**Achieving respiratory excellence in pre-school children with cystic fibrosis**

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A child with cystic fibrosis (CF) who begins school at 5-6 years of age in good respiratory health has established a strong framework for the rest of their life. Respiratory excellence has been achieved if a child is active and asymptomatic with normal chest radiology and a lack of CF pathogens from respiratory cultures. To achieve this goal, excellent nutrition is imperative and there is clear consensus on the approach to address pancreatic insufficiency.(1) This contrasts with airway management strategies, which are extremely variable across the globe. There is lack of robust evidence to guide airways management in this age group. The global expansion of newborn bloodspot screening for CF has thrown this into sharp perspective.(2) In this volume of the journal, four papers examine the issue of respiratory health in young children with CF.(Korten, Garratt, Pollak, Voldby refs from editors) This is a good addition to our knowledge, even if these papers generate rather more questions than answers.

Preventing respiratory symptoms in pre-school CF children is the mantra of most CF Paediatricians, and hence, the data presented by the Swiss are, on the face of it, quite unsettling.(Korten ref) The authors have undertaken multiple breath washout (MBW) to measure lung clearance index (LCI) on babies with CF between four and thirteen weeks of age comparing with a well-matched cohort of babies without CF. The number of successful tests reflects well on the research team and the sedative power of milk. The values are similar in both cohorts and reassuring. The group have then monitored both cohorts closely for the first year of life with weekly phone calls to generate a respiratory score. This is a robust methodology to collect these data and, somewhat surprisingly, there is little difference between the CF and non-CF infants. There are a lot of respiratory symptoms in both groups, with infants being symptomatic for around 20% of the first year of life. There was no relationship between symptom score and the MBW respiratory function measures at baseline. A repeat LCI measurement at 12 months would have been informative but would require a much stronger sedative than milk at this age! These data are helpful to my practice, in that they quantify the extent of symptoms in this age group with around two-three months of symptoms reported in the first year of life. I remain of the opinion that respiratory symptoms in pre-school children with CF are important, especially cough, and would like to see further data as this cohort moves into years 2-6. The headline of the study that early CF lung disease may not be captured by clinical presentation alone somewhat overstates the findings, but the data do suggest that we can’t be complacent with less symptomatic infants.

Respiratory surveillance and antibiotic management of airway infection are areas of even greater varied practice. Most CF paediatric centres in Europe and the US undertake some form of regular upper airway sampling as a proxy to lower airway infection, most commonly through naso-pharyngeal aspirate or cough swab. Some centres opt for less frequent but more accurate lower airway sampling with bronchoscopically obtained alveolar lavage (BAL) samples. The Australian BAL study and the Australian AREST-CF programme have provided insight into early CF airways infection, but the data do not support a strategy of routine lower airway sampling in the early years.(3, 4) Debate over surveillance strategy is mirrored by what to do when CF pathogens are isolated and the general approach to antibiotic therapy. One area on which there is agreement is the need for an intensive eradication strategy if *Pseudomonas aeruginosa* is isolated from any form of respiratory culture.(5) In this journal, Garratt *et al*. present data from the AREST CF programme reporting the outcomes of two intensive eradication regimens for *Pseudomonas aeruginosa* isolated from the lower airways with follow up BAL samples obtained 3 and 12 months post initiation of therapy.(Garratt) Neutrophil elastase (NE) is well known to CF scientists and reflects the intense neutrophil-dominated “acute” picture of inflammation in the CF airways.(6) The children with *Pseudomonas aeruginosa* isolated had significantly higher levels of NE in their BAL samples. Successful eradication was achieved in the majority of infants with no growth of pseudomonas aeruginosa at 3 months and there was a considerable reduction in NE measured in the BAL. For some infants, high NE levels persisted at the post-eradication sampling and, somewhat surprisingly, there wasn’t a clear relationship between this and unsuccessful eradication. However, the infants with persistently high NE were around twice as likely to have a recurrent isolation of *Pseudomonas aeruginosa* from the samples obtained 12 months later. What do these results mean for clinical practice. Measuring NE in BAL fluid is challenging, costly and undertaken routinely in few centres, mostly where there is an established research programme. These data may support an argument for measuring NE routinely to identify at risk infants and consider further treatment options, but most centres would not repeat bronchoscopy at the end of a three-month eradication regimen, so this opportunity would not arise. Determining the most appropriate further treatment for these at-risk infants would require robust trials. The authors suggest an anti-inflammatory approach (and provide some elegant *ex vivo* data to support this) but my bias would be towards prolonged anti-microbial treatment, possibly with a different nebulised antibiotic regimen. More work is needed on this important topic.

Another anxiety that has nagged me for the past few decades has been the use of routine pulmonary function tests (PFTs) for infants with CF to identify early onset airways disease and facilitate earlier treatments. The work of Pollak *et al*. (and others) reassures me that traditional infant PFTs using the raised volume compression technique do not have a place in routine clinical practice.(Pollak; (7)) This may not have been the case thirty years ago, but with our current cohort of well infants, an artificially produced forced expiration in infants does not correlate with standard spirometry when children are old enough to blow out candles or whatever incentive they are given. The emergence of multiple breath washout (MBW) has provided a measure (lung clearance index (LCI)) that does seem to give us a window into early airways involvement in infants with CF. It seems increasingly apparent that establishing this measure as a part of routine clinical practice may give CF Paediatricians early warning of CF lung disease even in an infant with normal radiology and little clinical concern. The SHIP trial undertaken by this group and others in North America was extremely valuable in demonstrating that use of hypertonic saline (7%) nebulised twice a day resulted in a reduction (improvement) in LCI of around 0.8 compared to infants that received nebulised normal saline.(8) Should all infants with CF have twice daily nebulised hypertonic saline based on the SHIP study results? In our service, we discuss this trial with our families and come to a decision in partnership considering the benefit in LCI value balanced against the daily drama of delivering a nebulised therapy to a pre-schooler. Undertaking MBW measurement in pre-school children requires a skilled team and appropriate equipment. I am told it is possible in 4-year-olds, tricky in 3-year-olds and very difficult in under 2s. The swiss group report good success in babies but the need for sedation in the older infants changes the risk:benefit equation. It is difficult to justify sedation outside of research programmes at present. There is now enough evidence to suggest that all CF centres should be aiming to routinely measure LCI before children go to school and this requires investment, training and expertise.

There is no evidence to support the routine use of nebulised dornase alfa for pre-school children with CF and the evidence for early school age children, who are well, is not robust.(9) This therapy has a very good safety profile and is routinely used in this age group despite lack of evidence of efficacy. Possibly it is better tolerated and easier to administer once daily than hypertonic saline. The main negative impact is the time and effort to deliver a therapy to a pre-schooler for which there is no clear evidence of efficacy.

The Danish group present data from a randomised trial of the intervention of stopping dornase alfa.(Voldby) As new therapies for CF emerge, stopping trials will become an increasingly important part of the CF landscape and it is important they generate outcomes that are meaningful to people with CF and their families.(10) The primary outcome for this trial was LCI measured one month after the stop intervention. The median age of the children was around 10 years and 14 completed the study in each arm. Children randomised to the stop arm had a significant increase their LCI value, whilst those who continued dornase alfa maintained their LCI. Although a small trial with no attempt at blinding the intervention to the families or health professionals, the difference is clearly significant, both statistically and clinically. This result mirrors data from adult studies demonstrating a reduction in FEV1 following withdrawal of dornase alfa therapy. The authors propose a plausible rationale, that ventilation inhomogeneity is exacerbated by the withdrawal of dornase alfa and that LCI is good measure to identify this change, in comparison to standard spirometry.(Voldby)

It has taken more than a decade but gradually CF Paediatricians are getting a handle on LCI as a measurement they can utilise in clinical practice to monitor early CF lung health. As we move to a new era of variant specific therapies, it is clear that maintaining health in the pre-school years remains critical to longer term well-being. Nutritional excellence is key in this age group, but approaches to maintaining airway health remain varied. There is good agreement about the importance of intensive eradication regimens for *Pseudomonas aeruginosa* and emerging confidence in LCI as a measure of early airways disease. There is some evidence that hypertonic saline may have a role as an early aerosolised therapy but less clear evidence in pre-school children for dornase alfa, albeit this is a safe and well tolerated therapy. Surveillance for CF pathogens is important and I remain convinced that persistent symptoms are important (especially persistent cough) and merit active investigation and treatment. But what the Swiss data tell us is that even in the asymptomatic infant we need to be vigilant.

**References**

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