Chronic *Stenotrophomonas maltophilia* infection and exacerbation outcomes in cystic fibrosis☆☆,☆☆,★

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Abstract

Background: Chronic *Stenotrophomonas maltophilia* infection is a risk factor for pulmonary exacerbation in cystic fibrosis (CF) but its impact on subsequent clinical outcomes is unknown. The aim of this study was to determine the effect of chronic *S. maltophilia* infection and associated antimicrobial therapy on the recovery of forced expiratory lung volume in 1 s (FEV₁) following pulmonary exacerbation.

Methods: This was a retrospective cohort study of patients with CF followed at The Hospital for Sick Children and St. Michael’s Hospital from 1997 to 2008. The primary outcome was the difference in FEV₁ percent predicted from baseline to follow up after a pulmonary exacerbation. Secondary outcomes for the effect of antimicrobial therapy included time to subsequent exacerbation.

Results: There were 1667 pulmonary exacerbations in 440 CF patients. Patients with chronic *S. maltophilia* infection did not recover their baseline FEV₁ following 31% of exacerbations and had an overall mean FEV₁ decline of 1.84% predicted after exacerbation. Older (p=0.02), female (p=0.02) patients with lower BMI z score (p=0.002) and *Burkholderia cepacia* complex infection (p=0.005), but not chronic *S. maltophilia* infection (p=0.86), had a greater decrease in follow up FEV₁% pred compared to baseline. The number of days of antibiotic therapy against *S. maltophilia* during a pulmonary exacerbation was not associated with a significant difference in the FEV₁ recovery (p=0.69) or with a longer time to subsequent pulmonary exacerbation (p=0.56).

Conclusions: Although CF patients experience a significant decline in lung function following exacerbation, chronic *S. maltophilia* infection and associated antimicrobial therapy do not affect subsequent lung function recovery.

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Keywords: Cystic fibrosis; *Stenotrophomonas maltophilia*; Pulmonary exacerbation
1. Introduction

Chronic *Stenotrophomonas maltophilia* infection in cystic fibrosis (CF) patients has recently been shown to be an independent risk factor for pulmonary exacerbation [1]. Antibiotic use, however, is a known risk factor for the isolation of *S. maltophilia* in the respiratory tract of CF patients and increased treatment of pulmonary exacerbations may simply be selecting out *S. maltophilia* in the airways of sicker CF patients [2–5]. The consequences of the increased number of pulmonary exacerbations in CF patients with chronic *S. maltophilia* infection are unknown.

Using the CF Foundation Patient Registry, Goss and colleagues have shown that a quarter of CF patients do not recover their baseline pulmonary function following an exacerbation and have identified risk factors associated with failure to recover baseline lung function [6]. We hypothesized that chronic *S. maltophilia* infection is associated with poorer outcome during pulmonary exacerbations in CF patients and that outcome may be influenced by whether or not specific antimicrobial therapy against *S. maltophilia* was initiated. The aim of this study was to determine the impact of chronic *S. maltophilia* infection on the recovery of forced expiratory lung volume in 1 s (FEV$_1$) following pulmonary exacerbation and the role of anti-*S. maltophilia* antimicrobial therapy on FEV$_1$ recovery.

2. Materials and methods

2.1. Study design and definitions

This was a retrospective cohort study using the Toronto CF Database of patients with CF followed at The Hospital for Sick Children and St. Michael’s Hospital (Toronto, Canada) from 1997 to 2008. Patients were included in the study if they had a confirmed diagnosis of CF based on the following: a) the presence of clinical features consistent with CF, or b) a positive family history for CF plus either 2 documented sweat chloride values $>$ 60 mEq/L measured by quantitative pilocarpine iontophoresis test, genetic testing showing 2 CF-causing mutations or a nasal potential difference consistent with CF [7]. Patients were excluded once they had received a lung transplant.

As previously, a pulmonary exacerbation was defined as a hospitalization for respiratory symptoms requiring antibiotics [1]. Each pulmonary exacerbation was classified into one of three groups based on previous definitions [1]: 1) chronic *S. maltophilia*: 2 or more positive sputum or bronchoalveolar cultures for *S. maltophilia* in previous 12 months, 2) intermittent *S. maltophilia*: 1 positive sputum or bronchoalveolar cultures for *S. maltophilia* in previous 12 months or a previous positive culture, and 3) never *S. maltophilia*: never having a positive sputum or bronchoalveolar culture for *S. maltophilia*. For baseline characteristics, patients were classified into one of these three groups based on respiratory tract culture results from the 12 months prior to the first year of observation.

The primary outcome was the difference in FEV$_1$ percent predicted from baseline to follow up after a pulmonary exacerbation in each of these three groups. Baseline FEV$_1$ was defined as the best FEV$_1$ in the 6 months before the hospitalization date for pulmonary exacerbation. Follow up FEV$_1$ was defined as the best FEV$_1$ in the 3 months following the hospitalization date for pulmonary exacerbation [6]. Hospitalization FEV$_1$ was defined as the worst FEV$_1$ 7 days prior or 4 days after the date of hospital admission for pulmonary exacerbation [8]. FEV$_1$ recovery was defined as a follow up FEV$_1$ greater than or equal to 90% of the baseline FEV$_1$ [6]. Consecutive pulmonary exacerbations within 3 weeks of antibiotic treatment were considered as a single event.

Antibiotic therapy for *S. maltophilia* was defined as the use of antibiotics with activity against *S. maltophilia*, such as trimethoprim–sulfamethoxazole, levofloxacin, ticarcillin–clavulanate and doxycycline [9,10], in the 14 days before or 21 days after the date of hospital admission for pulmonary exacerbation.

This study was approved by the Research Ethics Board at The Hospital for Sick Children (1000013759) and St. Michael’s Hospital (09-0876).

2.2. Statistical analysis

Analysis of variance (ANOVA) was used to compare continuous variables at baseline and chi-square independent test was used to assess the association to the three levels of *S. maltophilia* groups. A generalized linear mixed model (with appropriate covariance structures of power to account for the longitudinal nature of repeated data structure of FEV$_1$% of each subject) was generated to analyze the relationship between chronic *S. maltophilia* infection and change in FEV$_1$% predicted accounting for age, gender, BMI z score, pancreatic insufficiency, *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex or methicillin-resistant *Staphylococcus aureus* (MRSA) infection, allergic bronchopulmonary aspergillosis (ABPA) (as defined by the treating physician in combination with increased IgE levels), drop in FEV$_1$% predicted from baseline to exacerbation, time since baseline FEV$_1$ measurement, and use of antibiotic therapy specific for *S. maltophilia*, based on risk factors identified in previous studies [6,11]. Medicaid insurance was not included due to the existence of universal healthcare insurance in Canada. A second model, adjusting for significant variables identified in the first model, was generated to analyze the relationship between days of *S. maltophilia* antibiotic therapy during pulmonary exacerbation and change in FEV$_1$% predicted and time to subsequent pulmonary exacerbation.

2.3. Power analysis

This study had 80% power, at the 5% level of significance, to detect a minimum difference of 1.4% predicted in FEV$_1$ recovery between the never and chronic *S. maltophilia* groups. Linear regression power analysis demonstrated that, this study had greater than 87% power to detect a minimum difference in the slope of 0.1 for FEV$_1$% predicted (SD 8.30) and 80% power to detect a minimum difference in the slope for time to subsequent exacerbation (days) of 4.0 (standard deviation of up
to 429) regressed on the number of days of antibiotic therapy (SD 12.68).

3. Results

3.1. Baseline patient characteristics

From 1997 to 2008, of the 881 CF patients followed in the Toronto CF Database, 440 patients had at least one pulmonary exacerbation requiring hospitalization and antibiotics. Of these 440 patients, 23 (5%) patients had chronic S. maltophilia infection, 29 (7%) had intermittent S. maltophilia infection and 388 (88%) had never had S. maltophilia isolated from the respiratory tract. Baseline patient characteristics are summarized by S. maltophilia infection status in Table 1, demonstrating no significant differences. Of note, patients in each of the three groups had a similar average number of respiratory cultures taken per year (chronic 2.9, intermittent 3.4 and never 3.0 cultures/yr p = 0.49).

3.2. FEV1 recovery following pulmonary exacerbation

During the study period, there were 1667 pulmonary exacerbations identified that required hospitalization and antibiotics. Of these, 366 (22%) were in patients with chronic S. maltophilia infection, 184 (11%) were in patients with intermittent S. maltophilia infection and 1117 (67%) were in patients who never had S. maltophilia. The adjusted difference in FEV1% predicted from baseline to follow up after exacerbation is represented, according to S. maltophilia infection status, in Fig. 1. Patients with chronic S. maltophilia infection had a mean difference in FEV1% predicted from baseline to follow up of −1.84% pred (SE 1.49), patients with intermittent S. maltophilia infection had a difference of −1.86% pred (SE 1.53) and patients who never had S. maltophilia had a difference of −2.25% pred (SE 1.40).

The effect of chronic S. maltophilia infection on the difference in FEV1% predicted from baseline to follow up after each exacerbation was evaluated using a linear regression model, adjusting for the previous identified variables. In this model, older (p = 0.02), female (p = 0.02) patients with lower BMI z score (p = 0.002) and B. cepacia complex infection (p = 0.005), had a greater decrease in follow up FEV1% pred compared to baseline (Table 2). Patients who had a greater FEV1 drop from baseline to the time of exacerbation also had lower FEV1 in follow up after exacerbation (p < 0.0001). Of note, patients with ABPA had a greater FEV1 in follow up after exacerbation (p = 0.0008). Patients with chronic S. maltophilia infection (p = 0.86) or who had S. maltophilia antibiotic therapy (p = 0.53) did not have a significant difference in FEV1% pred recovery following exacerbation. Using previous definitions to dichotomize FEV1 recovery [6], our data showed that FEV1 was not recovered after 31% of exacerbations with chronic S. maltophilia infection, 23% of exacerbations with intermittent S. maltophilia infection and 31% of exacerbations with no S. maltophilia infection. Lower BMI z score, B. cepacia complex infection and greater FEV1 drop were identified as significant risk factors for failing to recover FEV1 in a generalized mixed model.

3.3. Effect of S. maltophilia antibiotic therapy on FEV1 recovery and time to subsequent pulmonary exacerbation

To examine the effect of antibiotic therapy directed against S. maltophilia on FEV1 recovery after a pulmonary exacerbation, a linear regression model was generated only for patients with S. maltophilia infection (chronic and intermittent S. maltophilia infections). Of the 366 exacerbations with chronic S. maltophilia...

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Table 1

Baseline characteristics of patients with pulmonary exacerbations.

<table>
<thead>
<tr>
<th></th>
<th>Chronic S. maltophilia (n = 23)</th>
<th>Intermittent S. maltophilia (n = 29)</th>
<th>Never S. maltophilia (n = 388)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. resp cultures/yr, mean (IQR)</td>
<td>2.9 (1–4)</td>
<td>3.4 (1–4)</td>
<td>3.0 (2–4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age in years, mean (IQR)</td>
<td>19.8 (11.7–26.9)</td>
<td>18.6 (12.3–21.9)</td>
<td>20.0 (10.0–27.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>52.2%</td>
<td>58.6%</td>
<td>50.1%</td>
<td>0.67</td>
</tr>
<tr>
<td>Pancreatic insufficient</td>
<td>91.3%</td>
<td>89.7%</td>
<td>86.6%</td>
<td>0.91</td>
</tr>
<tr>
<td>CFRD</td>
<td>4.3%</td>
<td>17.2%</td>
<td>13.7%</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean BMI z score (IQR)</td>
<td>−0.5 (−1.3 to 0.1)</td>
<td>−0.8 (−1.5 to 0.1)</td>
<td>−0.7 (−1.3 to 0.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean baseline FEV1% pred (IQR)</td>
<td>56.3 (42.5–67.3)</td>
<td>62.8 (47.4–73.8)</td>
<td>62.2 (45.3–77.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>P. aeruginosa positive</td>
<td>40.9%</td>
<td>57.7%</td>
<td>61.6%</td>
<td>0.05</td>
</tr>
<tr>
<td>B. cepacia positive</td>
<td>4.5%</td>
<td>15.4%</td>
<td>18.1%</td>
<td>0.20</td>
</tr>
</tbody>
</table>

IQR: interquartile range.
infection, 121 (33%) of them were treated with \textit{S. maltophilia} antibiotic therapy which eliminated \textit{S. maltophilia} for at least 1 year in only 31 (26%) of these exacerbations. Of the 184 exacerbations with intermittent \textit{S. maltophilia} infection, 26 (14%) of them were treated with \textit{S. maltophilia} antibiotic therapy which eliminated \textit{S. maltophilia} for at least 1 year in 15 (58%) of these exacerbations. Fig. 2 illustrates the number of days of \textit{S. maltophilia} antibiotic therapy received for every exacerbation (mean 20 days; median 14 days; range 1–134 days). The majority of these exacerbations (95%) were treated with only one \textit{S. maltophilia} antimicrobial agent and in most cases (76%), \textit{S. maltophilia} antimicrobial treatment was initiated on the day of hospitalization.

The difference in FEV$_1$% predicted from baseline to follow up after pulmonary exacerbations with chronic or intermittent \textit{S. maltophilia} infection was evaluated adjusting for significant variables from the previous model. In this adjusted model, patients with a greater FEV$_1$ drop from baseline to the time of exacerbation ($p<0.0001$) had a greater decrease in follow up FEV$_1$ and patients with ABPA had a greater FEV$_1$ in follow up after exacerbation ($p=0.03$). The number of days of antibiotic therapy against \textit{S. maltophilia} during a pulmonary exacerbation was not associated with a significant difference in the FEV$_1$ recovery following a pulmonary exacerbation ($p=0.69$). The results were similar when the gain in FEV$_1$% predicted from hospitalization to follow up after pulmonary exacerbation was evaluated.

For patients with chronic and intermittent \textit{S. maltophilia} infections, the time to subsequent pulmonary exacerbation was then determined. The estimate of the time to subsequent pulmonary exacerbation was 574.85 days (SE 113.45). A linear regression model was then generated to examine the relationship between time to subsequent exacerbation and number of days of antibiotic therapy against \textit{S. maltophilia} during the exacerbation, adjusting for the previously identified variables. Lower BMI z score ($p=0.04$) was significantly associated with a shorter time to subsequent pulmonary exacerbation. Antibiotic treatment against \textit{S. maltophilia} during a pulmonary exacerbation was not associated with a longer time to subsequent pulmonary exacerbation ($p=0.56$). When \textit{S. maltophilia} antibiotic therapy was dichotomized into $\geq 14$ days or $<14$ days of antibiotic therapy [12], the same variables were significant in evaluating FEV$_1$ and time to subsequent pulmonary exacerbation.

### 4. Discussion

We have previously shown that chronic \textit{S. maltophilia} infection in CF patients is an independent risk factor for pulmonary exacerbation requiring hospitalization and antibiotic therapy and this study confirms that there are more pulmonary exacerbations per patient with chronic \textit{S. maltophilia} infection [1]. This study showed that chronic \textit{S. maltophilia} status does not affect FEV$_1$ recovery and \textit{S. maltophilia} antibiotic treatment does not influence the recovery of, or the gain in, FEV$_1$ during a pulmonary exacerbation or the time to subsequent pulmonary exacerbation, regardless of the length of therapy.

Recurrent pulmonary exacerbations are associated with significant increases in morbidity and mortality in CF [11,13–16]. Similar to a previous study by Sanders et al., there was a failure to recover baseline FEV$_1$ in approximately 30% of exacerbations in our study [6]. As a population whole, patients had an approximately 2% predicted decrease in follow up FEV$_1$ compared to baseline; other studies have noted an approximately 3% decrease in FEV$_1$ following pulmonary exacerbations [8]. Adjusting for similar variables as previous analyses [6], this study noted that older age, female gender, lower BMI, \textit{B. cepacia} complex infection, and a larger drop in FEV$_1$ at the time of exacerbation, negatively affected lung function recovery after a pulmonary exacerbation. In contrast, patients with ABPA had improved lung function following pulmonary exacerbation, likely reflecting the effect of steroid therapy which was administered to the majority (59%) of them [17]. Although persistent \textit{P. aeruginosa}, \textit{B. cepacia} complex and MRSA were risk factors for worse lung function following exacerbation in the Sanders study, chronic \textit{S. maltophilia} infection was not a risk factor in our study. Thus, while CF patients chronically infected with \textit{S. maltophilia} have more pulmonary exacerbations [1], it does not appear as though they do worse, in terms of lung function, following a pulmonary exacerbation than patients who have intermittent or who never had \textit{S. maltophilia}. This is in

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression estimate</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>−0.06</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>−1.11</td>
<td>0.49</td>
<td>0.02</td>
</tr>
<tr>
<td>\textit{P. aeruginosa}</td>
<td>−1.23</td>
<td>0.82</td>
<td>0.13</td>
</tr>
<tr>
<td>\textit{B. cepacia} complex</td>
<td>−1.64</td>
<td>0.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Lower BMI z score</td>
<td>−0.65</td>
<td>0.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis (ABPA)</td>
<td>3.16</td>
<td>0.94</td>
<td>0.0008</td>
</tr>
<tr>
<td>Greater FEV$_1$ drop from baseline to exacerbation</td>
<td>−0.40</td>
<td>0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic \textit{S. maltophilia}</td>
<td>0.03</td>
<td>0.59</td>
<td>0.86</td>
</tr>
<tr>
<td>\textit{S. maltophilia} antibiotic treatment</td>
<td>−0.008</td>
<td>0.01</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Fig. 2. Histogram of total number of days of \textit{S. maltophilia} antibiotic therapy received per episode of pulmonary exacerbation in patients treated with \textit{S. maltophilia} antibiotic therapy.
keeping with our previous findings that the rate of FEV₁ decline over time is not greater in chronic *S. maltophilia* infected patients [1]. It is still not clear, however, how chronic *S. maltophilia* is associated with more exacerbations and more exacerbations are associated with greater FEV₁ decline [18] but chronic *S. maltophilia* infection is not associated with greater FEV₁ decline. Exactly how pulmonary exacerbations contribute to the rate of FEV₁ decline has yet to be determined.

Although the primary aim of this study was to examine the effect of chronic *S. maltophilia* infection on lung function recovery following pulmonary exacerbations, the inclusion of detailed information regarding antibiotic therapy permitted us to investigate, albeit in a limited retrospective manner, its effect on clinical outcomes. The goal of antibiotic treatment during a CF pulmonary exacerbation is to decrease the bacterial load in the airways (possibly eliminating the bacteria) and decrease the associated inflammation thereby improving lung function and prolonging the time to subsequent exacerbation [19,20]. Antibiotic therapy targeting *S. maltophilia* during pulmonary exacerbations did not affect the degree of FEV₁ recovery following the exacerbation or the time to subsequent exacerbation despite the fact that the median number of days of antibiotic therapy was 14 days, which is standard of care for the treatment of pulmonary exacerbations [12]. It is important to note, however, that there was a wide variation in the number of days of antibiotic therapy. In addition, almost all patients were treated with only one antimicrobial drug targeting *S. maltophilia*, resulting in elimination of *S. maltophilia* from the airways in only one quarter of chronic *S. maltophilia* pulmonary exacerbations. This raises the question of whether the antimicrobial treatment of *S. maltophilia* in these patients was truly effective. *S. maltophilia* is notorious for its intrinsic resistance to a broad spectrum of antimicrobial agents and it is often recommended to treat *S. maltophilia* infections with two antibiotics with different mechanisms of action [9]. In the analysis of the effect of antimicrobial therapy on clinical outcomes, patients with intermittent infection were included with patients with chronic infection due to the small sample size. It is possible that chronically infected patients may benefit more from antimicrobial therapy during exacerbations. Alternatively, it has been suggested that it is the occurrence of the pulmonary exacerbation itself, as evidenced by the initial drop in FEV₁ at the time of exacerbation, rather than any of the antimicrobial therapy we administer during an exacerbation, which is the most important determinant of long-term outcome. Other large epidemiologic studies have demonstrated that the duration of antibiotic treatment during pulmonary exacerbations does not affect the lung function decline seen after pulmonary exacerbations in CF patients [8,12]. Prospective interventional studies with measurements of sputum bacterial density are needed to definitively address the role of *S. maltophilia* antimicrobial therapy during exacerbations.

This study has several limitations. The definition of chronic infection was based on previous work which identified a specific serologic response to *S. maltophilia* in this group of patients [1]. It does not take into account, however, the number of respiratory cultures done per year. It is possible that sicker patients have more respiratory cultures taken, have more *S. maltophilia* detected as a result and chronic *S. maltophilia* status thus simply reflects a sicker patient population. Chronic definitions based on the percentage of positive cultures may therefore also be appropriate. However, the average number of respiratory cultures taken per year was similar in our three study groups. In addition, we did not do molecular typing on the *S. maltophilia* isolates as the isolates were not available due to the retrospective nature of the study. This limits our ability to state that these patients were truly chronically infected with the same clone of *S. maltophilia* over time. The study also had a limited number of patients with chronic *S. maltophilia* infection which may affect its power to identify risk factors for failing to recover FEV₁ [6]. However, the study was adequately powered to detect a minimum difference of 1.4% predicted in FEV₁ recovery between patients with chronic versus no *S. maltophilia* and for the effect of *S. maltophilia* antibiotic therapy, a difference of 0.1 in the slope for FEV₁% predicted and of 4 days in the slope for time to subsequent exacerbation, all clinically relevant minimum differences. In addition, this study analyzed repeated exacerbations which are not independent events and hence a generalized linear mixed model with an appropriate covariance structure was used to account for the longitudinal nature of the repeated data. Finally, antimicrobial susceptibility data for infecting *S. maltophilia* strains was not collected; it is possible that these strains were resistant to the antibiotics chosen to treat *S. maltophilia* during the exacerbation. However, the authors presume that antibiotics were chosen based on the most recent culture results and the role of sensitivity testing in chronic airway infection is being debated.

In conclusion, a significant proportion of CF patients do not recover their lung function following pulmonary exacerbation, particularly older, undernourished female patients infected with *B. cepacia* complex. CF patients with chronic *S. maltophilia* infection, however, are not at increased risk of lung decline after an exacerbation. In addition, currently used antimicrobial therapies directed at *S. maltophilia* during a pulmonary exacerbation do not appear to affect lung function recovery or time to subsequent exacerbation. Future clinical trials may be required to identify more effective therapies to prevent the increased rate of hospitalization seen in CF patients chronically infected with *S. maltophilia*.

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