

Assessment of the association between pediatric asthma and *Streptococcus pyogenes* upper respiratory infection

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ABSTRACT

This study was designed to determine the relationship between asthma and the risk of developing *Streptococcus pyogenes* infections of the upper respiratory tract among children and adolescents. We conducted a retrospective cohort study that followed a convenience sample of 340 healthy children who participated in the Rochester Family Measles Study. Comprehensive medical record reviews determined asthma status by applying predetermined criteria. All laboratory test results of cultures, rapid antigen, and polymerase chain reaction tests for *S. pyogenes* infections during the first 18 years of life were collected to compare the incidence of *S. pyogenes* infections between asthmatic and nonasthmatic subjects. A Poisson regression was fit to determine the association between asthma and *S. pyogenes* infections controlling for other risk factors. Of the 340 subjects, we enrolled 327 who were eligible for this study. Of the 327 subjects, 114 (35%) had asthma. The incidences of *S. pyogenes* infections for asthmatic and nonasthmatic subjects were 0.25 per person-year and 0.18 per person-year, respectively. The adjusted risk ratio for asthma was 1.40 (95% CI, 1.12–1.74; $p = 0.0029$). Asthma in children is associated with an increased risk of *S. pyogenes* upper respiratory infections. The impact of asthma status on susceptibility to microbial infections needs to be considered in the context of a possible causal relationship between asthma and microbial infections. The mechanisms underlying this risk need to be elucidated.

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Key words: Asthma, child, group A *Streptococcus*, infection, pharyngitis, *Streptococcus pyogenes*, susceptibility

Recently, it has been reported that patients with asthma have an increased risk of developing invasive pneumococcal disease (IPD) compared with those without asthma.^{2,3} These studies helped the Advisory Committee on Immunization Practices change the pneumococcal vaccine policy by including adult asthmatic patients in the pneumococcal vaccine eligibility criteria.⁴ The mechanisms underlying this increased risk of IPD have not been determined. At present, whether patients with asthma have an increased risk of developing other streptococcal infections, such as *Streptococcus pyogenes* infections, is not known. Because asthma is the most common chronic disease and a major morbidity, affecting 30 million people in the United States and 300 million people

globally,^{5,28,29} determining if an association exists between asthma and *S. pyogenes* infections should improve our understanding of asthma as a disease and our approach to asthmatic patients.

In the present study, we sought to determine the relationship between asthma and the *S. pyogenes* infections among children during their first 18 years of life. Our study setting and approach have epidemiological advantages, including a self-contained health care environment, a unified medical record system for research, and criteria-based asthma ascertainment.

METHODS

Study Design and Setting

The study was a retrospective cohort study. Rochester, MN, is centrally located in Olmsted County. Olmsted County had a recorded population of 124,277 during the 2000 Census. The population in Olmsted County was 90% white, compared with 89% white in Minnesota and 75% in the United States. Characteristics of the City of Rochester and Olmsted County populations were similar to those of the U.S. white population, with the exception of a higher proportion of the working population employed in the health care industry.^{6,7} Medical care in Rochester, MN, is virtually self-contained within the community with a unified medical record system between two medical centers for the past 90 years. This dossier-type medical record

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contains all inpatient and outpatient data that have been indexed in an automated form since 1935.⁸

Study Subjects

The study protocol was approved by the institutional review boards at both Mayo Clinic and Olmsted Medical Center. Study subjects were obtained from a sample of 876 children who were enrolled in the Rochester Family Measles Project, which was a convenience sample recruited from the Rochester School District in Rochester, MN, and the details about the original subjects were described in a previous study.⁹ The subjects for this study were a stratified random subset of 340 children from the original cohort who had undergone human leukocyte antigen typing. The original study cohort, aged 5–13 years, was enrolled in the study from schools in Rochester, MN, in 1993. At the time of our study, between 2002 and 2006, the study subjects were ≥ 14 years old. We excluded subjects whose medical records were designated with “no research authorization” cards at one more sites and those who were not Olmsted County residents for at least 1 year.

Identification of *S. pyogenes*

Ascertainment of *S. pyogenes* infection was made by laboratory test results of a patient’s throat swab. Each subject’s medical records were reviewed from birth to the 18th birthday. All incidents of *S. pyogenes* culture, rapid antigen detection test (RADT), or polymerase chain reaction (PCR) test for a throat swab were recorded by date along with the result, positive or negative. No distinction was made during analysis between positive test results obtained from a throat culture, RADT, or PCR. All negative results based on RADTs were followed up with a plated culture to prevent false negative results. The Mayo Clinic Microbiology Lab began using a rapid PCR-based test in August 2002 at which time all plated cultures and RADTs were discontinued.

Asthma Status

We conducted comprehensive medical record reviews for these children to determine their asthma status by applying predetermined criteria for asthma. These criteria are detailed in Table 1. The criteria for asthma based on medical record review were developed during a previous study by Yunginger *et al.*⁶ In the original study, to assess the reliability of the criteria, random samples of records were reviewed by different nurse abstractors and analyzed for interobserver reliability and agreement rates between abstractors and a high degree of concordance was found.¹⁰ Previous literature on asthma epidemiology research has used these criteria to define asthma.^{11–13} All subjects had lived in Rochester, MN, for at least 1 year before

Table 1 Asthma criteria

Patients were considered to have definite asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present and they were considered to have probable asthma if the first two of the following 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
3. Two or more of the following:
 - Sleep disturbed by nocturnal cough and wheeze
 - Nonsmoker (≥ 14 years old)
 - Nasal polyps
 - Blood eosinophilia $>300/\mu\text{L}$
 - Positive wheal-and-flare skin test results or elevated serum IgE levels
 - History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV₁ or FVC $<70\%$ predicted or methacholine challenge test showing $\geq 20\%$ decrease in FEV₁
 - Favorable clinical response to bronchodilator

FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity.

ascertainment of asthma status to avoid patients who were seeking tertiary care from outside of Rochester. In cases of definite or probable asthma status, the index date was defined as the date when a subject met the criteria for asthma according to the medical record.

Statistical Analysis

To address the study aim, the incidence density rates were calculated by dividing the number of infections by the total person-years based on the follow-up duration from the first registration date to the last follow-up date or 18th birthday, whichever comes first. All positive test results for *S. pyogenes* were considered incidents of *S. pyogenes* infections as discussed previously. The denominator (the total person-years) of the incidence density rate offsets the different number of *S. pyogenes* infection, which is a function of the follow-up duration. The incidence density rates follow the Poisson distribution because the responses were counted and, thus, we fitted data to a Poisson regression model to calculate risk ratios and their corresponding 95% CI adjusting for pertinent covariates and confounders. We summarized the incidence of *S. pyogenes* infection per person-year with 95% CI and compared the incidence

Table 2 Characteristics of study subjects and factors associated with the incidence of *Streptococcus pyogenes* infections based on a univariate Poisson regression model

Characteristics	No. (%)	<i>S. pyogenes</i> Incidence Rate (per person-year)	Unadjusted Risk Ratios (95% CI)	<i>p</i> Value
Asthma status				
No	213 (65)	0.18	Reference group	
Yes	114 (35)	0.25	1.38 (1.12–1.70)	0.003
Sex				
Female	159 (49)	0.21	Reference group	
Male	168 (51)	0.21	0.97 (0.78–1.19)	0.75
Race				
Nonwhite	21 (6)	0.08	Reference group	
White	306 (94)	0.22	2.89 (1.41–5.95)	0.004
Maternal education				
Unknown	110 (34)		Reference group	
High school or less	23 (7)	0.17	1.22 (0.83–1.79)	0.31
Some college	108 (33)	0.21	1.23 (0.78–1.94)	0.38
College degree	49 (15)	0.21	1.43 (0.90–2.27)	0.13
Grad degree	37 (11)	0.25		
Family history of asthma				
No	129 (39)	0.20	Reference group	
Yes	198 (61)	0.22	1.10 (0.88–1.36)	0.40
Family history of atopy				
No	106 (32)	0.20	Reference group	
Yes	221 (68)	0.21	1.06 (0.85–1.33)	0.59
Birth weight				
Unknown	2 (1)			
>2500 g	255 (78)	0.22	Reference group	
<2500 g	70 (21)	0.15	0.66 (0.49–1.89)	0.007
Likelihood of diagnosis				
Definite asthma	97 (85.1)	0.25	Reference group	
Probable asthma	17 (14.9)	0.27	0.92 (0.58–1.45)	0.71
Severity of asthma				
Unknown	10 (8.8)		Reference group	
Mild–moderate	94 (82.5)	0.25	1.12 (0.63, 1.97)	0.71
Severe	10 (8.8)	0.28		

density rates of *S. pyogenes* infections between children with asthma and those without asthma. A univariate Poisson regression was fit to identify other factors associated with an increased risk of *S. pyogenes* infections. A multivariate Poisson regression was then fit to determine the independent impact of asthma status on risk of *S. pyogenes* infections controlling for pertinent covariates and cofounders (birth weight and ethnicity) identified by univariate Poisson regression models,¹ by using the Greenland's variable entering criteria for a multivariate model.¹⁴ In addition, to assess the potential detection bias (*i.e.*, asthmatic patients might be more likely to seek medical evaluations and tests for *S. pyogenes* infections compared with nonasthmatic patients), we compared the incidence of *S. pyogenes* infections before and after the physician diagnosis of

asthma. Also, we compared the incidence of tests for *S. pyogenes* infections, including both positive and negative test results, before and after the physician diagnosis of asthma. All statistical significance was tested at a two-sided α -error of 0.05.

RESULTS

Of 340 children eligible for the study, 327 were eligible for this study. Thirteen children had medical records that were not authorized for review. The overall incidence of *S. pyogenes* upper respiratory infections was 0.21 per person-year in our study subjects. The subjects included 168 (51.4%) male patients and 306 (93.6%) white patients, which are similar to the overall demographics of Olmsted County in 1990.¹⁵ Of the 327

Table 3 Incidence of *Streptococcus pyogenes* infection based on a multivariate Poisson regression model

	Adjusted Risk Ratio (95% CI)	p Value
Asthma status		
Yes	1.40 (1.12–1.74)	0.0029
No	Referent	
Ethnicity		0.03
White	2.55 (1.09–5.97)	0.02
Nonwhite	Referent	
Birth weight (kg)	1.27 (1.04–1.57)	

subjects, 114 (34.9%) were asthmatic, among whom 97 (85.1%) met the criteria for definite asthma and the remainder met the criteria for probable asthma. None of the asthmatic subjects used more than two courses of inhaled or systemic corticosteroids in their first 18 years of life. Furthermore, none of the 15 (13%) asthmatic subjects who received a course of inhaled or systemic corticosteroids did so within 30 days of a positive *S. pyogenes* test. The other characteristics of the study subjects are summarized in Table 2.

The Relationship between Asthma and *S. pyogenes* Infection

The incidences of *S. pyogenes* infection for asthmatic and nonasthmatic subjects were 0.25 per person-year and 0.18 per person-year, respectively. According to a multivariate Poisson regression model, the adjusted risk ratio of patients with asthma in developing *S. pyogenes* infection was 1.40 (95% CI, 1.12–1.74; $p = 0.0029$) compared with those without asthma, controlling for birth weight and ethnicity (Table 3). The univariate analysis results for other factors associated with *S. pyogenes* infections are summarized in Table 2. The incidences of positive *S. pyogenes* infections for asthmatic patients before and after their index date and before and after their date of physician diagnosis were not significantly different. Likewise, the incidences of total *S. pyogenes* tests for asthmatic patients before and after their index date and before and after their date of physician diagnosis were also not significantly different (Table 4).

DISCUSSION

Our study results suggest that patients with asthma have a higher incidence of *S. pyogenes* upper respiratory infections (0.25 per person-year) than that for nonasthmatic patients (0.18 per person-year). Our incidence rates are in keeping with a previous published incidence rate for a group of school-aged children in Melbourne, Australia (0.14 per person-years),¹⁶ and

well below the incidence rate in a periurban slum community in northern India (0.95 per person-year).¹⁷ The risk ratio (*i.e.*, incidence ratio) in our study for patients with asthma developing *S. pyogenes* infections is 1.40 (1.12–1.74), controlling for birth weight and ethnicity, which were also associated with increased *S. pyogenes* infection. This is a significant impact considering the reported impact of environmental tobacco smoke on asthma incidence (OR, 1.13–1.31, depending on age of child),^{18,19} asthma prevalence (OR, 1.21–1.5, depending on smoking status of both parents),^{20,21} the prevalence of wheeze (OR, 1.24–1.47),^{20,21} and lower respiratory illness (OR, 1.5–1.72)^{20,22} in young children.²³

Our findings could be the result of detection bias that arises from a differential medical evaluation or test-seeking behavior between children with and without asthma. However, neither the incidences of *S. pyogenes* infection nor the incidences of tests for *S. pyogenes* before and after physician diagnosis of asthma are different in our cohort. In addition, two of our research group's recent prospective studies show that parents of asthmatic children are not more likely to seek medical evaluations for mild acute illnesses in their children when compared with parents of nonasthmatic children.^{24,25} Alternatively, our findings could also be caused by an effect of inhaled or short-term systemic corticosteroids. However, only 15 (13%) of the children with asthma in our study ever used inhaled or short-term systemic corticosteroids and none of them had a positive *S. pyogenes* test in the 30 days after the steroid use. In fact, previous studies have shown that both inhaled corticosteroid and short-term systemic steroid are associated with reduced upper respiratory tract infection-induced acute exacerbation of asthma.^{26,27}

Although there has been no previous cohort study examining the relationship between asthma and the incidence of *S. pyogenes* infections in the literature, Talbot *et al.* reported a significantly increased risk (adjusted OR of 2.4) of IPD among patients with asthma compared with those without asthma² and this finding has been recently confirmed by our research group.³⁰ Previous studies have also reported that children with asthma have increased colonization with *Streptococcus pneumoniae* and *Staphylococcus aureus*³¹ and increased evidence of previous *Legionella pneumophila* infection³² when compared with nonasthmatic patients. A previous cross-sectional study compared the positivity of culture or RADT in the presence of upper respiratory symptoms for children with and without asthma. The study reported an increased risk of *S. pyogenes* infections among asthmatic patients, OR of 1.36 (0.72–2.57), but was not statistically significant due to insufficient statistical power.³³ In contrast, our study assessed the long-term outcomes of the relationship between asthma status and *S. pyogenes* infection. Therefore, our

Table 4 Incidence of *Streptococcus pyogenes* infections before and after asthma occurrence

	Before Asthma Index Date (n = 112) Reference Group	After Asthma Index Date (n = 111)	Risk Ratio (95% CI)	p Value
Positive <i>Streptococcus pyogenes</i> infections (per person-year)	0.29	0.24	0.82 (0.62–1.09)	0.17
Total <i>S. pyogenes</i> infections episodes (per person-year)	0.93	0.87	0.94 (0.77–1.14)	0.52
	Before Asthma Physician Diagnosis (n = 96) Reference Group	After Asthma Physician Diagnosis (n = 94)		
Positive <i>S. pyogenes</i> infections (per person-year)	0.28	0.25	0.87 (0.65–1.18)	0.38
Total <i>S. pyogenes</i> infections (per person-year)	0.92	0.89	0.97 (0.78–1.19)	0.75

study findings on an increased risk of *S. pyogenes* infection among children with asthma appear to be consistent with what the literature supports.

Strengths of our study include epidemiological advantages in addressing the study questions, such as the self-contained health care environment and unified medical records for research among health care providers in our study setting. Also, our study assessed a long-term risk and the incidence of *S. pyogenes* infections among children with and without asthma during their first 18 years of life. Our study has an inherent limitation as a retrospective study, and our results are observational ones showing an epidemiological association, not necessarily a causal relationship between asthma and *S. pyogenes* infection, but this is an under-investigated area and the results should be a basis for a future experimental study. Another limitation of our study was the inability to differentiate *S. pyogenes* carriage versus infection. However, most instances of testing for *S. pyogenes* were caused by clinical symptoms or signs. Also, it is still noteworthy to observe the differential incidence of *S. pyogenes* carrier state or infection among children with asthma compared with nonasthmatic patients because it raises rational questions for the risk of *S. pyogenes* infection or carriage and other infections caused by *S. pyogenes* among those with asthma. Our study setting has a predominantly white population that may limit generalizability to other study settings. Finally, a physician would have to assess 15 asthmatic children for 1 year before diagnosing one extra case of *S. pyogenes* upper respiratory infection. Thus, our findings, while significant, do not suggest that a substantial change in current clinical practice should be made.

In conclusion, children with asthma are at an increased risk of *S. pyogenes* upper respiratory infections

compared with nonasthmatic patients. The risk of *S. pyogenes* infection is independent of the index date of asthma (*i.e.*, timing of the phenotypic development of asthma), suggesting that the immunogenetic predisposition to asthma may underlie the increased susceptibility to *S. pyogenes* infection. Additional studies are needed to elucidate the mechanisms underlying the increased risk of *S. pyogenes* upper respiratory infections.

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