

AGGRESSIVE TREATMENT STRATEGIES TO
OPTIMIZE PATIENT OUTCOMES

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ABSTRACT

The significant strides made in the understanding of cystic fibrosis (CF) and the availability of multiple therapies have dramatically improved patient outcomes, but these advances have also led to new challenges, particularly in regard to treatment selection for pulmonary manifestations of CF. This article reviews current, evidence-based treatment strategies, with a focus on recommendations from recently developed CF pulmonary guidelines and emerging trends in *Pseudomonas* infections. Inhaled antimicrobials targeting *Pseudomonas aeruginosa* and agents that aid in mucociliary clearance are mainstays in the management of CF lung disease, with anti-inflammatory agents also considered important in stabilizing lung function. Also discussed are future strategies, including new classes of nebulized antibiotics, dry powder inhalation delivery systems, and use of antibiotics based on biofilm susceptibility testing.

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CHANGING THE FACE OF CYSTIC FIBROSIS

The impression of cystic fibrosis (CF) as a fatal childhood disease has changed considerably, as demonstrated by a dramatic improvement in patients' life span over the past 30 years.¹ Since this disease was first characterized in the 1940s by sweat abnormalities, there has certainly been a significant acceleration in our understanding of the various CF manifestations, as well as the availability of multiple therapies (eg, recombinant human deoxyribonuclease [DNase], nonsteroidal anti-inflammatory drugs [NSAIDs], inhaled tobramycin, azithromycin, and hypertonic saline). Coordinated care at specialized CF centers is also considered a major contributor to the improved patient outcomes that are responsible for today's median life expectancy of greater than 37 years.¹ These centers are geared to optimize education regarding the full spectrum of CF (eg, diagnosis and good nutritional habits) and to provide family centered treatment of all disease manifestations, including pancreatic dysfunction (both exocrine and endocrine), hepatobiliary disease, symptoms within the gastrointestinal tract, loss of electrolytes in sweat, and male infertility. Because lung disease accounts for nearly 85% of mortality in CF, pulmonary care is clearly a key component of the improvements made in CF outcomes and is the main focus of this discussion.

The hallmark of advanced CF lung disease is bronchiectasis, which is characterized by dilated airways filled with mucopurulent material and diffuse sacular changes, producing airflow defects with an obstructive pattern. In line with these findings, therapies that are initiated and maintained in CF pulmonary care are aimed at reducing the development of bronchiectasis and managing its symptoms. Several rational treatment strategies are in use and under

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investigation, including those that enhance clearance of secretions, reduce infection, and temper inflammation.² Antimicrobials and agents that aid in mucociliary clearance are mainstays in the management of CF lung disease, with anti-inflammatory agents also considered important in stabilizing lung function.² Agents that specifically target ion transport and restore or improve function of the CFTR protein (the underlying cause of CF) are not yet available but are the subject of considerable research interest.

TREATMENT GUIDELINES FOR CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

One of the complexities of care in CF is determining which of the multitude of available therapies is best suited for a particular patient, and in facilitating this decision, the CF Foundation has developed CF pulmonary guidelines based on systematic reviews of original research, modified systematic reviews, and existing Cochrane reviews. The following section is focused on guideline recommendations, which summarize the quality of therapeutic data and strength of treatment recommendations (see Table 1 for ranking of recommendations).³ A comprehensive reference list to accompany the recommendations can be found in the published guidelines.³

Recombinant human DNase (dornase alfa), considered one of the more established therapies in CF, was developed to improve viscoelastic properties of airway secretions and to promote mucus clearance by degrading free DNA that accumulates within CF mucus.³ Most of the studies involving dornase alfa have been conducted in pediatric and older patients (>6 years), and can be grouped into those focusing on moderate-to-severe lung disease (forced expiratory volume in 1 second [FEV₁] <69%) or those focusing on mild lung disease (FEV₁ 70%–89%).³ Based on the number of patients studied (>3000) and the presence of both short-term and long-term outcome data in individuals with moderate-to-severe lung disease, the quality of evidence pertaining to dornase alfa in this stage of CF lung disease is considered good, and the benefit is considered substantial.³ In mild disease, however, fewer studies of dornase alfa are available, with a total of approximately 500 patients and only 1 study involving a large number of patients. As

a result, the quality of evidence is rated as fair and the benefit is considered moderate.³ In general, dornase alfa has become a mainstay in the management of CF and is used in patients regardless of infection with CF pathogens, because the agent's effects on lung function are independent of patients' microbiology status. Overall, dornase alfa is well tolerated, with voice alteration being the most common adverse effect.

Because chronic colonization of the airways with *Pseudomonas aeruginosa* is associated with a more rapid decline in lung function, aerosolized antibiotics are advocated for suppression of chronic infection.³ Inhaled tobramycin is the most widely used antibiotic in CF, with the majority of associated studies conducted in patients who are chronically infected with *P aeruginosa*, the most common pathogen found in CF. In moderate-to-severe disease, the quality of evidence supporting tobramycin use is considered good due to the number of strong clinical trials involving nearly 700 patients.³ In one large phase III study of 520 patients with CF, intermittent administration of tobramycin (300 mg twice daily for alternating 28-day cycles) improved pulmonary function, decreased the density of *P aeruginosa* in sputum, and decreased the risk of hospitalization.⁴ The results showed reductions in *P aeruginosa* density regardless of resistance to tobramycin, which serves as a reminder that susceptibility testing does not always predict antimicrobial effects in patients with CF. Nebulized tobramycin is generally well tolerated, with a low risk of aminoglycoside-associated side effects (ototoxicity and nephrotoxicity) and no accumulation in the serum. Due to limitations in the number of studies, the quality of evidence for use of inhaled tobramycin in mild disease

Table 1. US Preventive Services Task Force Recommendation Grades: Ranking of Evidence

Strength of Overall Evidence of Effectiveness	Estimate of Net Benefit (Benefit Minus Harms)			
	Substantial	Moderate	Small	Zero/Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Strength of recommendations (A > B > C > D; I).

I = insufficient evidence.

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and in children younger than 6 years of age is considered fair and poor, respectively.³ Several other inhaled antibiotics (eg, colistin) have been used for the management of chronic *P aeruginosa* infection, but the data have not demonstrated clear benefits and are, therefore, not currently recommended for routine use.

Hypertonic saline inhalation is gaining popularity as a way to improve mucociliary clearance by increasing hydration of airway surface liquid.³ The studies used to support this therapy have been conducted over the last 5 years and have included approximately 500 patients, mostly older than 6 years. Overall, the quality of evidence is considered fair. Only one of the trials evaluated a large number of patients over a prolonged period of time, demonstrating improved clinical stability and modest improvements in lung function.⁵ The most common side effects associated with hypertonic saline include cough and bronchospasm, but in general, this therapy is well tolerated, especially if patients are pretreated with an inhaled bronchodilator.³

Anti-inflammatory agents are used to reduce the excessive and persistent inflammatory response seen in CF airways. This inflammatory component is thought to be a major cause of airway destruction, ultimately leading to bronchiectasis and severe obstructive airway disease.³ Thus far, studies of inhaled corticosteroids (in adult and pediatric patients with CF) have not provided clear evidence of positive effects; therefore, the quality of evidence is considered fair, but the net clinical benefit has been noted as zero in the guidelines.³ Oral corticosteroids, which have been mostly studied in pediatric patients, are associated with some improvement in lung function, but steroid-related side effects result in a net negative overall effect, limiting long-term use. Studies examining systemic corticosteroids in young adults with CF are limited; therefore, chronic use in this population is not supported.³ NSAIDs (ibuprofen) have also been evaluated in CF, and although the number of patients examined has been relatively small, the duration of studies has been quite long (up to 4 years). Oral ibuprofen has been shown to reduce the rate of FEV₁ decline, with the quality of evidence supporting this therapy considered fair and the benefit moderate, particularly in children ages 6 through 18.³

Chronic use of macrolides in CF has become a mainstay of therapy, particularly in patients who are chronically infected with *P aeruginosa*. Nearly 300 patients have been evaluated in randomized, crossover, and open-

label studies. In one of these trials of patients with CF who are chronically infected with *P aeruginosa*, azithromycin produced a rapid and clear improvement in lung function that persisted during the treatment period (168 days), but was lost approximately 1 month after treatment discontinuation. Compared to those given placebo, patients receiving azithromycin experienced nearly a 50% reduction in pulmonary exacerbations.⁶ Due to the heterogeneity of dosing regimens examined and the limited number of studies, the overall quality of evidence for chronic azithromycin use is considered fair; however, chronic use of azithromycin is recommended for patients with CF who are 6 years and older with persistence of *P aeruginosa* infection.

Because *Staphylococcus aureus* is commonly identified in the sputum of children with CF, prophylactic use of antistaphylococcal antibiotics has been examined in the pediatric CF population. One of the major concerns with this preventive approach, however, is the observation that suppression of *S aureus* growth may accelerate acquisition of *P aeruginosa* infection, which has a clear negative impact on lung function over time.³

Bronchodilators are commonly used in CF, with β_2 -adrenergic receptor agonists considered to be of

Table 2. Agents Used in CF with Classes of Recommendations

In general, these recommendations are directed to patients with CF ≥ 6 yrs of age.

- Class A Recommendations (substantial benefit)
 - Recombinant DNase
 - Inhaled tobramycin (*PsA* +)
- Class B Recommendations (moderate benefit)
 - NSAIDs (ibuprofen)
 - Macrolides (azithromycin)
 - Bronchodilators (β_2 -adrenergic receptor agonists)
 - Hypertonic saline (7%)
- Class D Recommendations (no benefit or potential harm)
 - Oral corticosteroids (6–18 yrs, chronic)
 - Inhaled corticosteroids
 - Anti-staphylococcus antibiotics (chronic)
- Class I Recommendations (insufficient information)
 - Leukotriene antagonists, oral corticosteroids (adults), anticholinergics, N-acetylcysteine, and cromolyn

CF = cystic fibrosis; DNase = deoxyribonuclease; NSAID = nonsteroidal anti-inflammatory drug; *PsA* = *Pseudomonas aeruginosa*. Reprinted with permission from Flume et al. *Am J Respir Crit Care Med*. 2007;176:957-969.³

moderate benefit in improving lung function. Other airway therapies (eg, leukotriene modifiers, sodium cromoglycate, inhaled anticholinergic agents, and N-acetylcysteine) have been examined in a limited number of studies, with data too inconclusive to provide any formal recommendations.³ A summary of all major treatments used in CF, with classes of recommendations, is included in Table 2.³

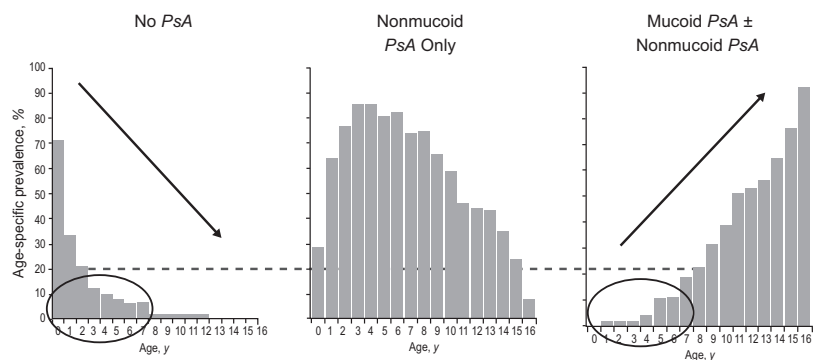
MONITORING PATHOGENS

Evidence of early lung disease in patients with CF can be seen in the form of infection and/or inflammation in bronchoalveolar lavage fluid, with most patients demonstrating colonization with at least 1 of the common pathogens (*Haemophilus influenzae*, *S aureus*, or *P aeruginosa*) by 1 year of age.⁶ *Pseudomonas* status has a tremendous impact on patient outcomes and is, therefore, a key factor to consider when choosing therapies in patients with CF, particularly when chronic management is being considered or as eradication strategies emerge. The natural course of *Pseudomonas* infection in patients with CF typically starts with transient, non-mucoid *P aeruginosa* infections several months after birth, which can occasionally self-resolve or be eradicated with aggressive antibiotic interventions. At a later point, however, *Pseudomonas* can achieve a phenotype that is difficult to eradicate with current regimens, which ultimately leads to an established chronic infection, escalating inflammation, and an accelerated loss of lung function.⁷ Once the pathogen has developed a mucoid and/or biofilm phenotype, eradication strategies are typically unsuccessful, and a clear loss of lung function (as observed by a steady decline in FEV₁) is expected.⁷ Biofilms are increasingly being recognized as contributing to CF pathogenesis, because bacteria in a biofilm state exhibit increased resistance to antibiotics and host defense factors.⁶ Communal bacteria in a biofilm can survive antibiotic concentrations as much as 1000-fold higher than the same bacteria in an individual, free-living state. As a result, clinically attainable antibiotic concentrations in the airways may be inadequate in clearing biofilm infections, thus allowing the bacteria to persist and spread.⁷

In general, a low percentage of patients are colonized with *Pseudomonas* early in life; however, as patients with CF age into adulthood, the majority of them become chronically infected. Prevention strategies for *Pseudomonas* infections are becoming common early in life, whereas management of chronic infection is frequently the focus later in life. However, as a result of more aggressive treatment of children with positive cultures for *P aeruginosa* (particularly prior to established infection), a small group of late teens and young adults that are not chronically infected is emerging. For these individuals, preventive strategies (eg, careful monitoring and aggressive strategies to manage new isolates) are critical, because the likelihood of acquiring mucoid *Pseudomonas* steadily increases throughout the teen years and into early adulthood (see Figure for age-specific prevalence of *P aeruginosa*) and remaining *P aeruginosa* negative is a strong positive predictor of better pulmonary outcomes.⁸

In addressing management of early *Pseudomonas* infection, one large ongoing trial (EPIC or Early *Pseudomonas* Infection Control study) is comparing a combination of nebulized tobramycin and oral ciprofloxacin with nebulized tobramycin alone in approximately 300 patients with CF aged 1 to 12.⁹ Within each of the arms, patients can be stratified into

Figure. Age-Specific Prevalence of *Pseudomonas aeruginosa* from Birth to Age 16



The arrows emphasize the change in PsA detection by age, and the circles include the age range of pediatric patients that are currently monitored aggressively for *Pseudomonas* infection. Over the coming years, this age range will continue to increase as successful PsA eradication protocols are defined and used.

PsA = *Pseudomonas aeruginosa*.

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those receiving regular treatment on a quarterly basis or those treated only after detection of new *Pseudomonas* isolates. Outcomes include proportion of recurrent *Pseudomonas*-positive cultures (at 18 months) and time to occurrence of pulmonary exacerbations. It is hoped that this study will provide CF healthcare providers clear guidance on appropriate eradication regimens that can be extended to the young adult CF population.

FUTURE STRATEGIES

With the recognition of inhaled tobramycin as a valuable tool in the treatment of CF lung infections, development of other inhaled antibiotics has emerged as a logical strategy to manage the disease.¹⁰ Antibiotic efficacy and side effects depend on the antibiotic class, the drug formulation, and the delivery system used, but in general, delivery of effective local airway drug concentrations via aerosolization decreases the risk of systemic side effects seen with long-term use of oral or intravenous antibiotics.⁹ Currently, tobramycin solution for inhalation (TSI) is the only US Food and Drug Administration-approved nebulized antibiotic for CF pulmonary infection with *P aeruginosa*, which although quite effective, has certain limitations. Because sputum inhibits the antimicrobial activity of tobramycin (due in large part to charge interactions), large doses are required to achieve bactericidal concentrations in airway secretions.¹¹ Availability of inhaled antibiotics from different classes would provide increased therapeutic options and may reduce the risk of treatment-emergent bacterial resistance that can occur with tobramycin monotherapy. One promising agent being developed for this purpose is aztreonam, a gram-negative active antibiotic in the monobactam class that is not inhibited by CF sputum and has demonstrated in vitro activity against pansensitive, multidrug-resistant and tobramycin-resistant *P aeruginosa* isolates.¹¹ Studies examining aztreonam lysine for inhalation in adolescents and adults with chronic *P aeruginosa* infection have shown a favorable safety and efficacy profile (eg, improved respiratory symptoms, pulmonary function, and clinical stability).^{11,12}

In addition to the development of new classes of nebulized antibiotics, development of novel drug delivery systems has emerged as a strategy to enhance patient adherence and subsequent outcomes. Delivery systems need to be flexible so that single devices can

deliver more than one type of treatment, possibly through the use of interchangeable components that modify the delivery system to match specific molecules.¹¹ Dry powder inhalation delivery systems, which have been viewed as an exciting alternative to nebulized medications, are being used to administer tobramycin and potentially other antibiotics.¹³ Tobramycin inhalation powder (TIP) delivers a high payload of tobramycin topically to the lungs for management of chronic *Pseudomonas* infections, and has been shown to result in faster and more efficient pulmonary delivery of tobramycin compared with TSI.¹⁴ However, TIP use has been associated with an increased rate of local respiratory tract symptoms, which might be expected with a high-concentration powder formulation.

Another area of interest is use of antibiotics based on biofilm susceptibility testing. This strategy is currently not routinely used to guide treatment of CF lung disease, but has been shown in one retrospective study to potentially have a role in the treatment of CF pulmonary exacerbations.¹⁵ When treatment response in patients with at least 1 biofilm-grown antibiotic-susceptible isolate was compared to those with none, there was a significant decrease in sputum bacterial density and length of stay, as well as a non-significant decrease in treatment failure.¹⁵ Some studies have also examined the role of synergy antibiotic testing to guide antibiotic choices, focusing on patients with CF colonized with pathogens that are resistant to multiple classes of antibiotics.¹⁶ Only one randomized trial has been performed to determine whether combination antibiotic susceptibility testing leads to improved clinical outcome in patients with CF who had acute pulmonary exacerbations. The results indicated that the approach was no more effective than treatment based on conventional culture and sensitivity testing.¹⁶

CONCLUSIONS

Advances in available pulmonary therapeutics and in the overall medical management of individuals with CF have improved patient outcomes, and have also served as a foundation for future clinical initiatives and research endeavors. For example, the emergence of a teen and young adult CF population that is not chronically infected with *Pseudomonas* would be considered a success story for modern day treatment, but would also require healthcare providers of older patients to

develop strategies for closer monitoring and treatment of new-onset *P aeruginosa* infections. Likewise, the increased life span of patients with CF has led to the need to manage new comorbidities and issues, such as infection with multidrug-resistant pathogens and diabetes. As with many other diseases, progress in CF has simultaneously improved prognosis and led to new challenges.

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