Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of *Chlamydia pneumoniae* infection

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Background: Persistent airflow limitation may develop in patients with asthma, particularly in adults with nonatopic (intrinsic) disease. Although the underlying mechanisms are still unknown, respiratory infections might be involved.
Objective: We investigated the annual loss of lung function in relation to seropositivity to *Chlamydia pneumoniae* in different subgroups of patients with severe asthma according to age at onset of asthma and atopic status.
Methods: One hundred one nonsmoking outpatients with a pulmonologist's diagnosis of severe asthma (32 men and 69 women; mean age, 46.0 years; range, 18-75 years) were included in a cross-sectional study. *C pneumoniae*–specific serum IgG and IgA were measured by means of ELISA. The estimated decline in lung function was calculated from the relationship between postbronchodilator FEV_1/vital capacity (percent predicted) and the duration of asthma and expressed as the slope of the regression line.
Results: Patients with adult-onset nonatopic asthma and positive IgG antibodies to *C pneumoniae* had a significantly steeper slope of the regression line compared with the other subgroups of asthmatic patients ($P = .001$), being indicative of a 4-fold greater estimated decline in postbronchodilator FEV_1/vital capacity (2.3% vs 0.5% predicted per year of asthma duration).
Conclusion: These results suggest that *C pneumoniae* infection might promote the development of persistent airflow limitation in patients with nonatopic adult-onset asthma. It remains to be established whether viable pathogens that are accessible for therapeutic intervention are still present in the lower airways. (J Allergy Clin Immunol 2001;107:449-54.)

Key words: *Asthma, severity of illness index, airway obstruction, prognosis, chronic disease, phenotype, Chlamydia pneumoniae, infection, immunology, human*

Abbreviation used
VC: Vital capacity

Bronchial asthma is generally considered a chronic inflammatory airways disease with variable and fully reversible airways obstruction. However, persistent airflow limitation may develop in a subgroup of patients with asthma without a significant history of smoking and despite optimal treatment.[1,2] In particular, adults with recent-onset nonatopic (intrinsic) asthma seem to be at higher risk for an increased decline in lung function.[3,4]

The nature of persistent airflow limitation is still unknown but is presumed to be due to structural changes within the airway wall associated with ongoing submucosal inflammation.[5] The inflammatory mechanisms promoting such airway remodeling are far from being clarified, but it has been suggested that persistence of microorganisms in the tracheobronchial tree might be involved.[6]

Airway inflammation, airway fibrosis, and airway wall thickening have been shown to develop in response to *Mycoplasma pulmonis* infection,[7] and evidence for persistent adenoviral infection in chronic obstructed airways has been demonstrated in children.[8] Also, *Chlamydia pneumoniae* has been associated with a broad spectrum of chronic diseases in human beings, including chronic obstructive pulmonary disease[9] and asthma.[10-13] In particular, adult-onset asthma[12] and severe longstanding nonatopic asthma[14,15] have been associated with serologic evidence of chronic *C pneumoniae* infection, suggesting that local immune responses to this intracellular pathogen might play a role in the severity and chronicity of asthma.[12,14,16]

In the present study we hypothesized that patients with severe adult-onset asthma without any evidence of atopy (intrinsic asthma) have persistent airway narrowing as a consequence of recurrent or chronic infection with *C pneumoniae*.

Therefore the aim of the present study was to compare patients with adult-onset, nonatopic, severe asthma with patients having equally severe early-onset or atopic asth-

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ma regarding *C pneumoniae* IgG and IgA antibodies and the decrease of lung function over time.

METHODS

Patients

Patients aged 18 to 75 years with severe bronchial asthma were asked to participate in this study. They were recruited from the outpatient pulmonary departments of 2 teaching and 8 nonteaching hospitals in the western part of The Netherlands between May 1998 and April 1999. Patients were eligible to enter the study if they had a diagnosis of asthma based on a history of episodic dyspnea and wheezing, a documented (recently or in the past 5 years) reversibility in FEV_1 of greater than 12% of predicted value,[17] or hyperresponsiveness to inhaled histamine (PC_{20} <8 mg/mL). All patients had to be symptomatic, with dyspnea, wheezing, cough, an impaired exercise tolerance, nocturnal symptoms, or frequent use of rescue medication. They had to use high doses of inhaled corticosteroids (dose ≥1600 μg/d beclomethasone or equivalent) combined with long-acting β_2-agonists or theophylline for more than 1 year. All had to have severe disease, requiring at least one course of oral corticosteroids during the last year or maintenance therapy with oral prednisone of 5 mg/d or greater. Current smokers and patients with a smoking history of more than 10 pack-years were excluded from participation. Early-onset asthma was defined as onset before the age of 18 years, and adult-onset asthma was defined as onset at 18 years of age or older, with the cutoff point of 18 years being the median age at onset for the whole group. The study was approved by the hospital medical ethics committee, and all patients gave informed consent.

Design

The study had a cross-sectional design. At entry into the study, patient characteristics were documented according to a structured questionnaire. The age at onset of asthma symptoms was used for the calculation of the duration of asthma. To judge the age at onset of asthma as accurately as possible, patients were questioned about a history of episodes of dyspnea, wheezing, or cough during childhood and puberty or lagging behind in physical education or other daily activities compared with classmates. In case of uncertainty, the earliest respiratory symptoms were taken into account. Furthermore, a blood sample was taken, and lung function measurements were performed.

C pneumoniae serology

C pneumoniae–specific IgG antibodies were detected in serum by using a purified *C pneumoniae* elementary-bodies ELISA (Savyon Diagnostics Ltd). Comparison of this ELISA with different commercially available ELISAs (with *C pneumoniae*-specific recombinant LPS antigens) and an in-house *Chlamydia* strain–specific microimmunofluorescence assay revealed a good correlation between the *C pneumoniae*–specific ELISAs, with the ELISA used in the present study comparing favorably with respect to interassay variation. For IgA antibody determination, anti-human IgA conjugated to horseradish peroxidase was used. All sera were tested in a blinded fashion and a single batch of ELISAs was used. Prevalence of anti-*C pneumoniae* IgG and IgA antibodies was based on cutoff values according to the instructions of the manufacturer to obtain positive and negative results. Positive control sera supplied by the manufacturer showed interassay OD value variation within 15%.

Atopy and total IgE

Atopic status was assessed by using specific IgE to a panel of common aeroallergens (house dust mite, grass and birch pollen, cat and dog dander, mugwort, and fungi; UniCAP, Pharmacia & Upjohn). A patient was considered to be atopic when showing a score of 1 or greater for at least one of the specific IgEs. Total IgE was assessed with a fluoroenzyme immunoassay (UniCAP, Pharmacia & Upjohn).

Pulmonary function

Bronchodilators were withheld, if possible, for at least 12 hours before pulmonary function tests were performed. All tests were conducted in the morning by an experienced technician. First, slow inspiratory vital capacity (VC) maneuvers were performed, followed by FEV_1 measurements, on a calibrated dry-rolling seal spirometer. The largest values from the first 3 technically satisfactory maneuvers were taken, with a difference between the 2 highest values of less than 5% or 0.1 L considered acceptable. FEV_1/VC was assessed before and 30 minutes after the administration of 400 μg of salbutamol and 80 μg of ipratropium bromide through metered-dose inhalers with a spacer device. Reversibility in FEV_1 was defined as follows:

$$(FEV_1\text{post} - FEV_1\text{baseline})/FEV_1\text{predicted},[17]$$

with an improvement in FEV_1 of larger than 12% of predicted value and exceeding 200 mL being indicative of a clinically significant improvement. The predicted values for FEV_1, VC, and FEV_1/VC were calculated according to the proposal by Quanjer et al.[17]

Statistical analysis

The 2 groups of patients with early-onset and adult-onset asthma were compared with respect to demographic data, RAST results, and lung function by using unpaired Student *t* tests, Wilcoxon rank tests, and χ^2 analyses whenever appropriate. The relationship between asthma duration and postbronchodilator FEV_1/VC (percent predicted) or FEV_1 (in milliliters) was investigated with regression analyses and Pearson correlation coefficients. Slopes of the regression lines (estimated regression weight) were interpreted as the annual decline in lung function. Differences in the slopes were assessed by using multiple linear regression analyses. All analyses were performed with the Statistical Package of the Social Sciences (SPSS-9.0) software. *P* values of less than .05 were considered statistically significant.

RESULTS

Patient characteristics

One hundred one patients with severe asthma participated in the study. Fifty-one percent of the patients had early-onset asthma, whereas 49% of the patients had asthma that started at or after the age of 18 years (Table I). About two thirds of the patients were women, and there was no significant difference in sex or age between the groups. As expected, patients with early-onset asthma had a significantly longer duration of their disease (median, 37 years) compared with that found in the patients with adult-onset asthma (median, 12 years). Thirty-one percent of the patients with early-onset asthma, as compared with 37% of those with adult-onset asthma, needed maintenance treatment with oral corticosteroids (median dose of 10 mg [range, 5-60 mg] vs 10 mg [5-40 mg] of prednisone a day, respectively [$P > .5$]). Seventy-nine percent of the patients with early-onset asthma had a positive RAST result, whereas the majority of patients with adult-onset asthma (65%) were nonatopic ($P < .001$). No significant differences were observed between the 2 groups with respect to baseline

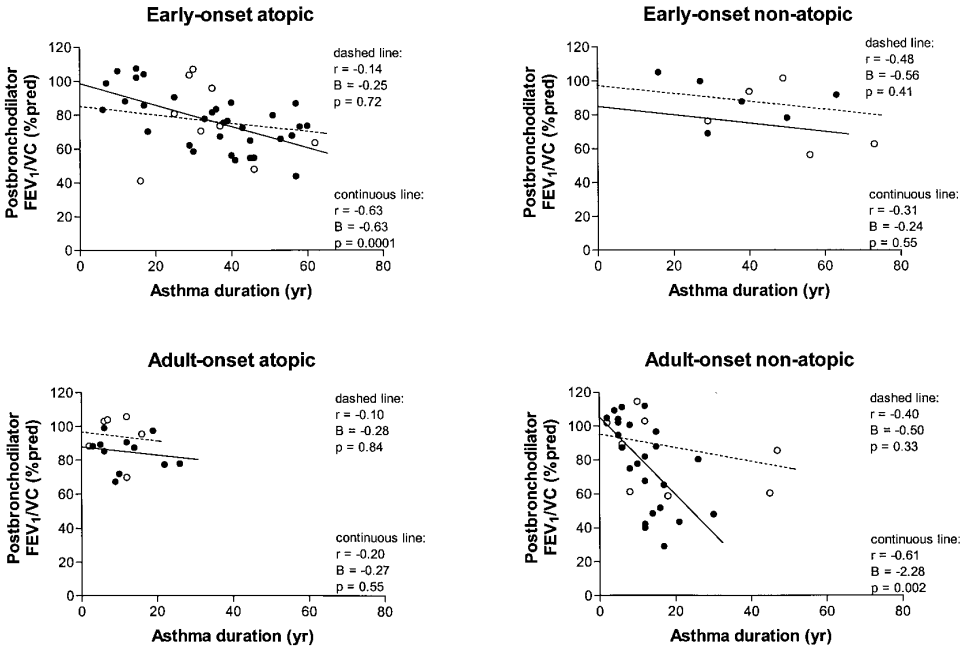


FIG 1. Relationship between asthma duration and postbronchodilator FEV_1/VC (percent predicted *[%pred]*) in different subgroups of patients with severe asthma according to age at onset of asthma, atopic status, and *C pneumoniae* IgG seropositivity (*filled circles* and *continuous lines*) versus seronegativity (*open circles* and *dashed lines*). Only in the subgroup of patients with adult-onset nonatopic asthma was a significant difference ($P = 0.03$) in the slopes of regression lines observed. *B,* Slope of regression line, with corresponding *P* value.

TABLE I. Comparison of patients with early-onset and adult-onset severe asthma

	Early-onset (<18 y), n = 52	Adult-onset (≥18 y), n = 49	*P* value
Age (y)*	45.5 ± 14.5	46.6 ± 11.9	.68
Sex (M/F)	15/37	17/32	.53
Asthma duration (y)†	37 (6-73)	12 (2-47)	<.001
Pack-years†	0 (0-10)	0 (0-10)	.14
Dose of inhaled corticosteroids†	1600 (1600-6400)	1600 (1600-4800)	.69
Positive RAST result (%)	78.8	34.7	<.001
Positive IgG to *C pneumoniae* (%)	73.1	71.4	.85
Positive IgA to *C pneumoniae* (%)	65.2	54.3	.29
Postbronchodilator FEV_1 (% pred)*	75.7 ± 22.6	78.6 ± 26.4	.56
Reversibility of FEV1 (% pred)†	10.6 (2-29)	9.1 (–1 to 44)	.21
Postbronchodilator FEV_1/VC (% pred)*	78.2 ± 17.7	82.3 ± 21.6	.29

P values are for differences between groups.
*Mean ± SD.
†Median (range).

FEV_1 or FEV_1/VC or postbronchodilator values of FEV_1 or FEV_1/VC (percent predicted).

C pneumoniae serology

The seroprevalence of *C pneumoniae*–specific IgG and IgA antibodies, as determined by ELISA, in the 101 patients with severe asthma was 73% and 60%, respectively (Table I). Seven patients showed IgA but no IgG antibodies directed against *C pneumoniae*, whereas 20 patients with *C pneumoniae* IgG antibody seropositivity lacked IgA antibodies. There were no significant differences in IgG or IgA seropositivity between patients with early-onset and adult-onset asthma as a whole.

C pneumoniae and loss of lung function over time

The annual loss of lung function, as calculated from the relationship between asthma duration and postbronchodilator FEV_1/VC (percent predicted) values, was assessed for different subgroups of patients with severe asthma according to age at onset of asthma, atopic status, and IgG seropositivity for *C pneumoniae* (Fig 1). There was a significant difference ($P = .03$) in the slopes of regression lines between patients with *C pneumoniae* IgG seropositivity and those with *C pneumoniae* IgG seronegativity in the subgroup of patients with adult-

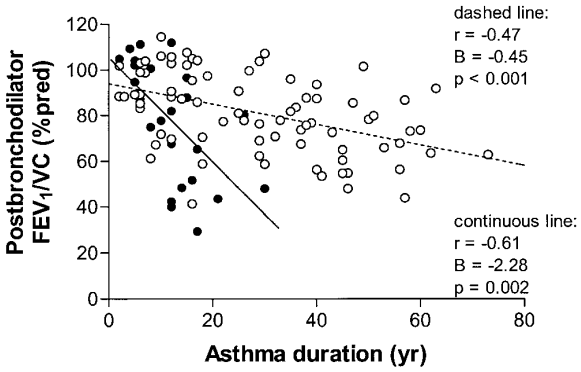


FIG 2. Relationship between asthma duration and postbronchodilator FEV_1/VC (percent predicted *[%pred]*) in patients with *C pneumoniae* IgG seropositivity and adult-onset nonatopic severe asthma (*open circles* and *continuous line*) versus the other subgroups (*filled circles* and *dashed line*). *B,* Slope of regression line, with corresponding *P* value (difference between the slopes, $P = .001$).

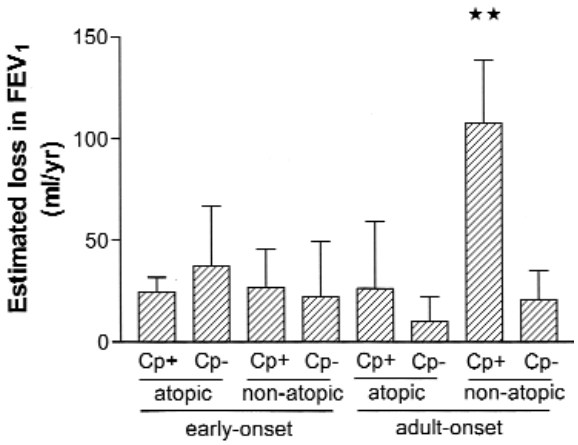


FIG 3. Estimated decrease in unadjusted FEV_1 (in milliliters) per year of asthma duration for 8 subgroups of patients with severe asthma according to age at onset of asthma, atopic status, and *C pneumoniae* IgG seropositivity. This decrease was calculated from the relationship between postbronchodilator FEV_1 and the duration of asthma and expressed as the slope of the regression line. *Bars* and *error bars* represent mean values and SEM. *Cp+* and *Cp–,* positive or negative *C pneumoniae* IgG antibodies, respectively. $**P < .01$ (patients with *C pneumonia* IgG seropositivity and adult-onset nonatopic asthma versus the other subgroups).

onset nonatopic asthma only, with the patients with IgG seropositivity showing increased airflow limitation for a given duration of asthma compared with those with IgG seronegativity.

For 7 of the 8 subgroups, the slopes of the regression lines were in a comparable range (slope of regression line, –0.25 to –0.63), corresponding with a mean decrease in postbronchodilator FEV_1/VC of about 0.5% predicted per year (Fig 2). The slope of the regression line observed in the patients with *C pneumoniae* IgG seropositivity and adult-onset nonatopic asthma was significantly steeper compared with those of the other subgroups (difference between the slopes, $P = .001$), showing a 4-fold greater estimated decline in postbronchodilator FEV_1/VC (2.3% of predicted value) per year of asthma duration. Similar results were obtained when reanalyzing the data with the postbronchodilator FEV_1 percent predicted as the outcome variable (data not shown). With respect to *C pneumoniae* IgA seropositivity, no significant differences between the slopes of the regression lines were found between the subgroups.

In Fig 3 the estimated decrease in unadjusted FEV_1 (in milliliters) per year of asthma duration is demonstrated for the 8 subgroups, showing an annual decline in FEV_1 (mean ± SEM) of 108 ± 31 mL in the patients with *C pneumoniae* IgG seropositivity and adult-onset nonatopic asthma. This is significantly higher compared with that found in the other subgroups, showing mean decreases of 21 to 37 mL in FEV_1 per year of asthma duration.

DISCUSSION

This study indicates that patients with adult-onset nonatopic (intrinsic) asthma have increased loss of lung function, which is related to the presence of circulating IgG antibodies against *C pneumoniae*. The estimated decline in FEV_1/VC (percent predicted) per year of asthma duration in this group of patients is about 4 times greater compared with that found in other patients with similar demographic and clinical characteristics and equally severe asthma. These findings fit in with the hypothesis that persistent airflow limitation in asthma is associated with chronic or recurrent infections with respiratory pathogens and suggest that *C pneumoniae* might be involved in the development of structural changes in the airway wall.

To our knowledge, this is the first study showing an association between serologic evidence of previous infection with *C pneumoniae* and persistent airflow limitation in patients with severe asthma. One earlier study showed that elevated IgG antibody levels to *C pneumoniae* were most prominent in asthmatic patients with a long duration of disease.[15] From 2 other studies, it appeared that chronic *C pneumoniae* infection was most likely to be associated with severe, longstanding, adult-onset asthma,[12,14] whereas one study in a general asthma population showed a weak but significant inverse correlation between the level of IgG antibodies to *C pneumoniae* and FEV_1 percent predicted.[16] Our findings confirm and extend these data by showing more specifically that only in the subgroup of patients with adult-onset nonatopic severe asthma seropositivity to *C pneumoniae* is an independent predictor of persistent airflow limitation.

The results of the present study do not seem to be biased by patient selection, design, or methods used. The patients were carefully selected to be nonsmokers with severe asthma, although a positive smoking history of up to 10 pack-years was allowed. An independent effect of smoking was, however, unlikely because the analysis showed that a positive smoking history was not a predictor of increased airflow limitation. The data on duration

of asthma were based on self-report and might therefore have been influenced by recall bias. Although we cannot fully exclude such bias, maximal attention was paid to this item, and all respiratory symptoms, such as cough, dyspnea, wheeze, and lagging behind in physical education or other daily activities compared with classmates, were taken into account. In addition, the observed differences in slopes between patients with or without IgG seropositivity within the subgroup of adult-onset asthma cannot be attributed to this bias factor. It can be argued that the use of cross-sectional data to investigate the loss of lung function over time might have influenced the results. However, when looking at longitudinal studies available on this issue, it appears that the estimated mean annual decline of lung function in our study was very similar to the unadjusted decline in FEV_1 of 38 mL[2] and 36 mL[18] per year found in adults with asthma of varying severity. Therefore it seems unlikely that the present findings were largely affected by the limitations of a cross-sectional study.

The striking association between seropositivity to *C pneumoniae* and increased decline in lung function in adult-onset asthma is compatible with the hypothesis that this respiratory pathogen might be involved in airway remodeling.[7,19] Chlamydiae are obligate intracellular microorganisms responsible for infections that are generally mild or even asymptomatic and may persist for long periods of time if untreated.[20] High serum titers of IgG or IgA antibodies to chlamydiae are considered as an indicator of recurrent or chronic infection.[21] In conjunctivae and fallopian tubes such recurrent or chronic infections with chlamydiae are known to be associated with tissue scarring.[22,23] *C pneumoniae* might therefore in turn lead to fibrosis in the airway wall by similar mechanisms, thereby causing loss of reversibility and enhanced airways obstruction.

Our observation of an increased loss of lung function over time in seropositive patients was restricted to those with adult-onset, nonatopic, so-called intrinsic asthma. The controversy over the existence of intrinsic asthma as a separate disease entity has been unresolved for decades.[24] Clinicians generally accept the existence of intrinsic asthma, referring to those asthmatic patients without an apparent underlying allergic disorder who characteristically have a later onset of symptoms and a more severe clinical course of the disease compared with those with allergic asthma.[25,26] The development of persistent airflow limitation in these patients is of particular concern because it is directly linked to morbidity and mortality.[27,28] Studies comparing the immunopathology of atopic (extrinsic) and nonatopic (intrinsic) asthma[29,30] have found more similarities than differences between the 2 disease subtypes.[25,31,32] Humbert et al,[25] who found evidence of local IgE production and abnormal macrophage activation in bronchial biopsy specimens from nonatopic asthmatic adults, postulated the existence of an ongoing immune response against an as-yet unidentified antigen, possibly infectious in origin. Our finding of an association between IgG seropositivity to *C pneumoniae* and increased airflow limitation in adult-onset nonatopic asthma only fits in with his hypothesis.

Our findings have implications for the clinical management of adult-onset asthma. About one third of the patients with severe asthma in our study had a fast decline in lung function and were thereby at risk for increased morbidity and mortality.[27,28] Yet these patients were treated with high doses of inhaled, oral, or both types of corticosteroids, suggesting that these patients with *C pneumoniae* IgG seropositivity and adult-onset nonatopic asthma were relatively steroid insensitive. In guinea pigs steroid resistance has recently been shown to be associated with latent adenoviral infection.[33] If respiratory pathogen-induced steroid insensitivity also occurs in patients with asthma, then alternative therapeutic approaches might be required.

In conclusion, the results from this cross-sectional study suggest that recurrent or chronic infection with *C pneumoniae* might promote persistent airflow limitation in patients with asthma, particularly in those with adult-onset nonatopic (intrinsic) asthma. If ongoing infection with this pathogen, a specific immune response to chlamydial antigens, or both can be confirmed in the bronchial mucosa of asthmatic patients with persistent airflow limitation, preventive strategies in young patients and vigorous antibiotic treatment in those already affected may provide an important perspective for future asthma management.

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REFERENCES

1. Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow obstruction. Thorax 1984;39:131-6.
2. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194-200.
3. Ulrik CS, Backer V, Dirksen A. A 10 year follow up of 180 adults with bronchial asthma: factors important for the decline in lung function. Thorax 1992;47:14-8.
4. Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. Am J Respir Crit Care Med 1994;150:629-34.
5. Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998;12:1209-18.
6. Reed CE. The natural history of asthma in adults: the problem of irreversibility. J Allergy Clin Immunol 1999;103:539-47.
7. McIntosh JC, Simecka JW, Ross SE, Davis JK, Miller EJ, Cassell GH. Infection-induced airway fibrosis in two rat strains with differential susceptibility. Infect Immun 1992;60:2936-42.
8. Macek V, Sorli J, Kopriva S, Marin J. Persistent adenoviral infection and chronic airway obstruction in children. Am J Respir Crit Care Med 1994;150:7-10.
9. Wu L, Skinner SJ, Lambie N, Vuletic JC, Blasi F, Black PN. Immunohistochemical staining for *Chlamydia pneumoniae* is increased in lung

tissue from subjects with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162(3 Pt 1):1148-51.
10. Cunningham AF, Johnston SL, Julious SA, Lampe FC, Ward ME. Chronic *Chlamydia pneumoniae* infection and asthma exacerbations in children. Eur Respir J 1998;11:345-9.
11. Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. JAMA 1991;266:225-30.
12. Hahn DL, Anttila T, Saikku P. Association of *Chlamydia pneumoniae* IgA antibodies with recently symptomatic asthma. Epidemiol Infect 1996;117:513-7.
13. Miyashita N, Kubota Y, Nakajima M, Niki Y, Kawane H, Matsushima T. *Chlamydia pneumoniae* and exacerbations of asthma in adults. Ann Allergy Asthma Immunol 1998;80:405-9.
14. Cook PJ, Davies P, Tunnicliffe W, Ayres JG, Honeybourne D, Wise R. *Chlamydia pneumoniae* and asthma. Thorax 1998;53:254-9.
15. von Hertzen L, Toyryla M, Gimishanov A, Bloigu A, Leinonen M, Saikku P, et al. Asthma, atopy and *Chlamydia pneumoniae* antibodies in adults. Clin Exp Allergy 1999;29:522-8.
16. Black PN, Scicchitano R, Jenkins CR, Blasi F, Allegra L, Wlodarczyk J, et al. Serological evidence of infection with *Chlamydia pneumoniae* is related to the severity of asthma. Eur Respir J 2000;15:254-9.
17. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;6(Suppl 16):5-40.
18. Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 1999;14:892-6.
19. Tang W, Geba GP, Zheng T, Ray P, Homer RJ, Kuhn C, et al. Targeted expression of IL-11 in the murine airway causes lymphocytic inflammation, bronchial remodeling, and airways obstruction. J Clin Invest 1996;98:2845-53.
20. Ward ME. The immunobiology and immunopathology of chlamydial infections. APMIS 1995;103:769-96.
21. Wong YK, Gallagher PJ, Ward ME. *Chlamydia pneumoniae* and atherosclerosis. Heart 1999;81:232-8.
22. Moore DE, Spadoni LR, Foy HM, Wang SP, Daling JR, Kuo CC, et al. Increased frequency of serum antibodies to *Chlamydia trachomatis* in infertility due to distal tubal disease. Lancet 1982;2:574-7.
23. Mabey DC, Robertson JN, Ward ME. Detection of *Chlamydia trachomatis* by enzyme immunoassay in patients with trachoma. Lancet 1987;2:1491-2.
24. Kroegel C, Jäger L, Walker C. Is there a place for intrinsic asthma as a distinct immunopathological entity? Eur Respir J 1997;10:513-5.
25. Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. Immunol Today 1999;20:528-33.
26. Rackemann FM. A working classification of asthma. Am J Med 1947;3:601-6.
27. Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1267-71.
28. Ulrik CS. Outcome of asthma: longitudinal changes in lung function. Eur Respir J 1999;13:904-18.
29. Virchow JC Jr, Kroegel C, Walker C, Matthys H. Inflammatory determinants of asthma severity: mediator and cellular changes in bronchoalveolar lavage fluid of patients with severe asthma. J Allergy Clin Immunol 1996;98:S27-33.
30. Walker C, Bode E, Boer L, Hansel TT, Blaser K, Virchow JC Jr. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. Am Rev Respir Dis 1992;146:109-15.
31. Tang C, Rolland JM, Ward C, Quan B, Walters EH. IL-5 production by bronchoalveolar lavage and peripheral blood mononuclear cells in asthma and atopy. Eur Respir J 1997;10:624-32.
32. Humbert M, Durham SR, Ying S, Kimmitt P, Barkans J, Assoufi B, et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against "intrinsic" asthma being a distinct immunopathologic entity. Am J Respir Crit Care Med 1996;154:1497-504.
33. Yamada K, Elliot WM, Brattsand R, Hogg JC, Hayashi S. The mechanisms of steroid-resistance induced by latent adenoviral infection in allergic lung inflammation in guinea pigs [abstract]. Am J Respir Crit Care Med 2000;161:A606.

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