High Tech Imaging Charts New Course for CF Care

New imaging techniques pioneered at Stanford are revealing previously undetected structural lung changes early in the life of persons with CF. Imaging of the chest using computed tomography (CT) is proving to be a sensitive tool for evaluating CF lung disease and measuring the impact of treatments, especially early in the disease process before lung function is impaired. In the past, measurement of CF lung damage has relied on less sensitive measures — chest x-rays and pulmonary function tests (PFTs) — that do not pick up early or subtle structural changes. Dr. Terry Robinson and the Cystic Fibrosis Foundation (CFF) Therapeutics Development Network have developed techniques using whole lung CT imaging to precisely measure structural changes. The results are underscoring the benefits of early, aggressive treatment of infections and strict adherence to CFF clinical guidelines, even when traditional measures indicate no or minimal lung disease. Results also suggest an important “window of opportunity” when lung damage may be reversible with aggressive treatment.

The Role of Imaging in CF

Historically, imaging has played a limited role in CF diagnostics. The CFF recommends chest radiography (x-rays) every 2–3 years for persons with stable lung function, and annual x-rays for persons with declining lung function or acute exacerbations to document disease progression or response to therapies. Systems for scoring changes in chest x-rays such as the Brashfield Score, measure and rate the severity of lung and airway abnormalities. But x-rays generally change slowly over time and do not pick up subtle damage. In the last ten years thin slice chest CT (also called high-resolution or HRCT) has increased our understanding of disease progression in CF using scans to score different aspects of disease such as bronchial wall thickness, bronchiectasis (loss of airway structural integrity), mucus plugging, and air trapping. CT technology also reveals regional changes in specific areas of the lungs before changes can be seen in PFTs or chest x-rays.

The new chest CT scoring systems and computerized analysis developed by Dr. Robinson and others precisely measure bronchial wall thickening related to airway inflammation, bronchiectasis, mucus plugging, air trapping and regional abnormalities that correlate strongly with disease severity. Dr. Robinson notes, “PFTs provide an overview of all regions of the lung; a person can have severe structural damage in one region yet have perfectly normal PFTs because the lung has such tremendous reserves. However, we are finding that although the lungs can sustain significant damage and still function normally, at some point in disease progression damage can reach a critical point, the reserve capacity nears its limit and lung function becomes severely compromised. Chest CT allows us to identify and document this process with a degree of specificity that can be lost in PFTs, particularly early in the course of CF. The information may allow us to shift the clinical care paradigm from treating damage to actually reversing the disease process and preventing bronchiectasis.”

HRCTs also are being used to identify potential biomarkers that measure the success of treatment regimens, such as Pulmozyme™ and TOBI™, and to measure the specific impacts of different types of bacteria on the lungs of people with CF.

CT scanners have evolved to allow low dose scans of the entire chest in 8–10 seconds using a technique called spiral CT that Continued on next page
Dr. Robinson has demonstrated reversible changes in HRCT scores after treatment with IV antibiotics and Pulmozyme™ — revealing reduced mucus plugging, improvement in airways, and reduced air trapping. Other research also suggests that bronchiectasis may be reversible in children with early/mild disease. Scientists suggest a new paradigm for CF lung disease as a spectrum with profound treatment implications: early pre-bronchiectasis defined by bronchial wall thickening followed by HRCT/CT-defined bronchiectasis with initial mild bronchial dilation (widening of the airway), and finally established bronchiectasis that does not resolve with specific interventions. They propose that reversal of airway disease may be possible in the first two phases: after one year of treatment, subjects getting Pulmozyme™ showed a 2–4% improvement in the extent and severity of bronchial wall thickness scores and a 6–9% decline in the extent and severity of bronchiectasis scores compared with essentially no change or worsening findings for the placebo group. The Pulmozyme™ study also demonstrated a 9–13% drop in quantitative air trapping at three months and a 15–16% drop at 12 months in subjects receiving the drug, compared with a 43–48% increase in air trapping at three months and a 50–61% increase at 12 months for the placebo group. These findings suggest a critical period for reducing and even reversing damage to CF lungs.

Early Disease Underestimated

These findings have significant implications for early treatment of persons with CF who have little apparent lung disease. PFTs underestimate the presence of mild and moderate disease. CFF-supported scientists recently hypothesized that more sensitive biomarkers are needed to assess new therapies and monitor disease because:

1. CF lung disease progresses despite stable or improving PFTs.
2. CF disease starts early, likely beginning with regional air trapping and bronchial wall thickness, progressing to bronchiectasis.
3. Progression may relate to bacterial colonization, especially Pseudomonas.
4. The “Window of Opportunity” is an important, new concept for clinical care.

To summarize, Dr. Robinson suggests, “If we are to address early changes in CF lung disease in order to prevent or possibly reverse early structural lung changes such as bronchiectasis, we have to be able to measure precisely and accurately the structural findings encountered in early CF lung disease. CT offers the technology to do this.”

Implications for Clinical Care

CF lung disease starts early in life with structural changes preceding changes in PFTs. Scientists hypothesize that there is a critical “window of opportunity” for therapies directed at prevention or potential reversal of early and progressive disease. These findings suggest that early, continuous assessment and monitoring is important, and that more aggressive intervention is critical to maintain optimum health in CF. Parameters to monitor may include:

- Low dose chest CT scanning and infant PFTs for early assessment with periodic follow-up;
- Aggressive surveillance of respiratory cultures to detect new infections quickly;
- Aggressive early intervention with antibiotic eradication protocols, mucolytics (e.g. Pulmozyme™) and/or ibuprofen, and airway clearance modalities.

Concerns about exposure to radiation have been addressed with new CT technology and lower dose protocols. Nonetheless, the expense and relatively early stage of the research mean that routine use of CT/HRCT has not been embraced. Stanford and the CFF plan further research to identify and document the value of CT in understanding the progression of CF and the effectiveness of various treatments. Drs. Robinson and Moss have been awarded a multi-year grant from Novartis Pharmaceuticals to document the natural history of CF in children with mild lung disease using CT, PFTs, bacterial cultures and other biomarkers.
**Vitamins and Minerals: An Important Link to Good Health**

Cystic Fibrosis creates unique nutritional needs that impact daily care and quality of life. Inadequate metabolism of many vitamins and minerals poses health risks, especially with the pancreatic insufficiency that affects 85–90% of people with CF. Without sufficient enzymes in the small intestines, valuable nutrients can’t be absorbed from food, including the fat-soluble vitamins (A, D, E, and K) and other vitamins and minerals such as B-6 and zinc. In addition, chronic inflammation and an increase in oxidative stress occurs in the lungs of persons with cystic fibrosis, possibly increasing the need for antioxidant vitamins such as vitamin C, vitamin E, beta-carotene (a precursor to vitamin A), zinc, and selenium. Research is revealing that some of these chemicals, also called micronutrients because of the very small quantities needed for normal functioning of the body, may play crucial roles in early lung development and even immune system function. This article initiates a series in our newsletter on the roles that vitamins and minerals play in CF, as well as current ideas on helpful — and harmful — dosing.

**How are vitamins and minerals monitored?**

Because of the well-known risk for deficiency of fat-soluble vitamins, the CFF Clinical Practice Guidelines recommend that blood levels of vitamins A, D, E, and K be monitored annually. Other vitamin and mineral levels typically are only measured if symptoms suggest deficiencies.

**Why can’t food provide enough vitamins?**

Even with the best enzyme therapy, some people with CF may fail to absorb 20% or more of the nutrients contained in food. Furthermore, nutrient losses vary since people differ in their degree of pancreatic insufficiency. In other words, adequate vitamin supplementation can be different from person to person, hence the need for regular monitoring of blood levels. That’s also why we recommend fat-soluble vitamin supplements for pancreatic insufficiency to ensure adequate absorption of vitamins. Commercial vitamin preparations of the fat-soluble vitamins are available in different forms and flavors that are tailored to persons with CF (sometimes called ADEKs). Our CF Center dietitian, Julie Matel, can help you select the right one. The CFF recommendations for fat-soluble vitamin supplements are in the table below.

**Stay Tuned**

Future newsletters will highlight a vitamin or mineral each issue with current information on how they are used in your body, dosing, sources, and risks of over- or under consumption.
North American CF Conference Highlights

Stanford sent a large contingent to the NACFC in October. Dr. Carol Conrad’s N-acetyl-cysteine [NAC] study results were a featured highlight. Subjects receiving pharmaceutical quality NAC experienced significant increases in GSH (glutathione) and decreases in neutrophil counts, elastase and IL8 in the lungs, all indicators of inflammation. Results were dose-dependent, and NAC was well-tolerated. To hear Dr. Conrad’s talk, visit www.cff.org/research/2005_nacfc/. Results of the study recently were published in the prestigious journal Proceedings of the National Academy of Sciences.

New studies presented at the conference and subsequently, published in the New England Journal of Medicine, confirmed the efficacy of inhaled hypertonic saline (HS). Small improvements in PFTs, significant reductions in exacerbations and improved quality of life with twice daily 7% HS inhalation were found in the large, multi-center placebo-controlled trials.

Basic science advances announced at the meeting included multiple sessions on biomarkers and proteomics in CF. Biomarkers are anatomic, physiologic, biochemical, or molecular parameters associated with the presence and severity of specific disease states and clinical symptoms. They are detectable and measurable by a variety of methods including physical examination, laboratory assays and medical imaging (such as the CT scoring system discussed in the cover story). Examples of biomarkers include tumor antigens in cancer, or changes in PFTs in CF. To study the effects of new drugs or treatments in clinical trials, traditional trial endpoints such as morbidity (e.g. number of hospitalizations or rate of decline in FEV1) and mortality (death), can be subjective, difficult to evaluate, or require large numbers of participants and very long timeframes to achieve statistical significance. Biomarkers in imaging may, in many instances, provide objective endpoints that may be confidently evaluated in a reasonable timeframe with smaller numbers of subjects. Proteomics is a growing aspect of biomarker research that identifies the thousands of proteins expressed in body tissues, fluids or even gases such as exhaled breath. A large body of research is underway to determine the role of these proteins in physiology and pathology of conditions such as CF. Dr. Moss attended a proteomics biomarker workshop at CFF in late November 2005.

Stanford In the News

Dr. Jeff Wine’s CF Research Laboratory (CFRL) at Stanford has been awarded a 5-year National Institutes of Health grant to clarify the functional role of CFTR in airway submucosal glands. This work is important because most people with cystic fibrosis (CF) die from complications caused by chronic infections of bacteria that reside in the mucus that is primarily produced by airway submucosal glands. Members of CFRL have developed optical methods to measure secretion rates from single glands and have shown that CF glands fail to respond to certain kinds of stimulation. To further clarify the role of CFTR in glands, CFRL will use an array of methods. Hallmarks of this research are the use of human tissues, dynamic imaging of cellular responses in living human glands, and direct comparisons between CF and non-CF glands.

Dr. Richard Moss served on the scientific organizing committee and attended the 2nd Annual Advances Against Aspergillus Conference in Athens, Greece in February, where he reviewed drug trials for ABPA.

Dr. Terry Robinson presented a talk entitled “Clinical Applications & Indications of HRCT/CT Scanning in Evaluation of CF and Lung Transplant Patients” in January. He also presented “Early Intervention In CF Care: A Paradigm Shift” at a CF Research Group University Meeting at UCSF, at John’s Hopkins University, National Medical Center in Washington D.C. and at A.I. Dupont Hospital for Children in Delaware.

Dr. John Mark presented a series of talks on complementary and alternative medicine and lung related issues to pediatric residents and at Grand Rounds at Packard, as well as at community hospitals in Salinas, Santa Cruz, Stockton, San Ramon and San Francisco.

Initial Hypertonic Saline dosing should be taken during a CF clinic visit so that dose tolerance and airway reactivity can be monitored before treatment is initiated.

Dr. Richard Moss

The CFF announced a major initiative to raise the bar on nutritional status through aggressive patient education, nutritional counseling and intervention. Growing evidence indicates early intervention to maintain weight improves lung function. The CFF is recommending use of Body Mass Index (BMI) standards rather than Ideal Body Weight (IBW) which is less sensitive to height since many persons with CF have lower than normal stature. A BMI greater than the 50th percentile is recommended for children, as well as goals of 23 or higher for men and 22 or higher for women. New protocols recommend earlier use of appetite stimulants and/or tube feedings before nutritional failure sets in. Closer monitoring of glucose tolerance is recommended, since CF-related diabetes may be a long-term consequence of malnutrition.

Current Research Studies

Please consider participating in a clinical trial for CF research. For more information, visit www.cfcenter.stanford.edu, contact our research coordinators or talk to your physician. The following trials are currently underway ("closed" indicates that recruitment is complete and a trial is in progress):• Infant and toddler pulmonary testing (closed)• Induced sputum: evaluation of anti-inflammatory agents• Inspire drug for correction of salt and water abnormalities (closed)• CF pre-diabetes intervention trial• NAC (closed)• Astreomycin for inhalation (closed)• EPIC trial for early treatment of pseudomonas• Upcoming Phase III trials at Stanford in mid-2006 TOBI® dry powder inhaler from Chiron, denfosol from Inspire, new pancreatic enzymes from Altus and Eurand
Clinic Initiative to Improve Care Management & Outcomes

The CFF Clinical Guidelines recommend a minimum of four visits to your CF Center each year to ensure early detection and prompt treatment of developing problems such as lung function declines, newly acquired bacteria and weight loss. Visit frequency consistently ranks as the single most important variable in health outcomes across CF centers around the world. It is also an area in which our Center falls short and must improve if we want to be among the best centers for outcomes. We need your help to improve visit frequency so that we can improve your clinical outcomes.

Letters will be followed up by calls from our nurses to underscore the importance of regular visits and to assist in making appointments. The LPCH physician appointment calendar has been revised to allow scheduling of physician visits six months in advance. Patients will also be encouraged to make their next appointment at the end of each visit. Patients now receive annual lab test orders several months in advance to facilitate scheduling and receipt of results prior to the annual visit. **Help us to help you become part of a top performing CF Center! Quarterly and Annual CF visits are important!**

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| 2004 CFF Registry Visit Comparisons Percent Meeting CFF Guidelines for 4+ Clinic Visits, 1+ Sputum Cultures & 2+ PFTs Annually |
| -------------------------------------------------- | -------- | -------- | ----------------- |
| Peer Group/Measure | LPCCH/ Stanford | National Average | Top 10 Centers |
| Children | | | |
| 5–17 yrs FEV1 Greater than 90% | 53.3% | 56.4% | 86.7% |
| 5–17 yrs FEV1 Less than 90% | 44.7% | 67.4% | 91.1% |
| Adults aged 18+ | | | |
| FEV1 Greater than 70% | 37.0% | 41.9% | 74.3% |
| FEV1 Less than 70% | 54.5% | 53.0% | 83.6% |

Pediatric patients who have not been seen at least quarterly, and all adult patients, will receive a letter summarizing the CFF Clinical Care Guidelines.

**Dollars for Scholars**

Go to the following websites to apply for scholarships for people with CF:
- [www.elizabethnashfoundation.org](http://www.elizabethnashfoundation.org)
- [www.cfscholarships.com](http://www.cfscholarships.com)
- [www.solvaypharmaceuticals-us.com/products/scholarships](http://www.solvaypharmaceuticals-us.com/products/scholarships)

**Cystic Fibrosis Center at Stanford**

Center Physicians: Richard Moss, Director; Carol Conrad, Terry Robinson, Lauren Witcoff, Nanci Yuan, John Mark, David Cornfield, Paul Mohabir (Adult CF physician)

- Clinic E Scheduling: (650) 497-8841
- Clinic Fax: (650) 497-8837
- Miguel Huerta, Patient Services Coordinator: (650) 498-2655
- Katherine Boyle, RN Pediatric Coordinator: (650) 736-1359
- Mary Helmers, RN Adult Coordinator: (650) 736-1358
- Kristin Shelton, Respiratory Coordinator: (650) 736-1905
- Joanne Asano, Social Work: (650) 736-1905
- Research Coordinators: (650) 736-0388

For Urgent Issues:
- Monday–Friday 8:30–5:00 pm contact RN Coordinator
- All Other Times (ask for Pulmonary Physician On-Call)
- (650) 497-8000

Visit our website at [http://cfcenter.stanford.edu](http://cfcenter.stanford.edu) for more information about our center and CF.

We gratefully acknowledge the leadership of friend and parent Penny Stroud in producing this publication.

To subscribe to this newsletter please call or email Judy Kirby at (650) 724-3474 or jkirby@stanford.edu

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