

Asthma remission: Does it exist?

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Subjects believed to have grown out of asthma often develop symptoms again later in life. Ongoing airway inflammation may determine the risk of relapse, although the mechanisms involved are still misunderstood. Additionally, patients with asthma during childhood may develop irreversible airflow obstruction (*ie*, airway remodeling) as a result of chronic airway inflammation. Recently, airway inflammation and remodeling could be demonstrated in bronchial biopsy specimens from young adults who considered themselves grown out of asthma. It is also shown that evidence of airway inflammation and remodeling can be obtained noninvasively, thereby providing the opportunity to monitor disease activity. If chronic airway inflammation and/or remodeling are consistent findings in asymptomatic subjects with a history of atopic asthma, the question arises whether natural history can be positively altered with prolonged antiinflammatory therapy. Benefits of long-term prognosis are, however, not yet shown. Since epidemiologic work has demonstrated that a certain percentage of subjects with apparently outgrown atopic asthma remains asymptomatic without needing therapy for the rest of their lives, it can be argued that "asthma remission does exist." The question is whether this percentage can be increased with prolonged antiinflammatory therapy and regular control. *Curr Opin Pulm Med* 2003, 9:15–20 © 2003 Lippincott Williams &

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Abbreviations

BAL	bronchoalveolar lavage
BHR	bronchial hyperresponsiveness
eNO	exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 second
HASM	human airway smooth muscle
MCh	methacholine
RBM	reticular basement membrane

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Atopic asthma symptoms often disappear around puberty [1,2]. Unfortunately, 30 to 80% of subjects who apparently have grown out of asthma develop symptoms again later in life [3]. Underlying risk factors are still unknown. Martinez *et al.* [4] suggested that chronic airflow limitation might contribute to symptom recurrence in adult life, even after long periods of clinical remission and especially among active smokers. Mechanisms leading to this persistent airflow limitation are, however, misunderstood. Recently, some authors have suggested that ongoing airway inflammation is the principal cause of progressing airway abnormalities [5,6] and, consequently, high relapse rate [7,8].

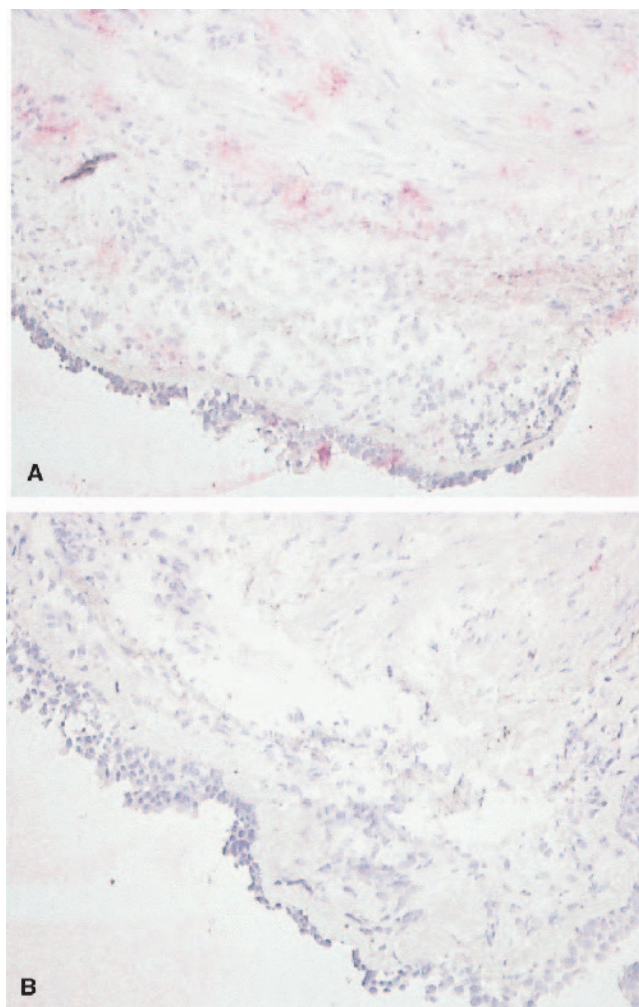
In this review, certain issues will be discussed, such as, the concept that ongoing airway inflammation and remodeling coincide during "remission" of asthma and the discrepancy between ongoing inflammation and the temporary absence of symptoms. Finally, the question whether the long-term prognosis of asymptomatic subjects with persistent inflammation can be altered with antiinflammatory therapy and intensified control is addressed.

In the last paragraph, we make an effort to answer the question, "will asthma ever go away," and propose a strategy for subjects who believe to have grown out of asthma.

Ongoing airway inflammation during clinical remission

Few studies have looked at asymptomatic subjects with a history of asthma. In 1978, Kerrebijn *et al.* [9] examined pulmonary function in 24 children who had not received treatment for over 1 year and still had no symptoms of asthma. Although clinical recovery from asthma seemed to be apparent, increased bronchial smooth-muscle tone was still present in these children. In 1994, Boulet *et al.* [10] demonstrated that most of a group of 30 ex-asthmatics considered in asthma remission showed a persistent increase in airway responsiveness to methacholine (MCh). It is, however, not clear whether these abnormalities were accompanied by ongoing airway inflammation or were solely due to structural changes as a late sequel of childhood asthma. To answer this question, we recently performed fiberoptic bronchoscopy in 18 subjects in clinical remission of asthma, 19 subjects with symptomatic asthma, and 17 healthy controls [7]. Biopsies were taken from the subcarinae of the main

Figure 1. Major basic protein density in bronchial biopsy specimens



Major basic protein (MBP) density in a bronchial biopsy specimen from a (A) subject in clinical remission of asthma and from a (B) healthy control. MBP is stained red.

bronchi. Immunohistochemical staining showed a significantly increased density of eosinophils (major basic protein staining) and mast cells (tryptase) in the bronchial mucosa of subjects in remission as compared with that from healthy controls (Figs. 1 and 2). Thus, the authors demonstrated the presence of ongoing inflammation despite the absence of symptoms.

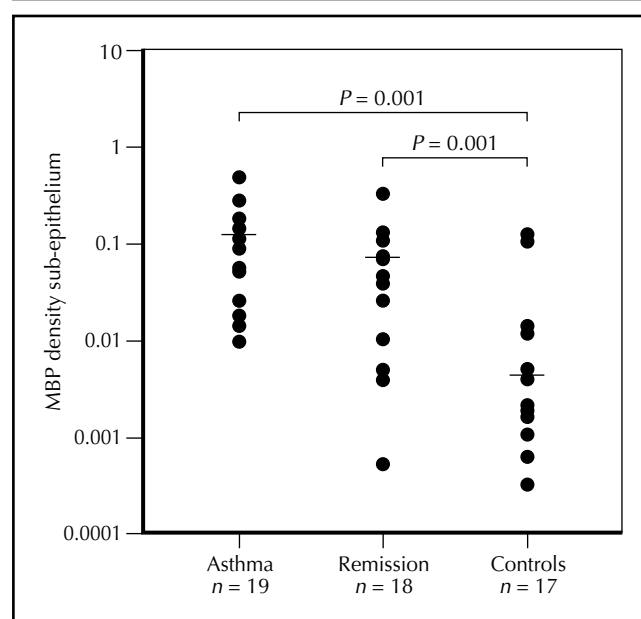
Recently, Warke *et al.* performed bronchoalveolar lavage (BAL) in 35 healthy children, 10 children with outgrown viral wheeze, and 25 children with outgrown asthma [8••]. They found elevated numbers of eosinophils in the BAL fluid of children who had apparently outgrown their asthma compared with controls ($P = 0.002$; Fig. 3). There was no relation between the length of remission and degree of airways eosinophilia. They speculated that ongoing airway inflammation might be a risk factor for future relapse.

Airway remodeling during clinical remission

The end result of asthmatic airway inflammation and its healing processes is an altered structure referred to as airway remodeling. This altered airway structure includes fibrosis and increased smooth muscle, mucus gland mass, vessel area, thickening of the reticular basement membrane (RBM), and epithelial desquamation [11]. As a consequence of these structural changes, the airway wall in asthma is usually thickened, which may result in permanent airflow obstruction. Cokugras *et al.* [12•] demonstrated thickening of the RBM even in 9-year old children with moderate asthma. Page *et al.* [13] recently described how human mast cells from asthmatic patients induce human airway smooth muscle (HASM) cell proliferation. They proposed that mast cells fulfill a central role in the remodeling process, which was also suggested by others [14,15].

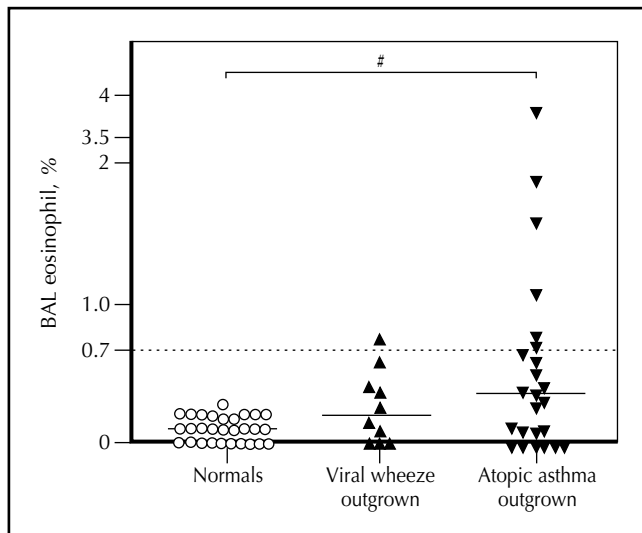
Invasively obtained “proof” of airway remodeling during clinical remission of asthma is scarce. In our study, thickness of the RBM in airway biopsy specimens from subjects in clinical remission of asthma differed significantly from those from healthy controls [7]. Also, occupancy of the RBM with epithelium differed between the study groups.

Figure 2. Ratio of major basic protein staining and subepithelium in bronchial biopsy specimens



Ratio of area of major basic protein (MBP) staining and total area of subepithelium in bronchial biopsy specimens from currently asthmatic subjects, subjects in clinical remission of atopic asthma, and healthy controls. Each dot represents one subject. Horizontal bars represent median values. Published with permission [7].

Figure 3. Bronchoalveolar lavage fluid for healthy children, viral wheeze outgrown, and atopic asthma outgrown



The value marked 0.7 (dashed line) corresponds to the previously defined upper limit of normal bronchoalveolar lavage (BAL) fluid eosinophil %, and solid lines represent median values. # $P = 0.002$. Published with permission [8•].

Monitoring disease activity during clinical remission

Since flexible bronchoscopy is not feasible as a routine monitoring tool, noninvasive markers that predict the degree of airway inflammation and/or remodeling are needed. Possible indices of airway inflammation include the level of sputum eosinophils, the presence of bronchial hyperresponsiveness (BHR) to inhaled stimuli, and exhaled nitric oxide (eNO) levels.

In 1995, Fahy *et al.* [16] demonstrated that analysis of induced sputum in subjects with asthma reveals information about eosinophil percentages qualitatively similar to those obtained by analysis of BAL fluid. A close relation between sputum eosinophils and eosinophil percentage in BAL fluid could also be demonstrated in a study by Grootendorst *et al.* [17].

BHR can be measured with different kind of stimuli. Provocation with adenosine 5'-monophosphate (AMP), as an indirect airway challenge, has been suggested to be a better marker of airway inflammation than direct challenges, such as provocation with MCh [18•,19]. Where MCh directly induces smooth muscle contraction, AMP is thought to have its effect through the stimulation of bronchial mast cells. In a study by Van den Berge and coworkers, PC₂₀ MCh and PC₂₀ AMP were measured in 120 patients with atopic asthma [20•]. In contrast to PC₂₀ MCh, PC₂₀ AMP could be predicted by the percentage of eosinophils in sputum. This is in agreement with our findings, where the density of mucosal eosinophils correlated significantly with BHR to AMP and with eNO levels, but not with BHR to MCh [7]. Also when mea-

suring the effect of allergen avoidance [21,22] and of antiinflammatory therapy [23–25] on airway inflammation, PC₂₀ AMP has been proven to be a useful monitoring tool. On the other hand, Sont *et al.* [26] could demonstrate a significant correlation between PC₂₀ MCh and eosinophil number in the lamina propria.

The response to MCh may, thus, provide information about active inflammation as well as structural airway changes as a consequence of airway remodeling [27–29]. In a study by Ward *et al.*, it was shown that an early improvement in BHR to MCh with fluticasone treatment was associated with early changes in inflammation, but the more progressive and larger improvement was associated with later improvement in airway remodeling [30••].

Recent articles on the subject have evidenced of a close relation between eNO levels and exposure to relevant allergens [31,32], or allergen avoidance [33] in atopic asthmatic subjects. Furthermore, eNO positively correlates with the level of blood- and sputum eosinophils in asthmatic subjects [34–36]. The observation that eNO levels in atopic asthmatic subjects are closely related to the eosinophil percentage in BAL fluid [37] and in bronchial biopsy specimens [7,38] from atopic asthmatic subjects indicates sufficiently that elevated eNO levels are highly associated with eosinophilic airway inflammation, thereby providing a unique tool in monitoring disease activity. It also seems to be justified to categorise asthma activity with the aid of eNO levels [39,40].

In conclusion, sputum eosinophils, eNO levels and BHR to AMP provide useful tools in monitoring disease activity, whereas BHR to MCh may also or merely reflect remodeling processes in the airways.

Symptom perception during clinical remission of asthma

Blunted symptom perception would provide a plausible explanation for the discrepancy between persistent airway inflammation and the absence of symptoms during clinical remission. Several studies have shown that the relation between asthmatic symptoms and other indices of asthma severity is poor. Teeter *et al.* [41] found asthma symptoms to correlate poorly with the level of airway obstruction. A low degree of “perceptiveness” for bronchoconstriction is especially demonstrated in subjects with severe asthma [42,43]. Bijl-Hofland *et al.* [43] hypothesized that either patients with more severe asthma show adaptation of “perceptiveness” for airway obstruction or, perhaps instead, that low perceptiveness leads to more severe asthma as a result of undertreatment. If, after years of symptomatic asthma, adaptation or loss of perceptiveness plays a role in subjects in clinical remission of asthma, it could possibly explain the discrepancy between the lack of symptoms and the ongoing airway

inflammation in these subjects. In a study from our group, however, BORG-scores after a 20% fall in forced expiratory volume in 1 second (FEV₁) during MCh- and AMP-induced bronchoconstriction were not different between subjects in clinical remission and subjects with symptomatic asthma [44], thereby making blunted dyspnea perception not a very likely explanation for the stated discrepancy. We suppose that the weight given by patients to breathlessness depends on many other factors, including age, where younger patients find it more troublesome than older ones [45]. Besides, a slow change in airflow obstruction is possibly less perceived than a fast deterioration due to provocation with MCh or AMP. This was also shown by Rietveld and Everaerd [46], who demonstrated that patients with prolonged airway obstruction perceived symptoms less well and were more vulnerable to negative effects of asthma than patients with acute onset airway obstruction.

Rationale for antiinflammatory therapy during clinical remission of asthma

Since some studies have evidenced of ongoing airway inflammation during clinical remission of atopic asthma [7,8], it has increasingly been a subject of debate that prolonged antiinflammatory therapy should be prescribed to these patients. Since airway inflammation is considered the cornerstone of asthma [47], inhaled steroids are widely accepted as first-choice therapy, even in the mildest forms of disease [48]. A down-regulating effect on several cell types in the bronchial mucosa [49,50], sputum eosinophils [51,52], exhaled NO [52,53] and bronchial hyperresponsiveness [54] has been demonstrated. Airway remodeling aspects such as collagen deposition and thickness of the RBM have also been shown to respond to some degree to antiinflammatory therapy [55,56]. If airway remodeling corresponds with progressing airway obstruction, a smaller decline in lung function with antiinflammatory therapy could possibly be reached, as shown by Grol *et al.* [57]. Several authors have focused their attention to the important concept that with the aid of inhaled corticosteroids natural history and final outcome of asthma might be altered [58–60]. Koh *et al.* [61••] studied the effect of inhaled budesonide on BHR to MCh of subjects in long-standing clinical remission of asthma. After 9 months of therapy no significant change on BHR was seen in this study. It was suggested that the mechanisms underlying BHR in this clinical setting could be different from those in symptomatic asthma. As BHR to MCh is in the first place thought to reflect structural changes in the airways, the absence of any effect of antiinflammatory therapy on this parameter could be due to irreversible remodeling of the airways in the subjects studied. On the other hand, De Kluijver *et al.* [62••] demonstrated that asymptomatic worsening of airway inflammation in subjects with mild asthma could be prevented by inhaled steroids.

Thus, it is unclear whether subjects, who seem to have grown out of asthma, but show evidence of ongoing disease, would benefit from prolonged antiinflammatory therapy. Since several study results indicate that inhaled steroids can positively influence progressive airflow limitation and long-term prognosis, this therapeutic modality should presumably also be (re) considered in subjects with subclinical airway inflammation. Whether this approach is really able to alter the natural history in subjects in clinical remission of asthma is as yet not known. Besides, therapy adherence in asymptomatic young adults will presumably be a major problem. Long-term controlled clinical trials are therefore needed to show benefits in terms of a reduced risk of relapse and/or of irreversible airflow obstruction later in life.

Does asthma ever go away?

There is ample evidence from the literature and our own studies that most young adults who consider themselves grown out of asthma just appear to be asymptomatic. The question remains whether true remission can be achieved, with or without the aid of antiinflammatory therapy. It may be that the absence of any signs of airway inflammation and airway remodeling is representative of true remission. This was only true for 10 or 15% of our population of asymptomatic subjects with a history of atopic asthma. Epidemiological data show that a small percentage of young adults in clinical remission remains asymptomatic for the rest of their lives. These may very well be the subjects in true remission. It is largely unknown whether “additional remissions” can be achieved with prolonged antiinflammatory treatment, and, if so, when this treatment can safely be stopped. Bahceciler *et al.* [63•] recently investigated which parameters would be useful in deciding whether inhaled corticosteroids therapy could be stopped. They demonstrated that only the duration of clinical remission prior to cessation of treatment had proven to be a useful parameter. In addition to their finding, Sont *et al.* [64] have shown that a better control of airway inflammation can be achieved when airway hyperresponsiveness is used as additional guide. Thus, long-term control at the outpatient clinic with noninvasive measurements reflecting airway inflammation and remodeling is presumably needed to decide whether antiinflammatory therapy should be started, continued or stopped.

We propose that adolescents who seem to have grown out of asthma should be monitored for years after symptoms have disappeared, thereby using noninvasive measurements of airway inflammation and remodeling, such as eNO levels, sputum eosinophils and the response to MCh and/or AMP. Treatment might be safely withheld in subjects without signs of airway inflammation or remodeling. In all other patients continuation of antiinflammatory therapy has the theoretical potential to positively alter the prognosis of atopic asthma. Long-term

studies are needed to examine the efficacy and safety of treatment on asymptomatic subjects with chronic airway inflammation.

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- 62 de Kluijver J, Evertse CE, Schrumpt JA, et al.: Asymptomatic Worsening of Airway Inflammation during Low-Dose Allergen Exposure in Asthma: Protection by Inhaled Steroids. *Am J Respir Crit Care Med* 2002, 166:294–300.
- In this study it was investigated whether "silent" allergen exposure induces and maintains airway inflammation and whether this can be prevented with inhaled steroids. Twenty-six atopic asthmatic patients inhaled low-dose allergen on 10 subsequent days. They were treated with 400 µg budesonide once daily ($n = 13$) or placebo ($n = 13$) from days -3 to 19. In the placebo group, allergen exposure resulted in a significant increase in sputum eosinophils ($P = 0.043$), ECP ($P = 0.011$), IL-5/IFN- γ messenger RNA ratio ($P = 0.04$), and eNO ($P = 0.001$), without worsening of symptoms and spirometry values. In the budesonide group, the changes in PC20, sputum ECP, and exhaled NO were significantly reduced as compared with changes in the placebo group ($P < 0.03$). The authors suggested that antiinflammatory therapy is beneficial during allergen exposure, even during asymptomatic episodes.
- 63 Bahceciler NN, Barlan IB, Nuhoglu Y, Basaran MM: Which factors predict success after discontinuation of inhaled budesonide therapy in children with asthma? *J Asthma* 2002, 39:37–46.
- In this study, urinary eosinophil protein X (UEPX) concentration, lung function, and BHR were determined in 40 asymptomatic asthmatic children treated with inhaled budesonide, to establish whether measurement of these parameters is useful in determining discontinuation of therapy. It was shown that duration of clinical remission was a more useful criterion than measurement of UEPX levels, lung function test, and assessment of BHR.
- 64 Sont JK, Willems LN, Bel EH, et al.: Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. *Am J Respir Crit Care Med* 1999, 159:1043–1051.