Poster #368

Phenotypes of Recurrent Wheezing in Young Children

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Abstract

RATIONALE:
Nearly 25% of preschool children have recurrent wheezing. Early identification of those who are at higher risk for exacerbations and respiratory infections is key.
METHODS:
To investigate early-onset wheezing in children aged 24-72 months, a review from a 7-year period in an asthma specialist clinic was performed. Criteria included presence of recurrent wheezing with a recent history of >2 systemic steroids (OCS) bursts per year and/or ≥3 courses of antibiotics (ABX) per 6 months. Both OCS and ABX treatments were for wheezing exacerbations prescribed by their PCP/ER staff. Patient characteristics and labs were collected, and questionnaires were sent to families to document subsequent use of OCS or ABX.
RESULTS:
Of 101 children (mean 51 months, 59% male) studied, 43% had >2 OCS/yr and 57% had ≥3 ABX/6months. At baseline, mean serum eosinophils was 233/uL, total IgE was 102 kU/L, and only 2 normal antibody titers to S. pneumoniae were present. Post-vaccination pneumococcal titers were responsive with 14 titers normalized. Other characteristics were presence of positive allergen sensitization 45%, eczema 39%, parental asthma 28%, and household pets 47%. Of 72 returned questionnaires, 82% responded with less bursts/use of OCS and ABX for wheezing exacerbations post-vaccination. Vaccine responder's baseline eosinophils was 215/uL, while non-responders were significantly higher at 370/uL. There was no significance in any other baseline values.
CONCLUSIONS:
Identification and vaccination for low pneumococcal titers in those with non-elevated eosinophil counts can reduce wheezing exacerbations. Higher eosinophil counts in young wheezers can identify those at higher risk for increased OCS and ABX use.

Introduction

Childhood asthma and wheezing are heterogeneous conditions with multiple phenotypes, arising from interactions between genetics, infections and environmental exposures. In children, 2-6 years of age, asthma phenotypes were originally classified into either transient early wheezing or persistent wheezing categories.[1]

Analysis of merged studies of preschool asthmatics have shown that with inhaled corticosteroid (ICS) treatment certain phenotypes reveal variations in the probability of exacerbations, which are divergent.[2] Phenotypes with minimal sensitization had more chances for asthma exacerbations with daily ICS use.

Early in life, certain microbiome compositions in respiratory flora are responsible for asthma exacerbations. Studies have shown that infants, who later had asthma, had an immune response to S. pneumoniae which increased IL-5 and IL-13 and decreased IL-17 and IL-10.[3] Further data in young children has shown that colonization with S. pneumoniae can contribute to the severity of asthma exacerbations with or without the presence of rhinovirus.[4]

In infancy, vaccination with PCV-13 initiated in 2010 in the US to replace the PCV-7 vaccine. But there is scant data on the immunogenicity of pneumococci in preschool asthmatics. Despite prior PCV vaccination, asthmatic children continue with a higher risk of invasive pneumococcal disease than their counterparts. Vaccine studies administering PPV-23 after PCV-13 showed improved antibody levels when boosted >10 months afterwards.[5] Recent recommendations from a meta-analysis of studies prior to 2011 suggested the need for supplemental PPV-23 vaccination in asthmatic children.[6]

We first proposed to evaluate the parent-report rate of exacerbation-prone preschool asthmatics with high frequency of antibiotic use and/or systemic steroid bursts. Secondly, we reviewed their baseline testing to attempt to elucidate phenotypic differences with varying outcomes in this age group.

Methods

Standard of medical care chart review and patient follow-up by phone/email with the family:

Inclusion Criteria:

- Documented history by clinician and parent of recurrent wheezing during past year
- Children, male or female, aged between 24 – 72 months of age
- Referral to allergy/asthma clinic by PCP or hospital between 2013-2019
- History of ≥ 3 steroid bursts (PO, IM) for wheezing exacerbations in the past year, and/or history of ≥ 6 antibiotic courses (PO, IM) for "infectious" wheezing in the past year
- Prior treatments based on prior diagnosis of asthma, pre-asthma, or reactive airways by PCP/ER
- Allergy specialist evaluation of allergen sensitivities and immune response

Exclusion Criteria:

- Systemic steroids within 4 weeks of evaluation
- Systemic antibiotics within 2 weeks of evaluation
- Steroid burst therapy for non-respiratory diseases
- Antibiotic treatment for non-respiratory etiologies
- Incomplete vaccination and immunization schedule during infancy
- Any known prior primary or secondary immunodeficiency

BASELINE

TOTAL COHORT		(n, SD)
Demographics		
	Number	101
	Age, mean months	51 (34-67)
	Males	59
	# CS use >3x/yr	44
	# Abx use >6x/yr	57
History		
	Parental asthma history	29
	Active or past eczema	39
	Presence of pets at home	47
Laboratory		
	WBC (x10 ^3/mcL)	9.1 (6.2-12.0)
	Eosinophils, serum (/mcL)	233 (81-385)
	Eosinophils, %	2.9 (0.8-5.0)
	IgG total (mg/dL)	799 (63-967)
	IgA total (mg/dL)	87 (49-125)
	IgM total (mg/dL)	96 (53-139)
	IgE total (IU/mL)	102 (5-229)
	S.pneumoniae titers (n >1.3mcg/mL)	2.4 (0.1-4.8)
Allergen Sensitivity		
	Positive PST/RAST food	33%
	Positive PST/RAST environment	27%

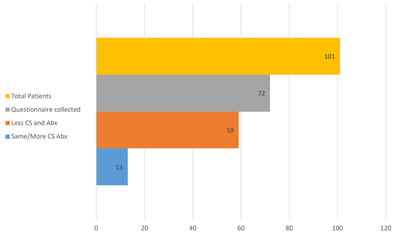
Results

Functional Antibody Responses

- All patients had incomplete or no response to Streptococcus pneumoniae despite prior completion of vaccine schedule with pneumococcal conjugate vaccine (PCV-13)
- Low titers were defined as (<1.3 mcg/mL) from S. pneumoniae functional antibody IgG response panel from Labcorp or Quest laboratories
- Mean number of antibody titers with response to PCV-13 was 2.4 ±2.3 (range 0-9)
- Baseline serotype titer responsiveness was most with serotype 23F and was lowest with Type 4
- All were administered a PCV-13 booster and/or PPSV-23, and a third had documented post-titer antibodies, which normalized to 14 ±5 (≥2 mcg/ml)
- Post-vaccination, no other markers were found to be different from their baseline measurements

Follow up questionnaire:

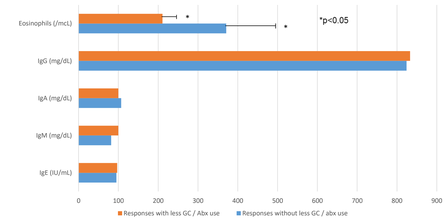
"Since your child's PCV/PPSV-23 vaccination, has he/she had (more, less, same)"
1. Number of infections, colds, and cough
2. Number of times treated with oral/IM steroids (i.e. prednisone)
3. Number of times treated with antibiotics

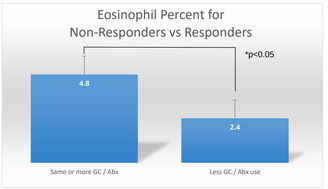


	RESPONDERS VS NON-RESPONDERS		
Demographics			
Age, mean months	54 +/-15	53 +/-17	n.s.
Males	60 %	75 %	n.s.
Positive PST/RAST	42 %	66 %	n.s.
Baseline (n, 95% C.I.)			
WBC (x10 ^3/mcL)	9.2 +/-2.8	9.1 +/-3.1	n.s.
Eosinophils, %	2.4 +/-0.4	4.8 +/-1.8	***p<0.05***
Eosinophils, serum (/mcL)	211 +/-36	371 +/-123	***p<0.05***
IgG total (mg/dL)	833 +/-173	814 +/-72	n.s.
IgA total (mg/dL)	91 +/-41	107 +/-41	n.s.
IgM total (mg/dL)	100 +/-46	86 +/-36	n.s.
IgE total (IU/mL)	97 +/-128	90 +/-82	n.s.
S.pneumoniae titers (n >1.3mcg/mL)	2.4 +/-0.6	4.1 +/-2.5	n.s.

Results

Serum total markers between responders and non-responders





Conclusions

- Young children with recurrent wheezing exacerbations which require frequent steroid bursts and/or antibiotics should be evaluated for low functional antibody responses in addition to asthma
- Despite prior complete vaccinations with PCV-13, this subset of young asthmatics with recurrent wheezing had poor antibody titer responses to S.pneumoniae
- Higher absolute eosinophil counts and percentages may distinguish those with atopic asthma that require closer monitoring from those with infection-induced wheezing and asthma
- By parental reporting, immunization with pneumococcal vaccine and the subsequent rise in antibody titers can reduce wheezing morbidity by decreasing systemic steroid bursts and antibiotic use
- Limitations of these results are that it is a retrospective review from one allergy/asthma clinic, and our future direction will be to perform this study prospectively with multiple study sites.

References

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