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eCysticFibrosis Review

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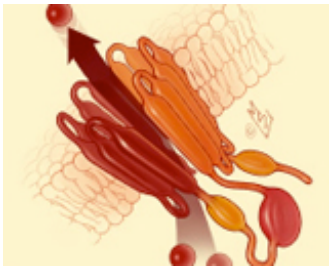

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eCysticFibrosis Review Volume 3 Issue 11

Emerging Pathogens in Cystic Fibrosis

In this Issue...

Pulmonary infection is a leading cause of death among patients with cystic fibrosis (CF). Recently, the prevalence of several potentially pathogenic microorganisms in the respiratory tracts of individuals with CF has increased considerably. Understanding the potential clinical impact, the pathogenesis, and the patient–to–patient transmission of these bacteria is extremely important to the maintenance of lung health in persons with CF.

In this issue, we review changes in the prevalence of organisms present in the airways of individuals with CF over the last 10 years, the impact of respiratory tract methicillin–resistant *Staphylococcus aureus* on survival; the association between lung transplantation or death and a virulent strain of *Pseudomonas aeruginosa* that can spread among patients; the impact of chronic nontuberculous mycobacterial lung disease on lung function; and the correlation between the mucoid status of *Burkholderia* cepacia complex bacteria and lung function

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the impact of methicillin–resistant *Staphylococcus aureus* infection on survival in patients with cystic fibrosis (CF)
- Identify the association between transmissible strains of *Pseudomonas aeruginosa* and survival in persons with CF
- Describe the effect of chronic nontuberculous mycobacterial lung disease, mucoid *Burkholderia cepacia* complex (BCC), and nonmucoid BCC infection on lung function in individuals with CF

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Release Date
June 19, 2012

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June 18, 2014

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IN THIS ISSUE

GUEST AUTHOR OF THE MONTH

In This Issue & Reviews:

Elliott C Dasenbrook, MD, MHS
Assistant Professor of Medicine and Pediatrics
The Connie and Jim Brown Chair in Pediatric Pulmonary Survivorship
Associate Director, Adult Cystic Fibrosis Program
Case Western Reserve University School of Medicine
University Hospitals Case Medical Center
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Guest Faculty Disclosure

Elliott C Dasenbrook, MD, MHS has indicated that he is an advisor to Savara Pharmaceuticals.

Unlabeled/Unapproved Uses

The author indicates that there will be a reference to unlabeled/unapproved uses of vancomycin and amikacin in the presentation.

Planning Committee Disclosures

COMMENTARY

Persons with cystic fibrosis (CF) are now living longer, with the median predicted survival age rising to 38 years. The most common cause of death in CF is respiratory failure, due most often to pulmonary inflammation and infection. *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex (BCC) are the pathogens most often associated with decreased survival among patients with CF. Recently, much interest has focused on the potential impact of methicillin–resistant *Staphylococcus aureus* (MRSA) and nontuberculous mycobacterial (NTM) infections on outcomes in CF.

A key driver of the success in describing microbiologic trends and associated clinical outcomes in CF is the international commitment to high–quality patient registries that have captured microbiologic and clinical data over decades. The articles reviewed in this issue have benefited from the US Cystic Fibrosis Foundation Patient Registry (1996 to 2008), a registry of individuals with CF from the province of Ontario, Canada (2005 to 2009), a CF registry from The University of North Carolina at Chapel Hill (2000 to 2007), and a registry of CF patients from Vancouver, Canada (1981 to 2007).

A literature review of recently published studies and microbiologic trends has identified the following important CF investigations that used patient registries:

(1) MRSA is a modifiable risk factor for death in CF.
As reported in the US Cystic Fibrosis Foundation Patient Registry (reviewed herein), perhaps the most dramatic trend in CF microbiology over the last 10 years has been the rise in MRSA infections. The prevalence in CF quadrupled from 6% in 2000 to 25% in 2010. In the study by Dasenbrook and colleagues (reviewed in this issue), the authors reported that detection of MRSA in the respiratory tracts of patients with CF was associated with shortened survival. Prior to this study, the association between MRSA and clinical outcomes had been unclear. One theory is that the clinical course of a patient with MRSA is similar to that of a patient with methicillin–sensitive *S. aureus* (MSSA). It has been shown that MSSA is associated with a milder disease course and with increased patient survival. [1] According to Dasenbrook and coworkers, the risk for death was greater among patients with MRSA compared with those with MSSA, suggesting that the course of a patient with MRSA is not similar to that of a patient with MSSA. Another hypothesis is that MRSA occurs in sicker patients who have worse outcomes.[2] In the MRSA survival analysis, MRSA was not an end–of–life marker, and even after adjustment for severity of disease, MRSA was still associated with an increased risk for death. Taken together, these data suggest that MRSA is an independent risk factor for mortality among persons with CF.

(2) Chronic NTM infection is associated with increased decline in lung function.
The prevalence of NTM in patients with CF is on the rise, now approaching 15%.[3] American Thoracic Society guidelines recommend that adult and adolescent patients with CF undergo periodic (at least yearly) screening cultures for NTM. [4] Furthermore, the guidelines also define clinical and microbiologic criteria for diagnosing NTM lung disease. As the diagnosis of NTM lung disease does not automatically imply immediate therapy, clinicians are faced with the difficult task of weighing the risks and benefits of treatment in each individual patient. The cohort study by Esther and colleagues (reviewed herein) provides important information on chronic NTM lung infection that lends additional support for the treatment of such patients, particularly those with *Mycobacterium abscessus* infection.

(3) A common transmissible strain of *P. aeruginosa* (Liverpool epidemic strain) infects patients with CF in Canada and the United Kingdom, and is associated with a greater risk for death or lung transplantation.
P. aeruginosa is the most important pathogen in CF and is thought to be acquired primarily from the environment. Researchers have reported[5], however, that some strains of *P. aeruginosa* are capable of spreading from patient to patient. One such transmissible strain is the Liverpool epidemic strain. After being discovered in Liverpool, England, further research revealed that cross–infection had occurred in 15 other centers in the United Kingdom. [5] The study by Aaron and associates (reviewed in this issue) documents that the Liverpool epidemic strain has reached North America. This fact is of particular concern, since the authors found that the transmissible Liverpool epidemic strain is associated with a higher risk for death or lung transplantation compared with unique (ie, nontransmissible) strains of *P. aeruginosa.* As this strain has previously spread throughout the United Kingdom, it is possible that it will or already has spread throughout North America. A survey of banked *P. aeruginosa* isolates from CF clinics should be undertaken, because the presence of this strain would result in a significant change in infection control policies for patients with positive cultures.

(4) Nonmucoid BCC infection is associated with a more rapid rate of decline in lung function.
BCC is the most feared pathogen in CF, based on its ability to spread among patients, its high level of resistance to antibiotics, and its capacity to cause rapid clinical deterioration. The prevalence of BCC in the US Cystic Fibrosis Foundation Patient Registry has been stable, at approximately 3%. As with *P. aeruginosa*, the clinical course of patients with BCC runs the spectrum from mild disease to severe infections. Investigators have been searching for host and bacterial explanations for this heterogeneity. Data from Zlosnik and colleagues (reviewed herein) suggest that nonmucoid BCC bacteria may help to explain some of the heterogeneity in the clinical spectrum of BCC disease. If confirmed in prospective evaluations, a simple test to determine the mucoid status of BCC would have important implications for the treatment of this infection.

In summary, identification of emerging pathogens is of critical importance in patients with CF. Research has demonstrated that chronic MRSA, chronic NTM, transmissible strains of *P. aeruginosa*, and nonmucoid BCC are all associated with worse clinical outcomes. Investigations are currently ongoing to address the optimal prevention and treatment strategies necessary to eradicate or suppress these infections, with the goal being to increase the length and quality of life of patients with CF.

Commentary References

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3. Olivier KN, Weber DJ, Wallace RJ Jr, et al; Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med.* 2003;167(6):828-834.
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5. Scott FW, Pitt TL. Identification and characterization of transmissible Pseudomonas aeruginosa strains in cystic fibrosis patients in England and Wales. *J Med Microbiol.* 2004;53(pt 7):609-615.

back to top

MICROBIOLOGIC TRENDS IN US PATIENTS WITH CYSTIC FIBROSIS

Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2010.* Bethesda, MD: Cystic Fibrosis Foundation; 2011. Accessed May 5, 2012.

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The US Cystic Fibrosis Foundation *Patient Registry Annual Data Report* for 2010 was published in October 2011. Data were collected from >26,000 individuals with CF who receive their care at 1 of the >110 CF care centers in the United States. Patients signed informed consent in which they agreed to share their de-identified data. The registry contains demographic and clinical data, including microbiologic assessments of respiratory cultures obtained from sputum, throat swab, and/or bronchoalveolar lavage fluid. The presence or absence of organisms is reported at each encounter throughout the year. The microbiology laboratories at accredited centers use standardized protocols to recover and identify CF pathogens.

The 2010 Patient Registry reveals several important microbiologic findings, particularly when compared with the 2000 report. First, the overall prevalence of *P. aeruginosa* continues to decline. In 2000, 59% of patients had *P. aeruginosa* detected in their respiratory tracts, while in 2010 that number dropped to 51%. When the 2010 prevalence of *P. aeruginosa* is broken down into 8 different age strata (>2 years, 2 to 5 years, 6 to 10 years, 11 to 17 years, 18 to 24 years, 25 to 34 years, 35 to 44 years, and 45+ years of age) and compared with 2000 data, the prevalence has declined in all age–groups. Multidrug–resistant *P. aeruginosa* is detected primarily in adolescents and adults. The overall prevalence is 19%, which has been consistent over the last several years (historical data is not available for comparison). The prevalence of MRSA has quadrupled over the last 10 years, increasing from 6.1% in 2000 to 25.7% in 2010. The prevalence of BCC has been steady over this time period, at 2.5%.

The overall health of patients with CF continues to improve, with the median predicted age of survival now at 38.3 years. The leading cause of shortened survival is respiratory failure due to respiratory infections. *P. aeruginosa* continues to be one of the most significant pathogens in CF, with the overall decreased prevalence and stable rate of multidrug–resistant *P. aeruginosa* encouraging, given the focus on eradication of this infection. The dramatic rise in MRSA prevalence, its transmissibility between patients, and recent associations of MRSA with

worse lung function decline and survival all render MRSA a very important emerging pathogen. Studies are ongoing to address the optimal prevention and treatment strategies. The overall prevalence of BCC remains low, which is reassuring, since this group of pathogens has the ability to rapidly spread among individuals with CF and cause severe clinical deterioration. Continued vigilance to CF microbiologic trends will be critical to the respiratory health of patients with CF.

back to top

MRSA INFECTION AND SURVIVAL IN PERSONS WITH CYSTIC FIBROSIS

Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. **Association between respiratory tract methicillin–resistant *Staphylococcus aureus* and survival in cystic fibrosis.** *JAMA.* 2010; 303(23):2386-2392.

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The impact of MRSA on outcomes in CF is unclear. The prevalence of respiratory tract MRSA, which is on the rise, now stands at 25%. In addition, MRSA is associated with virulence factors that may cause significant lung damage. The investigators of the current study set out to determine if patients with CF who have positive respiratory tract MRSA cultures have shorter survival times than do those who never have a positive MRSA culture. The authors used the US Cystic Fibrosis Foundation Patient Registry to conduct a cohort study between 1996 and 2008.

A total of 19,833 individuals with CF were enrolled in the study. Subjects with MRSA had worse survival than did those without MRSA. During follow–up, 5759 patients cultured positive for MRSA, while 14,074 remained MRSA–negative. Median estimated survival was 6.2 years shorter in MRSA–positive patients compared with MRSA–negative individuals. Since this was a cohort study and the differences in survival could be due to imbalances in the severity of illness between the 2 groups, Cox regression models were used to calculate hazard ratios of death that might account for possible differences in survival patterns. Even after adjustment for forced expiratory volume in 1 second (FEV_1) percent predicted, *P. aeruginosa*, BCC, gender, socioeconomic status, CF–related diabetes, and calendar year, the risk for death was 1.27 times higher in the MRSA–positive group than in the MRSA–negative group (95% confidence interval [CI], 1.11 to 1.45). As bias may be present in cohort studies, the authors also performed numerous sensitivity analyses to evaluate whether severity of illness differences between the groups might be responsible for the results. In these analyses, MRSA was not found to be an end–of–life marker, the hazard for death was greater in patients with MRSA than in those with MSSA, and persistent MRSA infection verus transient MRSA infection also increased the hazard for death. These analyses were all consistent with the conclusion that CF patients with MRSA experience poorer survival than do those without MRSA. The results of this study suggest that MRSA may be a modifiable risk factor for mortality in patients with CF. The adjusted and sensitivity analyses provided further evidence that MRSA is independently contributing to shortened survival, as opposed to being merely a marker of disease severity. These findings suggest that MRSA is a significant pathogen in CF and that patients may benefit from the aggressive treatment of MRSA infections. The next step is to determine whether prevention, eradication, and/or suppression of MRSA infection can improve lung function, prevent disease exacerbations, and enhance survival in patients with CF.

back to top

MYCOBACTERIUM ABSCESSUS INFECTION AND LUNG FUNCTION DECLINE IN PATIENTS WITH CYSTIC FIBROSIS

Esther CR Jr., Esserman DA, Gilligan P, Kerr A, Noone PG. **Chronic *Mycobacterium abscessus* infection and lung function decline in cystic fibrosis.** *J Cyst Fibros.* 2010;9(2):117-123.

NTM lung diseases are another group of infections in which the impact on clinical outcomes is unclear. The detection of NTM has been on the rise, with a recent large study reporting that 13% of patients had NTM–positive cultures [1]. In non–CF patients, NTM is known to cause respiratory disease. The objective of this study by Esther and associates was to examine the association between chronic NTM infection and clinical outcomes among individual with CF. Chronic infection was defined as ≥3 NTM–positive respiratory cultures over ≥3 quarterly visits. The investigators studied all patients with CF at The University of North Carolina at Chapel Hill between 2000 and 2007 who had ≥3 years of clinical data.

Chronic NTM infection in patients with CF is associated with a more rapid decline in lung function than in CF patients without NTM infection. In this single–center study, 536 NTM isolates were obtained from 166 patients over an average follow–up of 6.0 years. A total of 98 patients had at least 1 positive *M. avium* culture, whereas 68 patients had at least 1 positive *M. abscessus* culture. Even after adjustment for severity of illness, patients with chronic NTM infection (n=38) had an average decline in FEV_1 of 2.33% predicted/year, which was 42% more rapid than the 1.64% predicted/year in those without NTM infection (*P*=.01). Next, the authors analyzed the subgroup of patients with chronic NTM infection who had chronic *M. abscessus* infection (n=23). Patients with chronic *M. abscessus* infection exhibited a decline in lung function of 2.42% predicted/year, which was 48% more rapid than in those without NTM infection. In this study, the investigators combined *M. abscessus* and *M. massiliense*. Finally, the authors reported that patients with 1 positive *M. abscessus* culture were more likely to develop chronic NTM infection compared with those with 1 positive *M. avium* culture.

These results demonstrate that chronic NTM infection, particularly *M. abscessus*, may be associated with a more rapid rate of decline in lung function. Two factors suggest that these findings are due to chronic NTM infection contributing independently to lung function decline, as opposed to being a marker of severity. First, the lung function findings occurred even after adjusting for such important confounders as gender, pancreatic insufficiency, *P. aeruginosa* infection, nutritional failure, allergic bronchopulmonary aspergillosis, and CF–related diabetes. Second, the authors note that many patients were treated for NTM infection, especially *M. abscessus*. Since treatment would be expected to slow the rate of lung function decline, the results may actually be an underestimate of the true impact of chronic NTM infection on lung function. A limitation of this study is the fact that these data are derived from a single center and the results may not be generalizable to all CF centers. This study suggests that chronic NTM infection is increasing in prevalence and impacts key clinical outcomes. As NTM infections are notoriously difficult to treat, particularly *M. abscessus*, future research into the optimal timing and therapeutic approach of interventions will be required. For now, the importance of adult and adolescent patients with CF adhering to yearly screening recommendations for NTM is reinforced by this study.

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back to top

TRANSMISSIBLE STRAINS OF *PSEUDOMONAS AERUGINOSA* IN ADULTS WITH CYSTIC FIBROSIS

Aaron SD, Vandemheen KL, Ramotar K, et al. **Infection with transmissible strains of *Pseudomonas aeruginosa* and clinical outcomes in adults with cystic fibrosis.** *JAMA.* 2010;304(19):2145-2153.

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P. aeruginosa is one of the most important pathogens in CF, because it is detected in about half of all patients with the disease and is associated with increased morbidity and mortality. With the exception of transmission between siblings, *P. aeruginosa* is thought to be acquired primarily from the environment. Recent reports, however, have described transmissible strains of *P. aeruginosa* in the United Kingdom and Australia. To date, no transmissible strains have been identified in North American patients with CF. Aaron and colleagues set out to study all adult patients with CF in the province of Ontario, Canada, to determine whether transmissible strains of *P. aeruginosa* were detected and, if so, to establish any associations with clinical outcomes. The investigators evaluated 98% of all adult patients with CF in Ontario, Canada, between 2005 and 2008. Patients were followed for a total of 3 years through 2009.

Of the 446 patients evaluated, 102 (23%) were infected with 1 of 2 common, transmissible strains of *P. aeruginosa*. The first strain was the Liverpool epidemic strain, which had been previously described in the United Kingdom. The second strain had not been previously described. Over 3 years of follow-up, death or lung transplantation was reported in 13 patients (18.6%) infected with the Liverpool epidemic strain, 4 patients (11.4%) infected with the previously undescribed, transmissible strain, 19 patients (8.7%) infected with unique strains (ie, not transmissible), and 14 patients (11.1%) not infected with *P. aeruginosa*. Patients infected with the Liverpool epidemic strain had a greater 3–year risk for death or lung transplantation compared with those infected with unique strains of *P. aeruginosa* (adjusted hazard ratio, 3.26; 95% CI, 1.41 to 7.54). Infection with the previously undescribed strain was not significantly associated with a greater 3–year risk for death or lung transplantation compared with infection with unique strains of *P. aeruginosa*. Finally, the incidence of new infection with transmissible strains of *P. aeruginosa* among patients who were negative for the transmissible strains at baseline was low.

The authors reported that cross–infection with *P. aeruginosa* has occurred widely both within Ontario and between CF centers in the United Kingdom and Canada. Just because a strain can be spread among patients, however, does not imply that that strain is “more virulent.” For example, patients infected with the previously undescribed transmissible strain of *P.*

aeruginosa did not experience worse outcomes compared with those infected with unique strains of *P. aeruginosa*. Importantly, however, patients infected with the transmissible Liverpool epidemic strain of *P. aeruginosa* had a greater risk for death or lung transplantation. Given that close contact between patients is the most likely source of transmission, this finding has major implications for infection control. Should patients with the Liverpool strain of *P. aeruginosa* be subject to the same infection control policies as those with BCC? Prospective studies designed to determine whether transmissible strains of *P. aeruginosa* are present in other CF centers should be undertaken. The current study also provides another reminder about the importance of adhering to infection control policies in CF centers.

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back to top

NONMUCOID *B. CEPACIA* COMPLEX INFECTION AND LUNG FUNCTION DECLINE IN INDIVIDUALS WITH CYSTIC FIBROSIS

Zlosnik JE, Costa PS, Brant R, et al. **Mucoid and nonmucoid *Burkholderia cepacia* complex bacteria in cystic fibrosis infections.** *Am J Respir Crit Care Med.* 2011;183(1):67-72.

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Infection with BCC bacteria in patients with CF is associated with a variable rate of decline in pulmonary function. Some patients have a mild course punctuated by occasional exacerbations, whereas others can experience a rapid decline in lung function associated with sepsis and necrotizing pneumonias[1]. It is still unclear which host or bacterial factors are associated with a worse clinical course. Identification of any factors that are associated with worse clinical outcomes would help to identify prevention and treatment strategies, and thus improve the care of CF patients with BCC. The objective of this study by Zlosnik and coworkers was to determine the association between the mucoid phenotype of BCC and rate of decline in lung function. The investigators included patients at the CF clinics in Vancouver, British Columbia, between 1981 and 2007 who had BCC cultures and pulmonary function data.

Of the 62 patients eligible for evaluation, those infected with nonmucoid BCC had a more rapid decline in lung function than did those with mucoid BCC. Furthermore, patients with the nonmucoid phenotype of BCC had shorter survival times compared with those with the mucoid phenotype. A subgroup analysis of patients who switched between the mucoid and nonmucoid phenotypes further supported the primary conclusion, as the specific bacterial phenotype predicted the subsequent decline in pulmonary function (ie, patients switching from mucoid to nonmucoid BCC had a more rapid decline in lung function). In this study, the species of infecting BCC did not influence the rate of pulmonary function decline. Finally, *in vitro* incubation of BCC with ceftazidime and ciprofloxacin induced permanent switches from the mucoid to the nonmucoid phenotype. Exposure to meropenem at levels above the minimum inhibitory concentration did not induce a switch to the nonmucoid phenotype.

Nonmucoid BCC bacteria are associated with a more rapid rate of decline in pulmonary function in patients with CF. Although the mucoid status of BCC may be a key determinant in the progression of lung disease, the mucoid phenotype of BCC is not routinely reported in microbiology laboratories. This single–center, retrospective analysis provides the impetus for a multicenter, prospective study aimed at determining whether mucoid status impacts clinical outcomes in patients with CF and should be routinely performed in clinical microbiology laboratories. The nonmucoid phenotype hypothesis would also help to explain why after 20 years of BCC infection, some patients suddenly develop the much–feared “cepacia syndrome.” Interestingly, *in vitro* data suggest that ceftazidime and ciprofloxacin may convert BCC bacteria from the mucoid to the nonmucoid phenotype and thus enhance the virulence of the bacteria. Although not conclusive, it does suggest that other factors being equal, if a clinician treating a patient with BCC infection has the choice of either ceftazidime or meropenem, selecting meropenem may offer an advantage.

References

1. Cystic Fibrosis Foundation. Patient Registry Annual Data Report 2010. Bethesda, MD: Cystic Fibrosis Foundation; 2011. *Accessed May* 5, 2012.

back to top