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Original Article

Factors influencing the acquisition of *Stenotrophomonas maltophilia* infection in cystic fibrosis patients☆

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Abstract

Background: *Stenotrophomonas maltophilia* is one of the most common multi-drug resistant organisms causing pulmonary infections in CF patients. It is unknown whether *S. maltophilia* infection follows the same pattern and shares similar risk factors for acquisition as described for *Pseudomonas aeruginosa*.
Methods: We examined all clinical events from 1997 to 2008 in the Toronto CF Database to identify risk factors for the acquisition of *S. maltophilia* and to define distinct patterns of infection.
Results: We followed 601 patients over 12 years, during which time one quarter of subjects had at least one positive culture for *S. maltophilia*; the incidence rate was slightly higher in children (11.6/100 person years) compared with adults (10.6/100 person years). Using multi-variable Cox proportional hazards models, steeper rate of FEV_1 decline was a significant risk factor for *S. maltophilia* acquisition, whereas new infections were less likely to occur with greater oral antibiotic use and a history of *Burkholderia cepacia* complex infection.
Conclusions: This study illustrates the evolution of *S. maltophilia* infection over time in a large cohort of adults and children with CF. Younger CF patients, and those with greater lung function decline were at increased risk of *S. maltophilia* infection. The use of oral antibiotics to maintain lung function may be a way of decreasing the risk of infection. However, the optimal management of CF patients with persistent *S. maltophilia* infection is not yet known and requires further studies.

Keywords: *Stenotrophomonas maltophilia*; Epidemiology; Risk factors; Latent class models

1. Introduction

Despite improvements in survival over the past 20 years, the primary cause of death in CF is still respiratory failure secondary to chronic bacterial respiratory infection [1]. *Stenotrophomonas maltophilia* is one of the most common multi-drug resistant organisms causing pulmonary infections in CF patients [2,3]. We have recently demonstrated that chronic, but not intermittent,

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S. maltophilia infection in CF patients is associated with a specific systemic immune response to *S. maltophilia* and is an independent risk factor for hospitalization for pulmonary exacerbation [4]. The distinction between chronic and intermittent infection is important for other pathogens in CF as well; studies have shown that chronic methicillin-resistant *Staphylococcus aureus* (MRSA) and *Aspergillus fumigatus* infections are associated with clinical deterioration in CF patients [5,6].

To date, the evolution of airway infections with bacteria other than *Pseudomonas aeruginosa* is largely unknown. In the case of *P. aeruginosa*, CF patients are typically colonized with non-mucoid *P. aeruginosa* initially and if untreated, eventually develop chronic, mucoid *P. aeruginosa* infection that is very difficult to eradicate and is associated with clinical decline [7]. Risk factors for the development of mucoid *P. aeruginosa* infection in CF patients include female gender, number of delta F508 alleles, decreased lung function and lack of *S. aureus* on sputum culture [8]. Whether *S. maltophilia* infection follows the same pattern as described for *P. aeruginosa* and shares similar risk factors remains to be defined.

S. maltophilia infection is often considered to affect primarily older CF patients with more advanced lung disease [9]. However, recent studies describing high rates of *S. maltophilia* infection in pediatric CF patients highlight our lack of knowledge of this infection in the younger population [10]. Previous studies examining risk factors for *S. maltophilia* have found antibiotic use and poorer clinical status to be significantly associated with the presence of infection [6,11–13]. These previous studies have been limited to retrospective study designs where subjects were classified as ever positive for *S. maltophilia* infection, which may miss the complexity related to the acquisition of first infection, or subsequent infection patterns. Furthermore, it is also unclear whether current antimicrobial treatment directed against *S. maltophilia* alters the course of *S. maltophilia* infection in CF [6,11–13].

The aims of this study were thus to 1) determine the risk factors for initial acquisition of *S. maltophilia*, 2) characterize the patterns of *S. maltophilia* infection and 3) determine how clinical outcomes differ between the groups identified.

2. Materials and methods

2.1. Subject population and data collection

Pediatric and adult CF patients followed at Toronto CF clinics from 1997 to 2008 were included in the study (n = 751). Data were collected from the Toronto Cystic Fibrosis Database as previously described [14]. Patients were excluded if they were too young to perform spirometry (n = 38), if they were unable to produce sputum (approximately 9% of microbiology samples were excluded) or if they had received a lung transplant (n = 88). Subjects with a positive culture prior to 1997 were excluded for these analyses (n = 24). This study was approved by the Research Ethics Board at the Hospital for Sick Children (REB# 1000013759) and St Michael's Hospital (REB# 09-087c).

2.2. Definitions of variables

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 [15,16]. Antibiotic use was divided into terciles of cumulative number of courses of 1) non-ciprofloxacin oral antibiotics, 2) oral ciprofloxacin, and 3) intravenous antibiotics. Inhaled antibiotics were classified as 1) never, 2) intermittent and 3) chronic, and defined as more than 365 consecutive days of treatment. In adults body mass index (BMI) was categorized as normal (BMI > 18 and ≤ 25), underweight (BMI ≤ 18) and overweight (BMI > 25); in children, BMI centiles were calculated based on the CDC 2000 reference charts, underweight was defined as a BMI centile ≤ 12, normal (BMI centile > 12 and < 85) and overweight (BMI centile ≥ 85). Forced expiratory volume in 1 s (FEV_1) values were corrected for height, age and sex and analyzed as percent predicted and z-scores [17]. Thereafter FEV_1 was summarized as 1) baseline visit (i.e. first visit after January 1, 1997), 2) FEV_1 at the time of initial *S. maltophilia* acquisition and 3) the rate of FEV_1 change over the observation period determined for each subject. For patients with positive *S. maltophilia* cultures, the rate of decline was calculated for the period before the acquisition of *S. maltophilia* (baseline to first positive culture) and for the period after acquisition (first positive culture to end of follow-up period). A pulmonary exacerbation was defined, previously, as a hospitalization for respiratory symptoms requiring intravenous antibiotics [4]. Previous infection with *P. aeruginosa* was classified according to the Leeds criteria (never, ≤ 50% of cultures/year and > 50% of cultures positive/year). *Burkholderia cepacia* complex, *Haemophilus influenzae*, *S. aureus* and *Aspergillus* (identified as a risk factor for *S. maltophilia* acquisition in previous studies [6]) infections were classified as ever positive based on any positive culture prior to the first culture of *S. maltophilia* or the last follow-up date. MRSA infection was not included due to its low prevalence in the CF population in Canada and in our center [18,19]. All microbiology data was based on culture results from sputum or bronchoalveolar lavage samples.

2.3. Statistical analysis

Baseline characteristics were compared using non-parametric t-test (Mann–Whitney) for continuous variables and chi square test for categorical variables. Baseline characteristics for the cohort were defined from each subject's first year of observation. Cox proportional hazards survival models were used to identify univariable risk factors for initial *S. maltophilia* infection during the 12 year observation period. Subsequently, multivariable Cox proportional hazards survival models were fitted for any risk factors found to be significant or marginally significant on univariable analysis ($P < 0.15$) and those with strong a priori hypothesis (e.g. age, sex) for the same time period. A step-wise approach was used to calculate hazard ratios (HR), with 95% confidence intervals (CI), for the time to first respiratory specimen (sputum or bronchoalveolar lavage sample) positive for *S.*