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The early treatment of asthma was not greatly studied before the 1990s. Subjects included in intervention trials have usually had persistent asthma with a long duration of symptoms. Only a few studies have been done on early intervention. It has also become obvious that eosinophilic airway inflammation is common and does not always significantly affect lung function. If patients do not fulfill the functional criteria for asthma, they may not receive specific diagnosis and effective treatment. I have suggested the term "asthma-like inflammation" to describe the disorder of such patients. Bronchial obstruction and increased bronchial responsiveness are outcomes of the inflammatory process, and it may be argued that detection of eosinophilic inflammation is always late at the time asthma is diagnosed. The diagnosis of asthma is often severely delayed, a fact which influences the prognosis and efficacy of therapeutic interventions. The benefits of early treatment of symptomatic asthma have been shown, and several international guidelines recommend anti-inflammatory medication, preferably with inhaled steroids as first-line treatment to gain control of the disease as fast as possible. Very few studies, however, have addressed the long-term influence of various therapeutic approaches. Usually, the beneficial effects gradually disappear when treatment is withdrawn. There is no convincing evidence that any of the current pharmacologic therapies can change the natural course of asthma. Nevertheless, inhaled steroids seem to have a disease-modifying effect if started early enough, and there is a consensus that steroids abolish symptoms, improve lung function, and decrease the need for hospitalization and probably the mortality rate. In future, various combinations of immunologic and pharmacologic treatments may offer more permanent results in asthma therapy.

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Asthma and asthma-like inflammation in children, 7–12 years

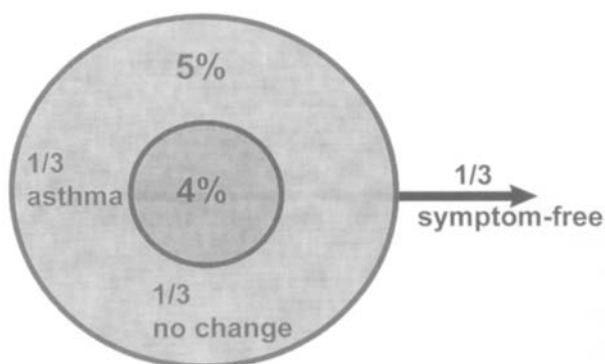


Figure 1. Outcome of asthma-like inflammation (symptoms but normal or nearly normal lung function) during follow-up of 2 years. One-third of children developed asthma.

The concept of early intervention in asthma has been useful in encouraging the development of treatment strategies which could alter the disease process. Obviously, the “golden period” for optimal intervention would be the time when symptoms of asthma begin. The term “early” has, however, been poorly defined. Most of the patients included in the studies have experienced symptoms for a long time before entry, and have persistent asthma. Moreover, newly diagnosed asthma and early asthma are not the same. Are patients with new asthma (e.g., with symptoms for less than 1 year) showing newly diagnosed asthma with a variable length of symptoms, or old asthma that has already been treated with several types of medication? Furthermore, early and mild asthma are not synonymous. Asthma may manifest itself with severe attacks from the very beginning or as only a mild, prolonged nuisance. The characterization of study populations is crucial, as study results are essentially dependent on the type of patients included.

In this paper, I will highlight the problems of detecting the early stages of asthma and the possibilities of early treatment, with special emphasis on the use of inhaled steroids.

Eosinophilic airway inflammation is common

Subjects with abnormal lung function (real asthmatics) comprise only a fraction of patients with recurring eosinophilic airway inflammation. Transient or variable eosinophilia of the bronchial mucosa may be quite

common, especially in atopic subjects, but does not always significantly affect lung function. Ryttilä et al. (1) characterized a patient group with symptoms indicating mild asthma and signs of eosinophilic inflammation, but with normal or close to normal lung function. This condition, which seems to be at least twice as common in clinical practice as asthma itself, needs a label. I suggest the term “asthma-like inflammation”; the terms “allergic cough” and “eosinophilic bronchitis” have also been used. Because these patients do not fulfill the functional criteria for asthma (2), they often do not receive specific diagnosis and effective treatment. In a Finnish study of children aged 7–12 years with symptoms indicating asthma but with normal or slightly deviated lung function, one-third developed clinical asthma during a 2-year follow-up period (3), one-third became free of symptoms, and the rest remained the same (Fig. 1). These results indicated that such patients with prolonged symptoms run a significantly increased risk of asthma.

A widened view of asthma, which takes into account patients with symptoms and signs of eosinophilic inflammation but normal lung function, would improve early detection of the disease and facilitate appropriate intervention. Whether this approach has an impact on the development of lung-function abnormality or asthma severity remains to be seen. However, it is reasonable to assume that it has.

Diagnosis is delayed

Bronchial obstruction or increased bronchial responsiveness are outcomes of the inflammatory process, and it may be argued that detection of eosinophilic inflammation is always late at the time asthma is diagnosed (4).

In September 1997, the clinicians of the outpatient department of allergology in Helsinki explored retrospectively the delay from the start of asthma symptoms to the actual diagnosis made by physicians. The estimate was based on patient files and personal interview. The average delay in children aged from 6 months to 16 years was 1 year 7 months (range 0–6 years, $n=34$). In adults aged from 16 to 70 years, the average delay was 5 years 4 months (range 0–30, $n=36$). In patients treated in the same department in 1992–3 ($n=333$, mean age 34 years), the delay from symptoms to diagnosis, estimated from the patient files, was found to be 3.6 years on average (range 0–30).

Irwin et al. (5) studied 102 patients who had had cough for more than 53 months. Of these patients, 31% had asthma,

and the average duration of the disease at the time of diagnosis was 4 years. Puolijoki & Lahdensuo (6) studied 182 patients with unexplained cough for more than 2 months; patients with asthma were carefully ruled out. After a follow-up of 4.4 years, 16% of patients were found to be asthmatic. History of atopy, allergic rhinitis, or asthmatic family members increased the risk by three- to fourfold. The increased number of eosinophils in blood, sputum, or nasal secretion also increased the risk by three- to fourfold. These authors also studied another 147 patients who had had prolonged cough for more than 2 months but had a normal chest radiograph (7). During a follow-up of 1 year, 34% of these were found to have asthma.

In Sweden, Larsson et al. (8) made a population-based survey in a small community and detected 666 asthmatic patients, of whom two-thirds had clinically mild disease, which, nevertheless, had a significant impact on their everyday life. Of these "mild" patients, 71% had consulted a doctor, but the correct diagnosis of asthma had been made in only 19%.

Doctors are not solely to blame for this situation. Asthma is perceived as a severe, life-long disease by the general public. Siponen (9) made a psychosocial study of asthmatic patients and concluded that patients hesitate to search for help and do not readily go to a doctor. They may pretend to have a common cold or allergy, rather than asthma, and may deny the possibility of asthma. They may also fear the label of a chronic disease and try to preserve the identity of a healthy person.

Treatment is wrong for long periods

This intolerable delay in making the diagnosis of asthma, and especially asthma-like inflammation, results in ineffective treatment being given for long periods. This is especially true in general practice, where huge numbers of coughing and wheezing patients are treated inadequately. Most patients with prolonged cough and mucus production, but normal or nearly normal lung function, receive repeated courses of antibiotics, expectorants, antitussives, antihistamines, and bronchodilators: everything, in fact, but adequate anti-inflammatory medication. This kind of treatment can continue for years. Anti-inflammatory medication with inhaled steroids or cromones is not usually considered before the patient shows definite signs of asthma verified by lung-function measurements. This is understandable because of the lack of convenient diagnostic methods of eosinophilic inflammation. However, intensive

What are we trying to control?

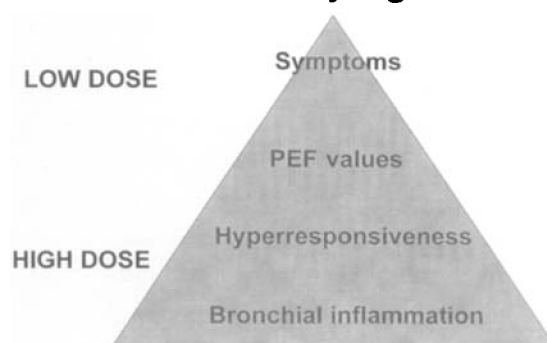


Figure 2. Symptoms and PEF values are improved when treatment with inhaled steroids is introduced, but low doses and short treatment periods may not significantly influence increased bronchial responsiveness and its cause: underlying mucosal inflammatory process.

research into the mucosal inflammatory process may offer new methods. To my mind, analysis of induced-sputum samples is the key. Sputum induced by hypertonic saline has been shown to be similar to lower respiratory secretions expectorated spontaneously (10), and to give comparable results to bronchoscopic methods (11).

Even when the diagnosis of asthma has been made, the condition is often severely undertreated. O'Byrne et al. (12) showed marked undertreatment of patients considered to have mild asthma in primary care practice. In an unselected population, Bousquet et al. (13) observed astonishing undertreatment of severe asthma: 85% of patients living in Paris, and 60% in Montpellier, were not receiving any anti-inflammatory treatment. Ferrante et al. (14) also found that inhaled anti-inflammatory drugs were insufficiently utilized in 13 899 young Italian males: only 16% of those who showed bronchial obstruction used inhaled steroids or cromolyn sodium. In Denmark, Gaist et al. (15) selected from a nationwide register those asthmatic patients who used β_2 -agonists extensively (more than 1600 inhalations per year). In 1991, 37% of such patients did not use inhaled steroids, and the situation had not improved by 1994: 33% were still without inhaled steroids.

Recent data confirm earlier observations that inhaled steroids confer significant protection against exacerbation of asthma leading to hospitalization (16). van Ganse et al. (17) found that, when overconfidence in β_2 -agonists and sub-optimal use of inhaled steroids were combined, the risk of hospitalization increased significantly (OR 5.5, CI 95% 1.1–26.1). Use of inhaled steroids also dramatically decreases hospitalization in children (18).

Anti-inflammatory treatment is effective but late

The severity of asthma fluctuates, even in the same patient, and the course of the disease is difficult to predict. The data available on the long-term benefits of different interventions are scanty. Even persistent asthma may have a more favorable natural course than expected. In one study, 12% of 285 adult asthmatic patients were symptom-free and showed normal lung function after a follow-up for 25 years (19). About two-thirds of mildly asthmatic children will outgrow their disease, while the remainder with more severe asthma will have persistent symptoms in adult life (20). There are surprisingly few data on the impact of various treatments on the "natural" course of childhood asthma.

Nevertheless, the benefits of early treatment of symptomatic asthma are obvious, and several recent guidelines recommend anti-inflammatory medication, preferably with inhaled steroids, as first-line treatment to gain control of the disease as fast as possible (2, 21, 22). Increasingly, the guidelines recommend inhaled steroids, not only in moderate and severe, but in mild asthma as well. Treatment is started as soon as the functional diagnosis of asthma has been established, and the so-called step-down approach is gaining currency. In this approach, high initial doses are followed with lower doses titrated to a level sufficient to control the condition. There is some evidence from a meta-analysis to support the policy of also treating mild steroid-naïve asthmatics with inhaled steroids from the very beginning (23), but more studies are needed, particularly to justify the step-down concept. Higher initial doses would probably have a better effect on the underlying inflammation and increased bronchial responsiveness than lower doses, which effectively reduce symptoms and increase PEF values (Fig. 2). In many immunologic or inflammatory diseases of long duration, the concept of induction treatment followed by maintenance treatment and treatment of relapses is followed: it could be applied to asthma treatment as well.

In contrast to β_2 -agonists, inhaled steroids reduce the eosinophilic inflammation in asthmatic airways (24–26). This has been observed in most patients with a wide spectrum of asthma severity. However, the long-term effect of steroid intervention may be quite different in patients with new disease (24) from patients with a longer history (25, 26). Whether steroids only suppress the disease or also modify the outcome may depend on the timing of the intervention. *Undertreatment of asthma for years* may result in permanent structural airway changes, at least in

some patients. The observation that inhaled steroids do not seem to have any permanent effect on the degree of bronchial hyperresponsiveness may be due to the inclusion in trials of patients with an asthma history for years before intervention with effective anti-inflammatory therapy (27, 28). For the same reason, inhaled steroids have not consistently influenced the thickness of the reticular basement layer, or the other elements of airway remodeling (25, 29, 30). "Scar" formation of the airways is probably a result of airway remodeling via chronic release of various inflammatory mediators and cytokines and, once established, is hardly reversible by pharmacologic intervention.

Increased bronchial responsiveness is probably a consequence of long-lasting or recurrent airways inflammation in susceptible individuals. Results from cross-sectional studies have shown a moderate correlation between the two (31–33). By high-resolution computed tomography, Boulet et al. (31) showed that, in subjects with a fixed component of airflow obstruction, there was an inverse correlation between the thickness of the airway wall and the PC₂₀ for methacholine. However, the correlation between clinical severity and subbasement membrane thickening is not straightforward. In the study of Chu et al. (34), the thickening was no greater in patients with severe asthma than in those with mild asthma. However, treatment aimed at increased bronchial responsiveness has been shown to reduce the number of activated eosinophils in bronchial lamina propria and the thickness of subepithelial collagen (35). Early treatment of eosinophilic inflammation could prevent the development of increased bronchial responsiveness caused by changes in airway structure.

Benefits of early treatment in adults

Early intervention with anti-inflammatory medication, particularly inhaled steroids, was not widely studied or discussed until the 1990s. Evidence that steroids modify the natural course of asthma is accumulating but is not yet conclusive. For early intervention, only a few relevant studies have been carried out.

Juniper et al. (36) studied patients with persistent asthma, but "with symptoms that were nontroublesome with β_2 -agonists alone". The patients showed an almost fourfold mean improvement in bronchial hyperresponsiveness when budesonide, 400 μ g daily, was introduced for 1 year. The symptoms also markedly improved. The study revealed severe undertreatment of patients who would usually be considered to have mild, controlled asthma. The patients

were steroid-naïve, but the duration of symptoms (presumably for years) was not given. It is questionable whether the study can be considered an early intervention study.

A directly relevant study of early intervention compared prospectively two treatment strategies: whether patients should be treated with inhaled steroid from the beginning, or whether treatment should be initiated with β_2 -agonist alone (37). Patients with asthmatic symptoms lasting less than 1 year and who had received no previous anti-inflammatory therapy inhaled either budesonide 1200 μg or terbutaline 750 μg daily as their first and only regular medication. Treatment with inhaled budesonide for 2 years resulted in almost complete clinical recovery and normalization of lung function, and was superior to β_2 -agonist treatment. Bronchial biopsies were taken from a subgroup of patients, and showed that after 3 months the budesonide-treated subjects had a significantly greater fall in the numbers of inflammatory cells than the terbutaline-treated patients (24).

This study was continued for a third year to investigate the effects of dose reduction or discontinuation of steroid treatment. A delayed introduction of inhaled steroid was also examined. The peak expiratory flow (PEF) was well maintained for year 3 in patients in whom the daily budesonide dose was reduced from 1200 μg by Nebuhaler[®] to 400 μg by Turbuhaler[®]. Most of the patients who switched from budesonide to placebo showed a gradual and slight decline in lung function, which became significant toward the end of year 3, but five patients did not deteriorate at all (38). The patients who were first treated with terbutaline for 2 years, and only subsequently treated with budesonide, did not reach the same level of lung function within year 3 as those who were treated with budesonide from the beginning of the study. Some functional reversibility was lost by delaying the start of steroid treatment.

Adult patients with persistent asthma or chronic obstructive pulmonary disease (COPD) (baseline FEV₁ about 60% of predicted), half of whom had already used inhaled steroids, received treatment for 2.5 years with bronchodilators alone or with β_2 -agonist (terbutaline) and steroid (beclomethasone) (39). The addition of inhaled steroid, but not an inhaled anticholinergic agent, to maintenance treatment with β_2 -agonist was very beneficial in terms of symptoms and bronchial responsiveness. However, the investigation can hardly be considered an early intervention study. The patients had pulmonary disease of at least moderate severity and a long history of symptoms (duration not mentioned).

The study was continued for 6 months after the first 2.5 years to investigate the effects of adding beclomethasone, 800 μg daily, to those patient groups that had not previously received inhaled steroids (40). Airway hyperresponsiveness showed no significant change after 6 months during the new intervention, whereas it had shown a significant improvement at 3 months in the patients who started beclomethasone in the first phase. It seems that institution of inhaled steroid should not be postponed in asthmatic patients with documented airways obstruction.

Osterman et al. (41) studied adult asthmatic patients who had had their asthma diagnosis established not more than 1 year before the study. However, most of these patients had persistent, albeit rather milder, disease with symptoms for several years. The patients inhaled budesonide, 400 μg daily by Turbuhaler for 1 year, and showed marked improvement in lung function and bronchial responsiveness compared with placebo treatment.

Selroos et al. (42) examined retrospectively the influence of the duration of pretreatment symptoms on the response to inhaled steroid treatment in steroid-naïve adult patients with asthma. The duration of symptoms ranged from less than 6 months to more than 10 years. Most of the 105 patients were treated with budesonide, 800 μg daily, for 1 year. During year 2, the dose was reduced when this was possible without a worsening of asthma control. The maximum effects were usually seen after 1 year's treatment, and control was maintained during year 2. A significant negative correlation was found between duration of symptoms and maximum increases in PEF and FEV₁. These results provided evidence that early treatment of asthma with inhaled steroid may prevent patients from developing chronic airway obstruction. However, the role of confounding by asthma severity at the initiation of treatment with inhaled steroids was not fully addressed.

Benefits of early treatment in children

The Dutch childhood study (28) included children with chronic obstruction and severe asthma. The aim was, in fact, not to investigate early intervention but to determine whether long-term treatment with a regular β_2 -agonist in addition to inhaled steroid was more effective than treatment with a β_2 -agonist alone. The results were quite conclusive: the steroid-treated group managed better in every respect, although full remission was achieved by only 60% of the children.

Agertoft & Pedersen (43) measured lung function and growth in 278 children with mild to moderate asthma during long-term treatment with inhaled budesonide, and compared their findings with those obtained from children not treated with steroids. The children were "old" asthmatics (mean duration of asthma 3.5 years), who had mainly used β_2 -agonists rather than steroids. The differences in FEV₁ and in many other outcome variables between the two groups were very significantly in favor of the budesonide-treated children. Interestingly, the annual increase in FEV₁ was greatest in those children whose asthma was of shortest duration when inhaled budesonide was started. Early intervention with inhaled steroid seemed to prevent the development of irreversible airway obstruction and reduce the risk of undertreatment. Again, the possible confounding by asthma severity at the initiation of treatment with inhaled steroids could not be judged.

König & Shaffer (44) observed during a 8.4-year follow-up of children from the age of 6.5 years that treatment with cromolyn sodium or inhaled steroid, but not bronchodilators alone on an as-needed basis, improved the long-term prognosis. However, the prognosis of mild childhood asthma is favorable even without any treatment. Oswald et al. (45) followed 286 children for 28 years and concluded that airway obstruction in mid-adult life was present mainly in those with moderately severe asthma. Subjects with relatively mild asthma who had not taken inhaled steroids did not appear to be disadvantaged in lung function.

Long-term influence little studied

One possible means of investigating the long-term effects of early intervention is to study what happens when treatment is stopped. The studies of Haahtela et al. (37, 38) provided only partial answers to the questions of how long steroid treatment should be continued after remission, whether the dose can be reduced, and what kind of dosage schedules can be employed. There are very few studies addressing these issues in adults or in children.

Short-term studies of the withdrawal of inhaled steroid therapy after treatment for periods of 4 weeks or less suggest that bronchial responsiveness increases within weeks of inhaled steroid reduction or withdrawal (46, 47). However, patients in these studies had persistent asthma with a long symptom history. It has been shown that considerably longer periods of treatment do not fully reverse the inflammatory changes in the airways, even in patients with relatively mild asthma (48, 49).

Juniper et al. (27) showed that the improvements in bronchial responsiveness induced by treatment with budesonide for 1 year were maintained for at least 3 months after cessation or reduction of treatment with an inhaled steroid. As mentioned earlier, the patients did not have early asthma, but rather a chronic disease with at least moderate severity.

van Schayck et al. (50) withdrew inhaled beclomethasone from a group of patients after 4 years of treatment. Before that, the patients had been treated with bronchodilators for the first 2 years, and with beclomethasone for the remaining 2 years. Some patients with poor lung function showed an accelerated rate of decline after withdrawal of the inhaled steroid, but those with good lung function showed no increase in the rate of decline of lung function. The investigators concluded that patients in the latter group could stop inhaled steroid after treatment for 2 years. Again, the patients had a long history of persistent asthma.

Osterman et al. (41) followed their patients after the treatment year for another 6 months without steroids. The budesonide-treated patients maintained about 50% of their achieved improvement in bronchial responsiveness during the follow-up period; however, only the patients with milder disease remained in the study, a fact which partially invalidated the observations. Overall, the effects of low-dose budesonide treatment for 1 year were mainly temporary. Again, most of the patients did not have "new" disease.

van Essen-Zandvliet et al. (28) included children with chronic obstruction and severe asthma. After treatment with inhaled budesonide for 28–36 months, inhaled steroid therapy was tapered off in some of the children over 6 months. The disease gradually worsened. All the patients used regular salbutamol while the dose of budesonide was reduced (51).

Simons (52) treated children with mild or moderate persistent asthma with beclomethasone, 400 μ g daily, for 1 year. The beneficial effect on increased bronchial responsiveness disappeared by 2 weeks after cessation of treatment.

Conclusions

Long-term treatment of asthma with inhaled steroid suppresses the disease, both in adults and children, by affecting the underlying airway inflammation. As a result, symptoms disappear, and lung function improves. Symptoms respond most rapidly to the initiation of inhaled steroid therapy; PEF values normalize more gradually, and in

patients with a long history bronchial responsiveness continues to decrease for many months or even years. Inhaled steroids modify the disease outcome if introduced early enough and for long enough [38, 43]. The persistence of this modifying effect has been shown in only a few selected patient groups, and the question of whether inhaled steroids can really change the course of asthma to a less troublesome disease remains essentially unanswered.

If inhaled steroid therapy is stopped, most patients will ultimately experience further symptoms of asthma. The speed of this relapse seems to be related to the length of symptom history before intervention, the severity of symptoms and signs at the outset, and the duration of the therapy. The impact of these clinical variables on steroid efficacy, however, has not been systematically studied.

Infiltration of inflammatory cells in the lamina propria of the airways has been shown to persist in patients with mild to moderate asthma, despite regular treatment with inhaled steroids [32], a finding which indicates a need for regular maintenance anti-inflammatory treatment. As asthmatic inflammation is a response to, and usually provoked by,

allergic reactions, infections, and other environmental factors, continued or repeated anti-inflammatory therapy is usually necessary for control of the condition.

A truly effective therapeutic intervention should be targeted on the initiating stage of asthma. Adult asthma often has roots in early childhood. The obstructive symptoms should be treated effectively, even during the first year of life. This was demonstrated by Kajosaari et al. [53], who treated small children (mean age 2.6 months) hospitalized because of RSV bronchiolitis symptomatically, or with nebulized budesonide for 1 week or nebulized budesonide for 2 months. After a follow-up of 2 years, asthma was diagnosed in 37% of the symptomatically treated children compared with 18% and 12% in the budesonide-treated children. These preliminary results should be confirmed in a better-controlled trial.

Asthma appears to be an immunologic disease, and several new immunologic approaches to treat asthma in childhood as well as in adulthood are entering clinical trials. In future, various combinations of immunologic and pharmacologic treatments may offer the key to more permanent results in asthma therapy.

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