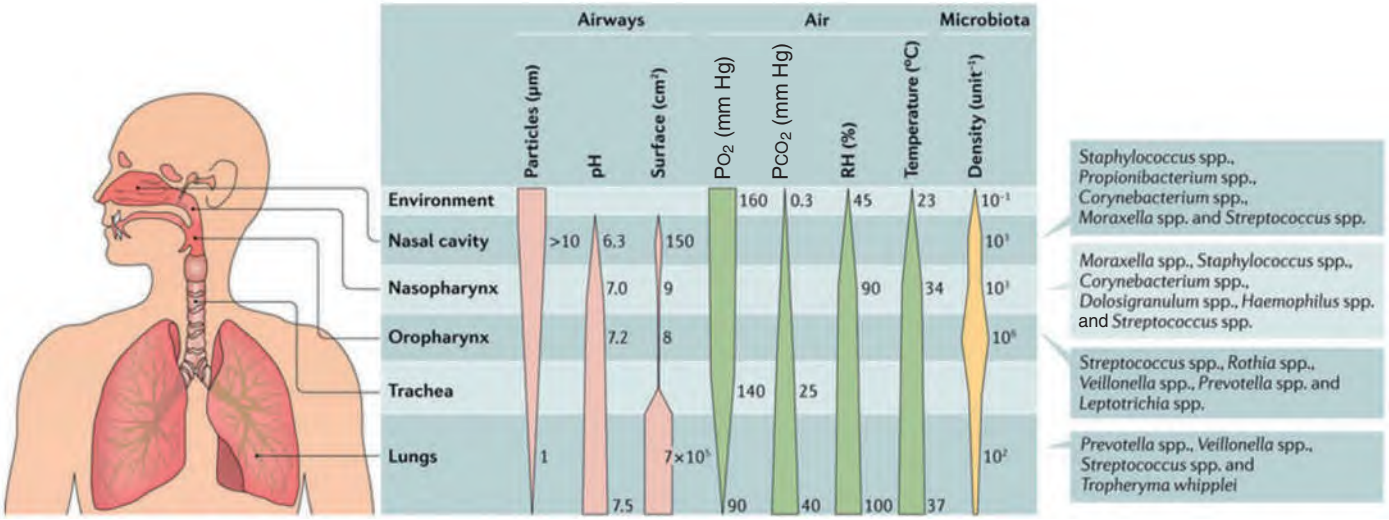

FIG. 69.1 Physiologic and microbial gradients along the respiratory tract. Physiologic and microbial gradients exist along the nasal cavity, nasopharynx, oropharynx, trachea, and lungs. The pH gradually increases along the respiratory tract, whereas most of the increases in relative humidity *(RH)* and temperature occur in the nasal cavity. The partial pressures of oxygen *(PO_2)* and carbon dioxide *(PCO_2)* have opposing gradients that are determined by environmental air conditions and gas exchange at the surface of the lungs. These physiologic parameters determine the niche-specific elective growth conditions that ultimately shape the microbial communities along the respiratory tract. The unit by which bacterial density is measured varies per niche; the density in the environment is depicted as bacteria per cubic centimeter of (indoor) air; density measures in the nasal cavity and nasopharynx are shown as an estimated number of bacteria per nasal swab; and the densities in the oropharynx and the lungs represent the estimated number of bacteria per milliliter of oral wash or bronchoalveolar lavage (BAL) fluid, respectively. *(From Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health.* Nat Rev Microbiol. *2017;15:259–270.)*

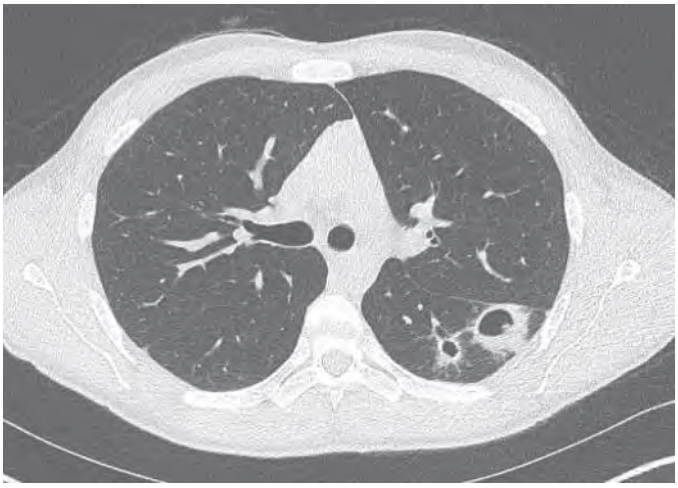

FIG. 69.2 A 28-year-old man with a history of intravenous heroin and cocaine use presented with 5 days of pleuritic chest pain. At computed tomography of the chest, he was found to have 18 cavitary lung nodules. An axial image containing two of the largest lesions is shown. He was ultimately diagnosed with *Staphylococcus aureus* tricuspid valve endocarditis complicated by septic pulmonary emboli. *(Courtesy Daniel Taupin, MD, NYU Langone Health.)*

prior insult to the lung are also more likely to be found in immunocompromised patients, although results from these studies may be biased by difficulties in isolating anaerobic bacteria.[16,17] Lung abscess can also occasionally form as a complication of intrathoracic surgery or flexible bronchoscopy. Nosocomial virulent organisms, as opposed to anaerobes, are typically involved in these iatrogenic lesions.[18,19]

EPIDEMIOLOGY

Because the great majority of lung abscesses result in hospitalization, hospital discharge summaries can be used to understand the incidence of the disease. Based on data from the National Hospital Discharge Survey of the Centers for Disease Control and Prevention for 2000 and 2010, between 10,000 and 15,000 hospital discharges in the United States per year included a diagnosis of lung abscess (International Classification of Diseases, Ninth Revision [ICD-9] code 513.0). The proportion of discharges with this diagnosis changed little over this time: 3.3 per 100,000 discharges in 2000 and 4.0 per 100,000 in 2010. Because the diagnosis of lung abscess in the discharge surveys is relatively nonspecific (cases of staphylococcal bacteremia or *Aspergillus* lung cavitation may be included), these rates overestimate the true occurrence rate of necrotic lung abscess. Consequently, lung abscess is a relatively uncommon diagnosis, with 21st century incidence rates lower than those reported in reviews from the 1970s.[20]

Lung abscesses are more common in males than in females. Surveys from the 1970s show a male to female ratio of 3:1 to 4:1. This sex difference in incidence was speculated to be related to higher rates of alcoholism, and therefore aspiration, among males.[21–23] In the more recent CDC discharge data, however, the male predominance was somewhat less prominent (69% male in 2000 and 52% in 2010). This equalization of the rates between sexes may reflect the increasing proportion of secondary abscesses occurring in immunocompromised hosts. In all studies, lung abscess is a disease of midlife or older. In the CDC discharge data, the mean ages of patients with lung abscess were 57.7 years (2000) and 50.1 years (2010). Approximately three-quarters of lung abscess diagnoses occurred in adults between the ages of 40 and 70 years.

Patients with primary lung abscess typically have risk factors for aspiration (Table 69.1). As mentioned previously, half of healthy individuals aspirate during sleep, and this increases to 70% of patients with altered consciousness.[7] Up to 78% of patients with lung abscess have a preceding episode of loss of consciousness typically due to alcohol use, seizure, stroke, drug use, or general anesthesia.[21,22,24–26] Alcohol use particularly enhances risk because it not only alters consciousness, but also induces vomiting and impairs neutrophil function.

Dysphagia caused by neurologic disease, such as amyotrophic lateral sclerosis or Parkinson disease, or esophageal disease, such as dysmotility or stricture, predisposes to aspiration even in the absence of altered consciousness.[23] Nasogastric tubes and other mechanical obstruction of anatomic barriers to aspiration also increase risk. Enteral tube feeding through the nasogastric tube magnifies the problem, particularly in the critically ill, who often have gastroesophageal reflux and decreased gastric

TABLE 69.1 Predisposing Factors for Development of Lung Abscess

Factors Associated With Aspiration
Alcoholism
Drug abuse
Sedating medications: general anesthesia, antipsychotics
Seizure
Stroke
Esophageal abnormality
Respiratory muscle dysfunction: Parkinson disease, amyotrophic lateral sclerosis
Periodontal disease
Enteral tube feeding
Factors Associated With Immunocompromise
Diabetes
HIV/AIDS
Steroids and immunosuppressive drugs
Local Factors
Bronchial carcinoma
Bronchiectasis
Pulmonary infarction

motility.[27] Furthermore, enteral tube feeds may have an impact on the oral microbiome, resulting in higher proportions of pathogenic flora in the oropharynx.[28] Proton pump inhibitors and histamine type 2 receptor antagonists, by increasing the pH of the stomach, can impair natural host defenses, resulting in higher bacterial burden.[29] If a subsequent aspiration event occurs in these settings, patients are more likely to deliver an inoculum of bacteria large enough to cause clinical infection.[27,29] Increasing the gastric pH can also alter the colonizing microbiota of the stomach and airway, favoring gram-negative organisms and modifying the causative organisms in aspiration pneumonia or lung abscess.[30]

Patients with lung abscess often have poor dentition. Historically, the majority (up to 82%) of patients with lung abscess have periodontal disease.[21,23] Gingivitis coincides with a high density of oral anaerobic organisms in the gingival crevice, leading to a potentially larger inoculum in the setting of aspiration. In contrast, primary lung abscess is rare in edentulous people. Because, in some studies, over 40% of edentulous patients with lung abscess had underlying bronchogenic carcinoma, a diagnosis of a lung abscess in an edentulous patient should prompt evaluation for underlying malignancy.[31]

As mentioned earlier, secondary abscess can occur in patients with underlying immunocompromise, such as those with diabetes mellitus or who are taking immunosuppressive medications including steroids. The presence of a primary lung pathologic condition that would predispose to stasis or necrosis, such as bronchiectasis, is also a risk factor.

CLINICAL PRESENTATION

Patients with lung abscess typically present with cough productive of foul-smelling sputum and fever.[11] Malaise, night sweats, and pleuritic chest pain are also reported. Bad breath can be a complaint, especially in the setting of putrid sputum. Patients typically have an indolent and subacute presentation, with the median duration of symptoms before presentation being 14 days but sometimes as long as 6 weeks.[11,14,22] Hemoptysis can occasionally be a presenting complaint.[22,32] In patients with chronic abscess, weight loss, anemia, and digital clubbing can be observed.[12,21] On physical examination, poor dentition is often noted. Patients with necrotizing pneumonia, particularly from a hematologic source, can occasionally present more acutely, within 1 week of symptom onset, with high fever.[10]

MICROBIOLOGY

The lung has an extant microbiome composed of upper respiratory organisms that transiently colonize the lower airways.[1,3] In adults, most organisms in the lung are those of the oropharynx (e.g., *Streptococci, Prevotella,* and *Veillonella*). Children's lungs also can be colonized with organisms from the nasopharynx such as *Moraxella, Haemophilus,* and *Staphylococcus.* These organisms are thought to enter the lung through microaspiration and to reside there only transiently with constant migration and elimination, never establishing rich, resident microbial communities. Organisms within the alveoli may prime the immune system and facilitate rapid microbial clearance.[1]

According to the findings of culture-based techniques, anaerobic pleuropulmonary infections contain an average of 3.5 different species of anaerobes and 1.7 different aerobes.[33] In the late 20th century, anaerobic bacteria accounted for 85% to 93% of organisms in lung abscess, with the predominant isolates being *Peptostreptococcus* species, *Fusobacterium nucleatum,* and *Prevotella melaninogenica,* formerly known as *Bacteroides melaninogenica.*[10,14,34,35,36,37] Microbiologic analysis from samples obtained by percutaneous drainage of abscesses confirmed the prevalence of anaerobic bacteria.[38] Obligate anaerobes including *Bacteroides* and *Prevotella,* which do not tolerate oxygen, are unlikely to grow in small lesions adjacent to well-oxygenated lung. Facultative anaerobes, which can use but do not require oxygen, constitute most of the organisms in a lung abscess and can grow and create the anaerobic environment for the obligate anaerobes.

Culture-based methods, however, may not tell the entire story. With 16S rRNA sequencing of bronchoalveolar lavage samples from patients with lung abscess, two-thirds of samples were classified as polymicrobial infections, and one-third were monomicrobial. Obligate anaerobes, which comprised the predominant phylotypes in 42% of samples, comprised at least 5% of microbiota in 86.5% of the polymicrobial infections. Among the pathogens identified by 16S sequencing, *Fusobacterium* species were the predominant phylotype, followed by *Streptococcus anginosus.*[38] *S. anginosus* was most likely of the frequent pathogens to be associated with monomicrobial infection.

The microbiology of lung abscess also varies by geography. For example, transthoracic aspiration from 90 patients with community-acquired lung abscess in Taiwan revealed a monomicrobial process in 79% of cases; *Klebsiella pneumoniae* was isolated in 33% of monomicrobial lesions, followed by *Streptococcus milleri* in 16%.[39] In a second study from Taiwan, only 26.2% of abscesses yielded anaerobic bacteria, as either a sole or a participating causative agent. *Streptococcus* spp. were the most commonly isolated organisms (59.8%); *Klebsiella* spp. accounted for 8.2% of community-acquired lung abscesses in this center.[23] Limitations of these studies included prior antibiotic use and the fastidiousness of anaerobes.[36] Despite these limitations, studies do suggest a change over time in the organisms involved in lung abscesses, from predominantly anaerobic to more virulent aerobic bacteria, and that regional variability in abscess microbiology may be important in determining etiology.[27,36,40]

Microbiology may also be quite different in nosocomial settings.[41] In critically ill intubated patients, gram-negative bacteria were found in tongue biofilm samples. These findings correlated with tracheal aspirate cultures in those who developed ventilator-associated pneumonia or aspiration pneumonia.[42] Similarly, patients on acid-suppressing medications have a greater propensity to colonization, and therefore aspiration pneumonia, with gram-negative organisms.[30] If necrotizing pneumonia or lung abscess develops in hospitalized patients, treatment against gram-negative organisms should be strongly considered.

Abscess etiologies in immunocompromised patients—with acquired immunodeficiency syndrome (AIDS), on chemotherapy, or after organ transplantation—are broad, as noted in Table 69.2. A retrospective study comparing immunocompromised patients with nonimmunocompromised patients noted a trend toward a greater proportion of aerobic bacteria isolated and a larger number of patients with multiple bacterial isolates. Conversely, in this group a low number of anaerobes were isolated, possibly in part owing to the methods of specimen collection.[16] Atypical pathogens can also cause abscess in immunocompromised hosts. In patients with impaired cell-mediated immunity, *Legionella, Nocardia,* and *Rhodococcus* are known causes of cavitary lesions. In patients with neutropenia, aerobic bacteria and molds such as *Aspergillus* and Zygomycetes are important pathogens. These pathogens are discussed in other chapters in this book.

DIAGNOSIS

Diagnosis of lung abscess is generally made through chest radiographs that show a lung cavity with an air-fluid level (Fig. 69.3). CT with contrast shows a thick irregular wall with a smooth internal border and

TABLE 69.2 Differential Diagnosis of a Cavitary Lesion on Chest Radiograph

Infectious Causes
Bacteria
Oral anaerobes Less commonly: *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa,* enteric gram-negative rods, *Pasteurella multocida, Burkholderia cepacia, Burkholderia pseudomallei, Haemophilus influenzae* types b and c, *Legionella,* group A *Streptococcus, Streptococcus pneumoniae, Streptococcus anginosus, Nocardia, Rhodococcus equi, Actinomyces, Clostridium, Capnocytophaga*
Septic Pulmonary Embolism
Originating in septic phlebitis, including Lemierre syndrome and vegetations from tricuspid endocarditis
Mycobacteria
Tuberculosis and nontuberculous pathogens
Fungi
Endemic mycoses (*Histoplasma, Coccidioides,* blastomycosis), *Cryptococcus, Aspergillus,* Zygomycetes
Parasites
Paragonimus westermani, Entamoeba histolytica, Echinococcus
Noninfectious Causes
Neoplasm
Primary lung cancer, metastatic carcinoma (particularly squamous cell) Pulmonary infarction caused by bland embolus
Vasculitis
Wegener granulomatosis, rheumatoid lung nodule
Airway Disease
Bullae, blebs, or cystic bronchiectasis Developmental cause Pulmonary sequestration
Other
Sarcoidosis, achalasia or transdiaphragmatic bowel herniation giving appearance of cavity with air-fluid level

Modified from Lorber B. Bacterial lung abscess. In: Bennett JE, Dolin R, Blaser M, eds. Principles and Practice of Infectious Diseases. *8th ed. Philadelphia: Elsevier; 2014;855–859.*

peripheral enhancement of the abscess. Consolidation in the adjacent parenchyma is found in half of all cases.[43] The majority of patients—70% to 96% in early case series—present with a single abscess.[21,22] The main localizations of these lesions mirror those of aspiration pneumonia, namely, the posterior segments of the right upper lobe, the middle lobe, and the superior segments of the inferior lobes.[21,22,43] These radiographic findings in a patient with aspiration risk factors and classic subacute presentation of fever, particularly with putrid sputum, are strongly suggestive of lung abscess and sufficient to clinch the diagnosis. In this case, empirical therapy targeting anaerobic organisms can be started in the absence of microbiologic studies.

If obtained, sputum cultures from patients with lung abscess typically yield polymicrobial respiratory flora. Specialized techniques such as transtracheal aspiration, transthoracic aspiration, and bronchoalveolar lavage with quantitative cultures are required for culturing of anaerobic organisms, but these are rarely performed in clinical practice. If empyema has developed, putrid smell of empyema fluid can be diagnostic and culture can be helpful in determining the microbes involved. If patients do not have the classic presentation or if they have secondary lung abscess, then cultures of expectorated sputum or bronchoalveolar lavage should be performed to evaluate for aerobic bacteria, mycobacteria, fungi, and occasionally parasites in the appropriate clinical situation. Furthermore, early bronchoscopy to evaluate for tumor should be considered if the abscess is in an atypical location or if the patient lacks risk factors for aspiration, is edentulous, lacks classic presenting symptoms, or has risk factors for lung cancer.

THERAPY

For primary lung abscess, prolonged treatment with antibiotics that cover oral microbiota, and anaerobes in particular, is necessary. The use of penicillin was a major advance in the treatment of primary lung abscess and for many years was the treatment of choice. In recent decades, production of penicillinase has led to penicillin resistance for many oral anaerobes, and other therapies have proved to be more efficacious. In the 1980s a small randomized clinical trial showed that 3 to 6 weeks of clindamycin was more effective than penicillin with a shorter febrile period, fewer days of putrid sputum, and a higher rate of clinical cure.[44] In a second randomized, controlled trial, 44% of patients who received penicillin failed to respond to therapy compared with only 5% of patients who received clindamycin. Furthermore, cultures obtained through transthoracic needle aspiration and/or bronchoscopic brushing revealed penicillin resistance in *Bacteroides* species that were all sensitive to

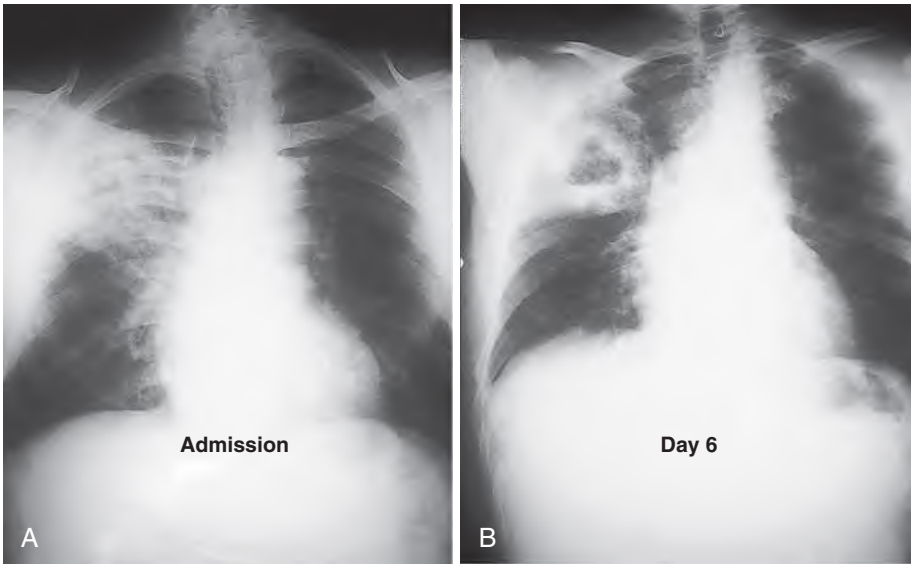

FIG. 69.3 (A) Admission chest radiograph from a 61-year-old man with fever, cough, and putrid sputum of 4 weeks' duration and a 12-pound weight loss. A large infiltrate, without obvious cavitation, is visible in the right lung. (B) A repeat radiograph on day 6 of hospitalization, after the patient began to produce copious sputum, shows a large, thick-walled cavity with an air-fluid level. Because the patient was a heavy smoker and had no aspiration risk and excellent oral hygiene, a bronchoscopy was performed, which showed a partially obstructing carcinoma. *(From Lorber B. Bacterial lung abscess. In: Bennett JE, Dolin R, Blaser M, eds.* Principles and Practice of Infectious Diseases. *8th ed. Philadelphia: Elsevier; 2014:855–859.)*

clindamycin.[38] Similarly, clindamycin compared with metronidazole showed a 90% versus 46% cure rate, respectively.[45] This discrepancy was likely secondary to metronidazole's lack of activity against the microaerophilic streptococci and anaerobic cocci that are often involved in anaerobic lung infections. Consequently, metronidazole is not considered adequate anaerobic therapy for lung abscess. More recently, treatment has shifted to β-lactam–β-lactamase combinations and fluoroquinolones. Intravenous, followed by oral, amoxicillin-clavulanate resulted in cure of 100% of patients.[46] Amoxicillin-clavulanate and clindamycin plus a cephalosporin were shown to have similar efficacy.[47] Moxifloxacin has also been shown to have equal efficacy to amoxicillin-clavulanate, and both treatments were well tolerated.[48,49] Of note, anaerobic resistance to clindamycin and moxifloxacin has been rising in the past few years.[50]

Other agents with excellent anaerobic coverage that should be considered, especially when resistant gram-negative organisms are present (i.e., in the setting of immunocompromise or nosocomial infection), include piperacillin-tazobactam and carbapenems.[51,52] Few data exist for these agents for lung abscess, but for aspiration pneumonia both have been shown to have good efficacy.[53,54]

Although patients have been cured with only oral therapy,[54] the general practice is to treat with intravenous antibiotics initially and then transition to oral therapy once clinical improvement is seen.

Duration of Therapy

Limited data direct duration of therapy for treatment of lung abscess. Levison and colleagues reported one relapse in patients receiving 3 weeks of penicillin compared with no relapse in patients receiving either 3 or 6 weeks of clindamycin or 6 weeks of penicillin.[44] In another study, moxifloxacin and amoxicillin-clavulanate were given through clinical and radiologic resolution of infection with mean duration of 30 and 35 days, respectively.[49] Other investigators advocate that the infection should be treated until there is clearance or small stable residual lesion on chest images.[11] In the absence of a body of clinical trials to guide decision making, a minimum of 3 to 4 weeks of treatment can be assumed, with close clinical monitoring to guide cessation of therapy. A longer duration of therapy should be considered for treatment of particularly large abscesses or in patients with underlying immunocompromise.

Surgical Intervention

Unlike abscesses in other areas of the body where drainage is required for cure, lung abscesses can be treated successfully with medical therapy alone in at least 80% of cases.[55,56] Spontaneous release of pus into the airway, as evidenced by putrid sputum expectoration, may serve as "natural" drainage.[11] In some instances, however, intervention may be required, such as in the setting of antibiotic failure, abscess secondary to neoplasm, or pulmonary hemorrhage.[56–58] Features that suggest risk for failure of medical therapy include associated malignancy, abscess diameter >6 cm, and involvement of resistant organisms.[58,59] Historically, patients who failed medical therapy underwent lobectomy (preferred), segmentectomy, or pneumonectomy. Mortality associated with surgical intervention, however, is as high as 15%.[60,61] More recently, minimally invasive approaches, including percutaneous and endoscopic drainage, have been explored.[62,63] Percutaneous drainage has a reported success rate of 84% with a mortality of 4%, suggesting that it is a reasonably safe alternative to surgical intervention.[63] Endoscopic drainage with pigtail catheter placement with or without antibiotic lavage has also been described with good outcomes.[62,64] This modality may be preferred in patients with coagulopathy, obstructing airway lesions, or centrally located abscesses.[63,64]

Response to Therapy and Prognosis

Typically, patients feel better within a few days of receiving appropriate antibiotics. Defervescence occurs within 7 to 10 days, although chest radiographs can show worsening in approximately one-third of patients during the first week of treatment.[10,22,65,66] Radiographic improvement often lags behind clinical resolution. Time to cavity closure is variable. The majority of cavities resolve on images by 6 weeks, but on rare occasions can take longer than this to close. Surrounding infiltrates may also take longer to resolve, typically at least 8 weeks.[66]

In the preantibiotic era, mortality associated with lung abscess was 33%. Since the advent of antibiotic therapy, mortality has fallen to 4% to 5%.[11,21,22] Prognosis is poorer in patients with obstructing airway lesions or in immunocompromised hosts.[67] Larger abscess size has also been associated with higher mortality rate.[59] In addition, abscesses involving resistant and/or more virulent organisms such as *Pseudomonas aeruginosa, Staphylococcus aureus,* and *K. pneumoniae* tend to have worse outcomes.[59] A recent study in geriatric patients suggested that oral microbiota dominated by *Prevotella* and *Veillonella* species had a higher pneumonia-related mortality rate than those dominated by *Neisseria* and *Fusobacterium*.[68] This suggests that the microbiome of the respiratory tract might play a more important part in the pathophysiology of and recovery from respiratory infection than previously thought.

PREVENTION

Sobriety, maintenance of good dentition, and prevention of aspiration are the best protection against lung abscess. Patients otherwise at risk should follow aspiration precautions. There is no evidence that administering antibiotics to patients who have been observed to aspirate prevents lung infections. Early recognition of lung infections and rapid initiation of antibiotic therapy, however, are crucial in preventing development of lung abscess.

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The complete reference list is available online at Expert Consult.

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70 Chronic Pneumonia

Peter G. Pappas

SHORT VIEW SUMMARY

Definition
- There can be persistent or progressive cough, dyspnea, often with chronic sputum production, with or without fever, lasting weeks or months rather than days.
- It is always associated with abnormal chest radiography.
- Constitutional symptoms, including weight loss and anorexia, are typical.
- Definition does not include asymptomatic solitary pulmonary nodules.
- It may be infectious or noninfectious.

Epidemiology
- Age, race/ethnicity, and gender are important considerations
- Underlying health issues and comorbid conditions
- Current and past residence, occupation, travel, and recreation history may be important
- Recent hospitalization or history of imprisonment
- Drug and alcohol history
- Recent prescription drug exposure

Microbiology
- Bacterial: anaerobes, microaerophilic and viridans streptococci; *Staphylococcus aureus;* selected community-acquired and nosocomial gram-negative bacilli; *Burkholderia pseudomallei*
- Higher-order bacteria: *Mycobacterium tuberculosis, Mycobacterium kansasii,* and other nontuberculous mycobacteria; *Nocardia* spp.; *Rhodococcus equi; Actinomyces* spp.
- Fungi: *Histoplasma capsulatum, Blastomyces* spp., *Emergomyces* spp., *Emmonsia crescens, Coccidioides immitis/posadasii, Paracoccidioides spp., Cryptococcus neoformans,* and *Cryptococcus gattii, Aspergillus* spp., *Lomentospora prolificans, Scedosporium* spp., *Mucorales* spp.
- Parasites: *Dirofilaria, Echinococcus granulosus, Paragonimus westermani,* filariasis
- Noninfectious causes: autoimmune diseases, neoplasia, drug induced, sarcoidosis, pulmonary alveolar proteinosis, silicosis, berylliosis, and a variety of other conditions

Diagnosis
- Careful clinical assessment, including detailed history, is essential.
- Clinical findings are generally nonspecific; rash, osteoarticular findings, and mucocutaneous and neurologic findings may provide helpful clues.
- Radiographic imaging, including routine chest radiograph or chest computed tomography, or both, are critical to diagnosis.
- Routine microbiologic studies, including sputum examination by Gram stain, potassium hydroxide, acid-fast stain, and preparations for ova and parasites, are important.
- Culture for routine bacteria, fungi, and acid-fast bacilli when possible. Multiplex polymerase chain reaction panels are available for respiratory specimens but are most useful for acute community-acquired pneumonia.
- Biopsy and culture of nonpulmonary specimens (e.g., urine, skin, bone, liver, prostate, or brain biopsy) in clinically relevant settings. Potentially important serologic studies include the interferon-γ release assays for tuberculosis; urine and serum *Histoplasma* antigen; serum and cerebral spinal fluid cryptococcal antigen; and serum galactomannan (GM).
- Bronchoalveolar lavage for acid-fast, modified acid-fast, and Gram stain; wet mount or calcofluor stain; cultures for bacteria, mycobacteria, and fungi; GM assay; and cytopathology.

Therapy
- Specific therapy is entirely dependent on the most likely etiologies, of which there are many possibilities, usually including antimicrobials.

Prevention
- In this broad category of disease, prevention generally entails the recognition and avoidance of circumstances that increase the likelihood of developing chronic pneumonia. In selected settings, such as high-risk patients receiving chemotherapy, prophylactic antimicrobials may be warranted.

Chronic pneumonia syndrome is a pulmonary parenchymal process that can be infectious or noninfectious, has been present for weeks to months rather than for days, and is manifested by abnormal chest radiographic findings and chronic or progressive pulmonary symptoms. Abnormal chest radiography, which may reveal any of several radiologic patterns, is probably the most important consideration in the diagnosis of chronic pneumonia. Indeed, in many patients, the diagnosis is based more on the pulmonary radiographic findings than on the pulmonary symptoms. However, asymptomatic patients who have abnormal radiographic findings, such as solitary or multiple nodules, should not be considered to have chronic pneumonia.

The emphasis in this chapter is on the chronic pneumonias caused by infectious agents. However, it is important to recognize the importance of noninfectious causes of chronic pneumonia, including the autoimmune diseases such as granulomatosis with polyangiitis; Churg-Strauss syndrome; Goodpasture syndrome and microscopic polyangiitis[1–6]; idiopathic pulmonary fibrosis and rheumatoid arthritis; neoplastic processes such as bronchogenic carcinoma, adenocarcinoma, and lymphoproliferative disorders[7,8,9–14]; prescription drugs, illicit drugs, and other chemicals[15–24]; radiation[17]; amyloidosis[25–27]; sarcoidosis[28,29,30,31]; pulmonary alveolar proteinosis[32] and forms of lipoid pneumonia[32–36]; chronic organizing pneumonia and hypersensitivity pneumonitis due to a wide variety of agents[37–40]; and other idiopathic interstitial pneumonias.[41–43]

CAUSES

The infectious causes of chronic pneumonia can be divided into two main groups: (1) those agents that typically cause acute pneumonia and are unusual causes of chronic pneumonia and (2) infectious agents that typically cause chronic pneumonia. Among those agents that typically cause acute pneumonia, anaerobic bacteria, selected microaerophilic streptococci,[44,45,46] *Staphylococcus aureus,* group F *Streptococcus, Haemophilus influenzae, Klebsiella pneumoniae, Burkholderia pseudomallei,* and *Pseudomonas aeruginosa* are the organisms most likely to produce persistent symptoms and chronic pneumonia. In these instances the pneumonia reflects a chronic necrotizing process that most commonly

occurs in patients with significant underlying disease (e.g., alcoholism, diabetes mellitus, intrathoracic malignancy, chronic obstructive lung disease), hospitalized patients, those requiring long-term ventilatory assistance, patients with chronic swallowing and reflux disorders, and others at risk for recurrent aspiration, such as patients with Parkinson disease and other neurologic disorders.[44,45–55] Acute pneumonia caused by most viral agents and by *Streptococcus pneumoniae, Mycoplasma pneumoniae, Legionella* spp., *Coxiella burnetii,* or *Chlamydia pneumoniae* rarely progresses to a chronic pulmonary infection.[56,57]

Table 70.1 lists the most common infectious and noninfectious causes of chronic pneumonia. In the otherwise healthy host, the most common considerations are tuberculosis[58–61] and nontuberculous mycobacteria (NTM)[59,62–66,67]; cryptococcosis due to either *Cryptococcus neoformans* or *Cryptococcus gattii*[68–70]; and the endemic fungal infections, including histoplasmosis,[71–73] coccidioidomycosis,[74–76] and blastomycosis.[77–80] In the appropriate geographic area, paracoccidioidomycosis, adiaspiromycosis, emergomycosis, and talaromycosis should be considered.[81–85] Lung abscess with mixed aerobic and anaerobic bacterial infections may warrant consideration,[45–47] as well as actinomycosis.[86–89] Aspergillosis (multiple species), scedosporiosis (caused by *Scedosporium apiospermum* and *Lomentopora [Scedosporium] prolificans),*[90,91] sporotrichosis,[92] emergomycosis (due to *Emergomyces africanus, Emergomyces pasteurianus,* and *Emergomyces canadiensis*), and adiaspiromycosis (caused by *Emmonsia crescens*)[93–96] are rare causes of chronic fungal pneumonia in the normal host. In the immunocompromised host, mycobacteria, especially *Mycobacterium tuberculosis,* remain common causes of chronic pneumonia.[97,98] Classic opportunistic infections associated with pneumonia, including nocardiosis,[99–102] *Rhodococcus*,[103] cryptococcosis,[69,104] aspergillosis,[105,106] and infections caused by other molds, such as the agents of scedosporiosis and mucormycosis, are also important in this population.[107,108] In the appropriate geographic areas, coccidioidomycosis, histoplasmosis, and blastomycosis are also important considerations in immunocompromised and noncompromised hosts.[73–78,109,110] In persons with acquired immunodeficiency syndrome (AIDS), coccidioidomycosis and histoplasmosis may be seen and are common AIDS-defining illnesses. Furthermore, in patients with AIDS, chronic pneumonia may be caused by *Rhodococcus equi, Pneumocystis jirovecii, Mycobacterium avium* complex, or noninfectious disorders, such as Kaposi sarcoma, lymphoma, and nonspecific interstitial pneumonitis.[111–117] The protozoa and helminths listed in Table 70.1 are uncommon causes of chronic pneumonia syndrome in persons living in industrialized countries, but they are important considerations for those who live in or have traveled to areas in which these agents are endemic.

EPIDEMIOLOGY

Age, Gender, and Race

A detailed history is an important first step toward establishing a specific diagnosis in patients with a chronic pneumonia syndrome. The significance of age and gender for patients with chronic pneumonia from other causes also usually relates, indirectly, to relevant epidemiologic factors. For example, an older adult is at higher risk of having a cerebrovascular accident, which in turn might predispose this patient to an aspiration episode and subsequent chronic bacterial pneumonia and abscess. Older debilitated patients are at higher risk for development of chronic necrotizing pneumonia caused by aerobic gram-negative bacteria.[49,51,54] Similarly, the gender of a given patient is likely to affect

TABLE 70.1 Causes of Chronic Pneumonia Syndrome

Infectious Agents That Typically Cause Chronic Pneumonia

Bacteria

Mixed aerobic and anaerobic bacteria (e.g., *Streptococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus anginosus* group, *Prevotella* spp., *Bacteroides* spp.)
Actinomyces spp.
Nocardia spp.
Rhodococcus equi
Burkholderia pseudomallei

Mycobacteria

Mycobacterium tuberculosis
Mycobacterium kansasii
Mycobacterium avium complex
Mycobacterium chelonae-abscessus complex
Mycobacterium szulgai
Mycobacterium xenopi
Mycobacterium malmoense
Mycobacterium terrae

Fungi

Aspergillus spp.
Blastomyces dermatitidis, B. gilchristii, B. helicus
Coccidioides immitis/posadosii
Cryptococcus neoformans
Cryptococcus gattii
Emergomyces spp. (*africanus, canadiensis,* and *pasteuriana*)
Emmonsia crescens, E. helica
Histoplasma capsulatum
Lomentospora prolificans
Paracoccidioides brasiliensis
Talaromyces marneffei
Pneumocystis jirovecii
Pigmented (dematiaceous) molds (see Chapter 268)
Scedosporium apiospermum
Sporothrix schenckii complex

Parasites

Dirofilaria spp.
Echinococcus granulosus, E. multilocularis
Filaria (tropical pulmonary eosinophilia)
Paragonimus westermani

Noninfectious Causes of Chronic Pneumonia

Neoplasia
Carcinoma (primary or metastatic)
Hodgkin disease and non-Hodgkin lymphoma
Other lymphoproliferative disorders
Cystic fibrosis
Sarcoidosis
Amyloidosis
Vasculitis (autoimmune diseases)
Systemic lupus erythematosus
Polyarteritis nodosa
Granulomatosis with polyangiitis (Wegener granulomatosis)
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
Goodpasture syndrome
Microscopic polyangiitis
Lymphomatoid granulomatosis
Progressive systemic sclerosis
Rheumatoid arthritis
Mixed connective tissue syndrome (overlap syndrome)
Chemicals, drugs
Radiation
Recurrent pulmonary emboli
Bronchial obstruction with atelectasis (e.g., tumor, foreign body)
Pulmonary sequestration
Pulmonary infiltration with eosinophilia syndrome
Löffler syndrome: usually transient
Pneumonia plus asthma (e.g., allergic bronchopulmonary aspergillosis)
Bronchocentric granulomatosis
Chronic eosinophilic pneumonia
Pneumoconiosis: asbestosis, berylliosis, silicosis, anthracosilicosis
Chronic form of extrinsic allergic alveolitis (hypersensitivity pneumonitis)

Other Lung Diseases: Cause Unknown

Chronic organizing pneumonia
Chronic interstitial pneumonia (fibrosing alveolitis, idiopathic pulmonary fibrosis)
Usual interstitial pneumonia (UIP)
Desquamative interstitial pneumonia (DIP)
Lymphocytic interstitial pneumonia (LIP)
Giant cell interstitial pneumonia (GIP)
Eosinophilic granuloma (pulmonary Langerhans cell histiocytosis X)
Lymphangioleiomyomatosis
Pulmonary alveolar proteinosis
Pulmonary alveolar microlithiasis
Idiopathic pulmonary hemosiderosis
Angiocentric immunoproliferative lesions

or determine occupation and hobbies and therefore the likelihood of exposure to certain infectious agents or other causative vehicles. Moreover, gender may predispose to certain rare chronic pulmonary disorders. For example, pulmonary lymphangioleiomyomatosis, a cause of chronic pneumonia, is a rare neoplastic disorder that occurs almost exclusively in adolescent and young adult women.[118] Racial and genetic characteristics are increasingly recognized as predisposing factors to severe disease manifestations from a variety of pathogens.[82,119–121] For example, chronic cavitary pulmonary tuberculosis is more common in blacks,[58,59] and disseminated coccidioidomycosis is much more likely in darker-skinned persons, including blacks, Filipinos, and Asians who have lived in or have traveled to an area endemic for *Coccidioides immitis* or *Coccidioides posadasii*.[74,76] Conversely, chronic cavitary histoplasmosis is much more likely in older white men with a history of emphysema.[71] Fungus ball (aspergilloma) of the lung occurs in a previously existing apical cavity in patients with prior sarcoidosis, histoplasmosis, tuberculosis, or other fibrocavitary lung disease.[88] Chronic necrotizing and invasive aspergillosis may occur in men with underlying chronic obstructive pulmonary disease and has been recognized as a postinfluenza complication.[88,122]

Occupation and Hobbies

An example of a condition linked to occupational and recreational behavior includes tuberculosis among health care workers and volunteers who work abroad in high-risk settings. Coccidioidomycosis may occur in desert rock collectors, laboratory technicians, archeologists conducting excavations, construction workers, hikers and campers, and others exposed to desert dust in the endemic area, which includes portions of northern Mexico, Argentina, California, Arizona, New Mexico, Utah, western Texas, and eastern Washington state. Histoplasmosis may occur in persons exposed to pigeon or starling roosts, those who clean out old chicken houses with dirt floors, those who cut and clear hollow trees, and those who demolish old buildings or explore caves inhabited by bats. Blastomycosis more often occurs in forestry workers, those who are earth-moving and heavy equipment operators, hunters, and other outdoorsmen. Unlike endemic fungal infections, cryptococcosis has *not* been strongly linked to occupational and recreational behavior,[123] perhaps reflecting the fact that *Cryptococcus neoformans* is a ubiquitous pathogen that is not geographically restricted. Moreover, good data suggest that a large proportion of the population is exposed to this organism early in life.[124] Furthermore, there has been no strong association between exposure to pigeon droppings and development of disease. Other associations include the following: echinococcosis in sheep herders; berylliosis in workers in the aircraft, electronics, and nuclear industries; the pneumoconioses (e.g., silicosis, asbestosis) in sandblasters and shipyard workers; and both chronic and acute pulmonary disease from repeated occupational or environmental exposure to the aerosolized organic antigens associated with extrinsic allergic alveolitis (hypersensitivity pneumonitis)[2,40,41] or to irritant gases, such as phosgene, ammonia, ozone, and nitrogen dioxide. Hypersensitivity reaction to *Mycobacterium avium* complex contaminating an indoor hot tub and causing interstitial pneumonia ("hot tub lung") occurs primarily in immunocompetent hosts.

Residence and Travel

Because the initial exposure to the microbiologic agents of many chronic or indolent infectious diseases may have occurred months or years before the disease appears, a detailed travel history is essential for any patient with chronic pneumonia. For example, if the patient has lived in the eastern half of the United States, especially the mid-South or upper midwestern regions, chronic pulmonary histoplasmosis and blastomycosis should be considered because the causative agents are endemic to that area. Likewise, coccidioidomycosis should be a strong consideration in a person with chronic cavitary pneumonia who has lived in or visited an area endemic for *Coccidioides immitis/posadasii*. Among patients with chronic pneumonia and a history of living in or travel to the US Pacific Northwest or British Columbia, infection due to *C. gattii* should be considered. Unlike some of the other endemic mycoses, where travel to the endemic area is sufficient to confer risk,[69,70] paracoccidioidomycosis should be realistically considered only for patients who have ever lived in Mexico, Central America, or the regions of South America that are endemic for *Paracoccidioides* spp.

In the setting of a potentially relevant travel history, in addition to identifying specific regions visited, it is often necessary to explore in detail rural versus urban exposure, the type of lodging, sources of drinking water, exposure to local foods, working environment, and other activities such as swimming and hiking. For example, a person who has lived or traveled extensively in Southeast Asia, particularly in low-lying or rice-growing areas, who manifests chronic pneumonia with pulmonary radiographic abnormalities resembling those of tuberculosis or a pulmonary mycosis, may be suffering from melioidosis.[125,126] Pulmonary paragonimiasis should be considered in the visitor to Southeastern Asia or the Philippines who consumes raw or partly cooked shellfish and who has chronic pulmonary symptoms plus dense, nodular lung opacities and ring shadows on the chest radiograph.[127]

Contacts, Habits, and Drugs

In the past few decades, most cases of pulmonary tuberculosis in the United States have been diagnosed in homeless persons, alcoholics, older adults, patients with human immunodeficiency virus (HIV), and immigrant population groups.[128,129] In patients and health care workers in whom tuberculosis is suspected, contacts among companions, relatives, or patients with tuberculosis should be sought. In addition, tuberculosis should be suspected in persons living or working in closed environments, such as jails and prisons, homeless shelters, drug rehabilitation centers, and nursing homes. Inquiry should be made into the patient's smoking and drinking histories and other personal habits. The likelihood of cancer of the lung and one of the invasive mycoses, such as aspergillosis and histoplasmosis, is greater in a smoker than in a nonsmoker. Aspiration pneumonia, chronic gram-negative bacillary pneumonia, tuberculosis, and pulmonary sporotrichosis are more likely to occur in an alcoholic than in a nondrinker. Intravenous drug users who inject heroin or other illicit agents are at risk for not only infection with HIV and subsequent development of AIDS but also septic pulmonary emboli associated with tricuspid or pulmonic valve infective endocarditis, necrotizing pneumonia, single or multiple lung abscesses, or an interstitial granulomatous reaction to the injected material, resulting in pulmonary hypertension (see Chapter 312). Similarly, frequent use of free-base (crack) cocaine has been reported to cause chronic organizing pneumonia, eosinophilic lung disease, interstitial pneumonitis, and pulmonary hemorrhage or infarction.[24,130]

More than 100 different pharmaceutical agents have been reported to cause acute and chronic pulmonary symptoms with radiographic abnormalities.[15–23,131–133] Early in the course of drug-induced pulmonary disease, the chest radiographic findings may be normal; later, an interstitial, nodular, or alveolar pattern (or a combination of these) may be present. Still later, chest radiography may reveal only a fibrotic pulmonary process. The agents that are most likely to cause chronic pulmonary disease include cytotoxic agents, such as bleomycin, busulfan, cyclophosphamide, methotrexate, nitrosoureas, noncytotoxic agents such as amiodarone, gold salts, nitrofurantoin, and penicillamine, as well as disease-modifying agents for rheumatologic disease, such as etanercept, infliximab, and leflunomide.[17–23] Because drug-induced pulmonary disease may develop after drug therapy has been discontinued, the physician should inquire not only about all drugs the patient is presently taking but also about those taken in the last 6 months.

Questions about recent antimicrobial therapy are critically important. Which antimicrobial(s) was used? Did the therapy result in radiographic or clinical improvement? If not, was the antimicrobial drug used in sufficient quantity and duration to cure the suspected process or alter its course? Was the appropriate agent used? What effect did the antimicrobial agent have on the results of cultures? Does the report of "normal flora" from the sputum culture merely reflect the elimination of a specific pathogen by antimicrobial therapy?

Underlying Disease

Pulmonary complications, including acute and chronic or refractory pneumonia, are especially common in persons with AIDS[111–116] and other conditions associated with impaired host immunity, such as high-dose corticosteroid therapy, cytotoxic therapy, hematopoietic stem cell and organ transplantation, Job syndrome, and chronic granulomatous disease.[134,135] Patients with poorly controlled diabetes mellitus or

preexisting chronic obstructive pulmonary disease are at higher risk for development of chronic or persistent bacterial pneumonia. Similarly, chronic obstructive lung disease commonly precedes fibrocavitary histoplasmosis or *M. avium* complex infection. Structural lung disease, such as preexisting bullae, bronchiectasis, and endobronchial lesions, may also predispose to chronic pneumonia. For example, recurrent or persistent pneumonia in the same area of the lung raises the suspicion of a local endobronchial lesion that may not be apparent on routine chest radiographs. Because aspiration may predispose to chronic pneumonia, inquiry should be made into a history of recent dental problems or manipulation, sinusitis with chronic nasal congestion, disorders of swallowing resulting from neurologic or esophageal disease, seizure disorders, recent anesthesia, quantity and frequency of alcohol consumption, and any illness leading to an unconscious state. Finally, it should be determined whether the chronic pneumonia is most likely community acquired or health care associated.

CLINICAL FEATURES

Symptoms

There are many causes of chronic pneumonia, and no single symptom complex is common to all causes. Often, nonspecific and constitutional symptoms, including fever, chills, and malaise, are present initially, followed by progressive anorexia and weight loss, indicating chronic illness. Pulmonary symptoms may be present early but frequently appear later in the course of the illness. Any patient with a prolonged illness and nonspecific constitutional complaints plus pulmonary symptoms, including a new or persistent cough, sputum production, hemoptysis, chest pain (especially pleuritic pain), or dyspnea, deserves medical evaluation, including a routine chest radiograph and, when findings on these studies are nonspecific and suggestive of a chronic parenchymal process, a computed tomography (CT) examination of the chest.

Evidence of extrapulmonary involvement should be explored with each patient. For example, chronic pneumonia with skin lesions should suggest coccidioidomycosis, blastomycosis, or, in the appropriate epidemiologic setting, paracoccidioidomycosis. Similarly, cryptococcosis, nocardiosis, histoplasmosis, talaromycosis, and Kaposi sarcoma should be important considerations for patients with skin lesions and with AIDS or other conditions associated with significant impairment of cell-mediated immune function. Mucous membrane lesions should also raise the possibility of histoplasmosis, paracoccidioidomycosis, talaromycosis, or Kaposi sarcoma. Monoarticular or polyarticular arthritis, polyarthralgia, or localized bone tenderness or pain may indicate systemic vasculitis or sarcoidosis. A history of chronic pneumonia with persistent headache and abnormal cerebrospinal fluid (CSF) should raise the suspicion of tuberculosis, cryptococcosis, or coccidioidomycosis involving the lungs and central nervous system (CNS). The presence of focal neurologic signs and symptoms is strong clinical evidence for a space-occupying lesion in the CNS; such findings in a patient with a cavitary infiltrate seen on a chest radiograph suggest the possibility of a brain abscess associated with chronic suppurative lung disease caused by nocardiosis[101–103] and microaerophilic or anaerobic bacteria, or an endemic fungal infection, such as blastomycosis, adiaspiromycosis, or histoplasmosis.[44,45,46,47] Similarly, the triad of skin nodules, pulmonary nodules, and CNS abnormalities suggests lymphomatoid granulomatosis.[7,8,9]

Signs

Although the findings on physical examination of the chest are usually not helpful in differentiating specific causes of chronic pneumonia, the presence of generalized wheezing or other signs of bronchospasm, in the absence of underlying lung disease, indicates an asthmatic component to the pulmonary illness and raises the possibility of a disorder causing both pneumonia and asthma, such as extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis, or allergic angiitis and granulomatosis (Churg-Strauss syndrome). Similarly, localized wheezing suggests the presence of an endobronchial obstructing lesion. The findings of tachycardia, cardiomegaly, gallop rhythm, and ankle edema provide evidence of cardiac disease, suggesting that the pulmonary symptoms and signs result at least in part from cardiovascular causes. The presence of skin lesions, clubbing, cyanosis, or phlebitis is not specific for any single pulmonary disorder but may help narrow the differential diagnosis, especially when considered along with other clinical and epidemiologic information. The presence of abnormal liver function, lymphadenopathy, hepatomegaly, and/or splenomegaly with chronic pneumonia suggests a systemic disorder involving the reticuloendothelial system, such as non-Hodgkin lymphoma, sarcoidosis, chronic disseminated histoplasmosis, or tuberculosis.

DIAGNOSTIC PROCEDURES

Initial Laboratory Studies

Routine laboratory studies can provide important clues to diagnosis. Pancytopenia suggests miliary tuberculosis, disseminated histoplasmosis, or a myelophthisic disorder, such as metastatic tumor or lymphoma involving the bone marrow. Isolated anemia is commonly associated with chronic pneumonia but is a nonspecific finding. A normal leukocyte count does not exclude infection. In particular, chronic fungal pneumonia may be associated with a normal or minimally elevated leukocyte count. Leukopenia or lymphopenia should raise the suspicion of an HIV infection. In addition, leukopenia is consistent with a diagnosis of sarcoidosis, systemic lupus erythematosus, tuberculosis, histoplasmosis, or neoplasia. A leukemoid reaction is nonspecific and may be seen in conjunction with almost any infectious cause of chronic pneumonia. Leukocytosis with polymorphonuclear cell predominance is suggestive of, but not specific for, a bacterial cause, including actinomycosis, but is also seen in granulomatosis with polyangiitis.

Routine laboratory tests that measure the function of other organs may provide more helpful information. Liver function studies, including bilirubin, alkaline phosphatase, and serum aspartate aminotransferase determinations and prothrombin time, should be performed for most patients. Urinalysis, with particular attention to the urinary sediment, plus tests of renal function, including measurement of blood urea nitrogen and creatinine, should also be done. Abnormalities of liver function (especially elevated enzyme levels), kidney function, or both should raise the suspicion of disorders that are not limited to the lung but are known to involve multiple other organs, including the liver and kidney. Such disorders include disseminated histoplasmosis and disseminated mycobacteriosis, as well as the vasculitides, sarcoidosis, and certain neoplastic diseases, especially the lymphoproliferative disorders.

In a patient with an abnormally low serum globulin level, a quantitative serum immunoglobulin determination should be obtained to evaluate for common variable immunodeficiency disorder or other disorders associated with hypogammaglobulinemia. Studies that should be performed in patients with suspected vasculitis include serologic tests for antinuclear antibodies, rheumatoid factor, cytoplasmic antineutrophil cytoplasmic autoantibodies (C-ANCAs), C-reactive protein, and erythrocyte sedimentation rate. In addition, measurement of serum angiotensin-converting enzyme may be useful, although it is a nonspecific test for which levels are increased in patients with a number of granulomatous disorders, including 30% to 80% of patients with sarcoidosis.[28,29]

Additional Studies

Basic core studies should be performed on all patients with chronic pneumonia, regardless of the suspected cause, but there should be flexibility in choosing additional tests or procedures to confirm a specific diagnosis. The orderly sequence of diagnostic studies described in the following sections necessarily results in oversimplification and consequently overlooks the unique aspects of a given patient's illness.

Chest Radiographic Studies

The chest radiograph, including posteroanterior and lateral films, is a reasonable screening procedure, but high-resolution CT[136] provides invaluable information. On occasion, magnetic resonance imaging is helpful, particularly in the evaluation of the noninfectious causes of chronic pneumonia. Positron emission tomography (PET) scanning (fluorodeoxyglucose PET), which measures metabolism by glucose uptake, has often proved disappointing in distinguishing malignant from infectious lung lesions. In Table 70.2, disorders are grouped according to the type of radiologic abnormality that is characteristic of the disease. In some disorders there is a spectrum of radiologic manifestations, and these disorders appear more than once in the table. Typical radiographic findings may provide clues to specific diagnoses. For

TABLE 70.2 Radiologic Patterns of Diseases: Common Causes of Chronic Pneumonia.

PATTERN OF DISEASE	FEATURES
Diseases That Cause Patchy Infiltrates and/or Bronchopneumonia or Lobar Consolidation	
Infectious Processes	
Aspiration pneumonia secondary to mixed aerobic and anaerobic infection	Usually dependent portions; superior or basilar segments of lower lobes, or posterior segments of upper lobes; pleural involvement with empyema common
Necrotizing pneumonia secondary to infection by Enterobacteriaceae, *Pseudomonas aeruginosa, Staphylococcus aureus,* or *Nocardia*	Any lobe or segment
Actinomycosis	Commonly involves lower lobes; cavitation frequently present; pleural involvement with empyema common, may extend into chest wall
Tuberculous exudative pneumonia	Not restricted to upper lobes; often bilateral, with perihilar distribution
Blastomycosis	Often a dense area of lobar or segmental consolidation; cavities may form; calcification and pleural disease infrequent
Cryptococcosis	Single or multiple infiltrates, often with sharp border, occasionally cavitary, rarely calcified; pleural effusions
Paracoccidioidomycosis	Asymptomatic bilateral fluffy infiltrates; may be extremely indolent and asymptomatic at presentation
Pneumocystis jirovecii	In addition to causing an acute diffuse pneumonia, *Pneumocystis* pneumonia may appear as dense infiltrates or nodules with granulomas resembling histoplasmosis on histopathology
Noninfectious Processes	
Chronic eosinophilic pneumonia	Rapidly progressive, dense infiltrates; usually peripheral (pattern is the reverse of pulmonary edema)
Bronchiolitis obliterans organizing pneumonia	Patchy nonsegmental areas of consolidation, often subpleural and bilateral; large irregular nodules
Diseases That Cause Pulmonary Cavitation	
Infectious Processes	
Pyogenic lung abscess complicating aspiration pneumonia	Usually single cavity; location same as aspiration pneumonia; air-fluid level common
Complicated necrotizing pneumonia	May involve any lobe; often multiple and bilateral, depending on route of acquisition of pneumonia
Tuberculosis-reactivation or adult type	Usually upper lobes; often bilateral; may be multiple; fibrosis and calcification common
Atypical mycobacterial disease	Radiologically indistinguishable from tuberculosis, except that cavitation may be more frequent
Melioidosis	May be acute or chronic and involve any lobe
Rhodococcal pneumonia	Simulates tuberculosis or nocardiosis; cavitation common
Histoplasmosis, chronic cavitary	Mimics tuberculosis; upper lobes frequently involved but any lobe can be involved; unilateral or bilateral
Coccidioidomycosis	Usually a single, thin-walled cavity with minimal involvement of surrounding lung; occasionally a thick-walled cavity surrounded by extensive parenchymal disease
Sporotrichosis	May mimic tuberculosis but can involve any lobe; cavitation is frequent
Aspergillosis	Single or multiple areas of pneumonia with or without central cavitation; not to be confused with pulmonary mycetoma ('fungus ball')
Paragonimiasis	Cystlike lesions and cavities, usually associated with linear or patchy infiltrates, fibrosis, and/or calcification
Echinococcosis	Single or multiple discrete, sharply defined, round lesions (cysts) with little surrounding inflammatory response; cavitation and/or calcification may occur
Noninfectious Processes	
Granulomatosis with polyangiitis and lymphomatoid granulomatosis	Often, multiple nodules with cavitation; may be unilateral or bilateral granulomatosis
Silicosis	Associated with conglomerate nodular densities, frequently in upper lobes; usually superimposed on background of diffuse nodulation; rarely, eggshell calcification of hilar nodes
Bronchogenic carcinoma	Thick-walled cavitation more common in squamous cell type
Lymphoma, especially Hodgkin's disease	Cavitation may occur in peripheral parenchymal nodules
Kaposi sarcoma	Small or large nodules associated with peribronchial cuffing and "tram track" opacities
Diseases That Cause One or More Dense, Well-Circumscribed Nodules	
Dirofilariasis (usually single)	—
Histoplasmosis (histoplasmoma)	May have calcification in center or in hilar nodes
Coccidioides spp. (coccidioidoma)	May have calcification in center or in hilar nodes
Cryptococcosis (cryptococcoma)	Often multiple, cavitation occasionally, calcification rare
Tuberculosis (tuberculoma)	May have calcification in center or in hilar nodes
Malignancy	—

TABLE 70.2 Radiologic Patterns of Diseases: Common Causes of Chronic Pneumonia.—cont'd

PATTERN OF DISEASE	FEATURES
Infectious and Noninfectious Diseases That Cause Chronic Diffuse Pulmonary Infiltration and Fibrosis	
Alveolar Pattern	
Bronchioloalveolar carcinoma	
Intrapulmonary bleeding (e.g., Goodpasture syndrome, diffuse alveolar hemorrhage)	
Pulmonary alveolar proteinosis	
Ground-Glass Pattern	
Sarcoidosis	
Early asbestosis or berylliosis	
Mycobacterium avium complex "hot tub lung" (hypersensitivity)	
Chronic organizing pneumonia (formerly bronchiolitis obliterans organizing pneumonia)	
Nodular Interstitial Pattern, Including Miliary Spherical Nodules	
Granulomatous infectious diseases (e.g., miliary tuberculosis, disseminated histoplasmosis)	
Sarcoidosis	
Lymphangitic carcinomatosis	
Granulomatosis and polyangiitis	
Lymphomatoid granulomatosis	
Allergic angiitis and granulomatosis	
Rheumatoid lung disease	
Pneumoconiosis (including asbestosis, silicosis, and berylliosis)	
Linear Interstitial Pattern, Including Fine Reticular Markings and Dense Fibrosis	
Chronic form of hypersensitivity pneumonitis	
Idiopathic pulmonary hemosiderosis	
Radiation injury—chronic	
Progressive systemic sclerosis	
Sarcoidosis	
Rheumatoid arthritis	
Idiopathic pulmonary fibrosis	
Honeycombing (Coarse Reticular Pattern With Cystic Air Spaces)	
Advanced form of fibrosing alveolitis	
Bronchiectasis	
Eosinophilic granuloma (pulmonary Langerhans cell histiocytosis X)	
Sarcoidosis	
Idiopathic pulmonary interstitial pneumonia	

example, demonstration of anterior mediastinal involvement argues strongly in favor of neoplasia, including lymphoma, thymoma, and metastatic carcinoma, as the cause of chronic pneumonia syndrome and argues against an infectious cause.

Tuberculosis and nontuberculous mycobacterial diseases, histoplasmosis, coccidioidomycosis, sporotrichosis, paragonimiasis, and the pneumoconioses, especially silicosis, are characteristically associated with fibrocavitary disease—a contracted area of lung with linear fibrosis, nodular or rounded densities, and cavitation.[137] In addition, tuberculosis, chronic fibrocavitary histoplasmosis, pulmonary mycetoma or "fungus ball," and silicosis characteristically involve the upper lobes. Many experts believe that anterior segment upper lobe involvement argues strongly against tuberculosis as a cause. A thin-walled parenchymal cavity is suggestive of coccidioidomycosis, sporotrichosis, or paragonimiasis, whereas a thick-walled cavity surrounded by an area of pneumonitis is more typical of tuberculosis, other mycobacterial infections, histoplasmosis, aspergillosis, melioidosis, nocardiosis, actinomycosis, pyogenic lung abscess, lung disease caused by *R. equi,* and squamous cell carcinoma. The presence of the "halo sign," a ring of enhancement surrounding a cavitary pulmonary lesion on chest CT in a severely immunocompromised patient, suggests invasive mold infection, especially invasive aspergillosis or mucormycosis.[138,139] The "reverse halo sign" may also be useful in this group and suggests pneumonia due to Mucorales.[140,141] Cavitation is seen but is less common in blastomycosis and cryptococcosis. Mediastinal and/or hilar lymph node calcification and occasionally parenchymal calcification are typical of tuberculosis, histoplasmosis, and coccidioidomycosis but are rare in actinomycosis, nocardiosis, blastomycosis, and cryptococcosis. Abscess of the chest wall or osteomyelitis of a rib adjacent to the pneumonia or pleural effusion (empyema necessitans) may be seen in actinomycosis, nocardiosis, blastomycosis, and tuberculosis. Although these radiographic manifestations of selected pulmonary diseases are typical in most patients, experience during the AIDS pandemic has shown that pulmonary diseases in these patients may be highly atypical in radiographic appearance and clinical course. Representative routine chest radiographs and chest CT images are shown in Figs. 70.1 through 70.15.

Patients With Radiographic Evidence of Localized Infiltrates or Cavitation

In all patients with radiographic evidence of localized infiltrates or cavitation in the setting of chronic pneumonia, examination of the sputum is essential. This is in striking contrast to the questionable value of sputum in the setting of acute community-acquired pneumonia.[142–144] The specimen of sputum must be a representative sample (i.e., a deep, coughed specimen). If the expectorated sputum is of adequate volume and is acceptable after cytologic screening, other procedures to obtain sputum may not be necessary. Microscopic examination of sputum may include the following:

1. Gram staining for bacteria and actinomycetes
2. Acid-fast staining for mycobacteria and modified acid-fast staining for *Nocardia*
3. Wet mount for fungi and eggs of *Paragonimus* (calcofluor white or potassium hydroxide preparation with phase contrast may enhance detection of fungi)
4. Cytologic preparations for neoplastic cells, eosinophils, and fungi

Generous volumes of expectorated sputum should also be sent to the microbiology laboratory for culture of bacteria, fungi, and mycobacteria. In addition, contacting the microbiology laboratory personnel directly to alert them to specific etiologic considerations is often helpful in confirming a suspected diagnosis. In this way, specimens can be inoculated on the most appropriate media, and the microbiologists can be made more aware of the likely pathogens.

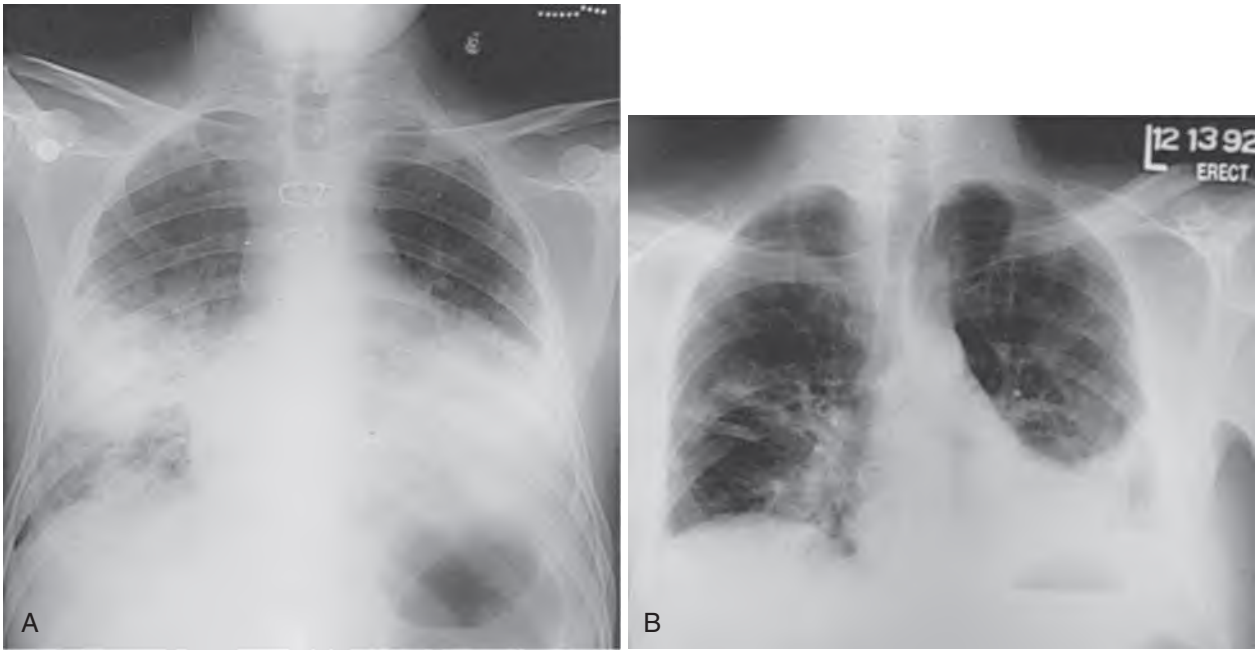

FIG. 70.1 (A) Chronic organizing pneumonia (COP) in a 32-year-old man who developed progressive chronic pneumonia several weeks after an open pericardiectomy to relieve cardiac tamponade associated with renal failure. Note the bilateral airspace consolidation. Bronchoscopy with transbronchial biopsy was nondiagnostic. The diagnosis of COP was established from tissue obtained at open lung biopsy. Corticosteroid therapy was dramatically beneficial. (B) COP in a 60-year-old man with a 1-month illness manifested by fever, malaise, weight loss, nonproductive cough, dyspnea, and bilateral subpleural nodular opacities. Both symptoms and radiographic abnormalities progressed during antibiotic therapy. A bronchoscopy with transthoracic biopsy was nondiagnostic. The diagnosis of COP was made from tissue obtained at open lung biopsy. Corticosteroid therapy was beneficial.

FIG. 70.2 Lymphangioleiomyomatosis. This 42-year-old woman had a 6-month history of progressive dyspnea and intermittent blood-streaked sputum. She denied fever or history of pneumothorax. Note the diffuse reticular pattern with areas of cystic dilatation and enlarged lung volumes. A pathologic diagnosis was made from lung tissue obtained by transbronchial biopsy.

FIG. 70.3 Atypical tuberculosis caused by *Mycobacterium avium* complex. This 52-year-old man had chronic obstructive pulmonary disease. He had an 18-month history of fever, weight loss, cough, intermittent hemoptysis, and progressive dyspnea associated with persistently positive acid-fast smears and cultures of expectorated sputum and worsening chest films despite appropriate antimycobacterial therapy. Note the bilateral lower lobe fibronodular disease, worse in the right lung, associated with cavitation.

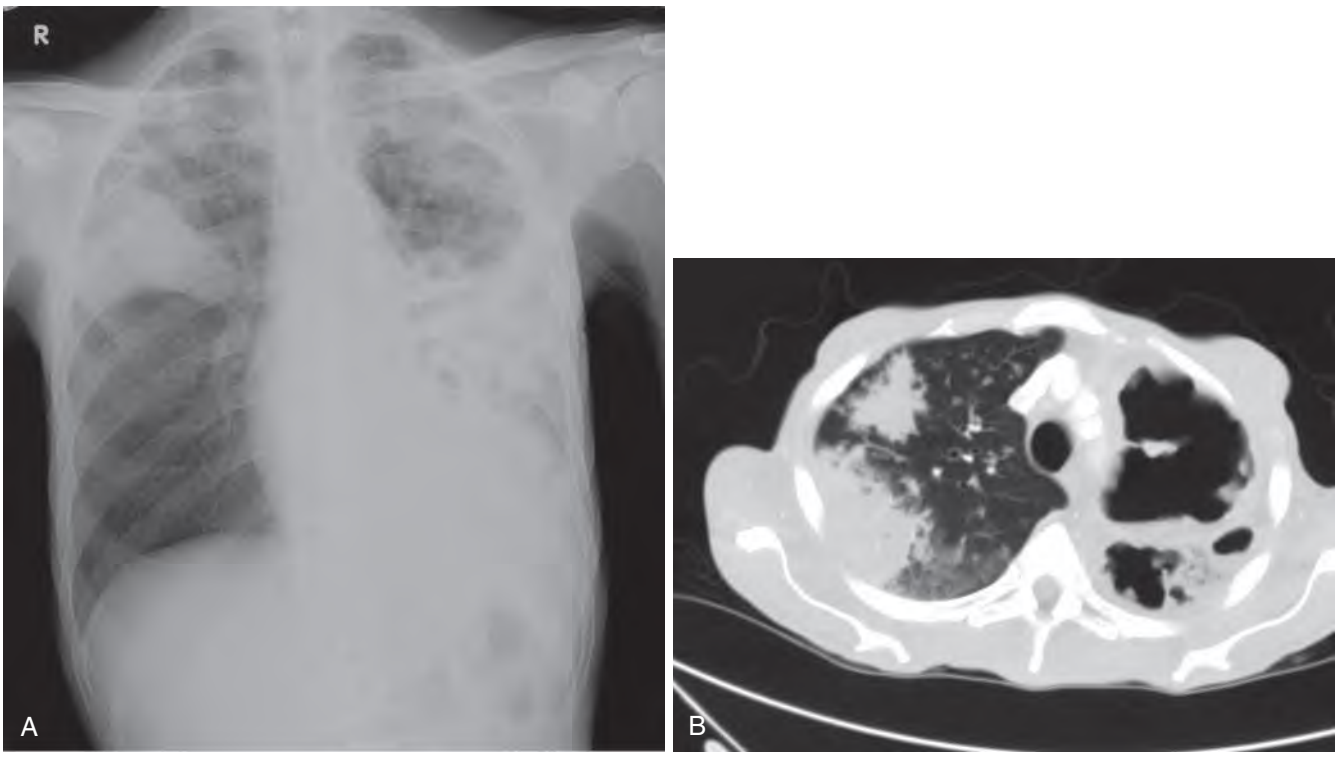

FIG. 70.4 (A) Pulmonary tuberculosis in a 45-year-old man with a 6-month history of cough, hemoptysis, fever, and a 35-lb weight loss. He was HIV negative. Sputum smears were positive for acid-fast bacilli, and cultures were positive for *Mycobacterium tuberculosis*. (B) Note bilateral parenchymal disease and near-total destruction of the left lung.

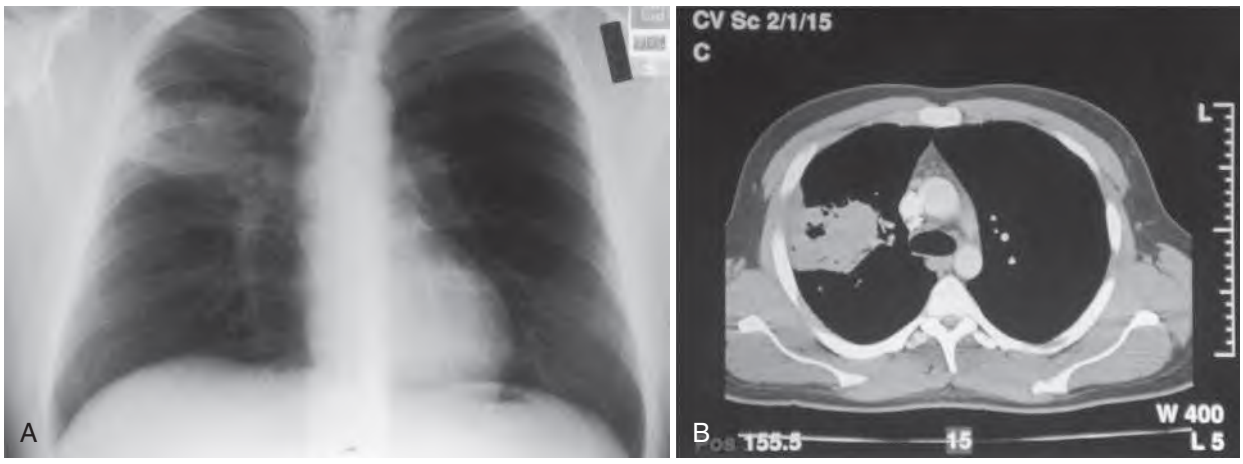

FIG. 70.5 (A) Pulmonary blastomycosis in a 24-year-old man who worked as a heavy equipment operator. He was also an avid hunter. He reported fever, night sweats, and a productive cough for 6 weeks unresponsive to outpatient antibacterial therapy. He had lost 25 lb during this time. He denied skin lesions or bone pain. Note the right upper lobe infiltrate on plain chest film. (B) Chest computed tomography scan shows a dense right upper lobe infiltrate with a central cavity not seen on plain films. Diagnosis was established by video-assisted thoracoscopy biopsy. Histopathology revealed broad-based budding yeasts, and cultures were positive for *Blastomyces dermatitidis*.

With appropriate communication, newer diagnostic techniques (e.g., rapid culture techniques, molecular probes, polymerase chain reaction [PCR], antigen detection assays, enzyme immunoassay [EIA]) can be used in a rational and thoughtful manner to facilitate laboratory diagnosis.[145–151] In particular, serum or urine antigen assays for the diagnoses of cryptococcosis, histoplasmosis, coccidioidomycosis, and blastomycosis are useful.[145–150] Nucleic acid–based tests for detection of *M. tuberculosis* are commercially available and diagnostically helpful (see Chapter 249).

When an infectious cause is being considered, cultures from other appropriate sources should be obtained. These may include the following: blood, urine, and pleural fluid from all patients with pleural effusion (pleural tissue should also be obtained for culture); CSF from all patients with CNS symptoms or signs; synovial fluid from all patients with joint effusion; and samples of skin, subcutaneous aspirate, mucous membrane, or any tissue obtained at biopsy.

If adequate sputum cannot be readily produced via spontaneous expectoration by the patient, consider these methods: (1) sputum induction by hypertonic aerosol and ultrasonic nebulization, hydration, chest physiotherapy, or postural drainage and (2) bronchoscopy for bronchial brushing, transbronchial biopsy, bronchoalveolar lavage (BAL), or protected specimen brush sampling of lower respiratory tract secretions.

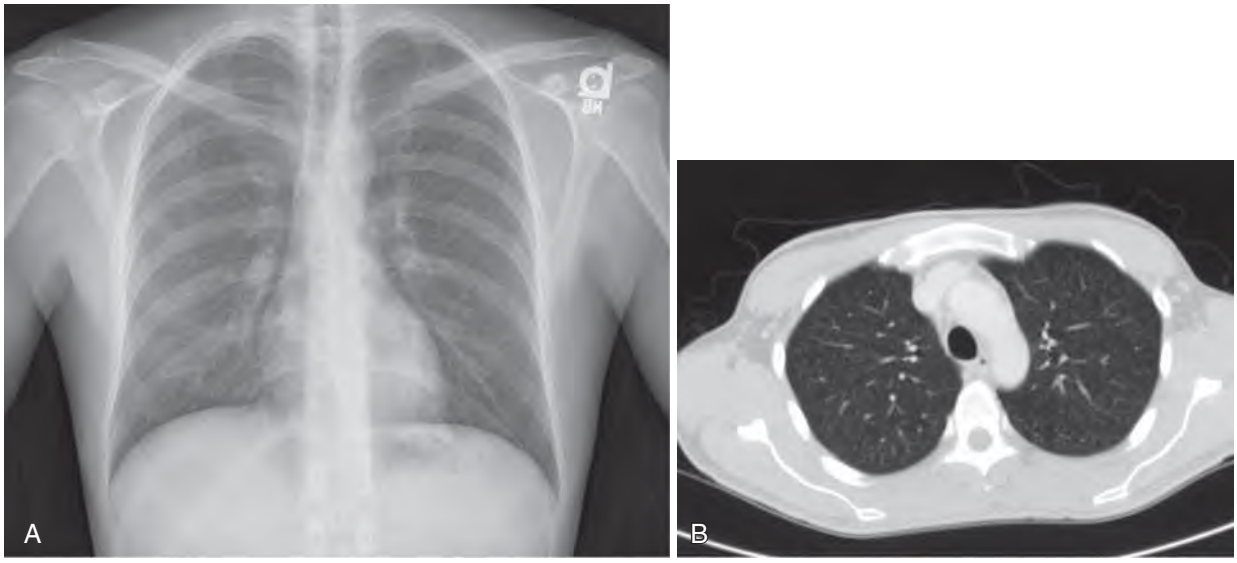

FIG. 70.6 (A) 68-year-old with fever, cough, and 20-lb weight loss over the past 6 months. Routine chest radiograph reveals a classic miliary pattern. Transbronchial biopsy revealed granulomata without organisms; cultures were positive for *Mycobacterium tuberculosis*. (B) Chest computed tomography on this patient reveals diffuse interstitial nodular findings consistent with miliary tuberculosis.

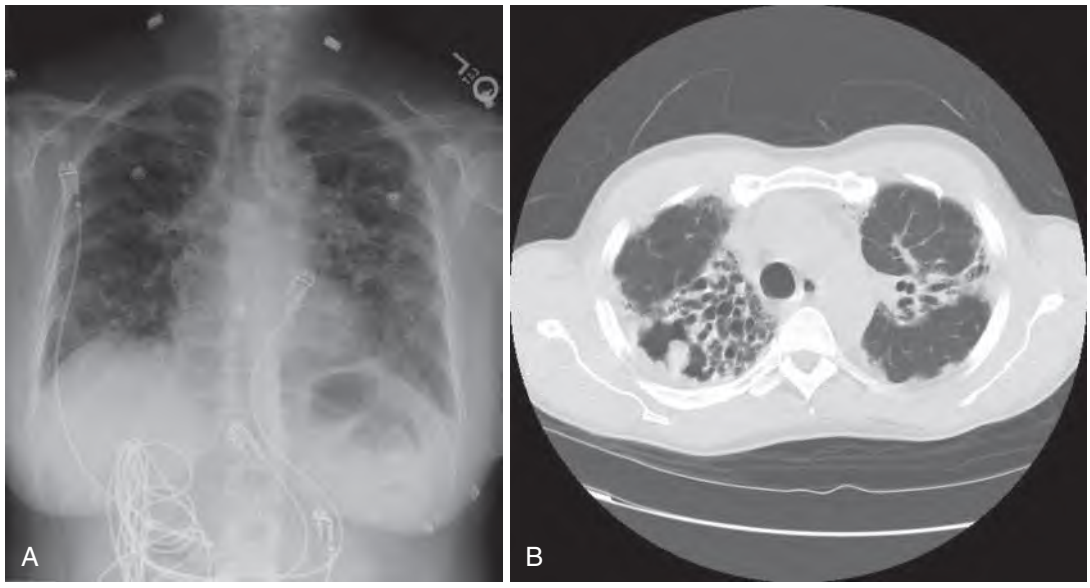

FIG. 70.7 (A) This 45-year-old woman with long-standing pulmonary sarcoidosis has had progressive exertional dyspnea and occasional cough productive of scant hemoptysis. She has received intermittent oral glucocorticosteroids with symptomatic relief but insidious disease progression. (B) A computed tomography scan of this patient reveals extensive fibrocavitary disease with honeycombing and bronchiectasis. There is a pulmonary aspergilloma (mycetoma) in the superior segment of the right lower lobe, noted to be the likely source of hemoptysis.

Quantitative PCR for *P. jirovecii* on BAL specimens is more sensitive than direct fluorescent microscopy, but low-level positivity occurs in patients who are pulmonary carriers (see Chapter 269). PCR on BAL specimens for *Aspergillus* have been used in some centers, largely in Europe, as one of the many factors considered in the diagnosis of invasive pulmonary aspergillosis, along with BAL galactomannan (GM). Standardization of the technique across centers is in progress.[152] Commercially available PCR kits for *Aspergillus* are available in some overseas countries.

Skin tests are appropriate when certain infectious causes are being considered. The tuberculin skin test with purified protein derivative and the interferon-γ release assays on blood are commonly used to detect exposure, although seriously ill patients may be anergic. Skin test antigens for the detection of infection with NTM and sporotrichosis are not commercially available. Skin tests of the tuberculin type are no longer commercially available for patients with suspected histoplasmosis. Coccidioidin is also no longer available, but the spherusol skin test has been US Food and Drug Administration approved for detecting exposure to *Coccidioides immitis*.

Serologic tests for HIV should be performed for all patients with unexplained chronic pneumonia. In addition, serologic tests may be helpful when other infectious causes, especially fungi, are considered. However, there may be problems with some of these tests, including delays in obtaining results and limited sensitivity and specificity. The lateral flow assay (LFA) for *Coccidioides* is a rapid new test that can screen for any form of coccidioidomycosis, but a positive result should

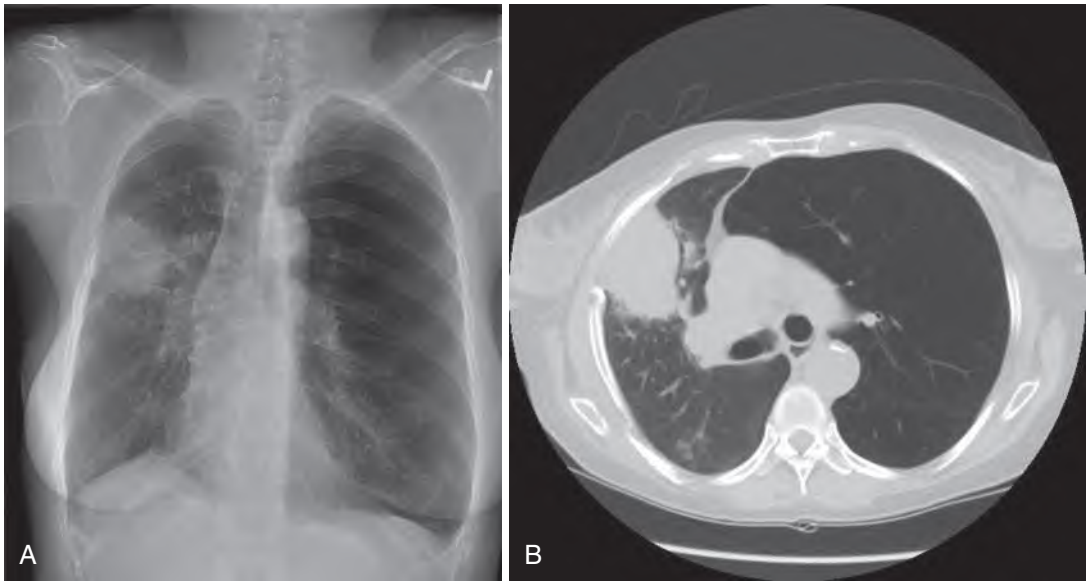

FIG. 70.8 (A) This 64-year-old black female who underwent single-lung transplantation for chronic obstructive pulmonary disease presented with fever and cough for 10 days. The chest radiograph revealed a dense and well-circumscribed nodular infiltrate in the right midlung zone. Blood and bronchoalveolar lavage cultures were positive for *Rhodococcus equi*. (B) A computed tomography scan of the same patient reveals a pleural-based, large, masslike lesion without cavitation in the transplanted lung.

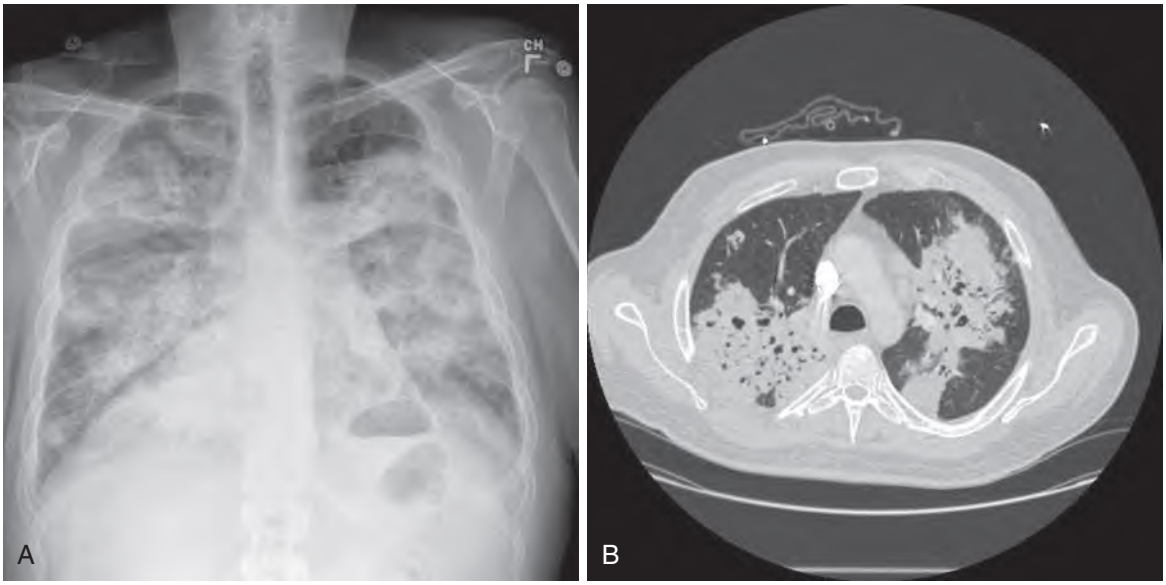

FIG. 70.9 (A) This 38-year-old white male landscaper with poorly controlled diabetes had progressive dyspnea, cough productive of yellowish sputum, fever, and weight loss over 2 months. His chest radiograph on presentation reveals diffuse infiltrates of both lungs with a somewhat nodular character. Sputum and bronchoalveolar lavage (BAL) fungal cultures were positive for *Blastomyces dermatitidis.* (B) A computed tomography scan obtained of the same patient reveals bilateral, dense, multilobar infiltrates with small areas of cavitation. A diagnosis of blastomycosis was initially suspected on the basis of finding broad-based budding yeasts on special stains of BAL fluid.

be confirmed with a more traditional EIA complement fixation or immunodiffusion assay for antibody to *Coccidioides* spp. These assays are especially helpful in patients with disseminated or fibrocavitary coccidioidomycosis but are usually not above background positivity in patients with a solitary pulmonary cavity (see Chapter 265). Serum cryptococcal antigen may be detectable in greater than 50% of nonimmunocompromised patients with pulmonary cryptococcosis; a greater proportion of patients with extrapulmonary disease will have positive serum cryptococcal antigen.[69] The availability of the LFA for cryptococcal antigen should facilitate the performance of this test in resource-poor environments.[153] This new assay is easily performed in 15 minutes, and it is generally more sensitive than the more cumbersome latex agglutination and EIA assays.[153] *Histoplasma* antigen in serum or urine is helpful in disseminated histoplasmosis but less commonly positive in infection confined to the lung, especially in nonimmunocompromised patients. Sensitivity depends on the laboratory performing the test. There is no standardization between laboratories. Serologic tests for paracoccidioidomycosis are available in the endemic area and useful. The serum and BAL EIA GM assay for early diagnosis of acute invasive aspergillosis is useful in hematologic malignancy and stem cell transplantation patients, but its utility in other patient populations is poorly established.[152,154–156] Among patients with suspected tuberculosis but with negative culture

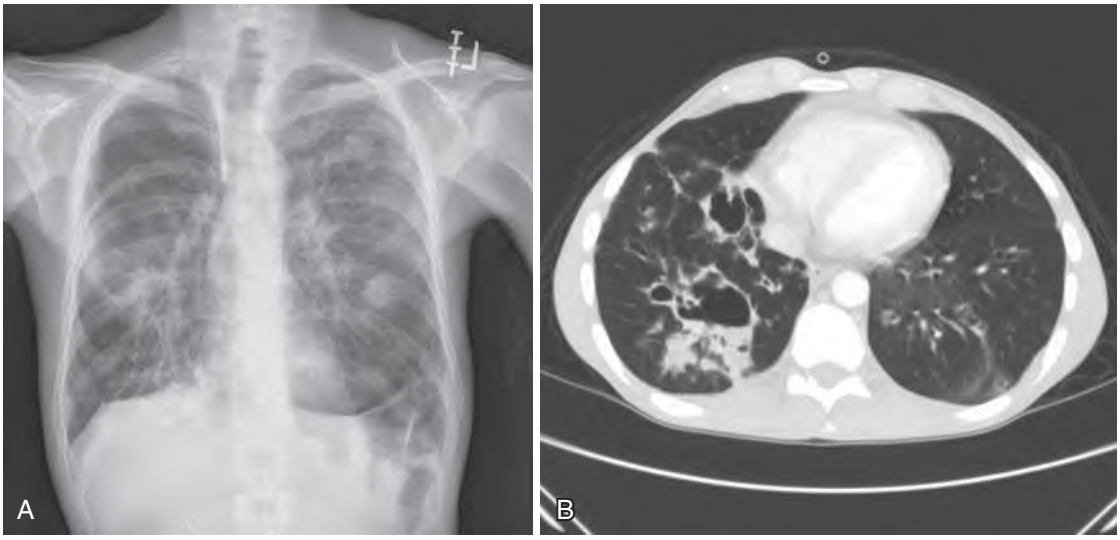

FIG. 70.10 (A) This 68-year-old white male with acute myelogenous leukemia had recently undergone myeloablative chemotherapy as part of his induction course. He experienced profound and prolonged neutropenia, and on the 21st day of fever and neutropenia he complained of cough and scant hemoptysis. A routine chest radiograph revealed multiple nodular lesions in both lungs, some with cavitation. A diagnosis of invasive aspergillosis was suspected, and a serum and bronchoalveolar lavage galactomannan were both positive (1.1 and 2.3, respectively), thus establishing a diagnosis of probable invasive pulmonary aspergillosis. (B) A computed tomography scan from the same patient reveals multiple cavitary lesions from the right lung consistent with invasive pulmonary aspergillosis. Extensive cavitation such as shown is not usually observed until neutropenia has improved or immunosuppression has lessened.

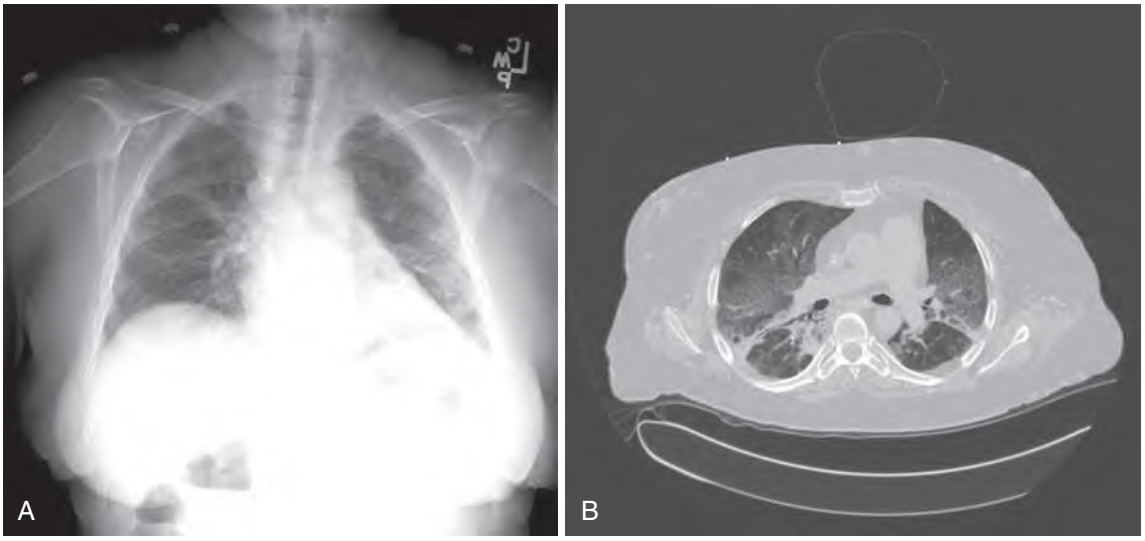

FIG. 70.11 (A) This 32-year-old white female is status postrenal transplant approximately 10 years ago and now presents with progressive, nonproductive cough and low-grade fever over the past 2 months. A routine chest radiograph reveals diffuse interstitial infiltrates without pulmonary nodules or a focal pulmonary infiltrate. (B) A computed tomography scan obtained on the same patient reveals diffuse interstitial infiltrates bilaterally with the "crazy-paving" pattern typical of pulmonary alveolar proteinosis. Diagnosis was confirmed by bronchoscopy with the finding of copious milky-white material on bronchoalveolar lavage. At that time she was also found to have a concomitant *Mycobacterium avium* complex pulmonary infection.

and histopathologic studies, the quantiFERON-Gold (Qiagen; Germantown, MD) in-tube test or the T-Spot TB assay may be a useful alternative to skin testing for detecting exposure to tuberculosis.[157–159] If hypersensitivity pneumonitis is suspected, serum can be examined for precipitating antibodies to various inhalant antigens and, if allergic bronchopulmonary aspergillosis is suspected, total serum immunoglobulin (Ig)E and serum IgG anti-*Aspergillus* antibody levels can be measured. Finally, serologic tests for rare causes of chronic pneumonia, such as *Legionella* spp., *Chlamydia pneumoniae,* and *Coxiella burnetii,* should be considered for appropriate patients. Multiplex PCR panels for respiratory samples are able to detect a variety of microbial agents but are most useful in acute, community-acquired pneumonia. Urine antigen testing for *Legionella* also should be considered in pneumonia of more acute onset.

Invasive Procedures

Certain clinical situations dictate a more aggressive diagnostic approach. In patients who are unable to raise sputum spontaneously and in whom attempts to induce sputum production are unsuccessful, invasive procedures may be necessary. Fiberoptic bronchoscopy is usually the initial procedure. It is diagnostically most helpful when accompanied by BAL and transbronchial biopsy, with appropriate microbiologic and histologic studies. Analysis of BAL fluid may increase the diagnostic yield of bronchoscopy, especially in immunocompromised persons, such as patients with AIDS and suspected opportunistic infections or patients with suspected noninfectious causes of chronic pneumonia. Continued bloody return on BAL confirms the diagnosis of diffuse alveolar hemorrhage in patients after allogeneic hematopoietic stem cell

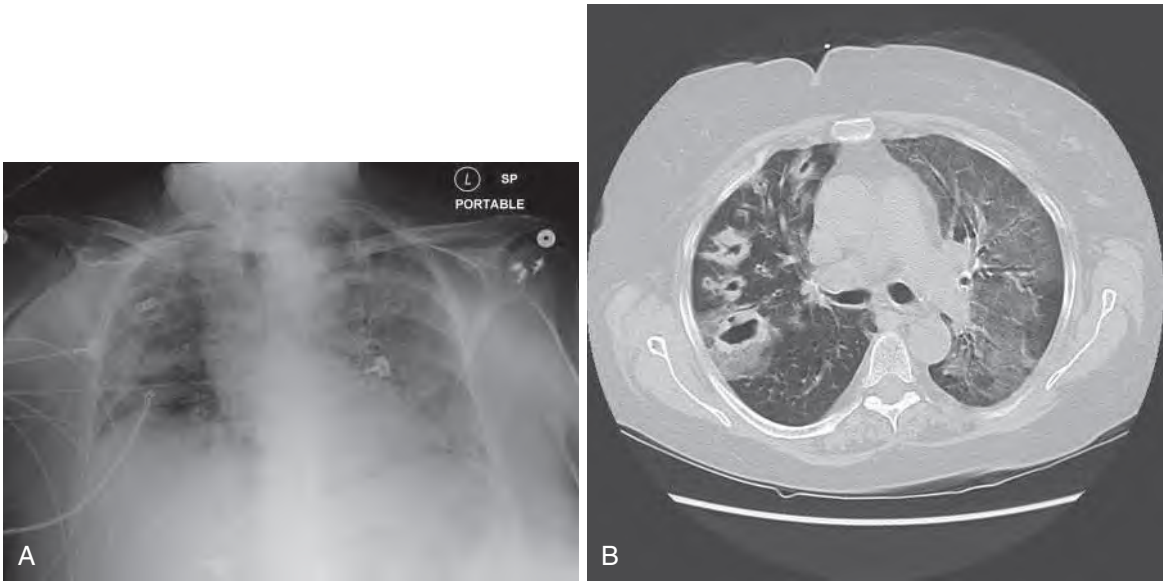

FIG. 70.12 (A) A 68-year-old former nurse presented with fever and cough productive of yellowish, blood-tinged sputum for 2 weeks. She is a smoker with chronic obstructive pulmonary disease and asthma. She received intermittent glucocorticosteroids for asthma exacerbations. Methicillin-susceptible *Staphylococcus aureus* (MSSA) was recovered from sputum, and a bronchoalveolar lavage revealed 4+ gram-positive cocci in clusters among sheets of neutrophils. Cultures were positive for MSSA. (B) A computed tomography scan from the same patient reveals bilateral alveolar infiltrates with well-circumscribed cavitary lesions consistent with the diagnosis of community-acquired MSSA pneumonia.

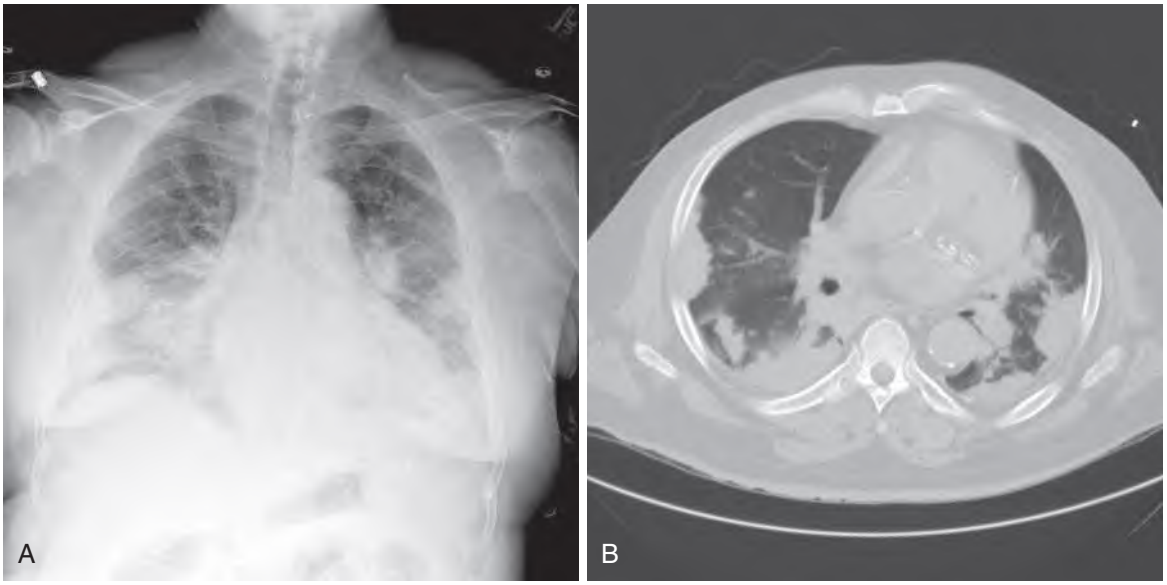

FIG. 70.13 (A) This 71-year-old black male with history of a renal transplant approximately 5 years ago presents with fever, cough, exertional dyspnea, and mild headache over the past 4 weeks. He is stable on his current immunosuppressant regimen. He works as a dairy farmer. Bronchoalveolar lavage and blood cultures at baseline were positive for *Cryptococcus neoformans.* Note the bilateral diffuse nodular lesions. Cerebrospinal fluid cultures and cryptococcal antigen assay were negative. (B) A computed tomography scan from the patient reveals multiple, bilateral parenchymal and pleural-based, noncavitary pulmonary nodules, consistent with a diagnosis of extensive pulmonary cryptococcosis.

transplantation.[160] Transbronchial biopsy can be especially helpful in patients with diffuse pulmonary infiltrates. In a patient with extensive pleural involvement, thoracentesis and pleural biopsy (or rigid thoracoscopy in selected situations) may be more helpful diagnostically than bronchoscopy. In some institutions, open lung biopsy is the procedure of choice for patients with interstitial lung disease and for immunosuppressed patients with unexplained pulmonary disease because of the large sample size, expediency of diagnosis, and safety of the procedure.[161–163] In contrast, in other institutions with experienced operators, CT-guided transthoracic fine-needle aspiration of solid lesions in the lung, particularly those near the pleura, can be diagnostic.[164,165] In patients with adequate ventilatory reserve, video-assisted thoracoscopic surgery (VATS)[166] is preferred to open lung biopsy and is associated with a low risk of complications and high sensitivity. All tissue specimens, regardless of source, should be submitted for the Gram stain, special stains for acid-fast bacilli and fungi, and culture. In patients with extrapulmonary disease, specimens from the extrapulmonary site(s) should be obtained for culture and histologic studies. In such patients the results from a diagnostic arthrocentesis, abdominal paracentesis, lumbar puncture, bone marrow biopsy, liver biopsy, lymph node biopsy, or skin biopsy may preclude the necessity of pursuing more invasive techniques.

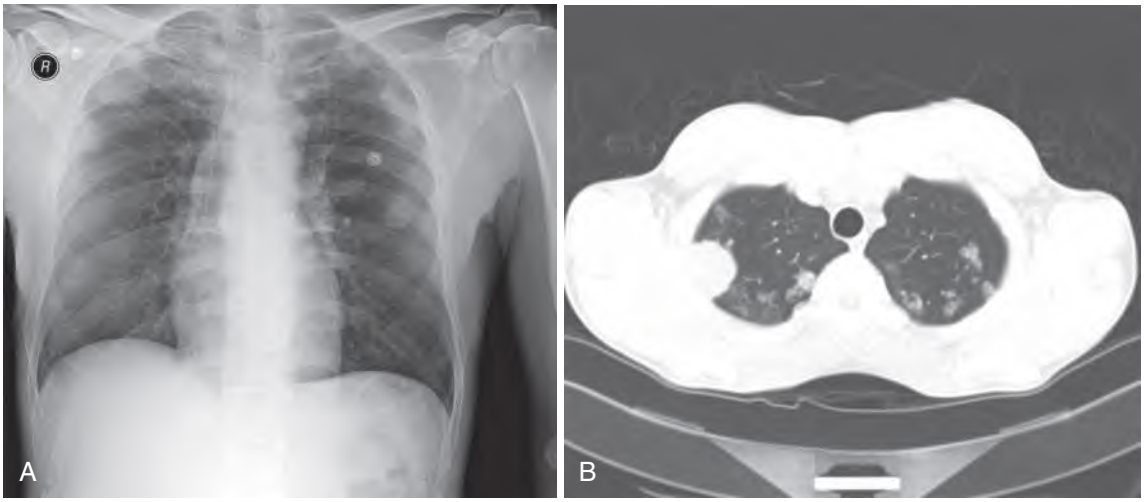

FIG. 70.14 (A) This 48-year-old white male with fever, nonproductive cough, and frontal headache has an extensive travel history, including military service in Southeast Asia, the Philippines, Australia, and California. Chest radiograph reveals multiple bilateral, nodular pulmonary lesions. Both serum and cerebrospinal fluid (CSF) and cryptococcal antigen assay were positive, and CSF eventually revealed *Cryptococcus gattii*. (B) A computed tomography scan of the chest in the same patient reveals multiple parenchymal, poorly defined nodules and one large pleural-based nodule typical for *C. gattii* pulmonary infection.

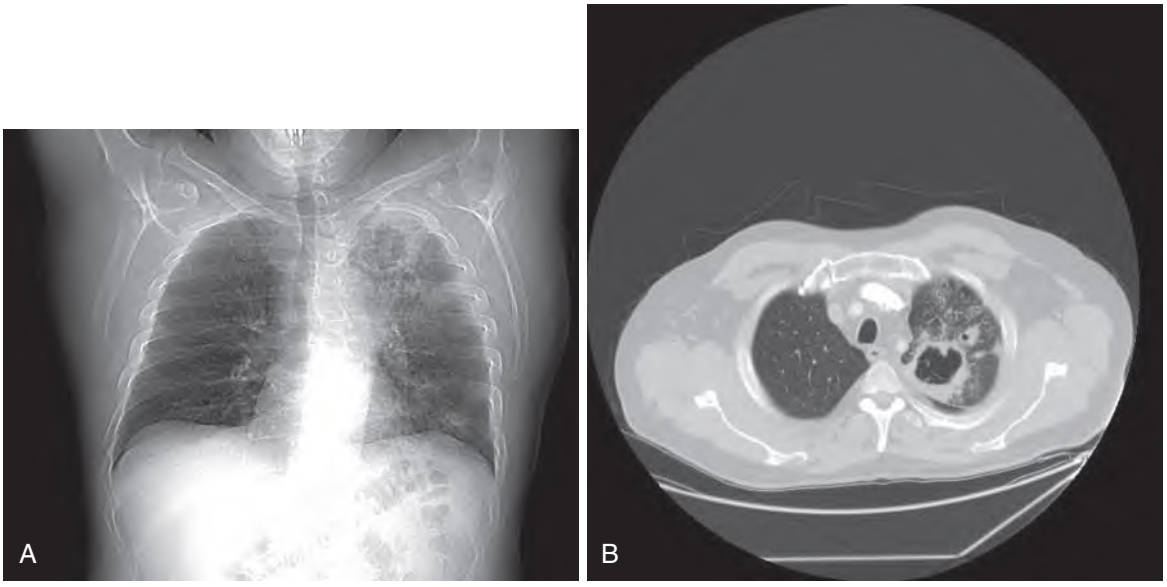

FIG. 70.15 (A) This 59-year-old white male has a recent diagnosis of small cell carcinoma upper lung involving the right lung and mediastinum. He is also noted to have a cavitary lesion and cough productive of yellowish sputum progressive over the past 6 months. He lives in southern Texas near the Mexican border. Serology was positive for *Coccidioides,* and the organism was isolated from multiple expectorated sputum samples. (B) A computed tomography scan from the same patient reveals a large cavitary lesion in the left upper lobe, with some surrounding parenchymal infiltrates consistent with a diagnosis of chronic fibrocavitary pulmonary coccidioidomycosis.

Patients With Radiographic Evidence of Diffuse Pulmonary Infiltration and Fibrosis

In patients whose chest radiographs show a predominantly diffuse infiltrative pattern of either the alveolar or interstitial type (see Table 70.2), pulmonary function studies may be critically important. These studies not only quantify the degree of pulmonary insufficiency but may help delineate the disease processes by virtue of the patterns of pulmonary function impairment. Pulmonary function studies are particularly useful in characterizing those diseases that impair gas transfer and predispose to ventilation perfusion inequalities, such as sarcoidosis or other interstitial lung diseases.[28,29]

Studies that may be especially useful in this group of patients include the following:

1. Arterial blood gas studies and exercise oximetry
2. Tests of pulmonary function, including spirometric measurements, measurements of lung volume, and measurement of pulmonary diffusing capacity
3. Studies on sputum, as previously outlined (cytologic examination is especially important)
4. Lung biopsy—the procedure of choice to make an accurate morphologic diagnosis (fiberoptic bronchoscopy with transbronchial biopsy, VATS, or [uncommonly] conventional thoracotomy for open lung biopsy)

THERAPY

Antimicrobial Agents

Most patients with a chronic, indolent illness and who are clinically stable do not require immediate empirical therapy. A methodical and thorough diagnostic evaluation is the initial priority. In a patient with bilateral upper lobe cavitary disease in whom the initial microscopic examinations are nonrevealing, the leading considerations include tuberculosis, histoplasmosis, and, in the right setting, coccidioidomycosis. If such a patient has a positive tuberculin skin response and/or a positive quantiFERON-Gold assay, then tuberculosis should be presumed

until proven otherwise, and the patient should be kept in respiratory isolation until the diagnosis can be reasonably excluded. Disseminated tuberculosis should be strongly suspected in any patient with unexplained fever and a chest radiograph showing a nodular interstitial pattern; prompt institution of antituberculosis therapy may be lifesaving in this otherwise fatal condition. Similarly, empirical antifungal therapy, usually with an amphotericin B formulation, may be indicated in any immunocompromised patient with severe or rapidly progressing chronic pneumonia due to the high risk of death associated with these infections.

Corticosteroids

The use of glucocorticosteroids for the treatment of a patient with chronic pneumonia is controversial. If the cause of the illness is an infectious agent, particularly a bacterium or fungus, steroids are not routinely indicated. However, some experts advocate a short course of glucocorticosteroid therapy, along with antituberculosis therapy for patients with advanced pulmonary tuberculosis and severe inanition. In general, higher-dose corticosteroids (>20 mg methylprednisolone equivalent daily) are beneficial in chronic pneumonia from noninfectious causes, such as the vasculitides,[3–6] sarcoidosis,[28,29] chronic eosinophilic pneumonia,[2] radiation injury, chronic organizing pneumonia,[36–39] and many of the fibrotic lung diseases, including chronic hypersensitivity pneumonitis, along with avoidance of exposure to the offending antigen.[40] Other immunosuppressive drugs, such as cyclophosphamide and azathioprine, may also be effective for some patients, especially those with pulmonary vasculitis or granulomatosis with polyangiitis.

Bronchoscopy and Surgery

Bronchoscopy is frequently used as a therapeutic adjunct, especially for patients who have thick, tenacious secretions that cannot be raised by noninvasive techniques. In other patients, mucus plugs or foreign bodies may predispose to atelectasis and chronic pneumonia, and therapeutic bronchoscopy may be necessary to expand the atelectatic lung.

Surgery plays a limited role in the management of chronic pneumonia. Lobectomy or pneumonectomy should be considered in a patient with chronic destructive pneumonia, multiple macroabscesses or microabscesses involving an entire lobe or lung, and a ventilation-perfusion scan indicating nonfunction of the involved lung (e.g., pulmonary gangrene).[167] Thoracotomy may also be indicated to decorticate the pleura in patients with significant pleural reaction and resultant restrictive lung disease.

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71 Cystic Fibrosis

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SHORT VIEW SUMMARY

Definition

- Cystic fibrosis (CF) is a genetically inherited autosomal-recessive disease resulting from mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), located on the long arm of chromosome 7. It is a multisystem disorder in which respiratory and gastrointestinal manifestations predominate.

Epidemiology

- CF is the most common genetically inherited orphan disease involving Caucasians. Current treatment strategies have led to improved clinical outcomes, in which the majority of CF patients now reach adulthood.

Microbiology

- Chronic airway infection and inflammation, most commonly associated with *Pseudomonas aeruginosa,* are strongly associated with increased morbidity and mortality. Many other pathogens, such as methicillin-resistant *Staphylococcus aureus, Burkholderia cepacia* complex, *Stenotrophomonas maltophilia,* and others, are also implicated in chronic progressive lung disease.

Diagnosis

- Newborn screening is now available in all 50 states.
- Measurement of immunoreactive trypsinogen and *CFTR* gene mutation analysis are the mainstays for newborn screening in CF. Positive screening is followed by sweat chloride testing.
- Acute pulmonary exacerbations are usually linked to progression of disease. Respiratory viruses may trigger pulmonary exacerbations.

Therapy

- Maintenance therapy for CF-related lung disease includes mucolytics, airway hydrating agents, chest physiotherapy, antiinflammatory drugs, and a combination of oral and inhaled antibiotics (see Table 71.1).
- Acute pulmonary exacerbation may be treated with oral and nebulized antibiotics as needed; more serious exacerbations will require a combination of intravenous antibiotics, intense airway clearance accompanying mucolytics and airway hydrating agents, and aggressive nutritional management while monitoring for complications.
- In addition to the US Food and Drug Administration–approved CFTR modulators—ivacaftor, lumacaftor-ivacaftor (Orkambi), and tezacaftor-ivacaftor (Symdeko)—for those with specific CFTR genotypes, new triple-combination small-molecule therapies will provide disease-modifying treatment to nearly 90% of CF patients.

Prevention

- Genetic counseling to help avoid offspring with CF and early diagnosis through newborn screening.
- Early eradication strategies may prevent chronic airway infection with PA and other pathogens associated with chronic progressive lung disease.

Chronic airway infection and inflammation remains a major contributor to progressive pulmonary disease in patients with cystic fibrosis (CF) and is strongly associated with increased morbidity and mortality. Better understanding of the underlying pathophysiology, role of early intervention, improved identification and treatment of acute pulmonary exacerbations (APEs), advances in chronic pulmonary therapies, a shift in treatment paradigms, and the use of cystic fibrosis transmembrane conductance regulator (CFTR) modulator drugs, have led to improvements in clinical outcome and life expectancy in CF patients, with greater than 50% of patients now being older than 18 years.[1,2] Despite these advances, there remain significant challenges to the management of acute and chronic lung infection.

CF is associated with mutations in the *CFTR* gene, the most common of which is F508del. Inheriting two mutations on opposite alleles, from the more than 1800 *CFTR* mutations identified, leads to a variable degree of salt and water imbalance in the majority of organs expressing CFTR. These mutations are categorized according to the functional defect: no CFTR translation (class I), defect in processing (class II), impairment in CFTR regulation (class III), abnormal conductance (class IV), decreased production (class V), or increased degradation (class VI).[3] For drug development and practical purposes, mutations outside of F508del and gating mutations are classified as minimal function and residual function, based on their responsiveness to available modulator drugs. Although pancreatic insufficiency is not typically associated with class IV, V, and VI defects, the ability to make other clinical predictions based on mutation profiles is limited.[4] In regard to manifestations of lung disease, there is unpredictability of phenotype based on genotype, with both rapid progressive phenotype patients (those with a steeper decline in forced expiratory volume in 1 second [FEV_1] over time compared to average) and long-term nonprogressive phenotype patients (those with stable FEV_1 over time) in cohorts carrying the same *CFTR* mutation, suggesting additional genetic and environmental factors are involved in health decline.[5,6]

The diagnosis of CF relies on clinical presentation in combination with diagnostic testing. Since it was first introduced in Wisconsin in 1994, all states in the United States have adopted newborn screening for CF, joining CF centers across Europe and Australia along with a growing number of other countries.[7–9] A positive screen includes evidence of elevated immunoreactive trypsinogen or identification of one or more disease-causing *CFTR* mutations.[10] Sweat chloride testing via pilocarpine iontophoresis and *CFTR* mutation analysis follows a positive screening test. A chloride concentration greater than 60 mEq/L is considered positive and concentrations are considered indeterminate down to a cutoff of 30 mEq/L, although rarely a patient diagnosed with CF can have chloride concentrations below the diagnostic range,[11] making the diagnosis of CF more challenging in certain cases. New terms to better define those patients who do not completely meet the diagnostic criteria have been established to identify those at risk for complications of CF and who continue to require close attention. Methodologies to help differentiate those at risk include the β-adrenergic sweat secretion rate and the nasal potential difference (a measure of bioelectric properties that reflect CFTR function using harvested epithelial cells from human bronchi and nasopharynx or intestinal organoids), which are offered at limited CF centers to provide additional insight but currently are available as research tools only.[12,13] *CF-related metabolic syndrome* is a term reserved for asymptomatic individuals who do not meet the diagnostic threshold of sweat chloride testing and *CFTR* mutation analysis. Depending on their clinical presentation or new diagnostic

results, these individuals may be redefined as having CF, having CFTR-related disorder (e.g., a patient with CF-related metabolic syndrome who is symptomatic), or not having CF.[10]

Pulmonologists are often the primary providers for CF patients, with infectious disease physicians involved as consultants. Each discipline approaches the disease according to its background training and experience, but we believe their cooperation is critical to optimally treat those suffering from CF. Increasing evidence-based data are available to help guide the CF caregiver. The Cystic Fibrosis Foundation (CFF), founded in 1955 to serve the CF community, created a Therapeutic Development Network in the late 1990s to support clinical trials, whether in cooperation with industry or physician initiated, harnessing the pooled resources of CF care centers. The armamentarium for the modern CF clinician includes new oral and inhaled antibiotics, airway hydrating agents, mucolytics, antiinflammatory drugs, CFTR modulators, and nutritional supplements (see Table 71.1 under "Treatment" later).

The present chapter describes key CF-related infectious diseases issues that are relevant to infectious diseases clinicians.

CLINICAL DISEASE

The clinical course of CF is frequently described by chronic progressive lung disease punctuated by APEs. These exacerbations may be triggered by infection, environmental exposures, or other events.[14] There is no universally accepted definition of an APE, and responses to a change in symptoms differ among clinicians (chest physiotherapy only, oral antibiotics, intravenous antibiotics, etc.).[15] However, for the purpose of clinical trials, an APE is frequently defined as the presence of four or more of the following criteria[16]:

- an increase in sputum volume or change in color
- new or increased hemoptysis
- increased cough
- increased dyspnea
- malaise
- fatigue or lethargy
- a temperature greater than 38.0°C
- anorexia or weight loss
- sinus pain or tenderness
- a change in sinus discharge
- a change in findings on physical examination of the chest
- a decrease in FEV_1 by 10% or more from baseline
- radiographic changes in support of a pulmonary infection

The focus of CF care is to avoid or reduce APEs, and a standardized definition of APEs would allow caregivers to recognize exacerbations and treat them early. Every APE has an impact on recovery of lung function.[17] In a cohort study involving the CFF Patient Registry, Sanders and colleagues demonstrated a 25% failure in FEV_1 recovery among 8479 exacerbations.[17] In a retrospective study of FEV_1 following an APE included 440 patients and a total of 1667 exacerbations requiring hospitalization and antibiotics, nearly one-third of all patients failed to return to baseline lung function.[18] Both studies correlated poor recovery with a greater drop in FEV_1 from baseline prior to treatment initiation; allergic bronchopulmonary aspergillosis (ABPA); concomitant infection with *Burkholderia cepacia* complex (BCC), *Pseudomonas aeruginosa* (PA), or methicillin-resistant *Staphylococcus aureus* (MRSA); and lower body mass index (BMI).

Prior to the widespread use of newborn screening, the vast majority of CF diagnoses were made based on respiratory symptoms, along with failure to thrive and steatorrhea and other gastrointestinal symptoms. Despite lack of pulmonary symptoms, there is evidence supporting neutrophilic inflammation in the airways of asymptomatic infants. Sly and coworkers observed the presence of increased neutrophil elastase activity in bronchoalveolar lavage (BAL) fluid from infants as young as 3 months of age, and it was associated with subsequent development of bronchiectasis at 36 months.[19]

In more typical CF patients, respiratory manifestations include a chronic suppurative cough, obstructive lung disease by spirometry, and hyperinflation on chest radiographs. Symptoms of cough and wheezing continue in varying degrees and correlate with progressive bronchiectasis. APE presents on top of chronic stable symptoms as noted earlier. Many patients present with digital clubbing, but it is by no means universal. Chronic sinus disease develops in most CF patients as soon as the paranasal sinuses develop.[20] Nasal polyposis is found in 10% to 32% of patients.[21] Chronic sinus disease may be found in patients with minimal lung disease or even those who do not quite meet CF diagnostic criteria and tends to constitute a reservoir for infection.

ABPA can be described as a hypersensitivity response to *Aspergillus fumigatus* and may be a cause of an APE. Although other fungi may produce a similar response, *Aspergillus*-related hypersensitivity is the most commonly recognized. ABPA leads to airway obstruction, bronchiectasis, and pulmonary fibrosis if not managed successfully and further impacts CF-related lung disease.[22] The diagnostic criteria include[23]:

1. An acute or subacute exacerbation (cough, wheeze, decline in pulmonary function, increased sputum) not attributable to another etiology
2. Cutaneous reactivity to *Aspergillus* or elevated *Aspergillus*-specific immunoglobulin (Ig)E antibodies
3. Elevated serum IgE greater than 1000 IU/mL
4. *Aspergillus* serum precipitins or elevated *Aspergillus*-specific IgG antibodies
5. New chest imaging abnormalities that do not resolve with antibacterial treatment or chest physiotherapy

The mainstay of treatment involves corticosteroid use with taper over a course of 2 to 3 months while monitoring response (IgE, respiratory symptoms, spirometry, chest radiography). It is important to manage concomitant infection, particularly in cases of poor response to therapy. Itraconazole, voriconazole, posaconazole, or isavuconazole can be used when there is a poor response or a relapse in ABPA, or when use of corticosteroids is not possible. Triazole-related drug-drug interactions are important to monitor with these agents, particularly in the age of CFTR modulators, but isavuconazonium may be a best option. Response to antifungal treatment is associated with pretreatment isolation of *A. fumigatus* from the respiratory tract.[24] Despite a lack of demonstrable evidence in CF patients, omalizumab is a non–US Food and Drug Administration (FDA)-approved option for some patients resistant to traditional ABPA therapy or suffering untoward side effects from steroids.[25]

Common nonrespiratory manifestations of CF include pancreatic insufficiency, which is progressive and found to some degree in up to 90% of patients by age 1.[26] It is characterized by frequent, copious, foul-smelling, greasy stools, as well as failure to thrive due to malabsorption of fat and protein. Untreated with pancreatic enzyme replacement therapy (PERT), patients may present with electrolyte abnormalities, protein-calorie malnutrition, and fat-soluble vitamin deficiency. Pancreatitis is a complication most commonly associated with those patients who have adequate or borderline pancreatic function. CF-related diabetes afflicts one-quarter of young adults and up to 50% of adults with CF.[27] Meconium ileus or bowel obstruction at birth in a nonpremature infant is highly suggestive of CF.[28,29] When this occurs in adolescents and adults, it is called distal intestinal obstructive syndrome or meconium ileus equivalent. Quick, aggressive medical attention to relieve the obstruction is crucial to avoid the surgical intervention required in severe cases. Rectal prolapse occurs less frequently and is associated with malnutrition, constipation, and poor adherence to PERT and also manifests in stool incontinence. Another symptom similarly impacting quality of life is urinary incontinence. Constipation can be a significant contributor, but often other measures are necessary to manage cough-associated urinary incontinence, such as physical therapy and cognitive behavior therapy.[30,31] Liver disease is common and related to biliary dysfunction due to inspissated bile and is associated with laboratory abnormalities such as elevations in alkaline phosphatase. Liver disease progresses in a small number of patients, rarely beyond early adulthood, leading to cirrhosis, portal hypertension, and development of esophageal varices. Rarely does cholelithiasis require surgical intervention other than prophylactic removal prior to lung transplantation.[32]

There are many risk factors for osteoporosis in men and women with CF. Malabsorption of vitamin D, malnutrition, decreased physical activity, glucocorticoid treatment, and hypogonadism contribute to the development of bone disease.[33] Pain associated with CF-related arthropathy occurs in a small number of patients but causes significant morbidity.

Hypertrophic osteoarthropathy is associated with abnormal proliferation of soft and osseous tissue at distal parts of extremities. It appears to share the same process as digital clubbing but is much less common, and its exact pathogenesis is unclear. Nephrolithiasis and nephrocalcinosis are common in CF patients as well. They are most frequently due to hyperoxaluria due to oxalate absorption in setting of inadequate PERT and decreased citrate excretion.[34]

PATHOGENESIS OF CYSTIC FIBROSIS–RELATED LUNG DISEASE

The CFTR protein, residing on apical membranes of epithelial cells, regulates salt and water balance. The mechanism of its impact on airway surface liquid is the subject of research, but it is recognized that the absence or dysfunction of CFTR in epithelial cells lining various ducts in the body leads to a hyperabsorptive state, which in turn is due to the osmotic gradient created by impaired chloride, sodium, and bicarbonate transport. In the lung, the depletion and dehydration of the airway surface liquid layer lead to impaired mucociliary transport with the development of thick, tenacious secretions. This in turn leads to an inability to clear bacteria and other debris from the lower airways. More recent data link reduced secretion of bicarbonate in the pathogenesis of CF. CFTR impacts pH by altering bicarbonate secretion, leading to reduced pH and a reduced ability for innate mechanisms to combat bacteria.[35] This impaired clearance leads to a chronic infection state, most commonly associated with *S. aureus* and PA. The negative bearing on innate defense results in an inflammatory response that includes polymorphonuclear leukocytes and antibodies.[36–38] While communicating with the lower airway, the sinuses can provide a separate environment for bacteria to inhabit. Segregated intrapulmonary habitats can also exist in focal areas of the lung, making it challenging to target specific organisms that may be responsible for APEs. These bacterial communities are only a small number of organisms representing the complex microbiome of the CF lung.

Similarly aged patient cohorts with the same *CFTR* mutation can have mild, moderate, or severe lung disease, thus genetic modifiers have been implicated, as well as environmental ones (smoke, socioeconomic class), but also variable microbiology.[39] It is difficult to identify and detect genetic modifiers due to significant variations in disease presentation and response to external stressors in the environment.

THE CYSTIC FIBROSIS MICROBIOME

Haemophilus influenzae and *S. aureus* are frequently cultured from the upper airway of children with CF, while worsening clinical outcomes are usually associated with chronic infections with PA, as well as chronic infections with other bacteria, including BCC species, *Achromobacter xylosoxidans,* and *Stenoptrophomonas maltophilia.*[40,41] There is an increased recognition of lung disease caused by nontuberculous mycobacteria (NTM) in CF patients. NTM are recovered with increasing frequency as they age, with *Mycobacterium abscessus* being the most concerning infection associated with worse outcomes.[42] Anaerobic organisms such as *Streptococcus, Prevotella, Actinomyces,* and *Veillonella* are also increasingly recognized as possible pathogens inhabiting the low oxygen concentration of mucoid airway surface liquid.[43,44]

The growing CF literature on airway microbiology reveals an undeniably complex and dynamic interaction between the CF airway and organisms inhabiting this environment.[41,45] Even organisms associated with CF lung infection for decades are recognized to be genetically and phenotypically diverse, even within the same patient and different parts of the lung.[46] Infection diversity likely impacts management, and the presence of two or more species inhabiting the same space appears to change the way individual bacterial species behave, through quorum sensing, and work in concert to drive disease progression. Limoli and associates elegantly demonstrated the change in PA motility via type IV pili and flagella activity when exposed to *S. aureus* in ex vivo sputum samples.[46a] In vitro coculture models involving PA and *S. aureus* also demonstrate enhanced antimicrobial resistance.[47] Their interactions, including sharing genetic data, have an impact on antibiotic susceptibility.[48] Particular bacterial pairs may be associated with better or worse outcome. New tools of molecular diagnostics have helped inform caregivers and researchers, including the role of viruses in APEs.[49,50]

Given the poor relationship between in vitro susceptibility and clinical outcome among CF patients, our current antimicrobial susceptibility testing may be inaccurate, and culture procedures may fail to identify other potential pathogens with diverse susceptibility patterns from different colonies of the same bacterial species. Biofilm susceptibility testing has not proven to be superior to conventional testing but warrants further evaluation.[51,52] DNA- and RNA-based deep sequencing methods can identify a greater diversity of bacterial species and variants, but the genomic knowledge determinant of antibacterial resistance remains limited.[53,54]

Beyond the traditional CF bacterial pathogens, there have been ongoing data highlighting the potential role of other bacteria and their association with CF exacerbations.[55] Anaerobes and oral flora are found in very high densities, including *Prevotella* and *Veillonella. Streptococcus milleri* has been associated with worse outcomes in CF, but is an organism not usually sought out by CF microbiology laboratories. Newly identified organisms such as *Gemella* and *Rothia mucilaginosa* have been associated with worse outcomes with *Rothia* detected more often than PA in many patients.[56,57]

Bacterial pathogens in CF airway are shown in Fig. 71.1. In the early days of CF, *S. aureus* was the only bacterium identified in lungs, but successful treatment soon led to the predominance of chronic infections with PA and BCC, which are associated with poor clinical outcomes. Even before the advent of CFTR modulators, there had been a steady decline in the prevalence of PA despite its being the predominant organism in adults over 25 years of age, while chronic infection with *S. aureus* continues to increase in prevalence. Chronic infection with MRSA and *Achromobacter* has plateaued over the last several years based on data in the CFF Patient Registry data from 2016 (see Fig. 71.1).[57a] We are able to identify bacteria from the respiratory tract utilizing standard culture techniques as well as molecular typing. A major question remains current: how do we identify whether bacteria identified in respiratory cultures are disease producing and impacting clinical outcomes? For example, it is well known that in sputum from CF patients, different bacterial colony morphotypes can be found that arise from the same bacterial strain.[58] This suggests that the bacteria in the lungs are constantly adapting a variety of described mechanisms (auxotrophy, motility, type III secretion system, lipopolysaccharide, antibiotic resistance, biofilm, hypermutability, quorum sensing, small-colony variants [SCVs]) that lead to these different phenotypes, and a dominant single bacterial strain may evolve.[59] We are beginning to understand the evolution of clonal populations. Multiple lineages coexist and multiple clones evolve separately with different lineages. Genomic and proteomic approaches may become helpful to better understand these communities.[60,61] These novel insights remain difficult to translate into clinical outcomes at this time.

Lungs themselves are also very heterogeneous in disease severity. Understanding the differences in regions of the lungs may help explain patient heterogeneity. Regions with mild and severe disease are infected by different subpopulations of PA. As an example, we can target factors that select infections with milder PA subpopulations. Most regions, however, contain a mixture of isolates and subpopulations, confounding this investigation.

The study of CF exacerbation with proteomics has contributed to our understanding of changes in bacteria during APEs.[46] While bacterial density remained stable, a decrease in bacterial diversity was associated with declining FEV_1. Looking at 27 consecutive sputum samples from the same patient, Carmody and colleagues demonstrated that microbial communities change.[56] They showed a decrease in abundance of dominant species, including PA, BCC, and *Achromobacter,* following antibacterial treatment. Zhao and coworkers found that interventions led to a change in bacterial diversity and were associated with age, disease severity, and antibiotic exposure.[62] Density of bacteria remained the same, while microbial diversity decreases.[56] In general, microbial diversity decreases with antibiotic exposure, but bacterial communities generally return to pretreatment configurations by 1 month after completion of antibacterial courses. Others have also demonstrated an association between microbial diversity and FEV_1 (Fig. 71.2), as well as the lack of correlation with total microbial abundance (Fig. 71.3).[63]

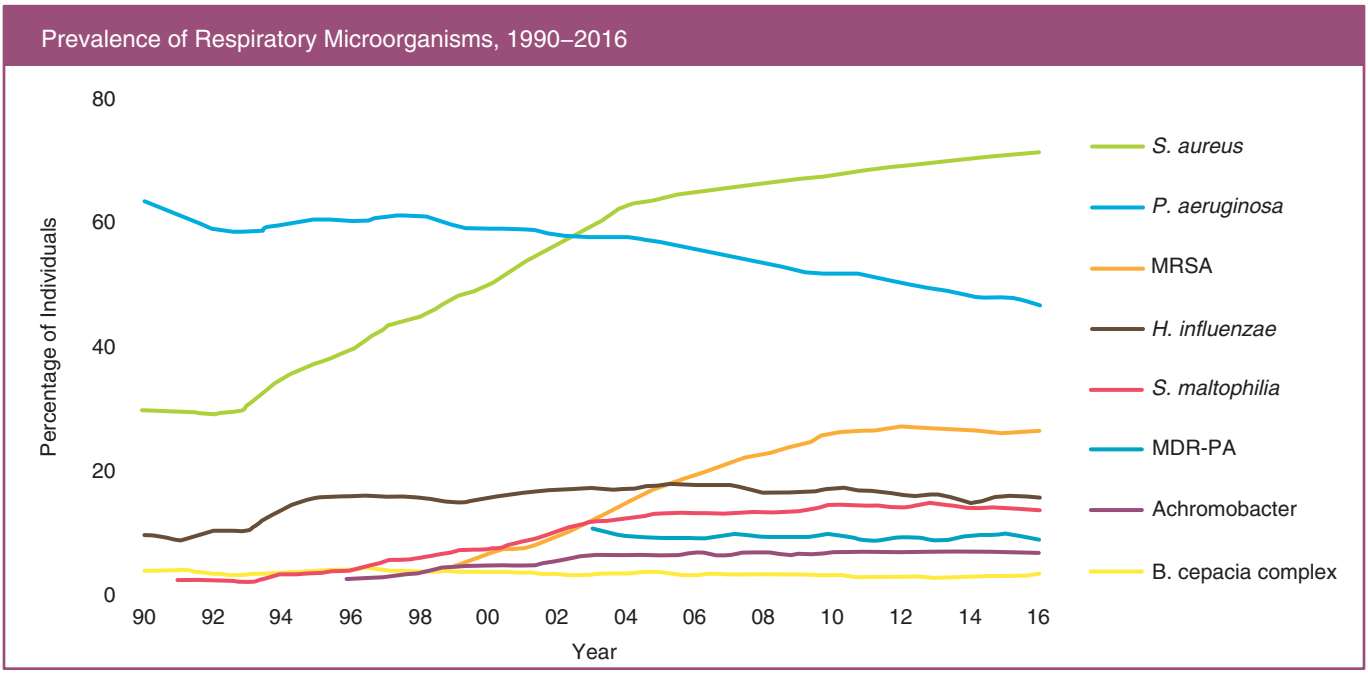

FIG. 71.1 The proportion of individuals in various age groups who cultured positive for the bacterial species indicated during 2016. *MDR-PA,* Multidrug-resistant *Pseudomonas aeruginosa; MRSA,* methicillin-resistant *Staphylococcus aureus. (Data from Cystic Fibrosis Foundation.* Patient Registry 2016 Annual Data Report. *Bethesda, MD: Cystic Fibrosis Foundation; 2016:29.* https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf. *Accessed January 3, 2019.)*

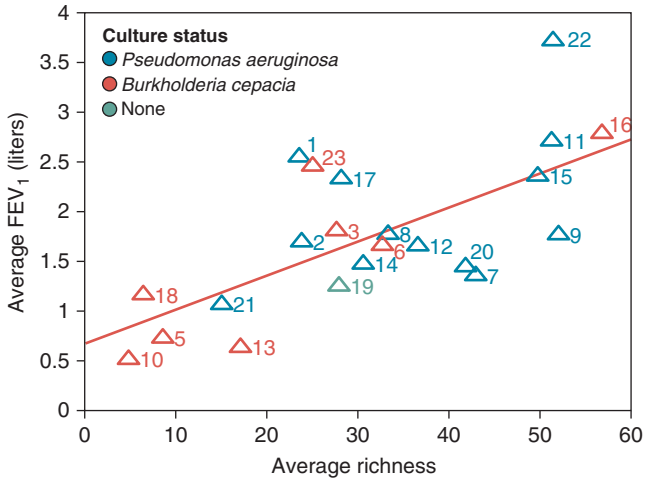

FIG. 71.2 Microbial richness in sputum samples is associated with decreased lung function. Shown is a plot of the average forced expiratory volume in 1 second (FEV_1) compared with average microbial richness in sputum for each patient. FEV_1 and microbial richness values were averaged across all time points for each patient. Numbers next to each symbol indicate patient ID. Symbols are color coded on the basis of patient culture status (*Pseudomonas aeruginosa*, *blue; Burkholderia cepacia* complex species, *red;* culture negative for both, *green*). Results from linear regression analysis (*red line*) indicate a significant correlation (coefficient of determination [r^2] = 0.42, $P = .0009$). *(Data from Fodor AA, Klem ER, Gilpin DF, et al. Adult CF airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations.* PLoS One. *2012;7:e45001.)*

Even with changes in clinical status, neither the Zhao and coworkers nor the Fodor and associates study observed a significant change in airway microbial community structure or bacterial abundance. The 23 patients included in the study by Fodor and associates were chronically infected with either PA or BCC, along with isolation of species belonging to the genera *Streptococcus, Prevotella, Rothia, Veillonella, Actinomyces,* and *Granulicatella.* The progression of disease with age, microbial diversity, and resistance to antibiotics supports this observation. As in the study by Zhao and coworkers, APEs or disease progression was not associated with increase in bacteria numbers, overgrowth of a specific organism, or the isolation of a new bacterial infection. Fodor and associates suggested that an APE represents the spread of infection to previously unaffected airways or adaptation by organisms that may lead to a change in the expression of virulence traits. For example, during chronic CF airway infection, PA can undergo conversion from a smooth to a mucoid colony phenotype, discussed in more detail below.[64] The coexistence of mucoid and nonmucoid PA variants suggests a protective benefit in evasion of host defense.[65,66] Data presented here provide insights into the CF airway microbiota, including initial diversification events in younger patients and establishment of specialized communities of pathogens associated with poor pulmonary function in older patient populations.

How do we decide on therapy based on this information? There is evidence that uncouples susceptibility testing from clinical outcome, and the evolving microbiota data may help explain the disconnect between in vitro testing and clinical outcomes[67,68] However, irrespective of susceptibility, including multidrug-resistant PA, similar clinical responses are observed to usual antimicrobial therapies.[69]

MAJOR CYSTIC FIBROSIS PATHOGENS

Staphylococcus aureus

The most common pathogen among CF patients in contemporary cohorts is *S. aureus,* with recovery from sputum at its height in children and adolescents (see Fig. 71.1).[57a] *S. aureus* was the dominant infection leading to respiratory failure in patients during the early to mid-20th century. The introduction of antistaphylococcal antibiotics led to selection of gram-negative organisms and observation of chronic infection with PA. Like PA, CF patients may culture methicillin-sensitive *S. aureus* (MSSA) from sputum repeatedly and it may represent the same isolate over time.[70] Outside of the United States, chronic management of CF at some centers includes routine treatment against MSSA with similar prevalence rates, but surprisingly, MRSA levels are significantly less in comparison.[71] Although some evidence suggests reduced exacerbation rates,[72] the CFF consensus guideline committee on chronic therapies

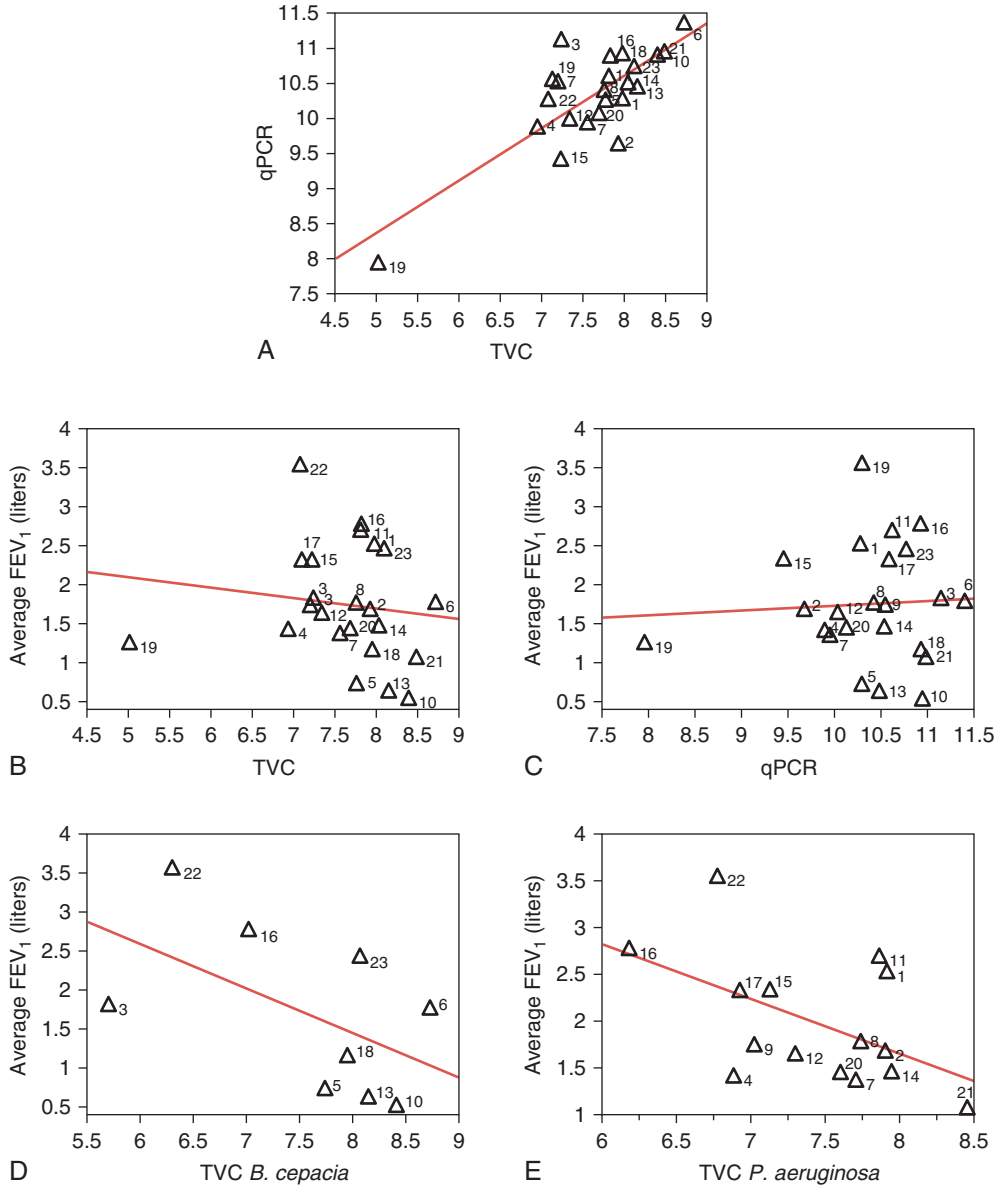

FIG. 71.3 Lung function is not correlated with total bacterial abundance. Measurements of total bacterial abundance in sputum by (A) timed vital capacity (TVC) and quantitative polymerase chain reaction (qPCR) are well correlated ($r^2 = 0.63$, $P < .0001$; $n = 23$). Forced expiratory volume in 1 second (FEV_1) is not correlated with (B) TVC ($r^2 = 0.017$, $P = .55$; $n = 23$) or (C) qPCR ($r^2 = 0.003$, $P = .8$; $n = 23$) and only modestly correlated with TVC from (D) *Burkholderia cepacia* complex species ($r^2 = 0.29$, $P = .13$, $n = 8$) and (E) *Pseudomonas aeruginosa* ($r^2 = 0.26$, $P = .05$; $n = 14$). Measurements for bacterial abundance and FEV_1 were averaged across time points for each of the 23 patients. Labels in each panel indicate patient ID. Lines indicate regression fit by linear least squares. Only TVC values >0 were included for *B. cepacia* and *P. aeruginosa* comparisons. TVC values represent log10 of total bacterial colony-forming units recovered per gram of sputum. qPCR values represent log10 copies of the bacterial 16S ribosomal RNA gene detected per gram of sputum. *(Data from Fodor AA, Klem ER, Gilpin DF, et al. Adult CF airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations.* PLoS One. *2012;7:e45001.)*

to maintain respiratory health recommended against routine antistaphylococcal treatment, given the observation of greater prevalence of PA in groups receiving chronic antistaphylococcal treatment and its consequences.[73] The annual prevalence of *S. aureus* was 71.1% (includes MRSA) in 2016 and increasing, while PA rates have continued to slowly decline.[57a] Despite the increased prevalence of MRSA over the last 20 years, the levels plateaued about 3 years ago. The prevalence mirrors that of community-acquired MRSA in our communities in general, although it is unclear whether this is the source of MRSA infection in CF.[74–76] Prevalence can vary; however, the most recent CFF registry data from 2017 suggest an overall prevalence of 26% and that prevalence is highest among adolescents and young adults.[76a]

With chronic infection and treatment of both MSSA and MRSA, the detection of SCV *S. aureus* is increasingly being recognized in patients with CF. These bacteria do not grow well on standard culture media and are not routinely identified by most clinical laboratories. A recent multicenter trial in the United States was conducted to evaluate the prevalence and clinical significance of SCV *S. aureus* and noted that 28% of patients enrolled were infected with SCV *S. aureus*. Those infected had significantly lower lung function, had increased odds of having an APE, and were more likely to have been treated by a sulfonamide antibiotic prior to detection. It is unclear whether SCV *S. aureus* infection causes or is an indicator of worse lung function. Additional studies are needed to evaluate whether prevention or treatment of SCV *S. aureus* improves clinical outcomes.[77] Our microbiology laboratory uses mannitol–salt agar to help identify this slow-growing variant. There is a positive association with the presence of SCV *S. aureus* and use of trimethoprim-sulfamethoxazole (TMP-SMX) and infection with PA.

Two recent studies demonstrated an association of SCV *S. aureus* with more advanced lung disease in children and adults.[78,78a]

Methicillin-Resistant *Staphylococcus aureus*

A study by Dasenbrook and colleagues reported worse survival in patients with sputum culture positivity for MRSA,[79] and others have reported lower absolute lung function when MRSA is compared to MSSA.[80] In the Dasenbrook and colleagues cohort study of longitudinal data obtained from the CFF Patient Registry that analyzed 19,833 patients, the reported risk of death was 1.27 times greater for individuals with at least one culture positive for MRSA reported compared to those in whom MRSA was never detected, adjusting for PA infection.[79] New and persistent infection with MRSA revealed a more rapid rate of decline in lung function among 8- to 21-year-olds, but this effect was not observed in those older than 21 years of age (Fig. 71.4).[81] The increased prevalence of MRSA in the last decade may explain the flattening of the overall CF median mortality curve.[57a] These findings underscore the importance of persistent MRSA infection in CF.

Routine MSSA-directed antibacterial prophylaxis is not uncommon in the United Kingdom and other parts of Europe. Despite this, the overall MRSA prevalence in the United States is much higher. Distribution of MRSA types in CF and non-CF differ for a given country.[82–84] A cross-sectional study showed that FEV_1 values declined faster in patients who became chronically infected with MRSA compared to those who experienced intermittent MRSA infection.[86] There is fluidity between community- and hospital-associated MRSA. The STAR-CF study looked at chronic MRSA infection based on staphylococcal protein A gene, staphylococcal chromosomal cassette mec (SCCmec), and Panton-Valentine leukocidin (PVL).[87] SCCmec type II is usually hospital associated, SCCmec type IV is usually community associated, and a majority of the pediatric CF population studied was determined to be positive for SCCmec II and PVL negative. There were no differences in gender, FEV_1, BMI, or rates of MSSA. The number of clinic visits was increased among SCCmec II–positive patients, while hospitalizations did not differ. Elizur and coworkers noted an increased rate of decline in FEV_1 and necrotizing pneumonia associated with PVL positivity.[88]

Several recent clinical trials have addressed questions related to acute and chronic infection with MRSA. The STAR-Too trial was a randomized, controlled, open-label study that compared the implementation of an early MRSA eradication protocol (two oral antibiotics, topical antibiotics, and instructions for environmental decontamination techniques) to an observation group receiving current standard of care. The study was stopped early by the data safety monitoring board due to a significant decrease in MRSA-positive screens at 28 days in the treatment group compared to controls.[89] The PMEP study was designed to look at eradication of persistent MRSA infection. Subjects were randomized to receive either inhaled vancomycin (250 mg twice daily) or placebo (taste-matched saline), along with rifampicin plus a second agent (TMP-SMX or doxycycline) and topical agents (mupirocin intranasal cream and chlorhexidine washes).[89a]

There is controversy over management of chronic MRSA infection, but directed treatment is usually employed for all exacerbations using same antibiotic choices as in non-CF patients. Teicoplanin and fusidic acid are used in Europe but are not available in the United States.[71]

Linezolid is active against most strains of MRSA and has been tested for the treatment of MRSA pneumonia in non-CF patients with overall similar outcomes when compared to intravenous vancomycin.[71,90,91] Successful use of linezolid for treatment of MRSA-associated APE has been reported in CF patients,[92] but development of breakthrough linezolid resistance has been frequently reported in CF patients.[93–95] Linezolid use for greater than 2 weeks is frequently associated with myelosuppression and other adverse effects, so longer term use in patients with MRSA infection may be difficult, but we use it in cases of a history of vancomycin hypersensitivity reactions or as step-down treatment in patients for whom intravenous administration is problematic.

Telavancin is a new antibacterial drug with several comparative studies with vancomycin in non-CF patients. Although not currently approved for CF, a recent study by Roch and associates demonstrated excellent bactericidal activity with low resistance profile in vitro against MRSA samples obtained from CF patients.[96] Another recent case series describes the utilization of telavancin for APE in three adolescents.[97] Currently there are ongoing investigations to further delineate the pharmacokinetics of telavancin in adults with CF.[97a]

Ceftaroline is a new antibacterial drug with activity against MRSA. Like telavancin, ceftaroline has not been approved for APE in CF; however, there is growing interest in its use. Autry and colleagues and Barsky and associates recently completed separate pharmacokinetic and pharmacodynamic studies investigating the dosing of ceftaroline in patients with CF. Their studies suggested 600 mg (15 mg/kg in children) every 8 hours administered over 60 minutes should be considered to reach a free drug concentration greater than the minimal inhibitory concentration (MIC) for 60% of the dosing interval.[98,99] It remains unclear, though, how ceftaroline should be adjusted in patients with impaired renal function, the effects of other antibiotics on the ceftaroline pharmacokinetic profile, and if this dosing regimen is associated with clinically significant outcomes.

Ceftobiprole is another new antimicrobial that may have a role in treatment of MRSA-associated APE.[100] Daptomycin is not recommended for pulmonary infections since it binds to surfactant. As noted earlier, there is a high prevalence of MRSA in the United States, and chronic infection may be associated with worse outcome and a risk factor in CF for increased health care utilization. The use of tedizolid or dalbavancin for treatment of MRSA infections in CF patients remain to be determined.

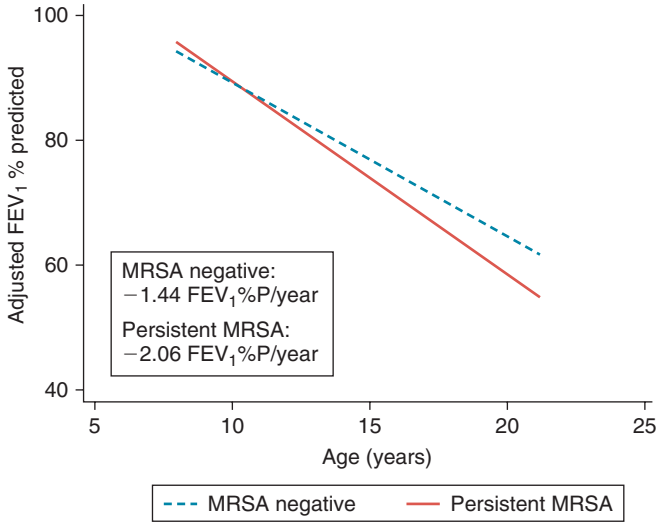

FIG. 71.4 Persistent methicillin-resistant *Staphylococcus aureus* (MRSA) cultures and forced expiratory volume in 1 second (FEV_1) percentage. Linear predictor of percent predicted decline of FEV_1 per year (FEV_1%P/year) for cystic fibrosis patients ages 8 to 21 years with persistent MRSA (≥3 MRSA cultures; *solid line*) compared with those without MRSA *(dotted line).* Average follow-up for each individual in the cohort was 5.3 years. FEV_1 was adjusted for group differences in the confounders. *(Data from Dasenbrook EC, Merlo CA, Diener-West M, et al. Persistent methicillin-resistant* Staphylococcus aureus *and rate of FEV1 decline in cystic fibrosis.* Am J Respir Crit Care Med. *2008;178:814-821.)*

Pseudomonas aeruginosa

In prospectively collected oropharyngeal cultures obtained at least every 6 months from patients diagnosed through neonatal screening,[101] PA has been recognized to be quite adaptable to inhabiting the CF respiratory tract. Since the first description of CF, PA has become the second most prevalent pathogen found in the respiratory tract of CF patients.[57a] The establishment of CF centers and cohorting of patients in hospitals is somewhat responsible for the emergence of this organism.[102] This observation has led to adoption of strict infection control and practice guidelines.[103–106] The neonatal screening program underway since 1985 was a collaboration involving two CF centers in Wisconsin, and its inception had implications for the prevalence

of PA infection.[7] Observation of screened and control groups were similar overall, but one center, which was located in an urban setting, showed significantly younger age for acquisition of PA. This clinic did not segregate patients by age, and perhaps allowed more opportunity for social interaction outside of the clinic. Although the overall study did not indicate a significantly increased risk for PA acquisition, it suggested risk factors associated with an urban center clinic. Patients identified with CF through neonatal screening had a median of 52 PA-free weeks in the urban CF center, while PA-free survival was 289 weeks at the nonurban center. The acquisition of PA impacts survival and is strongly associated with a decrease in FEV_1 and life expectancy.[107–109] Kerem and coworkers showed significant association of decreased lung function at age 7 in patients with PA infection compared to those uninfected with PA.[109] Also, a decrease in PA-positive cultures at a Danish center occurred when PA-infected and noninfected patients were segregated.[109a]

Despite the impaired but robust host inflammatory response and treatments directed toward PA, this organism comprises 60% to 70% of all CF respiratory infections by age 18,[57a] and chronic infection eventually leads to respiratory failure and death. Initial strains are usually unique and begin with strains from an environmental source.[110] This is followed by repeated airway infection and eventually chronic airway infection, as well as parenchymal infection, chronic bronchopneumonia, and necrotizing pneumonia.[49] The aggressive use of antipseudomonal antibiotics can substantially delay chronic infection.[38] The Early Pseudomonal Infection Control (EPIC) study was designed to determine the impact of the acquisition of PA and of four separate antibiotic regimens to eradicate the first positive PA culture: cycled therapy or culture-based therapy with inhaled tobramycin (300 mg twice daily) and ciprofloxacin or placebo.[112–114] No one therapy was superior to the others, but each led to decrease rates of PA recurrence.[115]

Strategies to prevent early PA acquisition from developing into chronic infection remain of interest. Despite efficacious eradication protocols, PA recurrence still develops in one-third of patients within 18 to 27 months. Nearly one-half of the children receiving eradication therapy experience pulmonary exacerbation within 18 months. Macrolide antibiotics have previously been shown to reduce the risk of pulmonary exacerbations and reduce PA biofilm formation. The OPTIMIZE trial investigated whether the addition of azithromycin to inhaled tobramycin during eradication therapy would reduce the risk of pulmonary exacerbation and delay recurrence of PA. Patients were randomized to receive 28 days of inhaled tobramycin with azithromycin or inhaled tobramycin monotherapy with plans to follow for 18 months. The study was stopped early by the data safety monitoring board after the azithromycin arm reached a prespecified monitoring boundary for efficacy. The study was amended and is currently being completed as an open-label study. The study revealed that the addition of azithromycin to eradication therapy with inhaled tobramycin increased the duration of time to pulmonary exacerbation, but did not reduce the frequency of exacerbations or affect the time to PA recurrence.[116]

There is evidence that respiratory syncytial virus (RSV) infection promotes biofilm formation and enhances PA antibiotic resistance (see "Respiratory Viruses" later).

The eventual chronic PA infection can occur through a separate, genomically distinct organism or, in a quarter of the cases, through the same genomic variant.[117–119] The source of recurrent pulmonary PA can be a persistent environmental source or a nonpulmonary reservoir, such as the sinuses. The eventual chronic infection is likely due to adaptive changes to PA and is associated with increased degree of inflammation and recruitment of neutrophils and other destructive proteases.[110]

The term *colonization* is frequently used to describe persistently positive bacterial cultures from the CF airway, but is not an accurate description. Although large bacterial colony counts exist in the airway (1×10^8/mL) without an acute illness and during periods of clinical stability, there is still an exaggerated inflammatory response leading to airway destruction and disease progression. The term *colonized* would suggest that failure to eradicate would not be associated with increased morbidity. Thus we prefer the term *chronic infection*. Extended airway residence leads to changes in gene expression, including formation of anaerobic biofilms such as alginate and progression of disease due to chronic infection.

Antibacterial discovery and use has been associated with improved survival in patients with CF, although the development of antibiotic resistance has not been shown to increase the rate of decline.[120] Even though they may arise from similar strains, PA phenotypic changes have an impact on response to therapy.[120] PA can adapt by altering gene regulation and proteomic expression to the environment in which it lives. The CF airway has significant complexity and promotes a chronic PA infection model. The regulatory pathways are very complex. One such mechanism is alginate overproduction, leading to mucoid-type PA. This is a result of *algT,* a gene that negatively regulates flagella, pili, and quorum sensing (Rhl signal and rhamnoloid). The type three secretion system positively regulates heat shock response, oxidative stress response, osmotic stress response, and alginate production. Neutrophils also cause reactive oxygen species and reactive nitrogen intermediates expression to promote stress on bacteria and PA.[121] CF epithelial cells are unable to efflux glutathione, the most prevalent antioxidant, and they poorly absorb other dietary antioxidants. Reactive oxygen species and reactive nitrogen intermediates can lead to damage in DNA, lipids, and proteins, which in turn can lead to selection of variants that helps PA survive in the microaerobic or increasingly anaerobic environment.[122,123]

Antibiotic tolerance or resistance is directly related to antibiotic exposure. PA was rarely seen early on when severe *S. aureus* infection led to morbidity in the early days of CF lung disease antibacterial treatment. However, effective antistaphylococcal treatment led to the emergence of PA as a dominant CF-associated pathogen. The use of antibiotics has also led to resistance.[124,125] Resistance to all clinically relevant classes of antibiotics is increasingly exhibited by PA isolates from patients with CF.[126] Given the clonal nature of most CF-associated PA infections and the apparently infrequent transmission between patients in the setting of strict infection control practices, it would seem that de novo evolution of antibiotic resistance in individual patients is common.[127–130] Folkesson and coworkers demonstrated the lineage of a single strain of PA evolving or diversifying into mucoid and nonmucoid.[120] These sublineages, found in different regions (sinus, central airway, and specific lobe), reflect the distribution and isolation in different compartments of the lung. The phenotype can be homogeneous despite the complicated evolution genetically. If anaerobic conditions or stress with high salt are added to culture media, PA can change from a nonmucoid to a mucoid phenotype. When the environment becomes favorable again, PA reverts to a nonmucoid phenotype. This is not observed with wild-type PA, but happens to PA obtained from CF airways, which have adapted to their changing environment.

When PA is grown in CF sputum, increased expression of quorum sensing signaling genes is observed, leading to increased expression of virulence factors.[131] PA does not grow alone in the CF airways, and spatial localizations are impacted by other bacteria around them.[132] When PA is in proximity to gram-positive bacteria, it becomes more virulent (e.g., by making piocyanin). Treating MSSA chronically may help keep PA quiescent and may explain the benefit of antistaphylococcal therapy on individual CF patients.

New antimicrobial agents are currently being investigated to target multidrug-resistant PA. Ceftolozane-tazobactam is a novel cephalosporin/β-lactamase inhibitor with activity against multidrug-resistant PA. Currently ceftolozane-tazobactam is only indicated for intraabdominal infections and complicated urinary tract infections in adults, although its utility in nosocomial pneumonia has been described in case reports. However, a study by Grohs and associates examined the in vitro activity of ceftolozane and ceftolozane-tazobactam against 58 nonduplicate clinical isolates of gram-negative bacilli (35 *P. aeruginosa,* 11 *A. xylosoxydans,* and 12 *S. maltophilia*) acquired from CF patients. Ceftolozane was found to be the most active agent against PA (MIC for 50% of isolates [MIC_{50}], 4 μg/mL, and MIC for 90% of isolates [MIC_{90}], 128 μg/mL), with 54% of multidrug-resistant strains being susceptible.[133] In a US surveillance study by Farrell and colleagues of hospital-acquired PA, 96.1% of isolates were inhibited with MIC ≤4 μg/mL and maintained good activity against multidrug-resistant PA, including 77% of ceftazidime-nonsusceptible isolates.[134,135] Two case

reports have described using ceftolozane-tazobactam in CF patients during APE[136,137]; further studies are needed to determine its clinical efficacy in CF APE.

Ceftazidime-avibactam is another novel cephalosporin/β-lactamase inhibitor with good activity against multidrug-resistant PA. In US surveillance studies, it was found to have greater than 90% susceptibility rates, including approximately 80% of ceftazidime-nonsusceptible isolates. In vitro studies of multidrug-resistant PA from CF patients revealed 71.9% susceptibility.[138] Further studies are needed to determine the clinical efficacy of this drug in CF APE.

Currently interest has increased in gallium and its role as an antiinfective and antiinflammatory treatment agent for patients chronically infected with PA. Gallium is structurally similar to iron, and its uptake by PA disrupts PA iron metabolism by blocking the further uptake of iron. Furthermore, gallium also functions by inhibiting bacterial DNA synthesis and catalase activity, which in turn increases its sensitivity to oxidants. In vitro studies have shown it to be effective against PA, including multidrug-resistant strains, stationary-phase bacteria, and biofilms. A recently completed study, the IGNITE trial, randomized adult CF patients to receive either 5-day continuous infusion of gallium or placebo therapy and evaluated its effects on lung function, PA colony density, and drug safety. The study revealed a statistically significant improvement from baseline FEV_1 at days 6 and 14 of therapy and a decrease in PA density at day 28 of therapy. The inflammatory marker data were collected, and the results are currently pending.[139]

Burkholderia cepacia Complex

BCC organisms pose a significant health risk to CF patients. Although BCC was described much earlier, its association with CF was not appreciated until the 1980s.[140–142] In a longitudinal study in Belfast, 19 patients chronically infected with BCC and 19 controls chronically infected with PA were studied over a 4-year period.[143] The FEV_1 and BMI deteriorated much more in the BCC-infected group as compared to the PA-infected group ($P = .001$ and $P = .009$, respectively). Pathogenic differences exist among BCC species. Those infected with *B. cenocepacia* tend to have a much greater decline in FEV_1 compared to patients infected with *B. multivorans*.[143,144] Most of the more than 60 species belonging to the genus *Burkholderia* are not pathogenic to humans, but we pay attention to those that can result in serious sinopulmonary infections in patients with CF. Identified by 16S ribosomal DNA and *recA* gene analysis, many belong to the BCC group, consisting of 17 species at the moment, with new ones being identified. Outside of the BCC group, *B. gladioli, B. pseudomallei,* and *B. fungorum* have been identified as pathogens causing disease in CF patients.[145]

The increasing prevalence and the first of many descriptions of the rapid spread of BCC infection were reported in the CF center in Toronto.[146] They also provided one of the first descriptions of the so-called *cepacia syndrome.* Cepacia syndrome is characterized by rapidly deteriorating lung function, fever, leukocytosis, elevated markers of inflammation, and BCC bacteremia. Although *B. multivorans* behaves more like PA, it too has been associated with cepacia syndrome.

B. cenocepacia and *B. multivorans* are the most frequent isolated species belonging to the genus *Burkholderia.* Our center has a particular interest in *B. dolosa* due to its significant virulence and transmissibility. Caraher and colleagues compared *B. dolosa*'s ability to invade lung epithelial cells and form biofilm in vitro along with other BCC organisms, specifically *B. cenocepacia* and *B. multivorans*.[147] Its behavior is similar to other clinically relevant BCC species that infect CF patients, and it resulted in an epidemic spread across a large CF center. Thirty-one patients chronically infected with *B. dolosa* were compared to unmatched patients with *B. multivorans* and those not infected with *Burkholderia* species. The baseline FEV_1 and rate of decline were similar but the decline in FEV_1 after acquisition of *B. dolosa* was significant (−7.1% per year vs. −2.1% prior to infection) compared to no significant change associated with *B. multivorans* and those infected with non-*Burkholderia* species. A recent retrospective review by Boyer and coworkers revealed that 11 patients infected with *B. dolosa* who underwent lung transplantation had survival rates of 73%, 53%, and 30% at 1, 3, and 5 years, respectively, with a median survival of 44 months.[148] Among the 42 patients eventually identified during the epidemic, only 12 are alive at this time. Of the 11 patients who received transplants, 4 remain alive, and of 8 remaining pretransplantation patients, 5 are either awaiting lung transplantation or facing end of life.

The prevalence of BCC or *B. gladioli* infection can reach 8% in some adult CF cohorts, but usually hovers around 3% to 4% (see Fig. 71.1). The treatment of these drug-resistant strains is difficult and typically requires three to six concurrent antibacterials, including simultaneous use of more than one β-lactam antibacterial. A typical regimen for patients being admitted for APE associated with chronic infection with *B. dolosa* includes prolonged infusion of ceftazidime and meropenem, minocycline, and TMP-SMX, with the addition of chloramphenicol in cases of treatment failure. Fluoroquinolones and other β-lactam antibiotics, such as piperacillin-tazobactam, cefepime, aztreonam, and imipenem, have been used. Most strains of BCC are resistant to colistimethate.

Other Bacteria

With new advances in bacterial taxonomy and genetics-based methodologies, we are identifying new species, including those previously identified as either *Pseudomonas* or BCC. *Herbaspirillium* is one such organism previous identified as belonging to the BCC.[149] Other organisms not explored in depth include *A. xylosoxidans* and *B. gladioli,* which may be associated with progression of lung disease and morbidity.

S. maltophilia is an increasingly recognized pathogen impacting CF patients. Chronic infection is an independent risk factor for recurrent need for antibiotics.[150] Patients who acquire *S. maltophilia* have more advanced disease and may experience an exaggerated decline in lung function.[151] A study by Waters and colleagues looked at the impact of chronic infection with *S. maltophilia* on mortality and the need for lung transplantation.[152] A longitudinal cohort study of 687 patients revealed a nearly threefold increase in mortality for those chronically infected with *S. maltophilia* (≥2 positive sputum cultures in the previous 12 months) and did not bear out in those with intermittent infection (1 positive culture in the previous year or history of culture positivity). Unfortunately, antibiotic resistance is common in *S. maltophilia* infections. This resistance is multifactorial and related to *S. maltophilia* having limited outer membrane permeability as well as the presence of multidrug efflux pumps and antibiotic-modifying enzymes (aminoglycoside-modifying enzymes and carbapenemases).[151] A Cochrane review was performed in 2016 to assess for the effectiveness of antibiotic treatment for *S. maltophilia* in patients with CF, but the review did not reveal any supportive evidence.[153] The decision to treat is driven largely by clinician judgment, previous provider experience, and current and previous sputum or BAL culture results or both. In our center, we routinely utilize ceftazidime, levofloxacin, TMP-SMX, and minocycline.

Nontuberculous Mycobacteria

During the mid-1990s the prevalence of NTM infection among CF patients was 13%, and most were identified as *Mycobacterium avium* complex (72%), followed by *M. abscessus* (16%).[154] Risk factors associated with NTM included older age and geographic location (higher incidence in the Southwest compared to the Northeast) as well as a relatively higher association in those patients infected with *S. aureus* and *A. fumigatus* as compared with PA. The relation of spirometry results to the likelihood of finding NTM-positive cultures is unclear, and studies have found no association, a positive association, or a negative association. CFTR dysfunction may, of itself, predispose to NTM infection, since the rates of heterozygosity for *CFTR* mutations within the non-CF population with pulmonary NTM disease is between 30% and 50%.[155] Recent data from the CFF registry revealed that the prevalence rate of NTM-positive cultures was 13%.[76a] Esther and coworkers reviewed 4862 CF culture data from patients older than 8 years and also found an 11% NTM prevalence rate.[156] However, 55.6% were due to *M. abscessus* and associated with a sharper decline in FEV_1. The risk factors leading to this increased prevalence may coincide with the increased use of azithromycin in CF patients. Interestingly, a study that included over 27,000 patients detected NTM in 20% of cases (64% *M. avium* complex and 36% *M. abscessus*), with chronic azithromycin use less likely to be associated with NTM culture positivity.[157] Despite this, it is still important to screen patients for NTM to help avoid drug resistance to azithromycin.

Recent reports cite the transmissibility of *M. abscessus* among CF patients at care centers in the United States and the United Kingdom.[158,159] Gross and associates at the Tripler Army Medical Center Hospital (Hawaii) described an outbreak among a large portion of their CF cohort.[160]

The diagnosis and treatment of NTM infections remain challenging given the clinical presentation of patients with CF. Active NTM infection should be considered in patients with repeatedly smear-positive respiratory cultures, compatible radiographic findings, and lack of clinical response despite appropriate antibacterial therapy.[161]

Respiratory Viruses

The impact of viral infection on CF lung disease cannot be underestimated.[162,163] Fifty to sixty percent of exacerbations are associated with respiratory virus infections in children and are associated with FEV_1 decline, prolonged antibiotic use, and increased respiratory symptoms. With rhinovirus (69%) and influenza A/H1N1 (16.7%) leading the way, there was a 9.7% prevalence of documented viral infection detected by polymerase chain reaction among a cohort of adult patients presenting with a pulmonary exacerbation.[164] These exacerbations were associated with more severe lung disease and less response to standard therapies, and time to next pulmonary exacerbation was significantly reduced (64 days vs. 107 days). Respiratory virus coinfection may be implicated in planktonic-to-mucoid PA phenotype switching, specifically related to RSV.[49,165,166] Biofilm growth is enhanced during RSV infection compared to absence of RSV infection.

Fungal Disease

The role of fungi in the respiratory tract, particularly *A. fumigatus*, is still being elucidated.[167] When not causing ABPA, there is an increased association with disease severity when measured by FEV_1, hospitalization rates, and radiographic abnormalities.[168] A retrospective cohort study of CF patients with *A. fumigatus* infection, defined as 2 or more sputum or BAL cultures positive within a given year, found a decreased FEV_1 when compared to uninfected subjects; *A. fumigatus* was an independent risk factor for hospitalizations, the primary outcome measure of the study.[167] The role of fungal markers in serum and airway secretions can be helpful in raising suspicion for invasive fungal disease, but false-positive test results due to concomitant antibiotic use, presence of PA, or environmental contaminants should also be considered. Treatment decisions should be based on a full clinical picture, including nodular lung disease and other computed tomography–based radiologic patterns.

TREATMENT (Table 71.1)

Antimicrobial Treatment

A relationship exists between antibacterial use and improvement in lung function and survival in CF patients.[169,169a] Improved survival correlates with the discovery and introduction of additional antibiotics over the last century. It may also be evident that CF care centers with current best pulmonary functions in CF populations are also associated with higher rates of drug resistance.[170] Interestingly, several comparative trials have not shown the impact of antibacterial therapy on lung function. However, the benefits of combination therapy and incongruity with clinical experience are probably due to study design, sample size, poor definition of respiratory exacerbation, and the tremendous variability of the CF study population. Some CF patients have been on chronic antibiotics that may not have been accounted for in these studies as well. Conway and colleagues demonstrated some benefit, but this study included three antibiotics, suggesting that different combinations of antibiotics may be necessary for minimizing FEV_1 decline.[170a] These studies likely placed too much importance on the microbiology data from a single sputum culture; the end points for studies comparing single versus combination therapies are likely also flawed.

TABLE 71.1 Summary of Recommendations for Chronic Pulmonary Therapies for Patients With Cystic Fibrosis, 2013

TREATMENT	RECOMMENDATION	CERTAINTY OF NET BENEFIT	ESTIMATE OF NET BENEFIT	RECOMMENDATION[a]
Inhaled tobramycin: moderate to severe disease[b]	For individuals with CF, 6 yr of age and older, with moderate-to-severe lung disease and *Pseudomonas aeruginosa* persistently present in culture of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa: moderate to severe disease[b]	For individuals with CF, 6 yr of age and older, with moderate-to-severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations.	High	Substantial	A
Ivacaftor[c]	For individuals with CF, 6 yr of age and older, with at least one G551D *CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function, improve quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled aztreonam: moderate to severe disease[b]	For individuals with CF, 6 yr of age and older, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Dornase alfa: mild disease[b]	For individuals with CF, 6 yr of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, 6 yr of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.	High	Moderate	B
Inhaled tobramycin: mild disease[b]	For individuals with CF, 6 yr of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B

Continued

TABLE 71.1 Summary of Recommendations for Chronic Pulmonary Therapies for Patients With Cystic Fibrosis, 2013—cont'd

TREATMENT	RECOMMENDATION	CERTAINTY OF NET BENEFIT	ESTIMATE OF NET BENEFIT	RECOMMENDATION[a]
Inhaled hypertonic saline	For individuals with CF, 6 yr of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and reduce exacerbations.	Moderate	Moderate	B
Inhaled aztreonam: mild disease[c]	For individuals with CF, 6 yr of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B
Chronic use of ibuprofen (age <18 yr)	For individuals with CF, between 6 and 17 yr of age, with an FEV_1 ≥60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/mL, to slow the loss of lung function.	Moderate	Moderate	B
Azithromycin without *P. aeruginosa*	For individuals with CF, 6 yr of age and older, without *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.	Moderate	Small	C
Inhaled corticosteroids	For individuals with CF, 6 yr of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.	High	Zero	D
Oral corticosteroids	For individuals with CF, 6 yr of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to improve lung function or quality of life, or reduce exacerbations.	High	Negative	D
Other inhaled antibiotics	For individuals with CF, 6 yr of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 yr of age and older, with *P. aeruginosa* persistently present in the culture of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Leukotriene modifiers	For individuals with CF, 6 yr of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled or oral *N*-acetylcysteine, or inhaled glutathione	For individuals with CF, 6 yr of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral *N*-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Inhaled anticholinergics	For individuals with CF, 6 yr of age or older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Chronic use of ibuprofen (age ≥18 yr)	For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.	Low	—	I
Chronic inhaled β_2-adrenergic receptor agonists	For individuals with CF, 6 yr of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.	Low	—	I
Oral antistaphylococcal antibiotics, chronic use	For individuals with CF, 6 yr of age and older, with *Staphylococcus aureus* persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.	Low	—	I

TABLE 71.1 Summary of Recommendations for Chronic Pulmonary Therapies for Patients With Cystic Fibrosis, 2013—cont'd

TREATMENT	RECOMMENDATION	CERTAINTY OF NET BENEFIT	ESTIMATE OF NET BENEFIT	RECOMMENDATION[a]
Ivacaftor	For individuals with CF, 2 yr of age and older, with class III gating mutations other than G511D or R117H (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D)	• Age 2–5: N/A • Age 6–18+ & FEV_1 <40: Very Low–Low • Age 6–11 & FEV_1 40–>90: Low • Age 12–18+ & FEV_1 40–>90: Moderate	—	• Age 2–5: Recommended For • Age 6–18+: Conditional For
Ivacaftor	For individuals with CF, 6 yr of age and older, with the R117H mutation	• Age 6–11 & FEV_1 <40–90: Very Low • Age 6–11 & FEV_1 >90: Low • Age 12–18+ and FEV_1 <40–>90: Very Low • Age 18+ & FEV_1 <40: Very Low • Age 18+ & FEV_1 40–90: Moderate • Age 18+ and FEV_1 >90: Low	—	• Age 6–11 & FEV_1 <40–90: Conditional For • Age 6–11 & FEV_1 >90: Conditional Against • Age 12–17 & FEV_1 <40–90: Conditional For • Age 12–17 & FEV_1 >90: Conditional Against • Age 18+: Conditional For
Ivacaftor-lumacaftor	For individuals with CF, 6 yr of age and older, with two copies of F508del	• Age 6–11: Very Low • Age 12–18+ and FEV_1 <40–90: Moderate • Age 12–18+ and FEV_1 >90: Low	—	• Age 6–11: Conditional For • Age 12–18+ & FEV_1 <40–90: Strong For • Age 12–18+ & FEV_1 >90: Conditional For

[a]Strength of Pulmonary Clinical Practice Guidelines Committee recommendations: *A,* substantial net benefit; *B,* moderate net benefit; *C,* small net benefit; *D,* no net benefit; *I,* the committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.
[b]Severity of lung disease is defined by FEV_1 percent predicted as follows: normal, >90% predicted; mildly impaired, 70%–89% predicted; moderately impaired, 50%–69% predicted; and severely impaired, <40% predicted.[176]
[c]CF Foundation personnel did not participate in any activity related to ivacaftor.
CF, cystic fibrosis; *CF Foundation,* Cystic Fibrosis Foundation; *FEV_1,* forced expiratory volume in 1 second.
Data from Mogayzel et al.,[177] *Rowe et al.,*[213] *and Sawicki et al.*[212]

Azithromycin

Reduction in morbidity and mortality from macrolide antibiotics in diffuse panbronchiolitis, a rare inflammatory lung disease similar to CF in many ways, led to a number of studies in CF patients, including a randomized controlled study involving 185 patients.[171] Participants in the treatment arm experienced fewer respiratory exacerbations at the end of 168 days and their FEV_1 improved. The mechanism of macrolide-associated improvement in lung disease is still uncertain, but azithromycin is thought to modulate inflammation and may in fact have some direct antimicrobial impact.[172,173] Assays to emulate the airway environment and bacterial biofilm, and nonconventional biofilm susceptibility testing, have been used to demonstrate azithromycin inhibition of PA in biofilm. The antiinflammatory impact of azithromycin has been described using distinct models and includes demonstration of a decrease in C-reactive protein and a reduction in BAL fluid neutrophil cell count, neutrophil elastase, interleukin-1β, interleukin-8, and other mediators.[174] Despite a recent study contradicting some of these observations,[175] there is overall wide acceptance of azithromycin's role as an antiinflammatory in CF. In 2007, guidelines on chronic pulmonary therapies were published and included a high recommendation for chronic azithromycin in those CF patients chronically infected with PA.[176] A follow-up publication in 2013 reiterated this recommendation and also reflected on studies of azithromycin for those not infected with PA.[177]

Inhaled Antibiotics

Aerosolized antibiotics have become a mainstay of acute and chronic therapy in patients with CF. Prior to FDA approval of various formulations of inhaled antibiotics, several drugs meant for intravenous use were being nebulized to treat airway infection.[178] Since FDA approval of tobramycin inhalation solution (TIS) in 1997 and the study on intermittent aerosolization of 300 mg of preservative-free tobramycin for patients chronically infected with PA, two other inhaled antibiotic formulations have been FDA approved, and a number of other formulations are in the CFF clinical trials pipeline.[179] The 24-week study of 520 patients receiving either TIS or placebo demonstrated improved FEV_1, decreased density of PA in expectorated sputum, and decreased rates of hospitalization. Despite an increase in drug resistance, there was no significant impact of emergent drug resistance on lung function. The recent EAGER trial studied the safety, efficacy, and convenience of tobramycin inhalation powder (TIP), and results led to FDA approval of TIP in 2013.[180] There was a higher drop-out rate in the TIP group due to cough, but overall, the new formulation has demonstrated better adherence since administration takes 4 to 6 minutes compared to 15 to 20 minutes with TIS.

Aztreonam lysine for inhalation (AZLI) was FDA approved in 2010 based on results from multiple studies, including a randomized, double-blind, placebo-controlled clinical trial.[181–183] AZLI resulted in significant improvement in FEV_1, reduced density of PA, and improvement in respiratory symptoms as measured by the Cystic Fibrosis Questionnaire–Revised (CFQ-R) Respiratory Scale in a study that involved 164 CF patients with moderate-to-severe lung disease.[181]

Colistin is the most well known antipseudomonal antibiotic not FDA approved, but widely used to treat acute exacerbations and chronic infection with PA. A recent death attributed to inhalation of colistimethate, the inactive prodrug of colistin, as noted in an FDA Alert in 2007, has led to more hesitancy to use inhalation of drugs intended for parenteral use. A number of other inhaled antibiotics are in various phases of active clinical trials, including inhaled levofloxacin and vancomycin.[179]

Liposomal inhaled amikacin (LIA) recently received limited approval by the FDA for patients infected with NTM disease. The approval was in part based on a phase II, randomized, double-blind, placebo-controlled clinical trial for treatment-refractory NTM with two treatment arms; one arm received LIA in addition to a multidrug antimicrobial regimen while the second arm did not receive LIA.[184] Despite not achieving the primary end point, more patients in the LIA group had negative sputum cultures at the end of the study period, and it was determined to be safe in a limited patient population with unmet medical needs, as

postulated by the Limited Population Pathway for Antibacterial and Antifungal Drugs under the 21st Century Cures Act.[184a] Further studies are required to determine whether LIA will be efficacious for those patients with acute or chronic infection with PA.

Cystic Fibrosis–Specific Antibiotic Treatment Approaches

There are many questions yet to be answered regarding the treatment of CF respiratory infections. Given susceptibility data in particular patients, how should providers go about selecting antibiotics and what is the optimal length of therapy? The latter question was studied during the STOP trial, a prospective observational clinical trial sponsored by the CFF to evaluate current physician treatment practices and patient outcomes. The multicentered study revealed substantial variation in treatment duration and regimen. The average treatment length was 15.9 days, and individuals with more advanced lung disease received longer treatment courses. Of note, the study revealed that the mean absolute increase in FEV_1 from admission was 9% predicted at the end of antibiotics, and only 39% of participants fully recovered lung function, and only 65% recovered 90% of lung function that was lost.[185] This study laid the ground work for the STOP2 trial, which is an ongoing randomized trial evaluating the effectiveness of different intravenous treatment lengths based upon changes in lung function.[185a] In many cases, susceptibility data from recent and prior bacterial colonies isolated in sputum or BAL are still used to help determine antimicrobial choices. However, the combination of previous patient experience, drug toxicities, and allergies, in addition to the susceptibility data, should also be incorporated into making decisions regarding APE treatment.

Due to the increased volume of distribution and enhanced renal clearance of antibiotics in CF patients, they generally require larger doses of antibiotics compared to the general population.[186]

Patients who develop APE receive treatment directed at current or recent respiratory bacterial isolates. Patients who have chronic PA infection receive a combination of at least two antipseudomonal agents, with the intent of minimizing emergence of resistance given high baseline bacterial density and treating subpopulations of PA that may have not been identified on sputum sampling. Patients chronically infected with *S. aureus* receive treatment directed at MSSA or MRSA. In addition, patients with acute pulmonary infections should be tested for respiratory viruses, especially during influenza season. Patients may develop noninfectious complications related to CF that need to be contemplated in the differential diagnosis of APE, such as hemoptysis, pneumothorax, lobar atelectasis, and pulmonary embolism.

The negative impact of chronic infection with PA on CF patients, and the benefit of delaying chronic acquisition, has led to investigations to identify and treat early infection with PA and improve efficacy of eradication protocols, as discussed earlier. The largest of these trials is the randomized EPIC study investigating four separate treatment arms.[112–115] All patients received an initial course of TIS with or without ciprofloxacin, followed either by cycled antibiotic therapy regardless of respiratory cultures or symptoms or by culture-based therapy only when PA was isolated. No significant differences in clinical or microbiologic outcomes were found, but the EPIC study has led to more universal acceptance of eradication as a strategy. Subsequent studies have confirmed the decrease in PA recurrence after early identification, but this practice has not necessarily led to decreased hospitalization rates when compared to less aggressive protocols predating the EPIC trial.[115] Caregivers continue to aggressively treat patients with new-onset PA, but treatment regimens continue to vary despite the EPIC data.

Once-daily aminoglycoside administration has been widely adopted following the results of the TOPIC study.[187] Once-daily administration of tobramycin (10 mg/kg/day) was shown to be as efficacious as three times daily in treating pulmonary exacerbations and potentially less nephrotoxic. It is not clear if there is increased risk for sensorineural hearing loss, associated with increased prevalence in CF patients exposed to topical or inhaled aminoglycosides, but once-daily dosing is currently under further examination.[188]

A recent study has raised concerns regarding the coadministration of azithromycin and tobramycin. A study looking at PA-associated cutaneous thermal injuries led to the observation that azithromycin reduced the antimicrobial activity of tobramycin.[189] This antagonism was not demonstrated with ciprofloxacin. Another recent study looked at the change in lung function, as well as time to subsequent antibiotic requirement, quality of life (as measured by the CFQ-R Respiratory Scale score), and change in sputum PA density.[190] The data for the study were based on the Gilead Sciences randomized comparator trial involving 268 patients comparing AZLI to TIS.[191] In vitro data suggested a potential drug-drug interaction between tobramycin and azithromycin, based on the effects of combination drugs (azithromycin plus tobramycin and azithromycin plus aztreonam lysine). Subjects randomized to TIS and on chronic azithromycin therapy demonstrated less improvement in FEV_1, decrease in time to next exacerbation, less improvement in disease-related quality of life, and no change in sputum PA density. Though not enough to change treatment practice just yet, these findings are provocative and may impact future management of PA infection in CF.

Prolonged or continuous infusion of β-lactam antibiotics has been utilized with more frequency. The short half-life and lack of significant postantibiotic effect of β-lactam antibiotics makes them an attractive alternative, and duration above MIC helps determine efficacy.[192–194]

Non–Antibacterial-Based Treatments

In addition to antimicrobials, a combination of antiinflammatories, mucolytics, airway hydrating agents, airway clearance techniques, and nutritional supplements, among others, have been studied and have been incorporated into CF clinical practice.

Recombinant human DNase (dornase alfa) has been a mainstay of chronic respiratory therapy in CF since the early 1990s.[195] Dornase alfa helps break down large amounts of DNA (human, bacterial) and improves the rheology of airway secretions, aids in mucolysis, and facilitates airway clearance. The use of dornase alfa is strongly recommended for CF patients, including asymptomatic patients or those with mild disease.[176]

Hypertonic saline improves hydration of the airway surface liquid layer and improves mucociliary clearance in patients with CF.[196] In a multicenter randomized controlled trial, Elkins and coworkers demonstrated the benefits of 7% saline for inhalation.[196] Although the improvement in lung function did not achieve significance, there was a significant reduction in pulmonary exacerbations and need for antibacterial treatments. Given the impact of inhaled hypertonic saline on the airway surface liquid layer and on the basic defect causing CF manifestation in the airway, another multicenter randomized controlled trial involving CF infants ages 4 to 60 months, the Infant Study of Inhaled Hypertonic Saline in CF (ISIS), was pursued. Though the study did not achieve it primary outcome, this was likely due to lack of reliable outcome measures in this age group.[197]

Given the association of an exuberant immune response and advancing lung disease, antiinflammatory agents continue to be commonly used to treat CF lung disease.[198] Inhaled steroids were used indiscriminately given their ease of delivery and presumed benefit without significant downside. Although no studies were able to demonstrate a benefit in patients other than those with airway hyperreactivity or ABPA, an inhaled corticosteroid withdrawal study did not demonstrate a difference between exacerbation rates among subjects.[199] Oral glucocorticoids are not recommended for routine use outside of ABPA or asthma. Despite the benefit in lung function stabilization, the observation of hyperglycemia and diabetes, growth retardation, cataracts, osteoporosis, and higher rates of PA culture positivity indicate that the risks outweighed the potential benefits.[200,201] Konstan and associates performed a randomized, double-blind, placebo-controlled trial that demonstrated a significant reduction in the rate of FEV_1 decline, with the impact greatest in subjects younger than age 13 and with no difference observed in an older cohort.[202]

The concern for renal toxicity exists for patients receiving other agents associated with nephrotoxicity (e.g., ibuprofen) or dehydration, but a recent study did not observe an elevation in biomarkers of kidney injury.[203] Despite one small randomized, placebo-controlled trial that showed an improvement in FEV_1 of 8%, the CFF guidelines committee recommended against routine use of ibuprofen.[177]

Restoring CFTR Function

CF has been an exemplar of precision medicine, which was underscored by the invitation of a medical student with CF to the 2015 State of the

Union, where President Barack Obama announced the National Institutes of Health Precision Medicine Initiative known as the All of Us Research Program.[205] The promise of gene therapy for CF was at the forefront following the discovery of the *CFTR* gene in 1989, but has failed to deliver a much-anticipated cure. While there is still hope for traditional gene therapy, recent advances in gene editing have demonstrated real promise. High-throughput screening of small molecules helped launch a new treatment paradigm. Instead of treating symptoms and the manifestations of the disease, new FDA-approved therapies target basic *CFTR* defects at the protein level, while promising clinical trials targeting DNA/RNA and stem cell biology are in progress. Our knowledge of the mechanism by which a mutation leads to a particular abnormal CFTR protein expression, or lack of it, has led to mutation-specific therapies. G551D, a mutation shared by just over 4% of CF patients, results in a gating defect or class III mutation.[57a] The small molecule ivacaftor (corrector molecule) was shown to correct the mutated CFTR protein on the cell surface.[206] A 48-week randomized, double-blind, placebo-controlled trial demonstrated significant improvements in lung function (FEV_1) and BMI, along with reduction in respiratory symptoms based on the CFQ-R, APE, and sweat chloride test.[207] FDA approval came in 2012, and ivacaftor became the first small molecule in a therapeutic pipeline to expand treatment eligibility from 4% to 90% by 2020.

The most common *CFTR* mutation—F508del, with a near 85% prevalence—was the next target of small-molecule therapy. A total of 1108 patients enrolled in two phase III clinical trials of ivacaftor in combination with lumacaftor, a potentiator molecule to "chaperone" the misfolded protein resulting from *CFTR* mutation F508del, led to a modest but significant improvement in lung function as well as exacerbation-free days and reduced hospitalizations.[208] However, drug-drug interactions, including oral contraceptives and antidepressants, as well as complications of airway hyperreactivity in a small subset of patients led to development of a second corrector molecule. Once-daily tezacaftor, in combination with twice-daily ivacaftor, was introduced as an alternative to lumacaftor and led to a similar but slightly greater improvement in lung function.[209] While lumacaftor-ivacaftor was approved for those patients who are F508del homozygous only, tezacaftor-ivacaftor expanded coverage to compound heterozygotes with F508del and a *CFTR* residual function mutation. While these therapies increased accessibility of modulator therapies to nearly 50% of the CF population, a significant portion are still left out. Next-generation correctors to complement tezacaftor-ivacaftor have demonstrated significantly superior outcomes in comparison to tezacaftor-ivacaftor alone. In addition to the results of the phase II trial, a recent press release from Vertex Pharmaceuticals Inc. reveals the promise of the triple combination therapies. Next-generation correctors VX-659 and VX-445, when combined with tezacaftor-ivacaftor for patients who are heterozygotes for F508del and the minimal function *CFTR* mutation (F508del/MF), demonstrated a 13.3-point and a 13.8-point increase in percent predicted FEV_1 ($ppFEV_1$), respectively.[210,211] For those patients with two copies of F508del (F508del/F508del) and already on tezcaftor-ivacaftor, addition of VX-659 and VX-445 resulted in a 9.7-point and an 11.0-point increase in $ppFEV_1$, respectively. Preliminary results from recently completed phase III clinical trials involving VX-659, tezacaftor, and ivacaftor revealed a 14.0-point increase in $ppFEV_1$ after 4 weeks for F508del/MF patients and a 10.0-point increase in $ppFEV_1$ for F508del/F508del patients. With the successes of small-molecule CFTR modulators, there are four other sponsors of modulators in early phase II clinical trials.[179] These therapies will not reverse damaged, bronchiectatic lungs, while children and those with very mild disease experience the biggest impact on morbidity and mortality. Earlier introduction of these therapies may significantly delay the impact of infectious complications and reduce the rate of disease progression, as observed with ivacaftor in patients with at least one copy of G551D[212] (Fig. 71.5). These effective therapies provide an opportunity to study the change in microenvironment and airway surface liquid of the lung and its impact on bacteria infecting the airways.

Ongoing longitudinal observation studies are in progress for patients on various combinations of modulators, including PROMISE, a new study to follow those patients on the next generation of CFTR modulators (awaiting submission). The G551D Observational Study (GOAL) involving patients with the *CFTR* mutation G551D prescribed ivacaftor is still providing a wealth of information on various outcome measures, including lung function, nutrition, mucociliary clearance, intestinal pH, sputum inflammation and microbiome, and sweat secretion rate, among others.[213] Though there are conflicting data from a cohort of 12 subjects in Ireland, where an eradication of or sustained reduction in PA sputum density was observed, the much larger GOAL study reveals a significant reduction in PA culture positivity: a 35% reduction compared to the year prior to initiation of ivacaftor, particularly associated with patients with a higher FEV_1 prior to starting ivacaftor[214] (Fig. 71.6). The impact on CFTR and alteration in the microenvironment of the airway may be playing a role, but antimicrobial properties of ivacaftor may also be

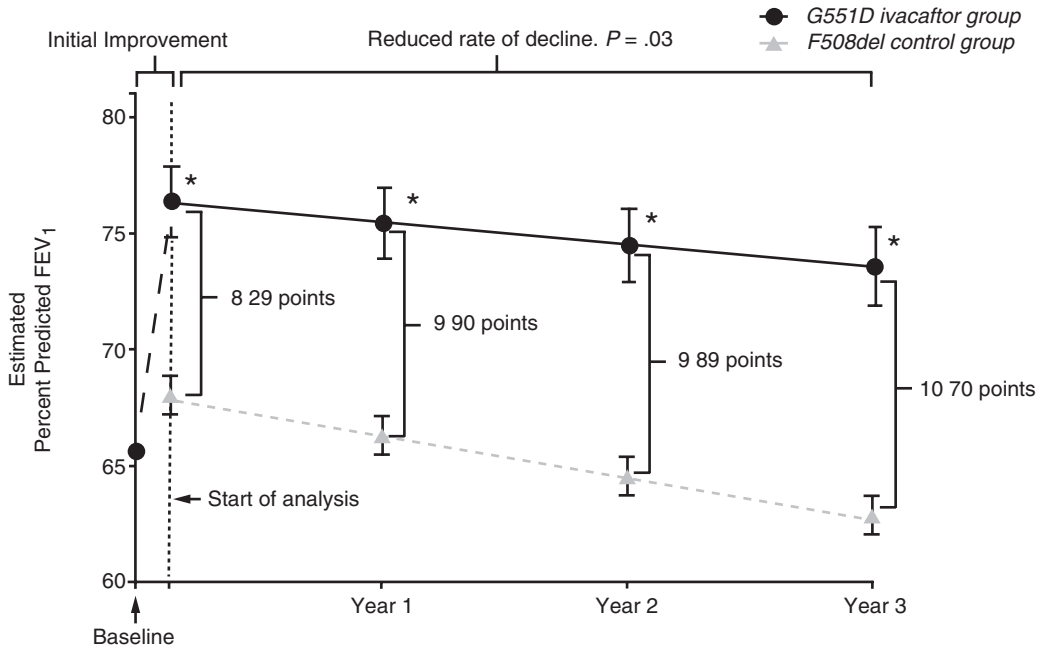

FIG. 71.5 Estimated percentage predicted FEV_1 measures (±SE) at years 1, 2, and 3. *$P < .001$. *FEV_1*, Forced expiratory volume in 1 second; *SE*, standard error. *(From Sawicki GS, McKone EF, Pasta DJ, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data.* Am J Respir Crit Care Med. *2015;192:836-842.)*

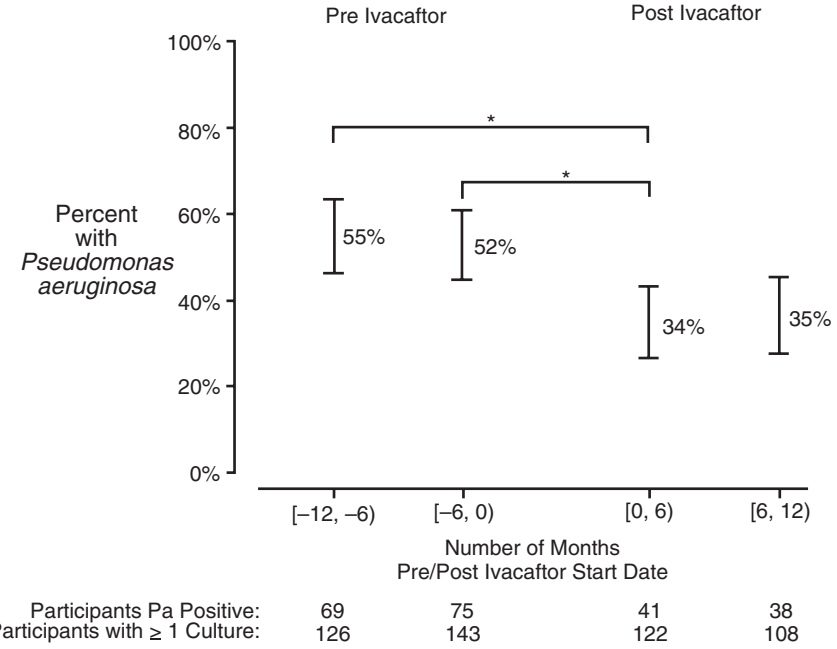

FIG. 71.6 Clinical measures obtained through the Cystic Fibrosis Foundation National Patient Registry in 6-month intervals before ivacaftor and after ivacaftor. *Pseudomonas aeruginosa* (*Pa*) positivity among those with a recorded respiratory culture in 6-month intervals. Means and 95% confidence intervals; *$P < .001$. *(From Rowe SM, Heltshe SL, Gonska T, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis.* Am J Respir Crit Care Med. *2014;190:175-184.)*

implicated.[208] Ivacaftor has a quinoline ring similar in structure to the quinolone antibiotics, and has demonstrated antimicrobial activity via reduced bioluminescence of bacteria such as *S. aureus* and PA. These properties were enhanced in combination with other antibiotics. The earlier introduction of more effective modulators will very likely have an impact on the epidemiology of infection in CF in years to come.

The therapeutic pipeline also includes a host of preclinical and phase I clinical trial studies, including gene editing techniques such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9) and stem cell biology. Despite the nearly 90% of CF patients worldwide who may have access to modulator therapies by the year 2020, there are a large number of CF patients with no clear therapeutic options in the near future. There is a great emphasis on developing *CFTR* mutation agnostic approaches to fixing CFTR to address this increasingly desperate option. Though some nonsense mutations may respond to small-molecule modulators, the great majority will require a different treatment paradigm that may also apply to other genetically inherited orphan diseases.[215]

INFECTION CONTROL

Transmission of pathogens among patients is a significant concern for CF centers and their patients. The CFF Consensus Conference on Infection Control Practices published recommendations in 2003 to help prevent patient-to-patient transmission.[216] Their suggestions apply not only to ambulatory clinics and inpatient setting, but to non–health care environments as well. Acquisition of new CF pathogens may come from the environment, but transmission from direct and indirect contact with CF patients has been demonstrated.[144] Outbreaks have involved PA, BCC, MSSA and MRSA, *Achromobacter, M. abscessus,* and others.[159,217] Updated 2013 CFF guidelines recommend that all CF centers review their quarterly surveillance reports to assess the incidence and prevalence of respiratory tract pathogens at their centers and perform molecular typing utilizing an appropriate genotyping method.[218] Recent studies have shown that aerosolized PA particles travel greater than 3 feet and can survive on surfaces for more than 2 hours.[219–222] Therefore the CFF Infection Prevention and Control 2013 guidelines recommend that all people with CF, regardless of their respiratory tract culture results, should be separated by at least 6 feet from other people with CF in all settings and wear a surgical mask when in health care settings to reduce the risk of droplet transmission. Contact precautions and placing patients with CF in a single-patient room, for both inpatient and ambulatory patients, remain mainstay measures. In the clinic setting, patients with CF should have minimal time in common waiting areas and be placed into an examination room immediately. As with all patients, health care providers should perform hand hygiene with an alcohol-based hand rub, or with antimicrobial soap and water, when hands might be contaminated with pathogens.[218]

LUNG TRANSPLANTATION

Lung transplantation is a treatment option for CF patients who develop end-stage lung disease, and successful transplantation is associated with an increased quality of life and probably increased life expectancy. Here we comment on infectious disease considerations relevant to CF patients who undergo lung transplantation.

Lung transplantation is a contaminated surgery, especially in patients with CF, during which airway and pulmonary secretions are expected to spill into the chest cavity. Bilateral lung transplantation is the norm for these patients. Most early infections in lung transplant recipients are surgical site infections associated with the pleural space, fractured ribs, or soft tissue and, more rarely, anastomotic site infections.

As part of the pretransplantation evaluation, all recent respiratory tract bacterial isolates are taken into consideration in preparing a tailored perioperative antimicrobial regimen. Similar to pretransplantation treatment of APE, two antipseudomonal antibacterials are administered perioperatively. If patients are chronically infected with multidrug-resistant PA strains (susceptible only to colistin), we typically administer a recent regimen that was associated with clinical improvement or stabilization, even if it does not contain colistin. This antibacterial regimen is continued for 2 weeks postoperatively and is adjusted by day-of-transplant bronchial cultures obtained from the recipient and donor. In addition, we give antibacterial prophylaxis for MRSA and continue treatment for 4 weeks if MSSA or MRSA is isolated on day-of-transplant cultures. All patients receive inhaled colistin or tobramycin during their initial hospitalization to minimize the risk of anastomotic site infection.

A majority of lung transplantation centers adopted "universal" prolonged voriconazole prophylaxis when this antifungal was approved in 2002. Although this has probably led to lower incidence of fungal

disease, most chronic toxicities of voriconazole use have been described in this population, especially phototoxicity, and periostitis probably from voriconazole-associated fluorosis. Analysis of fungal disease epidemiology in lung transplantation patients at our center pointed to the fact that most fungal disease was related to perioperative contamination with *Candida* and *Aspergillus,* and was not a result of increased immunosuppression. Given these data, we implemented a "targeted" strategy in which all patients receive micafungin as part of their perioperative antimicrobial regimen, beginning with induction of anesthesia and continued for 7 to 10 days. Patients also received inhaled amphotericin twice daily during their initial hospitalization or if they receive treatment for acute rejection. Once the explant pathology and day-of-transplant cultures are available, patients who had positive cultures for yeast or molds are treated with fluconazole or voriconazole, depending on fungal species isolated and susceptibilities, and are continued on this regimen for 3 to 6 months.[223] Patients whose cultures remain negative go home without any systemic antifungal. With this strategy, around 10% of transplanted patients go home on voriconazole, and the incidence of fungal disease is comparable to centers that use "universal" strategies.[224] *M. abscessus* infection in patients who undergo lung transplantation is infrequent, but highly problematic.[225] We continue TMP-SMX prophylaxis for life as *Pneumocystis jirovecii* and antibacterial prophylaxis.

Given infection control measures in place and younger age, CF patients tend to be cytomegalovirus (CMV) seronegative (R–), and thus are at higher risk of CMV disease when receiving lungs from CMV-seropositive donors (D+). The most common approach is to use valganciclovir prophylaxis for at least 1 year for patients who are CMV D+/R–, but 6 months of prophylaxis is likely sufficient for patients who are CMV R+.[226,227] Similarly, CF patients may be Epstein-Barr virus (EBV) seronegative at the time of lung transplant. This confers a very high risk (≥50%) of EBV-associated posttransplantation lymphoproliferative disease if they receive lungs from an EBV-seropositive donor.

Posttransplantation, lungs no longer contain CFTR-affected cells, but other CFTR-affected mucosal surfaces remain. Management of chronic sinusitis and polyposis associated with CF needs to continue posttransplantation. Sinusal chronic infections remain a reservoir for CF-associated bacteria. This requires judicious interpretation of cultures obtained during surveillance bronchoscopies, since cultures may represent oral or sinus contamination at the time of the procedures. Although some centers treat all BAL isolates, we do not pursue treatment of positive cultures in the absence of lung parenchymal or compatible respiratory symptoms.

FUTURE DIRECTIONS

Despite the numerous advances that have been made in CF care and treatment, there is still more work to be done. The Cystic Fibrosis Foundation is currently engaged in assisting with the development of the next generation of medications to aid in the treatment of CF. This drug development pipeline is robust and includes new modulator therapies, antiinflammatories, antiinfectives, mucociliary clearance medication, and gastrointestinal therapies (https://www.cff.org/Trials/pipeline).

At the 2018 North American Cystic Fibrosis Conference, the Cystic Fibrosis Foundation announced a commitment of 100 million dollars for the development of the Infection Research Initiative.[228] This initiative is envisioned to be a comprehensive approach to improve outcomes with infection through enhanced detection, diagnosis, prevention, and treatment. The Infection Research Initiative will take a multifaceted approach to advancing infection research, including identification of novel approaches to detect microorganisms and diagnose infection, and to enhance understanding of CF microorganisms and their acquisition. This is intended to develop safe and effective antiinfective agents, optimize currently utilized treatment regimens, evaluate the long-term impact of chronic antibiotic utilization, and characterize the effect of modulator therapy on infections.[228]

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The complete reference list is available online at Expert Consult.

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D Urinary Tract Infections

72 Urinary Tract Infections

Jack D. Sobel and Patricia Brown

SHORT VIEW SUMMARY

PATHOLOGIC CHARACTERISTICS

- With acute pyelonephritis there is suppurative necrosis or abscess formation.
- With chronic pyelonephritis there is uneven scarring.
- With papillary necrosis one or more pyramids may slough.

PATHOGENESIS

- Most urinary tract infections (UTIs) are the result of retrograde ascending infection, consequent to numerous behavioral factors.
- Because of efficient host defense mechanisms, bacterial pathogens capable of causing UTIs (uropathogens) are selected by virtue of genetically determined virulence factors.
- Virulence factors facilitate microorganism persistence in the urinary tract.
- Virulence factors include adhesins, bacterial capsules, aerobactin, cytotoxic necrotizing factors, hemolysins, and siderophore receptors.
- In functional and structurally compromised urinary tracts, there is reduced requirement for virulence factors in order to produce infection.

HOST DEFENSES

- Nonimmune mechanisms, especially antibacterial activity of urine, shearing force of micturition, and urine flow, are highly effective in reducing UTI frequency.
- Adaptive immunity—both antibody- and cell-mediated mechanisms—have a limited protective role.
- Innate immunity based on uroepithelial cells and response to adherent microbes reflects a complex recognition and reactive proinflammatory response consisting of multiple cytokines and inflammatory cells.
- Protective cytokine response is genetically determined and influences outcome spectrum from asymptomatic bacteriuria to suppurative renal disease.
- Genetic susceptibility to UTI is still minimally recognized and understood.

EPIDEMIOLOGY AND NATURAL HISTORY

- *Escherichia coli* is the most common infecting organism.
- Resistant *E. coli* and other resistant bacteria are increased in health care–related infection compared with community infection.
- Resistant bacteria are increased in complicated UTI.
- Asymptomatic bacteriuria is common and of little consequence except in a few groups.
- UTIs occur in 1% to 2% of infants, about 5% of girls, and 0.5% or less of boys.
- Renal damage is related to vesicoureteral reflux, which occurs in 30% to 50% of preschool children with infection; structural or functional obstruction also causes damage.
- UTIs are much more common in women than men and are most often asymptomatic.
- Up to 60% of women have symptomatic UTIs during their lifespan, and 10% of women have UTIs each year.
- Two percent to 5% of women have recurrent UTIs with a genetic predisposition.
- UTI in men is uncommon but often associated with structural or functional abnormality.
- Renal infection rarely causes end-stage renal disease without other underlying disease.

DIAGNOSIS

- Urine dipsticks for pyuria and bacteriuria are useful screening tests.
- A negative test for pyuria makes UTI unlikely.
- Negative tests for bacteriuria are common in UTI because of low titers of bacteria.
- Two urine cultures with greater than or equal to 10^5 of the same uropathogen/mL urine are required for diagnosis of asymptomatic bacteriuria.
- One culture with 10^2/mL or more of a gram-negative bacillary uropathogen is diagnostic in symptomatic UTI.
- One-third of young women with cystitis have fewer than 10^5 bacteria/mL urine.

MANAGEMENT AND TREATMENT

(see Table 72.6)

- All symptomatic UTIs are usually treated for relief of symptoms.
- Most asymptomatic infections should be neither sought nor treated because of lack of benefit; exceptions are during pregnancy and those persons who are to have traumatic urologic procedures. Controversial exceptions are some young children and after renal transplantation.
- Nonantimicrobial prevention measures are directed at reinfections and reducing risk factors. They include avoidance of spermicidal contraceptives and catheterization and use of topical estrogens in postmenopausal women.
- Treatment for infants younger than 3 months involves a β-lactam and an aminoglycoside intravenously.
- Treatment for infants older than 3 months is as mentioned previously for those seriously ill and an oral β-lactam or trimethoprim-sulfamethoxazole (TMP-SMX) for others.
- Treatment for acute, uncomplicated pyelonephritis in nonpregnant women is a urine culture and then fluoroquinolone.
- Treatment for uncomplicated cystitis in women is short-course therapy with nitrofurantoin, TMP-SMX, fosfomycin, or pivmecillinam.
- Treatment for complicated UTI is a urine culture and then fluoroquinolone. For cystitis, nitrofurantoin and fosfomycin are options.
- Treatment of relapses is prolonged therapy or chronic suppression. Complicated UTI or prostatitis is possible.
- Reinfections can be self-treated per episode or prevented using single-dose prophylaxis for intercourse or long-term prophylaxis.

PREGNANCY

- Asymptomatic bacteriuria of pregnancy requires therapy and posttreatment surveillance to reduce the risk of maternal pyelonephritis, hypertension, and preterm delivery.
- UTI treatment options are reduced given lack of availability of quinolones, tetracyclines, and sulfonamides (at term) as treatment options.

IMAGING

- The ever-improving quality and availability of renal ultrasonography has facilitated the diagnosis of renal complications and underlying urologic abnormalities. Excretory urography (intravenous pyelography) has fast disappeared, replaced by computed tomography scan and magnetic resonance imaging examinations.
- The use of imaging studies in infants and preschool children with febrile UTIs remains controversial, with reduced reliance on cystourethrography and the preference shifting to a "top-down" approach to selecting children who would most benefit from investigation.

Bacteriuria is a frequently used term and literally means "bacteria in the urine." The probability of the presence of infected urine in the bladder can be ascertained by quantifying the numbers of bacteria in voided urine or in urine obtained via urethral catheterization. *Significant bacteriuria* is a term that has been used to describe the numbers of bacteria in voided urine that usually exceed the numbers caused by contamination from the anterior urethra (i.e., $\geq 10^5$ bacteria/mL). The implication was that in the presence of at least 10^5 bacteria/mL of urine, infection must be seriously considered, and that with less than 10^5/mL, infection was unlikely. The 10^5 criterion was of significance historically. Currently it is of value only for diagnosing asymptomatic bacteriuria, which is important to treat in only limited circumstances.

TERMINOLOGY

The term *cystitis* has been used to describe the syndrome involving dysuria, frequency, urgency, and occasionally suprapubic tenderness. However, these symptoms may be related to lower tract inflammation without bacterial infection and can be caused by urethritis (e.g., gonorrhea, chlamydial urethritis). Furthermore, the presence of symptoms of lower tract infection without upper tract symptoms by no means excludes upper tract infection, which may also be present.

Acute pyelonephritis describes the clinical syndrome characterized by flank pain, tenderness, or both, and fever, often associated with dysuria, urgency, and frequency. However, these symptoms can occur in the absence of infection (e.g., in renal infarction or renal calculus). A more rigorous definition of acute pyelonephritis is the previously described syndrome accompanied by an indication of acute infection in the kidney.

Uncomplicated urinary tract infection (UTI) refers to infection in a structurally and neurologically normal urinary tract. The generally accepted definition of *complicated UTI* includes infection in the presence of factors that predispose to persistent or relapsing infection, such as foreign bodies (e.g., calculi, indwelling catheters or other drainage devices); obstruction; immunosuppression; renal failure; renal transplantation; and urinary retention from neurologic disease.[1,2] In addition, infection in men, pregnant women, children, and patients who are hospitalized or in health care–associated settings may be considered complicated. In the patient with complicated infection, infecting microorganisms are more likely to be resistant to antimicrobial agents. Recurrences of UTI may be relapses or reinfections. *Relapse* of bacteriuria refers to a recurrence of bacteriuria with the same infecting microorganism that was present before therapy was started. This is caused by the persistence of the organism in the urinary tract. *Reinfection* is a recurrence of bacteriuria with a microorganism different from the original infecting bacterium. It is a new infection. Reinfection may occur with the same microorganism, which may have persisted in the vagina or feces. This can be mistaken for a relapse.

The term *urosepsis* has been commonly used to describe the sepsis syndrome caused by UTI. Although used in the literature, this term should not be used in clinical documentation because it is not considered synonymous with sepsis for the purposes of coding. Utilizing the term *sepsis* and indicating the specific clinical syndrome to which the sepsis is secondary (e.g., pyelonephritis or acute prostatitis) is a better way to refer to sepsis secondary to infection in the urinary tract.

Increasingly the term *febrile urinary tract infection* is utilized; these infections can occur with or without concomitant sepsis.[3]

The term *chronic UTI* has little meaning in many patients. True chronic infection should really mean persistence of the same organism for months or years with relapses after treatment. Reinfections do not mean chronicity any more than repeated episodes of pneumonia indicate chronic pneumonia.

The term *chronic pyelonephritis* means different things to different authors. To some, chronic pyelonephritis refers to pathologic changes in the kidney caused by infection only. However, identical pathologic alterations are found in several other entities, such as chronic urinary tract obstruction, analgesic nephropathy, hypokalemic nephropathy, vascular disease, and uric acid nephropathy. Pathologic descriptions do not (and cannot) differentiate between the changes produced by infection versus those produced by these other entities.

Papillary necrosis from infection is an acute complication of pyelonephritis, usually in the presence of diabetes mellitus, urinary tract obstruction, sickle cell disease, or analgesic abuse. Papillary necrosis can occur in the absence of infection in some of these conditions. The necrotic renal papillae may slough and cause unilateral or bilateral ureteral obstruction. Intrarenal abscess may result from bacteremia or be a complication of severe pyelonephritis. Perinephric abscess occurs when microorganisms from the renal parenchyma or blood are deposited in the soft tissues surrounding the kidneys. Acute lobar nephronia, also called acute focal bacterial nephritis, is a radiologic diagnosis (most commonly on computed tomography scanning) consisting of edema and inflammation without liquefaction of one infected kidney lobe in a patient with the clinical syndrome of acute pyelonephritis.

PATHOLOGIC CHARACTERISTICS[4]

Acute Pyelonephritis

In severe acute pyelonephritis, the kidney is somewhat enlarged and discrete, yellowish, raised abscesses are apparent on the surface. The pathognomonic histologic feature is suppurative necrosis or abscess formation within the renal substance.

Chronic Pyelonephritis (Chronic Interstitial Nephritis)

In chronic pyelonephritis, one or both kidneys contain gross scars, but even when involvement is bilateral, the kidneys are not equally damaged. This uneven scarring is useful in differentiating chronic pyelonephritis from diseases that cause symmetrical contracted kidneys (e.g., chronic glomerulonephritis). There are inflammatory changes in the pelvic wall with papillary atrophy and blunting. The parenchyma shows interstitial fibrosis with an inflammatory infiltrate of lymphocytes, plasma cells, and occasionally neutrophils (Fig. 72.1). The tubules are dilated or contracted, with atrophy of the lining epithelium. Many of the dilated tubules contain colloid casts, which suggest the appearance of thyroid tissue ("thyroidization" of the kidney). There is also concentric fibrosis about the parietal layer of the Bowman capsule (termed *periglomerular fibrosis*) and vascular changes similar to those of benign or malignant arteriolar sclerosis.

Many studies have found little correlation between these pathologic findings and evidence for past or present UTI. Clearly, a better term for this pathologic entity would be *chronic interstitial nephritis* to encompass all the clinical states that can cause these changes. To incriminate infection as the sole cause of chronic interstitial nephritis, one needs evidence of past or present UTI and the absence of any other condition that can cause the pathologic picture of chronic interstitial nephritis. These criteria are seldom met and, even if they are, it is frequently impossible to establish whether infection is complicating interstitial nephritis of some unrecognized cause.

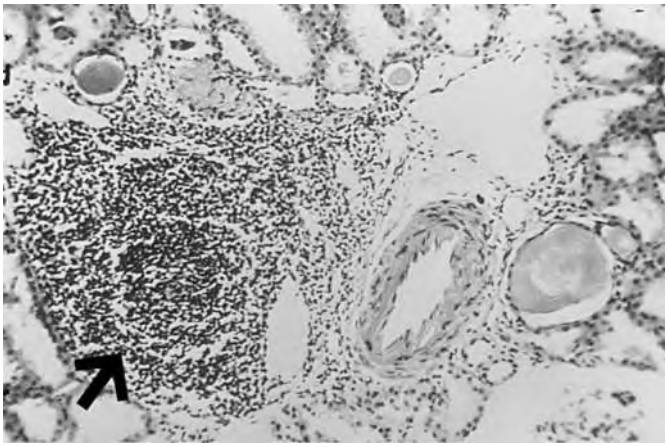

FIG. 72.1 Chronic pyelonephritis. Tubules are filled with eosinophilic casts and surrounded by a dense infiltrate of lymphocytes and plasma cells *(arrow)*.

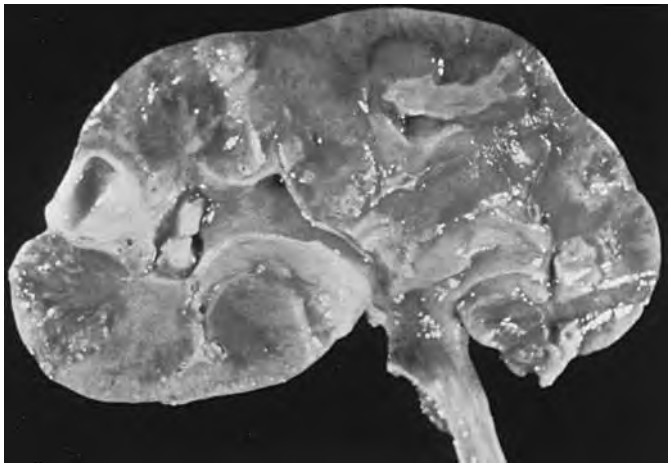

FIG. 72.2 Necrotizing papillitis (papillary necrosis) complicating acute pyelonephritis in a diabetic patient. The pelvis is hemorrhagic. Note large and irregular defects. *(Courtesy Dr. M. Bergeron.)*

Papillary Necrosis Caused by Infection

Frequently both kidneys are affected, and one or more pyramids may be involved (Fig. 72.2). The pyramids are replaced by wedge-shaped areas of yellow necrotic tissue, with the base located at the corticomedullary junction. As the lesion progresses, a portion of the necrotic papilla may break off, producing a calyceal deformity that results in a recognizable radiologic filling defect. The sloughed portion may be voided and, in some cases, can be recovered from the urine. Microscopically, edema is initially seen in the interstitium. Eventually, the lesion resembles an infarct with coagulation necrosis involving the entire pyramid. The collecting tubules are filled with bacteria and polymorphonuclear leukocytes.

PATHOGENESIS OF URINARY TRACT INFECTION

Urinary tract infections occur as a result of the interaction of bacterial virulence and host biologic and behavioral factors, superseding highly efficient host defense mechanisms. There are three possible routes whereby bacteria can invade and spread within the urinary tract: the ascending and hematogenous pathways.

For a discussion of catheter-associated UTIs, see Chapter 302.

Ascending Route

The ultimate source of uropathogenic *Escherichia coli* (UPEC) and other uropathogens is the intestinal tract acting as a fecal reservoir. Especially apparent in women, the next phase of the ascending route is bacterial colonization of the vaginal introitus and periurethral meatus tissue. Evidence links new and increased colonization with uropathogens originating from rectal microbiota just before UTI. Colonization occurs in parallel with concomitant loss of the normally predominant and protective vaginal *Lactobacillus* species. Both culture and microbe genomic-based studies confirm the prevalence of *Lactobacillus* spp. in vaginal microbiota.[5] Lactobacilli express protective efficacy by achieving low pH (4.0–4.5); by interference with uropathogen adherence to vaginal epithelial cells; and by production of bacteriocins, H_2O_2 and chloride anions, and myeloperoxidase.

The urethra is usually colonized with bacteria. Studies using suprapubic puncture techniques have revealed the occasional presence of small numbers of microorganisms in the urine of uninfected persons. Massage of the urethra in women and sexual intercourse can force bacteria into the female bladder. Condom use may heighten the traumatic effects. Furthermore, just one catheterization of the bladder results in UTI infection in about 1% of ambulatory patients,[6] and infection develops within 3 or 4 days in essentially all patients with indwelling catheters with open drainage systems. Both the contraceptive diaphragm with nonoxynol-9 contraceptive jelly in women and the condom catheter in men have been shown to predispose to infection.[7] Studies have implicated the spermicide rather than the diaphragm. Spermicides increase colonization of the vagina with uropathogens. Although the dominant *Lactobacillus* vaginal flora are more sensitive to nonoxynol-9 than is *E. coli,* it has not been proved that the high coliform presence in nonoxynol-9 users is caused by a loss of lactobacilli. Spermicide use also increases adherence of *E. coli* to vaginal epithelial cells.[5] Estrogen deficiency is now recognized as a predisposing factor to recurrent UTIs in postmenopausal women because of consequent vaginal microbiome changes with loss of protective lactobacilli, which are replaced by coliforms and other uropathogens.[8] As with younger women, recent sexual intercourse is strongly associated with incident UTIs in postmenopausal women.[9] Uropathogenic *E. coli* is not infrequently shared between heterosexual sex partners.

The fact that UTI is much more common in women than in men gives support to the importance of the ascending route of infection. The female urethra is short and is in proximity to the warm, moist, vulvar and perianal areas, making contamination likely. It has been shown that the organisms that cause UTI in women colonize the vaginal introitus and the periurethral area before urinary infection results. Once within the bladder, bacteria may multiply and then pass up the ureters, especially if vesicoureteral reflux is present, to the renal pelvis and parenchyma. Animal studies have also confirmed the importance of ascending infection. If bladder bacteriuria is established after unilateral ureteral ligation, only the unligated kidney develops pyelonephritis. Finally, studies have correlated intestinal carriage of urovirulent *E. coli* and susceptibility to UTIs in children.[10]

In addition to the fecal reservoir, experimental mouse models of UTI have demonstrated that UPEC invade the bladder epithelium and form intracellular bacterial communities. These communities constitute quiescent intracellular reservoirs associated with resistance to clearance by antimicrobial treatment and recrudescence of bacteriuria.[11]

Hematogenous Route

Infection of the renal parenchyma by bloodborne organisms clearly occurs in humans. The kidney is frequently the site of abscesses in patients with *Staphylococcus aureus* bacteremia or endocarditis, or both. Experimental pyelonephritis can be produced by the intravenous (IV) injection of several species of bacteria and *Candida.*[12] However, the production of experimental pyelonephritis by the IV route with gram-negative enteric bacilli, the common pathogens in UTI, is difficult. Additional manipulations, such as the creation of ureteral obstruction, are often necessary.[12] It would appear that in humans, infection of the kidney with gram-negative bacilli rarely occurs by the hematogenous route.

Urovirulence in Bacteria

Although UTIs are caused by many species of microorganisms, most are caused by *E. coli.* However, only a few serogroups of *E. coli*—01, 02, 04, 06, 07, 08, 075, 0150, 018ab—cause a high proportion of infections. This has led to the concept of UPEC clones, or lineages, to differentiate pathogenic populations from commensals, and clonal analysis has facilitated epidemiologic studies of the spread of antibiotic-resistant clones of *E. coli* and identified environmental sources of *E. coli,* including households.[13] Certain O, K, and H serotypes also correlate with clinical severity, especially pyelonephritis. Accordingly, certain strains of *E. coli* are selected from the fecal microbiota by the presence of virulence factors that enhance both colonization and invasion of the urinary tract. Virulence factors allow evasion of host defenses and have the capability to produce disease. Cystitis and pyelonephritic *E. coli* isolates are genetically distinct, exhibiting differences in O, K, and H antigens. Genetic differences among uropathogens may be responsible for different clinical outcomes. Johnson and colleagues[14] have confirmed that certain O, K, and H serotypes are associated with urovirulence and with the presence and expression of multiple chromosomal virulence factor determinants. Virulence is a critical determinant of clinical presentation. Recognized virulence factors include increased adherence to vaginal and uroepithelial cells[15]; resistance to serum bactericidal activity; a higher quantity of K antigens (K1, K5, K12) in capsules; and the presence of aerobactin *(iucC),* cytotoxic necrotizing factor type 1 *(cnf),* hemolysin *(hly)* production, and a siderophore receptor *(iroN).*[15]

A variety of bacterial toxins have been reported that breach epithelial barriers, including an α-hemolysin that inhibits protective cytokine production by bladder epithelial cells, and the importance of extracellular polysaccharide as a virulence factor has been suggested.[16,17] Capsular polysaccharide contributes significantly to bacterial survival by countering lytic effects of complement and phagocytes. Induction of indoleamine 2,3-dioxygenase by UPEC attenuates innate response to uroepithelial cell invasion, facilitating colonization and establishment of infection. Genes for the various urovirulence factors are often duplicated in uropathogens and frequently linked as large, multigene, chromosomal segments called *pathogenicity islands,* and are absent in coliforms found in normal fecal flora.[18,19] Other virulence genes for *E. coli* UTI include *usp,* coding a uropathogenic specific protein, and *iroN,* coding a catechol siderophore receptor homologue.[20] Urine is poor in iron and other minerals. All uropathogens are able to use urine as a growth medium. Urine is, however, an incomplete growth medium; hence, the synthesis of one or more nutritional factors by UPEC is essential. Bacterial synthesis of guanine, arginine, and glutamine is required for optimal growth in urine.[21] *Escherichia coli* with mutations that are insufficient to generate resistance, as measured in the clinical microbiology laboratory, may have a selective advantage in the physiologic conditions provided by urine.[22]

Adhesins

Fimbriae

Adhesive properties of bacteria influence the selection of bacteria capable of colonizing the colon[10,23] and reaching and colonizing the normal urinary tract, and they influence the anatomic level of infection in the urinary tract (Table 72.1). Accordingly, bacteria with enhanced adherence to vaginal and periurethral cells would be selected to colonize the anatomic regions adjacent to the urethral orifice. *Escherichia coli* pyelonephritis isolates adhere better than *E. coli* cystitis isolates, and urinary isolates tend to adhere more strongly to uroepithelial cells than do random fecal *E. coli* isolates. The adhesins of UPEC exist as filamentous surface organelles termed *pili* or *fimbriae* or as nonfilamentous proteins in the outer membrane (see Chapter 218). Numerous uropathogenic strains adhere in the absence of fimbriae.

P Fimbriae

The binding of *E. coli* to epithelial cell receptors containing globoseries glycosphingolipid accounts for the attachment of most strains causing kidney infection and is not inhibited by mannose; this binding is called mannose resistant. Fimbriae attaching to globoseries receptors are termed *P fimbriae* because the receptor is a constituent of the P blood group antigen complex present in human erythrocytes and uroepithelial cells. The glycosphingolipids, synthesized by specific glycosyltransferases, are components of the glycocalyx surrounding epithelial cells and consist of an oligosaccharide moiety on the cell surface covalently linked to a lipid position embedded in the outer leaflet of the plasma membrane. Glycosphingolipases are highly specific to a given host and play an important role in determining tissue tropism for microbial pathogens and an individual host's susceptibility to UTIs. The globoseries glycosphingolipid receptors (Gal-Gal) are distributed throughout the urinary tract, particularly in the kidney.

P fimbriae are frequently present in uropathogens; they augment the virulence of UPEC at different stages of infection, including remaining longer in the intestinal tract and spreading more efficiently to the urinary tract for purposes of colonizing and producing ascending infection.[10,24] Once in the urinary tract, P-fimbriated strains adhere, persist, and, despite enhancing epithelial cytokine response, invade the kidney and induce bacteremia.[24] P fimbriae invariably show the strongest association to acute disease severity with 90% or more of acute pyelonephritis–causing strains, but less than 20% of asymptomatic carriers express this phenotype. The *pap* gene *EFG* sequences encode the adhesin complex. Three molecular variants of PapG adhesin, encoded by *PapG* class I through IV alleles, exhibit subtle receptor-binding preferences influencing the clinical outcome. Allele class II predominates among strains causing pyelonephritis and bacteremia, and class III allele is more commonly found in children and women with cystitis.[25,26] P fimbriae confer enhanced ability of UPEC clones to colonize the colon and spread to the perineum. Although relatively resistant to phagocytosis by neutrophils, *E. coli* with P fimbriae paradoxically enhance the host inflammatory response after engaging Toll-like receptor 4 (TLR4) by inducing the elaboration of proinflammatory cytokines.[27,28] Neutrophils lack receptors for P fimbriae. P-fimbriated *E. coli* dominates as a cause of pyelonephritis and urosepsis, especially among blood isolates; nevertheless, downregulation of P fimbriae expression may occur in the bacteria when they are in the kidney, hence facilitating parenchymal persistence.[29] In the mouse model of pyelonephritis, antibodies directed against P fimbriae that block bacterial adherence to uroepithelial cells in vitro prevent upper tract infection in vivo. With the same model, a vaccine using P fimbriae demonstrated some encouraging results; however, no progress in humans has followed.

Type I Fimbriae

Binding of *E. coli* to mannose-containing host epithelial receptors, glycoproteins uroplakin I and II, is universal in UPEC strains and is essential for establishment of cystitis.[30] In fact, strains from cystitis

TABLE 72.1 Uropathogenic *Escherichia coli* Adhesins and Corresponding Epithelial Receptors

ADHESIN	GENETIC SEQUENCE	RECEPTOR	COMMENTS
Type 1 fimbriae (MS)	*Pil, fimH, fimB, fimE*	Mannosylated proteins on epithelial cells (uroplakin Ia) and PMNs	Bind to THP and SIgA
P fimbriae (MR)	*papG* (class Ia) ($papG_{J96}$) *papGAP* (class II) ($papG_{IA2}$) *papG* (class III) ($prsG_{J96}$)	Gal-α 1-4 (P blood group antigen)	Rare Strongly associated with pyelonephritis and bacteremia Cystitis; predominates among patients with urinary tract abnormalities and males
S/F1C fimbriae (MR)	*Sfa/fac*	Sialyl-(α-2-3) galactoside	Adherence inhibited by THP
Type 1c (MR)	*Foc*	Undetermined	Possibly associated with pyelonephritis
G fimbriae (MR)		Terminal *N*-acetyl-D-glucosamine	
M fimbriae (MR)		Galactose-*N*-acetylgalactosamine	
Type 3 fimbriae	*(mrkABCDF)*	Blood group M (glycophorin A)	Contribute to biofilm formation; *E* gene present in 16% of first-time cystitis isolates
Dr family (fimbriated and nonfimbriated)	*Drb* operon; adhesin (*E* gene); *AfaE1-5; AfaF*	Dr blood group antigen component of DAF (decay accelerating factor) and type IV collagen	

MR, Mannose-resistant; *MS,* mannose-sensitive; *PMN,* polymorphonuclear neutrophil; *SIgA,* secretory immunoglobulin A; *THP,* Tamm-Horsfall protein.

patients are more likely to bind than those from pyelonephritis patients. Fimbriae attaching to mannosylated proteins via *FimH* subunits are the common type 1 fimbriae (pili), and attachment is inhibited in the presence of mannose (mannose sensitive). Type 1 fimbriae bind mannose epitopes on secreted glycoproteins such as secretory immunoglobulin A (IgA) and urinary mucus, Tamm-Horsfall protein (THP), bladder uroplakin protein, integrins, and fibronectin.[31] Type 1 fimbriae are encoded by the *pil* or *fim* gene cluster, including nine genes that encode structural and regulatory proteins.[32] The gene *fimA* encodes the fimbrial subunit protein, which can be expressed independently of the *fimH*-encoded adhesin protein.[33] The *fim* DNA sequences encoding type 1 fimbriae occur in most clinical isolates; consequently, epidemiologic evidence of an association between type 1 fimbriae and the site or severity of infection is more difficult to obtain. Expression of type 1 fimbriae is not especially prevalent among pyelonephritogenic strains. Clinical correlation in childhood, use of human bladder epithelial lines, and experimental animal studies have correlated type 1 fimbriae with persistence of *E. coli* in the urinary tract, and the use of a *fimH* null mutant of a type 1–positive *E. coli* isolate resulted in rapid elimination of the mutant from the urinary tract. Adherent bacteria multiply into biofilm-like inclusions known as *intracellular bacterial communities* or enter a quiescent phase for later reemergence. Such organisms may be relatively protected from host immune defense, and may contribute to clinical relapse. Similarly, clinical correlations in childhood urinary infections suggest that type 1 fimbriae contribute to virulence in the urinary tract when expressed in the background of a fully virulent uropathogen. Paradoxically, *fimH* also promotes adhesion to phagocytic cells that should presumably result in early bacterial clearance because of enhanced intracellular killing. In fact, antibody-opsonized and internalized type 1 fimbriae–bearing *E. coli* are rapidly killed. This is likely to occur within renal parenchyma, and hence type 1–fimbriated *E. coli* are programmed to shed their fimbriae on reaching the renal pelvis. In contrast, *E. coli* internalized only by a type 1 fimbrial mechanism survive intracellularly within the phagocyte, resulting in parasitism. Once inside the macrophage, the bacterium is safe from antibiotic assault, only to emerge later and possibly contribute to the relapse of bacteriuria. Bacterial adherence to urinary catheters is also type 1 fimbriae dependent. Type 1 fimbriae–mediated attachment to mast cells and lymphocytes results in further release of cytokines, causing cell proliferation and secretion of antibodies.

P and type 1 fimbriae are inversely and coordinately regulated in individual strains, explaining how invading bacteria adapt extemporaneously and sequentially to different environmental conditions prevalent in the human urogenital tract (e.g., P fimbrial expression downregulates type 1 fimbrial expression).[34] Type 3 fimbriae in UPEC are thought to contribute to biofilm formation and to be important in urethral catheter infections.[35]

Other Adhesins

In addition to type 1 and P fimbriae, various adhesins, including S (7% of uropathogenic strains), type 1c, G, and Dr fimbriae and M and X adhesins,[36] with differing molecular binding specificities and serologic properties, have been identified on UPEC and are expressed in vivo in urine (see Table 72.1). S fimbriae bind sialic acid epitopes present in renal sialylated lipoproteins. The Dr hemagglutinin family includes fimbrial and nonfimbrial adhesins. Four genes (*draA, B, C,* and *D*) encoding the structural proteins and adhesins of the fimbriae have been identified. The adhesins bind to the Dr blood group antigen component of decay-accelerating factor, which is widely distributed along the urinary tract and mediates cellular invasion.[37] Dr-expressing uropathogens are of relatively low invasive potential and demonstrate low multiplication rates; however, Dr-positive *E. coli* persists in renal infections and may play a role in chronic pyelonephritis and interstitial nephritis.[36] Type 1 pili and the Dr adhesin have been linked to bladder epithelial cell invasion and intracellular persistence by UPEC.[14]

Studies with other species of bacterial uropathogens (e.g., *Proteus mirabilis, Klebsiella* spp.) have similarly demonstrated the significance of adherence in the pathogenesis of urinary infections. *Staphylococcus aureus* uncommonly causes cystitis and ascending pyelonephritis; in contrast, *Staphylococcus saprophyticus* is a frequent cause of lower UTIs. *Staphylococcus saprophyticus* adheres significantly better to uroepithelial cells than does *S. aureus* or *Staphylococcus epidermidis.*

Expression and Selection of Virulence Factors

Evaluation of urinary isolates for virulence characteristics in the presence of underlying structural abnormalities (e.g., severe reflux) frequently fails to demonstrate the typical bacterial virulence factors. Similarly, *E. coli* blood isolates obtained from patients with urosepsis after bladder instrumentation often lack virulence factors. Virulence determinants are more frequently expressed by urinary isolates of *E. coli* obtained from women with cystitis compared with fecal isolates from healthy women. No difference in the prevalence of *E. coli* virulence determinants was found between subjects with first-time cystitis and those with recurrent cystitis, suggesting that host rather than bacterial factors determine the risk for recurrent infection. It has been demonstrated that *E. coli* isolates that cause cystitis in women using diaphragms with spermicides have fewer virulence determinants than do isolates of nonusers, suggesting that the use of diaphragms with spermicides may allow infection with less virulent *E. coli.* In one study, quinolone-resistant UPEC was less virulent with decreased invasive capacity. In contrast, *E. coli* strains isolated from men with febrile UTI exhibited a significantly higher prevalence of virulence-associated phylogenetic groups, serotypes, and virulence genes.[38] Resistant organisms have been shown to have reduced type 1 fimbriae expression and proteolytic toxin Sat elaboration.[39] Trimethoprim-sulfamethoxazole (TMP-SMX), extensively used to prevent urinary infection, reduces the synthesis, expression, and adhesive function of type 1 fimbriae at concentrations well below the minimal inhibitory concentration. The importance of adherence as a virulence factor is not complete without consideration of the role of the host. A difference in adherence receptor density and specificity is linked to a difference in genetic susceptibility. In women and children with recurrent UTI, an increased avidity of bacterial attachment to vaginal, periurethral, and uroepithelial cells has been found.

Other Virulence Factors of Uropathogenic *E. coli*

Certain other characteristics of bacteria may be important in the production of upper tract infection. Motile bacteria, especially those with flagellae, can ascend in the ureter against the flow of urine, and the toxins of uropathogenic gram-negative bacilli have been shown to decrease ureteral peristalsis and possibly contribute to the renal parenchymal inflammatory response by phagocytic cell activation.[40] As a general principle, UPEC promote a more intense inflammatory response through greater activation of the innate immune system, resulting in symptomatic urinary tract inflammation. In *Proteus* spp., the production of urease by infecting microorganisms has been correlated with the ability to cause pyelonephritis. The presence of K capsular antigen protects bacteria from leukocyte phagocytosis. Most uropathogenic strains produce hemolysin, which facilitates tissue invasion and causes renal tubular epithelial and parenchymal cell damage, possibly making iron available to invading *E. coli.* The hemolysin gene is frequently located adjacent to genes encoding for serum resistance and sialic acid–specific (S) fimbriae, but the pathogenic role of hemolysis in pyelonephritis remains controversial. Aerobactin, an iron-scavenging protein or siderophore, is present with increased frequency in uropathogenic strains of *E. coli.*[12] Iron acquisition systems are often found in uropathogenic *E. coli,* presumably because conditions in the bladder are iron poor. Uropathogenic *E. coli* strains contain a greater number of iron acquisition systems than do fecal or commensal strains, which is reflective of the adaptation to the iron-limiting urinary tract environment. Genes have been identified that encode for these virulence factors: *hlya* (encoding hemolysin), *cnf1* (encoding cytotoxic necrotizing factor 1), and *iutA* (encoding aerobactin receptor). Cytotoxic necrotizing factor 1 has been associated with UTIs and prostatitis in clinical epidemiologic studies and causes pronounced bladder inflammation in animal models.[41] The iron-regulated gene homologue adhesin (Iha), an outer membrane protein encoded by *iha,* was shown to be a virulence factor in a mouse model of UTI.[42] Recent studies have indicated a fitness advantage for flagellated *E. coli* in mouse models of UTI facilitatory colonization. Of note, *E. coli* strains causing asymptomatic bacteriuria

appear to have lost their ability to express functional virulence-associated genes.[43]

Some UPEC strains downregulate responding neutrophil activity, hence evading the dominant acute immune response (i.e., suppressing neutrophil transepithelial movement and therefore recruitment), providing an important advantage for establishing infection. Additionally, UPEC resists phagocytic killing and dampens production of antibacterial reactive oxygen species by neutrophils. Downregulation is achieved by reduced expression of polymorphonuclear neutrophil (PMN) genes.

The greater the number of organisms delivered to the kidneys, the higher the chance of producing infection. The kidney itself is not uniformly susceptible to infection because few organisms are necessary to infect the medulla, whereas 10,000 times as many are necessary to infect the cortex. The greater susceptibility of the medulla may be caused by the high concentration of ammonia, which may inactivate complement, and by poor chemotaxis of PMNs into an area of high osmolality, low pH, and low blood flow.

Host Factors in Urinary Tract Infections

Host behavioral factors that contribute to UTI include sexual intercourse, including frequency; use of spermicides for contraception; a new sexual partner within the last year; and recent antimicrobial exposure. The latter factor not only increases risk of UTI but profoundly increases risk of acquisition of resistant bacteria. Finally, lack of estrogen is a major factor contributing to increased risk in postmenopausal women not receiving hormone replacement therapy. Loss of estrogen results in decreased or complete loss of vaginal lactobacilli. Key urogenital mucosal host defense mechanisms are also dependent on estrogen, including bladder contractibility and hence emptying capacity as well as antimicrobial peptides, which are increased following estrogen supplementation.[44] Finally, estrogen enhances epithelial cell barrier function, especially bladder cells.

HOST DEFENSE OF THE URINARY TRACT

With the exception of urethral mucosa, the normal urinary tract is resistant to colonization by bacteria and, for the most part, efficiently and rapidly eliminates pathogenic and nonpathogenic microorganisms that gain access to the bladder[45] (Table 72.2).

Innate Immunity

The antibacterial defense of the urinary tract relies almost entirely on innate immunity. Susceptibility to UTI is largely controlled by specific innate immune signaling and by promotor polymorphisms and transcription factors that modulate the expression of genes controlling these pathways. Innate immune response of the host is critically important, and bacterial clearance normally proceeds without sequelae. On the other hand, dysfunction—usually genetic in origin and often only slight—may actually contribute to enhancing inflammation and cause tissue destruction, especially in the kidney. Defects in innate immunity drastically increase UTI susceptibility both in mice carrying single gene deletion and in patients prone to pyelonephritis.[46,47] Uropathogenic clones elicit an inflammatory response at all levels in the urinary tract by stimulating uroepithelial and other cells to produce cytokines and other proinflammatory factors. The intensity and efficiency of the innate host response are genetically regulated and are critical factors for the host-organism interaction in the urinary tract.[48] The innate immune response is activated in a pathogen-specific manner (e.g., P fimbriae–mediated adhesion). Toll-like receptor 4 is essential for the defense against infection with gram-negative uropathogens leading to cytokine and chemokine responses with recruitment of inflammatory cells.[49] Systemic elaboration of interleukin (IL)-1β transcription factors such as interferon regulatory factor 3 and IL-6 may lead to fever and activation of the acute-phase response. Urine and serum IL-6 concentrations reflect the severity of infection, with highest levels in pyelonephritis and bacteremia.[50] The chemotactic cytokine IL-8 is released at the mucosal site recruiting PMNs, resulting in pyuria and contributing to the eradication of bacteriuria. Interleukin-8 receptor deficiency confers susceptibility to acute pyelonephritis.[51] Toll-like receptor 4 is activated by bacteria in urine either directly by lipopolysaccharide or following bacterial adhesion. This stimulates local urinary production of chemokines such as CXCL8, leading to migration of neutrophils and other responding inflammatory cells. Intensity of this response is one determinant of whether infection resolves or progresses as asymptomatic or symptomatic bacteriuria. Infection also stimulates expression of chemokines CXCR1 and CXCR2 by urothelial cells. CXCR1 is essential for the increased neutrophil migration across infected cell layers in vitro. Secretion of chemokines and cytokines, including CCL2, CXCL6, and CXCL8, follows.[52] Reduced TLR4 expression has been reported in children with asymptomatic bacteriuria.[53] By evading or modulating the activation of the host mucosal urothelial innate response, UPEC may provide a pathogenic advantage in reaching and persisting in the kidney, but paradoxically, if the inflammatory response is absent or attenuated, renal abscesses and symptomatic pyelonephritis may not follow.[54,55]

Direct contact between adherent bacteria and uroepithelial cells may also result in bacterial growth suppression. This antibacterial epithelial defense function is activated by transmembranous signals from bacteria attached to the host cell surface and involves adenylate cyclase activity.

Effectors of the innate immune response also include an array of molecules elaborated by epithelial cells or PMNs, which inhibit a wide range of microorganisms. These include α-defensins (HD5) in the kidney and upper ureter, β-defensins (HBD) in nephron tubules and collecting ducts, cathelicidin, and hepcidin.[56]

Urine and Bladder Defenses

An emerging concept is that the bladder, rather than representing a sterile environment, may in fact host a "urinary microbiome" of commensal organisms that may influence UTI. Although urine is generally considered to be a good culture medium for most bacteria, it does possess antibacterial activity. Anaerobic bacteria and other fastidious organisms that make up most of the urethral flora generally do not multiply in urine. It has been shown that extremes of osmolality, a high urea concentration, and low pH levels are inhibitory for the growth of some of the bacteria that cause UTI. Furthermore, the pH and osmolality of urine from pregnant women tend to be more suitable for bacterial growth than those from nonpregnant women, which in turn are more suitable for bacterial growth than those from urine from men. The presence of glucose makes urine a better culture medium, whereas the addition of prostatic fluid to urine inhibits bacterial growth. Furthermore, urine has been shown to inhibit the migrating, adhering, aggregating, and killing functions of PMNs.

The epithelial surface of the urinary tract is covered by a thin layer of urine and fluid secreted by the epithelial cells. The epithelial secretions possess antimicrobial properties, mainly the product of neutrophils providing a surveillance function. Neutrophil defensins are 3- to 5-kDa disulfide cationic peptides; their presence on epithelial surfaces may play a role in clearance of adherent bacteria. Another weapon against UTI is antimicrobial peptides; an example is ribonuclease 7, but its production is inhibited by certain bacterial strains.[57]

TABLE 72.2 Antibacterial Host Defenses in the Urinary Tract

Urine (osmolality, pH, organic acids)
Urine flow and micturition
Urinary tract mucosa (bactericidal activity, peptides, cytokines)—innate immunity
Inflammatory response
Polymorphonuclear neutrophils
Tamm-Horsfall protein
Cytokines
Low-molecular-weight oligosaccharides
Secretory immunoglobulin A
Lactoferrin
Peptides
Adaptive immune system
Humoral immunity
Cell-mediated immunity
Miscellaneous
Prostatic secretions