

## Cystic Fibrosis in 2006

a report by

**Susanna A McColley, MD**

*Division Head, Pulmonary Medicine, Director, Cystic Fibrosis Center, and Associate Chair for Clinical Affairs,  
Department of Medicine, Children's Memorial Hospital*

Cystic fibrosis (CF) is an autosomal recessive disorder that generally becomes symptomatic within the first year of life. Although it was originally described in the 1930s, the genetic abnormality underlying CF was not described until 1989 in a multinational collaborative effort using novel genetic techniques. The gene, called the cystic fibrosis transmembrane regulator (CFTR), codes for an epithelial cell protein that normally sits in the apical cell membrane and functions as a chloride channel and as a regulator of other apical chloride and sodium ion channels. Defective CFTR results in abnormal ion transport and dehydrated secretions in the airway, digestive, and urogenital systems. In the lung, this results in abnormal clearance of mucus, chronic suppurative pulmonary infection, and robust pulmonary inflammation. This process leads to bronchiectasis, which can be seen in asymptomatic children as early as the first year of life and which has been documented in children with normal pulmonary function, as measured by spirometry. On average, children with CF have near normal lung function, expressed as forced expiratory volume in one second (FEV<sub>1</sub>) at age six, but a decrease in lung function of 2–4% of predicted per year thereafter. Ninety per cent of affected individuals ultimately die from complications of lung disease. During the past 20 years, median life expectancy in the US has increased from about 25 years to almost 37 years of age. Survival is quite variable between individuals, and death still occurs in childhood and adolescence. A number of risk factors for decreased survival have been identified that may lead to specific interventions. Regardless of risk factors, it can be anticipated that survival will increase more rapidly over the next decades through three complementary strategies: widespread adoption of newborn screening to allow diagnosis and therapy before symptoms occur; quality improvement processes that promote best delivery of evidence-based care; and the use of available and new therapies targeted specifically to the abnormalities present in the CF lung.

### Predictors of Survival

While survival is steadily increasing in cystic fibrosis, there is significant variability in the clinical course of the

disease. Risk factors for increased morbidity and mortality can be separated into those inherent to the patient and those that can be modified with medical care. Those inherent to the patient include the presence of two severe CFTR gene mutations, those in class I, II, and III. Other genetic factors include female sex and 'genetic modifiers', or variations in genes other than CFTR. Modifier genes include a polymorphism in a gene that codes for transforming growth factor beta (TGF- $\beta$ ), a protein with numerous functional properties; presence of the polymorphism is associated with more severe lung disease. Other non-modifiable risk factors include age and symptoms at diagnosis, pancreatic insufficiency, and minority (non-Caucasian) ethnicity. Socioeconomic status (SES) is an important predictor of survival; people with CF from low SES as measured both by state insurance through the US Medicaid program and by median income in postal code have decreased survival; there is a striking 'dose-response' relationship between income and survival, with those with highest family incomes having longest survival. Modifiable predictors of survival include nutritional status: higher weight and body mass index (BMI) are associated with longer survival.

FEV<sub>1</sub> second is a strong predictor of survival; when FEV<sub>1</sub> falls below 60% of predicted, the annual risk of mortality doubles, and when FEV<sub>1</sub> falls below 30% of predicted, two-year survival is only 50%. Thus, therapies aimed at improving and stabilizing FEV<sub>1</sub> are extremely important. Chronic infection with *Pseudomonas aeruginosa* (PA), especially mucoid strains, is associated with more rapid decline in lung function and earlier mortality. Because the acquisition of mucoid PA can be delayed by early treatment of asymptomatic infection, frequent monitoring of infectious status by pharyngeal or sputum cultures, coupled with antibiotic therapy for positive PA cultures, is recommended. Diabetes mellitus is associated with more rapid decline in pulmonary function in female but not male individuals with CF, and leads to nutritional abnormalities; therefore, early detection and treatment of diabetes is also important.

### Newborn Screening

It has been long appreciated that infants diagnosed



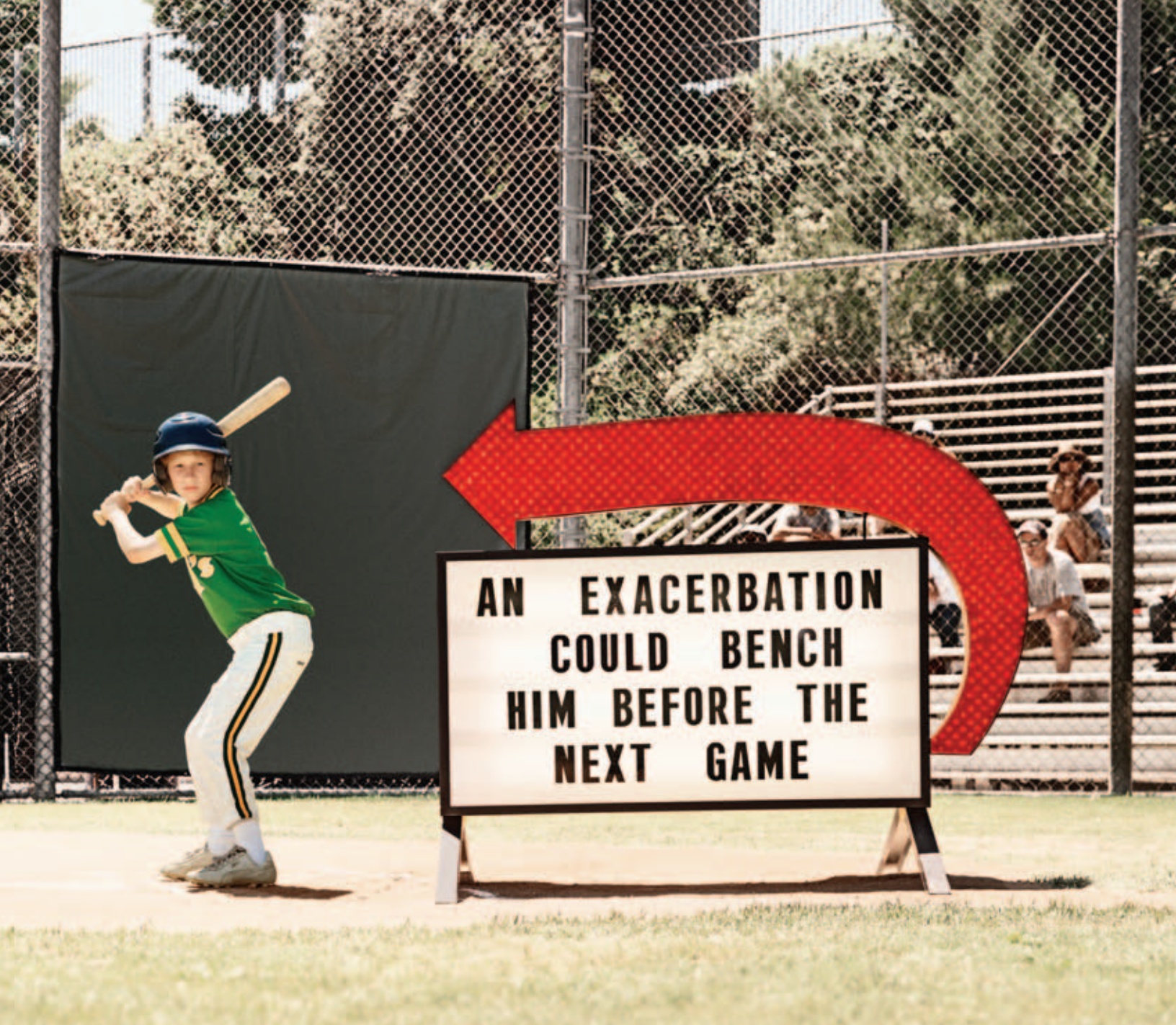
Susanna A McColley, MD, is Division Head of Pulmonary Medicine, Director of the Cystic Fibrosis Center, and Associate Chair for Clinical Affairs in the Department of Medicine at the Children's Memorial Hospital in Chicago. She is Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine. She is a member of the American Thoracic Society and has served on its International Conference Committee and its board of directors; she currently chairs its Strategic Planning Committee. She served on the Cystic Fibrosis Foundation Center Committee from 1997 to 2005 and was chairperson during the latter part of her appointment; she was Co-chair of the 2005 North American Cystic Fibrosis Conference. Dr McColley is a Fellow of the American Academy of Pediatrics and of the American College of Chest Physicians. She has diverse research interests including pathogenesis of *Pseudomonas aeruginosa* and angiogenesis and inflammation in cystic fibrosis, and has participated in numerous multicenter clinical trials of cystic fibrosis therapies.



**Indication:** Daily administration of Pulmozyme in conjunction with standard therapies is indicated in the management of cystic fibrosis (CF) patients to improve pulmonary function. In patients with an FVC  $\geq$ 40% of predicted, daily administration of Pulmozyme has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics. Safety and efficacy of daily administration have not been demonstrated in patients for longer than 12 months.

**Important Safety Information:** Pulmozyme is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product. Pulmozyme should be used in conjunction with standard therapies for CF. The most common adverse events reported include voice alteration, pharyngitis, laryngitis, rash, chest pain, and conjunctivitis.

Please see adjacent brief summary of prescribing information for additional information.



Early signs of lung damage aren't so obvious. But the need to delay exacerbations is.

Why wait to see the effects of cystic fibrosis? With Pulmozyme, you can help delay respiratory tract exacerbations and improve lung function in mild to moderate patients.<sup>1</sup> So treat these patients early with Pulmozyme — because every day matters.



**Every day matters**

**Reference:**

1. Pulmozyme [package insert]. South San Francisco, Calif: Genentech, Inc; 2001.

For more information, visit [www.pulmozyme.com](http://www.pulmozyme.com)



# Pulmozyme<sup>®</sup>

## dornase alfa INHALATION SOLUTION

### Brief Summary

The following is a brief summary. Before prescribing, please consult full prescribing information including DOSAGE and ADMINISTRATION.

### INDICATIONS AND USAGE

Daily administration of PULMOZYME<sup>®</sup> (dornase alfa) Inhalation Solution in conjunction with standard therapies is indicated in the management of cystic fibrosis patients to improve pulmonary function. In patients with an FVC  $\geq$ 40% of predicted, daily administration of PULMOZYME has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

Safety and efficacy of daily administration have not been demonstrated in patients for longer than twelve months.

### CONTRAINDICATIONS

PULMOZYME is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.

### WARNINGS

None.

### PRECAUTIONS

#### General

PULMOZYME should be used in conjunction with standard therapies for CF.

#### Information for Patients

PULMOZYME must be stored in the refrigerator at 2-8°C (36-46°F) and protected from strong light. It should be kept refrigerated during transport and should not be exposed to room temperatures for a total time of 24 hours. The solution should be discarded if it is cloudy or discolored. PULMOZYME contains no preservative and, once opened, the entire contents of the ampule must be used or discarded. Patients should be instructed in the proper use and maintenance of the nebulizer and compressor system used in its delivery.

PULMOZYME should not be diluted or mixed with other drugs in the nebulizer. Mixing of PULMOZYME with other drugs could lead to adverse physicochemical and/or functional changes in PULMOZYME or the admixed compound.

#### Drug Interactions

Clinical trials have indicated that PULMOZYME can be effectively and safely used in conjunction with standard cystic fibrosis therapies including oral, inhaled and/or parenteral antibiotics, bronchodilators, enzyme supplements, vitamins, oral or inhaled corticosteroids, and analgesics. No formal drug interaction studies have been performed.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis:** Lifetime studies in Sprague Dawley rats showed no carcinogenic effect when PULMOZYME was administered at doses up to 246  $\mu$ g/kg body weight per day. PULMOZYME was administered to rats as an aerosol for up to 30 minutes per day, daily for two years, with resulting lower respiratory tract doses of up to 246  $\mu$ g/kg per day, which represents up to a 28.8-fold multiple of the clinical dose. There was no increase in the development of benign or malignant neoplasms and no occurrence of unusual tumor types in rats after lifetime exposure.

**Mutagenesis:** Ames tests using six different tester strains of bacteria (4 of *S. typhimurium* and 2 of *E. coli*) at concentrations up to 5000  $\mu$ g/plate, a cytogenetic assay using human peripheral blood lymphocytes at concentrations up to 2000  $\mu$ g/plate, and a mouse lymphoma assay at concentrations up to 1000  $\mu$ g/plate, with and without metabolic activation, revealed no evidence of mutagenesis potential. PULMOZYME was tested in a micronucleus (in vivo) assay for its potential to produce chromosome damage in bone marrow cells of mice following a bolus intravenous dose of 10 mg/kg on two consecutive days. No evidence of chromosomal damage was noted.

**Impairment of Fertility:** In studies with rats receiving up to 10 mg/kg/day, a dose representing systemic exposures greater than 600 times that expected following the recommended human dose, fertility and reproductive performance of both males and females was not affected.

#### Pregnancy (Category B)

Reproduction studies have been performed in rats and rabbits with intravenous doses up to 10 mg/kg/day, representing systemic exposures greater than 600 times that expected following the recommended human dose. These studies have revealed no evidence of impaired fertility, harm to the fetus, or effects on development due to PULMOZYME. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

#### Nursing Mothers

It is not known whether PULMOZYME is excreted in human milk. Small amounts of dornase alfa were detected in maternal milk of cynomolgus monkeys when administered a bolus dose (100  $\mu$ g/kg) of dornase alfa followed by a six hour intravenous infusion (80  $\mu$ g/kg/hr). Little or no measurable dornase alfa would be expected in human milk after chronic aerosol administration of recommended doses. Because many drugs are excreted in human milk, caution should still be exercised when PULMOZYME is administered to a nursing woman.

#### Pediatric Use

Because of the limited experience with the administration of PULMOZYME to patients younger than 5 years of age, its use should be considered only for those patients in whom there is a potential for benefit in pulmonary function or in risk of respiratory tract infection.

#### Geriatric Use

Cystic fibrosis is primarily a disease of pediatrics and young adults. Clinical studies of Pulmozyme did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

### ADVERSE REACTIONS

Patients have now been exposed to PULMOZYME for up to 12 months in clinical trials.

In a randomized, placebo-controlled clinical trial in patients with FVC  $\geq$ 40% of predicted, over 600 patients received PULMOZYME once or twice daily for six months; most adverse events were not more common on PULMOZYME than on placebo and probably reflected the sequelae of the underlying lung disease. In most cases events that were increased were mild, transient in nature, and did not require alterations in dosing. Few patients experienced adverse events resulting in permanent discontinuation from PULMOZYME, and the discontinuation rate was similar for placebo (2%) and PULMOZYME (3%). Events that were more frequent (greater than 3%) in PULMOZYME treated patients than in placebo-treated patients are listed in Table 1.

### Pulmozyme<sup>®</sup> (dornase alfa) Inhalation Solution

In a randomized, placebo-controlled trial of patients with advanced disease (FVC <40% of predicted) the safety profile for most adverse events was similar to that reported for the trial in patients with mild to moderate disease. For this study, adverse events that were reported with a higher frequency (greater than 3%) in the PULMOZYME treated patients, are also listed in Table 1.

**Table 1**

Adverse Events Increased 3% or More in PULMOZYME Treated Patients Over Placebo in CF Clinical Trials

Adverse Event (of any severity or seriousness)	Trial in Mild to Moderate CF Patients (FVC $\geq$ 40% of predicted)			Trial in Advanced CF Patients (FVC <40% of predicted) treated for 12 weeks	
	Placebo n=325	PULMOZYME QD n=322	PULMOZYME BID n=321	Placebo N=159	PULMOZYME QD N=161
Voice alteration	7%	12%	16%	6%	18%
Pharyngitis	33%	36%	40%	28%	32%
Rash	7%	10%	12%	1%	3%
Laryngitis	1%	3%	4%	1%	3%
Chest Pain	16%	18%	21%	23%	25%
Conjunctivitis	2%	4%	3%	0%	1%
Rhinitis				24%	30%
FVC decrease of $\geq$ 10% of predicted*	Differences were less than 3% for these adverse events in the Trial in mild to moderate CF patients			17%	22%
Fever				28%	32%
Dyspepsia				0%	3%
Dyspnea (when reported as serious)	Differences were less than 3% for this adverse events in the Trial in mild to moderate CF patients			12%†	17%†

\*Single measurement only, does not reflect overall FVC changes.

†Total reports of dyspnea (regardless of severity or seriousness) had a difference of less than 3% for the Trial in advanced CF patients.

### Events Observed at Similar Rates in PULMOZYME and Placebo Treated Patients with FVC $\geq$ 40% of Predicted

**Body as a Whole** Abdominal pain, Asthenia, Fever, Flu syndrome, Malaise, Sepsis

**Digestive System** Intestinal Obstruction, Gall Bladder disease, Liver disease, Pancreatic disease

**Metabolic Nutritional System** Diabetes Mellitus, Hypoxia, Weight Loss

**Respiratory System** Apnea, Bronchiectasis, Bronchitis, Change in Sputum, Cough Increase, Dyspnea, Hemoptysis, Lung Function Decrease, Nasal Polyps, Pneumonia, Pneumothorax, Rhinitis, Sinusitis, Sputum Increase, Wheeze

Mortality rates observed in controlled trials were similar for the placebo and PULMOZYME treated patients. Causes of death were consistent with progression of cystic fibrosis and included apnea, cardiac arrest, cardiopulmonary arrest, cor pulmonale, heart failure, massive hemoptysis, pneumonia, pneumothorax, and respiratory failure.

The safety of PULMOZYME, 2.5 mg by inhalation, was studied with 2 weeks of daily administration in 98 patients with cystic fibrosis (65 aged 3 months to <5 years, 33 aged 5 to  $\leq$ 10 years). The PARI BABY™ reusable nebulizer (which uses a facemask instead of a mouthpiece) was utilized in patients unable to demonstrate the ability to inhale or exhale orally throughout the entire treatment period (54/65, 83% of the younger and 2/33, 6% of the older patients). The number of patients reporting cough was higher in the younger age group as compared to the older age group (29/65, 45% compared to 10/33, 30%) as was the number reporting moderate to severe cough (24/65, 37% as compared to 6/33, 18%). Other events tended to be of mild to moderate severity. The number of patients reporting rhinitis was higher in the younger age group as compared to the older age group (23/65, 35% compared to 9/33, 27%) as was the number reporting rash (4/65, 6% as compared to 0/33). The nature of adverse events was similar to that seen in the larger trials of PULMOZYME.

#### Allergic Reactions

There have been no reports of anaphylaxis attributed to the administration of PULMOZYME to date. Urticaria, mild to moderate, and mild skin rash have been observed and have been transient. Within all of the studies, a small percentage (average of 2-4%) of patients treated with PULMOZYME developed serum antibodies to PULMOZYME. None of these patients developed anaphylaxis, and the clinical significance of serum antibodies to PULMOZYME is unknown.

#### OVERDOSAGE

Single-dose inhalation studies in rats and monkeys at doses up to 180-times higher than doses routinely used in clinical studies are well tolerated. Single dose oral administration of PULMOZYME in doses up to 200 mg/kg are also well tolerated by rats.

Cystic fibrosis patients have received up to 20 mg BID for up to 6 days and 10 mg BID intermittently (2 weeks on/2 weeks off drug) for 168 days. These doses were well tolerated.

Pulmozyme<sup>®</sup>  
(dornase alfa)  
Inhalation Solution

7033603  
(4824301)

Manufactured by  
GENENTECH, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990

Code Revision Date: April 2005  
FDA Approval Date: January 2001  
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before the onset of symptoms have better outcomes than those diagnosed with symptoms; furthermore, those with respiratory and gastrointestinal symptoms at diagnosis fare worse than those with gastrointestinal symptoms alone. Diagnosis of pre-symptomatic infants can avoid 'catastrophic' diagnosis with failure to thrive or severe respiratory distress. Newborn screening has also been associated with decreased mortality.

### Delivery of Evidence Based Care

Variability in clinical monitoring and treatment has been documented in US CF care centers and also exists outside of the US. Only about half of children seen in US care centers receive recommended monitoring. Moreover, there is substantial variability in the use of therapies that have been proven to positively impact pulmonary function. More importantly, there is a wide range in average pulmonary function and BMI at US CF centers, suggesting an opportunity to improve outcomes. The Cystic Fibrosis Foundation has created an ambitious program to improve the quality of CF care and thus improve outcomes at US CF centers. Strategies include rigorous updating and dissemination of evidence-based guidelines and the funding of multicenter quality improvement collaboratives. An example of the former is the consensus statement on pediatric nutrition. Because one-third of children are under-nourished, frequent objective assessment of nutritional status and early intervention with any decline in weight or BMI are essential strategies. When nutritional goals are not met with these strategies, placement of a gastrostomy or nasogastric tube for nocturnal supplemental tube feedings is a very successful strategy for improving nutrition. This strategy should not be limited to patients with severe or refractory malnutrition, but used as an adjunct measure to achieve normal growth.

Appropriate care for pulmonary disease is also essential. A practice guideline on pulmonary care is currently being formulated by CFF. Observational studies from the Epidemiologic Study of Cystic Fibrosis showed that sites with better pulmonary function outcomes see patients more frequently, obtain more spirometric measurements and respiratory tract cultures, and use more intravenous (IV) antibiotic therapy than patients with lower pulmonary function. Use of specific therapies that improve lung function and reduce exacerbation therapy is felt to be important, but published studies show a strong bias toward use of these therapies in patients with more severe disease, confounding analysis.

### Therapies Targeted to the CF Lung

For many years, CF lung disease was treated with airway clearance techniques and with oral or IV antibiotics. In the US, antibiotics have primarily been used for pulmonary exacerbation therapy, while, elsewhere, oral antibiotics are given to young children to prevent infection with *Staphylococcus aureus*. Airway clearance techniques include chest physiotherapy with percussion and postural drainage, use of hand-held positive expiratory pressure (PEP) devices, including simple PEP devices and devices that also have an oscillating pressure, such as the Flutter™ and Acapella™ systems, high-frequency chest wall oscillation systems, autogenic drainage, and active cycle of breathing techniques. Most patients in the US are prescribed preventive airway clearance therapy after the time of diagnosis.

Pulmonary exacerbation has several different published definitions. The 1997 CFF Practice Guidelines define pulmonary exacerbation as "a change in respiratory signs and symptoms ... which necessitates treatment with antibiotics and augmented airway clearance. Increased chest congestion, decreased exercise tolerance, and onset of new or increased crackles ... usually associated with a decrease in [forced vital capacity] FVC and FEV<sub>1</sub> of greater than 10%." Treatment of pulmonary exacerbation depends on its severity and patient respiratory culture results. An increased frequency of airway clearance aids in clearing increased secretions and should be performed whether the patient is treated in the hospital or at home. Antibiotics are given to reduce sputum bacterial load and are associated with symptom resolution and improvement in pulmonary function. While oral antibiotics may be appropriate for mild exacerbations in patients with organisms that are sensitive to agents that may be administered orally, intravenous antibiotics are preferred for moderate or severe exacerbation. In patients with PA, combination antibiotic therapy results in more sustained improvement than monotherapy; usually, a third-generation cephalosporin, a carbapenem, or a semi-synthetic penicillin is given in combination with an aminoglycoside. The duration of therapy is a minimum of 14 days, and most practitioners also treat until there is resolution of both symptoms and pulmonary function decline.

Therapies targeted specifically to the CF lung have only recently been introduced and are anticipated to grow rapidly over the next decade. The first CF-specific therapy introduced was rh-DNase, or Pulmozyme™, which was approved by the FDA in 1993. The rationale of rh-DNase therapy is that there is robust neutrophilic inflammation in the CF lung. When neutrophils decay in the airways, abundant

DNA is released, increasing sputum viscosity and adherence. In a pivotal phase III clinical trial, administration of once-daily rh-DNase resulted in a modest but statistically significant improvement in pulmonary function in the treatment versus placebo arm. More importantly, subjects receiving rh-DNase had a significantly reduced risk of pulmonary exacerbation during the trial period. In order to assess the effectiveness of rh-DNase in young children with mild lung disease, a two-year, randomized, placebo controlled trial was performed in children aged six to ten years with normal forced vital capacity (FVC). Similar results were achieved in the rh-DNase group, with an even more striking reduction in pulmonary exacerbation frequency.

Other recently developed or adopted therapies are targeted to patients chronically infected with PA. Tobramycin solution for inhalation (TSI, TOBI™) was developed because laboratory investigation revealed that PA within CF sputum requires very high tobramycin levels to achieve adequate bacterial killing. Because high doses of tobramycin are toxic to the kidney and inner ear, a high-dose inhalation solution was developed. Pre-clinical studies and microbiologic principles suggested that the drug should be given intermittently rather than continuously. TSI was studied in a six-month, double-blind, placebo-controlled study of over 500 subjects with CF aged six to 30 years with FEV<sub>1</sub> 25–75% of predicted. Subjects took the inhalation solution twice daily for 28 days, followed by no solution for 28 days, for the duration of the study. Compared with subjects who received placebo, patients taking TSI had a clinically and statistically significant improvement in pulmonary function, averaging 12% predicted FEV<sub>1</sub>. A significant reduction in pulmonary exacerbation was also seen. A trial of subjects with milder lung disease was terminated when an interim analysis revealed a substantial reduction of pulmonary exacerbations in the treatment versus placebo arm of the study.

Azithromycin, a commonly prescribed and widely available macrolide antibiotic, has been studied in three placebo-controlled clinical trials in CF patients with chronic PA. Results of the trials show improvement in pulmonary function and reduction in pulmonary exacerbation, without a reduction in sputum PA density. It is hypothesized that azithromycin has an anti-inflammatory effect in the lung, but other mechanisms of action are being investigated. Preliminary reports suggest a role for azithromycin in patients without chronic PA, and the CFF has planned a large study of macrolide therapy in children without chronic PA colonization. The newest available therapy for CF lung disease is 7% hypertonic saline (HTS). The purpose of

this therapy is to provide an osmotic force on the airway surface to rehydrate airway secretions and enhance mucociliary clearance. A double-blind, placebo-controlled clinical trial of CF patients aged six and older and with FEV<sub>1</sub> greater than 40% of predicted showed improved pulmonary function and a reduction in pulmonary exacerbation in subjects taking 4cm<sup>3</sup> of 7% HTS twice daily compared with subjects taking normal saline at the same volume and schedule.

A number of potential new therapies for CF are currently being studied in clinical trials. Two agents have been designed to override the epithelial ion channel abnormality. Denufosal (Inspire Pharmaceuticals, Durham, NC) is a P2Y<sub>2</sub> receptor agonist. Activation of airway epithelial P2Y<sub>2</sub> receptors opens a non-CFTR apical ion channel, allowing rehydration of the airway epithelial surface. In phase II clinical trials, the drug was well tolerated, had a good safety profile, and led to improvement in FEV<sub>1</sub> in subjects receiving drug versus placebo. A phase III study is currently under way. 552-02 (Parion Sciences, Durham, NC) is an epithelial sodium channel agonist, developed with a similar rationale. The first phase II clinical trial is near completion.

Because of issues with antimicrobial resistance and emerging Gram-negative bacteria in the CF lung, additional antibiotic therapies are needed for chronic suppressive therapies. Furthermore, the administration time of TSI is 20-30 minutes, leading to patient dissatisfaction and non-adherence to therapy. Aztreonam, a monobactam with substantial activity against PA and *Burkholderia cepacia*, is being studied in several clinical trials. This agent has been developed for delivery via a highly efficient, hand-held, portable nebulizer system; this reduces nebulization time to about four minutes. Tobramycin inhalation powder has been developed with a goal of giving similar efficacy as TSI, but with dramatically shorter administration time; clinical trials are in progress.

A variety of new pulmonary therapies are being studied in pre-clinical and early clinical studies. The ultimate goal is to develop therapies that correct the CFTR defect or replace abnormal CFTR through protein or gene therapy. While these therapies may, in the future, dramatically change the clinical manifestations of CF, those currently affected will continue to have improving quality and length of life by use of available and emerging therapies with close attention to delivery of high-quality, evidence-based care. ■

*A longer version of this article containing references can be found in the Reference Section on the website supporting this briefing ([www.touchrespiratorydisease.com](http://www.touchrespiratorydisease.com)).*