The clinical management of cystic fibrosis (CF) has made great strides in recent years as a result of advancements in therapeutic options, methods of assessing lung health, and standardizing care. Earlier and more accurate diagnosis and tracking of disease progression are now made possible by physiologic methods such as specialized spirometry and gas mixing techniques, and imaging studies such as high-resolution computed tomography scanning, hyperpolarized Helium magnetic resonance imaging, and positron emission tomography \(^{[18F]}\) fluorodeoxyglucose scans. Clinical study data and research into the pathophysiology of this genetic disorder have broadened the spectrum of antibiotic therapies available (eg, disease- and target organ-specific aerosolized antibiotics), and introduced new agents to promote airway secretion clearance (dornase alpha and hypertonic saline) and to counteract inflammatory changes (such as macrolide antibiotics, high-dose ibuprofen, and glucocorticosteroids). This review article highlights these and other monitoring and therapeutic techniques, discusses the relationship between nutrition and lung function, and notes improved outcomes associated with proactive comprehensive CF center-based care.


Although a genetic disorder involving a mutation of the cystic fibrosis transmembrane conductance regulator gene (CFTR), individuals with cystic fibrosis (CF) are born with essentially normal lungs that quickly succumb to pathology thought to be secondary to a combination of early postnatal infection and inflammation. Increasing evidence points to early intervention—optimally even before infants with CF become symptomatic—to assure the best prognosis. Perfecting techniques aimed at establishing a diagnosis and then monitoring lung health poses a formidable challenge when working with infants and toddlers, yet bronchoscopy performed on infants only a few weeks old already reveals the presence of infection and inflammation, and this damage may be irreversible. Thus, early detection and reliable monitoring are now recognized as essential for this patient population. Traditionally, assessment of CF lung disease relied heavily upon history and physical examination and plain chest radiography until children were mature enough to cooperate with spirometry (usually around ages 5–6 years). Recently, new techniques have been developed to improve the evaluation of children in the preschool years. These include physiologic and imaging modalities. These techniques are currently under development and evaluation but not widely applicable for technical and cost reasons, in addition to lack of longitudinal validating.

Management of CF is based upon a multifaceted approach that includes techniques for accomplishing airway clearance, reducing mucus production, combating infection, and ameliorating inflammation. Quality-of-life issues are also key to the patient and family. This article will also discuss nutritional therapies as well as the evidence supporting the use of accredited multidisciplinary CF centers to improve outcomes for patients, such as reducing hospitalizations, emergency room visits, and the need for parenteral therapies, while increasing the quality and length of life.
MONITORING LUNG HEALTH

PHYSIOLOGIC METHODS FOR ASSESSING LUNG FUNCTION

Spirometry is the principal physiologic method employed to assess airway function in patients with CF once they are of school age. Serial evaluations can help track disease progression as well as response to therapy. The average decline in forced expiratory volume in 1 second (FEV₁) is currently approximately 2% per year, but there is very wide interpatient, and indeed intrapatient, longitudinal variability. In infants, the raised volume rapid thoracoabdominal compression (RVRTC) technique can now be used to accomplish the same task of measuring flow rates at differing volumes without patient cooperation. Using this method, it is possible to generate flow-volume curves in infants that closely resemble flow-volume curves in older children and adults. Studies of infants with CF undergoing RVRTC reveal that some demonstrate evidence of airflow obstruction before clinical or microbiological signs of disease become apparent. RVRTC requires sedation of the infant and specialized equipment and training, and cannot be used after approximately age 2 years. Several investigators have been able to perform reliable adult-type spirometry on normal and affected children between the ages of 2 and 4 years with rigorous technique and careful training of subjects. Analysis of data from these spirometric techniques suggests that there is “significant early loss of lung function in CF, probably in infancy, which is not reversed by intensive therapy over several years.”

Another physiologic method used to evaluate distal airway disease is gas mixing whereby the child inhales a fixed amount of an inert marker gas, such as sulfur hexafluoride, until an equilibrium is reached at which point gas intake is stopped and the concentration is measured as it is washed out during tidal breathing. From cross-sectional and longitudinal studies performed using this technique, gas mixing appears to be the most sensitive physiologic method, becoming abnormal before forced expiratory flows. However, it may be too sensitive for late-stage disease or may detect insignificant abnormalities.

IMAGING TECHNIQUES FOR ASSESSING LUNG HEALTH

Imaging techniques have advanced significantly over the past 20 years from a time when plain chest X ray was the sole radiologic study available to current methods that include high-resolution computed tomography (HRCT) scanning, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning. These newer techniques afford the ability to assess and quantify the progressive nature of CF lung disease well before conventional radiographic or pulmonary function abnormalities become apparent. Structural lung damage and abnormalities, such as air trapping, bronchiectasis, mucus plugging, ground glass, and parenchymal opacities, may affect select lung regions while sparing adjacent locations. This becomes evident using HRCT and other sensitive modalities.

QUANTITATIVE CHEST X RAYS

Current guidelines for chest X ray in patients with CF recommend studies every 2 to 4 years in stable individuals and annually in patients with frequent infections or declining lung function. Scoring systems may be used to quantify the degree of lung damage and to track changes in lung disease. Several studies have demonstrated that quantitative chest radiography may be more useful than pulmonary function tests in younger patients.

HIGH-RESOLUTION COMPUTED TOMOGRAPHIC SCANNING

Of all modalities, HRCT scanning has been found to be the most effective in diagnosing early disease due to its ability to detect subtle pathology in patients who are clinically asymptomatic with normal chest X rays and spirometry. It is also sensitive and accurate for tracking progressive changes over time. Although there were earlier concerns about serial HRCT scans leading to excessive exposure to radiation, there have now been advances in the equipment and techniques that allow radiation exposure not much greater than routine chest X rays. HRCT scoring systems now have been developed to assess parameters of CF pathology. Nasr et al monitored outcomes in children younger than 5 who had been treated with aerosolized dornase alpha, reporting a significant difference in HRCT scores in treated children. Robinson et al showed reduction in air trapping in a year-long controlled trial of dornase alpha in patients with CF with normal lung function using quantitative computer analysis of HRCT images. The Cystic Fibrosis Foundation has yet to issue guidelines for use of HRCT. However, it is certainly the most promising of the imaging techniques and may be used in conjunction with pulmonary function tests in managing patients where appropriate.
Magnetic resonance imaging is an attractive option for diagnosis and monitoring of patients with CF because it is noninvasive and requires no irradiation. It also has good contrast resolution. MRI is able to provide information regarding the function of the heart and pulmonary vasculature, in addition to the lungs. In the lungs, MRI may detect early mucus plugs or bronchiectasis, and differentiate between conditions that might be otherwise difficult to distinguish, such as mucoid impaction versus atelectasis or hilar adenopathy versus enlarged hilar vessels. Generally, MRI has not proven to be more useful than HRCT because it requires more time, sedation, and higher cost. However, in specific situations, MRI is an important addition to the diagnostic choices for patients with CF, such as for evaluating pulmonary hypertension and/or assessing lung perfusion changes that might indicate vascular abnormalities. Hyperpolarized helium magnetic resonance imaging may also be useful in older patients with advanced lung disease and has the advantage of not exposing these patients to additional radiation. Functional MRI correlates with spirometry and computed tomography scan results for such patients, as compared to children with lesser obstructive lung disease.

As noted in this article, CF can cause regional defects in airway structures and lung parenchyma. Regional lung inflammation has been found in adult patients with CF by PET scan, and it has been suggested that PET scanning may be a promising modality for early detection of infection and inflammation, in addition to a method of determining response to anti-inflammatory therapies. In combination with HRCT, it is possible to compare areas of inflammation noted on PET scan with areas of structural lung damage noted on HRCT.

Other detection and monitoring methods not specifically discussed in this review include oropharyngeal cultures and bronchoscopy with bronchoalveolar lavage to assess microbiology and inflammatory biomarkers, hematologic markers of infection and inflammation, and a variety of nutritional and metabolic assessment tools. Techniques that permit screening and/or earlier identification of pathology before patients are symptomatic are critical to improving outcomes. It is thought that there is a critical “window of opportunity” to intervene therapeutically before chronic lung disease develops or becomes irreversible. However, although early intervention is sound, it creates significant new challenges, including increased cost, treatment burden, and unintended consequences. It has the potential to slow or stop disease progression, but this must be balanced against the potential for adverse effects and high costs with uncertain benefits. In the sections that follow, clinical management of CF is discussed. Validating new therapies for early intervention, in part by validating new measures of lung health to assess these therapies, is but the first step on the road to further improving prognosis and quality of life for patients with CF.

As previously noted in this article, CF is a serious and lifelong condition that requires continual monitoring and management to prevent exacerbations and prolong life. The major complications of CF are pulmonary, and thus will be the focus of this article. According to the Cystic Fibrosis Foundation Clinical Practice Guidelines, the treatment goals for pulmonary disease include delaying the progression of lung disease and preserving lung function, proactive testing to identify organisms that cause infection, reducing acute respiratory exacerbations that lead to hospitalizations, and preventing complications. Because infection with associated inflammation occurs as early as the first weeks of infancy in patients with CF and appears to be the result of changes to the airways and adjacent lung tissue resulting in chronic obstruction and abnormal respiratory secretions, chronic therapies target infection, inflammation, and achievement of airway clearance as early in life as possible.

Overzealous host inflammatory responses (particularly excess neutrophil recruitment and activation in the airways) to infection with organisms (especially Staphylococcus aureus, nontypeable Haemophilus influenzae, and Pseudomonas aeruginosa) are thought to lead to the clinical symptoms of CF, such as cough induced by retention of thick purulent sputum, reduced exercise capacity, and shortness of breath.
Thus, physical therapy techniques aimed at airway clearance and physical training may be used as non-pharmacologic treatments for patients with CF. These are designed to enhance mucociliary clearance by dislodging mucus plugs from airways followed by cough clearance, to ease expectoration by increasing airway caliber and reducing mucus viscosity with accompanying bronchodilator and mucolytic therapy, and to improve exercise capacity, muscle strength, and reduce breathlessness. Bradley et al summarized the findings of 5 Cochrane systematic reviews of the evidence for the physical therapies commonly used for patients with CF. The airway clearance techniques evaluated included chest/conventional physiotherapy (traditional postural drainage, percussion, and vibration to loosen and encourage expectoration of secretions), positive expiratory pressure (PEP; using a device that makes the patient exhale against pressure), noninvasive ventilation (NIV; using a device connected to a generator that provides a set positive pressure on inspiration and expiration), and physical training (aerobic and nonaerobic). There appears to be evidence of at least a short-term benefit of airway clearance for patients with CF in that it increases mucus transport or secretion expectoration. In the analysis, compared to other methods, conventional chest physiotherapy was at least as effective, but patients tended to prefer techniques that promoted more independence, such as PEP, which was also found to be effective based on measures such as spirometry, plethysmography, amounts of mucus expectorated, blood oxygen levels, and/or numbers of respiratory exacerbations. However, NIV was found to be most effective, especially in patients with more severe disease. Both physical training and these various airway clearance techniques were found to be more effective than no airway clearance or physical training, but with neither one seemingly better than the other and with no long-term evidence of efficacy for either category.

Bradley et al point out that airway clearance should remain a component of the management plan for patients with CF, and that to improve adherence, techniques that foster self-care and independence are preferred when the patient is physically capable of doing this for himself or herself. In this regard, it is notable that in the United States, use of percussive “Vest” devices that allow patient independence and flexibility of duration and intensity of treatment have become extremely popular. With regard to physical training, both aerobic and anaerobic components should probably be included, with monitoring for adverse events, such as dyspnea, bronchospasm, and fatigue.

**MUCOLYTIC AND HYDRATING AGENTS: DORNASE ALPHA AND INHALED HYPERTONIC SALINE**

The breakdown of neutrophils results in the release of DNA, which in turn increases the viscosity of airway secretions in patients with CF. Dornase alpha is a recombinant human DNase that digests extracellular (but not intracellular) DNA and thus helps to alleviate this condition because the high viscosity of CF sputum is due in part to very high DNA content derived primarily from defunct host neutrophils. Hodson et al analyzed data from the Epidemiologic Registry of Cystic Fibrosis that had been compiled for 13,684 patients over 2.3 years. The authors found that dornase alpha was beneficial in terms of improving FEV\textsubscript{1}, in addition to reducing the occurrence of exacerbations. Specifically, untreated patients showed a decline in FEV\textsubscript{1} over this period, whereas treated patients were stable, and there were 25 fewer exacerbations requiring intravenous antibiotics per 100 treated patients per year. The authors stated that these findings supported what had been found in clinical practice, and that younger patients (6–13 years old) benefit most from this therapy.

Another therapy aimed at improving the chronic symptoms and pathophysiology of CF is inhaled hypertonic saline. The mechanism of action of hypertonic saline is controversial, as the hypothesis that it improves airway surface fluid volume has been questioned. It is also noted that sputum becomes less viscous when hypertonic saline is added to it because the saline separates DNA from its associated mucoproteins, which can then undergo natural proteolytic enzyme digestion. In addition, hypertonic saline induces cough that can also assist in eliminating mucus and facilitate sputum production (incidentally making it available as a method to obtain sputum for microbiological analysis). Studies have demonstrated that chronic use of 7% hypertonic saline inhalation 2 to 4 times a day improves lung function (as measured by FEV\textsubscript{1}) and reduces exacerbations, subsequently improving school and work attendance and reducing the need for antibiotics. The main difficulty with this therapy is its tolerability because it has been noted that some patients experience bronchoconstriction as a result of inhaling hypertonic saline, and complain of cough, chest tight-
ness, and pharyngitis. Thus, it is recommended that patients be premedicated with a bronchodilator before receiving hypertonic saline. This is a low-cost therapy with benefits that outweigh the adverse effects, at least for patients older than age 6 years. Use in younger patients is currently being studied.

**Antibiotic Therapy**

Patients with CF are prone to early and persistent endobronchial infection with specific types of bacteria. Classically, pulmonary parenchymal involvement (pneumonia) and systemic invasion (sepsis) rarely accompany these chronic airways infections. Early infections are most frequently caused by *S. aureus* and *H. influenzae* (nontypeable species not responsive to childhood immunization with *H. influenzae* type B vaccines), followed by *P. aeruginosa*, and less commonly, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, nontuberculous mycobacteria (particularly *Mycobacterium avium intracellulare* and *Mycobacterium abscessus*), and Aspergillus fungi (especially *Aspergillus fumigatus*). *P. aeruginosa* is the most significant pathogen in CF—up to 80% of patients are eventually infected, and its presence is associated with accelerated decline in lung function and a poorer prognosis. It is challenging to isolate pathogens and then determine antibiotic susceptibilities for patients with CF due to polymicrobial infections. Microbiology laboratories familiar with the use of specialized media for the isolation and identification of CF pathogens should be used.

Generally, clinicians first attempt to use oropharyngeal cultures in nonexpectorating patients, but sometimes must resort to bronchoalveolar lavage. Induction of sputum with hypertonic saline inhalation is increasingly used for detection of CF pathogens in nonexpectorating patients older than age 6 to 7 years. The Cystic Fibrosis Foundation recommends sputum culture and sensitivity testing every 3 months or sooner as needed. In other countries, serologic testing is also sometimes used to diagnose or follow *P. aeruginosa* infection, but these tests are not widely available in the United States outside of research facilities and remain of uncertain clinical utility.

Clinicians may prescribe antibiotics under a variety of clinical scenarios for patients with CF. Early in life they may be prescribed prophylactically to prevent chronic colonization, although this approach has not been validated by clinical trials. Antipseudomonal antibiotics may be used to eradicate early *P. aeruginosa* infection when detected in routine surveillance or illness episode respiratory cultures, an approach shown effective by many small studies and trials. However, the optimal antibiotic regime for *P. aeruginosa* eradication is unknown, and the long-term clinical benefit unproven; consequently, several large prospective trials addressing these questions are currently in progress in the United States and Europe. Antipseudomonal antibiotics may also be prescribed as a chronic maintenance (“suppressive”) therapy in an effort to slow disease progression and prevent exacerbations in patients with chronic, ineradicable *P. aeruginosa* infection. Antibiotics are utilized when patients experience serious microbial infections manifested by acute pulmonary exacerbations often requiring intravenous antibiotics and hospitalization to return to pre-exacerbation status. As with any use of antibiotics, prescription of antibiotics for patients with CF should be based on identification of the offending pathogen(s), susceptibility testing, and careful consideration of the specific regimen (including its length) to avoid unnecessary use.

In general, patients with CF may receive early antibiotic therapy aimed at preventing the onset of chronic *P. aeruginosa*. By contrast, the advisability of prescribing prophylactic or maintenance antibiotics active against *S. aureus* or *H. influenzae* is controversial. Although antistaphylococcal prophylaxis remains popular in the United Kingdom, most clinicians in the United States do not choose this option, after the largest multicenter controlled trial showed that reduced *S. aureus*-positive cultures were accompanied by increased *P. aeruginosa*-positive cultures and no clinical benefit. Antibacterial antibiotic maintenance therapy may be administered via inhalation—an option that is more appealing than the intravenous route. However, a variety of obstacles may be encountered via conventional jet nebulizer delivery systems, including induction of bronchospasm for irritating hypertonic solutions or difficulties with solubility of medications.

The main consideration with aerosolized drugs is that most of the nominal dose of the drug is either retained in the nebulizer, lost to the surrounding air, or deposited on the nasal or oropharyngeal mucosa and then swallowed—with only 1% to 10% being delivered to the respiratory tract by conventional jet nebulizer systems. Newer piezoelectric pore-based devices, such as the eFlow (PARI Pharma, Munich, Germany), may deliver up to 40% to 50% of the loaded dose to the air-
ways. Effective aerosol antibiotic treatment must deliver adequate amounts of the drug exceeding the target organism’s minimal inhibitory concentration (MIC) to the site of infection. High-dose inhaled tobramycin aerosol solution (300 mg/5 mL unit dose given twice daily) was the first US Food and Drug Administration-approved inhalational antibiotic for CF in patients 6 years old or older with chronic *P. aeruginosa* infection, and has been demonstrated to reduce bacterial density in amounts equal to or in excess of that achieved by parenteral therapy. Following the methodology of the pivotal clinical trials, it is usually given on alternate months and, in some patients, may be rotated with inhaled colistin and/or oral ciprofloxacin. Inhaled tobramycin improves lung function and reduces the numbers of pulmonary exacerbations requiring intravenous antibiotics (by 36% in 1 study).

The use of macrolide antibiotics (in particular azithromycin) has also generated great interest in terms of chronic therapy for *P. aeruginosa*-infected patients with CF and perhaps other subgroups. Although traditionally this class of drugs does not demonstrate enough activity against acute pseudomonal infections (MICs are not high enough), a number of studies have shown that azithromycin may improve lung function (FEV1) and decrease the frequency of exacerbations in *P. aeruginosa*-infected patients with CF. A variety of potential mechanisms have been proposed, such as a delayed bactericidal effect, interference with the organism’s quorum sensing capabilities, inhibition of protein synthesis, blocking of its ability to adhere to mucosa, or to be motile via flagella, or to maintain the protective biofilm state. For the host, neutrophil recruitment and expression of various inflammatory cytokines may be reduced by macrolides. Thus, macrolides (especially azithromycin) may also prove useful for chronic CF therapy.

When patients experience an exacerbation, generally marked by increased cough, sputum production, shortness of breath and/or spirometric evidence of worsening airflow obstruction, reduced exercise tolerance, anorexia, weight loss, and malaise (Table), they are generally hospitalized initially. Then, once stabilized, patients may be able to continue on parenteral antibiotics from home (if the proper resources are available) for a total period of 14 to 21 days. Exacerbations generally require 2 antibiotics (for *P. aeruginosa*, an antipseudomonal beta lactam and an aminoglycoside to achieve synergistic antimicrobial activity, along with intensified airway clearance and bronchodilators, nutritional support, and management of any comorbid conditions (eg, CF-related diabetes) or complications (eg, hemoptysis).2,43

**ANTI-INFLAMMATORY THERAPIES: CORTICOSTEROIDS, IBUPROFEN, AND OTHERS**

Although the exact underlying pathophysiologic mechanisms are still to be elucidated, endobronchial infection in CF is associated with intense and excessive inflammation that appears to persist after resolution of the acute infection. When infection is present, neutrophils increase as part of the body’s normal immune response; however, in patients with CF, apoptosis seems to be delayed, causing neutrophil levels to remain high. As these short-lived cells are activated and later as they break down, they release damaging intracellular contents, such as oxidants and proteases, which increase sputum viscosity and also are harmful to respiratory tissues. For example, neutrophil elastase digests elastin and other airway wall proteins, impedes cilia and phagocytosis, increases mucus, and promotes the generation of neutrophil chemoattractants such as interleukin-8, leukotriene B4, complement products, and leukocytosis.

**Table. Criteria for Pulmonary Exacerbations**

<table>
<thead>
<tr>
<th>Symptoms</th>
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<tr>
<td>• Increased frequency, duration, and intensity of cough</td>
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<tr>
<td>• Increased or new onset of sputum production</td>
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<tr>
<td>• Change in sputum space</td>
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<tr>
<td>• New onset or increased hemoptysis</td>
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<tr>
<td>• Increased shortness of breath and decreased exercise tolerance</td>
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<tr>
<td>• Decrease in overall well-being—increased fatigue, weakness, fever, poor appetite</td>
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<td>Physical signs</td>
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<tr>
<td>• Increased work of breathing—intercostal retractions and use of accessory muscles</td>
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<tr>
<td>• Increased respiratory rate</td>
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<tr>
<td>• New-onset or increased crackles on chest examination</td>
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<tr>
<td>• Increased air trapping</td>
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<tr>
<td>• Fever</td>
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<tr>
<td>• Weight loss</td>
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<tr>
<td>Laboratory findings</td>
</tr>
<tr>
<td>• Decrease in FEV1 of 10% or greater compared with best value in previous 6 months</td>
</tr>
<tr>
<td>• Increased air trapping and/or new infiltrate on chest radiograph</td>
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<tr>
<td>• Decreased SaO2</td>
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tumor necrosis factor alpha, and other proinflammatory cytokines, fueling a vicious cycle of infection and inflammation.\(^{44}\) Together, these circumstances result in progressive and irreversible airway obstruction, bronchiectasis, respiratory failure, and death.

Many think that treating the inflammatory response early in life is most effective—before such a cycle becomes entrenched and irreversible structural damage, such as bronchiectasis and fibrosis, occurs. The most commonly utilized anti-inflammatory therapies in CF include systemic and inhaled corticosteroids and ibuprofen. Anti-inflammatory effects of steroids include reduced mucus and edema, inhibition of chemotaxis, adhesion, and activation of leukocytes, and reduced synthesis or action of multiple inflammatory cytokines and mediators.\(^{44}\) A Cochrane review of systemic steroid use in CF concluded that oral steroids appeared to slow disease progression, but there were serious adverse effects, such as growth retardation, hyperglycemia, and the development of cataracts.\(^{45}\) Therefore, such adverse effects have sharply limited long-term use of systemic glucocorticosteroids to treat CF. By comparison, the result of a Cochrane analysis of inhaled steroid use was inconclusive with regard to benefit, and a recent multicenter trial in the United Kingdom demonstrated that inhaled corticosteroids could be withdrawn from most patients with CF previously treated without adverse consequences.\(^{46,47}\)

Ibuprofen, a nonsteroidal anti-inflammatory alternative, has also been studied. Interestingly, although high-dose ibuprofen (peak plasma concentrations of 50–100 µg/mL) has demonstrated significant usefulness in improving outcomes for patients with CF (significant reduction in the rate of FEV\(_1\) decline, fewer hospitalizations, and improved nutritional status), its use has not become widespread—perhaps due to concerns about adverse effects, including gastrointestinal hemorrhage and the need to obtain a pharmacokinetic study to initiate therapeutic dosing.\(^{48}\) Yet, its benefits outweigh its risks and inconveniences, and ibuprofen should be considered routine therapy for young patients with mild disease.\(^{49}\) Other anti-inflammatory therapies being studied include anti-inflammatory or regulatory cytokines and modulators of pro-inflammatory intracellular signaling, antioxidants, antiproteases, certain antibiotics (azithromycin), dornase alpha (which has anti-inflammatory effects independent of its mucolytic activity), ion transport regulators, and gene replacement therapy. Whatever the agent, several approaches working together may be most effective in fighting the enhanced inflammatory response of CF (eg, antibiotics to reduce the presence of bacteria, antiproteases to decrease the damaging products of inflammation, and dornase alpha to clear the airway).

### Nutritional Therapies

Data from the Cystic Fibrosis Foundation Patient Registry, a database that tracks the health of more than 23 000 people who receive care at CF Foundation-accredited care centers, reveal that body mass index (BMI) percentiles in children and BMI values in adults directly correlate with pulmonary function—both are strong predictors of patient status. Furthermore, malnutrition (inadequate weight gain and linear growth retardation) is a major clinical issue for patients with CF, affecting more than 22% of children who fall below the 10th percentile for weight (14% fall below the fifth percentile for height). This concern continues into adulthood. Nearly 61% of adults have BMIs below the recommended level, and 38.5% have nutritional failure (BMI <19 kg/m\(^2\)).\(^{49}\) Morbidity and nutritional status are linked, particularly with respect to the development of pulmonary disease. It has also been observed that patients with CF who have pancreatic insufficiency have more severe nutritional and pulmonary involvement.\(^{50,51}\) Studies indicate that in children the lack of adequate growth also affects growth and preservation of lung tissue, the presence of malnutrition precedes the development of lung dysfunction, maintaining good nutrition and a stable weight also maintains FEV\(_1\), and improving weight and nutritional status improves FEV\(_1\).\(^{51-55}\)

Overall, chronic infection and inflammation with poor appetite and high energy demands placed upon the body from the increased work of breathing, combined with chronic malabsorption that results from pancreatic insufficiency in most patients with CF, all contribute to the chronic malnutrition seen in many patients with CF. For some patients, other comorbidities also play a key role, such as CF-related diabetes mellitus (Figure).\(^{51}\) To compensate for these factors, it is recommended that patients with CF aim to achieve 120% to 150% of the typical recommended daily allowance for various nutrients in their diets—a scenario that is difficult for many patients with CF to achieve.\(^{54,55}\) However, a variety of nutritional interventions may be utilized to assist in the process. A meta-analysis of behavioral techniques, oral supplements, enteral supplements, and parenteral nutrition was conducted and, interestingly, all of the inter-
ventions were found to be equally effective in achieving weight gain to the same degree. However, it is important to implement aggressive nutritional therapies in the earliest stages of the disease to have the most benefit because it has been noted that malnutrition impacts lung deterioration, which in turn impacts overall morbidity and mortality. Specific therapies should be individualized for each patient depending on their particular caloric needs, pancreatic insufficiencies, gastrointestinal comorbidities, the possible presence of diabetes, and/or behavioral issues.

**PUTTING IT ALL TOGETHER: IMPROVING QUALITY OF LIFE**

Today, approximately 30,000 Americans are living with CF, and the mean life expectancy has increased from less than 1 year 40 years ago when the disease was first described to 36.9 years today, with more than 45% of patients in the United States being 18 years of age or older. In exploring the factors that influence the outcome of patients with CF, it appears that attendance in a specialized care facility that follows guidelines developed by the Cystic Fibrosis Foundation is beneficial. Such a facility generally includes a multidisciplinary team, including specialized physicians (pediatricians for children and internists for adults, most commonly pulmonologists), nurses, physical and respiratory therapists, nutritionists, social workers, and often gastroenterologists and endocrinologists. The Cystic Fibrosis Foundation recommends at least 4 visits annually, including spirometry every 6 months and respiratory tract microbial cultures every 3 months.

Examining data from the Epidemiologic Study of Cystic Fibrosis—a multicenter longitudinal observational study that collects detailed clinical, therapeutic, microbiological, and lung function data from more than 25,000 patients enrolled since 1993—it has been determined that sites that obtained spirometry, microbiologic cultures, and treated aggressively with intravenous (IV) antibiotics (ie, more frequently and for longer durations) had the best outcomes in terms of FEV₁ values. In addition, at these centers, more pediatric and adult patients received anti-inflammatory drugs (inhaled cromolyn or nedocromil and oral steroids), and more adults received bronchodilators, dornase alpha, and inhaled steroids. Data collected by Padman et al also noted that infants at CF care sites whose children demonstrated superior average lung function at ages 6 to 12 years were more likely to have been diagnosed by family history or newborn screening rather than by symptoms. These children were diagnosed earlier, and also had more office and sick visits, more respiratory tract cultures, more frequent use of IV antibiotics, steroids, mast stabilizers, supplemental oxygen, and mucolytics. The authors’ analysis suggests that because nutritional deficits may be detected before 2 months of age, and because malnutrition can affect lung function, pulmonary outcomes may be improved via interventions during the first 3 years of life. Also, more frequent respiratory cultures might lead to earlier detection and treatment of *P. aeruginosa*—a serious cause of pulmonary dysfunction. Thus, it seems prudent to implement newborn screening to assure capture of these infants as early on as possible, and then to follow the patients closely with respiratory cultures and assessment of lung health, to utilize infection control measures, and to employ early treatment of infections and malnutrition.

**THE FUTURE FOR PATIENTS WITH CYSTIC FIBROSIS**

**GENE AND CELL-BASED THERAPIES**

Clinicians and scientists have made great strides in the diagnosis and management of CF—markedly extending longevity and reducing morbidity; however, a cure remains elusive. One promising area for
research involves gene therapy. In 1989, the CFTR gene was sequenced and cloned. This was followed by the successful transfer of the gene to CFTR-deficient cultured cells in which the cyclic-AMP-activated chloride channel was produced. Early human trials showed some promise coincided with increased societal and government concern over possible adverse effects for gene therapy in general, and this slowed progress. More importantly, researchers discovered problems of vector limitations (toxicity or inefficacy) and barriers faced by the gene transfer vectors once in the airways, including extracellular barriers secondary to inflammatory responses such as mucus and immune surveillance aimed at preventing delivery of the genetic material; within the target cell, duration of transgene expression is an issue. Scientists have novel ideas regarding how to overcome these challenges, such as more efficient nonviral vectors and “stealth” viruses that can be re-administered, improved delivery systems, and new approaches to prolong transgene expression by means of alternative promoters or integrating vectors. It is also entirely possible that advances in stem cell therapy may eventually supersede gene therapy.

**Pharmacologic Advances**

Pharmacologic approaches to treatment of CF are focusing on a number of therapeutic options. These include correcting defective CFTR or bypassing it entirely with activation of alternate ion channels, mucolytic agents, anti-inflammatory agents, and finding new methods of treating P. aeruginosa, such as active or passive immunization against this organism. Lung transplantation is a treatment of last resort for patients with CF; despite a new allocation system based primarily on medical need, shortage of donor lungs remains a critical limitation. Chronic rejection continues to bedevil efforts to make lung transplantation as successful an option for end-stage CF as solid organ transplantation is for diseases of the kidney, heart, or liver.

Difficulties encountered in drug development include the global challenges faced by all new drugs, such as the tremendous time and expenditures involved in launching a new pharmaceutical and specific issues for the CF population, including gaining informed consent, cooperation, and evaluation of efficacy within the context of the unique behavior of the disease in infants and children.

**Conclusions**

Although primarily pulmonary in its complications, CF is a multisystem disorder caused by a genetic defect or defects in the CFTR gene that interferes with chloride transport and affects many other cell functions. It has only been in the past 25 years that researchers have been able to understand the genetics, pathophysiology, and clinical manifestations of this disease. As a result, we have seen a dramatic increase in life expectancy. This has been accompanied by new methods to screen for and diagnose CF early in life—often before symptoms become evident and infection and inflammation have taken hold. Early diagnosis has led to preemptive management, especially in the areas of nutritional and anti-infective therapies. Care at accredited CF centers takes a multisystem and multidisciplinary approach, with regular visits to a variety of specialists in the areas of medicine, nursing, nutrition, physical therapy, and social work. This, and increasing evidence-driven standardization of care, has resulted in better clinical outcomes for patients—a goal that we must continue to strive for and attain.

**References**
