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The Effect of Chronic Infection With *Aspergillus fumigatus* on Lung Function and Hospitalization in Patients With Cystic Fibrosis

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Background: The relevance of *Aspergillus fumigatus* in patients with cystic fibrosis (CF) not affected by allergic bronchopulmonary aspergillosis is unclear. Our aim was to determine the effect of persistent infection with *A fumigatus* on pulmonary exacerbations and lung function in children with CF.

Methods: This was a retrospective cohort study of patients with CF followed at The Hospital for Sick Children from 1999 to 2006. Persistent *A fumigatus* infection was defined as the presence of two or more positive sputum or bronchoalveolar cultures for *A fumigatus* in a given year. The primary outcome measure was the annual number of hospitalizations for pulmonary exacerbations.

Results: Two hundred thirty patients with CF were included in the analysis. The FEV₁ of patients persistently infected with *A fumigatus* was 3.61% ($P \leq .0001$) lower during the study period compared with uninfected patients. There was a significant interaction between *A fumigatus* and *Pseudomonas aeruginosa* on lung function ($P = .0006$). Patients not infected with either organism had the highest pulmonary function. Persistent *A fumigatus* infection (relative risk [RR] = 1.94, $P = .0002$) and CF-related diabetes (RR = 1.64, $P = .028$) were associated with an increased risk of pulmonary exacerbations requiring hospitalization, whereas there was no increased risk of pulmonary exacerbations among patients with allergic bronchopulmonary aspergillosis (RR = 1.02, $P = .94$). When adjusted for baseline pulmonary function, none of these variables were associated with a significantly increased risk of pulmonary exacerbations, with only chronic *A fumigatus* infection trending toward significance (RR = 1.40, $P = .065$).

Conclusions: Persistent *A fumigatus* infection is an independent risk factor for hospital admissions in patients with CF.

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Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; CFRD = cystic fibrosis-related diabetes; MRSA = methicillin-resistant *Staphylococcus aureus*; RR = relative risk

Cystic fibrosis (CF), one of the most common fatal autosomal recessive diseases, is characterized by chronic airways infection and inflammation. Pulmonary exacerbations are significant clinical events for

patients with CF and lead to lung function decline.¹ Pulmonary exacerbations are usually associated with a change in the bacterial density of the bacterial flora residing in the airways.^{2–5}

Aspergillus fumigatus is a ubiquitous fungus found worldwide in soil, decaying vegetation, foods, dust, and water. Normal hosts quickly clear *A fumigatus* upon exposure, whereas it often persists in the respiratory

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tracts of patients with CF.⁶ Reported prevalence rates for *A fumigatus* based on sputum cultures range from 10% to 57% in patients with CF.⁷⁻⁹ Prevalence of infection may depend on clinic geography as well as individual clinics' surveillance methods for endobronchial fungal infections.⁹ Culture positivity for *A fumigatus* has been associated with increasing age, antibiotic or steroid use, indwelling catheters, *Stenotrophomonas maltophilia* colonization, and geography.⁹⁻¹³

A subset of patients with CF infected with *A fumigatus* will go on to develop allergic bronchopulmonary aspergillosis (ABPA), an immune-mediated sensitization to *Aspergillus* resulting in symptoms such as wheezing, pulmonary infiltrates, and decline in pulmonary function.¹⁴ However, in the absence of ABPA, the impact of persistence of *A fumigatus* in the airways on the course of CF lung disease remains unclear.

The aim of this study was to assess if the persistent presence of *A fumigatus* in the lower respiratory tract of patients with CF is associated with more hospitalizations due to decline in pulmonary function and/or pulmonary exacerbations. We hypothesized that *A fumigatus* infection in the respiratory secretions of patients with CF may result in more pronounced airway inflammation, which leads to lower pulmonary function as well as more pulmonary exacerbations in patients with CF.

MATERIALS AND METHODS

Subject Population and Data Collection

The data for this study were extracted from the Cystic Fibrosis Database at The Hospital for Sick Children in Toronto, Canada. The database contains information for patients' sputum microbiology, medications, pulmonary function testing, and hospital admissions for intravenous antibiotics. Specific information that was unavailable from the database was retrieved through systematic review of the hospital health records charts by one of the study investigators.

All patients included in this study were younger than 19 years of age and had a confirmed diagnosis of CF. This was defined by: the presence of clinical features consistent with CF or a positive family history for CF plus either two documented sweat chloride > 60 mEq/L by quantitative pilocarpine iontophoresis test, a genotype showing two well-characterized disease-causing mutations, or a nasal potential difference consistent with CF.¹⁵⁻¹⁸ Patients were excluded from the study if they were unable to produce sputum, unable to perform reproducible spirometry, or had a history of lung transplantation. Patient data were censored at the first respiratory culture positive for *Burkholderia cepacia*.

Study Design

This was a retrospective cohort study of patients with CF followed at The Hospital for Sick Children from 1999 to 2006. This time period was chosen because hospital health record charts were available electronically for these years, which increased the

reliability of the data collected. Given that it is not feasible to differentiate *A fumigatus* infection and *A fumigatus* colonization, we have chosen to use the term infection throughout this article. Persistent *A fumigatus* infection was defined as the presence of two or more positive sputum or bronchoalveolar cultures for *A fumigatus* in a given year. Patients who developed persistent infection with *A fumigatus* were compared with those who did not over the study period. The primary outcome measure was the difference in FEV₁ in percent predicted between patients chronically infected with *A fumigatus* and those whose cultures were negative for *A fumigatus*. The secondary outcome was the number of hospital admissions for pulmonary exacerbations requiring intravenous antibiotics per year. The study was approved by The Hospital for Sick Children's Research Ethics Board.

Statistical Analysis

The initial analysis used descriptive statistics to characterize the study subjects. Baseline FEV₁ was defined as the best FEV₁ 1 year before the first observation in the follow-up period. Two separate regression models were generated. In the first model, a hierarchical linear model was generated to look at the effect of chronic *A fumigatus* infection on quarterly FEV₁, allowing for a random effect and slope for each patient. The second model assessed the effect of chronic *A fumigatus* infection on number of hospital admissions using Poisson regression. Multivariable analysis was performed to account for age, sex, BMI, baseline FEV₁, colonization with *Pseudomonas aeruginosa* (current, never, gone), infection with mucoid *P aeruginosa*, use of inhaled tobramycin, use of steroids (oral or inhaled), and use of intravenous antibiotics. Multivariable analysis was also performed to account for ABPA, CF-related diabetes (CFRD), and pancreatic status. ABPA was defined as treatment with a prolonged course of oral steroids in the context of an elevated IgE and clinical symptoms. An adjusted model for number of hospital admissions was then generated to adjust for baseline FEV₁.

RESULTS

Cohort Characteristics

Of 230 patients with CF included in the analysis, 37 of these patients (16%) were chronically infected with *A fumigatus* at baseline. Patient characteristics in the first year of follow-up were summarized by *A fumigatus* infection status in that year. Patients persistently infected with *A fumigatus* were not significantly different in age, sex, BMI *z* score, or pancreatic status compared with those sputum negative for *A fumigatus* (Table 1). Patients persistently infected with *A fumigatus* did have significantly lower FEV₁% predicted mean (79.2% vs 86.1% in the *A fumigatus*-negative group). Patients with CF who were persistently infected with *A fumigatus* had a significantly higher rate of ABPA, greater use of inhaled antibiotics, inhaled or oral corticosteroids, and *P aeruginosa* infection. The rate of mucoid *P aeruginosa* infection was not different between the two groups.

Pulmonary Function

A hierarchical linear regression model for FEV₁ demonstrated that persistent infection with both

Table 1—Cohort Characteristics in the First Year of Follow-up

	<i>Aspergillus</i> Positive (n = 37)	<i>Aspergillus</i> Negative (n = 193)	P Value
Age, mean (range)	10.9 (7.3, 17.68)	11.09 (7.1, 18.0)	ns
Sex (female)	48.7%	44.0%	ns
Pancreatic insufficiency	97.3%	88.6%	ns
BMI z score	−0.6 (−2.9, 1.8)	−0.2 (−3.6, 2.6)	ns
FEV ₁ mean (range)	79.2% (38.1, 113.2)	86.1% (23.2, 124.0)	.04
<i>Pseudomonas</i> positive	54.1%	44.1%	.01
Mucoid <i>Pseudomonas</i>	32.4%	25.4%	ns
CFRD	8.1%	2.6%	ns
ABPA	10.8%	1.0%	< .001

ABPA = allergic bronchopulmonary aspergillosis; CFRD = cystic fibrosis-related diabetes; ns = not significant.

A fumigatus and *P aeruginosa* were associated with lower lung function. Patients persistently infected with *A fumigatus* had an FEV₁ that was 3.61% ($P \leq .0001$) lower during the study period compared with those patients who were never infected with *A fumigatus*. Patients with transient *A fumigatus* infection had an FEV₁ that was 1.46% ($P = .019$) higher than patients with chronic *A fumigatus* infection, and 2.14% ($P \leq .001$) lower than those who were never infected with *A fumigatus* during the study period.

A model was then generated in which nonsignificant variables were removed, and the interaction between *A fumigatus* and *P aeruginosa* was examined. There was a significant interaction between *A fumigatus* and *P aeruginosa* ($P = .0006$) (Fig 1). Patients not infected with either *P aeruginosa* or *A fumigatus* had the highest pulmonary function. Patients currently infected with *A fumigatus* and *P aeruginosa* had the worst pulmonary function.

Pulmonary Exacerbations

A log linear model was generated to evaluate the effect of persistent infection with *A fumigatus* on pulmonary exacerbations. In a model unadjusted for baseline FEV₁, persistent *A fumigatus* infection (relative risk [RR] = 1.94, $P = .0002$) and CFRD (RR = 1.64, $P = .028$) were associated with an increased risk of pulmonary exacerbations (Table 2). The presence of mucoid *P aeruginosa* trended toward significance (RR = 1.45, $P = .086$). A diagnosis of ABPA was not associated with an increased risk of pulmonary exacerbations (RR = 1.02, $P = .94$). A second model was then generated that included the significant variables only (ie, chronic *A fumigatus* infection and CFRD) with ABPA excluded, and similar results were found.

An adjusted model controlling for baseline FEV₁ was then used to assess whether the severity of lung

disease explained these differences. In this model, none of the variables, which included CFRD or mucoid *P aeruginosa*, were associated with a significantly increased risk of pulmonary exacerbations. However, patients with chronic *A fumigatus* infection still showed an increased risk of pulmonary exacerbations that trended toward significance (RR = 1.40, $P = .065$).

The effect of transient *A fumigatus* infection (one positive culture in any given year) was also examined. Patients with transient *A fumigatus* infection had a significantly elevated risk of hospitalization compared with patients whose *A fumigatus* cultures were negative (RR = 1.43, $P = .047$) in univariate analysis. Transient infection with *A fumigatus* was not associated with elevated risk of hospitalization in the adjusted model, which controlled for baseline FEV₁.

DISCUSSION

Here, to the best of our knowledge, we demonstrate for the first time that patients with CF who are persistently infected with *A fumigatus* have a higher rate of hospital admissions for pulmonary exacerbations. Of note, these patients did not have ABPA. Patients persistently infected with *A fumigatus* had a lower FEV₁% predicted during the study period than controls. These findings were similar to the effects of *P aeruginosa* infection, although the difference in lung function was more pronounced for *A fumigatus*. Not surprisingly, patients who were uninfected with either organism had the highest pulmonary function. Therefore, persistent infection with *A fumigatus* during the pediatric years may have lifelong implications on the trajectory of FEV₁% predicted.

To the best of our knowledge there have been only two studies that have systematically assessed the effect of *A fumigatus* in the absence of ABPA in patients with CF.^{8,19} Kraemer et al¹⁹ reported the decline in lung function among pediatric patients with CF with *A fumigatus* sensitization to be intermediate between CF controls and patients with CF with ABPA. Sensitization to *A fumigatus* was defined as positive for specific IgE RAST class 2 or higher in serum and/or for increased specific IgE to recombinant allergens in serum and increased *A fumigatus*-specific IgG in serum, as determined by enzyme-linked immunosorbent assay.¹⁹ In the study by Mroueh and Spock,⁸ *A fumigatus* did not have a significant negative effect on either Brasfield radiograph scores or pulmonary function tests. However, the authors did not evaluate the effect of *A fumigatus* infection on hospital admissions, and the definition of *A fumigatus* infection did not differentiate between patients with a single positive culture for *A fumigatus* and those with persistent infection. *Aspergillus* can occasionally contaminate

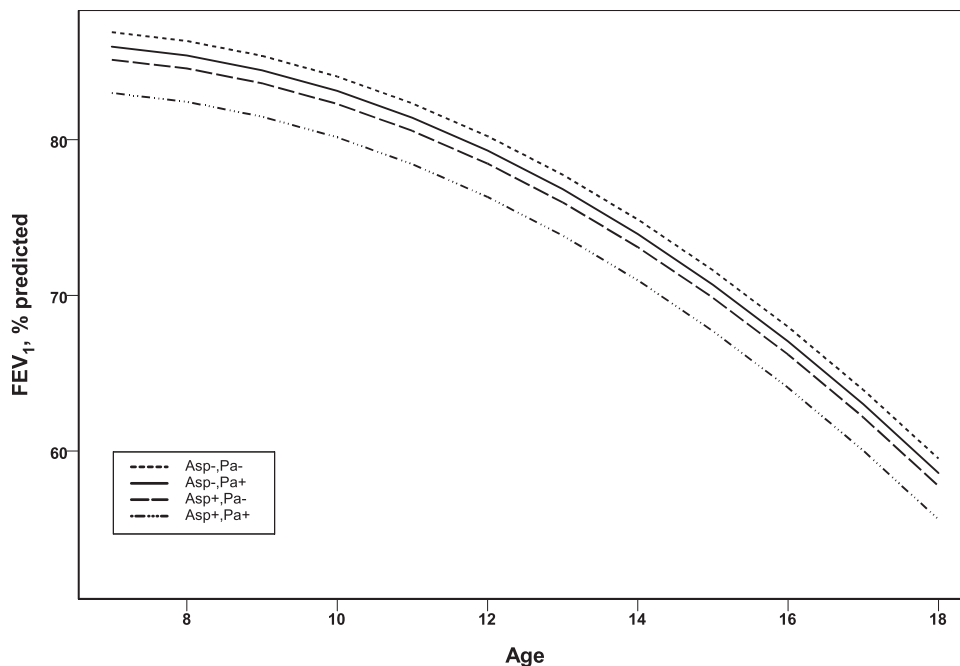


FIGURE 1. Decline in FEV₁ % predicted over time for the *Aspergillus fumigatus* and *Pseudomonas aeruginosa* interaction (baseline FEV₁ of 85% predicted and starting age of 7 years). Asp = *Aspergillus fumigatus*; Pa = *Pseudomonas aeruginosa*.

otherwise sterile sputum cultures; *A fumigatus* infection can be transient in a high percentage of cases, and this transient infection is less likely to have a significant clinical impact. As there is no validated definition available for persistent infection with *A fumigatus*, we adopted a model derived from *P aeruginosa* infection for this study.²⁰ Interestingly, using a similar approach, a recent study looking at the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) on lung function in CF also demonstrated a negative impact in patients with persistent MRSA infection that was not seen when all patients with any positivity MRSA

were included in the analysis.²¹ This concept of focusing only on those patients with persistent infection may also be useful for other emerging pathogens in CF whose role has been difficult to clarify to date.^{22,23}

There is increasing evidence that *A fumigatus* may be of clinical relevance in some individuals with CF who do not exhibit the typical manifestations of ABPA. Shoseyov et al²⁴ reported a group of patients with CF who experienced clinical deterioration with respiratory symptoms that did not respond to intravenous antibiotic therapy and demonstrated clinical improvement only after treatment with antifungal medications.²⁴ This entity was defined as *A fumigatus* bronchitis, but the authors were unable to identify clear risk factors for its development.²⁴ A retrospective cohort analysis was performed by Kanthan et al⁶ to assess the impact of *A fumigatus* sensitization in patients with CF. They reported a significant reduction in *A fumigatus* sensitization in a cohort of patients studied in 2001 compared with an earlier cohort; this reduction in sensitization was associated with improved pulmonary function. Interestingly, this finding was attributed to greater use of antifungal agents.⁶ This raises the question whether antifungal therapy may be a therapeutic option for patients persistently infected with *A fumigatus*. Although there is significant off-label use of this treatment strategy, no clinical trial that we are aware of has addressed this question to date. A multicenter trial using oral itraconazole is currently ongoing in Canada and will shed more light into this area.

Table 2—Pulmonary Exacerbation Risk Unadjusted for Baseline FEV₁ % Predicted and Adjusted for Baseline FEV₁ % Predicted

Variable	RR	SE	P Value
Unadjusted for baseline FEV ₁ % predicted			
Chronic <i>Aspergillus fumigatus</i>	1.94	0.34	.0002
Transient <i>A fumigatus</i>	1.43	0.25	.047
CFRD	1.64	0.37	.028
Mucoid <i>Pseudomonas aeruginosa</i>	1.45	0.32	.086
ABPA	1.02	0.34	.94
Adjusted for baseline FEV ₁ % predicted			
Chronic <i>A fumigatus</i>	1.40	0.26	.065
Transient <i>A fumigatus</i>	1.08	0.21	.71
CFRD	1.19	0.27	.45
Mucoid <i>P aeruginosa</i>	1.20	0.21	.29

RR = relative risk; SE = standard error. See Table 1 for expansion of other abbreviations.

Study Limitations

There are several potential limitations to our study. We could not address the relevance of *A fumigatus* in patients who could not produce sputum, since throat swabs are not a useful technique for *A fumigatus* detection. Another limitation of the study is its retrospective nature. Patients chronically infected with *A fumigatus* had significantly lower FEV₁% predicted than patients in the *A fumigatus*-negative group at baseline. It is possible that patients who are sicker at baseline with lower lung function are exposed to more antibiotic therapy, and that this then predisposes them to endobronchial acquisition of *A fumigatus*. Alternatively, it is possible that the acquisition of *A fumigatus* directly results in poorer pulmonary function. Therefore, further prospective study is needed to address this “chicken and egg” controversy.

CONCLUSIONS

This study assessed the relationship between persistent *A fumigatus* in patients with CF and hospital admissions as well as pulmonary function. At present, *A fumigatus* in the CF airway is largely assumed to be a benign organism. However, this study suggests that persistent *A fumigatus* infection is associated with more pulmonary exacerbations and lower lung function. Further studies need to be done to address the question whether the treatment of persistent *A fumigatus* infection will reduce pulmonary exacerbations in patients with CF.

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Dr Aaron: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and/or revising it critically for important intellectual content; and final approval of the version to be published.

Dr Ratjen: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and/or revising it critically for important intellectual content; and final approval of the version to be published.

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REFERENCES

1. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. *Thorax*. 2007;62(4):360-367.

2. Regelman WEG, Elliott GR, Warwick WJ, Clawson CC. Reduction of sputum *Pseudomonas aeruginosa* density by antibiotics improves lung function in cystic fibrosis more than do bronchodilators and chest physiotherapy alone. *Am Rev Respir Dis*. 1990;141(4 pt 1):914-921.
3. Smith AL, Redding G, Doershuk C, et al. Sputum changes associated with therapy for endobronchial exacerbation in cystic fibrosis. *J Pediatr*. 1988;112(4):547-554.
4. Wat DDI, Doull I. Respiratory virus infections in cystic fibrosis. *Paediatr Respir Rev*. 2003;4(3):172-177.
5. van Ewijk B, van der Zalm M, Wolfs T, van der Ent C. Viral respiratory infections in cystic fibrosis. *J Cyst Fibros*. 2005;4(2):31-36.
6. Kanthan SK, Bush A, Kemp M, Buchdahl R. Factors effecting impact of *Aspergillus fumigatus* sensitization in cystic fibrosis. *Pediatr Pulmonol*. 2007;42(9):785-793.
7. Schønheyder H, Jensen T, Højby N, Andersen P, Koch C. Frequency of *Aspergillus fumigatus* isolates and antibodies to *Aspergillus* antigens in cystic fibrosis. *Acta Pathol Microbiol Immunol Scand*. 1985;93:105-112.
8. Mroueh SSA, Spock A. Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. *Chest*. 1994;105(1):32-36.
9. Milla CE, Wielinski CL, Regelman WE. Clinical significance of the recovery of *Aspergillus* species from the respiratory secretions of cystic fibrosis patients. *Pediatr Pulmonol*. 1996;21(1):6-10.
10. Bargon J, Daultbaev N, Köhler B, Wolf M, Posselt HG, Wagner TO. Prophylactic antibiotic therapy is associated with an increased prevalence of *Aspergillus* colonization in adult cystic fibrosis patients. *Respir Med*. 1999;93(11):835-838.
11. Bhargava V, Tomashefski JF Jr, Stern RC, Abramowsky CR. The pathology of fungal infection and colonization in patients with cystic fibrosis. *Hum Pathol*. 1989;20(10):977-986.
12. Marchac V, Equi A, Le Bihan-Benjamin C, Hodson M, Bush A. Case-control study of *Stenotrophomonas maltophilia* acquisition in cystic fibrosis patients. *Eur Respir J*. 2004;23(1):98-102.
13. Simmonds EJ, Littlewood JM, Hopwood V, Evans EG. *Aspergillus fumigatus* colonisation and population density of place of residence in cystic fibrosis. *Arch Dis Child*. 1994;70(2):139-140.
14. Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis*. 2003;37(Suppl 3):225-264.
15. Rosenstein BJCG, Cutting GR; Cystic Fibrosis Foundation Consensus Panel. The diagnosis of cystic fibrosis: a consensus statement. *J Pediatr*. 1998;132(4):589-595.
16. Knowles MRPA, Paradiso AM, Boucher RC. In vivo nasal potential difference: techniques and protocols for assessing efficacy of gene transfer in cystic fibrosis. *Hum Gene Ther*. 1995;6(4):445-455.
17. National Committee for Clinical Laboratory Standards. *Sweat Testing: Sample Collection and Quantitative Analysis; Approved Guideline*. Villanova, PA: National Committee for Clinical Laboratory Standards; 1994.
18. Wilson DC, Ellis L, Zielenski J, et al. Uncertainty in the diagnosis of cystic fibrosis: possible role of in vivo nasal potential difference measurements. *J Pediatr*. 1998;132(4):596-599.
19. Kraemer R, Deloséa N, Ballinari P, Gallati S, Cramer R. Effect of allergic bronchopulmonary aspergillosis on lung function in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2006;174(11):1211-1220.
20. Lee TWRBK, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients. *J Cyst Fibros*. 2003;2(1):29-34.
21. Dasenbrook EC, Merlo CA, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant *Staphylococcus*

- aureus and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178(8):814-821.
22. Goss CHOK, Otto K, Aitken ML, Rubenfeld GD. Detecting *Stenotrophomonas maltophilia* does not reduce survival of patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2002;166(3):356-361.
23. De Baets FSP, Schelstraete P, Van Daele S, Haerynck F, Vanechoutte M. *Achromobacter xylosoxidans* in cystic fibrosis: prevalence and clinical relevance. *J Cyst Fibros*. 2007;6(1):75-78.
24. Shoseyov DBK, Brownlee KG, Conway SP, Kerem E. *Aspergillus bronchitis* in cystic fibrosis. *Chest*. 2006;130(1):222-226.

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