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eCysticFibrosis Review
Presented by
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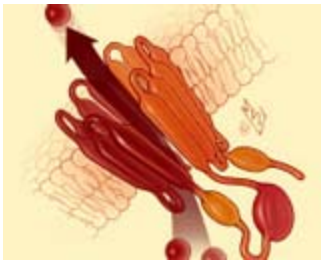

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November 2008: VOLUME 1, NUMBER 4

Emerging Pathogens in Cystic Fibrosis

In this Issue...

Over the last 25 years, significant advances have been made in the treatment of individuals with cystic fibrosis (CF). This has resulted in the current median predicted survival in patients with CF being >37 years of age and a corresponding greater number of adults living with the disorder than ever before, with >45% of affected individuals ≥18 years of age. A significant portion of the gains achieved in CF have been the result of early and more aggressive antibiotic therapy.

In this issue, we focus on one of the challenges resulting from this longer survival and more aggressive antibiotic therapy: the emergence of new and more resistant pathogens. We review 7 publications that provide both insight into the latest CF microbiologic trends and a greater understanding of CF pathogens, to assist CF caregivers in providing the best treatment and appropriate education for patients and their families.

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Credit Designations
Intended Audience
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Faculty Disclosures
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1.0 hours Physicians
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Release Date
November 13, 2008

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IN THIS ISSUE

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Michael P. Boyle, MD, FCCP has disclosed no relationship with commercial supporters.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

Newsletter:
- Identify emerging pathogens in cystic fibrosis (CF).
- Describe the effect of Methicillin-resistant *Staphylococcus aureus* infection on lung function in patients with CF.
- Explain the effect of *Burkholderia cepacia* complex infection on lung transplantation in patients with CF.

Podcast:

- Identify emerging pathogens in cystic fibrosis (CF).
- Describe the role of infection control and potential treatments in CF patients with MRSA.
- Explain the risk factors associated with development of multiple antibiotic-resistant *Pseudomonas aeruginosa* infection in CF.

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COMMENTARY

Cystic fibrosis (CF) caregivers expend a great deal of energy following microbiologic disease trends. This is both because pulmonary infection is the most important contributor to CF morbidity and mortality, and because early and appropriate treatment of pulmonary infection results in improved clinical outcomes. Although new pathogens and changing antibiotic strategies can make CF microbiology feel like a constantly moving target, a review of current microbiologic trends and investigations identifies the following 4 important principles:

(1) *Pseudomonas aeruginosa* is the most important CF pathogen, with evidence suggesting that early aggressive treatment of *P. aeruginosa* may be having an impact on age-specific prevalence. According to data from the current US Cystic Fibrosis Foundation Patient Registry, reviewed in this newsletter, 54.4% of all individuals with CF were infected with *P. aeruginosa* in 2007. The age at which individuals with CF acquire *P. aeruginosa* infection is increasing, however: in 2002, 50% of individuals with CF were infected with *P. aeruginosa* by the age of 8 years; by 2007, the age at which 50% of individuals were infected climbed to 10.5 years. This likely reflects increased efforts by US CF care centers to aggressively treat initial *P. aeruginosa* infections.[1]

(2) As reported in the CF Foundation Patient Registry, perhaps the most striking current trend in CF microbiology is the dramatic rise in Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, with the prevalence in CF increasing from 9.2% in 2002 to 21.2% in 2007. As discussed by Dasenbrook and colleagues, although one-third or more of all MRSA infections may be transient, this trend is of particular importance because epidemiologic studies suggest that persistent infection with MRSA is associated with an

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increased rate of decline in lung function.

(3) Studies of molecular epidemiology are providing insight into the clinical implications of specific infections, but additional longitudinal studies are needed. The clinical impact of molecular epidemiology is evident in *Burkholderia cepacia* complex infections, with studies by Alexander and associates and by Murray and coworkers demonstrating that the effect on lung transplantation outcomes varies by genomovar. The need for more in-depth studies on the association between molecular epidemiology and clinical outcomes is particularly highlighted in MRSA, where reports on the effect of the presence of the pathogen on the Panton-Valentine Leukocidin gene, addressed in studies by Glikman and colleagues and by Elizur and associates, have varied widely.

(4) Although all the aforementioned studies are ongoing, evidence is accumulating that fastidious infection control practices in patients with CF are more important than ever. As addressed in the article by Merlo and coworkers, reports of transmission of multiple antibiotic-resistant strains of *P. aeruginosa* and MRSA in CF are not uncommon. Infection control measures have been documented to limit the spread of known pathogens and represent first-line defense against emerging CF pathogens.[2]

References

1. Treggiari MM, Rosenfeld M, Retsch-Bogart G, Gibson R, Ramsey B. Approach to eradication of initial *Pseudomonas aeruginosa* infection in children with cystic fibrosis. *Pediatr Pulmonol.* 2007;42(9):751-756
2. Saiman L, Siegel J; Cystic Fibrosis Foundation Consensus Conference on Infection Control Participants. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Infect Control Hosp Epidemiol.* 2003;24(5 suppl):S6-S52.

MICROBIOLOGIC TRENDS IN THE US CYSTIC FIBROSIS PATIENT POPULATION

Cystic Fibrosis Foundation Patient Registry. **2007 Annual Data Report to the Center Directors.** Bethesda, Maryland. ©2008 Cystic Fibrosis Foundation.

2007 not available yet – only the 2006 report is online:

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The US Cystic Fibrosis (CF) Foundation Patient Registry Annual Data Report summarizes clinical and microbiologic trends in all individuals enrolled in the US CF Patient Registry, which is estimated to comprise nearly 90% of the total US CF population. This year's report, released in October 2008, includes summary data on 24,511 patients with CF—approximately 13,000 children and 11,000 adults (≥18 years of age). Data are collected and entered at all accredited CF care centers in the United States. Culture results include all respiratory cultures: throat, sputum, and bronchoscopic samples.

Several microbiologic trends were evident in this year's registry data. As expected, *Pseudomonas aeruginosa* continues to be the key pathogen, with 54.4% of all individuals with CF being infected. This represents a small decline from the prevalence of 57.9% reported in 2002. What is clear, however, is that the age at which patients with CF acquire *P. aeruginosa* infection is on the rise. In 2002, 50% of individuals with CF were infected with *P. aeruginosa* by 8 years of age. In contrast, in 2007, the age at which 50% of individuals with CF were infected with the pathogen increased to 10.5 years. Similarly, in 2002, 70% of individuals with CF were infected with *P. aeruginosa* by the time they were 15.5 years old. In 2007, that number increased by >2 years, with the 70% infected mark not being reached until the age of 18.

Although the age of onset of *P. aeruginosa* infection is on the rise, an increasing number of individuals infected with the pathogen have resistant organisms. In 2007, 18.4% of patients with CF were infected with multiple-resistant strains, defined as being resistant to all antibiotics tested in ≥2 classes (β-lactams, fluoroquinolones, and aminoglycosides). Whereas accurate, long-term historical data are not available for comparison, this number is known to represent an increase from the 16.4% prevalence in 2006.

Another striking microbiologic trend is the continued increase in the prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA). In 2007, 21.2% of individuals with CF in the CF Foundation Patient Registry had a respiratory culture positive for MRSA. This represents a significant increase from the 18.9% prevalence observed in 2006 and a dramatic increase from the 9.2% prevalence observed in 2002. There is a wide range of MRSA infection prevalence by CF care center, with 27 of the 185 centers reporting that >30% of their patients are MRSA-positive and 14 centers reporting that <10% of their patients are infected with the pathogen. Age-specific data on MRSA demonstrate that the prevalence increases throughout childhood, peaks at the age of 11, and then persists above 20% until approximately 30 years of age. Stenotrophomonas maltophilia (12.6%), Achromobacter xylosoxidans (5.9%), *Burkholderia cepacia complex* (Bcc [not *B. gladioli*] 2.9%), and nontuberculous mycobacteria requiring treatment (1.7%) complete the list of pathogens of particular interest in the 2007 CF Foundation Registry.

The 2007 CF Foundation Registry report highlights the continued significance of such known pathogens as *P. aeruginosa* and the growing importance of emerging pathogens, including MRSA. Perhaps the single most notable microbiologic trend in the 2007 CF Foundation Registry data is the more than doubling in MRSA prevalence among the US CF patient population since 2002. Whereas numerous investigations have focused on *P. aeruginosa* to help determine its impact on clinical outcomes and best treatment practices, much more about MRSA needs to be known. The CF Foundation Patient Registry allows us to recognize the increasing significance of MRSA and to evaluate aspects of its impact on clinical outcomes, but it is limited by the lack of accompanying MRSA molecular phenotyping data.

The older age at which 50% of individuals with CF are becoming infected with *P. aeruginosa* is encouraging. This likely reflects increased efforts by US CF care centers to aggressively treat initial *P. aeruginosa* infection, although it may also be associated with the overall improvement in lung function among younger age-groups during the same time period. The prevalence of Bcc has actually decreased slightly since 2002 (2.9% currently vs 3.1% in 2002), but this group of pathogens continues to be important in CF because of its potential significant impact on clinical outcome.

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EFFECT OF PERSISTENT MRSA INFECTION ON LUNG FUNCTION DECLINE IN PATIENTS WITH CYSTIC FIBROSIS

Dasenbrook EC, Merlo CA, Diener-West M, Lechtzin N, Boyle MP. **Persistent methicillin-resistant *Staphylococcus aureus* and rate of FEV_1 decline in cystic fibrosis.** *Am J Respir Crit Care Med.* 2008;178(8):814-821.

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Dasenbrook and colleagues conducted a cohort study of the Cystic Fibrosis (CF) Foundation national patient registry to determine if persistent Methicillin-resistant *Staphylococcus aureus* (MRSA) infection of the respiratory tract in children and adults with CF is associated with a more rapid decline in lung function. The patient registry was used to study 17,357 individuals from 1996 to 2005, of whom 1732 developed new, persistent MRSA respiratory tract infection. Persistent infection was defined as ≥3 MRSA-positive cultures. Decline in lung function was evaluated using 2 different comparisons: 1) the persistent MRSA cohort (n=1732) vs the MRSA-negative cohort (n=13,922); and 2) prior to detection of MRSA vs following detection of MRSA among the 1732 individuals with persistent infection. This is the largest study to date of individuals with CF and MRSA infection.

Two significant findings were reported from this study. First, the average rate of percent predicted forced expiratory volume in 1 second (FEV1%) decline was 46% more rapid in those with MRSA compared with those without the pathogen. After adjustment for confounders, in individuals aged 8 to 21 years, those with persistent MRSA had a decline of 2.06% predicted/year, whereas those without MRSA infection had a decline of 1.44% predicted/year (difference, -0.62% predicted/year; 95% confidence interval [CI], -0.70 to -

0.54; P<.001; see Figure 1). Second, approximately 50% of individuals with MRSA had transient infections (defined as ≤2 MRSA-positive cultures). Transient MRSA individuals were followed for an average of 2 years and had an average of 5 cultures performed after their last MRSA culture. One significant limitation to this study is the fact that the registry did not differentiate between hospital- and community-associated MRSA strains.

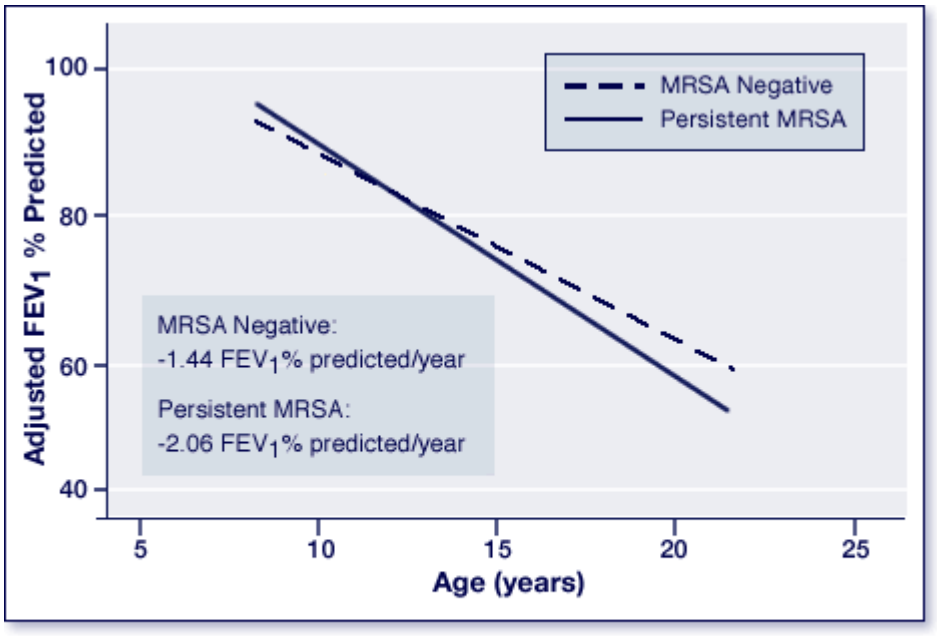

Figure 1. FEV_1% decline for patients with cystic fibrosis aged 8-21 years with persistent MRSA compared to those without MRSA, adjusted for severity of illness. Average follow-up was 5.3 years.

The authors concluded that new, persistent MRSA infection in patients with CF 8 to 21 years of age is associated with a more rapid rate of decline in lung function. This investigation, with its very large sample size, longitudinal design, and statistical adjustment for severity of illness, suggests that MRSA may be more than just a marker of disease severity and may actually be contributing to patient morbidity. Would it be wise, then, to initiate treatment protocols based on the results of this study? Given the observational design of the study, the authors state that "it would be premature to recommend antibiotic treatment of CF individuals aged 8-21 with persistent respiratory MRSA infection." It is not clear whether treating persistent MRSA infection can reverse lung function decline and potentially improve patient outcomes. The next steps will be interventional studies examining 1) the risks and benefits of an eradication protocol in those with CF who have new, persistent MRSA infection; and 2) the molecular epidemiology of persistent MRSA infection. These studies will need to take into account the transient nature of nearly half of all MRSA infections. At this time, with the increasing prevalence of MRSA, emphasis should continue to focus on the prevention of MRSA through infection control. Patients, families, and caregivers should continue to practice standard and contact precautions as currently recommended in the CF Foundation guidelines.[1]

References

1. Saiman L, Siegel J; Cystic Fibrosis Foundation Consensus Conference on Infection Control Participants. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission.

Infect Control Hosp Epidemiol. 2003;24(5 suppl):S6-S52.

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MOLECULAR EPIDEMIOLOGY OF MRSA IN PATIENTS WITH CYSTIC FIBROSIS

Glikman D, Siegel JD, David MZ, et al. **Complex molecular epidemiology of methicillin-resistant *Staphylococcus aureus* isolates from children with cystic fibrosis in the era of epidemic community-associated methicillin-resistant S aureus.** *Chest.* 2008;133(6):1381-1387.

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Elizur AR, Orscheln RC, Ferkol TW, et al. **Panton-Valentine Leukocidin-positive methicillin-resistant *Staphylococcus aureus* lung infection in patients with cystic fibrosis.** *Chest.* 2007;131(6):1718-1725.

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Glikman and colleagues compared the molecular types of Methicillin-resistant *Staphylococcus aureus* (MRSA) strains between pediatric patients with cystic fibrosis (CF; n=34) and those without the disease (n=331). All MRSA isolates were collected prospectively from 2 centers in 2004 and 2005. This cross-sectional study included only the first MRSA isolate from each patient during the trial period. Elizur and colleagues examined 226 pediatric patients with CF to determine the incidence and clinical characteristics of newly detected MRSA (n=40) at a single center from 2001 to 2004. Decrease in forced expiratory volume in 1 second (FEV1) was determined by comparing the value at the time of the culture with the patient's maximum value in the preceding year. In both studies, all CF MRSA respiratory isolates underwent susceptibility testing, multilocus sequence typing, Panton-Valentine Leukocidin (PVL) gene detection, and staphylococcal cassette chromosome *mec* (SCC*mec*) typing.

In the Glikman study, one-third (11/34) of the MRSA strains in patients with CF were community-associated MRSA (CA-MRSA). In contrast, 91% of the MRSA isolates in the non-CF pediatric population were community-associated SCC*mec* type IV strains. No differences in ciprofloxacin or clindamycin resistance rates were noted between the 2 groups when stratified according to SCC*mec* type. In the CF patient population, CA-MRSA strains were significantly more likely to be isolated from newly colonized CF patients than were the hospital-associated MRSA (HA-MRSA) strains (P=.02). Among the CF patients with MRSA, comparisons between surveillance and exacerbation cultures revealed no difference in PVL gene status (surveillance culture, 7/23; 30% vs pulmonary exacerbations, 3/11; 27%; P=1.0), suggesting that PVL status did not impact clinical outcomes.

In contrast, Elizur and colleagues concluded that acquisition of PVL-positive MRSA in individuals with CF was associated with acute, severe pulmonary involvement, including lung abscesses in 2 patients. PVL-positive MRSA was associated with significantly decreased FEV_1% compared with the maximum value in the previous year (17% decline in PVL-negative MRSA vs 41% decline in PVL-positive MRSA; P=.01). Interestingly, all MRSA infections in this study were associated with a significant decline in FEV_1%, regardless of PVL status. The authors did report, however, that those individuals treated with antibiotics had full recovery of their lung function despite the steep decline from the prior year.

These studies, which were conducted during the era of increasing prevalence of CA-MRSA, provide insight into the molecular epidemiology of this pathogen. Both studies suggest that approximately one-fourth to one-third of the MRSA detected in patients with CF are CA-MRSA strains. This provides a baseline from which we can observe changes over time in the molecular epidemiology of MRSA in pediatric patients with CF. There have been an increasing number of reports of transmission of CA-MRSA strains within hospitals, however, and given the high rates of exposure in the health care system, we must be aware that patients with CF may be particularly susceptible to an increasing CA-MRSA prevalence through this mechanism.

The main difference between the 2 studies is their conclusions about the effect of PVL gene status on clinical outcomes in patients with CF. Glikman and associates found that PVL-positive MRSA was not associated with exacerbations or necrotizing pneumonia, although the cross-sectional study design limits the ability to detect such an association. The Elizur study, on the other hand, clearly documented that at least a subset of PVL-positive MRSA infections are associated with severe pulmonary involvement in patients with CF. MRSA phenotypes may vary by community, making the findings of both studies less generalizable to other patient populations. The contrast in conclusions about the effect of PVL-positive MRSA highlights the need for future longitudinal studies that analyze the molecular epidemiology of MRSA in CF and its impact on clinical outcomes.

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RISK FACTORS FOR MULTIPLE ANTIBIOTIC-RESISTANT *P. AERUGINOSA* IN PATIENTS WITH CYSTIC FIBROSIS

Merlo CA, Boyle MP, Diener-West M, Marshall BC, Goss CH, Lechtzin N. **Incidence and risk factors for multiple antibiotic-resistant *Pseudomonas aeruginosa* in cystic fibrosis.** *Chest.* 2007;132(2):562-568.

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This investigation by Merlo and coworkers used the Cystic Fibrosis (CF) Foundation Patient Registry to identify risk factors for the acquisition of multiple antibiotic-resistant *Pseudomonas aeruginosa* (MARPA) infection among individuals with CF. The method used was a 5-year, retrospective cohort study of CF patients with new *P. aeruginosa* and subsequent MARPA acquisition from 1998 through 2002. MARPA was defined as any strain of *P. aeruginosa* resistant to ≥2 of the following antibiotics: tobramycin, ciprofloxacin, and meropenem. A time-to-event analysis using Cox proportional hazard modeling was used to assess risk factors for acquisition of MARPA after adjusting for differences between cases and controls in patient characteristics, including age, lung function, nutritional status, and pancreatic function.

During the time period studied, 4293 cases of new *P. aeruginosa* infection occurred, with 341 of those patients subsequently developing MARPA. Identified independent risk factors for acquisition of MARPA included multiple courses of intravenous (IV) antibiotics per year (hazard ratio [HR], 2.0; 95% CI, 1.4 to 2.8); ≥1 hospitalization per year (HR, 2.5; 95% CI, 1.8 to 3.5); and lower forced expiratory volume in 1 second (FEV1; HR, 1.7; 95% CI, 1.3 to 2.2). Use of inhaled tobramycin for longer than 1 year (HR, 2.1; 95% CI, 1.6 to 2.8); CF-related diabetes mellitus (HR, 1.6; 95% CI, 1.1 to 2.4); and care at a CF center in the top quartile for MARPA prevalence (HR, 2.0; 95% CI, 1.3 to 3.0) were all also identified as being independent risk factors for developing resistant *P. aeruginosa*. Risk for MARPA acquisition did not differ by gender or pancreatic status. Of interest, 26% of patients acquiring MARPA did so with their first positive *P. aeruginosa* culture.

This investigation confirms the suspected role played by frequent antibiotic exposure in the development of MARPA. This includes the effects of both IV and prolonged inhaled antibiotic exposure as risk factors. What is more novel is the identification of CF-related diabetes as an independent risk factor for acquisition of MARPA. Also of interest is the observation that receiving care at a CF center with a high MAPRA prevalence is an independent risk factor for acquisition. Although this may solely be the result of more frequent culturing and better detection methods at these centers, it also highlights the importance of meticulous infection control practices. The fact that MARPA was reported among 26% of patients with their initial *P. aeruginosa* infection suggests that antibiotic pressure alone may not account for MARPA prevalence. Some of the conclusions from this study must be viewed with caution, however, since the definition of MARPA used differs slightly from the current definition because of less extensive antibiotic sensitivity data being available in the CF Foundation registry during the time period studied.

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IMPACT OF *BURKHOLDERIA* INFECTION ON LUNG TRANSPLANTATION IN CF VARIES BY SPECIES

Alexander BD, Petzold EW, Reller LB, et al. **Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex.** *Am J Transplant.* 2008;8(5):1025-1030.

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Murray S, Charbeneau J, Marshall BC, LiPuma JJ. **Impact of *Burkholderia* infection on lung transplantation in cystic fibrosis.** *Am J Respir Crit Care Med.* 2008;178(4):363-371.

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The articles by Alexander and associates and by Murray and colleagues both evaluate the effect of *Burkholderia cepacia* complex infection on survival following lung transplantation in patients with cystic fibrosis (CF). These studies, which have been previously summarized in detail in the July 2008 eCystic Fibrosis Newsletter on lung transplantation, serve to remind us of the variability of clinical effect of *Burkholderia* infection in CF based on species.

The investigation by Alexander and colleagues studied 75 patients with CF undergoing lung transplantation between 1992 and 2002. Of the 16 infected with *B. cepacia complex* (Bcc), only those with *B. cenocepacia* had significantly worse post-transplant survival. These patients were 6 times more likely to die within 1 year of transplantation than were those with other Bcc species (P=.04) and 8 times more likely to die within 1 year than were those with no Bcc infection (P<.00005). The investigation by Murray and associates, which also studied the effect of Bcc on lung transplantation outcomes, determined that those with non-epidemic strains of *B. cenocepacia* have the greatest risk for post-transplant mortality. Of 74 transplant patients studied who developed Bcc, the HR for death vs uninfected patients was 2.52 (95% CI, 1.04 to 6.12). As in the Alexander study, those infected with Bcc species other than *B. cenocepacia* were not at increased risk for poor outcomes. Those without Bcc infection but with *B. gladioli* infection were found to be at increased risk for 1-year post-transplant mortality. Of 14 transplant patients with *B. gladioli* who were studied, the HR for death vs uninfected patients was 2.23 (95% CI, 1.05 to 4.74).

The results of these studies highlight the importance of differentiating species within *Bcc* infections when evaluating the potential impact on clinical outcomes. The Bcc consists of 9 phenotypically similar, but genotypically distinct, species. The most important genomovars in patients with CF are genomovar II (*B. multivorans*), genomovar III (*B. cenocepacia*), and genomovar VI (*B. dolosa*).

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At the conclusion of this activity, participants should be able to:

Newsletter:

- Identify emerging pathogens in cystic fibrosis (CF).
- Describe the effect of Methicillin-resistant *Staphylococcus aureus* infection on lung function in patients with CF.
- Explain the effect of *Burkholderia cepacia* complex infection on lung transplantation in patients with CF.

Podcast:

- Identify emerging pathogens in cystic fibrosis (CF).
- Describe the role of infection control and potential treatments in CF patients with MRSA.
- Explain the risk factors associated with development of multiple antibiotic-resistant *Pseudomonas aeruginosa* infection in CF.

To obtain ACPE credit the post-test for both newsletter and podcast must be completed successfully.

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