

ORIGINAL ARTICLE

The FACT score in predicting pneumococcal antibody levels in asthmatics

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Abstract

Background: There is no measure currently available to identify asthmatics with potential immune incompetence. **Objective:** We propose use of a novel scoring system called the FACT score, which is formulated based on four parameters: (1) Family history of asthma, (2) Atopic conditions, (3) Bacterial colonization and (4) Th1 versus Th2 immune profile. **Methods:** This was a cross-sectional study involving 16 asthmatics and 14 non-asthmatics. The first two parameters of the FACT score were obtained via a chart review and interview. For the third parameter, nasopharyngeal swab samples were cultured. The ratio of interleukin-5 to interferon-gamma for each patient was measured by peripheral blood mononuclear cells cultured with house dust mite. Antibodies to 23 pneumococcal antigens were used for humoral immunity. **Results:** The FACT scores for asthmatics (mean $\pm$ SD: 5.2 ± 1.87) were higher than those for non-asthmatics (mean $\pm$ SD: 3.3 ± 1.5) ($p = 0.008$). Of the 16 asthmatics, 7 (44%) had 12 or more positive serotype-specific polysaccharide antibodies, whereas 12 of 14 (86%) of non-asthmatics subjects had 12 or more positive serotype-specific polysaccharide antibodies ($p = 0.014$). Overall, the FACT score was inversely correlated with the number of positive serotype-specific antibody levels [ρ (p) = -0.38 , $p = 0.04$]. The proportions of subjects with 12 or more positive serotype-specific antibodies among non-asthmatics and asthmatics below and above the median of the FACT scores were 86, 50 and 38%, respectively ($p = 0.052$). **Conclusions:** The FACT score may help us identify a subset of asthmatics with immune incompetence. Study findings need to be replicated in a larger study.

Keywords

Asthma, epidemiology, FACT score, immunodeficiency, immunity, infection, pneumococcal

History

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Introduction

Streptococcus pneumoniae has a high morbidity and mortality worldwide. A recent CDC report estimated 40,000 cases and 4000 deaths due to *S. pneumoniae* in 2009 in the United States alone [1]. A study by Jounio et al. investigated 10 risk factors for microbial oropharyngeal carriage. They found that the only statistically significant risk factor for *S. pneumoniae* colonization was asthma [2]. It has been reported that up to 15% of children who acquire colonization with a new pneumococcal serotype develop infection within 2–3 days [3]. Furthermore, multiple studies have demonstrated an increased risk of invasive pneumococcal disease (IPD) in asthmatics [4–6]. The Advisory Committee on Immunization Practices (ACIP) now recommends a one-time immunization

with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) to those with asthma aged 19–64 years [7].

Individuals with asthma or other atopic conditions have been reported to have suboptimal humoral and cell-mediated immune functions [8,9]. For example, a previous study showed reduced vaccine responses to PPV23 in children with asthma [10]. We recently reported asthmatic patients have lower anti-pneumococcal antibody titers than non-asthmatics [6]. However, not all asthmatics have increased risk of infection or suboptimal immune responses. This raises the question, why do some asthmatics have increased risk of infections while others do not? There are a large number of factors that may potentially play a role. To address this question, we developed a scoring system to distinguish this particular subset of asthmatics.

Currently, there is no scoring system available to identify those asthmatics with potential immune incompetence. We hypothesized that a novel scoring system called the FACT score to help identify these individuals, which is calculated based on four parameters: (1) family history of asthma [8], (2) atopic conditions other than asthma [11], (3) colonization (bacterial) [2,12] and (4) Th1 versus Th2 immune profile [13–16].

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To test this hypothesis, we conducted this exploratory study which determined whether FACT score was positively correlated with the likelihood of immune incompetence (lower pneumococcal antibody levels).

Methods

This study was approved from the Mayo Clinic Institutional Review Board in accordance with federal regulations.

Study design

This was a cross-sectional study. The dependent variable (response variable) was 23 serotype-specific anti-pneumococcal polysaccharide immunoglobulin G (IgG), and the details were previously reported [6]. The independent variable (predictor variable) was the calculated FACT score.

Study subjects

The details of the study design and subjects were previously reported [6]. Briefly, this was a convenience sample involving a total of 30 patients, 16 asthmatic patients and 14 non-asthmatic patients aged 4–80 years old at the time of enrollment who were recruited from patients who received medical care from Mayo Clinic. Patients were excluded if they had (1) moderate or severe disability; ear, nose or throat anatomic abnormalities; immunodeficiency; or were currently on immunosuppressive therapy [17]; (2) receipt of immunoglobulin or other blood products within the preceding 3 months; (3) confirmed pneumococcal disease with antibiotic treatment in the preceding 1 month and (4) non-Olmsted County, MN, inhabitant [6]. Enrollment was delayed 2 weeks for subjects with upper respiratory infections or viral illness. Patients in receipt of prior pneumococcal vaccination were not excluded.

Dependent (response) variable

Measurement of 23 serotype-specific anti-pneumococcal polysaccharide IgG levels

Antibodies to 23 serotypes of *Streptococcus pneumoniae* as a dependent (response) variable were measured by microsphere photometry method at the Mayo Clinic Clinical Immunology Lab [18]. Cut-off values for adequate anti-pneumococcal levels were based on Sorensen et al., who suggested that serotype-specific anti-pneumococcal polysaccharide antibody (IgG) level at 1.3 µg/mL or greater is considered an adequate or positive response [19]. The individual serotype-specific pneumococcal antibody level was coded as a binary variable (0 versus 1). For analysis, we summed the number of positive serotype-specific antibody levels (i.e. 0 versus 1) using the criteria by Sorensen et al., and thus, the possible range of the number of positive serotype-specific antibody levels were 0–23.

FACT score

The first two parameters of the FACT score were obtained via a systematic chart review and interview at the time of enrollment. The patients were assigned 0 or 1 based on the absence or presence of a family history of asthma and 0 or 1

based on the absence or presence of any other atopic condition including allergic rhinitis, atopic dermatitis and/or food allergy.

For determination of the third parameter, patients underwent nasopharyngeal swab cultures and were assigned a number of 0 for no colonization, 1 for colonization with one organism and 2 for colonization with more than 2 organisms (from cultures for *S. pneumoniae*, *S. aureus*, *H. influenza* and *M. catarrhalis*).

Finally, interferon-γ (IFN-γ) and interleukin-5 (IL-5) release were measured from peripheral blood mononuclear cells (PBMCs) cultured with house dust mites for 4 days for assessment of the fourth parameter, Th1 versus Th2 immune profile. PBMCs were isolated and then incubated with 50 µg/mL of *Dermatophagoides pteronyssinus* (HDM) for 4 days at 37 °C and 5% CO₂. The cell-free supernatants were harvested and stored at –30 °C until cytokine measurement by ELISA. The patients were divided into quintiles based on their IL-5/INF-γ ratio and assigned a number of 0, 1, 2, 3 or 4 based on the quintiles. Based on the determination from these four parameters, the range of the FACT score was between 0 and 8.

Each patient was then tested for serotype-specific antibody to 23 pneumococcal polysaccharide antigens as measured by ELISA (seropositivity was considered ≥1.3 µg/mL) [18].

Ascertainment of asthma

Patients who fulfilled predetermined criteria in Table 1 were considered asthmatics and those who did not meet the criteria were categorized into non-asthmatics. This criteria for asthma has been used for asthma research in the past [6].

Data analysis:

Subjects were categorized into three groups for analysis: non-asthmatics, asthmatics below the median of the FACT score and asthmatics above the median of the FACT score. Comparisons of continuous variables (e.g. the number of seropositive anti-pneumococcal antibodies) among these three groups were made using Kruskal–Wallis test and adjusted *p* value for multiple comparisons. The association between categorical variables and the above three groups by the FACT score was assessed by chi-square or Fisher exact tests. The correlation between the FACT score and overall pneumococcal antibody levels in a discrete variable was made by Spearman's correlation coefficient analysis.

Results

The study subject characteristics are summarized in Table 2. The range of the FACT scores in this study was 0–8 (mean = 4.3 ± 1.93 and median = 4).

The FACT score and asthma status

The mean FACT score for asthmatic patients above and below the median of the FACT score was 6.8 (SD = 0.9) and 3.6 (SD = 1.1), respectively, and the mean FACT score for non-asthmatics was 3.3 (SD = 1.5) (*p* < 0.001) (Table 2). The adjusted odds ratio for FACT score in predicting asthma status was 2.03 per 1 point increment of FACT score (95% CI 1.13–3.67, *p* = 0.019) controlling for age.

Table 1. Definition of asthma.

Patients were considered to have asthma if a physician had made a diagnosis of asthma, and at least two of the following three conditions were present OR if each of the following three conditions were present:

1. History of cough, dyspnea, and/or wheezing, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
3. Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (14 years or older)
 - Nasal polyps
 - Blood eosinophilia higher than $300 \mu\text{L}^{-1}$
 - Positive wheal and flare skin tests OR elevated serum IgE
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher than 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
 - Favorable clinical response to bronchodilator

Table 2. Demographic and clinical characteristics of the study subjects.

	Non-asthmatics (n = 14)	Asthmatics below the median of FACT score (n = 8)	Asthmatics above the median of FACT score (n = 8)	p Value [†]
Demographics				
Age, mean ($\pm$ SD)	31.5 ($\pm$ 22.5)	31.0 ($\pm$ 19.4)	24.4 ($\pm$ 25.4)	0.76
Male gender, n (%)	7 (50)	6 (75)	3 (38)	0.31
Caucasian, n (%)	10 (71)	6 (75)	5 (63)	0.58
Atopy, co-morbid conditions, and corticosteroid therapy				
Atopic/sensitization status, n (%) ^a	1 (7)	8 (100)	8 (100)	<0.001
Comorbid conditions present, n (%) ^b	2 (14)	3 (38)	2 (25)	0.46
Inhaled corticosteroid therapy, n (%)	–	2 (25) ^c	4 (50)	0.33
Pneumococcal vaccination status				
Subjects receiving PCV-7 or PPV23 vaccination, n (%)	4 (29)	3 (38)	5 (63)	0.54
PCV-7	3 (21)	1 (13)	3 (38)	–
Pneum-23	1 (7)	2 (25)	2 (25)	–
FACT score				
FACT score, mean ($\pm$ SD)	3.3 ($\pm$ 1.5)	3.6 ($\pm$ 1.1) ^{†b}	6.8 ($\pm$ 0.9) [‡]	<0.001
FACT score individual parameters				
Family history of asthma, n (%)	4 (29)	7 (88)	5 (63)	0.024
Atopic conditions, n (%)	1 (7)	4 (50)	7 (88)	0.001
Colonization, n (%)	3 (21)	2 (25)	4 (50)	0.35
Th1/Th2 immune profile ratio, mean ($\pm$ SD) ^d	2.7 ($\pm$ 1.1)	1.9 ($\pm$ 1.0) ^b	4.6 ($\pm$ 0.7) ^c	<0.001

^aDetermined by positive ($>0.35\text{kU/L}$) serum-specific IgE levels to cat dander/hair, short ragweed, June grass, house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and *Alternaria Tenuis*.

^bComorbid conditions include renal disease, gastroesophageal reflux disease, chronic obstructive pulmonary disease, fibromyalgia, hypertension, depression, gout, arthritis, congenital cardiac abnormalities, spinal radiculopathy, specific antibody deficiency, cleidocranial dysplasia and von Willebrand disease.

^cOne subject was on both inhaled and oral corticosteroid therapy.

^dDetermined by the ratio of cytokines IL5/IFN gamma after 5 days of PBMC stimulation with house dust mite.

[†]p Value for overall comparison based on Kruskal–Wallis test for continuous variables and chi-square or Fisher Exact test for categorical variables.

[‡]p < 0.01 for comparison between asthmatics below and above median of FACT score.

[‡]p < 0.01 for comparison between non-asthmatics and asthmatics above the median of FACT score.

The FACT score and serotype-specific pneumococcal antibody levels

The FACT score was inversely correlated with the number of positive serotype-specific antibody levels [ρ (ρ) = -0.38, p = 0.04] (Figure 1). We assessed the proportions of subjects with 12 or more positive serotype-specific antibodies in relation to the FACT scores in quartile. The median numbers of seropositive pneumococcal antibodies by quartiles of the FACT scores were 18.5, 12.5, 15 and 7 in 1st (lowest FACT score), 2nd, 3rd and 4th (highest FACT score) quartiles, respectively (p value for overall comparison by Kruskal–Wallis test = 0.035, $p_{\text{corrected for multiple comparison}}$ = 0.004 for

1st versus 2nd quartiles, $p_{\text{corrected for multiple comparison}}$ = 0.03 for 1st versus 3rd quartiles and $p_{\text{corrected for multiple comparison}}$ = 0.014 for 1st versus 4th quartiles).

The relationship between the FACT score and serotype-specific pneumococcal antibody levels in asthmatics and non-asthmatics

Of the 16 subjects with asthma, 7 (44%) had 12 or more positive serotype-specific polysaccharide antibodies, whereas 12 of 14 (86%) of non-asthmatics subjects had 12 or more positive serotype-specific polysaccharide antibodies (p = 0.014). The proportions of subjects with 12 or more

positive serotype-specific antibodies among non-asthmatics, asthmatics below the median of the FACT scores and asthmatics above the median of the FACT scores were 86, 50 and 38%, respectively ($p=0.052$) (Table 3). Compared to non-asthmatics, the adjusted odds ratios for 12 or more positive serotype-specific pneumococcal antibodies in asthmatics below the median the FACT scores and those above the median of the FACT scores were 0.16 (95% CI 0.02–1.27, $p=0.084$) and 0.11 (95% CI 0.01–0.85, $p=0.035$), respectively, controlling for age.

Discussion

In this study, we describe a subset of asthmatics, identified by a higher FACT score, who have a relative decrease in immune function based on serotype-specific pneumococcal antibody titers. We found that the FACT score predicts asthma status. We also discovered that the FACT score was inversely correlated with the number of positive anti-pneumococcal antibody levels. The asthmatic subjects were then divided into quartiles based on their FACT score number. Subjects in the highest quartile (highest FACT score numbers) were found to have a significantly decreased number of positive anti-pneumococcal antibody titers, potentially identifying a subgroup of asthmatics with significant immune incompetence.

Prior studies have demonstrated an increased risk of IPD in asthmatic patients [4–6]. A recent large epidemiological study

by Inghammer et al. reported that the risk of IPD in asthmatics is double that of controls [19]. Overall, the above results observed in our study may support this data and suggest that asthmatics have suboptimal serotype-specific pneumococcal antibody levels versus non-asthmatics. This disparity was reflected in the differences in the FACT score, with significantly higher FACT scores in asthmatics than non-asthmatics. Our study further identifies a subset of asthmatics, classified by a higher FACT score, with a lower number of protective anti-pneumococcal antibody responses. This particular subset of asthmatics may represent a novel asthmatic phenotype distinguished by a relative decrease in immune function. Our study findings are unlikely to be due to the influence of pneumococcal vaccinations ($p=0.72$), steroid exposure ($p=0.69$) or comorbid conditions ($p=0.63$) since there were no significant associations of pneumococcal antibody titers with these variables. In fact, a higher proportion of asthmatics (38–63%), especially those above the median of the FACT score (63%) who had the lowest positive pneumococcal antibody titers, had received pneumococcal vaccine compared to non-asthmatics (29%). In addition, asthmatics above the median of the FACT scores were relatively younger than the other two groups but after adjusting for age, the results remain significant suggesting the FACT scores still useful for predicting asthma status and the likelihood of lower pneumococcal antibody titers.

Subsequent studies confirm that increased risk of infection in asthmatics is not limited to pneumococcal disease. A population-based retrospective case-control study by Capili et al. demonstrated that asthma status was significantly associated with an increased risk of pertussis (adjusted odds ratio: 1.73; 95% CI 1.12–2.67; $p=0.013$) [20]. A separate study demonstrated a significantly higher number of asthmatics with IgG and immunoglobulin A (IgA) antibodies against *Chlamydomphila pneumoniae*. Of the asthmatic subjects in which sputum analysis was obtained, 40% were found to have positive *C. pneumoniae* by PCR analysis [21].

A different study reported poor anti-viral responses in pediatric asthma patients. In a group of 47 children, rhinovirus-associated interferon (IFN) production was significantly lower in asthmatic patients when compared to controls. The authors also demonstrated an inverse correlation between IFN concentrations and total serum immunoglobulin E (IgE) and a positive correlation between rhinovirus RNA levels and total serum IgE levels, further supporting the claim that atopic patients have deficient immune function against

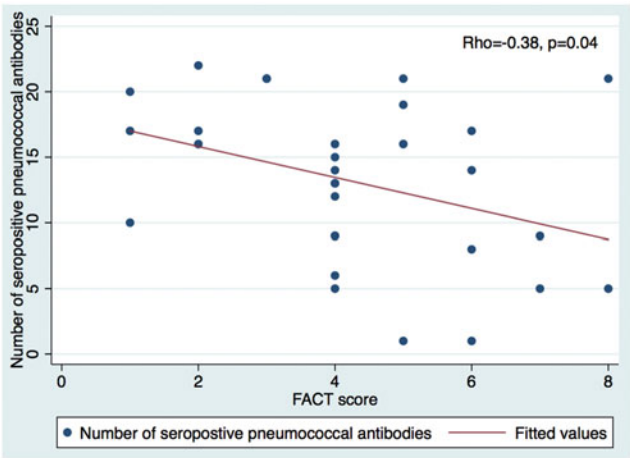


Figure 1. Correlation of the FACT score with the number of positive serotype-specific anti-pneumococcal responses.

Table 3. Number and percentage of 12 or more positive anti-pneumococcal serotype-specific antibodies.

	Non-asthmatics (n = 14)	Asthmatics below the median of FACT score (n = 8)	Asthmatics above the median of FACT score (n = 8)	p Value for chi-square
12 or more anti-pneumococcal serotype-specific Abs, n (%)	12 (86)	4 (50)	3 (38)	0.052
Odds ratio (95% CI) ^a	Referent	0.16 (0.02–1.27), $p=0.084$	0.10 (0.1–0.9), $p=0.035$	
The average number of positive pneumococcal antibodies out of 23	16	11	8.5	0.044
Regression coefficient, β (95% CI) ^a	Referent	–4.47 (–9.79 to 0.86), $p=0.097$	–5.59 (–10.96 to –0.22), $p=0.042$	

^aParameter estimates were adjusted for age.

rhinovirus [22]. A prospective case-control study found the percentage of rhinovirus viremia was significantly higher in asthmatics with upper respiratory infections versus other non-asthmatic children with upper respiratory infections [23]. Studies have shown the increased risk of infection seen in asthmatics extends beyond the respiratory tract. A cross-sectional study of 26,400 children aged 7–12 demonstrated that a history of acute gastroenteritis during infancy was associated with the later development of asthma [24].

The exact mechanism of increased susceptibility to infections in asthmatic patients is unknown. Proposed mechanisms include possible defects in both innate and adaptive immune systems [25]. Multiple studies have reported defects in interferon production leading to deficient anti-viral defense in asthmatics [23,26,27]. Moreover, certain studies have demonstrated significantly lower interferon levels as early as the neonatal period [28]. Two studies assessing innate immune function found dysfunctional alveolar macrophages in severe asthmatic children [29,30]. Recently, defects in toll-like receptor anti-microbial responses have also been reported in atopic patients [31].

Deficient adaptive immunity in asthmatic and atopic patients may be due, in part, to T helper 2 (T_H2) cell predominance in the respiratory tract [25,32]. In neonates with a family history of atopy, interleukin-5 responses (T_H2 cytokine) are associated with a higher risk of respiratory infections in comparison to interleukin-10 responses (an immunoregulatory cytokine) [33].

Some studies have addressed novel treatments for asthmatics with an immune-incompetent phenotype. One study demonstrated the potential benefit of IFN-beta in the treatment of rhinovirus infection in asthmatic respiratory epithelial cells. It confirmed improved anti-viral responses to rhinovirus *in vitro* [34]. Given prior reports of impaired alveolar macrophages in severe asthma, a study by Fitzpatrick et al. looked at the effect of the antioxidant, glutathione, on macrophage performance. With supplemental glutathione use, airway phagocytes demonstrated improved functionality [30]. Overall, impaired innate immune functions in asthmatics have been well documented, especially innate immune functions of bronchial epithelial cells. However, the role of adaptive immune function in asthmatics is relatively poorly understood. Given that it is difficult to assess impaired innate immune functions via bronchial epithelial cells, it may be challenging to identify a subset of asthmatics with innate immune incompetence in clinical practice. In this respect, measuring adaptive immune functions is relatively more feasible than innate immune functions at bronchial epithelial level (unless there is a surrogate easy measure for immune dysfunction of bronchial epithelial cells).

Our study results have a few important implications. In clinical practice, asthmatic patients with relative immune-incompetence or an immunodeficient phenotype may benefit from identification and classification with the FACT score. Potential consequences may be an increase in the frequency of pneumococcal vaccination (and likely other vaccinations, i.e. individualized vaccine schedule for asthmatics), closer monitoring of immunogenicity or durability after vaccinations, early identification and timely treatment of infections, and the development of novel treatment options. In research, we call

for future research assessing increased risk of infection and/or immune incompetence related to asthma as a distinctive phenotype of asthma in addition to the existing asthma phenotype. At present, this aspect is almost completely overlooked and failure to distinguish such phenotype deters advancing our understanding on the relationship between asthma and microbial infection or colonization. In public health, the role asthma in emerging and re-emerging infectious disease epidemiology needs to be assessed and monitored at a population level and asthmatics involved with these infections need to be further characterized to address the concern we raised above.

To our knowledge, this is the first analysis and scoring system to identify an asthmatic phenotype with immune dysfunction. Each individual component of the FACT score was chosen based on a compilation of literature findings. The preliminary data from this study support the hypothesis that there is, in fact, a difference in immune function between individuals with asthma and those without.

The main strength of this exploratory study is a novel hypothesis of developing the FACT score to identify a subset of asthmatics with immune incompetence. Another strength is predetermined criteria for asthma which was used for our extensive epidemiologic work including the previously reported association between asthma and serious pneumococcal disease so that the results of this study can be related to our previous work. There are some limitations to this study. Given the small sample size in this report, further studies are needed to replicate the study findings. Future studies determining the cost-effectiveness of this approach, given the multi-step process required to determine the FACT score, would also be helpful. Another limitation is lack of objective measure for asthma in all subjects primarily due to the consistency of utilizing the same criteria as previous epidemiologic investigations. The definition of asthma utilized in this study can be easily replicated and applied to future investigations and clinical practice. If a bias occurs in asthma ascertainment, it is likely to be a non-differential misclassification bias and unlikely to affect interpretation of our study results significantly.

Conclusion

The FACT score predicts asthma status and may help us identify asthmatics with immune incompetence against pneumococci from non-asthmatics and asthmatics with normal immune functions. Whether FACT can be extended to identify immune incompetence against other organisms in asthmatics needs to be studied.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The presented research work was supported by Bridge Award from Mayo Foundation.

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