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Infections in Cystic Fibrosis

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The incidence of cystic fibrosis (CF), the most common fatal genetic disease among caucasians, is approximately 1 in 2,000 to 2,500 live births, and affected individuals have a median survival of 28.9 years.[1] The CF gene on chromosome 7 has been cloned recently,[2] and the sequence of its gene product, the cystic fibrosis transmembrane regulator (CFTR), is known. The most common mutation, ΔF508, accounts for approximately 70% of all CF mutations in North America.[2-4] CFTR is a cyclic adenosine monophosphate (cAMP)–regulated chloride channel found in the apical surfaces of secretory epithelial cells,[5] including the airway epithelium. In CF patients, the mutation results in abnormally viscous, dehydrated airway mucous causing impaired mucociliary clearance and airway obstruction.[6-8] Although airway obstruction plays a role, the precise link between the CF gene defect and ultimate colonization of the lung by microorganisms is not known. However, once airways are colonized, polymorphonuclear neutrophils migrate from the vascular space into the endobronchial space, resulting in inflammation without eradication of the infection.[9] A vicious cycle of mucus hypersecretion, airway obstruction, persistent bacterial colonization, and brisk inflammation results in lung destruction. A better understanding of the role of infection in the complex pathogenesis of CF lung disease is critical because lung disease accounts for most deaths among CF patients.[10]

Although a variety of pathogens may infect patients with CF, it is surprising that only a few are common. The purpose of this review is to characterize the common pathogens, indicate recently detected ones, and summarize contemporary approaches to managing infections in CF patients.

Staphylococcus aureus

Because of the difficulty in obtaining sputum from children younger than age 6 years and because bronchoscopy usually is required to isolate the lung pathogen,[11] the first infecting agent in CF patients is not always known. However, *Staphylococcus aureus* is characteristically the first infectious agent isolated from the sputum of CF patients.[12] Its prevalence is 31% in CF patients 6 to 10 years old, and 19% in CF patients older than age 36 years.[13] The most common capsular types found in CF patients are type 8 and type 5; untypeable strains are less common.[14] Historically, *S aureus* has been a frequent cause of death in CF patients.[15] This occurs less often now, presumably because of therapy with antistaphylococcal antibiotics.

Several properties mediate the pathogenesis of *S aureus* in CF patients. The cell wall of *S aureus* is important in allowing it to colonize CF patients and avoid phagocytosis. It can survive and grow in high NaCl concentrations, and the growth of *S aureus* is enhanced by p-hydroxyphenylacetic acid and oleic acid, both of which are elevated in CF respiratory secretions.[16] It also produces exotoxins such as the alpha and delta toxins, which cause tissue injury. Although the association is not well characterized, *S aureus* colonization in CF patients may predispose to co-infection with *Pseudomonas aeruginosa.*

The indications for treating *S aureus* are not clear because isolation from sputum may be due to either colonization or infection. Furthermore, sputum cultures may not be accurate because recovery from a sputum sample may indicate upper airway colonization. Therefore, it is not surprising that investigations of treatment show varied results. Some physicians have proposed the prophylactic use of antibiotics. However, one double-blinded, placebo-controlled study showed a decrease in morbidity from *S aureus* and *Haemophilus influenzae* with a concomitant increase in mucoid *P aeruginosa* colonization.[17] Others recommend therapy of *S aureus* with an acute pulmonary exacerbation or on isolation from a sputum sample. A current 6-year, double-blinded, placebo-controlled clinical trial of continuous cephalexin therapy may elucidate the value of early empiric antistaphylococcal therapy in young CF patients.[18]

Haemophilus influenzae

The role of *H influenzae* in CF remains unclear.[19] In addition to CF, nonencapsulated *H influenzae* also are found often in patients with other chronic pulmonary diseases, such as bronchitis and bronchiectasis. However, Rayner et al[20] found that *H influenzae* was isolated more frequently in the lower respiratory tract of CF patients than in that of asthmatics. The investigators also found that an increase in the isolation of *H influenzae* preceded exacerbations, and that colonization was reduced after antibiotic therapy. Isolation rates vary and tend to be related to culturing techniques. Previous studies detected biotype 1 most frequently,[21] although other studies have questioned this result.[20] As with the *S aureus*, primary viral infection may precede colonization by *H influenzae*. *H influenzae* may infect the upper respiratory tract before the lower tract, and *H influenzae* endotoxin may cause tissue injury and inflammatory reactions that predispose to *Pseudomonas* colonization.

Pseudomonas aeruginosa

Although CF patients are colonized initially with nonmucoid strains of *P aeruginosa*, later isolates are mucoid.[22] Appearance of

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P aeruginosa in previously undiagnosed patients should lead the physician to suspect the diagnosis of CF.[23] Colonization with *S aureus* and *H influenzae* predisposes to colonization by mucoid strains of *P aeruginosa* not found in nature or in patients with other pulmonary diseases.[22] Eighty percent of CF patients older than age 26 years are colonized chronically with mucoid *P aeruginosa*.[13]

The mucoid phenotype of *P aeruginosa* is due to the exopolysaccharide alginate. Alginate protects the organism from host defenses by preventing antibody coating and phagocytosis.[24,25] Alginate also may maintain colony formation in the airway.[26] May et al[27] have characterized the regulatory mechanisms governing alginate biosynthesis, and have identified factors in the CF lung that may participate in the transition from nonmucoid to mucoid *P aeruginosa*.

Other factors also contribute to the virulence of *P aeruginosa*. *P aeruginosa* adheres to respiratory epithelium and to mucin in the respiratory tract.[28] *P aeruginosa* produces exoproducts and proteases, which produce an inflammatory response causing destruction of the airways and decline in pulmonary function. Many strains are nontypeable secondary to a deficiency in lipopolysaccharide (LPS) sidechains, although the pathogenic significance of this finding is not clear.[29] Cystic fibrosis patients with *P aeruginosa* have elevated levels of antibodies directed against *P aeruginosa* antigens; however, the antibodies do not protect against pulmonary infection.[30]

Meconium ileus is an important predictor of early colonization with *P aeruginosa*.[31] There is, however, no correlation between genotype in CF and *P aeruginosa* colonization. Early acquisition may be due to more severe disease, earlier hospital stays, early antibiotic use, or cross-infection.[31] Antibiotic therapy does not eliminate the mucoid strains.[32] Winnie and Cowan[33] correlated an increased anti-*P aeruginosa* titer with decreased pulmonary function tests. Impaired mucociliary clearance due to chronic inflammation and airway obstruction contributes to the inability to clear *P aeruginosa*;[28] however, disseminated *P aeruginosa* infections are rare.

Several approaches to prevent chronic *P aeruginosa* colonization are being investigated. Cohorting of noninfected patients has been used in attempts to prevent primary infection.[34] Immunizations with a lipopolysaccharide vaccine and a whole cell vaccine against *P aeruginosa* have shown limited success.[35-37] More recently, investigations have focused on characterizing the potential role of defined polysaccharide vaccines, including conjugated vaccines.[38,39] In this group, certain vaccines induce antibodies and are safe. However, the efficacy of these vaccines is still under investigation.

The prevalence of chronic *P aeruginosa* colonization was reduced using a 3-week course of oral ciprofloxacin and inhaled colistin given to CF patients at the time of their first positive sputum culture for *P aeruginosa*.[40] The duration of this study was short (27 months), and more studies are needed before this approach can be recommended as part of routine CF care.

Burkholderia (Pseudomonas) cepacia

Since 1980, when Rosenstein and Hall reported a case of *B cepacia* pneumonia and septicemia in a 17-year-old CF patient,[41] *B cepacia* has emerged as an organism associated with increased morbidity and mortality in the CF population.[42-44] Isles et al[42] found that *B cepacia* colonization increased from 10% in 1971 to 18% in 1981. In Philadelphia, the rate increased from 1.3% to 6.1% from 1979 to 1983.[44] One devastating aspect of *B cepacia* is the resistance it exhibits to many antibiotics.[45] Detection of *B cepacia* by culture is difficult. Before the use of selective media, Tablan et al[45] found that only 32% of the laboratories could detect *B cepacia* in a simulated sputum sample.

Although colonization with *B cepacia* is correlated with increased morbidity and an abruptly deteriorating clinical course has been described, acquisition of *B cepacia* does not always result in a detectable decline.[43] However, host or pathogenic factors that reliably predict the clinical course have not been identified. Person-to-person transmission of *B cepacia* has been demonstrated by ribotyping.[46] *B cepacia* also can be acquired from contaminated equipment.[47] However, the marked reduction in the acquisition of *B cepacia* after cohorting of patients, that is, separating patients with culture-positive *B cepacia* from those who are culture negative, suggests that person-to-person transmission is the dominant mode in large CF centers with a high prevalence. In our experience, patients may acquire *B cepacia* and remain culture negative for up to 24 months.[48] Species-specific polymerase chain reaction (PCR) ribotyping has been proposed to overcome the limitations of culture methods.[49]

As with *P aeruginosa*, attempts at eradication of *B cepacia* usually are unsuccessful. The organism contains an inducible β-lactamase,[50] and in vitro susceptibility testing does not necessarily reflect in vivo response.[51]

Xanthomonas maltophilia

The gram-negative bacillus *Xanthomonas maltophilia* was classified initially as *P maltophilia*. However, a more detailed taxonomic analysis resulted in reclassification.[52] This organism has been associated with meningitis, pneumonia, mastoiditis, endocarditis, and urinary tract infections.

Xanthomonas is isolated increasingly from compromised hosts.[53] The organism has been described with increasing frequency in mechanically ventilated patients in the intensive care unit and in patients with previous antimicrobial therapy.[54] Several studies have shown that *X maltophilia* is isolated increasingly from CF patients.[55,56] The increased detection may be due in part to improved selective media.

The importance of *X maltophilia* as a pathogen among CF patients is not well characterized. Isolation of the organism does not confirm established infection, and these remain difficult to distinguish in CF patients. The role of *X maltophilia* is especially difficult to characterize because most patients are co-colonized with *P aeruginosa* and/or *B cepacia*. Although isolation of *X maltophilia* from the blood necessitates therapy, therapy for isolation from the sputum should be dictated by the patient's clinical course. *X maltophilia* is resistant to numerous antibiotics, including the quinolones, nalidixic acid, chloramphenicol, doxycycline, and the β-lactam antibiotics.[57-59] Isolates may be susceptible to trimethoprim-sulfamethoxazole.[60] Treatment should be based on susceptibility testing.

Other Bacteria

Other bacteria have been isolated from the sputum of CF patients. However, they less frequently cause disease than the previously discussed organisms. Enterobacteriaceae are isolated from the sputum of CF patients, and these include *Escherichia coli, Klebsiella, Proteus, Enterobacter,* and *Citrobacter.*[11] *H parainfluenzae* as well as *Streptococcus pneumoniae* also are isolated.[20,61] Previously, *Legionella pneumophilia* had been considered to cause exacerbations in CF patients, based on increasing serum antibody titers.[62] However, it was later shown that *L pneumophilia* antibodies cross-react with *Pseudomonas* antibodies.[63] Therefore, the actual incidence of *Legionella* in CF remains to be characterized.

Mycobacteria

The incidence of *Mycobacteria tuberculosis* is not increased in CF patients, compared with the normal population.[10] However, there has been increasing evidence that nontuberculous mycobacteria, including *M fortuitus, M gordonae, M chelonii, M kansaii,* and *M avium-intracellular,* may cause disease in CF patients.[64-67] An earlier study found 1.3% of the CF patients colonized with nontuberculous mycobacteria,[68] but more recent studies have demonstrated a prevalence in adult CF patients of 12.5% to 19.5%.[69,70] The higher prevalence in more recent studies may reflect better isolation methods that reduce contamination by *P aeruginosa.*[71] It is unclear if these cases represent harmless colonization or infection. In the setting of repeated isolation of atypical mycobacteria on culture, especially when accompanied by positive acid-fast bacilli smears or chest radiograph progression with infiltrates or cavities that do not improve with routine antibiotic therapy, therapy for nontuberculous mycobacteria should be considered.[72]

Fungus

Although *Candida albicans* is isolated from CF patients, it usually does not require therapy, because it rarely is considered pathologic.[73] Isolation usually is related to antibiotic or steroid use. *Aspergillus fumigatus* is another fungus isolated from CF patients. Invasive aspergillus or mycetoma is uncommon in CF, and amphotericin treatment usually is not needed.[74] However, the incidence of allergic bronchopulmonary aspergillosis (ABPA) is 5% to 15% among CF patients.[75] Criteria used to diagnose ABPA in CF patients include bronchospasm, pulmonary infiltrates, peripheral eosinophilia, elevated serum IgE, and positive skin test to *Aspergillus.* The therapy for ABPA consists of corticosteroids, bronchodilators, and postural drainage.[75]

Viruses

Viruses have been implicated in predisposing the CF respiratory tract to bacterial colonization, especially with such organisms as *S aureus, H influenzae,* and *P aeruginosa.* It has been postulated that viral damage to the respiratory epithelium facilitates adherence and penetration of the bacteria.[76] Virus also may disrupt mucociliary clearance and cause bronchoconstriction.[77,78] Viral-induced exacerbations may result in airway obstruction from vascular engorgement, cellular infiltration, and cell sloughing.[79] One study found antibodies directed against respiratory syncytial virus, influenza virus, and parainfluenza virus in the serum of CF patients.[80] Other studies have detected antibodies against adenovirus, rhinovirus, Epstein-Barr virus, and coronavirus.[81-83]

Several studies have shown respiratory deterioration in patients with viral infections.[62,81,83,84] One study found that exacerbations associated with viruses generally were indistinguishable from those in which no virus was isolated; however, exacerbations associated with influenza virus generally were more severe than those associated with other viruses or exacerbations in which viruses were not isolated.[83] Likewise, infection with respiratory syncitial virus (RSV) has been shown to cause frequent early hospitalizations for respiratory distress, be associated with increased morbidity (prolonged hospitalizations and mechanical ventilation), and result in an increased frequency of chronic respiratory symptoms and worse chest radiograph scores.[81] Although vaccines for RSV currently are not available, commonly used vaccines include the inactivated egg-grown influenza vaccine and the live attenuated measles vaccine. The influenza vaccine is given yearly as a split-viron vaccine to patients younger than age 12 years and the whole virus to patients older than age 12 years. Its efficacy is approximately 80%. The measles vaccine is given as a single initial dose at 15 months and provides durable immunity for 90% of patients; a second dose is recommended to stimulate immunity among vaccine failures.

Routine Treatment of CF Pulmonary Exacerbations

A CF pulmonary exacerbation is an acute or subacute change in pulmonary symptoms related to increased airway secretions. An exacerbation usually is characterized by several of the following findings: (1) increase in productive cough; (2) change in the volume and character of sputum; (3) dyspnea; (4) reduced exercise ability; (5) decreased activity or lack of energy; (6) increased respiratory rate; (7) new chest auscultative findings; (8) new infiltrates on chest radiograph; (9) deterioration in pulmonary function tests or oxygen saturation; and (10) decreased appetite or weight loss.[85] Although there is not a universally accepted definition of an exacerbation, most CF clinicians would begin antibiotic therapy, aggressive chest physiotherapy, nutritional support and, in selected patients, bronchodilators if five or more of the above findings were present.

For the clinician to select appropriate antimicrobial therapy, all of the significant lower respiratory tract organisms must be identified and their sensitivity patterns determined. In young CF patients, adequate lower tract sampling is difficult, and most clinicians rely on throat swabs to detect pathogens. The throat swab is performed by placing the swab against the pharynx to collect secretions. Coughing may occur, resulting in lung secretions being coughed onto the swab. Therefore, the throat swab may contain only oropharyngeal flora, or if cough occurs, a lower airway specimen may be collected. Ramsey et al[86] evaluated the predictive value of oropharyngeal cultures for identifying lower airway bacterial colonization by simultaneously performing oropharyngeal cultures and bronchoscopy. The positive predictive value of a positive oropharyngeal culture in patients who

could not cough and expectorate sputum was 83% for *P aeruginosa* and 91% for *S aureus*. Unfortunately, the sensitivity of the upper airway culture was only 46% for *P aeruginosa* and 77% for *S aureus*. Therefore, oropharyngeal cultures yielding *P aeruginosa* or *S aureus* are highly predictive of lower airway colonization, but a negative culture does not rule out the presence of these organisms. In patients with CF who can expectorate sputum, sputum samples contain the same bacterial species as simultaneously collected bronchial secretions.[87]

Because *P aeruginosa* is a frequent colonizer of the CF lung, special media are used to prevent its rapid growth from obscuring other significant co-pathogens. For the recovery of *S aureus*, the use of mannitol-salt agar is recommended. PC agar, which contains antibiotics to suppress *P aeruginosa*, is used routinely for isolating the fastidious but typically multiresistant *B cepacia*. Decontamination of sputum using sodium hydroxide and oxalic acid is recommended before obtaining cultures for mycobacteria.[71] Other pathogens may be unculturable using these techniques. For example, the role of anaerobic bacteria, viruses, fungal agents, and other fastidious bacteria in CF lung disease is characterized poorly because of the detection difficulties associated with culturing them. The development of PCR-based detection methods may enable epidemiologic studies of these potentially difficult to culture pathogens. Currently, CF sputum or throat samples are cultured on routine media (blood agar plate, chocolate agar, MacConkey agar), mannitol-salt agar, and PC agar.

Antimicrobial therapy usually is guided by the identification and sensitivity patterns of isolated bacterial pathogens. Exacerbations associated with *P aeruginosa* usually are treated with a two-drug regimen consisting of an aminoglycoside and either a third-generation cephalosporin or semisynthetic penicillin. Additional therapy may be added if coverage for *H influenzae* or *S aureus* is needed. Multiresistant *P aeruginosa* is a special problem. Often, combinations of antibiotics may be synergistic and clinically effective, despite the pathogen's being resistant to each one individually.[88]

In general, the pharmacokinetics of CF patients indicate a larger volume of distribution and an increased total body clearance of aminoglycosides and β-lactams;[89] therefore, recommended dosages of antimicrobials for CF patients reflect this difference (Table 1). Antibiotics usually are given for 2 weeks, although trials supporting this approach are lacking. Longer courses (3 or 4 weeks) may be needed for sicker patients.

The fluoroquinolones, ciprofloxacin and ofloxacin, have become important agents for the treatment of bronchopulmonary infections in CF patients for several reasons: (1) they have broad-spectrum antibacterial activity including *P aeruginosa*, *S aureus*, and *H influenzae*; (2) they can be given orally, their bioavailability being 70%; and (3) they have remarkable properties of diffusion into the pulmonary tissue and bronchial secretions.[90] The pharmacokinetics of the flouroquinolones are similar in CF and non-CF patients, and therefore dosing is similar. Adverse reactions occur in 4% to 8% of patients and are reversible when the drug is discontinued. The most common adverse reactions are gastrointestinal, skin reactions, photosensitivity, and minor central nervous system disorders. Unfortunately, monotherapy with these agents is commonly associated with the development of drug resistance by *P aeruginosa* after 3 to 4 weeks of therapy.[91,92] A gradual recovery of drug sensitivity usually occurs over several months. To reduce the risk of resistance, flouroquinolones should not be given for more than 14 days to patients with CF.[90] Furthermore, because administration of quinolones to immature animals results in lesions of joint cartilage, quinolones are relatively contraindicated in children whose growth is not completed.

Table 1. Guidelines for Commonly Used Parenteral Antibiotics for Cystic Fibrosis Pulmonary Exacerbations

Antibiotic	*Dose (mg/kg/d)*	*Doses/ Day*	*Pathogens*
Aminoglycosides			
Tobramycin*	6-12	3	PA, SA, HI
Gentamicin*	6-12	3	PA, SA, HI
Amikacin†	20-30	3	PA, SA, HI
Penicillins			
Pipericillin	300-500	4	PA, HI
Ticarcillin	300-600	4	PA, HI
Timentin	300-600	4	PA, SA, HI
Carbenicillin	500	4	PA, HI
Nafcillin	200	4	SA
Cephalosporins			
Ceftazidime	150-200	3-4	PA, HI
Cefsulodin	200	3-4	PA, HI
Cefuroxime	100-150	3	SA, HI
Other			
Imipenem/cilastin	50-100	4	PA, SA, HI
Aztreonam	150	4	PA, HI
Vancomycin‡	30-40	2	SA

NOTE. Dosages may need modification for hepatic or renal impairment.
Abbreviations: PA, *Pseudomonas aeruginosa;* SA, *Staphylococcus aureus;* HI, *Haemophilus influenzae.*
*Tobramycin and Gentamicin: adjust after 3 days: peak, 8-10 mg/L; trough, <1-2 mg/L.
†Amikacin: Adjust after 3 days: peak, 25-30 mg/L; trough, <5 mg/L.
‡Vancomycin: Adjust after 3 days: peak, 25-40 mg/L; trough, <10 mg/L.

New Therapies in Cystic Fibrosis

Traditional therapy for exacerbations has included antibiotics, physician therapy, nutritional support, and specific therapy for organ failure. Several newly accepted and investigational approaches may significantly improve the prognosis of CF.

Recombinant Human DNase

Recombinant human DNase (rh DNase) has been developed recently for use in CF patients. Sputum from CF patients contains large amounts of extracellular DNA from degenerated polymorphonuclear neutrophils, adding to the viscosity.[93] In the 1950s, bovine DNase was shown to reduce the viscosity of respiratory secretions by degrading DNA,[94] but its use was associated with severe reactions.[95] Therapeutic administration of rh DNase was made possible by the cloning of human pancreatic DNase I from a human pancreatic cDNA library.[96] Human recombinant DNase has fewer side effects,[97-99] and early phase I and phase II trials demonstrated improvement in pulmonary function tests when given by aerosolization to CF

patients. A 24-week, phase III, parallel-design, placebo-controlled, double-blind study of rh DNase therapy in 968 adults and children with CF demonstrated both safety and efficacy.[100] The administration of rh DNase at a dose of 2.5 mg daily or 2.5 mg twice daily improved the mean forced expiratory volume in 1 second (FEV_1) by 5% to 6% and reduced the age-adjusted risk of respiratory exacerbations by approximately 30%.

Aerosolized Antibiotics

Recently, aerosolized antibiotics have been used to provide direct delivery of aminoglycosides to the lower airways of CF patients. By inhalation of aerosolized antibiotics, high concentrations of antibiotics reach the site of infection with decreased risk of systemic effects because of minimal absorption.[101] Ramsey et al[99] recently compared aerosolized tobramycin to placebo and demonstrated improvements in forced vital capacity (FVC), FEV_1, and forced expiratory flow during the middle half of the forced vital capacity ($FEF_{25\%-75\%}$), as well as a decrease in the density of *P aeruginosa* in the sputum. Aerosol administration is safe as indicated by the lack of detectable ototoxicity or nephrotoxicity.[99,102]

Anti-inflammatory Agents

Chronic infection in CF results in chronic inflammation and associated lung destruction. Anti-inflammatory agents have been studied in the CF population to limit the host response. Alternate-day therapy with prednisone has been tested in several clinical trials. In 1985, Auerbach et al[103] reported encouraging results with improved respiratory status and increased patient weight. However, a subsequent study by Rosenstein and Eigan[104] reported that prednisone 2 mg/kg on alternate days was associated with cataracts, growth retardation, and glucose abnormalities.

Ibuprofen currently is being investigated as an anti-inflammatory agent that inhibits neutrophil function and has fewer side effects than corticosteroids. A placebo-controlled, double-blind study demonstrated that ibuprofen can be safely dosed in children.[105] Ibuprofen administered consistently for four years slowed the growth of lung disease without serious adverse effects in a population of CF patients aged 15 to 39 years.[106]

Immunotherapy

As noted above, active immunization of CF children has been unsuccessfully attempted to prevent acquisition of *Pseudomonas*. Antipseudomonas therapy with passive immunization also has been examined. Infusion of intravenous immunoglobulin (IVIG) into CF patients has been recently tested for efficacy in reducing *Pseudomonas* infection and acute exacerbation in a double-blind study. Transient improvement in expiratory flow measurements in the treated group was detected. However, the length of hospital stay was not shortened.[107] Further investigations of passive and active immunization are needed.

Amiloride

Amiloride, a sodium transport blocker, ameliorates the basic CF airway defect in epithelial ion transport. Preliminary studies have shown improved mucociliary clearance and pulmonary function tests.[108]

Somatic Gene Therapy

Several groups are actively investigating somatic gene therapy for CF. The current strategy is to deliver the normal gene to the epithelium of the CF airway. Several viral vectors are being investigated for their utility in disseminating the genes into the airway. Preliminary studies are underway to determine the safety and efficacy of such therapy. Gene therapy may provide a significant advancement in reducing the need for antibiotics to treat the infections of CF by locally correcting the genetic defect.

Special Problems

Antibiotic Resistance

Antibiotics may be important in extending the survival of CF patients; however, the widespread use of antibiotics has been associated with the emergence of antibiotic-resistant bacteria. Because *Pseudomonas* has emerged as the most important pathogen in CF, resistance has been extensively studied in *P aeruginosa*. Resistance to β-lactam antibiotics, aminoglycosides, and quinolones has emerged.[109,110]

It is sometimes difficult to determine the significance of antibiotic resistance. Total eradication of antibiotic-sensitive bacterial species from CF patients treated with antibiotics rarely is achieved. However, these patients experience improvement in clinical symptoms and pulmonary function. Despite reduction in the sputum concentration of sensitive species, mortality in CF frequently is secondary to respiratory decompensation and infection. Multiresistant organisms may contribute to this unfortunate scenario.[45]

Communicability of Disease

Modes of transmission of infections in CF appear to be varied. LiPuma et al[46] demonstrated person-to-person transmission of *B cepacia*, and other studies have implicated acquisition at CF summer camps. Occasional contamination of equipment also has occured.[111] Govan et al[112] examined transmission within CF social groups, and also detailed *B cepacia* contaminating environmental surfaces within their clinics. Another study examined the transmission of *P aeruginosa* among CF patients and found a high rate of acquisition among CF siblings and patients attending CF camps and clinics.[113] Based on these and other similar studies, cohorting of CF patients with multiresistant organisms now is recommended.

Infections in Cystic Fibrosis Lung Transplantation

More definitive therapy in CF includes lung transplantion. Despite antibiotic therapy, CF patients develop severe pulmonary impairment, and lung transplantion becomes a consideration. The indications for CF lung transplantation are similar to those for other diseases. Patients usually have severe hypoxemia, oxygen dependence, reduced exercise tolerance, mean FEV less than 30%, and respiratory failure. These are accompa-

nied by repeated pulmonary infections, continued weight loss despite nutritional support, psychological instability, and other irreversible organ damage.[114]

After lung transplantation, CF patients develop opportunistic infections similar to those of non-CF patients. Initial reports did not show an increased incidence of *Pseudomonas* pneumonia. However, recent reports show that *P aeruginosa* is the predominant pathogen. *B cepacia* is an important source of morbidity and mortality, especially in patients who were not colonized with *B cepacia* before transplantion.[115] Certain groups have begun an aggressive program to limit this organism after transplantion by cohorting, antibiotic prophylaxis, aggressive antibiotic therapy for infections, and sinus drainage surgery.[115] The long-term efficacy of lung transplantation for patients with CF is not yet known.

References

1. FitzSimmons SC: Cystic Fibrosis Foundation Patient Registry Annual Data Report, 1993
2. Rommens JM, Iannuzzi MC, Kerem B, et al: Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 245:1059-1064, 1989
3. Kerem B, Rommens JM, Buchanan JA, et al: Identification of the cystic fibrosis gene: Genetic analysis. Science 245:1073-1080, 1989
4. Riordan JR, Rommens JM, Kerem B, et al: Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 245:1066-1073, 1989
5. Anderson MP, Rich DP, Gregory RJ, et al: Generation of cAMP-activated chloride currents by expression of CFTR. Science 251:679-682, 1991
6. Cotton CU, Stutts MJ, Knowles MR, et al: Abnormal apical cell membrane in cystic fibrosis respiratory epithelium: An in vitro electrophysiologic analysis. J Clin Invest 79:80-85, 1987
7. Knowles MR, Stutts MJ, Spock A, et al: Abnormal ion permeation through cystic fibrosis respiratory epithelium. Science 221:1067-1070, 1983
8. Waltner WE, Boucher RC, Gatzy T, et al: Pharmacotherapy of airway disease in cystic fibrosis. Trends Pharmacol Sci 8:316-320, 1987
9. Koch C, Hoiby N: Pathogenesis of cystic fibrosis. Lancet 341:1065-1069, 1993
10. Wood RE, Boat TF, Doershuk CF: Cystic fibrosis: State of the art. Am Rev Respir Dis 113:533-578, 1976
11. Rosenfeld M, Ramsey B: Evolution of airway microbiology in the infant with cystic fibrosis: Role of nonpseudomonal and pseudomonal pathogens. Semin Respir Infect 7(3):158-167, 1992
12. Chartrand SA, Marks MI: Pulmonary infections in cystic fibrosis: Pathogenesis and therapy, in Pennington JE (ed): Respiratory Infections: Diagnosis and Management. New York, NY, Raven, 1989, pp 276-297
13. FitzSimmons SC: The changing epidemiology of cystic fibrosis. J Pediatr 122:1-9, 1993
14. Albus A, Fournier JM, Wolz C, et al: *Staphylococcus aureus* capsular types and antibody response to lung infections in patients with cystic fibrosis. J Clin Microbiol 26:2505-2509, 1988
15. Anderson DH: Therapy and prognosis of fibrocystic disease of the pancreas. Pediatrics 3:406-417, 1949
16. May JR, Roberts DE: Bronchial infection in cystic fibrosis. Lancet 1:602-603, 1969
17. Loening-Baucke VA, Mischler E, Myers MG: A placebo-controlled trial of cephalexin therapy in the ambulatory management of patients with cystic fibrosis. J Pediatr 95:630-637, 1979
18. Marks MI: Clinical significance of *Staphylococcus aureus* in cystic fibrosis. Infection 18:53-56, 1990
19. Watson KC, Kerr EJC, Baillie M: Temporal changes in biotypes of *Haemophilus influenzae* isolated from patients with cystic fibrosis. J Med Microbiol 26:129-132, 1988
20. Rayner RJ, Hiller EJ, Ispahani P, et al: *Haemophilus* infection in cystic fibrosis. Arch Dis Child 65:255-258, 1990
21. Long SS, Teter MJ, Gilligan PH: Biotype of *Haemophilus influenzae*: Correlation with virulence and ampicillin resistance. J Infect Dis 147:800-806, 1983
22. Doggett RG: Incidence of mucoid *Pseudomonas aeruginosa* from clinical sources. Appl Microbiol 18:936-937, 1969
23. Mearns MB: Natural history of pulmonary infections in cystic fibrosis, in Sturgess JM (ed): Perspectives in Cystic Fibrosis. Toronto, Canada, Canadian Cystic Fibrosis Foundation, 1980, pp 325-334
24. Govan JRW: Alginate biosynthesis and other unusual characteristics associated with the pathogenesis of *Pseudomonas aeruginosa* in cystic fibrosis, in Griffiths E, Donachie WE, Stephen J (eds): Bacterial Infections of Respiratory and Gastrointestinal Mucosae. Oxford, IRL Press, 1988, pp 67-96
25. Marrie TJ, Harding GK, Ronald AR, et al: Influence of mucoidy on antibody coating of *Pseudomonas aeruginosa*. J Infect Dis 139:357-361, 1979
26. Ramphal R, Pier GB: Role of *Pseudomonas aeruginosa* mucoid exopolysaccharide in adherence to tracheal cells. Infect Immun 47:1-4, 1985
27. May TB, Shinabarger D, Maharj R, et al: Alginate synthesis by *Pseudomonas aeruginosa*: A key pathogenic factor in chronic pulmonary infections of cystic fibrosis patients. Clin Microbiol Rev 4:191-206, 1991
28. Marshall BC, Carroll KC: Interaction between *Pseudomonas aeruginosa* and host defenses in cystic fibrosis. Semin Respir Infect 6:11-18, 1991
29. Fomsgaard A, Conrad RS, Gulanos C, et al: Comparative immunochemistry of lipopolysaccharides from typable and polyagglutinable *Pseudomonas aeriginosa* strains isolated from patients with cystic fibrosis. J Clin Microbiol 26:821-826, 1988
30. Fick RB Jr, Naegel GP, Matthay RA, et al: Cystic fibrosis *Pseudomonas* opsonins: Inhibitory nature in an *in vitro* phagocytic assay. J Clin Invest 68:899-914, 1981
31. Kerem E, Corey M, Stein R, et al: Risk factors for *Pseudomonas aeruginosa* colonization in cystic fibrosis patients. Pediatr Infect Dis J 9:494-498, 1990
32. Doring G, Hoiby N: Longitudinal study of immune response to *Pseudomonas aeruginosa* antigens in cystic fibrosis. Infect Immun 42:197-201, 1983
33. Winnie GB, Cowan RG: Respiratory tract colonization with *Pseudomonas aeruginosa* in cystic fibrosis: Correlation between anti-*Pseudomonas aeruginosa* antibody levels and pulmonary function. Pediatr Pulmonol 10:92-100, 1991
34. Hoiby N, Pedersen SS: Estimated risk of cross-infection with *Pseudomonas aeruginosa* in Danish cystic fibrosis patients. Acta Pediatr Scand 78:395-404, 1989
35. Langord D, Hiller J: Prospective, controlled study of a polyvalent *Pseudomonas* vaccine in cystic fibrosis: Three year result. Arch Dis Child 59:1131-1134, 1984
36. Miller JU, Spilsbury FF, Jones RJ, et al: A new polyvalent *Pseudomonas* vaccine. J Med Microbiol 10:19-27, 1974
37. Pennington JE, Reynolds HY, Wood RE, et al: Use of *Pseudomonas aeruginosa* vaccine in patients with acute leukemia and cystic fibrosis. Am J Med 58:629-636, 1975
38. Cryz SJ Jr, Wedgwood J, Lang AB, et al: Immunizatin of noncolonized cystic fibrosis patients against *Pseudomonas aeruginosa*. J Infect Dis 169:1159-1162, 1994
39. Pier GB, DesJardin D, Grout M, et al: Human immune response to

Pseudomonas aeruginosa mucoid exopolysaccharide (alginate) vaccine. Infect Immun 62:3972-3979, 1994

40. Valerius NH, Koch C, Hoiby N: Prevention of chronic *Pseudomonas aeruginosa* colonization in cystic fibrosis by early treatment. Lancet 338:725-726, 1991
41. Rosenstein BJ, Hall DE: Pneumonia and septicemia due to *Pseudomonas cepacia* in a patient with cystic fibrosis. Johns Hopkins Med J 147:188-189, 1980
42. Isles A, Maclusky I, Corey M, et al: *Pseudomonas cepacia* infection in cystic fibrosis: An emerging problem. J Pediatr 104:206-210, 1984
43. Lewin LO, Byard PJ, Davis PB: Effect of *Pseudomonas cepacia* colonization in survival and pulmonary function of cystic fibrosis patients. J Clin Epidemiol 43:125-131, 1990
44. Tablan OC, Chorba TL, Schidlow DV, et al: *Pseudomonas cepacia* colonization in patients with cystic fibrosis. J Pediatr 107:382-387, 1985
45. Tablan OC, Martone WJ, Doershuk CF, et al: Colonization of the respiratory tract with *Pseudomonas cepacia* in cystic fibrosis: Risk factors and outcomes. Chest 91:527-532, 1987
46. LiPuma JJ, Dasen SE, Nielson DW: Person-to-person transmission of *Pseudomonas cepacia* between patients with cystic fibrosis. Lancet 336:1094-1096, 1990
47. Smith DI, Gumery LB, Smith EG, et al: Epidemic of *Pseudomonas cepacia* in an adult cystic fibrosis unit: Evidence of person-to-person transmission. J Clin Microbiol 31:3017-3022, 1993
48. LiPuma JJ, Marks-Austin KA, Holsclaw D, et al: Inapparent, high-frequency transmission of *Pseudomonas cepacia* among cystic fibrosis patients. J Pediatr Infect Dis 13:716-719, 1994
49. Kostman JR, Edlind TD, LiPuma JJ, et al: Molecular epidemiology of *Pseudomonas cepacia* determined by polymerase chain reaction ribotyping. J Clin Microbiol 30:2084-2084, 1992
50. Heidt A, Monteil H, Richard C: O and H serotyping of *Pseudomonas cepacia*. J Clin Microbiol 18:738-740, 1983
51. Prince A: Antibiotic resistance of *Pseudomonas* species. J Pediatr 108:830-834, 1986
52. Pugliese G, Lichtenberg DA: Nosocomial bacterial pneumonia: An overview. Am J Infect Control 15:249-265, 1987
53. Villarino ME, Stevens LE, Schable B, et al: Risk factors for epidemic *Xanthomonas maltophilia* infection/colonization in intensive care unit patients. Infect Control Hosp Epidemiol 13:201-206, 1992
54. Marshall WF, Keating MR, Anhalt JP, et al: *Xanthomonas maltophilia*: An emerging nosocomial pathogen. Mayo Clin Pro 64:1097-1104, 1989
55. Klinger JD, Thomassen MJ: Occurrence and antimicrobial susceptibility of gram-negative nonfermentative bacilli in cystic fibrosis patients. Diagn Microbiol Infect Dis 3:149-158, 1985
56. Bauernfeind A, Bertele RM, Harms K, et al: Qualitative and quantitative microbiological analysis of sputa of 102 patients with cystic fibrosis. Infection 15:270-277, 1987
57. Lecso-Bornet M, Pierre J, Sarkis-Karam D, et al: Susceptibility of *Xanthomonas maltophilia* to six quinolones and study of outer membrane proteins in resistant mutants selected in vitro. Antimicrob Agents Chemother 36:669-671, 1992
58. Mett H, Rosta S, Schacher B, et al: Outer membrane permeability and beta-lactamase content in *Pseudomonas maltophilia* clinical isolates and laboratory mutants. Rev Infect Dis 10:765-769, 1988
59. Yu VL, Rumans LW, Wing EF, et al: *Pseudomonas maltophilia* causing heroin-associated infective endocarditis. Arch Intern Med 138:1667-1671, 1978
60. Morrison AJ Jr, Hoffmann KK, Wenzel RP: Associated mortality and clinical characteristics of nosocomial *Pseudomonas maltophilia* in a university hospital. J Clin Microbiol 24:52-55, 1986
61. Hoiby N, Hoff GE, Jersen K, et al: Serological types of *Diplococcus pneumoniae* isolated from the respiratory tract of children with cystic fibrosis and children with other diseases. Scand J Respir Dis 57:37-40, 1976
62. Efthimiou J, Hodson ME, Taylor P, et al: Importance of viruses and *Legionella pneumophila* in respiratory exacerbations of young adults with cystic fibrosis. Thorax 39:150-154, 1984
63. Tenover FC, Edelstein PH, Goldstein LC, et al: Comparison of cross-staining reactions by *Pseudomonas* spp. and flourescein-labeled polyclonal and monoclonal antibodies directed against Leginella pneumophilia. J Clin Microbiol 23:647-649, 1986
64. Hjelte L, Petrini B, Kallenius G, et al: Prospective study of mycobacterial infections in patients with cystic fibrosis. Thorax 45:397-400, 1990
65. Efthimiou J, Smith MJ, Hodson ME, et al: Fatal pulmonary infection with mycobacyerium fortuitum in cystic fibrosis. Br J Dis Chest 78:299-302, 1984
66. Smith MJ, Efthimiou J, Hodson ME, et al: Mycobacterial isolations in young adults with cystic fibrosis. Thorax 39:369-375, 1984
67. Boxerbaum B: Isolation of rapidly growing mycobacteria in patients with cystic fibrosis. J Pediatric 96:689-691, 1980
68. Hoiby N: Microbiology of lung infection in cystic fibrosis patients. Acta Paediatr Scand Suppl 301:33-54, 1982
69. Aitken ML, Burke W, McDonald G, et al: Nontuberculous mycobacterial disease in adult cystic fibrosis patients. Chest 103:1096-1099, 1993
70. Kilby J, Gilligan P, Yankaskas JR, et al: Nontuberculous mycobacteria in adult patients with cystic fibrosis. Chest 102:70-75, 1992
71. Whittier S, Hopfer RL, Knowles MR, et al: Improved recovery of mycobacteria from respiratory secretions of patients with cystic fibrosis. J Clin Microbiol 31:861-864, 1993
72. Kinney JS, Little BJ, Yolken RH, et al: *Mycobacterium avium* complex in a patient with cystic fibrosis: Disease vs. colonization. Pediatr Infect Dis J 8:393-396, 1989
73. Przyklenk B, Bauernfeind A, Horl G, et al: Serologic response to *Candida albicans* and *Aspergillus fumigatus* in cystic fibrosis. Infection 15:308-310, 1987
74. Mearns M, Longbottom J, Batten J: Precipitating antibodies to *Aspergillus fumigatus* in cystic fibrosis. Lancet 1:538-539, 1967
75. Knutsen A, Slavin RG: Allergic bronchopulmonary mycosis complicating cystic fibrosis. Semin Respir Infect 7:179-192, 1992
76. Petersen NT, Hoiby N, Mordhorst CH, et al: Respiratory infections in cystic fibrosis patients caused by virus, *Chlamydia* and *Mycoplasma*—Possible synergism with *Pseudomonas aeruginosa*. Acta Paediatr Scand 70(5):623-628, 1981
77. Carson J, Collier AM, Hu SS: Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N Engl J Med 312:463-468, 1985
78. Hall CB, Hall WJ, Gala CJ, et al: Long term prospective study in children after respiratory syncytial virus infection. J Pediatr 105:358-364, 1984
79. Prober CG: The impact of respiratory viral infections in patients with cystic fibrosis. Clin Rev Allergy 9:87-102, 1991
80. Wright PF, Khaw KT, Oxman MN, et al: Evaluation of the safety of amantadine-HCl and the role of respiratory viral infections in children with cystic fibrosis. J Infect Dis 134:144-149, 1976
81. Abman SH, Ogle JW, Butler-Simon N, et al: Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. J Pediatr 113:826-830, 1988
82. Winnie GB, Cowan RG: Association of Epstein-Barr virus infection and pulmonary exacerbations in patients with cystic fibrosis. Pediatr Infect Dis J 11:722-726, 1992
83. Pribble CG, Black PG, Bosso LA, et al: Clinical manifestations of exacerbations of cystic fibrosis associated with non-bacterial infections. J Pediatr 117:200-204, 1990
84. Wang EE, Prober CG, Manson B, et al: Association of respiratory

viral infections with pulmonary deterioration in patients with cystic fibrosis. N Engl J Med 311:1653-1658, 1984
85. Smith AL, Redding G, Doershuk C, et al: Sputum changes associated with therapy for endobronchial exacerbation in cystic fibrosis. J Pediatr 112:547-554, 1988
86. Ramsey BW, Wentz KR, Smith AL, et al: Predictive value of oropharyngeal cultures for identifying lower airway bacteria in cystic fibrosis patients. Am Rev Respir Dis 144:331-337, 1991
87. Iacocca VF, Sibinga M, Barbero G: Respiratory tract bacteriology in cystic fibrosis. Am J Dis Child 106:115-124, 1963
88. Saiman L, Niu WW, Heu HC, et al: Antibiotic strategies to treat multi-resistant *Pseudomonas aeruginosa*. Program and Papers of the 6th Annual North American Cystic Fibrosis Conference, Washington, DC, Cystic Fibrosis Foundation, 1992 (abstr 191)
89. de Groot R, Smith AL: Antibiotic pharmacokinetics in cystic fibrosis: Differences and clinical significance. Clin Pharmacokinet 13:228-253, 1987
90. Grenier B: Use of the quinolones in cystic fibrosis. Rev Infect Dis 11:S1245-S1252, 1989 (suppl 5)
91. Goldfarb J, Stern RC, Reed MD, et al: Ciprofloxacin monotherapy for acute pulmonary exacerbations of cystic fibrosis. Am J Med 82:174-178, 1987
92. Scully BE, Nakatomi M, Ores C, et al: Ciprofloxacin therapy in cystic fibrosis. Am J Med 82:196-200, 1987
93. Potter JL, Spector S, Matthews LW, et al: Studies in pulmonary secretions. 3. The nucleic acids in whole pulmonary secretions from patients with cystic fibrosis, bronchiectasis and laryngectomy. Am Rev Respir Dis 99:909-916, 1969
94. Elmes PC, White JC: Deoxyribonuclease in treatment of purulent bronchitis. Thorax 8:295-300, 1953
95. Raskin P: Bronchospasm after inhalation of pancreatic dornase. Am Rev Respir Dis 98:597-598, 1968
96. Shak S, Capon DJ, Hellmiss R, et al: Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 87:9188-9192, 1990
97. Aitken ML, Burke W, McDonald G, et al: Recombinant humane DNase inhalation in normal subjects and patients with cystic fibrosis: A phase I study. JAMA 267:1947-1951, 1992
98. Hubbard RC, McElvaney NG, Birrer P, et al: A preliminary study of aerosolized recombinant human deoxyribonuclease I in the treatment of cystic fibrosis. N Engl J Med 326:812-815, 1992
99. Ramsey BW, Astley SJ, Aitken MJ, et al: Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. Am Rev Respir Dis 148:145-151, 1993
100. Fuchs HJ, Borowitz DS, Christiansen DH, et al: Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 331:637-642, 1994
101. Maclusky I, Levison H, Gold R, et al: Inhaled antibiotics in cystic fibrosis: Is there a therapeutic effect? J Pediatr 108:861-865, 1986
102. Cooney GF, Lum BL, Tomaselli M, et al: Absolute bioavailability and absorption characteristics of aerosolized tobramycin in adults with cystic fibrosis. J Clin Pharmacol 34:255-259, 1994
103. Auerbach HS, Williams M, Kirkpatrick JA, et al: Alternate-day prednisone reduces morbidity and improves pulmonary function cystic fibrosis. Lancet 2:686-688, 1985
104. Rosenstein FJ, Eigen H: Risks of alternate day prednisone in patients with cystic fibrosis. Pediatrics 87:245-246, 1991
105. Konstan MW, Hoppel CL, Chai B, et al: Ibuprofen in children with cystic fibrosis: Pharmacokinetics and adverse effects. J Pediatr 118:956-964, 1991
106. Konstan MW, Byard PJ, Hoppel CL, et al: Effects of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med 332:848-854, 1995
107. Winnie GB, Cowan RG, Wade NA: Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. J Pediatr 114:309-314, 1989
108. Knowles MR, Church NL, Waltner WE, et al: A pilot study of aerosolized amiloride for treatment of lung disease in cystic fibrosis. N Engl J Med 322:1189-1194, 1990
109. Zabner R, Quinn JP: Antimicrobials in cystic fibrosis: Emergence of resistance and implications for treatment. Semin Respir Infect 7:210-217, 1992
110. McLaughlin FJ, Matthews WJ, Strieder DJ, et al: Clinical and bacteriological responses to three antibiotics regimens for acute exacerbation of cystic fibrosis: Ticarcillin-tobramycin, azlocillin-tobramycin, and azlocillin-placebo. J Infect Dis 147:559-567, 1983
111. Nelson JW, Doherty CJ, Brown PH, et al: *Pseudomonas cepacia* in patients with cystic fibrosis. Lancet 338:1525, 1991
112. Govan JRW, Brown PH, Maddison J, et al: Evidence for transmission of *Pseudomonas cepacia* by social contact in cystic fibrosis. Lancet 342:15-19, 1993
113. Tummler B, Koopmann U, Grothues D, et al: Nosocomial acquisition of *Pseudomonas aeruginosa* by cystic fibrosis patients. J Clin Microbiol 29:1265-1267, 1991
114. Shennib H, Adoumie R, Noirclerc M, et al: Current status of cystic fibrosis lung transplant. Arch Intern Med 152:1585-1588, 1992
115. Snell GI, de Hoyos A, Krajden M, et al: *Pseudomonas cepacia* in lung transplant recipients with cystic fibrosis. Chest 103:466-471, 1993