14. Quinton LJ, Walkey AJ, Mizgerd JP. Integrative physiology of pneumonia. *Physiol Rev* 2018;98:1417–1464.
15. Mijares LA, Wangdi T, Sokol C, Homer R, Medzhitov R, Kazmierczak BI. Airway epithelial MyD88 restores control of *Pseudomonas aeruginosa* murine infection via an IL-1-dependent pathway. *J Immunol* 2011;186:7080–7088.
16. Burnham KL, Davenport EE, Radhakrishnan J, Humburg P, Gordon AC, Hutton P, *et al*. Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med* 2017;196:328–339.

Developmental Milestones in Pediatric Research: A Case for Including Efficacy as Part of Interventional Trials in Infants with Cystic Fibrosis

In a study reported in this issue of the *Journal*, Stahl and colleagues (pp. 1238–1248) provide new evidence for the safety, tolerability, and potential efficacy of inhaled 6% hypertonic saline in infants with cystic fibrosis (CF) (1). PRESIS (Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis), a randomized, double-blinded trial, included just over 40 subjects enrolled at an average age of 3 months and followed for 1 year after being assigned to inhalation of twice daily nebulized isotonic versus hypertonic saline. No subject experienced a study-related serious adverse event or withdrew from the trial for intolerance. Studies done in children so young are often limited to safety and tolerability, but the PRESIS investigators were able to move beyond this and include measures of potential benefit to pulmonary health.

The study found that 6% hypertonic saline nebulized twice a day for 52 weeks provided a statistically significant improvement in lung function as measured by the primary efficacy outcome, lung clearance index (LCI). When compared with infants assigned to isotonic saline, those given 6% saline experienced a reduction (i.e., improvement) in LCI that was sustained over the 12-month observational period. The improvement in LCI, although not large, is similar to the difference reported between healthy children and those with CF at this age (2, 3). Larger improvements in LCI were seen in a small number of preschool-aged children after they started ivacaftor, but most of the children had higher (i.e., worse) baseline LCI values, and the few patients with normal baseline LCI tended to show little change with therapy (4).

The feasibility and successful use of LCI in the PRESIS study is perhaps as informative as the results. This is the first publication to report the successful use of LCI in a multicenter, randomized controlled clinical trial in infants. A single-center pilot substudy within the Infant Study of Inhaled Saline trial previously demonstrated that subjects receiving inhaled 7% saline had better LCI values than those receiving isotonic saline, but the participants had a median age of >2 years at enrollment (5). Stahl and colleagues now extend the argument that LCI can identify the health impacts of pulmonary interventions in trials that include very young children across multiple centers. Although the clinically meaningful change in LCI at this age is uncertain, they should be commended for this work requiring repeated study-related procedures for both LCI and chest magnetic resonance imaging (MRI).

There are a number of interesting observations beyond the key findings reported in this study. The PRESIS trial was set up to take advantage of early diagnosis of CF after newborn screening, with the goal of delaying or reducing the development of CF lung disease. This demonstrates the need for sensitive measures such as LCI to detect relatively small differences in lung function when focused on very young patients who may have been diagnosed before the onset of any pulmonary symptoms. Such measures were not available in initial studies of the effect of newborn screening on CF lung disease (6). Improvement in LCI was not associated with improvement in lung morphology as measured by MRI or the risk of predefined acute pulmonary exacerbations. Caution against overinterpreting data from a study of this size is necessary, but the findings suggest that either lung functional and structural abnormalities at this age do not align or lung imaging outcome measures may have less value in a population this young. Clearly, alternative interventions or imaging modalities may produce different results, but prior research also found a poor correlation between results from LCI and computed tomography imaging in subjects under 1 year old (7, 8). Less than one-third of children with CF appear to have bronchiectasis on computed tomography at 1 year of age (9).

The modified Fuchs criteria were used to define acute pulmonary exacerbation in this trial. This definition is a common, valuable tool in CF clinical research (10), but it may be less useful in such young children. One recognizes that infants, even when acutely ill, often lack many of the symptoms required by the Fuchs criteria (e.g., change in sputum, hemoptysis, dyspnea, sinus pain, chest X-ray changes, and change in lung function), which may explain why less than half of the subjects in the trial experienced a protocol-defined exacerbation over the 12-month period. Although hypertonic saline may not significantly impact the risk of acute pulmonary exacerbations in young children (11), this also underscores the ongoing need to consider alternative quantitative efficacy measures for the youngest populations. The CF community has recently been encouraged, if not surprised, by potentially important benefits reported in studies testing CFTR (cystic fibrosis transmembrane conductance regulator) modulator drugs in infants and toddlers with CF (12). Thus, accumulating evidence suggests that using chronic preventive therapies before the onset of observable symptoms may provide clinically meaningful benefits. More work is needed to understand long-term safety and whether

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or not the first year or two of life represents a window of opportunity during which any particular therapy may provide health gains that are not recoverable if treatment is delayed.

The PRESIS investigators also reported improved weight and weight-for-length with the use of 6% versus 0.9% inhaled saline. It is uncertain how this occurred, and the authors reasonably argue that such improvements may represent a systemic benefit from lessened pulmonary disease. Indeed, chronic airway or intestinal inflammation in people with CF appears to correlate inversely with nutritional status (13–15), and hypertonic saline may lessen the inflammatory state in older individuals (16). Without a direct measure of airway inflammation in the present study, this remains speculative, and it is worth recognizing that four subjects (19%) who were randomized to 6% saline were pancreatic sufficient, compared with one subject in the isotonic control group. Prior larger studies of drugs that improve mucociliary clearance in older children and adults have not identified nutritional gains (11, 17, 18). Ultimately, this interesting finding in infants treated with hypertonic saline will need to be replicated and better understood.

Regardless of the impact on weight, the PRESIS investigators have provided evidence of safety and tolerability, and have strengthened the rationale to pursue additional testing of chronic therapies, including hypertonic saline, in infants with CF. The need for sedation to obtain LCI measurements (or advanced imaging such as MRI) in infants will need to be carefully considered. Nonetheless, the PRESIS investigators are recognized for completing a challenging clinical trial that supports both the need for early intervention studies in young patients and the rationale to consider more than safety and tolerability in these trials. Efficacy data may not be important for regulatory approval and drug access in all countries, but they are very helpful when patients and providers wrestle with important issues such as treatment burden and cost. ■

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References

1. Stahl M, Wielputz MO, Ricklefs I, Dopfer C, Barth S, Schlegtendal A, *et al*. Preventive inhalation of hypertonic saline in infants with cystic fibrosis (PRESIS): a randomized, double-blind, controlled study. *Am J Respir Crit Care Med* 2019;199:1238–1248.
2. Hoo AF, Thia LP, Nguyen TT, Bush A, Chudleigh J, Lum S, *et al*.; London Cystic Fibrosis Collaboration. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. *Thorax* 2012;67:874–881.
3. Davies G, Stocks J, Thia LP, Hoo AF, Bush A, Aurora P, *et al*.; London Cystic Fibrosis Collaboration (LCFC). Pulmonary function deficits in newborn screened infants with cystic fibrosis managed with standard UK care are mild and transient. *Eur Respir J* 2017;50:1700326.
4. Ratjen F, Klingel M, Black P, Powers MR, Grasemann H, Solomon M, *et al*. Changes in lung clearance index in preschool-aged patients with cystic fibrosis treated with Ivacaftor (GOAL): a clinical trial. *Am J Respir Crit Care Med* 2018;198:526–528.
5. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, Davis S, *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: 456–460.
6. Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, *et al*. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003;168: 1100–1108.
7. Ramsey KA, Rosenow T, Turkovic L, Skoric B, Banton G, Adams AM, *et al*.; AREST CF. Lung clearance index and structural lung disease on computed tomography in early cystic fibrosis. *Am J Respir Crit Care Med* 2016;193:60–67.
8. Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, *et al*.; AREST CF. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. *PLoS One* 2011;6:e23932.
9. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, *et al*.; AREST CF Investigators. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* 2013;368:1963–1970.
10. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, *et al*.; The Pulmozyme Study Group. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331:637–642.
11. Rosenfeld M, Ratjen F, Brumback L, Daniel S, Rowbotham R, McNamara S, *et al*.; ISIS Study Group. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA* 2012;307:2269–2277.
12. Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, *et al*.; ARRIVAL study group. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med* 2018;6:545–553.
13. Visca A, Bishop CT, Hilton S, Hudson VM. Oral reduced L-glutathione improves growth in pediatric cystic fibrosis patients. *J Pediatr Gastroenterol Nutr* 2015;60:802–810.
14. Ranganathan SC, Parsons F, Gangell C, Brennan S, Stick SM, Sly PD; Australian Respiratory Early Surveillance Team for Cystic Fibrosis. Evolution of pulmonary inflammation and nutritional status in infants and young children with cystic fibrosis. *Thorax* 2011;66:408–413.
15. Ionescu AA, Nixon LS, Evans WD, Stone MD, Lewis-Jenkins V, Chatham K, *et al*. Bone density, body composition, and inflammatory status in cystic fibrosis. *Am J Respir Crit Care Med* 2000;162: 789–794.
16. Reeves EP, Williamson M, O'Neill SJ, Greally P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis. *Am J Respir Crit Care Med* 2011;183:1517–1523.
17. Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, *et al*.; 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.
18. Quan JM, Tiddens HA, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, *et al*.; Pulmozyme Early Intervention Trial Study Group. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;139:813–820.