Pulmonary and Critical Care Updates

Update in Cystic Fibrosis 2007

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Cystic fibrosis (CF) is a chronic condition involving several organ systems that results in life-long morbidity and premature mortality (1). CF is caused by abnormalities in the gene that codes for the CF transmembrane conductance regulator (CFTR), a membrane glycoprotein found in secretory and absorptive epithelial surfaces. CFTR is a chloride channel, but also participates in regulating ion flux through interactions with other proteins. Lung disease in CF, believed to be caused by dehydration of airway surface liquid layers, is the major killer through a complex process involving impairment of mucociliary clearance, infection, inflammation, and structural injury. This update of studies reported during 2007 focuses on issues in clinical care and clinical research relating to CF, but with some attention to basic investigations through model systems.

CLINICAL CARE

Clinical care issues in CF that received particular attention in 2007 are listed in Table 1. As with other medical conditions, clinical practices in CF are under scrutiny through the lens of evidence-based approaches. Flume and colleagues, in conjunction with the U.S. Cystic Fibrosis Foundation (CFF), reviewed practices related to chronic pulmonary treatments in CF (2). This is important for several reasons. Treatment practices, for example, are not uniform across centers. By providing guidance for center physicians, a careful review of the evidence could help bring treatments to patients who need them. In addition, families are experiencing increased burdens of treatment in terms of time and cost. Unsupported treatments should come under greater scrutiny. This systematic review found that, in appropriate settings, the use of inhaled tobramycin and inhaled dornase alfa both achieved ratings of substantial benefit supported by good evidence. The evidence for inhaled hypertonic saline and chronic macrolide use was deemed only fair, but it was recognized that they carried moderate benefit. Inhaled β_2 -adrenergic agents agonists were seen as having moderate benefit on the basis of good evidence. No separation was made, however, between short-acting and long-acting preparations. Future documents will address other aspects of care in CF. Oral nonsteroidal antiinflammatory therapy (ibuprofen) was viewed as carrying moderate benefit on the basis of fair evidence. This is discussed further in sections below dealing with two studies of ibuprofen reported in 2007.

Early diagnosis of CF through newborn screening received a great deal of international attention in 2007. Guidelines for performing screening on a statewide basis were reported and the economic benefits of screening were also noted (3, 4). Early diagnosis carries the promise of early treatment. It is known that CF lung disease begins in infancy. Markers of airway disease are needed in preschool children. Further understanding of the relationship between different markers of disease is also needed. Toward this end, Davis and coworkers examined computerized tomography (CT) imaging along with bronchoalveolar lavage (BAL) of lobes identified through the imaging (5). They found that imaging identified lobes with more inflammation as assessed through BAL. In addition, there was improvement in CT score of the lung with treatment. Taken together, these observations show that CT holds promise as an outcome measure in young children even over the short term.

Metabolic abnormalities are frequent in CF. Trace element, fat-soluble vitamin, and electrolyte abnormalities can exist in infancy. Adults are clearly prone to diabetes and low bone mineral density. Sermet-Gaudelus and colleagues provide evidence that low bone mineral density is present even in preschool children with CF (6). They also demonstrated that the abnormality in bone density was not related to lung function or nutritional status. It is clear from this study that more needs to be done to understand and treat the bone disease in CF beginning in early childhood.

The increasing use of CT imaging in CF raises the question of increased risk of cancer over a lifetime. de Gonzalez and coworkers, in a careful study, estimate that the risk of cancer is less than 0.5% in both males and females, assuming annual examinations and survival of 50 years (7). This is a lower risk than previous estimates. Nevertheless, the authors do not recommend routine monitoring until there is clear demonstration that the benefits outweigh the risks. Another treatment option that came under detailed inquiry was lung transplantation in children. Liou and colleagues, using CFF patient registry data of more than 500 children older than 12 years, found that very few patients actually benefited in terms of survival, calling into question the practice of transplantation in children (8). This study, however, covered a period when patients received transplantation based on time listed. The current approach is to perform transplantation on the sickest patients. Thus, the findings of Liou and colleagues' study may not pertain to current approaches.

Care for adults with CF is developing into a unique subspecialty bringing its own challenges (9). A key concern is how to attract adult pulmonologists into the field. Pregnancy is a particularly perplexing issue in adult care. Wexler and associates provide a detailed structure for dealing with this issue at many levels. Medical, ethical, and social questions should be considered before pregnancy (10). The CF care center physician should play an important role in these discussions.

CLINICAL AND MODEL SYSTEM INVESTIGATIONS

Clinical investigations in CF provide clues to pathogenesis and set the stage for structured clinical trials. Exploration of CF

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TABLE 1. HIGHLIGHTED CYSTIC FIBROSIS CLINICAL CARE ISSUES IN 2007

Issues	Reference
• Evidence-based medicine and standards of care	Flume and colleagues (2)
• Early diagnosis through newborn screening	Comeau and colleagues (3), Sims and colleagues (4)
• Early lung disease	Davis and colleagues (5)
• Metabolic abnormalities	Sermet-Gaudelus and colleagues (6)
• Radiation risk	de Gonzalez and colleagues (7)
• Lung transplant in children	Liou and colleagues (8)
• Cystic fibrosis in adults including pregnancy	Boyle (9), Wexler and colleagues (10)

model systems including tissue culture and animal studies also contributes to our understanding of pathogenesis and provides preclinical rationale for studies in patients. Representative CF clinical and model system investigations in 2007 are given in Table 2.

The pathogenesis of CF, in particular, is still incompletely understood. Moskwa and coworkers offered a new hypothesis emphasizing the role of reactive oxygen species in host defense against airborne bacteria (11). They found that CF epithelia failed to secrete thiocyanate, a key component of the oxidant defense system. This intriguing observation suggests that failure of epithelial oxidant defense should be considered together with dehydration of airway surface liquid and failure of antimicrobial peptides as a potential mechanism of lung disease in CF.

Another epithelium-based hypothesis for persistence of infection in CF was reported by Kowalski and coworkers (12). They found that major vault protein is recruited to lipid rafts when epithelia are infected with *Pseudomonas*. Bacterial binding to CFTR participates in this process. Major vault protein was required for clearance of *Pseudomonas*. This article provides a biologic function for major vault protein as well as a fascinating clue to CF pathogenesis.

It is often considered paradoxical that the CF airway contains high numbers of neutrophils but infection persists. Hartl and colleagues demonstrate that neutrophil-derived proteases can cleave chemokine receptors on neutrophils that essentially disable neutrophil killing of bacteria. In addition, antiprotease treatment restored neutrophil killing (13). Thus, there is a true vicious cycle in the airway that leads to failure to clear infection despite plentiful neutrophils. This study provides further impetus for trials of antiproteases in CF.

The role of mucus biology and, in particular, submucus glands in CF lung disease is also still unclear. Choi and coworkers demonstrated several abnormalities in CF airway glands that could contribute to a failure of host defense (14). In particular, normal glands produce a “housekeeping” or “background” level of mucus that CF glands do not produce. Moreover, synergy

between two stimuli to gland production in normal glands is lost in CF. Thus, abnormalities in regulation of mucus production from submucosal airway glands could contribute to lung disease. In addition to these questions raised about regulation of mucus production in CF, whether or not mucus from individuals with CF is different from normal in composition also has not been resolved. For example, MUC5AC and MUC5B, key airway gel-forming mucins, are decreased in CF in periods of stability compared with mucus from normal individuals. Henke and associates demonstrated that levels of these mucins increased during periods of exacerbation, suggesting that the CF airway can at least increase their production (15).

In a sense, the search for improved biomarkers and outcome measures is the central problem in CF research. There are now many proposed treatments, and they cannot all be tested in phase 3 trials. In addition, there is urgency in testing new therapeutic approaches. Ways to evaluate treatments in smaller number of patients over shorter periods of time are clearly needed, which explains the intense interest in biomarkers and outcome measures (16, 17). Mayer-Hamblett and coworkers examined biomarkers in sputum by studying sputa from 269 patients collected in the control limb or the run-in period for clinical trials (18). This study examined biomarkers of inflammation, neutrophil counts, neutrophil elastase, and IL-8, as well as biomarkers of infection, colony forming units of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Neutrophil elastase emerged as the best correlate of lung function both cross-sectionally and longitudinally. Neutrophil count and IL-8 also showed a relationship with lung function. Interestingly, the association of biomarkers of inflammation to lung function was greater than the association to biomarkers of infection. This study suggests that neutrophil elastase levels in sputum may have some value as a biomarker in phase 2 trials. In addition, the analysis provides further evidence that airway injury in CF is related to protease activity.

It is clear that phenotype in CF is not determined solely by the CF gene mutation. The relative role of the environment and heredity is still hotly debated. A very strong argument for the role of heredity was put forth by Vanscoy and colleagues who made use of the largest study to date of twins and siblings (19). Genetics played a substantial role in each of the lung function outcomes examined. This work suggests that modifier genes may be useful in prognosis and clinical trial stratification as well as in suggesting treatments.

CLINICAL TRIALS

Selected phase 1 (or pilot studies), phase 2, or phase 3 studies in CF are shown in Table 3. Moss and coworkers found no effect of an adenoassociated virus vector trial of gene therapy in CF (20). Duramycin inhalation, which acts through an alternative chloride channel to presumably improve ion transport across the airway in CF, showed encouraging results in a phase 1 study (21). Denufisol, a selective agonist of an alternative chloride channel, was well tolerated and improved lung function in patients with mild lung disease in a phase 2 study (22). A phase 3 trial of this agent is underway. Dry powder tobramycin for inhalation was well tolerated in an early phase study and is currently in later phase development (23). The use of the dry powder formulation decreases time of administration. A phase 3 trial of a flagella-based *Pseudomonas* vaccine decreased occurrence of positive *Pseudomonas* cultures but chronic *Pseudomonas* infection was uncommon in control and treated groups, probably related to changes in inhaled antibiotic treatment of *Pseudomonas* (24). Thus, the clinical impact of the vaccine may be small. A phase 2 study of inhaled α -antitrypsin demonstrated a decrease in airway inflammation and likely should be studied in a larger trial (25).

TABLE 2. REPRESENTATIVE CYSTIC FIBROSIS CLINICAL AND MODEL SYSTEM INVESTIGATIONS IN 2007

Investigations	Reference
• Clues to Pathogenesis	Kowalski and colleagues (12), Linde and colleagues (29)
- Impaired oxidant host defense	Moskwa and colleagues (11)
- Mucus biology	Choi and colleagues (14), Henke and colleagues (15)
- Neutrophil- <i>Pseudomonas</i> interactions	Hartl and colleagues (13)
• Biomarkers and outcome measures	Alton and colleagues (16), Ramsey (17), Mayer-Hamblett and colleagues (18)
• Gene modifiers	Vanscoy and colleagues (19)

TABLE 3. SELECTED PHASE 1 (OR PILOT STUDY), PHASE 2, OR PHASE 3 TRIALS IN CYSTIC FIBROSIS REPORTED DURING 2007

Primary Targeted Mechanism	Phase 1 (or pilot study)	Phase 2	Phase 3
Gene therapy		Adeno-associated virus, Moss and colleagues (20)	
Ion transport	Duramycin, Grasemann and colleagues (21)	Denufosal, Deterding and colleagues (22)	
Infection	Dry powder tobramycin, Geller and colleagues (23)	<i>Pseudomonas</i> vaccine, Doring and colleagues (24)	
Inflammation		α_1 -Antitrypsin, Griese and colleagues (25)	Ibuprofen, Lands and colleagues (26), Konstan and colleagues (27)
Metabolism		Growth hormone, Schnabel and colleagues (28)	

High-dose ibuprofen was studied in a phase 3 trial. There were some difficulties with enrollment and a statistically significant change in the primary endpoint—rate of decline in FEV₁—was not achieved (26). Decline in FVC was less in the ibuprofen group. It is not yet clear whether the results of this study will influence practice. Ibuprofen was the subject of another important investigation by Konstan and coworkers in a careful retrospective study (27). They examined the CFF registry and found that ibuprofen-treated patients had less decline in FEV₁ than matched control subjects. There was a slight increase in gastrointestinal bleeding in the ibuprofen-treated group. Even though this is a retrospective study, the large numbers of patients examined (1,300) is likely to lead more centers to use ibuprofen. A phase 2 trial of growth hormone in children with CF demonstrated increased linear growth, but no change in weight or lung function (28). This trial could contribute to the decision to use growth hormone in patients with CF and impaired growth.

It is likely that we will see the first results from trials of small druglike molecules with CFTR activity in 2008. In anticipation of these studies, Linde and coworkers found that, among patients carrying the W2182X stop mutation, there are differences in underlying transcript levels that correlate with response to gentamicin in terms of read-through (29). Thus, careful patient selection and characterization may be necessary in trials of agents with CFTR activity. In addition, we will need easier and better biomarkers and perhaps even outcome measures for CFTR effect.

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