Early Intervention for Newborns Screened for Cystic Fibrosis

Despite more than 10 years of newborn screening for cystic fibrosis (CF), recent recommendations on management of newborns screened for CF are almost entirely based on expert consensus with low-grade level of evidence (1, 2). More specifically, newborn screening has led to reports of improved nutritional outcomes and decreased burden of care (3), but benefits with regard to respiratory status remain contentious. Important longitudinal studies have demonstrated that inflammation and structural lung disease may develop and progress during infancy and preschool years, often in the absence of respiratory symptoms (4). Therefore, the advent of early diagnosis of CF enables early interventions aimed at preventing or potentially improving pulmonary insults. To facilitate the development of effective interventions, we must first develop safe robust outcomes, feasible and suitable for young children. Important insight has been gained into potential candidates from the Infant Study of Inhaled Saline (ISIS).

In the main study, Rosenfeld and colleagues examined the effectiveness of 48 weeks of twice daily nebulized 7% hypertonic saline (HS), compared with isotonic saline (IS, control), in 321 infants and preschoolers (aged less than 6 yr) recruited across multiple North American sites (5). The primary outcome was a reduction in rate of pulmonary exacerbation, a choice of outcome supported by evidence from a recent study that described correlation between exacerbation rate in the first 2 years of life and lung function outcomes at age 5 years (6). However, ISIS failed to achieve a reduction in exacerbations, despite large study numbers, which contrasts with the beneficial effects with HS on exacerbation rate reported in older age groups (7).

Suitability and reliability of exacerbation rate as an outcome measure in infants and preschoolers has since been debated. CF exacerbations related to underlying CF lung damage and characteristic CF bacterial organisms might be mimicked by the usual viral-induced respiratory infections of early childhood. It is clear that due to these reported ISIS results, benefits seen with HS in older populations cannot be extrapolated at present to management strategies used in younger subjects with CF. However, the smaller ISIS substudies examining the change in infant lung function measures (plethysmography, forced expiratory flows, and volumes) and multiple-breath washout (MBW) provide interesting insight that functional benefits may yet be proven with HS if future appropriately designed studies choose the right physiological outcome measure.

In the ISIS infant lung function subgroup (n = 45 infants), only one index demonstrated a statistically significant change ($FEV_{0.5}$) (5). After adjustment for baseline lung function, sex, age, height, and weight, $FEV_{0.5}$ exhibited a mean 38 ml larger increase (or 23% relative to the mean baseline value) in the HS group compared with IS (5). The potential signal from a physiological test, albeit small in magnitude, is reinforced by the observed changes in the lung clearance index (LCI) with HS presented by Subbarao and colleagues (pp. 456–460) in this issue of the *Journal* (8). MBW was performed at baseline and at the end of 48 weeks of HS treatment (n = 25, comprising 10 infants and 15 preschool children). Excellent feasibility was demonstrated in this setting (25 out of 27, 93%). In this small cohort, the treatment effect of HS did not reach statistical significance when LCI was expressed as an actual change (mean, 1.43 [95% confidence interval, 0.13–2.99]; $P = 0.07$); however, when expressed as z-score change, statistical significance was achieved (mean, 2.0 [95% confidence interval, 0.25–3.76]; $P = 0.03$). The small study numbers and the lack of infants with abnormal LCI at enrollment mean that results should not be overinterpreted, but it reinforces the exciting potential utility of LCI as an interventional outcome measure recently described in older CF pediatric cohorts, over shorter treatment periods (9, 10).

Several discussion points emerge from this study regarding LCI utility in these younger populations. The use of z scores in preference to actual units (lung turnovers) is supported by recent studies describing LCI variation across age ranges: LCI decreased markedly during the first 6 years of life, using pooled SF_6-based MBW data from three sites collected on the same equipment as used by Subbarao and colleagues (11), and in a separate study, LCI slowly increased between 7 and 70 years, using validated commercial nitrogen (N_2)-based MBW (MBNW) equipment (12). Reference data collected using different inert gases are not interchangeable (13), but trends described are likely to be present across different inert gases. Custom-built SF_6 respiratory mass spectrometer–based MBW equipment remains expensive and limited to specialized centers internationally (six at present to our knowledge). Targeting feasibility for large multicenter studies and obtaining generalizable LCI results ideally requires validated robust equipment, which is widely available at an affordable price. Close liaison with manufacturers during the development of the recently published European Respiratory Society/American Thoracic Society consensus statement (13) has facilitated more affordable validated commercial MBNW equipment (14). However, technical issues remain to extend this MBNW equipment use down to infancy and preschoolers. Aspects to address include the age-dependent effect of equipment dead space volume and the reported adverse effects of 100% oxygen on infant breathing patterns (15).

To complicate things further, Subbarao and colleagues describe a differing pattern of response between infants and preschoolers with CF, suggesting that beneficial effects in early disease (all infants had normal LCI z scores at baseline) may lie in prevention of disease progression, whereas in those with established lung disease in the preschool years (9/15, or 60%, with abnormal LCI z scores at baseline), improvement in LCI may be achievable.

Methodological factors also support examination of these age ranges separately. There is current uncertainty about the effect of patient interface, testing position, or use of sedation on LCI results as we look longitudinally: from infancy (facemask, supine, sedated) to preschool (facemask, sitting, distracted by DVD), and subsequently to school age (mouthpiece, not facemask). Until these issues are addressed, preschool studies may need to be targeted first or, alternatively, future studies designed with sufficient numbers of both infants and preschool children to enable separate analysis according to age.

Issues exist for each of the candidate outcome measures for early CF intervention studies (computed tomography, infant lung function, and MBW). Lack of appropriate normative values for available commercial equipment remains a significant concern for infant lung function (16), as does further minimization of radiation exposure associated with computed tomography scans, despite recent advances and dose reduction. MBW remains the most attractive of these options at present (17). Our success with addressing outstanding issues for each of these outcomes will govern the overall design and success of future studies.

Author disclosures are available with the text of this article at www.atsjournals.org.

Nicole Beydon, M.D.
APHP, Unité Fonctionnelle de Physiologie-Explorations Fonctionnelles Respiratoires et du Sommeil
Hôpital Armand Trousseau
Paris, France

Paul D. Robinson, M.D., Ph.D.
Department of Respiratory Medicine
The Children's Hospital at Westmead
Sydney, Australia

References

1. Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, Michel SH, Parad RB, White TB, Farrell PM, *et al.*; Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr* 2009; 155(6, Suppl): S73–S93.
2. Castellani C, Southern KW, Brownlee K, Dankert Roelse J, Duff A, Farrell M, Mehta A, Munck A, Pollitt R, Sermet-Gaudelus I, *et al.* European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros* 2009;8:153–173.
3. Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A; United Kingdom Cystic Fibrosis Database Steering Committee. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics* 2007;119:19–28.
4. Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, Robertson CF, Ranganathan SC, Sly PD, Stick SM; AREST CF. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. *Thorax* 2012;67:509–516.
5. Rosenfeld M, Ratjen F, Brumback L, Daniel S, Rowbotham R, McNamara S, Johnson R, Kronmal R, Davis SD; 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.
6. Byrnes CA, Vidmar S, Cheney JL, Carlin JB, Armstrong DS, Cooper PJ, Grimwood K, Moodie M, Robertson CF, Rosenfeld M, *et al.* Prospective evaluation of respiratory exacerbations in children with cystic fibrosis from newborn screening to 5 years of age. *Thorax* 2013;68:643–651.
7. 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.
8. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, Davis S, Brumback L, Gustafsson P, Ratjen F. 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.
9. Amin R, Subbarao P, Lou W, Jabar A, Balkovec S, Jensen R, Kerrigan S, Gustafsson P, Ratjen F. The effect of dornase alfa on ventilation inhomogeneity in patients with cystic fibrosis. *Eur Respir J* 2011;37: 806–812.
10. Amin R, Subbarao P, Jabar A, Balkovec S, Jensen R, Kerrigan S, Gustafsson P, Ratjen F. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. *Thorax* 2010;65:379–383.
11. Lum S, Stocks J, Stanojevic S, Wade A, Robinson P, Gustafsson P, Brown M, Aurora P, Subbarao P, Hoo AF, *et al.* Age and height dependence of lung clearance index and functional residual capacity. *Eur Respir J* 2013; 41:1371–1377.
12. Houltz B, Green K, Lindblad A, Singer F, Robinson PD, Nielsen KG, Gustafsson P. Tidal nitrogen washout ventilation inhomogeneity indices in a reference population aged 7–70 years. *Eur Respir J* 2012;40:694s.
13. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, Thamrin C, Arets HG, Aurora P, Fuchs SI, *et al.* Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J* 2013;41:507–522.
14. Singer F, Houltz B, Latzin P, Robinson PD, Gustafsson PM. A realistic validation study of a new nitrogen multiple-breath washout system. *PLoS ONE* 2012;7:e36083.
15. Schibler A, Schneider M, Frey U, Kraemer R. Moment ratio analysis of multiple breath nitrogen washout in infants with lung disease. *Eur Respir J* 2000;15:1094–1101.
16. Stocks J, Modi N, Tepper R. Need for healthy control subjects when assessing lung function in infants with respiratory disease. *Am J Respir Crit Care Med* 2010;182:1340–1342.
17. Stick S, Tiddens H, Aurora P, Gustafsson P, Ranganathan S, Robinson P, Rosenfeld M, Sly P, Ratjen F. Early intervention studies in infants and preschool children with cystic fibrosis: are we ready? *Eur Respir J* (In press)

DOI: 10.1164/rccm.201306-1023ED

Diamonds in the Rough: Identification of Usable Donor Lungs

Despite considerable success in long-term patient survival, transplantation in all solid organ systems continues to be hampered by persistent organ shortages (1). Of this limited resource, centers ultimately transplant only 15–20% of potential donor lungs. The reasons for this low use are complex. Preexisting donor lung disease, pneumonia, and chest trauma render some organs currently unsalvageable. Additionally, data to define reliable surrogate measures of donor lung function do not exist, and therefore, relatively stringent traditional donor selection criteria may prevent the use of suitable donor lungs. Moreover, implementation of the Lung Allocation Score (LAS) has resulted in transplantation of higher-acuity recipients who may be less likely to tolerate a significant reperfusion injury. Thus no simple algorithm can be used to guide acceptance or refusal of a particular donor offer.

In this issue of the *Journal*, Castleberry and colleagues (pp. 466–473) analyzed the United Network of Organ Sharing database to investigate whether the use of lungs from brain-dead donors after cardiac arrest results in acceptable recipient outcomes (2). This is a key question to address because organs from this group of donors appear to be underused. In this study, lung recipients were 1:1 propensity score matched to provide a recipient risk–adjusted comparison of the two groups. Importantly, analysis included only recipients after the implementation of the LAS, a scoring system designed to rank lung recipients based on medical urgency adapted in May 2005. Median survival, 30- or 90-day mortality, and postoperative complications were similar in both groups, suggesting that use of lungs from brain-dead donors after cardiac arrest results in acceptable recipient outcomes. The study is limited by its retrospective nature and the inability to measure other confounders not recorded in the database that may affect postoperative outcomes as well as the complex nature of organ use decisions. Nevertheless, it provides the first large-scale analysis of the use of lungs from brain-dead donors after cardiac arrest. Perhaps more importantly, these data suggest that lungs from brain-dead out-of-hospital cardiac arrest victims may be safe to transplant as well. Every year in the United States, between 1,800 and 7,200