Hypertonic saline for cystic fibrosis: worth its salt?

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Jennifer L Goralski
Cystic Fibrosis Research and Treatment Center, The University of North Carolina at Chapel Hill – Medicine, UNC CF Center, CB #7248 101 Manning Drive, Chapel Hill, NC 27599, USA

Scott H Donaldson
Author for correspondence: Cystic Fibrosis Research and Treatment Center, The University of North Carolina at Chapel Hill – Medicine, UNC CF Center, CB #7248 101 Manning Drive, Chapel Hill, NC 27599, USA, scott_donaldson@med.unc.edu

Airway dehydration in cystic fibrosis (CF) leads to chronic inflammation, ongoing infection and progressive lung disease. Restoration of airway hydration by inhalation of an osmotic agent (hypertonic saline) has been shown to be safe, effective and well-tolerated in adults with CF. Although the safety of hypertonic saline in infants and young children with CF has also been established, recent studies have reported inconclusive evidence about its efficacy. In this editorial, we discuss the evidence behind hypertonic saline use for adults, children and infants with CF.

Despite ongoing improvements in clinical care and life expectancy, lung disease remains the main cause of morbidity and mortality in children and adults with cystic fibrosis (CF). Structural lung disease begins well before symptom onset, as evidenced by cross-sectional imaging studies in infants diagnosed with CF via newborn screening [1,2]. This underscores the need for interventions that target the pathogenesis of lung disease early in childhood to slow its progression. In CF, impaired CF transmembrane regulator (CFTR) function leads to abnormal ion transport activities across epithelia and altered luminal secretions in multiple organs. In the lung, CFTR is an important ion channel that provides regulated chloride (and water) secretion down an electrochemical gradient in epithelial cells. CFTR also asserts an inhibitory influence over the epithelial sodium channel and impacts airway surface liquid pH through its role as a bicarbonate channel, further demonstrating its multifaceted role in airways. In the absence of functional CFTR, the dysregulation of chloride secretion, sodium absorption, transepithelial water flow and pH contributes to the development of a thick, viscous mucus layer overlying airway epithelia. The dehydrated mucus layer eventually becomes adherent to the airway surface, thus interfering with mucus clearance via cilia and cough-dependent mechanisms. A dehydrated mucus gel, as a consequence of its smaller mesh size, also impairs neutrophil migration to the site of bacterial infection within luminal secretions, and therefore promotes persistent bacterial infection and inflammation. Administration of an osmotic agent, such as hypertonic saline (HS), is a conceptually simple way to draw water into luminal secretions, restore mucus clearance and thereby reduce disease exacerbations and slow progressive airway obstruction. Additional effects of HS beyond improved mucociliary clearance (MCC) have also been proposed, including direct effects on inflammation and infection [3]. However, in vivo evidence that inhaled HS directly impacts quantitative microbiology or sputum inflammation/cytokines is lacking and requires further validation.

As early as 1996, clinical testing [4,5] of HS in CF patients was underway. Initial studies showed that HS acutely accelerated MCC in proportion to the concentration/mass of the inhaled salt [6]. Short-term administration was associated with improved lung function and appeared to be well tolerated [6,7]. In 2006, two seminal studies solidified the role of 7% HS in the treatment of CF lung disease. One study demonstrated that repeated use provided acute and sustained (>8 h) improvements in MCC...
while improving lung function after 2 weeks of treatment [7]. Although the sustained effect of HS on MCC is likely responsible for the observed clinical benefits, our understanding of the mechanism is incomplete. The ability of dehydrated secretions to accept and store water and then donate it back to the periciliary layer as determined by the osmotic pressure gradients that exist between the mucus layer and the periciliary layer [8] could help explain this beneficial phenomenon. The second critical study of HS [9] demonstrated important clinical benefits with chronic HS, including a marked reduction in the frequency of pulmonary exacerbations and fewer days missed from work/school. Quality of life was also enhanced, with significant improvements in mental health, emotional, role and health domains on the SF-36 following chronic therapy with HS. Subsequently, a retrospective analysis of 340 CF exacerbations at a single center confirmed this effect on pulmonary exacerbations in the patients using HS, even at the most severe lung disease (FEV1 < 40%) [10]. Finally, a study of HS used during hospitalization for CF exacerbations showed that nebulized HS sped recovery of lung function [11]. Together, these studies led HS to become an important treatment element for the CF population, and it is currently used by greater than 50% of CF patients in the USA (Port CF data). However, as these studies were heavily weighted by data from adults with CF, use in children has been limited by a lack of evidence supporting its efficacy.

More recently, clinical studies of HS in children with CF, including both infants and school-aged children, have shown acceptable safety and tolerability profiles [12–14]. However, because infants and children typically have less advanced lung disease, questions remain whether HS provides clinical benefit to this population. Although there is strong data to support the enhancement of MCC by HS in adult patients, a single-dose study of HS in CF children between 7 and 14 years old showed negligible acute MCC effects [15]. Interestingly, a recent trial of HS (6% NaCl vs 0.12%; 4 ml, three times daily for 4 weeks via the investigational eFlow device) in a pediatric CF population with normal lung function again showed little impact on MCC measured 2 h after the first dose, yet demonstrated a significant acceleration of MCC lasting >12 h after the final dose [16]. This sustained phenomenon is quantitatively similar to that observed in the earlier study of adult CF patients with more substantial disease [7] and suggests that the effects of repetitive dosing might not be predicted by single-dose studies of MCC in CF. In another study, lung clearance index (LCI) obtained by the multiple breath washout technique was used to assess ventilation heterogeneity in CF patients aged 6–18 with mild disease. Once again, this study demonstrated significant improvement in this index of ventilation inhomogeneity following 4 weeks of treatment with HS [17]. Together, these data provide physiologic evidence that HS may benefit children and adolescents with CF, even though documentation in other clinical endpoints has been difficult to establish in these mildly affected patients.

In an even younger population, the large multicenter ISIS trial [18] administered 7% HS or 0.9% isotonic saline to 321 infants with CF aged 4 to 60 months for 48 weeks. In ISIS, HS treatment did not improve the specified primary endpoint of pulmonary exacerbation frequency. However, in two ISIS sub-studies that assessed physiologic outcomes, both infant pulmonary function testing (FEV0.5) and LCI improved. These physiologic outcomes suggest that HS reduced airway obstruction even in the setting of early disease [19,20]. Interestingly, the youngest infants in the LCI sub-study uniformly had normal values at baseline, whereas 60% of preschoolers were already elevated at baseline. The pattern of treatment responses in these two groups suggested that HS tended to prevent worsening of LCI in infants, whereas it generally improved the abnormal LCI values in preschoolers. These data highlight the heterogeneity of disease even in young children with CF and the need to tailor endpoints and study designs to specific age ranges. A key question that arises, then, is whether the failure of ISIS to meet its primary outcome (reduced exacerbation frequency) reflects a true drug failure or, instead, signifies an inadequate outcome measure. One may argue that the pulmonary exacerbation definition, modified from studies in older CF subjects, primarily captured self-limited, viral upper respiratory tract infections that are common and unrelated to CF disease pathogenesis. The frequency of these events might be expected to overwhelm any HS effect on ‘true’ pulmonary disease exacerbations. Clearly, more needs to be done to identify and validate meaningful outcome measures in young children with CF. Although MCC, infant pulmonary function testing and LCI are all intuitively attractive as CF biomarkers, none have been fully validated as an outcome measure that will allow us to confidently predict clinical benefits. In the absence of better-defined endpoints, however, physiologic improvement after HS treatment should not be ignored, and should spur further research. Ultimately, we need to determine whether HS administered to patients with mild disease leads to slowing of disease progression when given over long periods of time (e.g., delaying development of bronchiectasis). Studies that address this question are needed.

Much remains to be learned about the use of HS in CF. Treatment regimes, including optimal dose, concentration, rate of delivery and order of administration, have not been clearly defined [21]. Several different concentrations are clinically available, ranging from 3 to 10% NaCl. Although an acute dose–effect relationship has been demonstrated between inhaled NaCl concentration and MCC [6], there is no data to support better or worse clinical efficacy with concentrations other than 7% HS. However, as intolerability due to oropharyngeal irritation and bronchospasm generally relates to the concentration of HS and its rate of delivery, selection of a dose for an individual patient is typically made by determining the maximally tolerated concentration. How this dose is practically determined may vary from a subjective assessment of symptoms reported by the patient to more objective testing that may include pre/post-dose spirometry. Because the
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Editorial

Despite bronchodilator pretreatment, approximately 5% of CF patients tolerate 7% HS well, particularly following bronchodilator pretreatment, it is reasonable to begin treatment at 7% HS, while being prepared to reduce this concentration in patients with evidence of non-severe adverse reactions that would likely limit adherence. Despite bronchodilator pretreatment, approximately 5% of CF patients will experience bronchospasm that limits use [9].

At present, we must weigh evidence of physiologic benefits with HS against lack of data providing definitive proof of clinical efficacy. Given the limitations of the data available in early lung disease, but a reasonably large body of work showing safety in all age groups and relatively low cost, clinicians would do well to consider HS as a safe and effective therapy for CF patients at any stage of disease.

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References
1. Sly PD, Brennan S, Gangell C, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med 2009;180(2):146-52
2. Stick SM, Brennan S, Murray C, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. J Pediatr 2009;155(5):623-8; e621
3. Reeves EP, Molloy K, Pohl K, McElvaney NG. Hypertonic saline in treatment of pulmonary disease in cystic fibrosis. ScientificWorldJournal 2012;2012:465230
4. Robinson M, Regnis JA, Bailey DL, et al. Effect of hypertonic saline, amiloride, and cough on mucus clearance in patients with cystic fibrosis. Am J Respir Crit Care Med 1996;153(5):1503-9
5. Eng PA, Morton J, Douglass JA, et al. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. Pediatr Pulmonol 1996;21(2):77-83
6. Robinson M, Hemming AL, Regnis JA, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax 1997;52(10):900-3
7. Donaldson SH, Bennett WD, Zeman KL, et al. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006;354(3):241-50
8. Button B, Cai LH, Ehre C, et al. A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia. Science 2012;337(6097):937-41
9. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med 2006;354(3):229-40
10. Dmello D, Nayak RP, Matuschak GM. Stratified assessment of the role of inhaled hypertonic saline in reducing cystic fibrosis pulmonary exacerbations: a retrospective analysis. BMJ Open 2011;1(1):e000019
11. Dentice R, Elkins M, Bye P. A randomized trial of hypertonic saline nebulisation during hospitalisation for pulmonary exacerbation in adults with cystic fibrosis. Pediatr Pulmonol 2012;47(Suppl 35):257
12. Dellon EP, Donaldson SH, Johnson R, Davis SD. Safety and tolerability of inhaled hypertonic saline in young children with cystic fibrosis. Pediatr Pulmonol 2008;43(11):1100-6
13. 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(7):666-71
14. 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(5):471-6
15. Laube BL, Sharpless G, Carson KA, et al. Acute inhalation of hypertonic saline does not improve mucociliary clearance in all children with cystic fibrosis. BMC Pulm Med 2011;11:45
16. Donaldson SH, Samulski D, Lafave C, et al. Sustained effect of hypertonic saline on mucociliary clearance in cf children with mild lung disease. Pediatr Pulmonol 2013;48(5):210
17. Amin R, Subbarao P, Jabar A, et al. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. Thorax 2010;65(5):379-83
18. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. JAMA 2012;307(21):2269-77
19. Subbarao P, Stanojevic S, Brown M, et al. Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis: a pilot study using inhaled hypertonic saline. Am J Respir Crit Care Med 2013;188(4):456-60
20. Davis SD, Rosenfeld M, Brumback L, et al. Infants PFTs as an endpoint in the infant study of inhaled saline randomized controlled trial. Pediatr Pulmonol 2012;47:225
21. Elkins M, Dentice R. Timing of hypertonic saline inhalation for cystic fibrosis. Cochrane Database Syst Rev 2012;2:CD008816