Children with Recurrent Upper Respiratory Infections and Impaired Pneumococcal Polysaccharide Responsiveness; Clinical and Serologic Response to the 23-Valent Polysaccharide Pneumococcal Vaccine (Pneumovax®).

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Introduction

Adequate pneumococcal prophylaxis continues to be a moving target.[1,2] Introduction of Prevnar® (PCV7, Wyeth Lederle Vaccines, Madison, NJ), a 7-serotype pneumococcal conjugated vaccine, in 2000 significantly decreased the incidence of invasive pneumococcal infections and increased herd protection worldwide. However, increasing prevalence of non-PCV7 pneumococcal serotypes and drug resistant serotypes led to the development and recent introduction of Prevnar13® (PCV13, Wyeth Lederle Vaccines, Madison, NJ) that includes 6 additional pathogenic pneumococcal serotypes. The long-term effects of PCV13 on pneumococcal disease incidence and herd protection are unknown. Pneumovax®, (PPV23 Merck Vaccines, Whitehouse, NJ), another pneumococcal vaccine available since 1977, consists of a mixture of purified capsular polysaccharides from the 23 most prevalent and invasive types of *Streptococcus pneumoniae* including the serotypes present in PCV13. PPV23 is currently indicated in children aged 2-18yrs with underlying medical conditions such as asplenia or HIV. PPV23 is also indicated for pneumococcal prophylaxis in adults. The clinical and serological response to PPV23 in patients with recurrent upper respiratory infections and pneumococcal antibody deficiency have been known for the last 30 years. There is, however, no information concerning the use of PPV23 in children and adolescent with recurrent respiratory infections and pneumococcal antibody deficiency despite appropriate immunization with PCV7.

Materials and Methods

Patient Population

We did a retrospective analysis of 72 patients between 2 and 25 years of age, referred to our subspecialty clinic for evaluation of recurrent respiratory infections between 12/2002 and 1/2011. The following data was gathered: sex, age, ethnicity, type and frequency of respiratory infections, medical and surgical history, family medical history and immunization record to PCV7. Blood was drawn for IgG and IgG subclasses, IgA, IgM, IgE levels; pneumococcal, *Haemophilus Influenzae* type b, tetanus, and diphtheria antibody titers. Institutional review board approval was obtained prior to the study.

Assessment of Clinical Response

Frequency and type of respiratory infections were documented at first visit. Patients with four or more upper respiratory infections treated with antibiotics per year; 4 or more acute otitis media episodes treated with antibiotics per year, or 2 or more episodes of sinusitis per year fulfilled the criteria for recurrent URI's and were included in the study. Most patients had a combination of recurrent otitis media and rhinosinusitis. Changes in frequency, type and severity of infections were recorded at first and subsequent visits for 6 months after administration of PPV23. A clinical response was considered positive if the parents reported complete resolution of the infections or more than 50 per cent decrease in the frequency according to the above criteria.

Pneumococcal Antibody Testing and Response

All patients had a 12-14 serotype pneumococcal antibody panel drawn to assess their pneumococcal antibody status as part of the initial evaluation. The pneumococcal antibody titers for each of the serotypes were analyzed by enzyme-linked immunosorbent assay (ELISA) for anti-pneumococcal IgG by a reference laboratory. The antibody levels were considered protective if the specific IgG titer was more or equal than 1.3 micrograms/ml in at least 50% of the serotypes in children 2 to 5 years of age, and in more than 70% of children older than 6 years of age. Based on these criteria, patients with nonprotective pneumococcal antibodies levels were given a dose of PPV23. A positive IgG antibody response to a given serotype was defined as a postimmunization antibody concentration of 1.3 micrograms/ml or greater, or a fourfold increase over the preimmunization value. Written parental consent for treatment was obtained prior to PPV23 administration. In order to assess the serological response, pneumococcal antibody levels were drawn at approximately 1, 3 and 6 months post immunization.

Patient characteristics

Measure	Number (%)
Age (years)	
2 – 5	41 (57)
> 6	31 (43)
Sex	
Females	26 (36)
Males	46 (64)
Ethnicity	
Caucasians	31 (43)
Hispanics	36 (50)
African American	5 (7)
Type of Infections[a]	
Otitis Media	48 (67)
Rhinosinusitis	71 (98)
Pharyngitis	18 (25)
Bronchitis	5 (7)
Pneumonia	3 (4)
Comorbidities	
Asthma	22 (30)
Allergies	8 (11)
Atopic Dermatitis	2 (3)
Surgical Procedures	
Myringotomy tubes	18 (25)
T&A	11 (15)
Sinus	5 (7)
PCV7	
3 – 4 doses	45 (62)
None	27 (37)

Abbreviations: T&A, Tonsillectomy and Adenoidectomy. [a] Patients presented with one or combinations of the various types of recurrent infections.

Results

Pre Immunization Antibody levels	N of Patients (%)
Non-Protective	64 (89)
Low-Range Protective	8 (11)
Antibody Response	
Protective	60 (83)
Partial	12 (17)
Clinical and Serological Response	
Positive Clinical Response	69 (96)
Positive Clinical Response with Partial Serology	12 (17)
No Clinical Response despite Protective Serology	3 (4)
Patients 2 – 5 Years of Age	41 (57)
Positive Clinical Response with Protective Serology	36 (88)
Positive Clinical Response despite Non-Protective Serology	2 (5)
No Clinical Response despite Protective Serology	3 (7)
Patients 6 Years and older	31 (43)
Positive Clinical Response with Protective Serology	21 (68)
Positive Clinical Response despite Non-Protective Serology	10 (32)
Patients Given PCV7 (3 – 4 doses)	45 (62)
Positive Clinical Response with Protective Serology	37 (82)
Positive Clinical Response despite Non-Protective Serology	5 (11)
No Clinical Response despite Protective Serology	3 (7)
Non-Prevnar Group	27 (37)
Positive Clinical and Serological Response	20 (74)
Positive Clinical Response despite Non-Protective Serology	7 (26)

Results

In this retrospective, descriptive study, we report the clinical and serological response to PPV23 in 72 children and teens seen in our clinic for evaluation of recurrent upper respiratory infections, who had evidence of pneumococcal antibody deficiency and normal immunoglobulins levels, IgG subclasses and responses to protein antigens. Forty-five (63%) of these patients had received PCV7 as part of their immunization schedule. Administration of PPV23 benefited 69 of the 72 patients (96%) with resolution of the infections in most cases including the 27 patients (37%) who did not receive PCV7. The positive clinical effect was most evident during the first 6 months after administration of PPV23. In 60 patients (83%) the clinical response was associated with a protective antibody response according to the criteria outlined above while 12 patients had a positive clinical response despite nonprotective serology (Table 2). Pneumococci frequently causing otitis media include serotypes 6B, 14, 19A and 23F, which are the same serotypes found to have developed resistance to antibiotics in the United States and elsewhere. These serotypes are included in the PPV23, which may explain the positive clinical and serological responses seen in our patients. Eleven per cent (5/72) of our patients had clinical improvement after PPV23 despite nonprotective serology while 3 patients (7%) had no apparent clinical response to PPV23 despite protective serology (Table 2). The infections in these patients may have been due to pneumococcal serotypes other than the 12 to 14 that we were able to measure.

Conclusions

Despite vaccination with PCV7, many children still suffer from recurrent acute otitis media, rhinosinusitis, bronchitis and pneumonia due to *Streptococcus pneumoniae*. Increasing prevalence of non-PCV7 pneumococcal serotypes and drug resistant serotypes have been implicated. It is expected that the new vaccine PCV13 will overcome these issues. There is, however, a group of patients who are unable to develop a normal response to pneumococcal and_other polysaccharides. Prior to the introduction of PCV7, it was estimated that approximately 5 to 10% of patients over 2 years of age who presented with recurrent respiratory infections belonged to this group.

Since polysaccharide non-responsiveness may be a feature of a variety of systemic illnesses and other immunodeficiency disorders, the term SADNI or selective antibody deficiency with normal immunoglobulins is currently used to characterize patients older than 2 years of age with recurrent upper respiratory infections in which polysaccharide non-responsiveness is the only identifiable immunological abnormality. Prior to the introduction of PCV7, SADNI was the most frequently identified immunodeficiency in patients with recurrent upper respiratory infections. The syndrome of specific antibody deficiency is defined using the combined response to all the serotypes tested. Normal children between 2 and 5 years of age are expected to have an adequate response to at least 50% of serotypes tested, while older patients should respond to at least 70% of serotypes tested.

Only 17 percent of our patients (12/72) can be characterized as having SADNI since they generated protective antibody titers to fewer than the expected numbers of serotypes for their age group after administration of PPV23; two patients in the 2 to 5 years of age group and 10 in the older than 6 years of age group were poor responders. Notwithstanding, the two patients in the 2 to 5 years of age group and the 31 patients in the older than 6 years of age had positive clinical responses including the 10 patients who were poor serological responders.

Our study showed that despite appropriate immunization schedules with PCV7, there is still a population of children who are seen frequently in the pediatrician's office for recurrent otitis media and sinopulmonary infections. They receive multiple courses of antibiotics per year and many of them undergo surgical procedures including placement of ear tubes, tonsillectomies and adenoidectomies, and sinus surgery with little or no relief. The poor responders to PCV7 can be identified by measuring their pneumococcal antibody titers, preferably the 14 serotype panel, which is commercially available. Children with evidence of impaired pneumococcal responsiveness and otherwise normal antibody responses should receive a dose of PPV23. Clinical and serological responses should be evaluated 4 to 6 weeks from immunization. Children who fail to respond to PPV23 may have the immunodeficiency known as SADNI and may benefit from other treatment options such as monthly infusions of gammaglobulin.

Our data is relevant due to the high cost of pneumococcal prophylaxis with the new conjugated pneumococcal vaccines. Inclusion of PPV23, a much more affordable vaccine, in the routine pneumococcal immunization schedule of children, and its use in the treatment of children with recurrent upper respiratory infections despite PCV7 and PCV13, should be considered.

Selected references

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