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The Microbiology Associated With Cystic Fibrosis

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Cystic fibrosis (CF) is the most common genetic disease affecting the Caucasian population of the United States. It is believed to be transmitted as an autosomal recessive disorder and has an incidence of 1 in 2000 live births in this country (5). It affects males and females equally and has been found with varied incidence in all racial and ethnic groups. The disease is characterized by malabsorption, chronic obstructive pulmonary disease, and a high salt content of the sweat. The disease affects the endocrine gland secretions throughout the body. Although it impacts on multiple body systems (gastrointestinal, endocrine, neurological), the most important and life threatening effects involve the lungs. Thus, CF is a major cause of chronic pulmonary disease in children, and a major cause of morbidity and mortality in young adults. Patients with CF have a lifetime of bacterial bronchitis, despite aggressive multiple antibiotic therapy. Typically, these children present with recurrent lower respiratory tract infections and a very characteristic sputum bacteriology. Although most patients carry multiple strains of normal oropharyngeal flora in their secretions, a variety of specific organisms are associated with lower respiratory tract infection in patients with CF.

Staphylococcus aureus

Prior to 1950 and the use of antibiotics, *Staphylococcus aureus* was the organism most frequently isolated from the sputum of patients with CF (19). The predominance changed dramatically to *Pseudomonas aeruginosa* over the past 4 decades, undoubtedly because of antibiotic use. *S. aureus* continues to be a frequent isolate from patients with CF. Infants with CF usually acquire *S. aureus* as part of their respiratory flora within the first few years after birth. Once colonized, they appear to carry the organism for life. Long-term colonization with the same phage type is typical, but the phage types associated with CF are not unique, and are similar to those seen in the community (11).

Because CF patients carrying *S. aureus* have a greater number of infections and require hospitalization more often than those not colonized with this organism, the isolation of *S. aureus* from respiratory secretions and sputum should always be reported by the clinical microbiology laboratory, regardless of the number of colonies isolated. In general, the *S. aureus* isolates from CF patients are no more resistant to antibiotics than those seen in the community.

Pseudomonas aeruginosa

Just as antibiotic use was responsible for the decreasing prevalence of *S. aureus* in cultures of sputum from patients with CF it is also responsible for the increasing prevalence of *P. aeruginosa*. *P. aeruginosa* was not associated with CF before the use of antimicrobial therapy (7). Now, more than 70% of all patients with CF carry *P. aeruginosa* in their lungs.

The colonial morphology of many of the *P. aeruginosa* strains isolated from CF patients is unique in that over half of the strains are mucoid. These colonies appear to have a slime coating, a factor thought to contribute to the persistence of *Pseudomonas* in the lungs of CF patients (14). It is believed that nonmucoid strains of *P. aeruginosa* initially colonize the respiratory tract of CF patients and that the later transition to a mucoid strain is associated with chronic infection and a poorer prognosis. Like *S. aureus*, *P. aeruginosa* colonization is not lost in patients with CF, and the prevalence of *P. aeruginosa* in sputum cultures from these patients increases with age.

In This Issue

Early CF investigators classified *P. aeruginosa* strains as being rough, classic, smooth, and mucoid, but in present terminology mucoid and nonmucoid are used to simplify reporting. Patients with CF usually harbor a mixture of mucoid and nonmucoid strains. Colonization and/or infection by two or more *P. aeruginosa* strains is common in CF patients. Such strains isolated from the same patient have been shown to be of the same O antigen type. (14).

The mucoid *P. aeruginosa* strains isolated from the respiratory secretions of over 59% of patients with CF appear to be specific for the disease and are considered by many to be pathognomonic. Mucoid *P. aeruginosa* strains are usually nonpigmented and produce an exopolysaccharide that appears to be a polymer of guluronic and mannuronic acid (15). The production of this substance was originally thought to be related to the presence of a bacteriophage, but it now appears that production of mucoid material is chromosomally determined (8). In vitro, the slime production by mucoid strains is unstable and usually lost on repeated subculture, but in vivo, organisms appear to retain the ability to produce the exopolysaccharide indefinitely.

Mucoid strains of *Escherichia coli* and *Klebsiella ozaenae* have also been isolated from CF patients (2, 13, 17). The mucoid substance purified from *E. coli* isolates is biochemically and antigenically different from the *P. aeruginosa* polymer. The lungs of patients with CF appear to offer an environment conducive to the production of a mucoid coating by a number of gram-negative rods. In general, *Enterobacteriaceae* rarely constitute the predominant gram-negative respiratory flora seen in CF patients.

Mucoid and nonmucoid variants of *P. aeruginosa* from the same patient appear to be of the same serotype, pyocin type, and phage type, and they share biochemical properties. Using in vitro susceptibility testing methods mucoid strains of *P. aeruginosa* have been found to be more susceptible to antibiotics than nonmucoid strains (27), but not all laboratories have observed this difference. Frequently, discrepancies occur between in vitro susceptibility test results of *P. aeruginosa* isolates and the clinical response to antibiotic therapy (21). Because CF patients are usually colonized with multiple strains of *P. aeruginosa*, it is not unlikely that the strains selected for in vitro testing in the laboratory do not represent all the strains present in the patient's lungs. Most laboratories attempt to minimize this problem by selecting and separately testing a wide cross-section of mucoid and nonmucoid *P. aeruginosa* strains for their in vitro susceptibility.

A number of investigators have attempted to type the *P. aeruginosa* isolates from CF patients using either the Homma or International serotyping systems (4, 12, 26, 33). Some investigators have indicated the prevalence of specific serotypes of *P. aeruginosa* in their CF patients while others have reported a wide heterogeneity in serotypes seen. These data are conflicting and confusing, and there appears to be no ideal system at this time for typing *P. aeruginosa* strains from CF patients.

Pseudomonas cepacia

In many CF centers, *Pseudomonas cepacia* has recently emerged as a cause of severe and frequently fatal pneumonia (25). Because a number of CF patients have exhibited rapid clinical deterioration and death following *P. cepacia* colonization, this organism is of great concern to those working with CF patients. *P. cepacia* colonization of patients with CF has clearly been shown to be associated with increased morbidity and earlier death. Like *P. aeruginosa*, *P. cepacia* appears to be able to colonize the lungs of CF patients for long periods of time without severe effects or signs of infection. Present estimates are that as many as 9% of CF children less than 10 years of age, and 21% of those greater than 10 years of age have *P. cepacia* in their sputum (3). Prior to its appearance in the CF population, *P. cepacia* had been implicated in nosocomial outbreaks and was noted to be the cause of respiratory tract infections, peritonitis, and occasional bacteremia. *P. cepacia* colonization and/or infection in patients with CF does not, however, appear to be a result of hospital outbreaks (25). A number of risk factors including patient age, severity of CF, antecedent use of aminoglycosides, recent hospitalization, sibling colonization, and nebulizer and disinfectant contamination have been associated with the acquisition of *P. cepacia*, but it is still unclear how patients with CF become colonized.

Because *P. cepacia* is such a significant isolate in patients with CF, most laboratories dealing with CF patients have adopted the routine use of *P. cepacia* selective media when culturing respiratory specimens. A number of excellent selective media are available and most centers have noted an increased isolation rate and awareness of *P. cepacia* once a selective medium is employed (9, 32).

This organism tends to grow slowly and may take as long as 72 h to appear on selective media. Some strains of *P. cepacia* are able to produce phenazine pigments like those of *P. aeruginosa*, but for those unfamiliar with the organism, the use of a selective and differential medium makes initial recognition of the organism much easier. *P. cepacia* strains can be characterized by bacteriocin production, biotyping, and serotyping systems. The two biotyping systems separate the

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strains into either four or eight biovars (6, 22). Several serotyping schemes for *P. cepacia* have been proposed, one of which is a classification based on seven somatic (O) and five flagellar (H) antigens (10). None of the serotyping systems appear to be in popular use at this time, and all should be considered preliminary.

P. cepacia tends to develop resistance to most antibiotics. Most patients colonized with the organism seem to have more severe lung disease and a poorer prognosis than patients colonized only with *P. aeruginosa* and *S. aureus*. *P. cepacia* is normally resistant to the polymyxins, aminoglycosides, first and second generation cephalosporins, and the antipseudomonal penicillins such as carbenicillin and ticarcillin. Resistance to chloramphenicol and trimethoprim-sulfamethoxazole appears to vary with the isolate, but imipenem, aztreonam, ciprofloxacin, and a number of third generation cephalosporins have demonstrated some in vitro activity against *P. cepacia*. As with *P. aeruginosa*, complete eradication of *P. cepacia* appears to be impossible even when the strain is susceptible to specific antibiotics.

Laboratorians should be aware of this organism's multiple resistance as the usual profiles of antibiotics used for in vitro antibiotic susceptibility testing may not be adequate when dealing with *P. cepacia*.

Haemophilus spp.

Haemophilus spp. are frequently isolated from the respiratory tract of patients with CF. In most studies, *Haemophilus* spp. are isolated from 10 to 38% of patients (16, 18). Of these isolates, approximately 85% are *H. influenzae*, 11% *H. parainfluenzae*, 3% *H. parahaemolyticus*, and 1% *H. aphrophilus*. Most of the *H. influenzae* isolates are nontypable strains and as many as 40 to 60% of these are resistant to ampicillin due to β-lactamase production. Nontypable *H. influenzae* strains have been isolated from transtracheal specimens, lung aspirates, and empyema fluid of CF patients with acute pulmonary exacerbations. Although rare, chloramphenicol resistance has been noted in two isolates of nontypable *H. influenzae* from patients with CF (18). Both isolates were also resistant to ampicillin, erythromycin, and tetracycline.

The distribution of *H. influenzae* and *H. parainfluenzae* biotypes in patients with CF has also been studied (29). Within this patient population, biotype I of *H. influenzae* predominates. This finding is noteworthy because, in general, β-lactamase production is much more common among biotype I strains of *H. influenzae* than any other biotype. In addition, biotype II *H. influenzae* strains were less common among the CF isolates when compared with isolates from children who did not have CF. No clear biotype predominates in *H. parainfluenzae* isolates. Because the role of *Haemophilus* spp. in acute exacerbations in patients with CF has not been determined, antibiotic prophylaxis for *Haemophilus* is not usually recommended. Instead, isolates associated with acute disease are treated at the time of infection based on their individual antibiotic susceptibilities.

Mycobacteria

Mycobacterium tuberculosis is rarely seen in patients with CF. The CF lung appears to be resistant to this organism, and many believe that this is due to hypoxemia present within the lungs. In one study involving over 700 patients, only two cases of active pulmonary tuberculosis were documented over an 18-year period (30). A number of investigators have isolated *M. fortuitum* from sputum cultures obtained from CF patients, but all have been considered to be saprophytic colonizers (1, 30). Given the lung physiology and poor nutritional state of patients with CF, in theory, pulmonary tuberculosis could be a serious complication of the disease. Studies indicate, however, that this is not the case and that the isolation of *M. tuberculosis* from CF patients occurs infrequently.

Allergic Bronchopulmonary Aspergillosis

Although other fungi, including *Candida* spp., are infrequently seen in patients with CF, the incidence of allergic bronchopulmonary aspergillosis (ABPA) has been reported to be as high as 10 to 14% (28). Originally thought to affect only older adolescent and young adult patients, ABPA is now being seen in younger CF patients as well.

Patients with ABPA present with typical symptoms of asthma, usually cough and wheezing. They may also have fever, malaise, and pleuritic chest pain. Unfortunately, all of this can be a typical course for a patient with CF experiencing a pulmonary exacerbation. For this reason, the diagnosis of ABPA in patients with CF can be very difficult.

If a CF patient experiencing exacerbation does not improve after appropriate antibiotic treatment and continues to have pulmonary infiltrates, wheezing, increased cough, and eosinophilia, the diagnosis of ABPA should be considered. The diagnostic features of ABPA include: 1) elevated serum IgE (average episodic peak of 1000 IU/ml); 2) precipitating IgG antibody to *Aspergillus* antigen; 3) serum eosinophilia (greater than 1000/mm^3); 4) immediate type hypersensitivity to *Aspergillus* antigen; and 5) acute pulmonary infiltrates or atelectasis (24).

The pathogenesis of ABPA is not completely understood, but it is believed that *Aspergillus* spores are deposited in the thick respiratory secretions of the patient. As the spores grow, the host response is largely an allergic immunologic reaction. Because this reaction involves complement activation, pulmonary damage and eosinophilic pneumonia are often seen. A variety of *Aspergillus* spp. have been reported as causes of ABPA, but *A. fumigatus* is the most common.

CF patients commonly have an increased frequency of positive skin tests, sputum cultures, and precipitating antibodies to *Aspergillus* (23). In general, patients with CF have a higher colonization rate of *Aspergillus* spp. than non-CF populations (28). Thus, many of the criteria used to diagnose ABPA are also strongly associated with CF in the absence of ABPA, and the isolation of *Aspergillus* spp. from culture alone is not a sufficient criterion. Acute changes in chest radiograph and in-

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creased serum IgE levels are considered to be reliable indicators of ABPA, but all isolations of *Aspergillus* spp. from patients with CF should be reported.

Viruses, Mycoplasma, Chlamydia

The role of viruses, mycoplasma, and chlamydia as lower respiratory pathogens of children and adults with CF has not been extensively evaluated. In one study of children with CF, 39% of severe exacerbations were shown to be associated with viral infections, primarily respiratory syncytial virus (RSV) and influenza A virus (31). Influenza virus infections are thought to be a significant cause of death in patients with CF, and influenza vaccine is now routinely given to most CF patients.

A second study correlating the incidence of acute respiratory exacerbations with possible etiologic agents showed that 76% of the episodes were associated with bacteria and 20% with nonbacterial respiratory agents (20). The nonbacterial episodes were caused by RSV (9%); parainfluenza virus (5%); influenza virus (3.6%); adenovirus (2.4%); mycoplasma (0.6%); and chlamydia (0.6%). Unfortunately, only serological evidence was used to implicate the nonbacterial agents, and neither study examined the role of rhinoviruses or coronaviruses.

The microbiology of the lower respiratory tract of patients with CF is extremely complex with many different organisms contributing to disease pathogenesis. Patients with CF are clearly at high risk for developing severe and life-threatening respiratory infections from a variety of pathogens throughout their lives.

The mechanism of pathogenesis of the bacterial infections is for the most part unknown. *S. aureus* is acquired early in life, followed by *P. aeruginosa*. *P. aeruginosa* persists as the dominant pathogen causing pulmonary disease of CF patients. Once colonization of *P. aeruginosa* is established, eradication appears to be impossible. Consequently, most patients receive antistaphylococcal and antipseudomonal therapy continuously.

H. influenzae infections are also common as are RSV infections. In patients with advanced pulmonary disease, it is not uncommon to find a variety of *P. aeruginosa* strains, *S. aureus*, and *Aspergillus* spp. in their sputum cultures. The most alarming new pathogen is *P. cepacia*, and its full impact on patients with CF is yet to be appreciated.

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Editorial

Clinical Laboratory Versus Industry: The View from Both Sides

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As clinical microbiologists who have left the hospital laboratory and now work for a company that manufactures products for our field, we have often been asked by friends, "What is it like to go into industry?" The questions range from, "Why did you want to leave the clinical laboratory?" "Why did you go commercial?" "Were you burnt out?" to "Do you like it?" and, "What is it really like?" The answers to these questions are not necessarily straightforward or simple and probably vary among individuals who work for different companies.

Both of us had been in clinical microbiology for more than 10 years. At the time we left, we both were senior laboratory supervisors at university medical centers with staffs of approximately 25. Our work in progressive clinical laboratories was challenging and stimulating, but also often frustrating and exhausting. Managing a clinical laboratory is not an easy task, but it can be gratifying. We both were able to conduct small-scale research/evaluation projects, teach microbiology to various types of students, and attend continuing education seminars and national meetings. So why did we leave the laboratory?

We both felt a need for a change; new challenges, new experiences, and new ways to have a professional impact on clinical microbiology. We felt that, without a doctoral degree, we could not advance much further in the clinical laboratory. Because microbiology remained our profession of choice, we independently sought positions in a diagnostic products company. Our present individual positions within the company are quite different; one in marketing and one in product development. Both paths have given us opportunities for growth and professional development. We will attempt to convey our impressions about working for a company that manufactures products for the clinical microbiology laboratory.

There are some general differences between the hospital and the industrial environment. In the most simplistic terms, a company's goal is to make money, while the hospital's goal is to cure the patient (although hospitals are becoming increasingly "business-like"). These basic goals affect the work environment/culture. For example, when instituting a certain test in the hospital, factors considered are based on clinical relevance and cost-effectiveness. Within a company, factors considered for developing and selling a given product include market size, development costs, production costs, and product competitiveness.

In the clinical laboratory, the amount and mix of work is dictated by the workload, which is a function of the physicians' propensity to order tests as well as the patient population in the hospital at the particular time. In industry, the work is dictated by "The Market," that is, a composite of all customers. What an individual customer needs or desires is a company's major concern, but because of the economic need to make universal products, the needs of individual laboratories must be balanced against the needs of all microbiology laboratories.

In the clinical laboratory, the crises tend to be day-to-day (such as a patient with some unusual test results or an instrument failure). In industry, the crises tend to be more lengthy, such as a change in a raw material that could affect product performance. Tracking down the exact component that is causing trouble and then finding an alternative component or making a formulation change can take months.

To a great extent, in a hospital environment, the technical information one is trying to communicate is understood by physicians, nurses, and other allied health-care workers. In an industrial setting one has to communicate to diverse groups of people and disciplines. For example, in our company, probably only 10 to 15% of the people who spend their work day making and supporting microbiology products really know what *Escherichia coli* is. On the other hand, shuffling papers and attending meetings seem to be universal functions in any institution.

A successful business provides useful, cost-effective, high-quality products that the customer wants. For a laboratory, the product is a timely, accurate test report of clinically useful information for the physician. For our company, the goal is to make products that enable the laboratory to generate results easier, faster, and more accurately. The laboratory is our immediate

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