

Pulmonary and Critical Care Updates

Update in Cystic Fibrosis 2005

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Cystic fibrosis (CF) is a complex, hereditary disease involving several organ systems (1). CF is caused by mutations in the gene that codes for the CF transmembrane conductance regulator (CFTR), a membrane glycoprotein that contributes to regulation of ion flux at certain epithelial surfaces. Lung disease results in most of the morbidity and mortality in CF. Advances in CF over the past several decades have recently been reviewed with an emphasis on the development and importance of CF care centers and on opportunities for new treatments (2).

The many threads of CF research in 2005 can be appreciated in Figure 1, showing the general headings (1) Molecular and Cellular Biology and Genetics, (2) Pathophysiology, and (3) Clinical Care and Treatment, along with several subheadings. This brief update reviews representative, significant articles in 2005.

MOLECULAR AND CELLULAR BIOLOGY AND GENETICS

State-of-the-art techniques are yielding information concerning normal and abnormal CFTR structure, potentially providing targets for drug therapy (3–5). CFTR function continues to be an important focus of investigation that includes interactions among CFTR domains as well as with associated proteins and signaling pathways (6, 7). New technologies, including small interfering RNAs and high-throughput screening, have been used to understand CFTR pathophysiology and to develop small molecules that improve CFTR function (8–10). In addition, studies of the use of stem cells to repopulate the airway offer promise of cell-based therapy in CF (11, 12).

Clinical outcome in CF is variable, even after controlling for CFTR mutation. This has led to the search for modifier genes. In a landmark study, Drumm and coworkers carefully examined putative modifier genes in large populations of patients with very good pulmonary outcome as well as in those with poor outcome (13). They found that of 10 previously reported modifier gene candidates, only mutations in the gene encoding transforming growth factor β 1 (TGF- β 1) could be conclusively demonstrated to influence outcome. Increased expression or activity of TGF- β 1 was associated with poorer outcome, providing more evidence for a role for the host response to infection in CF. Although this report examined previously identified modifier genes, new candidate genes have also appeared. A particularly intriguing candidate is a key antiinflammatory mediator, macro-

phage inhibitory factor (MIF), as reported by Plant and coworkers (14). In a study of several hundred patients with CF, a novel polymorphism conferring less promoter activity in MIF was associated with decreased *Pseudomonas* infection and less pancreatic insufficiency, further confirming an important role for inflammation in CF outcome.

PATHOPHYSIOLOGY

Infection

An improved *in vitro* model of the CF airway surface, incorporating features of periciliary liquid homeostasis, interactions with the mucus layer, and infection was reported (15). Bacterial biofilms continue as an active area of research (16). Progress was also made in elucidating the relationship between Toll receptor stimulation and inflammation in CF (17).

Inflammation

Most airway injury in CF is believed to be mediated by neutrophil products, including proteases and oxidants, liberated by the abundance of neutrophils in the CF airway at almost all ages. The role of the endothelium in contributing to the neutrophil influx has not, however, been well studied. Solic and colleagues examined heparin sulfate-containing proteoglycans in CF and control lungs and found that interleukin 8 (IL-8), likely the major chemoattractant in CF, has a prolonged lifetime in CF endothelium (18). This study opens the door for further investigations of the role of the circulation in maintenance of inflammation in CF.

The nitric oxide pathway has received attention in CF because of its potential role in both inflammation and infection. Grasemann and coworkers examined the role of arginase, an enzyme that competes for the important nitric oxide precursor L-arginine, in CF (19). They found increased arginase levels in sputum from patients with CF, suggesting a role for this enzyme in nitric oxide abnormalities in CF.

Mucus Plugging

Mucus plugging is a key clinical and pathophysiologic feature of CF and yet the mechanisms are not well understood. Harris and coworkers studied the expression of Bcl-2, an inhibitor of apoptosis, in goblet cells from human tissue as well as in rats and mice (20). Their results indicate that expression of Bcl-2 is associated with increased goblet cell hyperplasia in CF, likely contributing to mucus plugging.

Epithelial Injury and Repair

Although it is clear that epithelial injury is intimately involved in airway pathophysiology in CF, there have been few studies of epithelial injury and repair. Vovnow and coworkers recently provided evidence that the basal cell is the key cell involved in epithelial proliferation in CF (21). The marked difference in epithelial cell proliferation index between CF and control samples

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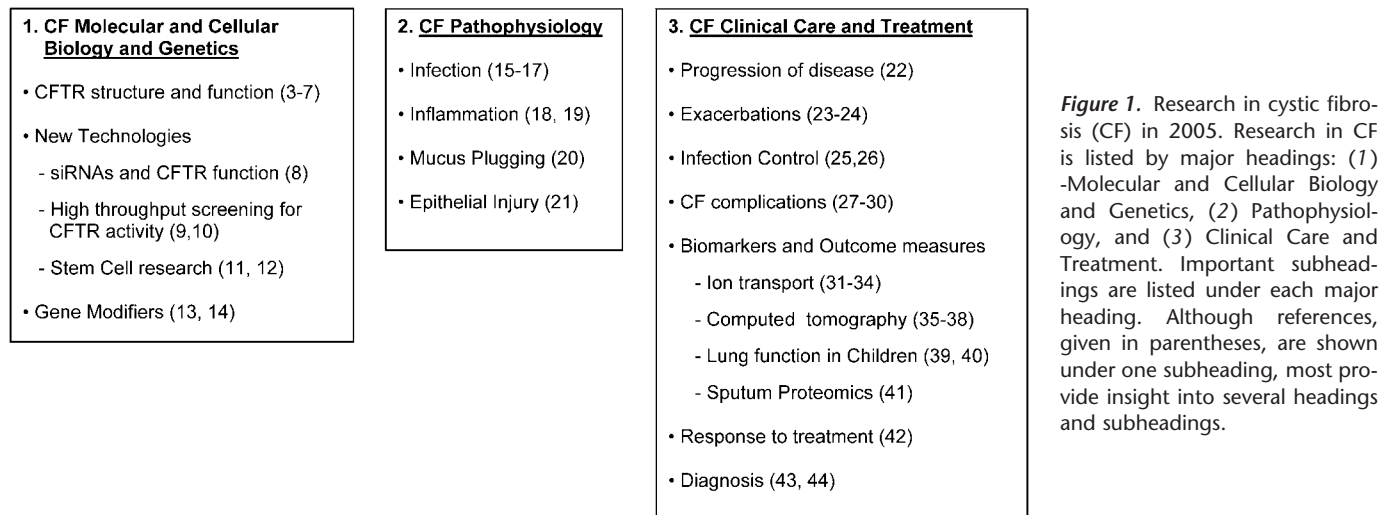


Figure 1. Research in cystic fibrosis (CF) in 2005. Research in CF is listed by major headings: (1) -Molecular and Cellular Biology and Genetics, (2) Pathophysiology, and (3) Clinical Care and Treatment. Important subheadings are listed under each major heading. Although references, given in parentheses, are shown under one subheading, most provide insight into several headings and subheadings.

in this study underscores the importance of further research in this area.

CLINICAL CARE AND TREATMENT

Progression of Disease

Among the goals of treatment in CF is to preserve lung function. Kulich and coworkers recently reported disease-specific longitudinal lung function equations for patients with CF based on the U.S. Cystic Fibrosis Foundation Patient Registry (22). These disease-specific equations will ultimately be used to provide patients and families information on where an individual with CF stands with respect to other patients nationwide. This is very much in keeping with the national trend toward data transparency. It is also hoped that this tool for patient education will provide an impetus for compliance with treatments. Because lung function changes with age in CF, previous clinical trials using a single lung function cut-off for stratification likely under-represented some ages. The equations developed by Kulich and colleagues may rectify this in future trials.

Exacerbations

In addition to the progressive decline in lung function evident over years, lung disease in CF is characterized by acute pulmonary exacerbations lasting several weeks and accompanied by dramatic decreases in lung function. The relationship between long-term decline in lung function and short-term exacerbation is not well understood. Ellaffi and coworkers studied severe exacerbations in CF to determine risk for mortality and also effect of exacerbation on clinical course (23). Risk factors for mortality included recent rapid decline in lung function and infection with *Burkholderia cepacia* along with need for more intensive support. Interestingly, however, severe exacerbation was not associated with progression of lung function decline in those patients who survived. This finding raises the issue, clearly requiring further study, of which exacerbations actually contribute to lung function decline in CF. Other deleterious effects of exacerbations in CF were investigated by Dobbin and colleagues who demonstrated abnormalities in sleep and neurobehavioral performance in adults with CF during an acute pulmonary exacerbation (24). This study argues that exacerbations should be treated promptly and thoroughly to avoid difficulties in daily life that are accompanied by sleep abnormalities.

Infection Control

Infection control remains a key issue in CF. In particular, patient-to-patient transmission of *Pseudomonas aeruginosa* continues to receive attention. Griffiths and colleagues have studied the effects of segregation on a particularly virulent epidemic strain of *Pseudomonas* that was associated with several deaths in early childhood (25). They found that segregation by culture status led to marked decrease in transmission of this strain, thus providing further evidence that cohorting is of benefit. Jones and coworkers examined the transmission of *Pseudomonas* in an adult CF clinic over 4 yr (26). They found that segregation by culture status was better than infection control techniques that did not include segregation. The move to segregate patients by infection status gained impetus through these studies published in 2005.

CF Complications

Important complications of CF include CF-related diabetes, CF-related bone disease, exocrine pancreatic insufficiency, and undernutrition. Evidence is accumulating that CF-related diabetes contributes to the lung disease and worse outcome. In addition, classical diabetic complications are being reported in CF. Glucose control is therefore a major issue. Brennan and coworkers recently took an important first step in evaluating glucose control in patients with CF by comparing glycosylated hemoglobin levels with continuous glucose monitoring. Patients with CF had results similar to patients with type 1 diabetes (27). As Brennan and colleagues note, however, we do not yet know what level of hyperglycemia leads to diabetes-related complications in CF.

CF bone disease is an increasingly important problem in adults. Boyle and coworkers found that even high-dose supplementation of ergocalciferol did not correct the deficiency of 25-hydroxy vitamin D present in a majority of patients with CF (28). This study points to the need for further investigations of bone metabolism and related nutrient absorption in CF. Significant reports of limitations in our current treatment approaches to exocrine pancreatic insufficiency and undernutrition in CF were also reported in 2005 (29, 30).

Biomarkers and Outcome Measures

As new treatments are proposed in CF, improved outcome measures are needed to provide proof of concept and demonstrate efficacy as quickly as safety permits. Because ion transport abnormalities are a hallmark of CF pathophysiology, the use of

airway potential difference as an outcome measure is under intense study. Davies and colleagues described the usefulness of lower airway potential differences in distinguishing children with CF from control children using a carefully performed bronchoscopic technique (31). Baseline potential difference distinguished patients with CF from control patients in the trachea but not in more distal airways. The response to zero chloride solution and isoprenaline in the third to seventh generations of airways did, however, distinguish patients with CF from control subjects. This study adds greatly to the armamentarium of outcome measures in young children with CF. A role for the CFTR in response to differing airway surface tonicities was also found in a nasal potential difference study during 2005 (32).

Several trials of macrolide antibiotics have demonstrated benefit in CF, but the mechanism of action is unclear. Barker and coworkers found no effect of two macrolide antibiotics on nasal potential difference in CF, suggesting that the mechanism of action of macrolides in CF is not related to ion transport (33). In a novel but sobering study, Sermet-Gaudelus and coworkers examined nasal potential difference in individuals heterozygous for CFTR mutations but without clinical features of CF (34). In addition, they performed imaging of nasal cell chloride transport. They found that significant numbers of heterozygous patients had nasal potential difference abnormalities when compared with control individuals. This study calls into question the relationship between nasal potential difference abnormalities and the clinical features of CF, clearly inviting further research.

Another potential surrogate outcome measure in CF is computed tomography (CT) analysis of the remarkable lung structural changes accompanying this disease. Brody and coworkers recently reviewed the current status of CT scanning in CF and concluded that effective techniques are available to allow CT scanning to be useful as a sensitive outcome measure for clinical trials in all ages (35).

The importance of CT-determined structural change in CF is illustrated by the attention it received in 2005 in a number of articles. De Jong and coworkers provided important steps toward quantifying CT-determined airway structural injury in CF through longitudinal analysis of 23 young patients (36). They found increases in airway luminal diameter and wall thickness compared with control subjects. Brody and colleagues contributed an important study toward validation of CT scoring as a potentially useful outcome measure in CF by showing a better relationship between the occurrence of exacerbation through use of a CT scoring system than with lung function (37). Martinez and colleagues extended the use of quantitative CT to infants and toddlers (38). They found that increased airway wall thickness coupled with decreased luminal diameter distinguished patients with CF from control individuals. The CT findings in this study correlated with infant lung function measures of airway obstruction. Taken together, the CT studies in CF suggest that early pathophysiology is one of decreased airway luminal diameter and bronchial wall thickening, which subsequently develops into increased airway luminal diameter in patients with CF compared with control subjects, consistent with development of bronchiectasis.

As it is increasingly clear that lung disease in CF begins early in life, treatments will need to be applied early. Measurement of lung function in preschool children has always been a difficult problem. Aurora and coworkers compared three means of determining lung function in CF (39). Approximately three-fourths of children could cooperate sufficiently for measurement of all three techniques. Multiple-breath nitrogen washout was more sensitive in separating individuals with CF from control individuals than spirometry or plethysmography. These findings demonstrate the feasibility of lung function testing in preschool children

and illustrate that inhomogeneities in the distribution of ventilation are an important early feature of CF lung disease with potential as an outcome measure. Further evidence in support of the importance of ventilation homogeneities in CF was provided by Kraemer and colleagues who demonstrated that lung clearance index was the best predictor of progression of disease in school-age children and adolescents with CF (40).

Another area of promising biomarker research in CF is the proteomic analysis of clinical specimens. Proteomics, the study of many proteins at once, provides a relatively unbiased investigation into differential protein content. Sloane and coworkers in a proteomic study of sputum from patients with CF in exacerbation found that myeloperoxidase and immunoglobulin fragments were the proteins in sputum best correlated with exacerbation (41). It is not yet clear, however, whether these protein determinations are better than sputum neutrophil count in detecting an exacerbation.

Response to Treatment

A key clinical issue in CF is how to decide which patients respond to a given treatment. Saiman and coworkers demonstrated that this is by no means an easy decision (42). Through use of a large multicenter azithromycin study, it was found that patients could achieve a reduction in the number of exacerbations without improvement in lung function. Thus, lung function improvement cannot be used to decide benefits of treatment in an individual patient. In addition, this study suggests that future treatment trials should look at outcome measures in addition to lung function.

Diagnosis

Improved clinical suspicion and genetic diagnosis has led to identification of patients with CF in adulthood. Rodman and coworkers investigated differences in patients with CF older than 40 yr identified before or after age 20 (43). They found significant differences between the two groups in genotype distribution, pancreatic insufficiency, and lung function. In addition, however, nontuberculous mycobacterial infection was a prominent feature of patients diagnosed after 20 yr of age. This study illustrates the importance of genotyping patients who have nontuberculous mycobacterial infection and who are not recognized as having CF.

In 2005, numerous studies dealing with newborn screening for CF appeared. Campbell and White reviewed the benefits of early diagnosis, including improved growth, better cognitive outcome, and avoidance of complications, as well the implementation of newborn screening programs (44). It is likely that early diagnosis through newborn screening will allow application of new and established treatments when they are most likely to be of benefit, before irreversible lung disease occurs.

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