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Original Article

The changing prevalence of pulmonary infection in adults with cystic fibrosis: A longitudinal analysis

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Abstract

Background: Increased patient longevity and aggressive antibiotic treatment are thought to impact on the microbial composition of the airways of adults with cystic fibrosis (CF). In this study, we sought to determine if a temporal change in the airway microbiology of adults with CF has occurred over time.
Methods: Longitudinal analysis of sputum microbiology results was undertaken on patients attending a large adult CF centre. Clinical status and health outcomes of transitioning patients were also assessed.
Results: A decrease in the prevalence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacia* complex and Aspergillus spp. ($p = 0.001$, $p < 0.001$, $p = 0.002$ and $p < 0.001$, respectively) occurred. Improvements in lung function among transitioning patients infected with *P. aeruginosa* were observed.
Conclusion: Overtime, a decline in the prevalence of many CF airway pathogens has occurred. Significantly, an incremental improvement in lung function was reported for transitioning patients with current *P. aeruginosa* infections.

Keywords: Paediatric; Lung function; *Pseudomonas aeruginosa*; Transition; Prevalence

Abbreviations: BMI, Body mass index; CF, Cystic fibrosis; CFRD, Cystic fibrosis-related diabetes; CFTR, Cystic fibrosis transmembrane conductance regulator; CI, Confidence interval; FEV_1% predicted, Forced expiratory volume in one second; FVC % predicted, Forced vital capacity; IQR, Interquartile range; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; NTM, Nontuberculous mycobacteria; RCH, Royal Children's Hospital; TPCH, The Prince Charles Hospital.

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1. Introduction

Cystic fibrosis (CF) is a multisystem disease, in which a great burden of the morbidity and mortality results from chronic suppurative lung disease. Pathophysiologically, the disease is characterised by dehydration of the airway surface liquid, elevated mucus production and increased susceptibility to infections [1,2]. A number of microorganisms are associated with CF airway infections, the prevalence of which varies according to patient age [1,3,4]. *Haemophilus influenzae* and methicillin-sensitive *Staphylococcus aureus* (MSSA) are frequently the earliest pathogens isolated in children and this is often [5–7] followed by *Pseudomonas aeruginosa* [1,3,4]. Early infection in children can progress to a chronic infection where eradication cannot be achieved. Thus, early treatment aims to prevent or delay the time to chronic infection. Aggressive antibiotic therapy is recommended at the time of *P. aeruginosa* acquisition and is usually successful in achieving initial eradication [8–10]. Programs aimed at eradicating early *P. aeruginosa* infection have been widely adopted over the past two decades with rates of *P. aeruginosa* infection progressively declining in young people especially in children and adolescents with CF [7,11–13]. It is less clear what impact these early changes are having on adult populations on rates of *P. aeruginosa* and other pathogens such as nontuberculous mycobacteria (NTM) infection, methicillin-resistant *S. aureus* (MRSA) and emergent bacteria (*Stenotrophomonas maltophilia* and Achromobacter spp.) [6,7,13–16].

P. aeruginosa remains the most prevalent microorganism isolated from adults with CF [4,6,7,13–16]. Once established, *P. aeruginosa* infections are difficult to eradicate and classically have been associated with accelerated lung function decline and poorer survival [17]. Several studies have defined the term chronic infection to provide a basis for diagnosing persistent infection [18,19]. Despite the ongoing debate about a strict definition to describe chronic *P. aeruginosa* infection, this term is now widely used including in some CF Data Registries to stratify infection status. Clinically, this definition may guide the physician in determining a therapeutic approach for the patient. However, the utility of these definitions in clinical practice is limited by the inability of some patients to provide sufficient sputum samples within a given time period, inadequate sample quality and limited follow-up review. Furthermore, such criteria are yet to be validated in adults with CF.

The aims of this study were to determine the prevalence of infection in an adult population of patients with CF and to assess the utility of the Leed's criteria in adults within a clinical setting to define chronicity of *P. aeruginosa* [18]. We were particularly interested in the clinical and microbiological characteristics of young adults at the time of transition to adult care, to determine if changes had occurred during the modern era of eradication therapy.

2. Methods

2.1. Study population

All patients with CF attending The Prince Charles Hospital (TPCH) Adult CF Centre located in Queensland, Australia, between 1st January 2001 and 31st December 2014 were included in the study. Clinical measurements were excluded following transplantation. The centre provides care for Queensland, the Northern Territory and northern New South Wales adults with CF, with national standards of care recommending a minimum of four multi-disciplinary outpatient reviews per year [20].

In 2013, there was a median of six (interquartile range [IQR]: 2–11) outpatient attendances at TPCH Adult CF Centre. Sputum samples were collected at each review and at the beginning and completion of all intravenous antibiotic treatment courses (inpatient and or hospital-in-the-home). Expectorated sputum was primarily collected with induced sputum sampled in selected non-productive patients with unexplained clinical decline (total 3260 samples from 469 patients). Induced sputum samples were unable to be differentiated from expectorated sputum as both were coded in the same way. Bronchoscopy samples were rarely collected and usually when unexplained clinical decline had occurred. During the study period, 51 bronchoscopic samples (bronchoalveolar lavage and bronchial washings) from 34 patients were collected representing 1.5% of the total samples submitted for culture. The sampling frequency from bronchoscopy samples did not change over time. Upper airway samples for bacteriological analysis were not routinely performed. This study was approved by TPCH, Human Research Ethics Committee (HREC/13/QPCH/51).

2.2. Sample collection and microbiological analysis

Only expectorated sputum sample results were included in this study. Sputum culture and microbiological identification was undertaken by a routine diagnostic laboratory using a combination of best practice standard phenotypic and molecular techniques [21]. Apart from the introduction of bacterial identification using the bioMerieux VITEK® MS (Mass spectrometry microbial identification system) in 2011, all other isolation and identification techniques remained consistent.

All fungal species reported were grown on routine bacterial culture media and specific NTM testing using standard solid, and liquid culture media for mycobacteria were undertaken in the Mycobacterial Reference Laboratory when requested by the treating physician (i.e., annually, when clinically suspected or when NTM had previously been cultured).

2.3. Microbiological and clinical data collection

Sputum microbiology results were obtained electronically from the Pathology Queensland Clinical and Scientific Information System (AUSLAB). In the first instance, clinical data were obtained from the TPCH CF patient database and hospital medical records, and if unavailable, information from either the Australian CF Data Registry or the referring CF centre at the time of transition were used. Notably, centres enter clinical and microbiological data into the Australian CF Data Registry on an encounter-basis allowing the capture of all sputum samples collected in each year. Of the 217 transitioning patients, sputum microbiological results were obtained from letters provided at the time of health-care facility transition (n = 6), the Australian CF