Asthma and Chlamydial Infection: A Case Series

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Background. Adult-onset asthma is frequently associated with antecedent respiratory symptoms that could represent either previously undiagnosed asthma or previous lung infections that result in subsequent asthma. To further investigate a reported association of *Chlamydia pneumoniae* infection and adult reactive airway disease, we looked for evidence of atypical infections in patients with acute wheezing and nonwheezing respiratory illnesses.

Methods. Pharyngeal cultures and acute and convalescent serology for *C pneumoniae* and *Mycoplasma pneumoniae* were obtained from 131 primary care outpatients (mean age, 36 years) with acute wheezing or nonwheezing respiratory illnesses. Peak flow measurements were obtained in patients with cough or wheeze. Spirometry before and after bronchodilator use was obtained to substantiate the diagnosis of chronic asthma in patients who had persistent wheezing and dyspnea after enrollment.

Results. Twelve (9.2%) of 131 patients were classified as having chronic asthma, 5/12 developed chronic asthma for the first time during the study period. Thirty (22.9%) patients were classified with acute asthmatic bronchitis, and 89 (67.9%) had nonwheezing illness. Two of the newly diagnosed asthmatics met serologic criteria for acute *C pneumoniae* infection, and one had serologic evidence for acute *M pneumoniae* infection. Compared with patients with nonwheezing respiratory illnesses, *C pneumoniae* seroreactivity was significantly ($P < .001$) associated with both chronic asthma and with acute asthmatic bronchitis.

Conclusions. Acute wheezing illness was encountered frequently in this primary care setting. Although most acute wheezing respiratory illness resolved without obvious chronic sequelae, some patients had persistent symptoms and were diagnosed with chronic asthma. *C pneumoniae* seroreactivity was associated with both acute and chronic wheezing, suggesting that pulmonary infection with this intracellular pathogen plays a role in the natural history of reactive airway disease.

Key words. Asthma; bronchitis; *Chlamydia pneumoniae*; *Mycoplasma pneumoniae*. (*J Fam Pract 1994; 38:589-595*)

The cause of asthma, a common chronic inflammatory airway condition, is not well understood. It was once thought that infection played an important causative role in asthma,[1–3] but there are no convincing scientific studies documenting "bacterial allergy" as a cause.[4] More recent epidemiologic studies and clinical reports have documented that respiratory diagnoses including bronchiolitis,[5] acute bronchitis,[6] chronic bronchitis[7] and pneumonia[8] are associated with the development of subsequent asthma in both adults and children. Some reports have presented preliminary evidence that atypical bacteria (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) may play a role in these reported associations.[5,9] Given these preliminary results and our limited understanding of asthma etiology, it is worthwhile to investigate further the possibility that atypical infections are involved in the initiation and exacerbation of asthma, or even the promotion of asthma in persistently infected, susceptible individuals.

Mycoplasma pneumoniae infection is a recognized cause of acute respiratory illnesses, including atypical pneumonia and tracheobronchitis, and may also cause asymptomatic infection in about 20% of cases.[10] *M pneumoniae* infection is more common in children than in adults,[11] and has been associated with varying proportions of acute infectious exacerbations of asthma, usually in children[12–14] but also sometimes in adults.[15] A prolonged carrier state beyond several months postinfection

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in immunocompetent patients has not been documented,[16] making it unlikely that persistent *M pneumoniae* infection frequently promotes chronic asthma.[5]

Another atypical respiratory pathogen, *Chlamydia pneumoniae*, has emerged as an important cause of acute respiratory illness, including bronchitis and pneumonia.[17] Like *M pneumoniae*, most primary infections occur in younger age groups. Unlike *M pneumoniae*, however, the majority of patients with *C pneumoniae* infections are asymptomatic or only mildly symptomatic,[18] and repeat infections are common and occur throughout adulthood.[19] Chronic intracellular infection is typical for chlamydiae.[20] Persistent infection has been documented for *C pneumoniae*[21] and has been implicated in some chronic cardiopulmonary diseases including sarcoidosis,[22] coronary artery disease,[23–25] and adult-onset asthma.[9]

In a previous prospective study designed to assess the role of acute *C pneumoniae* infection in bronchitis and atypical pneumonia, we found post hoc associations of *C pneumoniae* seroreactivity with wheezing, asthmatic bronchitis, and adult-onset asthma.[9] We now report results of culture and serology for *M pneumoniae* and *C pneumoniae* in a series of patients with asthma confirmed by pulmonary function testing, studied during a *M pneumoniae* epidemic. Asthma patients are compared with patients who had acute asthmatic bronchitis or acute nonwheezing respiratory illnesses.

Methods

Study Setting

One hundred thirty-one patients who visited a primary care office with complaints of respiratory illness between October 1989 and January 1991 (16 months) were enrolled in the study. The study site was a community-based, four-physician family practice office affiliated with a large multispecialty, multisite group practice located in a metropolitan area of south central Wisconsin (Dane County), with a predominantly white, middle-class population.

Enrollment Criteria

Enrollment was offered to all patients who were encountered by the clinician-investigator during the course of usual practice and who had laryngitis, biphasic illness (pharyngitis and/or laryngitis, followed by bronchitis or pneumonia), wheezing, or atypical pneumonia. Patient refusal was not documented but is believed to be minimal. Enrollment of patients with other respiratory illnesses was less systematic. The proportions of acute asthmatic bronchitis (23%) and asthma (9%) in this study are greater, therefore, than comparable figures (13% and 3%, respectively) from our previous study, which enrolled all patients systematically.[9]

Our definition of "asthmatic bronchitis" differs from that used in some standard references of pulmonary medicine. Thus, asthmatic bronchitis has been used to describe patients in whom the diagnoses of chronic bronchitis and asthma coexist, or are difficult to distinguish.[26] The term "wheezy bronchitis," as used in another reference,[27] denotes episodes of wheezing during acute bronchitis, occuring mainly in children. Acute asthmatic bronchitis, as used in this paper, refers to the latter type of wheezing during acute bronchitis but is not limited to children, since there is mounting evidence that a significant proportion (15% to 30%) of episodes of acute bronchitis in adult outpatients from primary care settings may involve bronchospasm or wheezing.[6,9,28,29]

Pulmonary Function Measurement and Diagnosis of Asthma

Patients with acute asthmatic bronchitis had peak expiratory flow measurements documented (best of three values) using a Wright peak flow meter (Armstrong Industries, Inc, Northbrook, Ill). Standardized normal values for age, sex, and height were also recorded. Patients with persistent wheezing and dyspnea in whom a diagnosis of asthma was suspected had spirometric testing performed using a spirometer (System 21, Gould Medical Products Inc, Dayton, OH). This study employed American Thoracic Society (ATS) guidelines for the diagnosis of asthma and chronic obstructive pulmonary disease (COPD).[30,31]

Clinical diagnoses of acute asthmatic bronchitis and asthma and serologic results of patients (n = 50) enrolled between October and December 1989 were included in our first report associating *C pneumoniae* infection with reactive airway disease.[9] The results of pulmonary function testing for this group have not been published previously. When these original patients were compared with the 81 patients enrolled after December 1989, there were no significant differences in mean age, sex, history of smoking, *C pneumoniae* seroreactivity, titer category or acute antibody, or diagnoses of acute asthmatic bronchitis, asthma, or COPD.

Bacteriologic and Serologic Data

Acute sera for microimmunofluorescence (MIF) testing for *C pneumoniae* and complement fixation (CF) testing for *M pneumoniae* and oropharyngeal culture for *C pneumoniae* and *M pneumoniae* were obtained at the time of study enrollment for all patients. Because 17 patients

failed to return for follow-up testing, convalescent sera were available from only 114 patients (87%). Serologic criteria for acute *C pneumoniae* infection were (1) a four-fold titer rise in either IgM seroreactivity or polyvalent (mixture of IgM, IgG, and IgA) seroactivity in the MIF test (using the TW-183 strain as antigen), or (2) any IgM titer ≥1:16, or (3) any polyvalent titer ≥1:512. Currently, there are no clearcut serologic criteria for chronic *C pneumoniae* infection. *C pneumoniae* titer category of patients not meeting serologic criteria for acute infection was defined as the greater of the acute or convalescent titer, or the acute titer if the convalescent was not available (<1:16 [seronegative], 1:16, 1:32, 1:64 and ≥1:128). Serologic criteria for acute *M pneumoniae* infection were (1) a four-fold or greater difference between acute and convalescent CF titers, or (2) a single acute CF titer of 1:128 or greater. Oropharyngeal cultures were transported from the study clinic to the Wisconsin State Laboratory of Hygiene in Madison for culture on McCoy cells as described previously.[9]

Clinical Categorization of Patients

Respiratory diagnoses made at enrollment and during the 6-month periods preceding and following enrollment were recorded for all subjects. A 6-month period was chosen to allow identification of patients who developed persistent asthma following the enrollment illness. Medical records were also completely reviewed for evidence of previous asthma and COPD. Based on this information, patients were classified into one of three diagnostic groups:

Group 1, Asthma (n = 12): This group included patients who had persistent wheezing and dyspnea and who met ATS criteria for reversible airway obstruction after inhaling albuterol or ingesting oral steroids. Five (41.7%) group 1 asthma patients were given a diagnosis of asthma for the first time during the postenrollment period, and the other 7 (58.3%) had exacerbations of previously diagnosed asthma.

Group 2, Acute asthmatic bronchitis (n = 30): This group consisted of patients who had cough and wheezing, a diagnosis of acute bronchitis with wheezing, or a diagnosis of asthmatic bronchitis at enrollment, and who did not have persistent asthma symptoms during the 6 months following enrollment.

Group 3, Nonwheezing respiratory illness (n = 89): This group included other patients with acute respiratory illness and no clinical evidence for either acute asthmatic bronchitis or asthma.

Respiratory diagnoses at enrollment and for the 6-month period before and after enrollment were tabulated by a medical record reviewer who was unaware of the culture and serologic results. Serologic results were unavailable at the time of study enrollment, and therefore could not have influenced enrollment or preenrollment diagnoses. Because the clinician-investigator became aware of serologic results sometime during the 6-month postenrollment period, diagnostic bias after that time cannot be excluded. However, other clinicians in the practice setting who may have made respiratory diagnoses in study patients were not aware of serologic results. Also, other than those enrolled, no other adult patient encountered by the principal investigator in this primary care practice reported asthma symptoms in association with acute respiratory illness during the study period. Therefore, bias related to exclusion of seronegative asthma patients with respiratory illness is possible but seems unlikely.

Statistical Methods

The chi-square test was used to analyze tabular data containing more than five items per category; otherwise, Fisher's exact test was used to analyze 2 × 2 tables, and a Monte-Carlo procedure (Bill Engels, Genetics Department, University of Wisconsin, Madison) was used to estimate the probabilities for NxK tables (minimum of 10,000 iterations per table). Analysis of variance was used to test differences in mean ages, and the Kruskal-Wallis test and the Mann-Whitney U test were used to compare geometric mean titers of subgroups. In the analysis of geometric mean titers, titers reported as <1:16 were coded as 1:8. Associations between diagnostic groups and seroreactivity were controlled for age, sex, and current smoking status using logistic regression.[32] Two-sided *P* values ≤.05 are reported as significant.

This study was approved by the human subjects committee of St Marys Hospital Medical Center, Madison, Wisconsin, and all patients gave informed consent. Further details of the study population, data collection methods, and microbiologic and serologic techniques have been published elsewhere.[9]

Results

Patient Characteristics

Mean age of the 131 patients was 36.4 years (range 11 to 78, standard deviation [SD] 13.5), 43.5% were male and 29.1% were smokers. One hundred twenty-seven (97%) subjects were 15 years of age or older. Eighty-three

Table 1. Characteristics of Asthma Patients and Description of Respiratory Illnesses That Preceded the Diagnosis of Asthma

Case No.	Age (y)	Sex	Chlamydia Titer Category*	COPD Category	Antecedent Respiratory Illnesses
1†	31	F	32	None	Bronchitis
2†	36	F	32	None	Pneumonia
3†	46	M	256	None	Bronchitis
4†‡	52	M	256	Moderately severe	Episodes of asthmatic bronchitis
5†§	57	M	32	Moderate	Pneumonia
6	58	F	64	Very severe	Wheezing exacerbations of COPD
7	59	F	32	Moderate	Bronchitis
8‡	60	M	512	Moderately severe	Sore throat, gradual onset of wheezing, and dyspnea
9	63	M	32	Severe	Wheezing with a "cold"
10	73	F	128	Mild	Episodes of asthmatic bronchitis
11	73	F	256	Mild	Chronic cough and sinusitis
12	75	F	64	Severe	Chronic bronchitis with episodes of pneumonitis; possible interstitial lung disease

**Greater of the* C pneumoniae *acute or convalescent polyvalent titer.*
†Newly diagnosed asthma.
‡Acute C pneumoniae *infection (serologic criteria).*
§Acute M pneumoniae *infection (serologic criteria).*
COPD denotes chronic obstructive pulmonary disease.

(63.4%) of 131 patients had *C pneumoniae* seroreactivity of 1:16 or greater in the polyvalent MIF test (72% of 49 men and 57% of 82 women, $P = .10$). Serologic evidence for acute *C pneumoniae* infection was present in 7 (5.3%) patients, and acute *M pneumoniae* infection was found in an additional 10 (7.6%) patients. There were no positive oropharyngeal cultures for *C pneumoniae* or *M pneumoniae*.

Clinical Findings in Patients with Atypical Infections and Asthma

Nine of 10 patients with acute *M pneumoniae* infection had atypical pneumonia confirmed by an infiltrate on chest x-ray film. The remaining patient with acute *M pneumoniae* infection had a diagnosis of bronchitis, but since he did not have a chest radiograph, it is possible that pneumonia might have been missed. Two patients with acute *M pneumoniae* infection had coexisting COPD, and one of these patients had prolonged dyspnea with spirometric evidence for reversible airway obstruction, which persisted during the postenrollment period but subsequently resolved (Table 1).

The clinical presentations of the seven patients with acute *C pneumoniae* infection were heterogeneous. Three patients had bronchitis (two also had pharyngitis or laryngitis), one patient had atypical pneumonia, and two patients had acute asthmatic bronchitis (one of these had a biphasic illness presentation). One of the patients with acute asthmatic bronchitis at enrollment later presented with another wheezing episode and rapidly developed severe, disabling, steroid-dependent asthma. The seventh patient with acute *C pneumoniae* antibody presented with mild pharyngitis and a history of gradual onset of wheeze and dyspnea. He required oral theophylline and inhaled bronchodilator therapy because chronic asthma developed and persisted until his death from other causes.

Clinical data for asthma patients are individually summarized in Table 1. The asthma diagnosis was preceded by a variety of acute or chronic respiratory illnesses in each case. COPD tended to be age related, as younger patients did not have it. Cases 2, 3, 7, and 10 had strong family histories of asthma. None of the asthma patients described in Table 1 had a history of childhood asthma, nor did any of them have histories implicating aeroallergens as triggers of asthma symptoms. In case 1, skin testing with a battery of common aeroallergens produced negative results. IgE and blood eosinophils were not measured in this study. Therefore, the atopic status of these patients, as indicated by skin testing, IgE levels, and eosinophilia, was not determined. All asthma patients improved clinically with standard antiasthma medication (inhaled albuterol, oral theophylline, and/or steroids).

Comparison of Wheezing and Nonwheezing Respiratory Illness Groups

Table 2 compares clinical and serologic data for patients with asthma, acute asthmatic bronchitis, and nonwheezing respiratory illness. Asthma patients were significantly older ($P < .001$) and had COPD more often ($P < .001$) than did patients with asthmatic bronchitis or nonwheezing respiratory illness. Four asthma patients had mild to moderate COPD, and five had moderately severe to very severe COPD accompanying their asthma diagnosis. There were no significant differences between groups in the prevalence of previous asthma, which did not appear to be reactivated by acute respiratory illness in group 3.

Table 2. Study Group Characteristics and Associations with Atypical Infection by Diagnostic Category

Characteristic	Group 1 Asthma (n = 12)	Group 2 Asthmatic Bronchitis in Patients Without Asthma (n = 30)	Group 3 Nonwheezing Respiratory Illnesses* (n = 89)	*P* Value
Age, (y), mean (range)	56.9 (31–75)	32.2 (15–50)	34.9 (11–78)	<.001
Sex (% male)	41.7	40.0	44.9	NS
Current smoker (%)	41.7	43.3	23.3	NS
Previous diagnoses (%)				
Asthma†	58.3	16.7	7.9	NS
COPD	75.0	6.7	4.5	<.001
C pneumoniae				
Serologic acute infection (%)	16.7	3.3	4.5	NS
Seroreactivity (%)	100	80.0	52.8	<.001
Geometric mean titer	76.1	29.2	18.9	.0001
M pneumoniae				
Serologic acute infection (%)	8.3	0.0	6.9	NS

**Pharyngitis (28.1%), laryngitis (22.5%), sinusitis (27.0%), influenza-like illness (6.7%), biphasic illness (5.6%), bronchitis (43.8%), atypical pneumonia (25.8%). Excluding bronchitis, distribution of diagnoses was not significantly different for other groups. Percentage adds to greater than 100 because some patients had multiple diagnoses.*
†Group 1: 7 (58.3%) of 12 had an exacerbation of previous asthma, and 5 (41.7%) had asthma diagnosed for the first time during this study; Group 2: 5 (16.7%) of 30 patients with a previous diagnosis of asthma did not have persistent symptoms during this study; Group 3: 7 (7.9%) of 89 had a previous diagnosis of inactive asthma.
NS denotes not significant.

C pneumoniae seroreactivity, whether measured as seroprevalence or as geometric mean titer, was significantly ($P < .001$ and $P = .0001$, respectively) more common in asthma patients and in patients with asthmatic bronchitis than in patients with nonwheezing illnesses. Using nonwheezing patients as controls, logistic regression analysis showed that these significant differences persisted after adjusting for age, sex, and smoking status. Significant dose-response associations of *C pneumoniae* titer with both acute asthmatic bronchitis ($P < .05$) and asthma ($P < .01$) were also noted. After excluding the four asthmatic patients with documented improvement in FEV_1 ranging from 12% to 14%, a significant ($P = .02$) difference in the prevalence of *C pneumoniae* seroreactivity between group 1 and group 3 patients persisted.

Comparable logistic regression models were developed for indicators of *M pneumoniae* infection. In these analyses, no significant associations with asthma or acute asthmatic bronchitis were found for (1) CF seroreactivity (1:8 or greater), or (2) CF titer for *M pneumoniae*. "Preexisting" *M pneumoniae* infection could not be measured because of the nature of the test, and therefore any possible relationship of "old" antibody with reactive airway disease could not be assessed.

Dividing the study group into patients enrolled between October and December 1989, and those enrolled after December 1989, acute asthmatic bronchitis remained significantly associated with *C pneumoniae* seroreactivity, titer category, and geometric mean titer within each subgroup analyzed separately.

Discussion

The case series reported here is consistent with previous observations that bronchitis often precedes the diagnosis of adult-onset asthma[6,33] and that asthma presenting after age 40 is often difficult to distinguish from, or coexists with, obstructive airway disease.[34] The association of asthma with previous respiratory disease has been interpreted as evidence that preceding symptoms were actually due to undiagnosed asthma.[7] Currently, there is little evidence that bacterial respiratory illnesses are related to the development of asthma or that any one specific pathogen is responsible for a significant proportion of the respiratory illnesses preceding the development of asthma in adults.[4]

Our study coincided with an epidemic of *M pneumoniae*. Nevertheless, *M pneumoniae* infection was associated with only one case of asthma in our study, and no antibody associations could be demonstrated. In studies by other investigators, *M pneumoniae* infection has been associated with infectious exacerbations of asthma in less than 1% of older adults (mean age, 48 years),[35] in 21% of younger adults (mean age, 34 years),[15] and in 25% of children and adults less than 30 years of age.[14] Our results provide further evidence that *M pneumoniae* infection plays a minor role in asthma in older adults.

Observations on our case series of patients with asthma and acute asthmatic bronchitis confirm and extend previous findings,[9] suggesting that *C pneumoniae* infection, as measured by seroreactivity, is associated with reactive airway disease. Our initial study, which did

not employ pulmonary function testing, showed an association of *C pneumoniae* seroreactivity with wheezing and with the clinical diagnosis of acute asthmatic bronchitis.[9] Serologic evidence for acute secondary *C pneumoniae* infection was also found in some patients with newly diagnosed asthma as well as in patients with an exacerbation of previously diagnosed asthma. The case series reported here included a significant association of *C pneumoniae* seroreactivity with asthma confirmed by pulmonary function tests. This association of *C pneumoniae* seroreactivity with asthma persisted after adjusting for age, sex, and smoking status, or when a more stringent criterion for reversible airway obstruction was used (15% or greater increase in FEV_1 following bronchodilator therapy, rather than the 12% or greater value currently suggested by the ATS).[30]

It is unclear whether these serologic associations reflect previous exposure or persistent infection. The usefulness of serologic diagnosis without culture confirmation of *C pneumoniae* has been questioned recently, as serologic criteria have been found to be problematic in some studies in children.[36] However, most investigators performing microimmunofluorescence testing for *C pneumoniae* feel that serologic criteria for acute primary infection in adults are sensitive.[37] Serologic diagnosis of secondary or chronic *C pneumoniae* infection, on the other hand, is difficult when four-fold titer changes or a convalescent titer is absent because of lack of an IgM response. There are also inherent problems in interpreting an arbitrary serologic cutpoint.[37]

Our studies employed a polyvalent (mixture of IgM, IgG and IgA) antibody test. Since most of the patients reported here had IgM antibody titers of less than 1:16, the findings in this study reflect associations of reversible airway disease with IgG and/or IgA class antibody. IgA antibody has recently been suggested as a marker for chronic *C pneumoniae* infection in coronary heart disease.[23] Further study is needed to determine whether the polyvalent antibody associations with asthma and asthmatic bronchitis reported here reflect IgA or IgG antibody activity.

We did not succeed in culturing *C pneumoniae* from the oropharynx of any of our patients. It is possible that nasopharyngeal swabbing rather than oropharyngeal swabbing, as well as improved transport of specimens to the laboratory, would have more likely yielded positive cultures. Optimization of sampling, specimen handling[38] and culture techniques,[39–41] and use of polymerase chain reaction testing[18] are necessary before concluding that *C pneumoniae* is absent from the upper respiratory tract of symptomatic asthma patients. Chronic chlamydial infections may involve deep tissues only.[25] It is possible that some categories of asthma patients have deep-seated lung infection without having nasopharyngeal infection. If so, bronchoscopic sampling of pulmonary macrophages[42] or of tissue samples from the lower respiratory tract is necessary to exclude chronic *C pneumoniae* infection in asthma patients.

Since patients with chronic lung disease may be susceptible to infection by a variety of microorganisms, it is possible that *C pneumoniae* seroreactivity is a result of asthma rather than an antecedent risk factor for asthma. However, seroreactivity was also associated with acute wheezing illness in many patients without evidence of chronic lung disease in our study. Either persistent infection with *C pneumoniae* or sensitization of T cells by previous chlamydial infection could plausibly contribute to asthmatic inflammation. Ongoing chlamydial infections cause inflammatory reactions at the site of infection.[43] Inflammatory damage might result from reactivation of previously sensitized lymphocytes by cross reaction with other infectious agents[44] or with human antigens to cause autoimmune inflammation.[45] As examples, chlamydial infection causes inflammatory damage responsible for blindness in trachoma and infertility and ectopic pregnancy in pelvic inflammatory disease.[20] Delayed hypersensitivity to a highly immunogenic chlamydial protein (called "heat shock protein") has been strongly implicated in the pathogenesis of trachoma,[45,46] probably is involved in tubal damage in chlamydial pelvic inflammatory disease,[44,47,48] and may possibly be involved in the pathogenesis of sexually acquired reactive arthritis.[49]

Although the serologic associations reported here do not distinguish current infection from previous exposure, they do suggest that *C pneumoniae* infection plays a role in the natural history of adult-onset asthma. Further studies of this important association are warranted.

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