Conference Summary

Respiratory Care and Cystic Fibrosis

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The 43rd RESPIRATORY CARE Journal Conference brought together experts from the United States, Canada, and the United Kingdom to review the art and science of cystic fibrosis (CF). This is the first time that CF was the topic for the Journal Conference, and it came about 6 decades after the disease was named, and 20 years after the gene was discovered on chromosome 7. Though CF is a multisystem disease, it is the chronic and progressive lung disease that causes most of the morbidity and mortality. The participants at the conference reviewed the epidemiology, pathophysiology, treatment, and novel therapies in the pipeline for CF lung disease. They also emphasized the many crucial roles that the respiratory therapist plays in CF, including diagnostic testing, aerosol therapies, airway clearance, infection control, patient and peer education, and patient advocacy. The May and June 2009 issues of the Journal reflect how diligently the participants worked to provide up-to-date reviews and lively discussions of these topics. *Key words: cystic fibrosis.* [Respir Care 2009;54(6):796–800. © 2009 Daedalus Enterprises]

Introduction

Unlike the millions of people diagnosed with asthma and chronic obstructive pulmonary disease, cystic fibrosis (CF) affects only about 30,000 individuals in the United States. Thus, the knowledge and experience of health-care professionals (including respiratory therapists [RTs]) regarding CF ranges from "ancient" memories of skinny, barrel-chested, coughing kids, to an in-depth understanding of this disease as participants in modern CF care teams. The objective of the 43rd RESPIRATORY CARE Journal Conference on CF was to provide a state-of-the-art review of the respiratory disease in CF and to look at the past, present,

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Dr Geller has disclosed relationships with Novartis, Bayer, Mpex, Pari, Aerogen, NanoBio, Aradigm, Genentech, CSL Behring, Boehringer Ingelheim, Trudell Medical International, Monaghan Medical, and Respironics.

Dr Rubin has disclosed relationships with Pfizer, Ventaira, Trudell Medical International, Monaghan Medical, GlaxoSmithKline, Medihale, Pharmaxis, Syntaxin, Bayer, Hill-Rom, Boehringer Ingelheim, and RegeneRx.

Dr Rubin presented a version of this paper at the 43rd RESPIRATORY CARE Journal Conference, "Respiratory Care and Cystic Fibrosis," held September 26-28, 2008, in Scottsdale, Arizona.

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and future of respiratory care in CF. These 2 issues of the Journal dedicated to CF can serve as a primer for those less familiar with the disease, and as an up-to-date review for those who are more involved in CF care.

Volsko reminded us that it has been about 60 years since the disease was first named, and about 20 years since the identification of the primary gene defect on chromosome 7, which codes for the protein called cystic fibrosis transmembrane conductance regulator (CFTR).[1] CF is a multisystem disease that is associated with pancreatic insufficiency, malabsorption, liver disease, chronic sinusitis, CF-related diabetes, male sterility, and osteoporosis, among others. But it is the chronic pulmonary inflammation and infection that cause most of the CF morbidity and mortality.

Since the discovery of the gene, our knowledge of CF respiratory disease has evolved tremendously. Over the years, the treatment paradigm has shifted from reacting to acute declines in respiratory health, to a proactive approach of preventing exacerbations and the loss of lung function. The result has been a continuing rise in the median age of survival for CF patients, now just under 38 years. RTs have made important contributions to the progress that has been made in CF care. The role of the RT in CF diagnostics, airway-clearance regimens, aerosol therapies, hospital and home care, patient and peer education, and research was emphasized throughout the conference.

Pathophysiology

The pathophysiology of CF is quite complex, and the disease course can be highly variable between affected individuals. Ratjen summarized the cascade of events in CF, starting with the gene mutation that codes for the CFTR protein, an important chloride channel that also regulates sodium and water flux across epithelial membranes, and interacts with many other cellular functions.[2] Though there are more than 1,500 described mutations for CF, they can be grouped into 6 different classes. Depending on the type of mutation, CFTR is either absent, deficient, or dysfunctional. The proposed low-volume hypothesis of CF lung disease suggests that CFTR dysfunction in apical epithelial membranes causes abnormal chloride, sodium, and water transport, leading to depletion of airway surface liquid that is required for normal ciliary function.[2] Ratjen,[2] Rubin,[3] and Davies[4] reviewed how this may be in part responsible for the ensuing cycle of phlegm retention, infection, and exaggerated inflammation that seems to perpetuate itself and leads to increasing airway obstruction and eventual respiratory failure. Rubin reminded us that "mucus is good," and "phlegm is bad." In the case of CF, the lower-airway secretions resemble pus more than mucus, with high levels of neutrophil-derived DNA and F-actin that co-polymerize and form tenacious, sticky secretions that are difficult to clear. In addition, absence of intact airway mucins may make it easier for bacteria to adhere to airway epithelium and establish a foothold, leading to chronic endobronchial infection.[3] Davies reviewed the different pathogens that can infect the airways in CF, and how the anaerobic environment in airway secretions favors the development of mucoidy in *Pseudomonas,* and subsequent development of biofilms, which protect the bacteria from immune defenses and antibiotics.[4] She also reviewed the possible roles of other organisms in CF lung disease, including non-tuberculous mycobacteria, *Burkholderia cepacia* complex, and emerging pathogens that are resistant to many antibiotic classes.

Monitoring the Lung Disease

Davies gave a comprehensive overview of the ways that we currently monitor the progression of lung disease and response to therapies, and how we may be looking at it in the future.[5] Spirometry, chest radiographs, and sputum cultures are the standard techniques for following the functional, anatomic, and microbiologic changes in the lungs, but all of these lack the sensitivity to detect early disease or small changes in disease progression over time. Davies said we need measures that are more sensitive, to allow very early detection, using techniques that are reproducible, easy to use, noninvasive, well tolerated, and applicable across all age groups. We need complementary information to look at lung function, inflammation, and bacterial infection as part of an entire package, not only for individual patient care, but also as outcome measures for clinical trials.[5]

Davies described the lung-clearance index, which uses an inert gas such as sulfur hexafluoride to look at ventilation heterogeneity, as a more sensitive measure of small-airway function. The lung-clearance index appears to be very sensitive even when forced expiratory volume in the first second (FEV_1) is not; it detects much earlier disease and is very sensitive to changes after therapy.[5] It can also be performed in very young children, in whom preventive strategies may have the most impact. Infant pulmonary function tests are also described to test early airway changes. These techniques are available only at a few centers, and are currently very expensive. High-resolution computed tomography scans are more sensitive than chest radiographs at detecting changes such as gas trapping and airway thickening, dilation, and mucus plugging. Some centers are now using computed-tomography scans routinely, while others are reluctant to do so because of the higher dose of radiation, though this is improving with newer scanners. Special magnetic resonance imaging and positron emission tomography scanning techniques are also being considered to monitor CF lung disease.[5] Davies also pointed out that, while we use respiratory cultures to detect patho-

gens for purposes of eradication or to tailor antibiotic treatments, many patients cannot expectorate sputum, and there is a disconnect between in vitro sensitivity tests and response to treatment. She mentioned molecular microbiologic techniques, exhaled breath tests, exhaled breath condensate tests, and measurement of bronchial mucosal blood flow as potential ways of improving our accuracy in following infection and inflammation in CF.[5]

Treatment

Several of the conference participants described current and experimental treatments that improve lung function and slow the progression of lung disease in CF. The therapies include gene replacement; CFTR modifiers; airway wetting agents; and treatments to improve airway clearance, inflammation, and infection. Ratjen discussed the therapies that target the "top" of the CF cascade (ie, the abnormal gene and the physiologic consequences of the CFTR mutations).[2] Gene replacement therapy generated a lot of enthusiasm shortly after the discovery of the CF gene in 1989, but there have been numerous challenges with the various viral and non-viral vectors used to deliver the gene. The most ambitious gene therapy trial is currently being conducted in the United Kingdom, using a cationic lipid-based vector.[2] Ratjen also discussed the exciting experimental treatments that affect CFTR expression, trafficking, or function. Class I mutations occur in about 5% of CF patients and result in incomplete protein transcripts that are destroyed intracellularly. An aminoglycoside derivative called PTC124 is showing promise to override the defect and produce complete CFTR transcripts to improve chloride transport. Other drugs in development (called correctors) reduce degradation and improve trafficking of CFTR to the cell membrane. In patients with CFTR present in the cell membranes, drugs such as VX770 (called potentiators) improve CFTR gating function, and showed promising results in a small group of patients with the G551D mutation.[2] Correctors and potentiators, alone or in combination, hold promise for other CF genotypes as well. Ratjen pointed out that CFTR is not the only chloride channel in the cell. Drugs such as denufosol and lancovutide activate alternate chloride channels, and showed positive results for improved lung function in early studies.[2] Studies of drugs that inhibit sodium absorption have been disappointing, but such drugs with longer half lives are in development. Finally, another way to address the underlying defect in CF is by using an inhaled osmotically active agent such as hypertonic saline or dry-powder mannitol to improve airway surface liquid level and airway clearance.[2,3]

Rubin[3] and Lester[6] both addressed the importance of removal of abnormal secretions from the airways in the maintenance of lung health in CF. Rubin discussed the abnormal properties of CF phlegm, and how different treatment strategies can alter those characteristics to enhance clearance. In addition to the hyperosmolar medications, he discussed the clinical effects of dornase alfa (Pulmozyme, Genentech), which cleaves extracellular DNA, and in clinical studies it improved pulmonary function and reduced exacerbations. He discussed macrolide antibiotics as mucoregulatory agents, and showed the data on azithromycin in CF (improved lung function, body weight, reduced exacerbations). While pointing out that inhaled thiol mucolytic agents such as N-acetyl cysteine have no proven benefit in CF, he reviewed other promising therapies such as thymosin beta 4 (decreases sputum cohesivity) and inhaled surfactant, both of which improve cough clearance.[3]

Lester was on the committee to establish the CF Foundation guidelines on airway clearance (published in RESPIRATORY CARE[7]), and discussed the mechanical techniques for airway clearance.[6] Some of the techniques require a caregiver (hands-on chest physiotherapy), and others allow the individual to be more independent. These techniques include vibratory chest percussion (vest therapy); positive-expiratory-pressure (PEP) and vibrating PEP devices; and breathing techniques such as autogenic drainage, active cycle of breathing, and directed coughing or huffing. Exercise has a positive effect as an adjunct to one of these other techniques. She emphasized the bottom line: the airway-clearance technique that works the best is the one that the patient will incorporate into their daily regimen. Since patients have different needs, they should be taught a variety of techniques, to improve adherence and to allow greater versatility should their situation change.[6]

The treatment of airway infection is a very important aspect of CF care. Of course, the best way to treat an infection is to prevent it from occurring in the first place. O'Malley did a comprehensive review of infection-control principles and how they apply to the CF population.[8] She reviewed the routes of transmission for microbes, and the guidelines for prevention, including standard precautions, transmission-based precautions, careful hand hygiene, patient cohorting, and cleaning and disinfecting respiratory equipment.[8] Geller then reviewed the treatment of airway infections with inhaled antibiotics.[9] The rationale for inhaled antibiotics is to get high concentrations at the site of infection in the airways, but low systemic levels, to limit adverse effects. Most of the evidence for inhaled antibiotics is for eradication of early infection or the long-term treatment of chronic infection with *P. aeruginosa*. The only approved inhaled antibiotic in the United States is tobramycin solution for inhalation (TOBI, Novartis), and in the United Kingdom inhaled colistin is also approved. With the threat of increasing microbial resistance and the emergence of other pathogens, it is clear that we need more tools to fight airway infection, so other inhaled antibiotics, including aminoglycosides, fluoroquinolones, and

β-lactams are in clinical development.[9] Inevitably, most people with CF will have increased symptoms from infectious exacerbations, despite chronic maintenance therapies. Newton reviewed the strategies for treatment of these exacerbations in the hospital, including the use of intravenous antibiotics and more aggressive airway clearance.[10] In some cases, noninvasive ventilation has been used to assist these patients through an acute event. He also emphasized the cleaning of respiratory equipment to avoid cross-contamination.

Many of the existing aerosol drugs for CF are delivered by liquid nebulization. In addition, some of the drugs in the CF therapeutic pipeline are delivered by inhalation. The time burden that this places on the patient is enormous, and is likely to result in non-adherence and suboptimal outcomes. The challenges of aerosol delivery in CF, including time-burden, were reviewed by Kesser.[11] CF patients come in different ages and sizes, and have differences in anatomy, disease severity, breathing patterns, and cognitive ability. Clearly this is not a "one-device-fits-all" scenario. Some new device technologies were discussed that try to solve some of the challenges and improve targeting and precision of aerosol delivery. These include soft-mist devices, vibrating-mesh devices, new dry-powder formulations, and electronic devices that slow the inhalation to improve lower-airway deposition.[11] Many of the aerosol drugs in development for CF are paired with a new-generation device. The frightening part is that patients may end up with a cupboard full of different devices, each for a different drug and each requiring its own care and cleaning ritual.

Complications and Transplantation

The natural history of CF lung disease includes chronic inflammation and infection, episodic exacerbations, structural airway changes (bronchiectasis), and increasing airway obstruction. As the lung disease worsens, there is an increased chance of serious respiratory complications, including pneumothorax, massive hemoptysis, and respiratory failure.[12] Flume described the epidemiology, pathophysiology, and management of these complications. The annual incidence of pneumothorax and massive hemoptysis is $< 1\%$ each, with about 75% of the cases occurring in adults 18 years and older. These complications can have a negative impact on pulmonary function and survival. There is a high recurrence rate with pneumothorax, such that about 70% of patients may ultimately need pleurodesis. Hemoptysis is often treated as a respiratory exacerbation, and if bleeding doesn't stop spontaneously, then bronchial artery embolization is often performed. Even with intervention, there is a high recurrence rate of over 50%.[12] Many caregivers stop airway-clearance maneuvers for a while after a pneumothorax or a bleed. That may not be necessary, but the technique may need to be altered. For example, PEP therapy may make a pneumothorax worse; this is an example where specific breathing techniques would be useful.

Respiratory failure is the result of progressive lung injury, and therapies include oxygen, nutritional support, airway clearance, antibiotics, and usual maintenance therapies. Intubation and mechanical ventilation of patients with mild or moderate lung disease and acute respiratory failure is appropriate, whereas in patients with severe lung disease it is discouraged unless they can receive a lung transplant in short order. However, noninvasive ventilation is being used more in CF, both for in-patients and in the ambulatory setting, to improve comfort or as a bridge to lung transplantation.[10,12]

Lung transplantation is an option for those patients who are not expected to survive 2 years. Models to predict survival have been developed and incorporate a number of factors. Characteristics of patients who are likely to benefit include FEV_1 less than 30% of predicted, rapidly worsening lung disease, increasing hospitalizations, hypercapnia, oxygen requirement, pulmonary hypertension, and recurrent hemoptysis.[12,13] Rosenblatt also noted that 5-year survival post-transplant is about 50%, and may be negatively impacted by several variables, including airways infection with *B. cenocepacia*. He also described how the development of the lung allocation score by the United Network for Organ Sharing in 2005 has decreased the waiting time for CF patients by about two thirds.[13]

The Cystic Fibrosis Foundation

We were privileged to have Bruce Marshall present the history of the CF Foundation and the incredible contributions that the organization has made to every facet of CF care and research. Started by a few CF families in 1955, the CF Foundation has grown into a large enterprise that supports basic science research, drug discovery and development, clinician and patient education, and patient advocacy. The CF Foundation has an accreditation process for CF clinical centers to provide centralized care with a team approach. The CF Foundation created the Therapeutics Development Network to coordinate and facilitate clinical trials of new therapeutics for CF. The CF Foundation also sponsors a patient registry to follow practice patterns in the United States, and hosts consensus conferences to develop evidence-based guidelines for the various aspects of CF diagnosis and management. The CF Foundation holds 2 annual conferences where scientists, clinicians, and industry can interact, share new information, and form new liaisons. The CF Foundation also provides educational resources for caregivers, patients, and families; a legal hotline; a patient advocacy manual; a CF pharmacy; and even a patient assistance program.[14] The mission of the CF

Foundation is, "*to assure the development of the means to cure and control cystic fibrosis and to improve the quality of life for those with the disease.*" Without the guidance of the CF Foundation, it would have been impossible to make the "great strides" in knowledge and treatment that we have seen to date.

What is the Role of the Respiratory Therapist?

All of the participants in this conference emphasized the important role that the RT plays in CF. Volsko illustrated that the role of the RT has progressed from the old days of mist tents and oxygen to the modern era, where RTs are crucial members of multi-specialty CF teams intimately involved in all aspects of CF respiratory disease. The RT plays a role as a diagnostician, caregiver, educator, researcher, and patient advocate.[1,14]

For patients who cannot provide sputum samples, the RT uses sputum-induction protocols or assists with bronchoscopies to obtain specimens for microbiology, inflammatory markers, or research protocols. Spirometry is routinely performed by RTs, and many of the newer techniques, such as infant pulmonary function testing and lung-clearance index, will be in the RT realm of expertise.[5]

The administration of aerosol medications and use of airway-clearance techniques are the most common bedside responsibilities in patient care. It is important for the RT to understand the different aerosol delivery systems: how they work, which one to use for which drug, and how to clean and disinfect them. The RT should be knowledgeable about various airway-clearance techniques so that the most appropriate ones can be used in individual patients. For inpatients, RTs spend considerable time at the bedside, giving them the opportunity to educate patients and families about nebulizer use and care, the proper order of inhaled medications, and airway-clearance techniques.[2,3,6,8-10] The face time with patients also promotes good will and trust between patients and caregivers, and often results in valuable insights into the psychosocial dynamics of the families, which may help with adherence to therapy.[14] Volsko and Newton pointed out that respiratory care protocols decrease the misallocation of services, decrease unnecessary care, and identify those who may need additional care.[1,10] RTs must know the 10 commandments of infection-control guidelines and be role models when it comes to hygiene, secretion precautions, and respiratory equipment handling.[8] Finally, RTs are the experts at setting up and teaching oxygen therapy and noninvasive ventilation.[10,12] This may involve therapists who work in an inpatient or out-patient setting, or in home care.

RTs also are integral participants in the research process in CF. This could involve the assessment of different airway-clearance devices,[1,6] bench testing of aerosol drug-device combinations,[11] quality-improvement projects, or participating as a research coordinator at the CF care center.[11,14] It is also important that RTs stay abreast of new research so that they understand the new devices and therapies: how they work, and what they do.[11] Finally, RTs are contributing on a national level by involvement with CF Foundation guidelines and education committees, benchmarking teams, and mentoring programs for RTs new to CF.[14]

The role of the RT in CF is multi-faceted; clearly RT's are very important members of the CF community. What was not discussed at the Journal Conference is just as important: what can CF do for the RT? The answer can be found in the facial expression of an RT as he or she meets the fiancé of one of the patients they cared for as a kid. Look at their smile and sense of pride as they look at pictures of patients at college graduation, running marathons, or raising families of their own. The care of CF patients, in particular, is personally gratifying and emotional. CF is a disease that killed most children by age 10 about 50 years ago. To be a part of the nurturing process of people with this genetic disease from infancy to adulthood, and to assist them in achieving their life goals is a truly amazing gift: a gift we hope will be shared by more and more caregivers in the future.

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