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## Treatment of Mild Asthma With Inhaled Corticosteroids: Is Discontinuation of Therapy Possible?

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**Background:** *This study investigated if long-term therapy with inhaled corticosteroids could be discontinued in mild asthma when patients are in a clinically stable phase of the disease. Data were derived from a 2-year randomized, controlled, bronchodilator intervention study in family practice. Methods:* The experimental (stop-steroid) group consisted of 19 asthmatic patients who had used inhaled corticosteroids daily during at least the year preceding this study and who stopped using these drugs because of participation in the bronchodilator intervention study. The control (no-steroid) group consisted of 70 patients with asthma who had not used corticosteroids in the year preceding the study. At the start of the study (8 weeks after stopping steroids), the two groups were completely comparable in all other relevant characteristics. During the 2-year study, patients were treated only with a bronchodilator (salbutamol or ipratropium bromide). Outcome measures were: exacerbations, symptoms, annual decline in forced expiratory volume in 1 second (FEV<sub>1</sub>), annual change in nonspecific bronchial responsiveness (PC<sub>20</sub>-histamine), and the need for additional corticosteroid therapy because of symptoms of increased airway obstruction. **Results:** In the stop-steroid group, 12 of 19 patients (63%) dropped out during the study period because of a deterioration of their clinical condition and need for additional (inhaled) corticosteroid treatment. In the no-steroid group, only eight patients dropped out for this reason (11%). In the stop-steroid group, who did not use steroids for at least 1 year, the annual FEV<sub>1</sub> decline was much larger than in the comparison subjects (165 vs 40 ml/yr). **Conclusions:** Stopping maintenance treatment with inhaled corticosteroids may not be advisable in all patients with mild asthma. Instead of stopping or interrupting treatment, family physicians are advised to determine the minimal effective daily dose of inhaled corticosteroids for each individual patient that provides adequate control of the disease.

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The current understanding that inflammation is a major pathophysiologic mechanism in asthma<sup>1</sup> has resulted in a shift in treatment policy toward the early introduction of inhaled corticosteroids.<sup>2,3</sup> In addition, some recent studies<sup>4-6</sup> have suggested that inhaled corticosteroids can improve the long-term outcome of asthma. The tendency toward early use of inhaled steroids is strengthened by the finding in two independent studies that continuous therapy with bronchodilators,

the usual alternative to steroid treatment, may have adverse effects on the control of asthma<sup>7</sup> and the progression of asthma.<sup>8</sup> Since continuous therapy with bronchodilators may be detrimental, treatment with inhaled corticosteroids is probably the only currently available therapy that has been shown to improve the long-term course of asthma.

Since the majority of patients with asthma are treated in family practices,<sup>9,10</sup> family physicians will be prescribing this therapy for a growing number of patients. An important question for family physicians and patients is whether treatment with inhaled corticosteroids can be interrupted or stopped when patients are in a stable phase of their disease. Since inhaled steroids do not have a direct

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symptom-relieving effect, patient compliance with this medication is a major problem,<sup>11</sup> and patients may even ask their family physician to stop maintenance treatment with inhaled steroids when their asthma is stable. Although inhaled steroids have relatively mild side effects, oral candidiasis, hoarseness, and irritation of the oropharynx may occur, and systemic effects may develop when doses of 800 µg or more are used.<sup>12</sup> All these aspects make the above question very relevant.

If corticosteroids "cure" the underlying mechanisms of asthma and chronic bronchitis to some extent, steroid treatment can probably be interrupted. If they only suppress inflammation temporarily, discontinuation of steroids might be difficult. Some information is available about the effects of stopping treatment with inhaled corticosteroids in patients referred for specialist treatment. In one study with moderate-to-severe asthmatic children, stopping inhaled steroids appeared to cause trouble.<sup>13</sup> Haahtela et al showed that discontinuation of treatment with inhaled steroids in mild asthma often was accompanied by exacerbation of the disease and may have resulted in irreversible loss of lung function.<sup>14</sup> In another study with mild asthmatic adults, it was shown that improvements in asthma caused by 1 year's use of inhaled steroids could be maintained for at least 3 months after stopping steroid treatment.<sup>15</sup> No studies have been performed with patients from family practice who had not been referred for specialist treatment. Since most of these patients probably have mild asthma, it seems relevant to investigate the possibilities of stopping inhaled steroids in these patients.

This study assessed the effects of stopping treatment with inhaled corticosteroids on long-term control and progression of asthma in a family practice. Data on 89 patients with asthma from a previously published large intervention study were evaluated.<sup>8</sup>

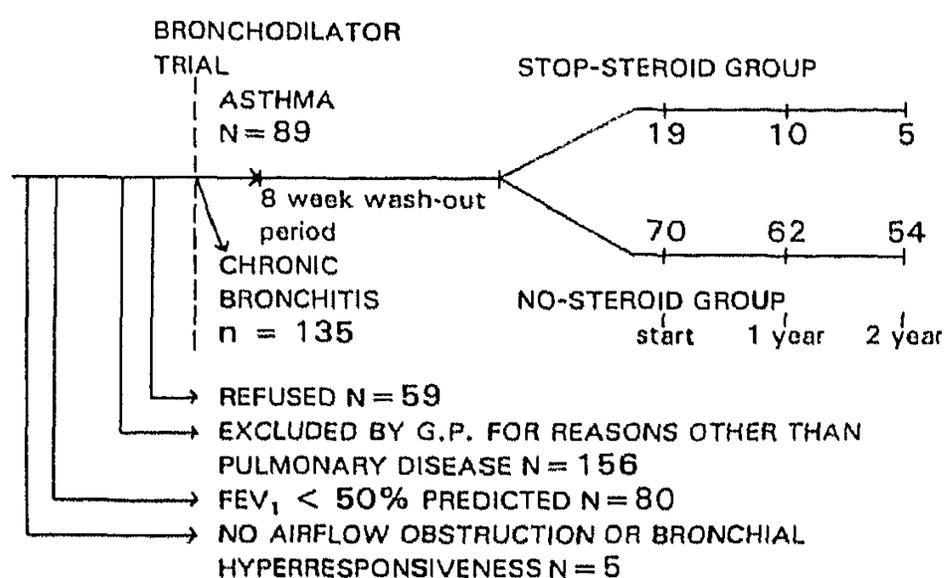
## Methods

### Patients

The study population consisted of 89 asthma patients who entered a 2-year randomized, controlled study of bronchodilator therapy in family practice.<sup>8</sup> Figure 1 shows the enrollment of the subjects. Patient selection and the inclusion and exclusion criteria of the intervention study have been described in detail elsewhere.<sup>8</sup> Twenty-nine family physicians were asked to select all their patients aged 30 or older with symptoms of asthma or chronic bronchitis. Inclusion criteria included only patients with a mild-to-moderate airway obstruction (forced expiratory volume in 1 second [FEV<sub>1</sub>] or FEV<sub>1</sub>/FVC' at least two standard

Figure 1

### Enrollment of Study Subjects



A total of 524 patients were selected at the start of the 2-year bronchodilator trial; 300 patients did not participate in the study for several reasons (see arrows). Of the 224 patients who eventually took part in the bronchodilator trial, only patients with asthma (n=89) were used in this study. No dropouts occurred in the 8-week washout period. At the start of the study, the stop-steroid group had 19 asthmatic patients. Due to dropout after 1 and 2 years of study, only 10 and 5 patients remained, respectively. The no-steroid group had 70 asthmatic patients. After 1 and 2 years of study, only 62 and 54 patients remained, respectively.

n = number of patients

FEV<sub>1</sub> = Forced expiratory volume in 1 second

deviations below their predicted value<sup>16</sup> but more than 50% of the predicted value) and/or bronchial hyperresponsiveness to histamine (provocative concentration of histamine that produces a 20% fall in FEV<sub>1</sub> [PC<sub>20</sub>], and PC<sub>20</sub> ≤ 8 mg/ml). Exclusion criteria were: dependency on oral corticosteroids, chronic heart failure, malignant disorders, or other life-threatening diseases. Only patients with airway reactivity due to asthma were included. The criteria for the diagnosis of asthma were based on the standards of the American Thoracic Society.<sup>17</sup> Asthma was defined as the combination of: 1) reversible obstruction (FEV<sub>1</sub> increased by more than 15% of the baseline value 60 minutes after the administration of 80 µg ipratropium bromide and 400 µg salbutamol), 2) bronchial hyperresponsiveness to histamine (PC<sub>20</sub> ≤ 8 mg/ml), 3) dyspnea, and 4) allergy and/or wheezing.

The experimental (stop-steroid) group had 19 asthmatic patients who had continuously used (inhaled) corticosteroids daily during at least 1 year preceding the study and stopped because of participation in the bronchodilator intervention study. These patients had been given permission by their physician to stop corticosteroids, and they entered an 8-week washout period before the start of the bronchodilator study.

during which inhaled corticosteroid treatment (and other pulmonary medication) was stopped. During this period, only as-needed inhaled salbutamol or ipratropium bromide were prescribed. No patients had an exacerbation during this washout period and were therefore not excluded from the study.

The control (no-steroid) group consisted of the remaining 70 asthmatic patients who had not used inhaled corticosteroids in the year preceding the study. The clinical characteristics of the stop-steroid and no-steroid groups are shown in Table 1. At the start of the study, the two groups had no significant differences.

The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.

### Outcome Measures

The stop-steroid and no-steroid groups were followed for 2 years while receiving standard bronchodilator treatment. The main outcome measure during this period was the annual decline, if any, in FEV<sub>1</sub>. On the basis of earlier research,<sup>6,8</sup> it was determined that the minimum detectable difference in FEV<sub>1</sub> decline was 120 ml/yr, with an individual standard deviation of the FEV<sub>1</sub> decline of 100 ml. With an alpha of .05 and a power of .8, the number of patients who could be evaluated had to be at least 10 in each study group.

Secondary outcome measures during this period were the number of exacerbations, severity of symptoms, and annual change in nonspecific bronchial responsiveness (PC<sub>20</sub>-histamine). An important outcome measurement and endpoint in this study was the need for corticosteroid therapy due to too severe or too many exacerbations. The category "too severe exacerbations" was defined as exacerbations not sufficiently treated by a 10-day course of oral prednisone, adding broad spectrum antibiotics if necessary. The category "too many exacerbations" was more than two exacerbations annually.

### Measurements

**Respiratory Symptoms.** The severity of respiratory symptoms (cough, phlegm, dyspnea) was assessed weekly by each subject on a scale of 0–4 and recorded in a diary. A score of "4" indicated worst symptoms and "0" indicated no symptoms. The total score was computed by adding the cough, phlegm, and dyspnea scores (maximum 4 points each) to yield a total score. The highest (most symptomatic) possible score was 12.

**Exacerbations.** Exacerbations were defined according to Fletcher et al,<sup>18</sup> with the modifications of Boman et al<sup>19</sup> as the occurrence of mucopurulent sputum, cough, and at least one of the following symptoms: general malaise, symptoms of common cold, fever, dyspnea, increased sputum production, increased sputum thickness, foul-tasting sputum, or increased difficulty of expectoration. In case of an exacerbation,

Table 1  
Patient Characteristics\*

Variable	Experimental "Stop-steroid" Group	Control "No-steroid" Group
Number	19	70
Age, years	56 (12)	51 (12)
Gender, male/female	6/13	35/35
Symptom score	4.6 (1.5)	4.9 (1.7)
# of packs/year of smoking	12 (10)	12 (16)
Smokers, yes/no/no data	2/8/9	27/38/5
Allergy,** yes/no/no data	5/6/8	24/40/5
FEV <sub>1</sub> % predicted	71 (19)	72 (20)
FEV <sub>1</sub> /IVC, %	62 (15)	61 (11)
Reversibility FEV <sub>1</sub> , % predicted	17 (10)	14 (11)
PC <sub>20</sub> -histamine, mg/ml	.6	1.3

\* Characteristics are of the 19 patients of the stop-steroid group (continuous use of inhaled corticosteroids during the year preceding the study) and the 70 patients of the no-steroid group (no use of corticosteroids during the pre-study period). Standard deviations or ranges are in parentheses. Differences in dichotomic variables were statistically compared using the chi-square test and were compared in normally distributed variables using the unpaired Student's *t* test. No statistically significant differences were present.

\*\* Allergy was defined as at least one positive test out of seven RAST (Radio Allergo Sorbent Tests).

FEV<sub>1</sub>—Forced expiratory volume in 1 second as a percentage of the predicted value

IVC—Inspiratory vital capacity

PC<sub>20</sub>-histamine—Provocative concentration of histamine (the dose of histamine producing a 20% fall in FEV<sub>1</sub>). Geometric mean PC<sub>20</sub> is given.

a 10-day tapering-down course of oral prednisone was given. (25, 25, 20, 20, 15, 15, 10, 10, 5, 5 mg).

**FEV<sub>1</sub>, PC<sub>20</sub> Histamine and Reversibility of Airway Obstruction.** No bronchodilating medication was taken for at least 8 hours before the assessments of airway obstruction. Measurements of FEV<sub>1</sub> were performed with the Microspiro HI-298 spirometer® (Chest Corporation, Japan) by two qualified laboratory technicians.<sup>20</sup> Patients had to perform three satisfactory forced vital capacity (FVC) maneuvers on all occasions. Data were taken from the curve with the highest sum of FVC and FEV<sub>1</sub>. The bronchial responsiveness to histamine was measured using the method described by Cockcroft et al<sup>21</sup> and expressed as the PC<sub>20</sub>-histamine value. After the FEV<sub>1</sub> had returned to baseline value, the increase in FEV<sub>1</sub> 60 minutes after the inhalation of both 400 µg salbutamol and 80 µg ipratropium bromide was assessed.

**Smoking Behavior.** The number of cigarettes smoked per day was recorded by the patients in a weekly report. The smoking history was retrospectively assessed and quantified in pack years.

**Table 2**  
Number of Dropouts, Period of Dropout, and Reasons for Dropout During the 2-year Study<sup>a,b</sup>

		Experimental "Stop-steroid" Group n=19	Control "No-steroid" Group n=70
		n (%)	n (%)
0-6 months	• Too severe or too many exacerbations (needing steroids)	8 (42)	4 (6)
	• Other reasons <sup>a,b</sup>	1 (5)	4 (6)
6-12 months	• Too severe or too many exacerbations (needing steroids)	0 (0)	0 (0)
	• Other reasons <sup>a,b</sup>	0 (0)	0 (0)
12-24 months	• Too severe or too many exacerbations (needing steroids)	4 (21)	4 (6)
	• Other reasons <sup>a,b</sup>	1 (5)	4 (6)

<sup>a</sup> In both the stop-steroid and no-steroid groups

<sup>b</sup> Lack of motivation, emigration, malignancy, side effects of bronchodilator study medication

**Table 3**  
Effects of Stopping Treatment With Corticosteroids

	Experimental "Stop-steroid" Group n=10	Control "No-steroid" Group n=62	P Value
FEV <sub>1</sub> decline, ml/year	165 (50)	40 (20)	.022
PC <sub>20</sub> decline, doubling dose/year	.33 (.62)	.33 (.22)	1.000
Exacerbations, number/year	1.1 (.31)	.8 (.1)	.216
Symptom score	2.0 (.51)	2.2 (.3)	.697

Table shows the effect of stopping treatment with corticosteroids on symptoms, exacerbations, the annual decline in FEV<sub>1</sub> (forced expiratory volume in 1 second), and PC<sub>20</sub> (provocative concentration of histamine producing a 20% fall in FEV<sub>1</sub>) in patients with mild asthma who could stop using corticosteroids at least during 1 year. Standard errors of the mean are in parentheses. Differences were tested by means of the unpaired Student's *t* test.

**Treatment During 2-year Follow-up**

All patients received bronchodilator therapy alone during the 2-year study period, either continuously (salbutamol 400 µg or ipratropium bromide 40 µg, four times daily) or on demand (only dry powder capsules of salbutamol 400 µg or ipratropium 40 µg during complaints or exacerbations).<sup>5</sup> No inhaled steroids or cromoglycate were permitted. Patients using salbutamol during the first year crossed over to ipratropium bromide during the second year and vice versa.<sup>8</sup>

**Analysis**

The scores of cough, phlegm, and dyspnea were combined in the total symptom score. The annual FEV<sub>1</sub> decline was determined by linear regression of FEV<sub>1</sub> over the course of time (maximum of seven measurements). PC<sub>20</sub> values were <sup>2</sup>log transformed prior to analysis. The annual changes of PC<sub>20</sub> were estimated by linear regression of <sup>2</sup>log PC<sub>20</sub> in the course of time (maximum of five measurements).

The influence of stopping treatment with inhaled corticosteroids on the outcome variables was assessed by multiple analysis of variance (MANOVA), adjusting for age, gender, height, smoking, pack years, allergy, initial PC<sub>20</sub> and FEV<sub>1</sub>, reversibility of obstruction, and bronchodilator treatment during the study.<sup>22</sup> The relation between clinical characteristics and the annual FEV<sub>1</sub> decline after stopping treatment with steroids in the stop-steroid group was also investigated by means of MANOVA. The effects of stopping steroids on decline in lung function and change in bronchial hyperresponsiveness, exacerbations, and symptoms were only investigated in subjects who could stop using steroids for at least 1 year (explanatory analysis, no intention-to-treat analysis).

**Results**

In the stop-steroid group, 12 of the 19 patients (63%) dropped out during the 2-year study period because of a deterioration of their clinical condition and need for additional (inhaled) corticosteroid treatment, vs only eight of the 70 patients (11%) in the no-steroid group (chi-square=20.1, *P*<.0001). Of the 12 dropouts from the stop-steroid group, eight needed additional corticosteroids during the first 6 months of the bronchodilator trial (Table 2).

When the patients who could continue bronchodilator therapy without inhaled steroids during at least 1 year were analyzed, the following data were found (Table 3). The annual FEV<sub>1</sub> decline was larger in the stop-steroid group (165 ml/yr) than in the no-steroid group (40 ml/yr) (*P*=.022). No differences between groups were found with respect to symptoms, exacerbations, and the annual change in PC<sub>20</sub>.

No feature could predict the effect of stopping inhaled corticosteroids at the start of the study. Allergy, initial FEV<sub>1</sub> and PC<sub>20</sub>, reversibility of obstruction, and smoking behavior before and during the study were all unrelated to the difference in annual decline in FEV<sub>1</sub> in the stop-steroid and no-steroid groups.

### Discussion

Long-term treatment of asthma with inhaled corticosteroids is becoming increasingly important for family physicians. Two recent guidelines about the therapeutic management of asthma advocated the early introduction of inhaled corticosteroids in patients with asthma.<sup>2-3</sup> Since most patients with asthma are treated in primary care practices,<sup>9-10</sup> and indications for the use of inhaled corticosteroids are increasing, family physicians will have to prescribe this kind of therapy for a growing number of patients. For family physicians, an important therapeutic question about treatment with inhaled corticosteroids is whether maintenance therapy with these drugs can be discontinued when adequate control of the disease has been achieved. This question has not yet been addressed in a long-term follow-up study in patients selected from family practice. Therefore, it seemed appropriate to study the ability to stop steroid therapy under close observation, as we did in this study.

This study shows that it is difficult to stop treatment with inhaled corticosteroids in patients with mild asthma. Of the 19 patients in whom steroids were stopped, 12 (63%) needed additional inhaled corticosteroids during the 2-year study period, mostly during the first 6 months after stopping. This percentage was much higher than in the group of subjects not using steroids regularly (11%). In the patients who stopped steroids and were able to continue treatment with bronchodilators alone (without inhaled steroids) for at least 1 year, the annual decline in ventilatory function was much higher than in the no-steroid group. However, no increased deterioration in bronchial hyperresponsiveness was found in the patients stopping inhaled corticosteroids. Perhaps the PC<sub>20</sub> had already declined during the washout period just before the start of the study.<sup>23,24</sup>

The high percentage of patients who needed additional corticosteroid therapy and the large decline of FEV<sub>1</sub> in the patients stopping treatment with steroids suggests that inhaled steroids do not cure but only suppress underlying disease processes. It even suggests the existence of a "rebound" increase in airway inflammation and a consequent excessive increase in airway obstruction after the withdrawal of steroids. Short-term studies in asthma demonstrated a decline in FEV<sub>1</sub> and an increase in nonspecific bronchial responsiveness after withdrawal or dose reduction<sup>15</sup> of inhaled steroids.<sup>23-25</sup> One long-term study in patients with asthma referred to specialist treatment also

showed a decline in FEV<sub>1</sub> level after stopping inhaled steroids.<sup>14</sup> After stopping treatment with oral steroids or replacement by inhaled corticosteroids, fatal asthma<sup>26</sup> and severe asthma relapse<sup>27</sup> may occur as late as 4-8 months after discontinuation. Fortunately, none of the stop-steroid group in our study had fatal or near-fatal asthma after cessation of steroids. The syndrome of pseudorheumatism (myalgia, arthralgia, joint swelling, etc) in some asthmatic patients stopping treatment with oral steroids<sup>28</sup> might also suggest a rebound increase in systemic and local inflammatory processes.

In origin, this study had another research question, and the information presented in this report represents a reanalysis of study data. A disadvantage of such a reanalysis is that the study protocol was not specifically designed for the purpose for which we used it. Therefore, the research reported here can only serve as an observational study. As a consequence, the study (stop-steroid) and comparison (no-steroid) groups do not really have a true experimental-control relationship. Measuring dropouts as an outcome might have interfered with the main outcome measures of the study (FEV<sub>1</sub> decline, PC<sub>20</sub> decline, etc), since the study was unblinded and not randomized. Patients in the stop-steroid group had already taken an inhaled steroid for at least 1 year and could easily drop out during the study on the basis of this pre-study medication experience. However, despite the many dropouts from the experimental (stop-steroid) group, we were still able to show a significantly faster decline of FEV<sub>1</sub> in this group than in the no-steroid group (165 vs 40 ml/yr). A better design to answer this paper's question would have been a randomized, controlled, double-blind study in which one group of patients would continue and another group would discontinue the medication. Before firm conclusions can be drawn about the possibility of stopping inhaled steroids, such a study is absolutely necessary.

In spite of this limitation, we believe this study suggests that physicians should be careful in their decision when to stop inhaled steroids in patients with asthma. For this study, we selected only those patients who had mild degrees of airway obstruction (FEV<sub>1</sub> was 75% of the predicted value), mild symptoms, and who, in the opinion of the responsible family physician, could potentially stop the use of inhaled corticosteroid therapy. No measured differences were detected in characteristics at the start of the study between the patients who had used inhaled corticosteroids and those who had not, 8 weeks after stopping the steroid treatment. During this 8-week washout period, we observed whether the symptoms were well controlled by bronchodilators alone and if no exacerbations or signs of increasing airway obstruction developed. If patients had not responded well to this bronchodilating therapy alone, they would have been excluded from the study. However, this did not occur.

As mentioned earlier, at the start of the study the stop-steroid and no-steroid groups were identical for all relevant characteristics. As a consequence, their needs for steroid therapy should also be identical. Therefore, the use of steroids seems to pose a risk in patients in that future discontinuation of the drug is associated with a deterioration in lung function. The majority of the stop-steroid group had been referred to the lung specialist before the start of the use of steroids. Therefore, we could overtake the mean initial FEV<sub>1</sub> of this group of patients. The mean FEV<sub>1</sub> percentage predicted was 71%, the same level as at the start of this study. However, the reason for referral in the stop-steroid group could have been an unstable (steroid-dependent) asthma. Theoretically, it is possible that the deterioration in lung function of the stop-steroid group was caused by this fact. In that case, an 8-week washout period would not have been long enough to eliminate the protective effect of steroids on the airways. Nonetheless, this study's data suggest that if a physician is considering stopping inhaled steroid therapy in a patient with apparently mild (stable) asthma, the patient must be monitored closely for at least 6 months after stopping.

### Conclusions

Stopping maintenance treatment with inhaled corticosteroids in patients with mild asthma might be troublesome. In this observational study, about 60% of the patients needed additional inhaled corticosteroids after discontinuation of the drug, most of them during the first 6 months after stopping. In the patients who could continue without corticosteroids for at least 1 year, the annual decline in ventilatory function was much larger than in the comparison group. Instead of stopping inhaled steroids, family physicians are advised to determine the minimal effective daily dose of inhaled corticosteroids that provides adequate control of the disease in individual patients.

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### REFERENCES

- Djukanovic R, Roche WR, Wilson JW, et al. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990;142:434-57.
- British Thoracic Society. Guidelines for management of asthma in adults: I. Chronic persistent asthma. *Br Med J* 1990;301:651-3.
- Anonymous. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992;5:601-41.
- Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Bryne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
- Haahela T, Järvinen M, Kava T, et al. Comparison of a beta2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
- Dompeling E, van Schayck CP, van Grunsven PM, et al. Slowing the deterioration of asthma and COPD during bronchodilator therapy by adding inhaled corticosteroids. *Ann Intern Med* 1993;118:770-8.
- Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
- Schayck CP van, Dompeling E, Herwaarden CIA van, et al. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised, controlled study. *Br Med J* 1991;303:1426-31.
- Lamberts H. Morbidity in general practice. Utrecht, The Netherlands: Huisartsenpers, 1984.
- Royal College of General Practitioners. Office of Population Censuses and Surveys. Department of Health and Social Security. Morbidity statistics from general practice 1981-1982. Third national study. Series MB5 no. 1. London: Her Majesty's Stationery Office, 1983.
- Dompeling E, Grunsven PM van, Schayck CP van, Folgering H, Molema J, Weel C van. Treatment with inhaled steroids in asthma and chronic bronchitis: long-term compliance and inhaler technique. *Fam Pract* 1992;9:161-6.
- Toogood JH. Complications of topical steroid therapy for asthma. *Am Rev Respir Dis* 1990;141:suppl 89-96.
- Waalens HJ, Essen-Zandvliet EF van, Hughes MD, et al. Cessation of inhaled corticosteroid (budesonide) after long-term treatment in children with asthma results in rapid deterioration. *Am Rev Respir Dis* 1993;148:1252-7.
- Haahela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
- Juniper EF, Kline PA, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;87:483-9.
- Quanjer PH. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;19(s5):7-10.
- American Thoracic Society. Standards for diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-43.
- Fletcher C, Peto R, Tinker C, Speizer FE. The natural history of chronic bronchitis and emphysema. Oxford, England: Oxford University Press, 1976.
- Boman G, Bileker U, Larsson S, Melander B, Wähländer L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis* 1983;64:405-15.
- Dompeling E, Schayck CP van, Folgering H, Hoogen HJM van den, Weel C van. Accuracy, precision, and linearity of the portable flow-volume meter Microspiro III-298. *Eur Respir J* 1991;4:612-5.
- Cockcroft DW, Killian DN, Mellon JA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
- Mardia KV, Kent JT, Bibby JM. Multivariate analysis. London: Academic Press, 1979.
- Kraan J, Koëter GH, Mark TW van de, Sluiter HJ, Vries K de. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985;76:628-36.
- Vathenen AS, Knox AJ, Wisniewski A, Tattersfield MA, Hargreave FE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991;143:1317-21.
- Haahela T, Alanko K, Muittari A, Lahdensuo A, Sahlström K, Vikka V. The superiority of combination beclomethasone and salbutamol over standard dosing of salbutamol in the treatment of chronic asthma. *Ann Allergy* 1989;62:63-6.
- Mellis CM, Phelan PD. Asthma deaths in children—a continuing problem. *Thorax* 1977;32:29-34.
- Maunsell K, Pearson RSB, Livingstone JL. Long-term corticosteroid treatment of asthma. *Br Med J* 1968;1:661-5.
- Hargreave FE, McCarthy DS, Pepys J. Steroid pseudorheumatism in asthma. *Am Rev Respir Dis* 1979;120:87-92.