexpensive and safe additional therapy for people with CF.

The use of a formula containing 7% HS and 0.1% hyaluronic acid (HA) [basing its use on the protective effects of HA against elastin injury and on a greater ease of administration (i.e., the perceived acceptability of inhalation)], showed no significant differences in the prevalence of moderate/severe symptoms of cough, saltiness, and throat irritation in pulmonary functions tests after 28 days (Brivio A, 2016).

In people with cystic fibrosis (pwCF), regular nebulisation of 6% or 7% saline improves lung function; however, these concentrations are not always tolerable. Indeed, some subjects report using lower concentrations of saline to improve tolerability, but the effects of lower concentrations of NaCl are unknown. A recent randomised, blinded, placebo-controlled, parallel-group, multicentre study from Australia aimed to evaluate the relative effectiveness and tolerability of 0.9% *versus* 3% *versus* 6% saline nebulised twice daily with an eFlow rapid nebuliser. 3% saline significantly improved lung function and increased the time to first pulmonary exacerbation compared with 0.9% saline but did not improve quality of life. 6% saline had similar benefits to 3% saline but also significantly improved quality of life compared with 3% saline. Only 6% saline delayed the time to intravenous antibiotics for pulmonary exacerbation. Tolerability and adherence were similar. In conclusion dilution of 6% saline to 3% maintains the benefits for lung function and exacerbation prevention, but the positive impacts of 6% saline on quality of life and time to *i.v.* antibiotics for pulmonary exacerbations are lost (Dwyer TJ, 2023).

Low cost is a relevant property of HS.

***Regarding issue 4***

There is evidence to recommend the use of HS in CF but it should not be used in preference to rhDNAse. At this stage the benefit

appears to be a reduction in pulmonary exacerbation frequency, though evidence does not exist to say it works in patients with frequent exacerbations. There are no data on the effects of HS in combination with rhDNase.

A recent review (Southern KW, 2019) explores the evidence supporting the use of dornase alfa, hypertonic saline, and mannitol in improving mucus clearance in patients with CF from different age groups with differing disease severity and the unanswered questions regarding the optimal use of these agents.

A research question that also in the modulator era could be significant, in particular for people with severe lung disease and/or subjects not eligible to CFTR modulation, is:

**Did people with CF and received dornase alpha and Hypertonic Saline (HS) have better preserved lung function than those treated with DA only?**

Two studies evaluated this issue:

1) A registry study from US, involving patients followed between 2006 and 2014 (pre-CFTR modulators era) shows that subjects with CF $_{F508del}$ had no significant difference in lung function when nebulized HS was added to dornase for 1-5 years (Kaditis AG, 2023).

2) A registry study using UK CF Registry data from 2007 to 2018, emulated a target trial. The authors included people aged 6 years and over who were prescribed DNase without HS for 2 years. Moreover they investigated the effects of combinations of DNase and HS over 5 years of follow-up. Inverse-probability-of-treatment weighting was used to control confounding. The study concluded that for individuals with CF prescribed DNase, no evidence was found that adding HS had an effect on $FEV_1$% or prescription of intravenous antibiotics. (Granger E, 2023)

***Regarding issue 5***

A CDSR is available on this issue (Elkins M, 2020).

Some theoretical problems could afflict this issue: nebulisation of HS during physiotherapy could increase the complexity and the length of the overall session of airway clearance. Administration of HS after physiotherapy could reduce tolerability because of more direct interaction with the respiratory epithelium than with the mucus layer. Morning delivery may increase coughing during school or job whereas nocturnal administration could induce sleep disturbance.

The HS should also be inhaled after a short-term bronchodilator, because it has previously been established that this is necessary to prevent bronchoconstriction (Bye PTP, 2007).

While outcomes such as lung function did not show any difference between the regimens, people with cystic fibrosis perceived that inhaling hypertonic saline before or during airway clearance techniques may be more effective and satisfying than inhaling hypertonic saline after airway clearance. No studies comparing morning and evening inhalation were found.

In conclusion, timing of hypertonic saline inhalation makes little or no difference to lung function (low?certainty evidence). However, inhaling hypertonic saline before or during airway clearance techniques may maximise perceived efficacy and satisfaction. The long?term efficacy of hypertonic saline has only been established for twice?daily inhalations; however, if only one dose per day is tolerated, the time of day at which it is inhaled could be based on convenience or tolerability until evidence comparing these regimens is available.

The identified trials were all of very short intervention periods, so longer?term research could be conducted to establish the effects arising from regular use, which would incorporate the influence of changes in adherence with long?term use, as well as generating data on any adverse effects that occur with long?term use.

***Regarding issue 6***

A multicenter study compared the effect of NaCl 6.0% vs NaCl 0.9%. The patients were randomized to receive sinonasal vibrating inhalation of either NaCl 6.0% or NaCl 0.9% for 28 days, having a symptom score as primary outcome (Mainz JG, 2016). Sinonasal inhalation with NaCl 6.0% did not lead to superior results vs NaCl 0.9%.

***Regarding issue 7***

A recent study compared the aerosol characteristics of HS delivered by nebulizers of different operating principles (Breath-enhanced nebulizers [BEN] vs breath-actuated nebulizers [BAN] vs continuous-output nebulizers [CON]. The study showed that HS aerosols generated with the BEN and BAN devices were similar, while that generated with the CON was different. Airway delivery was similar between different brabds of BEN devices, but higher than that observed with the BAN and CON devices.

***Regarding issue 8***

The SIMPLIFY study aimed to assess the effects of discontinuing nebulised hypertonic saline or dornase alfa in individuals using the CFTR modulator elexacaftor plus tezacaftor plus ivacaftor (ETI). The SIMPLIFY study included two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials at 80 participating clinics across the USA in the Cystic Fibrosis Therapeutics Development Network. Individuals with cystic fibrosis aged 12-17 years with percent predicted $FEV_1$ ($ppFEV_1$) of 70% or more, or those aged 18 years or older with $ppFEV_1$ of 60% or more, if they had been taking ETI and either (or both) mucoactive therapies (?3% hypertonic saline or dornase alfa) for at least 90 days before screening were included. The main results was that in individuals with CF on ETI with relatively well preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for 6 weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment (Mayer-Hamblett N, 2023). In a SIMPLIFY substudy, gamma scintigraphy was used to determine whether discontinuation of either HS or DA was associated with deterioration in the rate of in vivo mucociliary clearance (MCC) in participants ?12 years of age. While no significant differences in MCC endpoints were associated with HS discontinuation, significant improvement in whole and peripheral lung MCC was observed after discontinuing DA. These results suggest that pwCF on ETI with mild lung disease do not experience a subclinical deterioration in MCC that could later impact health outcomes after discontinuing HS, and in fact may benefit from improved MCC after stopping DA treatment (Donaldson SH, 2024).

On this basis, although the costs of DA and HS are smaller compared with ETI, reduction in use would lead to substantial prescription drug cost savings and reduce the treatment burden. However, individual benefits of these therapies should be considered, and decisions regarding changes in therapy remain an important discussion between people with CF and their providers (Gold LS, 2024).

A further substudy of the SIMPLIFY study assessed the safety of discontinuation HS in subjects with lower lung function (LLF, ppFEV1 40 - 59%). This substudy recruited only 23 subjects in two arms according to discontinuation or continuation of HS for 6 weeks. Participants of both arms had similar, rare adverse events and not significant differences in mean change of ppFEV1 from week 0 to week 6 (Nichols D, 2023).

To evaluate the impact of discontinuing both hypertonic saline (HS) and dornase alfa (DA) versus continuing both therapies, a subgroup of participants in the SIMPLIFY study who sequentially participated in trials evaluating the independent clinical effects of discontinuing HS and DA was studied. Forty-three participants discontinued both therapies by the end of SIMPLIFY, and 63 remained on both. In conclusion, SIMPLIFY participants who sequentially discontinued both HS and DA experienced no meaningful changes in clinical outcomes and reported decreased treatment burden as compared with those who remained on both therapies (Mayer-Hamblett N, 2024 ).

Introduction of novel therapies for cystic fibrosis (CF), raises the question whether traditional treatments can be withdrawn. A research question is: In the pre-modulator era, did people with CF who were F508del homozygous ($CF_{F508del}$) and received dornase alpha and Hypertonic Saline (HS) have better preserved lung function than those treated with DA only? A recent registry study from US, involving patients followed between 2006 and 2014 (pre-CFTR modulators era) shows that subjects with $CF_{F508del}$ had no significant difference in lung function when nebulized HS was added to dornase for 1-5 years (Kaditis AG, 2023).

## Unresolved questions

Long-term clinical trials are needed to evaluate the effect of HS in achieving sustained reductions in exacerbation frequency and to determine whether this translates into more compelling improvements in quality of life.

Future research should prioritize several key areas. First, trials should assess the effect of HS on individuals with frequent pulmonary exacerbations to determine whether this subgroup demonstrates enhanced treatment response. Second, studies are needed to identify patient subgroups that respond preferentially to HS versus other mucociliary clearance agents, particularly recombinant human DNase (rhDNase), to enable more personalized treatment approaches. Third, future trials should evaluate HS in conjunction with other mucociliary clearance regimens, or specifically target individuals who fail to derive benefit from rhDNase treatment.

The efficacy of combination mucociliary therapies also requires systematic investigation. Additionally, randomized controlled trials comparing HS inhalation before versus after airway clearance physiotherapy should be conducted, as should studies examining optimal timing of administration (morning versus evening dosing).

A significant contemporary issue concerns treatment discontinuation patterns among individuals with CF receiving CFTR modulator therapy. Patients treated with ivacaftor demonstrate reduced likelihood of continuing concurrent treatments, including inhaled antibiotics, dornase alfa, hypertonic saline, chronic oral antibiotics, and supplementary feeding, compared to those not receiving ivacaftor (Granger et al., 2021). Notably, differences in dornase alfa and hypertonic saline utilization between ivacaftor-treated and non-ivacaftor-treated individuals are more pronounced among patients with higher baseline lung function.

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The SIMPLIFY trials have established precedent for treatment discontinuation studies. The Streamlining Treatment Or Reducing Medication (CF-STORM) trial, a randomized open-label study conducted in England and Northern Ireland, is currently evaluating the safety of discontinuing HS, dornase alfa, or both treatments over a 12-month period (EudraCT 2020–005864–77). This trial aims to provide evidence that cessation of these nebulized therapies does not result in clinically significant decline in lung function over 12 months. (https://www.cfstorm.org.uk/).

Additional real-world observational studies are providing broader insights into long-term treatment patterns. The Home-Reported Outcomes in Cystic Fibrosis 2 (HERO-2) study in the United States (ClinicalTrials.gov identifier NCT04798014) and the National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO) study in the United Kingdom (NCT05519020) are evaluating long-term therapeutic strategies and will contribute essential evidence to inform clinical decision-making.

## Keywords

Airway clearance drugs -expectorants- mucolytic- mucociliary-;