AREST – Consumer version of Concise Clinical Review by Helen Lester, consumer representative, AREST-CF.

Early lung disease in infants and children with CF: Looking to the future

Sarath Ranganathan, Graham Hall, Peter Sly, Stephen Stick, and Tonia Douglas undertook the Concise Clinical Review on behalf of Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF).

Very early treatment of children with cystic fibrosis is key if we are to help them live longer and have a better quality of life, a clinical review has found.

The Review by senior Australian paediatric CF clinicians has established lung damage occurs very early in life, often without symptoms or signs. Because of this, the specialists now believe early childhood is a critical period for intervention to delay or stop the start of irreversible damage.

As well as future research strategies, doctors are also considering immediate changes to clinical practice based on the Review. They believe it's not feasible to await the results of future studies before intervening. Logic and experience, they believe, mean certain initiatives can be started to improve care of infants and children with CF, even if direct evidence is not yet available.

As a result, parents possibly face potentially increased surveillance and treatment of their healthy-looking children. Parents in this situation may benefit from psychosocial support, the Review says.

Because doctors now know that lung disease develops very early in life, the Review makes the case that they are therefore obliged to provide better CF education and support for parents and families after diagnosis.

Doctors examined a decade of research findings about early lung disease in children with CF to set up research and therapy directions for the future. They found irreversible, progressive lung disease develops *early* in life in CF because of a genetic defect that leads to dysfunction in the CF transmembrane regulator (CFTR), causing mucus in various organs to become thick and sticky.

Lung inflammation, infection and structural lung damage are common in infants and preschool children, and the Review found clinical approaches so far had failed to stop most children with CF having established bronchiectasis (permanent lung scarring) by the age of five.

Future studies will be designed to alter early disease progression to stop lung damage before it becomes irreversible. Areas of focus include treating lung inflammation, minimising lung function decline and preventing infection using environmental strategies.

The exact mechanisms linking the basic CF defect to organ damage (including irreversible damage to the lungs) are unclear, but data from intensive CF early surveillance programs, such as those developed by the Australian Respiratory Early Surveillance Program for Cystic Fibrosis, have provided important insights into the biological mechanisms and natural history of lung disease in early life.

Review findings at a glance

Pulmonary Inflammation

- Lung inflammation in infancy and the preschool years is associated with worse nutritional status, undesirable organisms in the lower respiratory airways, bronchiectasis, and lung function abnormalities.
- Infection is a key contributor in inflammation. Its increase with age during the preschool years appears to be relatively independent of current or previous infection.
- Normal lung defence mechanisms are overwhelmed by inflammation and infection, creating the potential for lung structure weakening.
- Research is examining the role of thick, sticky mucus in the cause of inflammation. The challenge is to identify and trial potential therapies for reducing inflammation and infection as a way to prevent future lung disease.

Infection

- Bacteria such as *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are thought to cause respiratory infection in CF, but the role of these organisms in the development and progression of structural lung disease and lung function decline remains unknown.
- The eradication of chronic *P. aeruginosa* (a significant pathogen in declining health and increased death) during the preschool years does not appear sufficient to prevent the development of structural lung disease or lower lung function.
- *S aureus* is commonly cultured shortly after diagnosis and in up to 30% of infants during the first six months of life.
- The environment may play a part in acquiring infections. Living in a regional versus a metropolitan area is a significant risk factor for the first acquisition of *P. aeruginosa.* It's possible *P. aeruginosa* infection may occur in those who already have worse lung disease or disease susceptibility. It remains unknown whether the *number* of a particular organism as opposed to the *presence* of the organism present in the airways, is important in CF lung disease.

Structural Lung Disease

- Structural lung damage caused by infection and inflammation is difficult to assess in its early stages, and until now has not been the main focus for doctors. Advances in technology have markedly improved the sensitivity with which structural lung disease can be detected.

Lung Function

- Infants who avoid lung infections during infancy experience lung growth similar to that of healthy children. It's likely that lung clearance index (LCI) may be useful to monitor structural lung disease in preschool and school-age children.

Implications for Clinical Practice

- Despite normal FEV_1, almost 80 per cent of children with CF show evidence of bronchiectasis by the time they reach school age.
- New treatments will be aimed at preventing the onset and delaying the progression of bronchiectasis, inflammation and lung function decline during the preschool years. The next target for treatment arising from newborn screening for CF is to develop genuine primary prevention strategies intended to avoid the development of the disease.

Clinical Care and Future Strategies

- Change in attitude in CF clinics is needed, with attention being given to the critical role of intervention in the early years.
- The Review advocates the development of policies and guidelines for a unified proactive approach to care in apparently 'healthy' CF children without symptoms. It says the detection of lung abnormalities in early life makes a persuasive argument for intervention, even if evidence for specific treatments is scarce.
- Therapeutic options may include antibiotics for CF pathogens detected in both symptomatic and asymptomatic individuals.

While using therapies earlier and more intensively seems an appropriate response to current scientific evidence, there is the potential risk of treatment-related side effects and increasing health costs.

Currently, treatments are recommended for the majority of patients because of the inability to predict a child's risk of disease progression. Being able to target children with the greatest need for such treatments would not only save money, but would reduce the potential risk of side effects from unnecessary treatments. The Review argues identifying better predictors of severity of disease from time of diagnosis should remain a crucial aspect of further research. New, potentially disease-modifying treatments are likely to be extremely expensive and may have as-yet-unknown side effects.

If early intervention is to succeed, appropriate tools are also required to safely and effectively monitor disease progression and the effect of treatments.

The main takeaway from the Review is that maximising the benefits provided by newborn screening programs through the early introduction and implementation of new CF treatments is important if we are to improve the longevity and quality of life for the next generation of people with CF.