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Original Article

Pneumococcal polysaccharide vaccine responses are impaired in a subgroup of children with cystic fibrosis

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Abstract

Background: Pneumococcal immunization is recommended in children with cystic fibrosis (CF). To date, however, there are no published studies on the efficacy of pneumococcal vaccination in this group of patients.
Methods: We carried out a retrospective study of serotype-specific pneumococcal antibody responses to immunization with Prevenar 7 and Pneumovax II in a cohort of children with CF.
Results: Nine children had been immunized with Prevenar 7, and all had serotype-specific pneumococcal antibody levels in the protective range (>0.35 mg/L) to all 7 immunizing serotypes. In contrast, only 7 of 33 patients (21%) immunized with Pneumovax II made protective antibody responses to all 7 serotypes, and 3 failed to make protective antibodies to any of the serotypes. Controlling for age as a confounder in the analysis, children with impaired antibody responses to pneumococcal polysaccharide (Pneumovax II) immunization had lower Shwachman–Kulczycki scores than children with normal polysaccharide antibody responses. All isolates of *Pseudomonas aeruginosa* occurred in patients with impaired anti-pneumococcal antibody responses, and a broader range of respiratory pathogens was isolated from these children.
Conclusions: Impaired antibody responses to immunization with Pneumovax II are common in children with CF and this may be associated with increased disease severity.

Keywords: Cystic fibrosis; Pneumococcus; Vaccine; Vaccination; Antibody; Polysaccharide

1. Introduction

Cystic fibrosis (CF) lung disease is characterized by a progressive decline in lung function, due to recurrent exacerbations of lower respiratory tract infections. Bacteria like *Staphylococcus aureus* and *Haemophilus influenzae* cause most of the early respiratory tract infections, before *Pseudomonas aeruginosa*

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; ELISA, enzyme linked immunosorbent assay; FEV_1, forced expiratory volume in one second; Ig, immunoglobulin; S–K, Shwachman–Kulczycki.

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becomes the predominant pathogen [1–3]. *Streptococcus pneumoniae* is rarely isolated from CF sputum and therefore its pathogenic role in CF is controversial. The prevalence of *S. pneumoniae* in the CF respiratory tract may however be underestimated, as the organism is difficult to isolate from sputa often heavily infected with other organisms [4,5].

Pneumococcal immunization of patients with CF is recommended by the European Cystic Fibrosis Society Vaccination Group [5], the American Academy of Pediatrics [6], and the UK Health Protection Agency [7]. Vaccination with polysaccharide vaccines confers only transient immunity and revaccination has been recommended by the European Cystic Fibrosis Society Vaccination Group every 3–5 years in patients with a more rapid decline in antibody titres and those of increased risk for invasive disease [5]. However, there are no published studies on the efficacy of pneumococcal vaccination in children or adults with CF [8]. Impaired immunoglobulin production has been described in a subgroup of children with CF [9–12]. It is important therefore to establish whether children with CF mount normal antibody responses to immunization against pneumococcus.

To evaluate the efficacy of pneumococcal vaccination, we conducted a retrospective analysis of antibody responses to vaccination in children with CF attending our CF centre.

2. Materials and methods

2.1. Subject population and study design

All of the children included in the study had a diagnosis of CF, confirmed by sweat testing and/or the presence of two disease-causing mutations in the *CFTR* gene. The data for this retrospective, cross-sectional study were extracted from University Hospitals of Leicester NHS Trust databases. The data used were obtained at an annual review between June 2009 and May 2010. The FEV_1% predicted was assessed by standard spirometry following ATS/ERS guidelines [13], and BMI-z scores were calculated from height and weight values. The chest radiograph Northern score [14] was assigned by a consultant paediatric radiologist, and Shwachman–Kulczycki (S–K) scores (based on a combination of scores for general activity, physical examination, nutrition, and chest radiograph findings) were calculated for each child [15]. Clinicians assigning Northern scores and S–K scores were blinded to the result of the pneumococcal antibody responses to immunization. Airway microbiology was reviewed for the 12 month study period. Review and anonymized use of patient clinical data were approved by the East Midlands Research Ethics Committee, reference number 12/WM/0285.

2.2. Pneumococcal antibody testing

Serotype-specific pneumococcal antibody titres were measured to the 7 serotypes of pneumococcus present in both Prevenar 7 and Pneumovax II (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), plus a further 6 serotypes included in Pneumovax II but not Prevenar 7 (serotypes 1, 3, 5, 7F, 8 and 19A), using a multiplex fluorescent bead assay (BioPlex Protein Array System, BioRad Laboratories, Hercules, CA), as described by Willcocks *et al.* [16]. The Food and Drug Administration (FDA) standard reference serum (89SF) was used as calibrant in validating the serotype-specific anti-pneumococcal antibody levels.

2.3. Pneumococcal vaccines and criteria used to assess antibody responses

Two pneumococcal vaccines are available in the UK: Pneumovax II, an unconjugated polysaccharide vaccine incorporating capsular polysaccharide from 23 pneumococcal serotypes; and Prevenar, incorporating capsular polysaccharide antigens from 7 serotypes (prior to 2010; 13 serotypes after 2010) conjugated to a protein carrier molecule (diphtheria toxoid). Prevenar has been included in the childhood vaccination schedule in the UK since 2006. Serotype-specific pneumococcal antibody levels >0.35 mg/L are considered by the WHO to represent protection against invasive pneumococcal infection [17]. In line with the recommendations for pneumococcal immunization [5–7], we routinely measure pneumococcal antibody levels at the CF annual review. Where antibody levels are deemed inadequate, we recommend booster immunization with Pneumovax II in children >2 years, with post-immunization pneumococcal antibody testing four to six weeks following the immunization. An adequate response to immunization is taken as a post-immunization titre >1.3 mg/L, in accordance with a recent American Academy of Allergy, Asthma and Immunology (AAAAI) guideline [18]. Patients aged two to five years are expected to achieve this antibody level to 50% or more of the immunizing serotypes, and patients six years or older should achieve this target antibody level to 70% or more of the immunizing serotypes tested [19,20].

2.4. Other laboratory tests

Serum immunoglobulins and IgG subclasses were measured on a BNII nephelometer (Dade Behring, UK). Age related normal ranges were applied. Specific antibodies to tetanus toxoid and Hib were measured by commercial ELISA (Binding Site, UK). All laboratory tests of immune function were carried out in accordance with the test manufacturers' protocols in diagnostic immunology laboratories that were accredited by Clinical Pathology Accreditation (CPA) UK. Microbiological testing was performed by the Department of Microbiology, University Hospitals of Leicester NHS Trust, following guidelines issued by the CF Trust [21]. *Pseudomonas* status was defined in line with Lee *et al.* [22].

2.5. Statistical analysis

All data were entered into a secure Excel database (Microsoft, Redmond, WA) and analysed using GraphPad (version 3.02; GraphPad Software Inc., La Jolla, CA) or Stata Statistical Software (release 11, 2009; StataCorp LP, TX). Descriptive statistics were used to describe cystic fibrosis patients and results of immunological and microbiological tests. Geometric means (with 95% confidence intervals) were calculated for serotype-specific pneumococcal polysaccharide antibody levels. Mann–