



MEDICAL

Early intervention in CF: When to start treatment and how to measure response?

By Professor Eitan Kerem, M.D.

The survival of patients with CF has improved dramatically in the last 40 years. It is estimated that a child born with CF now has over 80% chance of reaching the age of 40 years. This improved survival has been achieved by intensive and aggressive therapy. It has been shown that care at a specialized center, and input from a team of trained and experienced health professionals are essential for optimal patient management and improved outcome.

Improved outcomes result from frequent clinical evaluations, monitoring for complications, and aggressive interventions by physicians and other healthcare workers, specifically trained in the management of CF. Standards of care should define the service provision necessary to deliver a satisfactory level of care. Several guidelines* have been written with the aim of assisting CF caregivers in the evaluation and monitoring of patients, detection of complications and prevention of clinical deterioration.

In early life, CF is quite often (though not always) characterized by well being, minimal symptoms and functional stability. With the introduction of modern therapy in CF, the apparent progression of lung disease is slow. Pulmonary function tests are usually normal in early childhood. However, smoldering sub-acute decline may be present with or without the acute exacerbations (or flare-ups).

“ ...patients and their parents might be reluctant to adhere to tedious treatments in order to prevent the slow and non apparent decline”

Aggressive treatment of acute exacerbations is a common practice in CF care. However, patients and their parents might be reluctant to adhere to tedious treatments in order to prevent the slow and non apparent decline. Such therapies may require daily tiresome and time consuming practice of physiotherapy, inhalations and nutritional support that is very difficult to perform for many patients with CF and their parents. The feeling or appearance of well being gives a false sense that the disease is not active and therefore reduces the motivation to adhere to daily CF care. The smoldering sub-acute decline is associated with bronchial inflammation and bacterial growth which will lead to further lung damage and the development of bronchiectasis, a situation which is irreversible.

“ the implementation of effective hygienic measures inside and outside of CF centers”

Early and aggressive therapy instigated at the stage when there are no apparent signs of significant lung disease may delay the development and progression of the disease.



The current strategies for early intervention include:

- 1 early diagnosis,
- 2 early initiation of antibiotic and anti-inflammatory therapy,
- 3 early drug assisted augmentation of mucous drainage,
- 4 early nutritional support and the implementation of
- 5 effective hygienic measures inside and outside of CF centers

Studies designed to evaluate the effect of different therapies on early lung disease, need to include a large number of patients and need to follow them for many months or even years, in order to demonstrate a small effect. Therefore, it might be impossible to evaluate the effect of therapy on the early course of CF unless more sensitive tests can be found that will evaluate the effectiveness of treatment and monitor the progression of early lung damage.

The clinical endpoints for determination of response to treatment include assessment of infection, inflammation or structural changes. The current substitute markers that have been used to assess the effect of early treatment in CF include:

- 1 Pulmonary function tests
- 2 Sputum cultures
- 3 Inflammatory markers
- 4 Chest X-rays, HRCT
- 5 Nutritional status
- 6 Exacerbations rate and need for antibiotic therap
- 7

Pulmonary function tests

Pulmonary function is an important measure of disease severity and prognosis in CF. Spirometry is regarded as the best predictor of lung disease in CF and should therefore be measured at each clinic visit. The measurements provided include FEV₁ (forced expiratory volume in one second), and FEV₁ has been shown to be the strongest clinical predictor of mortality in CF and has been the primary outcome measure in many clinical trials. Spirometry requires coordination and the patient's collaboration, and can be performed in children over 5-6 years of age. Recent reports demonstrated that children as young as 2 years of age can produce reliable Spirometry. However, in most children of this age, the results are normal and in most cases cannot document underlying inflammation and/or minimal structural changes. Therefore spirometry is not a good outcome measure to evaluate the response to early treatment.

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The role of lung function testing during infancy remains unclear. Several studies have shown that compared to normal infants, infants with CF have changes in lung volumes and maximal flows indicating early inflammation in the small airways. However, these measurements require sedation, and they lack standardized equipment and technique that prevents their routine use. Thus, pulmonary function, regarded as the gold standard for lung disease in CF is insufficient to demonstrate early damage and response to therapy.



Bacterial cultures

Acute and especially chronic lung infections caused by bacteria are responsible for most of the morbidity and mortality of patients with cystic fibrosis. To prevent chronic pseudomonas infection, early 'intensive' anti-pseudomonal therapy has been recommended to eradicate intermittent colonization. Infants and small children often have respiratory infections, therefore early diagnosis of bacterial lung colonization or infection is crucial. The CF team should take the opportunity to discuss ways of increasing adherence to recommended therapy with parents and patients at this time. Prophylactic antibiotic therapy should be introduced in a timely manner, and effective hygienic measures taught to parents and patients.

“BAL...appears to be the most sensitive and accurate method to obtain respiratory cultures in infants and small children”

Some of the bacterial species may also cause cross-infection between patients with CF when attending CF centers or during social activities. Therefore, it has been recommended that sputum cultures are obtained at every routine clinic visit. Infants and young children do not expectorate sputum readily and other methods need to be used in order to obtain specimens that will identify the type of bacteria present in the lower respiratory system. These methods include:

- 1 nasopharyngeal aspirates***
- 2 cough swabs***
- 3 sputum induction aspirates***
- 4 serological test***

However, bronchoscopy and broncho-alveolar lavage (BAL is a saline wash of the airways and air sacs (alveolae) for recovery of inflammatory cells), appears to be the most sensitive and accurate method to obtain respiratory cultures in infants and small children. Several studies that performed tracheal aspirates or BAL cultures have documented the growth of bacterial pathogens in respiratory specimen cultures from infants who did not have apparent lung disease. Results from a recent multi center North American study that performed bronchoscopies annually from diagnosis in infancy showed that at the age of 1 year, bacterial pathogens were grown in BAL cultures in 65% of the infants, in 13% the growth was dense. The rate of dense growth increased to nearly 40% of the children at 2 and 3 years of age, with increase in the rates of pseudomonas from 8% at one year to nearly 20% at 3 years of age. Thus, bacterial pathogens are present in the respiratory tract of a minority of infants, even though many of them are asymptomatic.

“..performing bronchoscopy in infants and small children requires anesthesia and the procedure is regarded relatively invasive.”

Monitoring the growth of bacteria in infants following therapies might be beneficial to evaluate the response to therapy. However, performing bronchoscopy in infants and small children requires anesthesia and the procedure is regarded relatively invasive.



Complications including aspiration or spread of infection may also occur. Therefore it is not routinely used to assess response to early intervention or new therapies in patients with CF.

Chest X-rays and High resolution CT (HRCT) scans.

Imaging studies can define changes that might be early and pre-symptomatic. They are effort independent and can be performed at all ages, and can identify regional differences, and airway abnormalities. Chest X-rays are not regarded as a sensitive measure of lung disease. Early changes are non specific, difficult to define in a standardized manner and insensitive to the detection of early changes.

HRCT scores show better correlation with respiratory tract flare-ups and are more sensitive to follow the progression of lung disease

HRCT can show early structural abnormalities in infants before they have any symptoms. HRCT can identify lung disease in children whose lungs are evaluated as normal by pulmonary function tests (PFT). In one study, 14% (5 of 37) children with normal PFTs had bronchiectasis in four or more of the five lobes of the lungs. HRCT scores show better correlation with respiratory tract flare-ups than pulmonary function tests or X-rays, and are more sensitive for following the progression of lung disease. To monitor CF lung disease in clinical trials by using HRCT, standardization of the procedure and scoring is required, so that comparisons can be made between studies. Young children need sedation to perform this test and it is necessary to determine the risk of radiation exposure and balance that against the precision, accuracy and reliability of HRCT in measuring early asymptomatic disease.

Inflammatory markers

“..The ability to obtain specimens through induced sputum or nasal washing may enable the exploration of this promising method for assessment of the effect of therapies and at an early stage”.

BAL studies in screened infants with CF have demonstrated early pulmonary inflammation even before the development of bacterial colonization. These studies found that inflammation was present in infants as young as 4 weeks (with no bacterial colonization), and if there was colonization by a CF related pathogen, the inflammatory response was further enhanced. There was no clear relationship with clinical status or severity of symptoms. Since inflammation can be demonstrated in early stages of lung disease in CF, it might serve as a good marker of early disease. Several studies designed to assess the effects of interventions in CF have shown that in a small number of patients there has been improvement in the levels of inflammatory markers following therapy. Given that specimens can be obtained from children through induced sputum or nasal washing, it may be possible to explore this promising method for assessment of the effect of therapies at an early stage.



CF Patients' registries

Since the rate of progression of lung disease in patients with mild disease is slow, a large number of patients are required in order to detect small changes. The advantage of using data from CF patients' registries is that registries provide information on many patients. This enables the division of patients into subgroups such as gender, age groups and genotypes. Analyzing thousands of patients may compensate for the flaws that arise from a retrospective study, where details of the intervention are frequently not known. Standardization of care according to recent guidelines may improve the quality of data derived from registries. Collecting data on pulmonary function, radiographic scores, nutritional parameters, number of exacerbations or proportions of patients being free of exacerbations would be useful to evaluate minimal changes in patients with early disease. Ideally, a global patient registry that will collect data from patients around the world, would be the most powerful tool to investigate small changes in subgroups.

In conclusion, various methods of investigation can indicate early presence of infection, inflammation and structural changes in the lungs of young patients with CF. Early intervention, at the stage when these changes might not be apparent, might inhibit or reverse the progression of disease. The current methods to assess early changes in CF lung disease have limitations. Their sensitivity to detect early changes is low, and they have limited ability to assess the exact nature and type of infection or disease. Many of these investigations cannot be performed in uncooperative young children. Given that it is currently difficult and invasive to test infants for early lung damage, and in many centres some of these tests are not available, early intervention with physiotherapy, mucolytics and antibiotics should be considered on asymptomatic children without the use of these sophisticated tests. Accurate and simple to use markers are needed to assess early disease in children, preferably before disease becomes symptomatic. It is likely that early intervention will inhibit the progression of disease, but it is yet to be determined if early intervention will lead to reversal of early disease.

Professor Eitan Kerem, M.D. graduated from the Hebrew University Hadassah Medical School in 1982. He completed a pediatric residency and took a three-year fellowship in Pediatric Pulmonology at the Chest Division, the Hospital for Sick Children, Toronto, Canada. He is currently Associate Professor in Pediatrics at the Hebrew University, Hadassah Medical School and Head of the Department of Pediatrics at Hadassah University Hospital, Jerusalem. He is also on the board of the ECFS. His research concerns the association between genotype and phenotype in respiratory diseases, and the interaction of environmental factors with genetic diseases and their influence on disease severity.

1 * Kerem E, Conway S pi, Elborn S pi, Heijerman H pi, Consensus study group. Standards of care for patients with cystic fibrosis: A European consensus. J Cyst Fibros 4:7-26, 2005.



Editor's Note: For a list of references and further reading, email editor@cfww.org