The Clinical Approach to Lung Disease in Patients with Cystic Fibrosis

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ABSTRACT

There is strong evidence that early, aggressive therapy of lung disease leads to improved quality and quantity of life for patients with cystic fibrosis (CF). The treatment of pulmonary disease associated with CF is multifactorial, encompassing prophylaxis, aggressive treatment of infection, use of antiinflammatory agents, and treatment of severe complications. Chest physiotherapy on a regular basis, perhaps using new modalities that allow patient autonomy, is also crucial. This review covers the pathogenesis of CF lung disease and current approaches to therapy, highlighting guidelines recently published by the Cystic Fibrosis Foundation. Clinicians caring for patients with CF should maximize current therapies with the goal of preserving lung function until the time a more definitive curative or controller medication is developed. Empowering patients in the process of providing their own care is a key to achieving this goal.

KEYWORDS: Cystic fibrosis, inflammation, antibiotic therapy, treatment, prophylaxis, pathogenesis

Cystic fibrosis (CF) is the most common lethal heritable disorder in Caucasians. Birth prevalence generally runs around one in 3000 for North American and western European populations but ranges worldwide from one in 900 in regions of Quebec, Canada, to one in 350,000 in Japan.[1] For those persons with CF, pulmonary issues account for the majority of the morbidity and almost all of the mortality.

PATHOGENESIS OF CF LUNG DISEASE

There are several hypotheses regarding the onset of CF lung disease, including dehydration of airway surface liquid, inadequate clearance of bacteria by airway innate immune mechanisms, and a hyperinflammatory response to infection.[1] Polymicrobial infection is common even within the first year of life.[2] Infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus* leads to increased airway inflammation.[3] Neutrophils are recruited to the infected airways; they contribute to the injury of the airways but are also disabled by bacterial exotoxins,[4,5] and extracellular DNA derived from damaged neutrophils contributes to the tenacity of the phlegm that obstructs the airways. Thus the pulmonary disease is a consequence of the vicious cycle of obstruction, infection, and inflammation (Fig. 1).

Studies using infant pulmonary function tests (PFTs), chest x-rays, computed tomography (CT), and bronchoalveolar lavage demonstrate that CF lung disease begins early, often in the first few months of life, prior to obvious symptoms.[6–9] With the advent of newborn screening for CF, it is now commonplace for infants with CF to be diagnosed before they have developed overt symptoms. This offers physicians the

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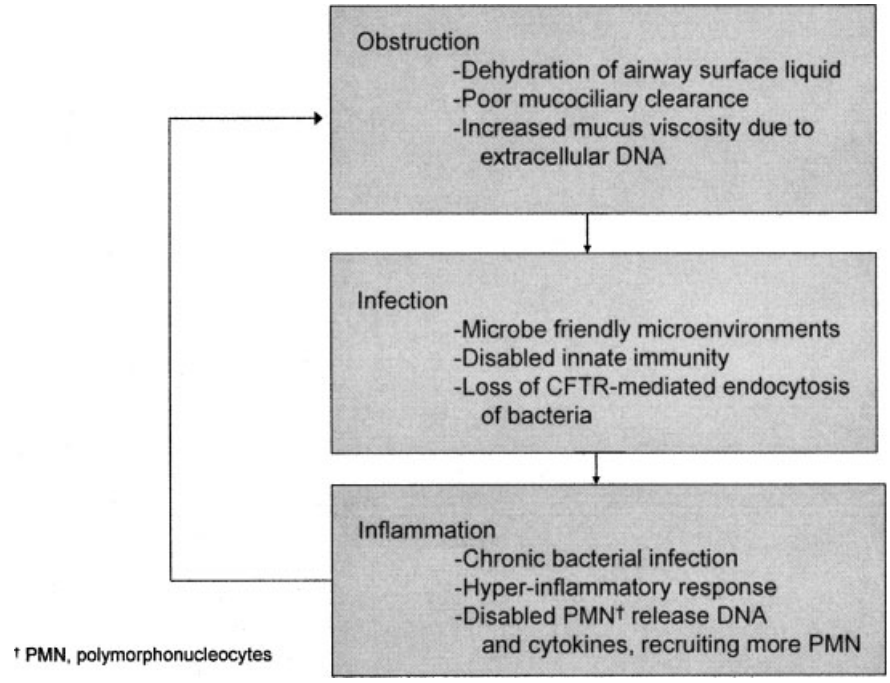

Figure 1 Vicious cycle of obstruction–infection–inflammation that leads to respiratory failure in cystic fibrosis.

opportunity to implement treatment early in the course of the cycle of inflammation, obstruction, and infection before irreversible tissue damage has occurred. Unfortunately, there are few published studies regarding treatment of children less than 6 years of age. However, there are two statements that can be made without doubt: (1) good nutrition early in life is associated with better lung function at school age,[10,11] and (2) exposure to environmental tobacco smoke is harmful for all children, especially those with CF.[12]

The benefit of an aggressive approach to CF care has been demonstrated by two epidemiological studies showing an association between higher PFT results, more frequent clinic visits, more frequent sputum cultures, and greater use of antibiotics.[11,13] The value of prescribing more medications and more therapies for patients must be balanced against the risk of toxicity, unintended consequences (e.g., selection of deleterious infectious pathogens), and the burden of care (e.g., time, cost). Table 1 highlights recommended chronic therapies for patients with CF. Not all therapies will be appropriate for all patients.

TREATMENT OF OBSTRUCTION

Although there is not great evidence of efficacy, airway clearance techniques are universally recommended for older children and adults. The U.S. Cystic Fibrosis Foundation guidelines highlight the following areas: (1) airway clearance therapy is recommended for all patients with CF, (2) no one airway clearance technique has been proven to be better than another, (3) airway clearance therapy should be based on patient preference, and (4) aerobic exercise is beneficial for overall health but does not take the place of airway clearance therapies.[14]

The selection of an airway clearance therapy is dependent upon many factors. Some therapies require patient participation and so may not be available for the very young; other therapies (e.g., percussion and postural

Table 1 Chronic Therapies for Cystic Fibrosis

Inhaled
Tobramycin solution for inhalation 300 mg twice a day, 28-day on–off cycles
Colistin 75 mg twice a day (reconstitute just prior to delivery)[a]
7% hypertonic saline, 4 mL twice a day (pretreat with albuterol)
Dornase alfa (rhDNase) 2.5 mg once a day
Albuterol MDI (meter dose inhaler) two puffs twice a day[b]
Oral
Azithromycin 500 mg Monday/Wednesday/Friday (>40 kg) 250 mg Monday/Wednesday/Friday (<40 kg)
Ibuprofen (dose adjusted based on pharmacokinetic measures[53])
Chest physiotherapy
Minimum of once a day when well
Two or three times a day when ill

[a]The Cystic Fibrosis Foundation (CFF) guidelines committee found insufficient evidence to recommend this medication[21]; however, it is used frequently in clinical care.
[b]Long-acting β-agonists (LABAs) have also been found to be efficacious for patients with CF.[21] The benefits of the use of LABAs in CF should be weighed against concerns regarding the safety of LABA use without concomitant inhaled corticosteroids in patients with asthma.[93,94]

drainage) require a partner. Because patient preference is important, it is wise to introduce patients to all available therapies so they may choose a therapy that they feel is most efficacious.[15] Although there is no evidence that any airway clearance is effective in infants, the guidelines have recommended teaching the parents how to perform percussion and postural drainage shortly after the diagnosis of CF is made.[14] Head-down positioning in this age group should be avoided due to the risk of gastroesophageal reflux and aspiration.[16] The CF center should have a strategy for introducing other forms of airway clearance as the patient ages.

Hypertonic saline has been demonstrated to improve mucociliary clearance in the laboratory setting.[17] The mechanism of action of this simple therapy is to replace the salt missing from the airway surface, presumably drawing water out of respiratory epithelial cells and rehydrating the airway periciliary layer; this lifts mucus off the epithelium, allowing more normal function of cilia and improved cough clearance.[18] Increasing concentrations of saline have been shown to improve airways clearance of labeled particles in CF patients.[19] In general, nebulization of 4 mL of 7% hypertonic saline twice daily is well tolerated, although the concentrated salt solution can precipitate coughing and bronchospasm, an effect that is somewhat ameliorated by pretreatment with a bronchodilator. Clinical trials of hypertonic saline (7%) have demonstrated modest improvement in lung function and increased time between exacerbations of pulmonary disease,[17,18,20] and it has been recommended as a chronic therapy.[21] An alternate inhaled medication with osmotic properties (i.e., mannitol) is under investigation as a possible therapy for CF.[22,23]

Airway clearance can be enhanced by the use of dornase alfa, an aerosolized enzyme that breaks down the extracellular DNA released by senescent polymorphonucleocytes, a contributing factor to the tenacity of CF sputum. Cleaving extracellular DNA into short fragments alters the properties of airway phlegm making it more readily cleared by cough and ciliary action. The benefit of dornase alfa, 2.5 mg via nebulizer daily, on lung function has been well established, and it is highly recommended for patients with moderate to severe lung disease.[4,21,24,25] There is also evidence of benefit when dornase alfa is used regularly by young patients with mild disease; there is a modest improvement in lung function as well as an increased time between respiratory tract exacerbations.[26] This drug is also recommended for use in patients who are asymptomatic or who have mild lung disease.[21]

It makes empirical sense that inhaled dornase alfa, which decreases the tenacity of airway phlegm, and hypertonic saline, which acts to rehydrate the periciliary water layer, could improve lung function if implemented early in life before infection and inflammation are well established. These agents have been shown to be safe for infants in small studies.[27,28] Whether they are efficacious or truly safe when used in large populations for prolonged periods is unknown.

TREATMENT OF INFECTION

Use of antiinfective agents is keystone to treatment of patients with CF. Infection in the airways of CF children follows a stereotypical pattern, with initial infections caused by vaginal and fecal gram-negative organisms, which are rapidly displaced by *Haemophilus influenzae* and *Staphylococcus aureus*. Approximately 18% of CF patients have methicillin-resistant *S. aureus* (MRSA) present in sputum cultures.[29] What role MRSA plays in the pathogenesis of CF lung disease is not known with certainty. One study of a large cohort of patients revealed an association between the presence of MRSA and frequent treatment with antibiotics, but there was no detectable effect on the rate of lung function decline.[30] In contrast, Dasenbrook et al[31] found a more rapid decline in lung function in individuals (ages 8 to 21 years) after they became chronically infected with MRSA compared with those patients who never grew the organism in culture.

There is a great deal more known about the adverse effects of chronic infection of the airways by *Pseudomonas*. *P. aeruginosa* is associated with a more rapid deterioration in lung function,[32] poor growth,[33] a reduced quality of life, increased hospitalization, and an increased need for antibiotic treatment.[34–36] *P. aeruginosa* has been shown to be a risk factor associated with decreased lung function in children and adolescents.[37]

Prophylactic Antibiotics

The early presence of *S. aureus* in CF airways led to studies of prophylactic treatment with oral antistaphylococcal agents. Two small studies of infants (up to 2 years) in the United Kingdom demonstrated fewer respiratory illnesses in the group receiving prophylactic flucoxacillin compared with placebo.[38,39] A longer (6 years) and larger study in the United States compared prophylactic treatment with cephalexin to placebo and found no difference between the two groups.[40] There was concern for an apparent increased incidence of *P. aeruginosa* in the group receiving daily antibiotic therapy. Given the absence of benefit and the potential for earlier acquisition of *Pseudomonas* infection, the US Cystic Fibrosis Foundation guidelines committee recommended against the use of daily, prophylactic antistaphylococcal therapy.[21]

Some have considered strategies to prevent *Pseudomonas* infection in patients with CF using both oral and inhaled antibiotics. Prophylactic antibiotics for the prevention of *Pseudomonas* infection have been sparsely

investigated.[41] Inhaled gentamicin was used in 28 patients over 3 years; none of the 12 patients who remained on this therapy for the entire study period acquired *P. aeruginosa*, whereas seven of 16 (43.8%) who discontinued the therapy developed chronic *Pseudomonas* infection, all after they stopped the antibiotic.[42] At this time it is not standard practice to offer prophylactic antibiotics to prevent *Pseudomonas* infection.

Treatment of Early *Pseudomonas* Infection

Because chronic infection with *P. aeruginosa* has been shown to be a predictor of poor outcome in CF,[32] there is great interest in early detection and eradication of this pathogen before it establishes chronic infection. Large, multinational studies are under way to assess the best way to treat first isolation of *P. aeruginosa* from CF sputum/throat culture. The treatment strategies typically include aerosolized antibiotics (tobramycin or colistin) with or without an oral antipseudomonal antibiotic.[43–45] Frequent cultures must be performed to identify early infection. In general, oropharyngeal swabs are an adequate means by which to assess *P. aeruginosa* infection, but bronchoalveolar lavage should be considered for those patients with signs or symptoms of lung disease in whom the presence of *P. aeruginosa* is suspected but not proven.

Chronic Suppressive Therapy

By 3 years of age nearly all infants have evidence of at least transient infection with *P. aeruginosa*.[46] The antiinfective agent tobramycin (given as tobramycin solution for inhalation 300 mg twice a day via nebulizer in alternating blocks of 28 days on and 28 days off) has been shown to decrease pulmonary exacerbations and improve pulmonary function test results in patients chronically infected with *P. aeruginosa*.[47] The Cystic Fibrosis Foundation (CFF) guidelines have recommended inhaled tobramycin in patients who have chronic airways infection with *P. aeruginosa*.[21] Other intravenous antibiotics have been used by the aerosolized route, but there is not enough evidence to provide a recommendation for their use.

TREATMENT OF INFLAMMATION

The inflammatory response in the airways is excessive in the CF patient, and it is the inflammation that contributes considerably to the injury of the airways. Corticosteroids have been frequently used to reduce inflammation for many other illnesses, and they have been tried in patients with CF. A large, multicenter, placebo-controlled trial of every-other-day oral prednisone showed a slower decline in lung function and fewer hospitalizations in the treated group; however, there were side effects including glucose intolerance, growth retardation, and cataracts.[48] Because systemic corticosteroids had such side effects, inhaled steroids have been tried in patients with CF. The largest and most comprehensive study of inhaled corticosteroids in patients with CF was a withdrawal study involving 171 patients.[49] Patients withdrawn from their inhaled steroids did not have more pulmonary exacerbations nor did they have a significant change in forced expiratory volume in 1 second (FEV_1). In contrast, a retrospective study of data collected prospectively for a CF registry showed an association between use of inhaled corticosteroids and a slower rate of decline of FEV_1.[50] Unfortunately, patients receiving inhaled corticosteroids also had decreased linear growth and increased insulin/hypoglycemic medications use. Therefore, neither oral nor inhaled corticosteroids are recommended for routine use in CF patients due to an unacceptable adverse event profile of oral corticosteroids and lack of proof of efficacy for the inhaled medication.[21,48,51]

Ibuprofen has direct effects on polymorphonucleocytes, including inhibition of neutrophil migration, decreased activation of the proinflammatory promoter nuclear factor-κB (NFκB), decreased production of arachidonic acid metabolites (e.g., leukotrienes and prostaglandins), and decreased activation of peroxisome proliferator activating receptors (PPARs).[52] This makes it a potentially potent agent for treatment of CF-associated airways inflammation. High-dose oral ibuprofen has been studied in two large, long-term, placebo-controlled trials.[53,54] In a single-center study, Konstan et al[53] showed a decrease in the rate of loss of lung function over 4 years in the treated group, with the largest benefit seen in younger patients (5 to 13 years). A multicenter trial in Canada enrolled patients between 6 and 18 years of age with mild lung disease.[54] In this study there was no significant impact of ibuprofen therapy on the primary end point, FEV_1, although the ibuprofen-treated group spent fewer days in the hospital (1.8 vs 4.1 days/year). In neither of these studies were significant adverse events reported; however, a retrospective report from another institution showed that many patients treated with high-dose ibuprofen chose to discontinue treatment, often due to gastrointestinal side effects.[55]

Macrolide antibiotics (e.g., azithromycin) demonstrate direct effects on bacteria, including modulation of bacterial virulence factors,[56] decrease in biofilm production, and even bactericidal effects on *P. aeruginosa* in its stationary growth phase.[57] Azithromycin also has direct effects on the host immune system, including downregulation of NFκB expression, tumor necrosis factor-α (TNFα) mRNA levels, and TNFα secretion from CF epithelial cells.[56] Macrolide antibiotics have been used for many years to treat patients with diffuse panbronchiolitis, a disease that shares many features with CF.[58] Four studies have addressed the chronic

use of macrolides in CF[59–62]; the largest of these demonstrated improvement in FEV_1 and a reduction in pulmonary exacerbations when thrice weekly azithromycin was compared with placebo in *P. aeruginosa*–positive patients.[62] The CFF guidelines committee for chronic pulmonary therapies recognized the limitations of the studies of macrolides in patients with CF but recommended its chronic use to improve lung function and decrease exacerbations.[21]

TREATMENT OF EXACERBATIONS OF PULMONARY DISEASE

The natural history of CF lung disease is one of progressive decline of lung function with episodes of acute worsening of respiratory symptoms, often referred to as pulmonary exacerbations. Unfortunately, what constitutes a pulmonary exacerbation of cystic fibrosis is not clearly defined.[63–66] Table 2[67] shows a useful mnemonic of signs and symptoms that can alert clinicians to the presence of an exacerbation. Generally, an exacerbation comes on insidiously over many weeks or months signaled by a slow decline in pulmonary function, increase in cough and sputum production, loss of appetite and weight, and changes in physical examination findings. Pulmonary exacerbations are generally thought to be due to bacterial infection of the lower airways with *P. aeruginosa*, *S. aureus*, or *H. influenzae*. Occasionally, there may be another factor that triggers the exacerbation such as an acute viral respiratory infection, a break in adherence to chronic medications, or a concomitant respiratory problem such as allergic bronchopulmonary aspergillosis, infection with an atypical mycobacterial strain, or acute mucous plugging.

Treating flares of CF lung disease aggressively improves pulmonary outcomes.[13,68,69] Therapy for a pulmonary exacerbation generally includes antibiotics (oral, inhaled, or intravenous), increased use of airway clearance techniques, and improved nutrition. Intravenous antibiotic therapy has been shown to decrease sputum *Pseudomonas* density and improve pulmonary function.[69] Combination antibiotic therapy with agents displaying different modes of action is preferred to avoid emergence of resistant strains, with therapy lasting ~14 days.[41] Because most patients with exacerbations will harbor *P. aeruginosa* in their airways, the usual in-hospital therapy is a combination of a β-lactam, which interferes with cell wall biosynthesis, and an aminoglycoside, which binds bacterial ribosome subunits and inhibits protein production[41]; however, addition or substitution of other antibiotics specific for *S. aureus*, *H. influenzae*, or MRSA may be necessary. It is important to obtain routine sputum or oropharyngeal cultures at office visits and at admission to the hospital in order that antibiotic treatment can be targeted appropriately during an exacerbation of symptoms.

Domiciliary treatment with intravenous antibiotics is feasible and may be equivalent to hospital-based therapy.[70,71] Unfortunately, home therapy can lead to more family stress and does not always produce results as good as in-hospital therapy, likely due to less complete adherence to prescribed antibiotic and chest physiotherapy.[72–74] Therefore, home therapy is recommended only if it can offer intensity of therapy similar to that provided in the hospital.

Table 2 Signs and Symptoms of an Acute Pulmonary Exacerbation in Cystic Fibrosis

C = Cough, increase or change in character
F = Fever, low-grade elevation in body temperature
P = Pulmonary function tests (decrease in forced expiratory volume in 1 second)
A = Appetite, decrease in appetite
N = Nutrition, weight loss
C = Complete blood count, increase in white blood cell count
R = Radiograph, new findings on chest radiograph
E = Examination, new crackles or wheezes
A = Activity, decrease in activity level
S = Sputum, increase in quantity or change in quality

This mnemonic is based on Dorothy Anderson's original description of cystic fibrosis as "cystic fibrosis of the pancreas."[67]

Complex Pathogens: *Burkholderia*

Bacteria in the *Burkholderia cepacia* complex (Bcc) present a particularly difficult challenge for CF therapy. These organisms are inherently resistant to antibiotic therapy, and although most Bcc infections are acquired from the environment, strict infection control policies should be enforced to obviate patient-to-patient spread. Infection with Bcc can cause acute pulmonary deterioration and even overwhelming septicemia.[75,76] In vitro multiple combination bactericidal testing may suggest a specific combination of three or more drugs that act synergistically to kill this organism.[77,78]

Complex Pathogens: *Aspergillus*

Aspergillus is a fungus that frequently colonizes diseased airways. An intense allergic response to *A. fumigatus* known as allergic bronchopulmonary aspergillosis (ABPA) is seen in 1 to 15% of CF patients.[79,80] ABPA manifests with wheezing, pulmonary infiltrates, and central bronchiectasis. Minimal diagnostic criteria for ABPA are acute or subacute clinical deterioration, total serum immunoglobulin E (IgE) concentration >500 IU/mL (1200 ng/mL), immediate cutaneous reactivity to *Aspergillus*, and one of the following: (1) precipitins to *A. fumigatus* or IgG antibody to *A. fumigatus*, or (2) abnormalities on chest radiography or CT

scan that have not cleared with standard antibiotic therapy.[79] Treatment of ABPA consists of long-term corticosteroids to ameliorate the allergic reaction. There is evidence that use of an antifungal agent may lessen *A. fumigatus* carriage and allow for the use of lower-dose, shorter-duration steroid therapy.[81]

TREATMENT OF PULMONARY COMPLICATIONS

Major pulmonary complications of CF include hemoptysis and pneumothorax. Hemoptysis can range from occasional minor blood streaking of mucus to massive bleeding. Life-threatening hemoptysis may be defined as any hemoptysis that: (1) is >100 mL in 24 hours; (2) causes abnormal gas exchange/airway obstruction; or (3) causes hemodynamic instability.[82] Medical treatment includes administration of vitamin K and fresh frozen plasma to correct coagulation defects, which can be a consequence of vitamin K malabsorption secondary to pancreatic insufficiency. Most clinicians feel that chest physiotherapy should be discontinued until bleeding has resolved for 24 to 48 hours. Because airway infection and inflammation can contribute to tissue breakdown and hemoptysis, intravenous antibiotics are commonly initiated to treat infection. Anecdotal reports have suggested that use of antifibrinolytic agents such as tranexamic acid and aminocaproic acid (Amicar, Wyeth, Madison, NJ) may be helpful.[83]

Attempts should be made to localize bleeding. Chest radiographs may demonstrate focal consolidation consistent with pulmonary hemorrhage. Bronchoscopy may be necessary to identify the site of bleeding if patient reports and radiography are not helpful. Keeping the affected lung in the dependent position helps to avoid contamination of the uninvolved lung. If bleeding persists despite medical management, selective bronchial artery embolization may be clinically indicated.[84] The radiologist must be careful to identify all feeding branches.[85] Bronchial artery embolization can be complicated by embolization of esophageal arteries, leading to postprocedure pain and swallowing dysfunction. Furthermore, care must be taken to identify spinal arteries because some may arise from the same trunk as the bronchial artery to be embolized.

Pneumothorax is a relatively frequent complication associated with CF with a lifetime incidence of ~10%.[86] The complication occurs more commonly in older patients with more severe lung disease. Patients usually present with acute onset of chest pain and dyspnea. Chest radiographs help delineate site and size, but occasionally CT of the chest is necessary to prove the diagnosis.[87] Management depends on the size of the pneumothorax and stability of the patient. Observation may be appropriate for small pneumothoraces (<20%) that are asymptomatic.[86] Chest tube placement is indicated for larger, more symptomatic pneumothoraces. Pleurodesis is necessary for persistent or recurrent pneumothorax.

The natural history of lung disease in CF leads to respiratory failure, initially presenting with abnormalities of gas exchange. Hypoxemia and hypercapnia initially become clinically significant during sleep, and become diurnal as the patient's disease progresses. Pulmonary hypertension and cor pulmonale eventuate. Treatment with supplemental oxygen improves attendance at school or work and leads to improved exercise tolerance.[79] Short-term oxygen therapy during sleep and exercise improves oxygenation but at the cost of a mild, likely clinically irrelevant, increase in pCO_2.

Patients with hypercapnic respiratory failure may benefit from ventilatory support. Patients with advanced-stage lung disease who are intubated for respiratory failure generally have unfavorable outcomes.[88] If the patient has listed for lung transplantation, there is a favorable experience with transplantation for patients on assisted ventilation.[89,90] Noninvasive positive pressure ventilation (NIPPV) is an option for the treatment of patients with moderate to severe lung disease suffering from hypoventilation.[91] NIPPV may rest the respiratory muscles by increasing the tidal volume,[92] and improves the quality of life by reducing exertional dyspnea, decreasing chest pain, and improving exercise tolerance.[91]

In conclusion, therapy for patients with CF requires attention to detail with early institution of therapies to augment airway clearance. Close monitoring for acquisition of pathogenic bacteria and aggressive therapy to try to eradicate them (particularly *P. aeruginosa*) is important. Identification and treatment of pulmonary exacerbations is a requisite. Complications such as hemoptysis and pneumothorax may occur no matter how well a patient is managed. Unfortunately, in 2009 deterioration in lung function over time is obligatory. The goal of therapy is to slow this decline and to improve the quality of the patient's life. It is hoped that therapies now on the horizon will turn CF into a chronic manageable disease.[1]

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