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Original Article

The association between *Staphylococcus aureus* and subsequent bronchiectasis in children with cystic fibrosis

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Abstract

Background: Staphylococcus aureus (*S. aureus*) may be related to more rapid progression of cystic fibrosis (CF) lung disease.
Methods: In the AREST CF cohort study, children diagnosed with CF undergo annual bronchoscopies with bronchoalveolar lavage and ultra-low-dose, chest computed tomography (CT) up to 6-years-old. Spirometry was assessed 3-monthly from the age of 4 years. Associations between de novo *S. aureus* acquisition before school age and CT and lung function at ages 5–7 years were investigated. Models were adjusted for multiple markers of disease severity at baseline.
Results: De novo *S. aureus* acquisition at 3-years-old (n/N = 12/122) was associated with increased bronchiectasis score at age 5–6 years. This association decreased but remained significant after adjustment for confounders. *S. aureus* at 3 was associated with significantly reduced $FEF_{25–75}$ at age 5–7 years, but not with FEV_1-%-predicted.
Conclusion: De novo *S. aureus* acquisition at age 3 is associated with later bronchiectasis and $FEF_{25–75}$ in children with CF.

Keywords: CT scan; Structural lung damage; Infection and inflammation; Lung function

1. Introduction

Features of cystic fibrosis (CF) lung disease are inflammation and chronic pulmonary infection. *Staphylococcus aureus* (*S. aureus*) has been identified as one of the earliest and most common bacterial pathogens in airways of children with CF [1,2]. The deleterious effect of chronic *P. aeruginosa* infection on pulmonary structure and function has been repeatedly described, but knowledge of the impact of other pathogens, particularly *S. aureus*, in the development of early CF lung disease is lacking [2,3]. Consequently there is no international consensus on the need for *S. aureus* prophylaxis or eradication, even if the organism is detected in the lower airways.

There are in vitro and in vivo data showing an association between *S. aureus* and airway inflammation [4–6], reduced lung

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function [7,8] and reduced nutritional status [9]. Therefore, despite a lack of evidence for a causal role, pulmonary infections with *S. aureus* are generally believed to contribute to the cycle of infection, inflammation and destruction of lung tissue. Previous intervention trials using prophylactic anti-staphylococcal antibiotic treatment have not shown any positive effects on clinical outcomes in infancy or up to the age of 6 years [10–12]. Importantly, the spirometry outcomes used in these studies have repeatedly been demonstrated to be less sensitive for detecting early CF lung disease than chest CT scans [13].

The Australian Respiratory Early Surveillance Team for cystic fibrosis (AREST CF) surveillance program is a birth cohort of CF patients in Melbourne and Perth, with annual bronchoalveolar lavage (BAL) and CT scans up to the age of 6 years. Using these data we aimed to investigate the complex associations between lower airway *S. aureus* infections in early life and the later development of CF lung disease, taking into account the possible underlying pathophysiologic pathways. We hypothesised that newly acquired *S. aureus* infection in infants and young children with CF is not merely a marker for underlying CF disease severity, but an important independent factor for disease progression as reflected in later chest CT scan and/or spirometry. An important clinical implication of this would be that a more aggressive treatment of *S. aureus* may be indicated, possibly including eradication strategies as currently advised for *P. aeruginosa*.

2. Methods

2.1. Study population

The AREST CF program operates in the Royal Children's Hospital, Melbourne and Princess Margaret Hospital, Perth, Australia. Upon detection at new-born screening or presentation of symptoms suggestive of CF, a sweat test is conducted to confirm the diagnosis [14]. The surveillance program commences at 3 months of age and annually thereafter up to the age of 5 years (Melbourne) or 6 years (Perth). Since 2005, this program includes an annual bronchoscopy with BAL and ultra-low-dose chest computed tomography scan (CT) performed under general anesthesia. Assessment of clinical spirometry is attempted every 3 months in CF children starting at the age of 4 years. The current study used data collected in children born between 2005 and 2016. More detailed descriptions of the study protocol have been published previously [15,16] and the relevant routines have not changed since.

2.2. Data collection

In the program, baseline perinatal data are collected retrospectively at enrollment. At each 3-monthly clinic visit, questionnaire data are collected on respiratory symptoms and medication use. BAL is performed at 3 months, 1 year and yearly thereafter under general anesthesia. BAL fluid is sent for microbial cultures and analyses of inflammatory markers.

2.3. Outcome variables

The main outcome variable was defined as CF-CT bronchiectasis score at 6 years if available, or at 5 years otherwise. Volume-controlled, volumetric or limited slice chest CT images are obtained under anesthesia before BAL is performed, with images at end inspiration (trans-respiratory pressure = 25 cmH_2O) and end expiration (trans-respiratory pressure = 0 cmH_2O) as described previously [16]. If the CT was missing at both 5 and 6 years the outcome was considered missing. A simplified CF-CT scoring method was used [15,17]. Of the children with a CT scan available at age 5 or 6 years 85% had a full volumetric scan available, in the remaining 15% results from limited slice CT scan were used.

Spirometry is performed according to international guidelines on a 3-monthly basis when the child is able to achieve acceptable and repeatable measurements [18]. Results were expressed as %-predicted calculated using the Global Lung Initiative reference equations, the validity of which has been verified in the Australian population [19,20]. Measurement with the highest recorded FEV_1-%-predicted were selected from each year.

2.4. Exposure and confounder variables

The primary exposure variable was defined as de novo (i.e. first time) acquisition of *S. aureus* from BAL culture, regardless of culture density. Possible confounding and/or preceding factors included: CF-CT bronchiectasis, air trapping and bronchial wall thickening scores in previous year; homozygous Delta508 gene abnormality, pancreatic insufficiency & meconium ileus at baseline; BAL markers for inflammation in previous year (neutrophil elastase and interleukin 8); and positive BAL bacterial cultures for other bacteria (including *P. aeruginosa*) in previous years. Medication use was assessed by parental report, but those results were not available for the entire study period. During the study entire period it was standard practice at both centres to prescribe amoxicillin/clavulanate prophylaxis during the first two years of life. Prophylaxis could be continued beyond 2 years of age at the physician's discretion.

2.5. Statistical analysis

Statistical analyses were conducted using STATA version 14.0 (StataCorp). Associations between de novo *S. aureus* and bronchiectasis score were analysed using linear regression. In order to reduce the risk of reverse causation and confounding, previous *S. aureus* infections were excluded and associations were adjusted for markers of disease severity at time of de novo *S. aureus* acquisition. Multiple imputation was used for the multivariate analyses to avoid selection bias due to missing data on confounder variables (see Fig. S1 in online supplement for flowchart), using the multivariate normal regression procedure (mi impute mvn) in STATA 14.0 (creating 100 imputed datasets). Associations between *S. aureus* and repeated measures of spirometry were assessed using linear mixed models.

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