Infectious Asthma: A Reemerging Clinical Entity?

David L. Hahn, MD
Madison, Wisconsin

Background. In the primary care setting, patients often report that their asthma began after an acute respiratory infection such as bronchitis, pneumonia, or an influenza-like illness ("infectious asthma"). Preceding respiratory illnesses such as bronchitis and pneumonia are also epidemiologic correlates of asthma in both children and adults. These associations suggest the possibility that respiratory infection is involved in the initiation of asthma in addition to the already acknowledged role of infection in asthma exacerbations. The purpose of this study was to investigate whether a history of infectious asthma influenced clinical and pulmonary function characteristics of patients with chronic asthma.

Methods. Conducted in a community-based primary care practice, this is a clinical descriptive study of 92 middle-class patients who had a mean age of 37.7 years (standard deviation 15.4 years), a clinical diagnosis of chronic asthma, and baseline pulmonary function test results available for analysis.

Results. There was sufficient history available to classify asthma as infectious in 41 (45%) of 92 patients. Patients with infectious asthma reported a much shorter duration of asthma symptoms than did patients with atopic, occupational, and exercise-induced asthma (5.6 vs 13.3 years, $P=.001$). Nevertheless, patients with infectious asthma had significantly worse percentages of predicted FEV_1 and $FEF_{25\%-75\%}$, both before and after bronchodilator therapy.

Conclusions. Infectious asthma was common in this primary care setting. Compared with patients with other asthma syndromes, those with infectious asthma had worse pulmonary function despite a shorter duration of symptomatic disease. Further studies of the cause and prognosis of this clinical entity are warranted.

Key words. Asthma, bronchitis, pneumonia, pulmonary function testing; respiratory function tests.
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Asthma, an important cause of respiratory morbidity and mortality, is an inflammatory condition of the airways whose underlying etiology is not completely understood. Recognition of the significance of inflammation in asthma has led to recommendations for more widespread use of anti-inflammatory therapy.[1] It is important to acknowledge, however, that current asthma therapies are palliative, not curative. Research into new possible underlying causes for asthma are therefore warranted.

Earlier in this century, many clinicians believed that respiratory infection played a significant role in asthma etiology.[2-5] Recent clinical studies have also suggested that bronchitis and pneumonia are associated with subsequent asthma.[6-8] Results of cross-sectional[9-12] and prospective[13,14] epidemiologic studies have found that preceding respiratory illnesses, including bronchitis, chronic bronchitis, and pneumonia, are associated with subsequent asthma in both children[9,12-14] and adults.[9,10] Smith[15] has recently proposed a viral hypothesis for the onset of allergic diseases and asthma. Busse,[16-18] Bardin et al,[19] and Sheth and Busse[20] have reviewed potential mechanisms whereby infection may exacerbate and possibly even initiate asthma. It has further been suggested that the adult acute asthmatic bronchitis syndrome may be a risk factor for the subsequent development of asthma.[21]

Discovery of bacterial etiologies for some diseases of previously unknown origin (for example, *Helicobacter pylori* in peptic ulcer disease) have led to greater acceptance of the concept that infection might be involved in the etiology of other chronic inflammatory conditions of un-

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From The Dean Medical Center, Madison, Wisconsin. Requests for reprints should be addressed to David L. Hahn, MD, Arcand Park Clinic, 3434 East Washington Ave, Madison, WI 53704.

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known cause.[22] Acute respiratory infection is acknowledged as a common cause for asthma exacerbations, but there is less evidence that infection is the *initiating* event for asthma. Since the etiology for asthma remains unknown, it is reasonable to ask whether further clinical definition of infectious asthma (reflecting infection associated with the *initiation* of asthma rather than solely with later exacerbations) will advance our understanding of the underlying cause and optimal management of this disease. This report describes clinical and spirometric findings in a consecutive series of 92 primary care outpatients with a diagnosis of chronic asthma who had pulmonary function tests recorded, and compares the clinical and spirometric findings in patients with chronic asthma classified as infectious and noninfectious.

Methods

Study Setting and Patients

The study site was a community-based primary care (family practice) office affiliated with a multisite, multispecialty group practice located in and around a mid-sized midwestern city, the population of which is predominantly white and middle class. Between 1988 and 1993, inclusive, the author recorded encounters with 97 patients who had a clinical diagnosis of symptomatic chronic asthma. Following each encounter, clinical data from the medical record and results of pulmonary function, if available, were entered into a database for later analysis. The goal was to record data for all encountered patients who reported symptomatic asthma. Whether any such patients were missed is unknown.

This case series includes 92 (95%) patients for whom baseline pulmonary function testing was also recorded. For this group, previous medical records were available for 89 (97%) group practice patients. Three (3%) patients were referred from outside the group practice, and they provided copies of medical records for review.

Pulmonary Function Measurements

Spirometric testing was performed according to American Thoracic Society guidelines,[23] using a Gould spirometer (System 21, Gould Medical Products, Inc, Dayton, Ohio). Baseline testing was performed for all 92 study group patients and in 84 (91%) patients after treatment with inhaled albuterol or a course of oral steroids. In most cases, the author performed spirometric testing. Sometimes pulmonary function was performed elsewhere in the medical center using a comparable apparatus and technique.

Classification of Asthma Syndromes

Patients with intermittent or persistent wheeze, cough, and dyspnea triggered by a variety of stimuli, who responded to inhaled beta-adrenergics and/or oral or parenteral steroids, received a diagnosis of chronic asthma based on clinical criteria of the American Thoracic Society.[24] Patients reporting that initial asthma symptoms were associated with an acute respiratory illness (usually bronchitis, pneumonia, or an influenza-like illness) were classified as infectious. Patients with atopic, occupational, and exercise-induced asthma, who did not report associations with respiratory infection when symptoms were first noticed, were classified as noninfectious. This classification refers only to associations with respiratory infection at the time asthma symptoms first began and does not refer to later exacerbations of asthma symptoms caused by respiratory infections. Some patients could not be classified because of lack of recall, unavailability of relevant medical records, or both.

Classification as infectious or noninfectious asthma was based on medical record evidence and patient recall of respiratory illness at the time asthma symptoms (usually wheeze and dyspnea) first occurred, regardless of whether a diagnosis of asthma was made at that time or later. As part of the typical patient workup, the author asked questions regarding possible infectious initiation of asthma. First, an open-ended question ("Tell me about the *very first time* you ever noticed any of your symptoms of asthma") was asked. Second, a more specific confirmatory probe ("So when you noticed your very first symptoms, they happened/did not happen after respiratory illness?") was used. Medical record data pertaining to initial recorded symptoms were often shared with the patient during this interview process.

Statistical Methods

Fisher's exact test was used to analyze 2×2 tables. Analysis of variance (ANOVA) was used to test for subgroup differences in means of continuous variables. A multivariate regression model was used to test for subgroup differences in pulmonary function values, while simultaneously controlling for the effects of current smoking and the reported duration of asthma symptoms. Two-sided *P* values of $<.05$ were reported as significant.

Results

Table 1 summarizes the clinical findings for the 92 study-group patients with chronic asthma encountered during the 6-year study period. Seventy-eight (85%) patients

Table 1. Clinical Characteristics of Patients Classified as Infectious and Noninfectious Asthmatics

	Total Group (N=92)	Clinical Category		*P* Value
		Infectious* (n=41)	Noninfectious† (n=36)	
Age, y [mean (SD)]	37.7 (15.4)	41.7 (14.1)	35.9 (17.1)	NS
Male, %	46	44	44	NS
Current smoker, %‡	25	40	15	.03
Age when asthma symptoms first reported, y [mean (SD)]	28.9 (16.4)	36.1 (15.8)	22.3 (14.5)	<.001
Duration of asthma symptoms, y [mean (SD)]	8.9 (9.9)	5.6 (6.6)	13.3 (12.5)	.001

**Infectious asthma: first symptoms of asthma reported following a respiratory illness (usually bronchitis, pneumonia, or an influenza-like illness).*
†Noninfectious asthma: atopic, occupational, or exercise-induced asthma without an infectious presentation. Classification was not possible for 15 (16.3%) patients for whom sufficient clinical history was unavailable.
‡Data on current smoking status were available for 81 (88%) patients, including 35 infectious and 33 noninfectious asthmatics.
SD denotes standard deviation; NS, not significant.

were over 20 years of age, 46% were male, and 25% were current smokers; data concerning previous smoking were not recorded. Age-of-onset data were available for 89 (97%) patients: 27 (30%) reported onset before age 20, 40 (45%) between ages 20 and 40, and 22 (25%) after age 40. Calculated asthma duration (current age minus age at onset) varied as follows: 5 years or less (45%), 5 to 15 years (30%), and more than 15 years (25%). Current age, age at onset, and asthma duration were significantly intercorrelated as follows: R (age vs age at onset)=.81 ($P<.001$), R (age vs duration)=.22 ($P=.036$), and R (age at onset vs duration)=−.40 ($P<.001$).

Based on available information, 77 (84%) patients could be classified as either infectious or noninfectious (Table 1). Patients with infectious asthma tended to be older than those with noninfectious asthma (41.7 vs 35.9 years of age, P=NS), were older when asthma began (36.1 vs 22.3 years of age, $P<.001$), and had a much shorter duration of symptoms (5.6 vs 13.3 years, $P=.001$). Patients with infectious asthma were also more likely to be current smokers (40% vs 15%, $P=.03$), but the sex distributions were approximately equal (44% male). Of the 41 subjects with infectious asthma, 14 (34%) reported some clinical history of allergy not associated with asthma initiation (mostly allergic rhinitis or allergic triggers for subsequent asthma episodes).

There were no significant differences for any of the variables reported in Table 1 between the 92 patients in the study group and the 5 patients who were excluded because they had not had pulmonary function tests.

Pulmonary Function Test Results

Table 2 presents pre- and post-bronchodilator pulmonary function results (as percentage of predicted FEV_1 and $FEF_{25\%-75\%}$) for the entire study group and for the subgroups of patients with and without infectious asthma. Twenty-eight (30.4%) patients had moderately severe baseline pulmonary function as indicated by a pre-bronchodilator FEV_1 of less than 65% of the predicted value. Pre-bronchodilator FEV_1 of less than 65% predicted was present in 42% of infectious asthmatics and in 22% of

Table 2. Pulmonary Function Test Results for Patients Classified as Infectious and Noninfectious Asthmatics

	Total Group (N=92)	Clinical Category		*P* Value‡
		Infectious* (n=41)	Noninfectious† (n=36)	
FEV_1, % predicted (SD)				
Pre-bronchodilator	74.4 (20.2)	67.7 (15.4)	77.9 (21.8)	.016
Post-bronchodilator§	90.6 (14.4)	86.5 (10.4)	94.9 (15.1)	.047
$FEF_{25-75\%}$, % predicted (SD)				
Pre-bronchodilator	50.2 (27.6)	41.8 (19.7)	52.4 (28.1)	.044
Post-bronchodilator§	64.7 (25.4)	61.4 (19.1)	72.8 (27.6)	.040
FEV_1/FVC, % (SD)	77.9 (8.6)	77.1 (7.7)	78.4 (9.1)	NS

**Infectious asthma: first symptoms of asthma reported following a respiratory illness (usually bronchitis, pneumonia or an influenza-like illness).*
†Noninfectious asthma: atopic, occupational or exercise-induced asthma without an infectious presentation. Classification was not possible for 15 (16.3%) patients for whom sufficient clinical history was unavailable.
‡Adjusted for asthma duration and current smoking.
§Post-bronchodilator results were available for 84 (91.3%) patients with chronic asthma, 40 (97.6%) patients with infectious asthma, and 32 (88.9%) patients with noninfectious asthma.
FEV_1 denotes forced expiratory volume in 1 second; FEF, forced expiratory flow; FVC, forced vital capacity; SD, standard deviation; NS, not significant.

noninfectious asthmatics (P=NS). When analyzed as continuous variables, pre- and post-bronchodilator FEV_1 and $FEF_{25\%-75\%}$ were all significantly worse for patients with infectious asthma as compared with those with noninfectious asthma. These differences remained significant after simultaneous adjustment for current smoking and asthma duration (Table 2).

For the total study group, post-bronchodilator FEV_1 increased 21.8%. There were no significant differences in bronchodilator response for patients with infectious and noninfectious asthma or for the degree of fixed obstruction, as measured by the ratio of FEV_1 to FVC (forced vital capacity) (Table 2).

Discussion

Acute respiratory infections preceding asthma have been frequently documented, but pathogenetic mechanisms remain speculative.[13] Possible initiation of asthma by a variety of agents including respiratory syncytial virus,[20] adenovirus,[25] *Mycoplasma pneumoniae*,[26] and *Chlamydia pneumoniae*[27] has been discussed. Chronic infection as a cause for persistent asthma symptoms has also been suggested for adenovirus[25] and chlamydia species.[27,28]

This study reported primarily on adult patients with chronic asthma drawn from a primary care population. The age distribution of asthma patients was a function of the practice, which contained fewer childhood asthmatics than one would expect from sampling the general population. Therefore, study results may not apply to childhood-onset asthma. Compared with patients having noninfectious asthma, infectious asthmatics developed symptoms at a later age and had worse baseline and post-bronchodilator pulmonary function, despite a much shorter duration of symptomatic disease. This pattern resembles previous descriptions of adult-onset asthma, which is associated with worse symptoms and a poorer prognosis when compared with asthma in younger patients.[5,29]

Several limitations of this study require comment. This was a clinical descriptive study in a single primary care practice, and as such, is subject to selection bias. Classification bias cannot be ruled out. Classification as infectious or noninfectious was made independently of knowledge of pulmonary function test results, and no a priori hypothesis was made regarding the significant association between infectious asthma and worse pulmonary function. Recall bias is a serious consideration, with patients ill for a shorter period possibly having a better recollection of the antecedent event. This limitation was overcome partially by the availability of previous medical records for some patients, and addressed by adjusting for asthma duration. Patient recall was supported by medical records, which often spanned decades, or occasionally a lifetime, representing one of the advantages of performing retrospective clinical research in a family practice setting. Results remained significant after controlling for duration of disease in a multivariate model. It is possible that smoking was related to worse pulmonary function in infectious asthmatics. Since smoking is known to be associated with chronic obstructive pulmonary disease (COPD), it is possible that smoking contributed to lower FEV_1 in infectious asthmatics, who had a higher prevalence of current smoking. There was no difference, however, between patients in the infectious and noninfectious groups in the ratio of FEV_1 to FVC (a measure of fixed obstruction in COPD). Furthermore, patients with a clinical diagnosis of COPD who also had asthma were excluded from this report. Finally, results remained significant after controlling for smoking in the multivariate model. Pulmonary function test results (as percentages of predicted values) are already normalized by age, sex, race, and body mass index. Therefore, in the author's opinion, further controlling for these variables in the multivariate model used in this analysis was not indicated.

This study found that infectious asthma had worse baseline pulmonary function compared with other forms of asthma, despite a significantly shorter duration of symptoms for infectious asthma (5.6 v 13.3 years). This pattern of findings could be explained by worse pulmonary function at the time infectious asthma became symptomatic, by a greater rate of loss of function after symptoms began, or by a combination of these mechanisms. Regarding a possible accelerated loss of function, infectious asthma could be associated with a severe acute insult, which is stable and unchanged over time, or with a continuing, progressive loss of function. Concern has been raised recently over the long-term use of inhaled steroids for asthma whose cause might involve chronic persistent infection.[28] These issues can be resolved only by means of prospective longitudinal studies.

This cross-sectional clinical study can offer only hypotheses for future research, not conclusive proof. The classification of infectious asthma, as employed here, is novel and its association with worse pulmonary function requires confirmation. Since causative factors of asthma are unknown, and inhaled corticosteroid therapy is now being advocated[1] despite the therapy's unknown effects on ultimate pulmonary function,[30] it is worthwhile to perform further studies on the reemerging clinical entity of infectious asthma. If this avenue of research proves fruitful and treatable infectious causes of asthma are identified, the possibility of "cure" may exist for some asthma patients for whom only palliative therapies are currently available.

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