Infection With Transmissible Strains of *Pseudomonas aeruginosa* and Clinical Outcomes in Adults With Cystic Fibrosis

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**Context**  Studies from Australia and the United Kingdom have shown that some patients with cystic fibrosis are infected with common transmissible strains of *Pseudomonas aeruginosa*.

**Objectives** To determine the prevalence and incidence of infection with transmissible strains of *P. aeruginosa* and whether presence of the organism was associated with adverse clinical outcomes in Canada.

**Design, Setting, and Participants** Prospective observational cohort study of adult patients cared for at cystic fibrosis clinics in Ontario, Canada, with enrollment from September 2005 to September 2008. Sputum was collected at baseline, 3 months, and yearly thereafter for 3 years; and retrieved *P. aeruginosa* isolates were genotyped. Vital status (death or lung transplant) was assessed for all enrolled patients until December 31, 2009.

**Main Outcome Measures** Incidence and prevalence of *P. aeruginosa* isolation, rates of decline in lung function, and time to death or lung transplantation.

**Results** Of the 446 patients with cystic fibrosis studied, 102 were discovered to be infected with 1 of 2 common transmissible strains of *P. aeruginosa* at study entry. Sixty-seven patients were infected with strain A (15%), 32 were infected with strain B (7%), and 3 were simultaneously infected with both strains (0.6%). Strain A was found to be genetically identical to the Liverpool epidemic strain but strain B has not been previously described as an epidemic strain. The incidence rate of new infections with these 2 transmissible strains was relatively low (7.0 per 1000 person-years; 95% confidence interval [CI], 1.8-12.2 per 1000 person-years). Compared with patients infected with unique strains of *P. aeruginosa*, patients infected with the Liverpool epidemic strain (strain A) and strain B had similar declines in lung function (difference in decline in percent predicted forced expiratory volume in the first second of expiration of 0.64% per year [95% CI, −1.52% to 2.80% per year] and 1.66% per year [95% CI, −1.00% to 4.30%], respectively). However, the 3-year rate of death or lung transplantation was greater in those infected with the Liverpool epidemic strain (18.6%) compared with those infected with unique strains (8.7%) (adjusted hazard ratio, 3.26 [95% CI, 1.41 to 7.54]; *P* = .01).

**Conclusions** A common strain of *P. aeruginosa* (Liverpool epidemic strain/strain A) infects patients with cystic fibrosis in Canada and the United Kingdom. Infection with this strain in adult Canadian patients with cystic fibrosis was associated with a greater risk of death or lung transplantation.

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unrelated patients with CF. Transmission of *Pseudomonas aeruginosa* between siblings with CF has been well documented; however, with the exception of siblings, most patients are thought to be infected with genotypically unique strains of *P. aeruginosa* acquired from the environment. However, reports first emerged in 1996 of a transmissible strain of *P. aeruginosa* discovered among patients with CF in Liverpool, England. This transmissible strain was later referred to as the Liverpool epidemic strain. Further studies showed evidence of cross-infection with the Liverpool epidemic strain between patients with CF located in 15 centers in the United Kingdom. Recent reports of transmissible epidemic strains of *P. aeruginosa* have also originated from Australian CF clinics in Melbourne and Brisbane and from a CF clinic in Manchester, England.

Transmissible strains of *P. aeruginosa* have not been described in North American patients with CF. One study from British Columbia, Canada, found that with the exception of sibling pairs with CF, patients in British Columbia were infected with unique rather than common strains of *P. aeruginosa*. The objective of our study was to perform a multi-year prospective study of all adult patients with CF in the province of Ontario (total population: 13 million) to determine whether patients with CF were infected with transmissible strains of *P. aeruginosa*, and if so, to determine the prevalence of infection and the incidence rates of new infection with these strains. Our second objective was to determine if infection with these strains of *P. aeruginosa* was associated with clinically important adverse outcomes.

### METHODS

From September 2005 to September 2008, all adult patients with confirmed CF who attended 1 of the 7 Ontario adult CF clinics or smaller outreach clinics were approached for the 3-year prospective observational cohort. These 7 clinics and their outreach programs provide secondary and tertiary care to more than 98% of all adult patients with CF in Ontario. Patients were included in the study if they were aged 18 years or older, able to spontaneously produce sputum, and if they had a confirmed diagnosis of CF made via genetic analysis and/or sweat testing. Patients were followed up prospectively for 3 years or until December 31, 2009, when the study ended. Study follow-up was coordinated during regularly scheduled appointments at the patients’ CF clinic. The research ethics boards of the participating centers approved the study, and all participants provided written informed consent.

**Sputum Processing and Microbiologic Methods**

Patients provided sputum samples on entry to the study, at 3 months, and yearly thereafter for 3 years. Sputum samples were transported on ice to the central laboratory in Ottawa, Ontario, Canada. Sputum was plated onto selective and nonselective media to detect *P. aeruginosa* and other bacterial pathogens. If *P. aeruginosa* was present in the sputum, 2 distinct *P. aeruginosa* colony morphotypes from each sputum sample were selected for molecular typing, and 5 *P. aeruginosa* isolates derived from each sputum sample were stored frozen in a mixture of brain heart infusion broth and glycerol (20%) at −70°C. A subsequent sputum culture, taken from the same patient 3 months later was similarly processed. In this fashion, 4 *P. aeruginosa* isolates were typed from each patient over the initial 3-month period of the study to determine prevalence of infection with transmissible strains in the inception cohort. Similar procedures were followed for sputum samples obtained at 1, 2, and 3 years postenrollment.

Clinical data, including spirometry, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and exacerbation history were collected from each patient at baseline and then annually for 3 years. Pulmonary exacerbations were defined as acute or subacute worsening of a patient’s respiratory symptoms that were severe enough to warrant oral or intravenous treatment with antibiotics, which was provided at the discretion of the patient’s physician. Patients who underwent lung transplantation before the 3-year end-of-study date did not contribute spirometry, BMI, or exacerbation data after their lung transplant date. Spirometry was performed according to the American Thoracic Society’s standards and predicted values from Crapo et al froze were used.

Molecular genotyping of each *P. aeruginosa* isolate was performed using pulsed-field gel electrophoresis (PFGE). Genomic DNA was prepared using a modification of a described method. The restriction fragment profiles were compared visually and also using BioNumerics computer software (Applied Maths, Kortrijk, Belgium), and were interpreted based on guidelines recommended by Tenover et al. Isolates with identical restriction fragment profiles were considered to represent a single strain. Isolates with restriction profiles that differed by 1 to 3 fragments were considered to be closely related strains evolving from a single clone. Isolates with profiles differing by 4 or more fragments were considered different strains and therefore assumed to be unrelated.

All patients who had sputum cultures positive for at least 1 common transmissible *P. aeruginosa* strain isolated from 1 of the 2 initial sputum samples taken 3 months apart were considered to be infected with a transmissible Ontario strain in the inception cohort. For patients who could be potential new incident cases of infection with a transmissible strain, we retrieved and genotyped all 10 frozen *P. aeruginosa* isolates from the sputums collected at baseline and at 3 months to ensure that we had not missed infection with a transmissible strain at the initial assessment. By doing this, we minimized the risk of falsely labeling a case as an incident infection when the infection may have been present at the initial assessment.
Multilocus sequence typing (MLST) was performed to rule out environmental or nosocomial acquisition of transmissible strains. Exposure to other patients with CF was ascertained via a patient questionnaire and deidentified data were linked to the study database to determine if incident cases had reported exposure to other patients known to be infected with epidemic strains.

Statistical Analysis
Patients were grouped according to the following infection status categories: (1) did not grow *P aeruginosa* in their sputum; (2) infected with unique strains of *P aeruginosa*; and (3) infected with either transmissible *P aeruginosa* strain A or B. Statistical comparisons between groups were limited to the strain A and B groups compared with the group infected with unique strains of *P aeruginosa* because these were the most clinically relevant comparisons. Continuous variables between the groups were compared using *t* tests and proportions were compared using *χ²* tests as appropriate. Random-effects mixed-linear models were used to compare the rates of decline in forced expiratory volume in the first second of expiration (FEV₁) and BMI over the 3-year study period in the patients infected with each of the 2 transmissible strains of *P aeruginosa* vs the corresponding rates in those patients infected with unique strains of *P aeruginosa*. Group × time interactions were analyzed using SAS PROC MIXED (SAS Institute Inc, Cary, North Carolina). Potential confounding effects of age, sex, BMI, baseline FEV₁, CF comorbidities (pancreatic insufficiency, diabetes, and chronic liver disease), infection with *Burkholderia cepacia* complex, and chronic treatment with azithromycin, dornase alfa, inhaled tobramycin, and inhaled colistin were assessed in the mixed-linear models. These confounding variables were decided a priori. Kaplan-Meier survival methods were used for between-group comparisons of unadjusted time to death or lung transplant. Cox proportional hazards models adjusted for the patient covariates were used to compare time to death or lung transplant. The clinical outcomes assessed were all decided a priori before data exploration. All statistical testing was 2-sided and was performed at a significance level of .05 using SAS software version 9.0 (SAS Institute Inc).

RESULTS
Of 580 patients approached to enter the study, 446 patients were enrolled (Figure 1). The mean (SD) age of the 446 enrolled patients was 29.3 (9.6) years and 255 were male (57%). The mean duration of study follow-up for patients infected with strain A of *P aeruginosa* was 853 days, strain B was 890 days, and unique strains was 868 days. Full 3-year follow-up was not available for 61 patients infected with *P aeruginosa* (14 infected with strain A, 8 infected with strain B, 1 infected with both strains A and B, and 38 infected with unique strains), who enrolled in the study after January 2007. These patients were followed up until December 2009. Vital status (death or lung transplant) was assessed for all enrolled patients until December 31, 2009.

Strains A and B of *P aeruginosa* were found in patients receiving care in 6 of 7 Ontario CF clinics. One small CF clinic located in Kingston, Ontario, Canada, which contributed only 8 patients to the study, did not contribute any patients infected with either transmissible strain. However, other patients living in this region and who were attending CF clinics in Toronto or Ottawa were found to be infected with strain A.

Transmissible Strains of *P aeruginosa* From Ontario vs the United Kingdom and Australia
The MLST was used to determine if the 2 transmissible strains isolated in Ontario were similar to the transmissible strains identified in the United Kingdom or in Australia. The MLST typing of the Ontario transmissible strain A isolates identified them as either ST type 146 or ST type 683. Both ST 146 and ST 683 have been identified as belong-
ing to the Liverpool epidemic strain of *P aeruginosa*. To verify that patients in Ontario were infected with the Liverpool epidemic strain of *P aeruginosa*, we obtained 8 known Liverpool epidemic strain isolates from CF centers in the United Kingdom. All 8 Liverpool strain isolates had identical PFGE band patterns to strain A isolates identified from Ontario. Five of the 8 Liverpool strain isolates from CF centers in the United Kingdom were infected with the Liverpool epidemic strain of *P aeruginosa*. All 8 Liverpool strain isolates from Ontario were infected with the Liverpool epidemic strain of *P aeruginosa*. The MLST typing of Ontario strain B isolates identified half of them as ST type 146.

The MLST typing of Ontario strain B isolates identified half of them as ST type 439. This ST type has not been previously described as a transmissible strain of *P aeruginosa* and it has never been described to infect patients with CF. The remaining 50% of Ontario strain B isolates had previously undescribed sequence types. Fifteen randomly chosen isolates from Ontario patients infected with unique strains of *P aeruginosa* as determined by PFGE also were typed using MLST. All 15 isolates showed unique MLST profiles and none were identified as being associated with transmissible *Pseudomonas* strains.

We also obtained isolates from the Midlands, Manchester, and Clone C epidemic strains from the United Kingdom. None of these other UK strains had PFGE banding patterns or MLST sequence types that matched Ontario *P aeruginosa* strains A or B. Similarly, we obtained isolates from the Melbourne, Brisbane, and Tasmania epidemic strains from Australia. Again none of these Australian strains had PFGE banding patterns or MLST sequence types that matched Ontario *P aeruginosa* strains A or B.

**New Infections With Transmissible *P aeruginosa* Strains A or B**

Thirteen patients developed possible new infections with *P aeruginosa* strain A or B that we discovered during annual sputum surveillance over the 3-year follow-up period. For 6 of these 13 patients, the transmissible strain was discovered to have been present in at least 1 of the 10 frozen sputum isolates recovered during the initial 3-month study period. Thus, a total of 7 patients developed new infections with *P aeruginosa* strains A or B over the 3-year follow-up period (Figure 1). The incidence rate of new infections with transmissible *P aeruginosa* strains was 7.0 per 1000 person-years (95% confidence interval [CI], 1.8-12.2 per 1000 person-years).

Environmental sampling of the incident patients’ homes, including sink and shower taps, and sampling from the incident patients’ CF clinics, including pulmonary function equipment and examination room sink taps, revealed positive culture evidence of *P aeruginosa* in 65 of 136 samples (48%), but no transmissible strains of *P aeruginosa* were recovered. All of the incident cases denied having relatives or friends with CF. Similarly, all denied social contact with any other patients with CF. Three patients had been hospitalized for CF in the 12-month period prior to incident infection, but all denied close contact with other patients with CF during their hospitalization. One patient had attended a CF fundraising event and may have had contact with other patients with CF.

**Clinical Outcomes**

TABLE 1 depicts the clinical characteristics of patients infected with *P aeruginosa* strain A, strain B, and unique strains and those not infected at study entry. Those patients not infected with *P aeruginosa* at study entry were more likely to be infected with other bacteria such as *Staphylococcus aureus* and *B cepacia* complex.

Patients infected with strain A were slightly younger and had a lower mean BMI at study entry compared with those infected with unique strains of *P aeruginosa*. Baseline lung function (measured as percentage predicted of FEV1 and forced vital capacity) was not significantly different in those with strain A or B compared with those infected with unique strains.
Patients infected with \textit{P aeruginosa} strain A had a slightly lower mean BMI compared with those infected with unique strains at study entry and this difference was maintained throughout the course of the study (Figure 2). However, mean and median BMI did not decrease in any of the 3 groups over the 3-year study. Rates of decline in BMI were not significantly different for patients with \textit{P aeruginosa} strain A vs those infected with unique strains (unadjusted difference: 0.17% [95% CI, −1.52% to 2.80%]; \textit{P} = .56; adjusted difference: 0.13% [95% CI, −0.25 to 0.44%]; \textit{P} = .58), or for those with \textit{P aeruginosa} strain B vs those infected with unique strains (unadjusted difference: 0.04% per year [95% CI, −0.50 to 0.43%]; \textit{P} = .87; adjusted difference: 0.06% per year [95% CI, −0.37 to 0.48%]; \textit{P} = .80).

Patients infected with \textit{P aeruginosa} strain B actually had slightly fewer pulmonary exacerbations (1.35 exacerbations/year; 95% CI, 0.89-1.81 exacerbations/year) compared with those infected with unique strains (1.93 exacerbations/year; 95% CI, 1.72-2.14 exacerbations/year; \textit{P} = .04; Table 2). Otherwise, there were no significant differences in exacerbation or hospital admission rates in the \textit{P aeruginosa} strain A or B groups compared with the group infected with unique strains.

Of 446 patients, 50 died or received a lung transplant (11.2%) over the course of 3 years. Death or lung transplant occurred in 13 patients infected with \textit{P aeruginosa} strain A (18.6%), 4 patients infected with strain B (11.4%), 19 patients infected with unique strains (8.7%), and 14 patients not infected with \textit{P aeruginosa} (11.1%). There were no deaths or lung transplants among the 7 incident cases or among the 3 patients initially infected with both \textit{P aeruginosa} A and B strains.

Table 1. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Patients Infected With \textit{Pseudomonas aeruginosa}</th>
<th>Patients Not Infected (\textit{n} = 126)</th>
<th>\textit{P} Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain A (\textit{n} = 70)</td>
<td>Strain B (\textit{n} = 35)</td>
<td>Unique Strains (\textit{n} = 218)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>27.5 (7.1)</td>
<td>27.9 (7.1)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>36 (51)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>167.6 (7.9)</td>
<td>169.2 (9.5)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>59.7 (10.5)</td>
<td>62.1 (13.0)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)\textsuperscript{a}</td>
<td>21.2 (3.0)</td>
<td>21.5 (2.8)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, mean (SD) \textsuperscript{b}</td>
<td>2.14 (0.92)</td>
<td>2.15 (0.93)</td>
</tr>
<tr>
<td>FVC, mean (SD), % predicted</td>
<td>74.3 (20.8)</td>
<td>73.8 (22.0)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (27)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>68 (97)</td>
<td>33 (94)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>4 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Infections, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{Staphylococcus aureus}</td>
<td>11 (16)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>\textit{Burkholderia cepacia} complex</td>
<td>6 (9)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>\textit{Aspergillus fumigatus}</td>
<td>14 (20)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Medications, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>23 (33)</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Inhaled tobramycin</td>
<td>50 (71)</td>
<td>27 (77)</td>
</tr>
<tr>
<td>Dornase alfa</td>
<td>11 (16)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Inhaled colistin</td>
<td>7 (10)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Calculated as weight in kilograms divided by height in meters squared.

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Infection with *P. aeruginosa* strain A was associated with a greater 3-year risk of death or lung transplantation compared with patients infected with unique strains (unadjusted hazard ratio [HR] 2.27 [95% CI, 1.12-4.60] \( P = .02 \); adjusted HR, 3.26 [95% CI, 1.41-7.54]; \( P = .01 \)). Infection with *P. aeruginosa* strain B was not significantly associated with a greater 3-year risk of death or lung transplantation compared with patients infected with unique strains (unadjusted HR, 1.37 [95% CI, 0.47-4.02] \( P = .57 \); adjusted HR, 1.10 [95% CI, 0.34-3.63] \( P = .87 \); Figure 3).

**COMMENT**

The results of our study indicate that a sizable minority of adult Canadian patients with CF living in the province of Ontario are infected with 1 of 2 common strains of *P. aeruginosa*. The most prevalent transmissible strain found was the Liverpool epidemic strain, which was found to infect more than 15% of Ontario patients. This same strain is known to infect approximately 11% of patients with CF who receive their care in 1 of 15 CF clinics in England and Wales. Our study is the first report to suggest that common strains of *P. aeruginosa* are shared among patients located on different continents. Our data suggest that cross-infection with *P. aeruginosa* has occurred widely both within Ontario and between CF centers in the United Kingdom and Canada. It is currently unknown if infection with the Liverpool epidemic strain or with other transmissible strains of *P. aeruginosa* is prevalent among US patients with CF. Epidemiological studies on infection with transmissible strains of *P. aeruginosa* in the CF population in the United States have not been published.

Presumably cross-infection with transmissible strains of *P. aeruginosa* may be resulting from close patient-to-patient contact among infected and noninfected patients. Studies of patients with CF have shown that viable *P. aeruginosa* is easily isolated from the cough aerosols of patients with CF, and that 70% of these aerosols are of respirable size (<3.3 µm in diameter). This suggests that coughing may serve as a potential mechanism for airborne transmission of *P. aeruginosa* from patient to patient. Aerosol dissemination of epidemic strains of *P. aeruginosa* has also been documented from room air samples in which patients perform spirometry and airway clearance, implying that close physical contact between patients may not be required to spread infection with epidemic strains within CF clinics. Recent reports have documented spread of the Liverpool epidemic strain of *P. aeruginosa* from a CF patient to both of her parents who did not have CF, suggesting that persons without CF can also serve as temporary reservoirs of infection. Finally, spread of the Liverpool epidemic strain from a CF patient to a pet cat has been recently described, suggesting that family pets can also serve as reservoirs for transmissible strains within the community.

**Figure 2.** Annual Unadjusted Median of Forced Expiratory Volume Percent Predicted in the First Second of Expiration (FEV1) and Median Body Mass Index

The blue lines indicate the rate of decline and were generated from the fitted slopes and intercepts generated from the mixed models. The top and bottom of the box plots represent the interquartile ranges and the horizontal lines represent the median values. The error bars extend 1.5 interquartile range from the 25th and 75th percentiles. Circles indicate outliers. For the FEV1 comparison of strain A vs unique strains, \( P = .01 \); strain B vs unique strains, \( P = .22 \). For the body mass index comparison of strain A vs unique strains, \( P = .49 \); strain B vs unique strains, \( P = .87 \). Body mass index is calculated as weight in kilograms divided by height in meters squared.
There is precedence for cross-infection of bacterial organisms between Canadian and British patients with CF. Epidemiological studies of *Burkholderia cenocepacia* conducted in the early 1990s revealed that the same ET12 strain of *B cepacia* infected patients with CF in Edinburgh, Scotland, Manchester, England, and Toronto, Ontario, Canada. Later studies from London, Ontario, Canada confirmed that attendance of patients at CF summer camps was strongly correlated with infection among Canadian and UK patients may have occurred in the early 1990s at CF summer camps or elsewhere. Our laboratory revealed that the same ET12 strain of *B cepacia* clonal strain. Later studies from London, Ontario, Canada confirmed that attendance of patients at CF summer camps was strongly correlated with *B cepacia* infection among Canadian pediatric patients with CF. It is impossible to know whether infection with the Liverpool epidemic strain of *P aeruginosa* originated in Canada or in the United Kingdom and it is difficult to identify in hindsight how the infection may have spread from one continent to another. The Liverpool strain was first identified in Liverpool in 1996 because of its unusual phenotypic properties; isolates displayed a relatively high level of resistance to conventional antipseudomonal antibiotics. By that time, Canadian CF summer camps had been disbanded because of infection-control concerns. However, molecular typing of *P aeruginosa* was not widely available until the late 1990s, and it is theoretically possible that cross-infection between Canadian and UK patients may have occurred in the early 1990s at CF summer camps or elsewhere. Our laboratory first picked up the presence of a possible transmissible *P aeruginosa* strain infecting Canadian patients in 2004, and this served as the stimulus for the present study. With the advent of MLST, it became possible to definitively identify this dominant Canadian transmissible strain as the Liverpool epidemic strain.

Although knowledge of infection with transmissible strains of *P aeruginosa* among patients with CF is important because of its implications for infection control, a sense of urgency about this issue would only be justified if infections with transmissible strains were shown to be associated with adverse clinical outcomes or prognosis. Our study is the first large, prospective cohort study to examine this issue.

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**Table 2.** Pulmonary Exacerbations and Hospital Admissions Over 3 Years

<table>
<thead>
<tr>
<th>Patients Infected With <em>Pseudomonas aeruginosa</em>, Mean (95% CI)</th>
<th>Strain A vs Unique Strains</th>
<th>Strain B vs Unique Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of exacerbations/y</td>
<td>Mean Difference (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Overall</td>
<td>1.77 (1.37 to 2.17)</td>
<td>−0.16 (−0.59 to 0.27)</td>
</tr>
<tr>
<td>Requiring home IV antibiotics</td>
<td>0.26 (0.11 to 0.41)</td>
<td>0.03 (−0.13 to 0.18)</td>
</tr>
<tr>
<td>Time spent in hospital annually, d</td>
<td>10.72 (4.82 to 16.63)</td>
<td>4.17 (−0.63 to 8.98)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IV, intravenous.

**Figure 3.** Comparison of Time to Death or Lung Transplant

Infection with strain A was associated with a greater 3-year risk of death or lung transplantation compared with patients infected with unique strains of *Pseudomonas aeruginosa* (unadjusted hazard ratio [HR], 2.27; 95% confidence interval [CI], 1.12-4.60; *P* = .02) (adjusted HR, 3.26; 95% CI, 1.41-7.54; *P* = .01). Infection with strain B was not significantly associated with a greater 3-year risk of death or lung transplantation compared with patients infected with unique strains of *P aeruginosa* (unadjusted HR, 1.37; 95% CI, 0.47-4.02; *P* = .57) (adjusted HR, 1.10; 95% CI, 0.34-3.63; *P* = .87). The vertical lines indicate censored observations.
respective case-control study of 12 patients infected with the Liverpool epidemic strain suggested that patients infected with the Liverpool strain had a greater annual loss of lung function compared with control patients with CF. However, an 8-year single-center study from a Manchester, England clinic compared 28 patients with CF with transmissible strains of P. aeruginosa (21 infected with the Manchester A strain and the other 7 infected with the Liverpool strain of P. aeruginosa) with 52 patients infected with unique strains of P. aeruginosa. This study did not show differences in survival or annual changes in lung function or BMI, although patients infected with transmissible strains did receive more intravenous antibiotics compared with those infected with sporadic strains.

Results of our study shed more light on the clinical implications of infection with common transmissible strains of P. aeruginosa. Those patients infected with Ontario strain A (also known as the Liverpool epidemic strain) were twice as likely to go on to death or lung transplant over the 3-year observation period compared with those infected with unique strains of P. aeruginosa (19% vs 9%). Somewhat surprisingly, our study did not show that patients infected with either transmissible strain experience an accelerated decline in lung function over 3 years compared with those infected with unique strains. How do we reconcile the fact that death or lung transplant is more common in patients infected with the Liverpool strain, but lung function appears to decline at the same rate as those infected with unique strains? We think the likeliest explanation is the healthy survivor effect. Patients who died or had lung transplants did not contribute annual lung function data following these events. Because a greater proportion of patients infected with the Liverpool Epidemic strain experienced these events, censoring of the sickest patients from the Liverpool strain cohort may have resulted in apparently lower rates of decline in lung function among the healthy survivors. Similarly, because most cases of transmissible strains were prevalent cases, it is possible that the sicker patients with transmissible strains died prior to 2005, and this other form of survivor bias could explain why lung function did not decline at an accelerated rate in those with transmissible strains.

There are potential limitations of our study. The annual decline in FEV1 percent predicted tended to be steeper in patients infected with P. aeruginosa strain B compared with those infected with unique strains; however, the relatively small numbers of patients infected with strain B resulted in limited power to show a statistical difference for this comparison. Also, although most patients had at least 10 isolates of P. aeruginosa genotyped over the course of the study, it is possible that some prevalent or incident cases of strain A or B could have been missed. Unmeasured confounders may also have influenced outcomes.

In summary, our study has shown that cross-infection with transmissible common strains of P. aeruginosa has occurred widely both within Ontario, Canada and between CF centers in the United Kingdom and Canada. Infection with the Liverpool epidemic strain was associated with a greater risk of death or lung transplant. Differences in prognosis among patients with CF infected with P. aeruginosa may be due in part to differences in specific strain types infecting individual patients.

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Author Contributions: Dr Aaron had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Aaron, Vandemheen, Ramotar, Chan, Doucette, Fergusson.

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There is only one solution if old age is not to be an absurd parody of our former life, and that is to go on pursuing ends that give our existence a meaning—devotion to individuals, to groups or to causes, social, political, intellectual or creative work.

—Simone de Beauvoir (1908-1986)