Unusual Lung Infection, Bronchiectasis, and Cystic Fibrosis

Gene G. Ryerson, MD, FCCP

Objectives:

1. To address the causes of bronchiectasis.
2. To discuss therapeutic options for the treatment of bronchiectasis.
3. To review the genetic aspects of cystic fibrosis (CF).
4. To define organ involvement in CF.
5. To consider the newer therapeutic approaches to the treatment of CF.
6. To discuss the treatment of Nocardia infection in the lung.
7. To review the chest radiographic findings of actinomycosis of the lung.

Key words: actinomycosis; bronchiectasis; cystic fibrosis; cystic fibrosis transmembrane regulator; Nocardia

Unusual Lung Infections

Nocardia

Nocardiosis refers to invasive disease caused by members of the genus Nocardia. Respiratory tract disease and extrapulmonary dissemination are the most common manifestations. Other presentations include cellulitis, lymphocutaneous syndrome, actinomycetoma, and keratitis. Nocardia organisms are aerobic, nonmobile, and nonspore-forming. In tissue specimens, the organisms reveal delicate branching filamentous forms that are Gram-positive and usually acid fast if weak decolorizing agents are used for the stains. Seven species have been associated with human disease. *Nocardia asteroids* is the most common species associated with invasive disease. *N farcinica* is less common and is associated with dissemination. A recently described species, *N pseudobrasiliensis*, is now felt to be responsible for infections previously attributed to *N brasiliensis*.

Epidemiology: Nocardia species are common natural inhabitants of the soil throughout the world. Epidemics within the hospital environment are rare and person-to-person transmission has only rarely been suggested. Although Nocardia can occur as a primary pulmonary pathogen in patients with no underlying disease, it is frequently recognized as an opportunistic disease, especially among patients with cell mediated immune deficiencies. This includes a transplantation, lymphoma, and AIDS. In HIV positive persons, nocardiosis most often presents with a CD4+ lymphocyte concentration of less than 250/μL. Nocardiosis has also been reported to be associated with pulmonary alveolar proteinosis, mycobacterial diseases, and chronic granulomatous disease.

Radiographic Manifestations: The chest radiographic patterns are variable. The most frequent manifestation is an air space pneumonia, usually homogeneous, but occasionally patchy. Nodules, either single or multiple, may be confused with metastatic carcinoma. The most common radiographic manifestation is cavitation found in both consolidations and nodules. Pleural involvement with an empyema is present in approximately one third of the cases.

Clinical Manifestations: Nocardial pneumonia is the most common respiratory tract syndrome. Although the clinical course may be acute in immunosuppressed patients, typically, the patient has a subacute presentation of several weeks of symptoms. Cough, purulent sputum, occasional blood-streaked hemoptysis, night sweats, and pleuritic pain are common symptoms. Superior vena caval syndrome, mediastinitis, and pericarditis have been reported from direct spread from the lungs. Nocardia rarely involves the chest wall. In approximately 50% of pulmonary cases, extrapulmonary dissemination occurs. In a significant number of cases of disseminated disease, the initial respiratory tract involvement does not elicit symptoms. Nocardiosis has the propensity for dissemination to the brain, but other extrapulmonary sites include the skin, bone, and muscle. In the central nervous system, Nocardia brain abscesses may be single or multiple. Nocardia is not usually recovered from the cerebrospinal fluid.

Diagnosis: In most cases of pneumonia, sputum smears are negative. Bronchoscopy may be necessary to obtain an adequate specimen for the characteristic Gram-positive filaments that may

be acid fast and often take up silver stains. Cultures for Nocardia require special handling since colonies may not appear for 2 to 4 weeks. Blood cultures require incubation aerobically for up to 4 weeks. Isolation of Nocardia from the sputum in a nonimmunosuppressed patient without radiographic abnormalities may represent colonization. However, a positive Nocardia sputum culture in an immunosuppressed patient more often indicates disease. At this time, no serologic test is available for the diagnosis of Nocardial infection.

Treatment: Sulfonamides remain the drug of choice for nocardiosis; sulfadiazine or sulfisoxazole at 6 to 8 g/d and then decrease to 4 g/d as the disease is controlled. The combination of trimethoprim and sulfamethoxazole is felt to be an equally effective alternate choice. Minocycline is an alternative choice for an oral mediation in those patients who have sulfa allergies. Intravenous regimens include amikacin, ceftriaxone, cefotaxime, ceftizoxime, and imipenem. Because of the risk of relapse, patients who have intact host defenses are generally treated from 6 to 12 months, while deficient host and those with CNS involvement are treated for 12 months.

Actinomycosis

Actinomycosis is a slowly progressive infectious disease caused by anaerobic or microaerophilic bacteria from the genus actinomyces. These organisms colonize in mouth, colon, and vagina. Infection results from mucosal disruption and can occur at any site in the body. Infection is characterized by a pyogenic response and necrosis, followed by intense fibrosis.

Epidemiology: The organisms are a normal inhabitant of the human oropharynx and are frequently found in dental caries and at the gingival margins of persons with poor oral hygiene. Actinomycosis of the respiratory tract is acquired by aspiration. Most infections occur in individuals who are not immunocompromised. However, some cases have been reported with impaired host defenses. Actinomycosis is most commonly caused by *Actinomyces israelii*. Most actinomycotic infections in the lung are usually polymicrobial. In tissue, actinomycosis infection grows in microcolonies or granules. Because these granules are yellow, they are often called sulfur granules, although they contain minimal amounts of sulfa.

Radiographic Manifestations: The usual pattern of acute pulmonary actinomycosis consists of air space pneumonia commonly in the periphery of the lung and often in the lower lung fields. If not treated with appropriate antibiotics, a lung abscess may develop, and the infiltrate may extend into the pleura with an associated empyema. Subsequently, actinomycosis will extend into the chest wall with osteomyelitis of the ribs and abscess formation. Actinomycosis is often mistaken for pulmonary carcinoma.

Clinical Manifestations: Pulmonary actinomycosis usually presents with an indolent progressive course. The initial manifestations include a nonproductive cough and low grade fever, subsequently followed by a productive cough with blood streaked hemoptysis. With chest wall involvement, the patient will develop pleuritic pain. Rarely, a sinus tract may appear as a bronchocutaneous fistula. Late in the disease, the patient may present with weight loss, anemia, and clubbing of the digits. Actinomyces most commonly presents as disease of the cervicofacial region following dental extraction, with osteomyelitis of the mandible or a soft tissue abscess that drains through the skin.

Diagnosis: Since actinomycosis often mimics malignancy, diagnosis may not be made until surgical resection. Since these organisms are normal oropharyngeal flora, isolation in the sputum or bronchial washings is not considered significant, except if sulfa granules are found. Histologic examination of lung tissue by either transbronchial lung biopsy or open lung biopsy may be necessary to confirm the diagnosis. Cultures of tissue must be delivered to the laboratory under anaerobic conditions.

Treatment: Actinomycosis requires prolonged treatment with high doses of antimicrobials. Penicillin is the drug of choice. Regimens include IV administration of 18 to 24 million units of penicillin for 2 to 6 weeks, followed by an oral penicillin for an additional 6 to 12 months. Actinomycosis has a tendency to relapse, and prolonged therapy optimizes the likelihood of a cure. Some cases may require both medical and surgical therapies.

Bronchiectasis

Bronchiectasis is defined as an irreversible dilatation and destruction of one or more bronchi and inadequate clearance and pooling of mucous

in the airways. Bronchiectasis is also characterized by persistent microbial infection and inflammatory response with release of microbial toxins and immune mediators.

Classification: A system of classification has been devised by Reed. This system classifies bronchiectasis according to anatomic and morphologic patterns of airway dilatation as follows: (1) Cylindrical bronchiectasis: uniform dilatation of bronchi, thick walled, and extending to the lung periphery without normal tapering. On high resolution CT, parallel "tram track" lines or "signet ring" appearance; (2) Varicose bronchiectasis: irregular and beaded outline of bronchi with alternating areas of constriction and dilatation similar in appearance to saphenous varicosities; (3) Cystic bronchiectasis: the most severe form, common in cystic fibrosis (CF). Bronchial dilatation and clusters of round air and fluid filled cysts, honeycomb appearance in CF; and (4) Follicular bronchiectasis: extensive lymphoid nodules and follicles within thickened bronchial walls.

Cystic, cylindrical, and varicose forms may co-exist in the same patient. The fourth pattern, follicular bronchiectasis, usually occurs following childhood pneumonia, measles, pertussis, or adenovirus infection.

Etiology: The most common cause of bronchiectasis in the United States is CF. Other causes are listed in Table 1.

Patients with focal bronchiectasis, which is localized to a segment or lobe, should undergo bronchoscopy to eliminate an obstructing bronchial lesion.

Radiographic findings by high resolution CT of the chest (HRCT) have been described in patients with *Mycobacterium avium* complex (MAC). The most noble finding in bronchiectasis is the presence of small nodular opacities or "tree in bud" appearance. Abnormalities are most often in the lower lung fields. Treatment with multiple antimicrobial agents may lead to resolution of these abnormalities, but prolonged therapy for up to 18 months may be necessary.

Patients with human immunodeficiency virus (HIV) infection have been found to have a high incidence of bronchiectasis, which may in part be due to recurrent bacterial infections. The bronchiectasis observed in HIV-infected patients is particularly aggressive.

In a group of patients with bronchiectasis, measurement of immunoglobulins, including IgG subclasses, demonstrated a high incidence of IgG subclass deficiencies, even when total IgG levels were normal.

Allergic bronchopulmonary aspergillosis predisposes patients to bronchiectasis as a consequence of a persistent complex immune response to airway colonization by Aspergillus. This type of bronchiectasis most commonly involves central airways, distinguishing it from other types of bronchiectasis. Patients with chronic asthma are also predisposed to bronchiectasis.

Table 1—*Predisposing Factors for Bronchiectasis*

Cause	Disease Example
Localized	
Airway obstruction	Foreign body aspiration External compression Stenosis Lung Tumors
Necrotizing pneumonia	
Diffuse	
Congenital	Intraluminal webs Absent cartilage Pulmonary sequestrations
Cystic fibrosis	
Young's Syndrome	
Dyskinetic cilia syndrome	
Kartagener's syndrome	
Deficiency in host defenses	Agammaglobulinemia Human immunodeficiency virus Chronic granulomatous disease IgG subclass deficiency Subclasses 2, 3, and 4
Immunologic abnormality	Allergic bronchopulmonary aspergillosis
Rheumatologic diseases	Rheumatoid arthritis Sjogren's syndrome
Post infections	Measles infection Pertussis infection Tuberculosis Pneumonia MAC infection
Posttoxic bronchitis	Ammonia inhalation Aspiration of gastric contents
Lung fibrosis	Sarcoidosis After radiation therapy Tuberculosis

Clinical Manifestations: Clinical findings found in a retrospective chart review of confirmed patients with bronchiectasis included cough (90%), chronic daily sputum production (76%), dyspnea (72%), hemoptysis (56%), and pleuritic chest pain (46%). The most common physical findings were crackles (70%) and wheezing or rhonchi (less than 50%). HIV-positive patients with confirmed bronchiectasis by CT reported daily cough and sputum production in less than 39% of cases.

Pulmonary function studies may be normal if the involvement with bronchiectasis is localized and mild. With diffuse disease, pulmonary function tests may reveal an obstructive ventilatory defect with hyperinflation and impaired carbon monoxide diffusing capacity. Some patients, on the other hand, with diffuse disease may present with a combined obstructive and restrictive ventilatory defect. Pulmonary function tests are not useful in distinguishing bronchiectasis from other airway diseases.

Laboratory studies in bronchiectasis include a mild degree of leukocytosis, usually without a left shift, an increase erythrocyte sedimentation rate, mild anemia, and hypergammaglobulinemia.

Radiographic Findings in Bronchiectasis: Routine chest radiographs are abnormal in approximately 50% of patients with proven bronchiectasis. The classic finding of "tram tracks" that represent thickened dilated bronchial walls is best seen on the lateral film. Other findings include hyperinflation and air trapping, increased linear markings, rounded opacities that represent areas of focal pneumonia, and ring shadows that represent dilated airways seen en face. HRCT has become the diagnostic standard for detection of bronchiectasis. It is both highly sensitive and specific for the diagnosis of bronchiectasis.

Differential Diagnosis: Bronchiectasis should be distinguished from COPD. Both diseases present with cough, sputum production, wheezing, and dyspnea. Exacerbations are common in both disorders, although the volume of sputum production is greater in patients with bronchiectasis. Recurrent fever and hemoptysis are less likely to be found in patients with chronic bronchitis. According to Fiel, the incidence of *Pseudomonas aeruginosa* is present in approximately 31% of patients with bronchiectasis, but only 2 to 4% of patients with COPD.

Bronchiectasis can also be confused with interstitial fibrosis, especially patients with a honeycomb appearance since on chest radiograph in end-stage fibrosis. This honeycomb parenchymal appearance may mimic the air-filled cyst of bronchiectasis.

Therapy for Bronchiectasis: The objectives of management for bronchiectasis are relief of symptoms; prevention of complications; control of exacerbations; and a reduction in mortality.

1. Antibiotics: Antibiotics are the cornerstone for the treatment of exacerbations of bronchiectasis. Bacterial flora include *Streptococcus pneumoniae* and *Haemophilus influenzae,* which can be treated with trimethoprim-sulfamethoxazole, ampicillin-clavulanate acid, or one of the newer macrolides. In patients colonized with Pseudomonas, oral therapy requires the use of a fluoroquinolone. In some cases, IV administration of antipseudomonal antibiotics is required. Whether prophylactic antibiotic therapy is necessary remains an unresolved question. Strategies for prophylaxis range from daily low dose antibiotics to 1 week out of each month. Daily inhaled antibiotic prophylaxis is now recommended in patients with CF colonized with *P aeruginosa*.
2. Bronchodilators: Most patients with bronchiectasis have significant airway hyperresponsiveness, presumably as a result of transmural airway inflammation. Routine use of bronchodilators has added potential advantage of the simulation of mucociliary clearance which is associated with the use of ß-adrenergic agents. Both aerosolized ß-agonist therapy and aerosolized anticholinergic therapy should be tried when there is evidence of reversible airway obstruction.
3. Anti-inflammatory agents: Although intense airway inflammation characterizes bronchiectasis, few studies have looked at the efficacy of corticosteroids in this disorder. Inhaled steroids have been suggested as an alternative and may be useful in some patients, especially those with significant airway hyperreactivity. It has been shown that inhaled corticosteroids can reduce inflammatory mediators and improve dyspnea, cough, and pulmonary function in severe bronchiectasis. Short courses of oral corticosteroids are often used during acute exacerbations. Nonsteroid anti-inflammatory agents, such as indomethacin, have been used in Europe, either orally or by inhalation (not available in the United States).
4. Airway clearance techniques: Possible drainage and chest physiotherapy are useful to enhance

gravity-aided clearance of secretions. Alternative treatment includes the use of a flutter device, positive expiratory pressure mask, chest oscillation, and humidification of inspired air.

5. Mucolytic agents and hydration: Adequate oral hydration and the use of nebulized solutions may improve airway mucous clearance. Acetylcysteine is beneficial in some patients. To date, there are no randomized, controlled clinical trials to show mucolytics to be of benefit in the treatment of non-CF bronchiectasis. Recombinant human DNase breaks down DNA released from degenerating bacteria and neutrophils. DNA has a tendency to form thick viscous gels. DNase improves clearance of secretions and pulmonary function and reduces hospitalizations in CF patients but has not been found to be useful in non-CF bronchiectasis. A recent study suggested that DNase was ineffective and potentially harmful in more than 300 adult outpatients with idiopathic bronchiectasis who are in stable condition.

Surgery for Bronchiectasis: In patients with localized bronchiectasis, surgical removal of the most affected segment or lobe may be considered. The major indications for surgery include the partial obstruction of a segment or lobe due to a tumor or the presence of a highly resistant organism in the affected area, such as MAC or Aspergillus. Patients require significant pulmonary function to withstand surgery. Surgery may also be performed for massive hemoptysis in patients with adequate pulmonary reserve, although the increases success of bronchial artery embolization for hemoptysis makes surgery less desirable.

Lung Transplantation for Bronchiectasis: Patients with bronchiectasis and CF were initially considered not to be good transplant candidates due to concerns about overwhelming infection after the use of prolonged immunosuppression. However, double lung transplantation has been successful in CF patients, and the St. Louis International Transplant Registry lists over 1,000 CF patients and over 200 non-CF bronchiectasis patients who have had lung transplant with a 1- year survival rate of 72% and a 4- year survival rate of 49% in CF patients.

Cystic Fibrosis

Genetics: CF is the most common genetic disease in the United States, with an incidence of 1 in 2,000 to 3,000 births. It is an autosomal recessive disorder with variable penetrance. Carriers of the CF gene are phenotypically normal. About 5% of the white US population are carriers of the CF gene, and approximately 30,000 individuals are affected by this disorder.

The CF gene, sequenced in 1989, is located in the long arm of chromosome number seven and encodes for the CF transmembrane regulator protein (CFTR). CFTR is located at the cell surface and acts as a regulated chloride channel.

CFTR may also regulate the function of other epithelial cell proteins. Defective transport of ions across the epithelial membrane leads to thick viscous secretions in many organs and to excessive chloride concentration in the sweat of patients with CF. This abnormality is the basis for the laboratory test most frequently performed to diagnose this disorder.

Over 700 mutations of the *CFTR* gene have been described, some in a single individual. The ΔF508 mutation is the most common and accounts for about 90% of CF chromosomes in patients of northern Europe descent but for only 60% of chromosomes worldwide. It is due to the deletion of a single phenylalanine residue at position 508. CFTR is expressed in all epithelial cells affected in CF, including the lung, pancreas, sweat glands, and liver. It is also found in the large intestine and testes.

Pathogenesis: CF is initiated by a defect in the gene normally responsible for encoding CFTR which is necessary for the flow of electrolytes and fluid across cell membranes. The resultant abnormalities in salt and water transport lead to alteration in the composition of secretions in the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and other exocrine tissues. In the lung, these alterations change the properties of the mucus layer lining the epithelia and the composition of the airway surface fluid, ultimately resulting in the clinical features of CF. These features include impaired mucociliary clearance, persistent bacterial infection, host inflammatory response (characterized by the accumulation of leukocyte-derived DNA and secretions rich in elastase), and airway obstruction, leading to progressive lung destruction.

Nonpulmonary Clinical Manifestations: In the pancreas, dysfunction of the exocrine portion leads to fat malabsorption and to malnutrition. Glucose intolerance is present in as many as 50 to 70% of older patients with CF. Diabetes mellitus occurs in

about 15%. Malabsorption of fat-soluble vitamins such as A, D, E, and K can lead to vitamin deficiency and coagulopathy.

The liver is affected with biliary cirrhosis as a result of thick secretions in the biliary ducts. This is manifested by abnormal liver function tests. Diffuse liver involvement can lead to portal hypertension.

Meconium ileus is present in about 40% of infants with CF and is pathognomonic for this disorder. A similar syndrome occurs in older CF patients due to inspissated mucus in the GI tract. This results in the distal intestinal obstruction syndrome (DIOS), often requiring surgical treatment.

About 95% of male CF patients are infertile. Although sperm maturation is normal, the Wolffian structures are often not developed. The vas deferens is often completely absent. This may indicate a role for the CFTR in the development of the male genital tract. In fact, in subjects with congenital bilateral absence of vas deferens but without any other abnormalities of CF, mutations in the *CFTR* gene have been reported.

Females with CF are not infertile, although they may have difficulty conceiving due to thick cervical mucus and/or unovulatory cycles if their nutritional status is poor. Pregnancies can be successful, and maternal function has not been found to deteriorate after pregnancy.

Pulmonary Manifestations: Pulmonary disease is present in 98% of patients with CF by the time they reach adulthood. Despite the great advances in the management of this disorder, the majority of the patients succumb to respiratory complications. A recurrent cough that becomes persistent is often the first manifestation. Airway hyperreactivity and wheezing are common in children. Bronchodilator responsiveness tends to decrease with age, perhaps as a result of destruction of the cartilage.

Pansinusitis with opacification of the paranasal sinuses is a universal finding in patients with CF. Nasal polyps are present in up to 30% of CF patients.

The lung in CF is normal at birth, but infection occurs early in life and is persistent. The abnormal ionic environment and chronic airway obstruction by thick secretions promote colonization with pathogenic bacteria, which leads to the accumulation of inflammatory cells. These cells release inflammatory mediators that cause inflammation and damage to the airway wall, with the development of bronchiolitis and subsequently bronchiectasis.

H influenzae, S aureus, and later, *P aeruginosa*, are the common pathogens found in CF airways. The abnormal CFTR may be partly responsible for colonization with Pseudomonas, as the normal CFTR appears to be involved in clearance of this organism from the airways. The high sodium content of CF secretions may contribute to chronic infection, as low sodium content is required for the effective killing of bacteria in airway epithelia.

Colonization with *P aeruginosa* is not benign, as it has been found to be an independent risk factor for accelerated loss of lung function and decreased survival. Colonization with *Burkholderia cepacia* denotes an even worse prognosis.

The mucoid appearance of Pseudomonas is due to production of alginate. This bacterium is difficult to eradicate, due to the poor penetration of antibiotics into purulent airway secretions and to the interference in phagocytic killing by alginate. Bacteria may have native or acquired antibiotic resistance.

Pharmacokinetics differ in CF patients, as the volume of distribution of hydrophilic drugs (penicillins, cephalosporins, aminoglycosides) is increased due to decreased adipose tissue. Renal clearance of aminoglycosides is increased, and therefore, dosage has to be adjusted, usually at triple the normal dose. Once-daily administration is not recommended.

Diagnostic Tests:

1. Sweat test (pilocarpine iontophoresis): The results of this test are abnormal in the large majority of patients with CF. A level > 60 mEq/dL is usually diagnostic for CF. However, the test must be repeated at least twice, and an adequate sample containing at least 50 mg of sweat must be collected over a 45-min period. About 1% of CF patients have normal sweat chlorides. Abnormal sweat tests are seen in other disorders, as listed in Table 2. Therefore, a diagnosis should only be made if the clinical history is suggestive of CF. Diagnostic criteria for CF are listed in Table 3.
2. Molecular diagnosis: Genetic screening is not recommended in CF. Many mutations have been identified after sequencing the entire gene in a research laboratory. Genotyping at commercial labs usually can only identify the 20 to 30 most common mutations. This accounts for <90% of

CF mutations in the general population.

3. Potential difference (PD) across the respiratory epithelium: This is a research tool that may be available at few centers to aid in the diagnosis of CF. Abnormal transport of chloride leads to a very negative potential differences across the nasal epithelium. Measurement of this potential difference can establish a CF diagnosis. Nasal perfusion with amiloride hydrochloride and with chloride-free solutions leads to characteristic changes in the PD.
4. Immunoreactive trypsin (IRT): Elevated levels of IRT are present in the blood of infants with CF. This radioimmunoassay or enzyme-linked immunosorbent assay can be performed on dried blood obtained for newborn screening.

Prognosis: Most patients still die of respiratory complications. The degree of pulmonary impairment is predictive of survival. In 1992, Kerem et al published the results of a study that demonstrated that when the FEV_1 decreased below 30% of predicted, the 2-year survival was less than 50%. Females appear to have a greater deterioration of lung function with age.

When the first accurate description of CF was published by Andersen in 1938, more than 80% of patients died within 1 year of birth. Since then, advances in diagnosis and therapy have been accompanied by a gradual improvement in prognosis and increased survival time. According to data from the CF Patient Registry, median survival in the United States was approximately 20 years in 1970 and has increased to 30.1 years by 1995. Recent estimates have projected a median survival of 40 years for children born in the United States in 1990 who are receiving current standard therapy for CF.

Management of Chronic Lung Disease:

1. Antibiotics: Prophylactic antibiotics against *S aureus* are not recommended. In a multicenter study evaluating the use of cephalexin in children with CF, there was no improvement in pulmonary function or rate of infection, but there was increased incidence with *P aeruginosa*. Inhaled tobramycin at a dose of 300 mg twice daily alternating every 4 weeks has been effective in improving pulmonary function and decreasing bronchitic exacerbations in patients colonized with Pseudomonas.
2. Anti-inflammatory agents: Oral corticosteroids have been shown to improve pulmonary function in children with CF but are associated with an unacceptable rate of side effects, such as growth retardation, cataracts, and glucose intolerance, and are not routinely used. Inhaled steroids have been studied, with controversial results: in 49 CF patients randomized to receive 1,500 μg/d of inhaled beclomethasone or standard therapy, there was no improvement in pulmonary function tests at 30 days. Fifty-five CF patients randomized to receive budesonide at 1,600 μg/d or placebo showed a statistically significant improvement in FEV_1 after 3 months. Inhaled steroids are used in patients with airway hyperreactivity. High-dose

Table 2—*False-Positive Sweat Tests*

Adrenal insufficiency
Anorexia nervosa
Atopic dermatitis
Autonomic dysfunction
Celiac disease
Familial cholestasis
Fucosidosis
Glucose-6-phosphate dehydrogenase deficiency
Glycogen storage disease, type I
Hypogammaglobulinemia
Hypoparathyroidism
Hypothyroidism (untreated)
Klinefelter's syndrome
Mucopolysaccharidosis, type I
Malnutrition
Nephrogenic diabetes insipidus
Nephrosis
Prostaglandin E1 infusion, long-term
Pseudohypoaldosteronism

Table 3—*Criteria for Diagnosis of CF*

Elevated sweat chloride level on two occasions
—OR—
Identification of mutations known to cause CF in both *CFTR* genes
—OR—
In vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium
—PLUS—
One or more phenotypical features of CF Sino-pulmonary disease Characterstic GI or nutritional disorders Obstructive azoospermia Salt loss syndrome
—OR—
Sibling with CF
—OR—
Positive newborn screening

ibuprofen was studied in 85 patients with mild lung disease in a randomized, placebo-controlled study. After 4 years, the rate of loss of FEV_1 was 1.5% vs 3.6%. This therapy is recommended in some pediatric patients.

3. Dornase alfa: Dornase alfa recombinant inhaled solution has been shown to improve FEV_1 by 6% and to decrease the frequency of respiratory exacerbations by 37%. It is administered by nebulization once daily at a dose of 2.5 mg via an approved aerosol delivery system.
4. Airway clearance: Postural drainage and chest physiotherapy are the traditional methods used to facilitate clearance of secretions. Mechanical devices include the positive expiratory pressure mask, the flutter device, or a vibrating vest. Autogenic drainage uses forced expiratory maneuvers at different lung volumes to improve expectoration.
5. Supplemental oxygen: Recommended for patients with exercise-induced or resting hypoxemia.

Management of Acute Pulmonary Exacerbations: Acute exacerbations usually occur with increased cough and sputum volume, sometimes associated with hemoptysis, and are often accompanied by systemic symptoms such as decreased energy, anorexia, and weight loss. Spirometry demonstrates a decrease in lung function.

Parenteral antibiotics are generally administered for 14 to 21 days to reduce the burden of bacteria, to decrease symptoms, and to improve lung function. Cephalothin and nafcillin are used for treatment of infection with *S aureus*, and vancomycin is used for patients with penicillin allergy. For patients colonized with Pseudomonas, an antipseudomonal penicillin is combined with an aminoglycoside. Combination therapy reduces the risk of the development of resistance.

Intensified bronchodilator therapy and chest physiotherapy are indicated during treatment of exacerbations. Steroids may be used in patients with hyperreactive airways, but they have not been systemically studied.

Complications of CF Lung Disease:

1. Hemoptysis: Hemoptysis occurs frequently during bronchitic exacerbations and usually is self-limited. Conservative measures such as bed rest, cough suppression, antibiotics, and correction of coagulopathy, if present, are adequate treatment for most patients. Massive hemoptysis is associated with a high mortality, but it may respond favorably to bronchial artery embolization. It is successful in as many as 90% of the cases, but recurrences can occur in about 20%. Repeated procedures can be done if necessary. If this proves unsuccessful, lung resection of the involved lobe may be the only alternative, but it is often difficult to ascertain with certainty which lobe or segment is responsible for the hemorrhage.
2. Pneumothorax: Spontaneous pneumothorax occurs in about 16% of patients with CF. The vast majority of these patients have severe pulmonary involvement antecedent to the pneumothorax, with an FEV_1 less than 50% predicted. The average recurrence rate is nearly 50% and, despite treatment, mortality is high at 30 to 60%. This high mortality relates more to the severe underlying parenchymal involvement than to the pneumothorax itself. Chemical pleurodesis may be necessary for recurrences.
3. Nontuberculous mycobacterial infections: Recently, there has been a marked increase in the isolation of nontuberculous Mycobacteria species (primarily *Mycobacterium avium intracellulare* complex and *Mycobacterium chelonei*) in adult patients with CF. Several centers have reported positive cultures from up to 18% of patients studied. Distinguishing airway colonization from infection can be difficult. High resolution HRCT may be useful in evaluation. Nodular opacities or "tree in bud" appearance suggests the presence of infection rather than colonization. Transbronchial lung biopsies may be required to demonstrate the presence of infection. If pulmonary function declines and atypical Mycobacteria are cultured from at least three sputum samples, treatment with antimycobacterial agents is recommended.
4. Allergic bronchopulmonary aspergillosis: A small portion of patients in the United States (1.8% in a 1995 report) develop allergic bronchopulmonary aspergillosis (ABPA). ABPA should be suspected if there is evidence of bronchospasm, peripheral eosinophilia, sputum cultures for *A fumigatus,* and immediate skin test response to *A fumigatus*. Diagnosis is confirmed by total serum IgE levels >1000 ng/mL and specific IgE or IgG to *A fumigatus*.
5. Respiratory failure and cor pulmonale: Respiratory insufficiency develops as lung disease

progresses, initially with hypoxemia on exercise, then at rest, and eventually with carbon dioxide retention. Right ventricular failure represents the culmination of the pathologic sequence of lung disease with progressive respiratory failure. In most cases, this process heralds the terminal stage in a patient's course with only limited survival beyond a few months.

Transplantation: CF patients are generally good transplant candidates, as they are young and otherwise healthy and are used to complex medical regimens. The transplanted lung does not develop the CF defect. These patients require bilateral lung transplantation using a clamshell incision.

Indications for transplantation include deteriorating respiratory status despite aggressive medical therapy and FEV_1 <30% predicted in compliant patients with good nutritional status and no other organ impairments. The average wait for transplantation is about 2 years. In 1997, the actuarial survival for CF patients was 72% at 1 year and 49% at 4 years.

Contraindications to transplantation include other organ failures, noncompliance with therapy, psychosocial instability, profound malnutrition, or active infection with Aspergillus or atypical Mycobacteria. Increased risk for transplantation is associated with colonization with resistant organisms (particularly *B cepacia*), previous thoracic surgery or pleurodesis, the need for mechanical ventilation, and diabetes mellitus.

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Recently, typical radiographic findings by high-resolution CT (HRCT) of the chest have been described in patients with infection with Mycobacterium avium *complex (MAC). The most notable finding in bronchiectasis is the presence of small nodular opacities and "tree in bud" appearance. Treatment with multiple antimycobacterial agents may lead to resolution of these abnormalities, but prolonged therapy for 12 to 18 months may be necessary.*

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Kerem E, Reisman J, Corey M, et al. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992; 236:1187-1191

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This article discusses issues of importance in maximizing successful application of lung transplantation to the CF population, including the appropriate timing for referral of patients, selection of suitable candidates, and expansion of the current donor pool through the controversial use of living donors.

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