

Review article

Relation between inflammation and symptoms in asthma

Asthma symptoms are the main reason for healthcare utilization and are a fundamental parameter for the evaluation of asthma control. Currently, asthma is defined as a chronic inflammatory disease. A French expert group studied the association between inflammation and asthma symptoms by carrying out a critical review of the international literature. Uncontrolled asthmatics have an increased number of polynuclear eosinophils in the induced sputum and an increased production of exhaled NO. Control by anti-inflammatory treatment is accompanied by a reduction in bronchial eosinophilia and exhaled NO. Asthma symptoms are the result of complex mechanisms and many factors modify their perception. Experimental data suggest that there is a relationship between the perception of symptoms and eosinophilic inflammation and that inhaled corticoid therapy improves this perception. Although they are still not applicable in routine practice, follow-up strategies based on the evaluation of inflammation are thought to be more effective in reducing exacerbations than those usually recommended based on symptoms and sequential analysis of respiratory function. Inhaled corticosteroid therapy is the reference disease-modifying therapy for persistent asthma. Recent studies demonstrated that adjustment of anti-inflammatory treatment based on symptoms is an effective strategy to prevent exacerbations and reduce the total number of doses of inhaled corticosteroids.

**I. Tillie-Leblond¹, D. Montani²,
B. Crestani³, J. de Blic⁴, M. Humbert²,
M. Tunon-de-Lara⁵, A. Magnan⁶,
N. Roche⁷, J. Ostinelli⁸, P. Chanez⁹**

¹Respiratory Diseases Department, Hôpital Albert Calmette, Lille; ²Pneumology Department, Hôpital Antoine Bécclère, Université Paris-Sud 11, Clamart; ³Pneumology Department, Hôpital Bichat-Claude Bernard, Paris; ⁴Pediatrics Department, Hôpital Necker Enfants Malades, Paris; ⁵Respiratory Diseases Department, Université Bordeaux 2 Victor Segalen, Hôpital Haut-Lévêque, Bordeaux; ⁶Institut du Thorax, INSERM UMR 533, Nantes; ⁷Respiratory Diseases Department, Hôpital Hotel Dieu, Paris; ⁸Laboratoire AstraZeneca; ⁹Respiratory Diseases Department, Hôpital Sainte Marguerite, Marseille, France

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I. Tillie-Leblond
Respiratory Diseases Department
Hôpital Albert Calmette
Boulevard du Pr. Jules Leclercq
59037 Lille Cedex
France

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Asthma symptoms represent the main reason for healthcare utilization. They constitute an essential element for asthma control and currently form the basis of the recommended strategy (1). However, these same recommendations define asthma as a chronic inflammatory disease of the airways. It therefore seemed important to evaluate the true relation between inflammation and asthma symptoms by conducting a critical review of the international literature. A group of French experts undertook to study this association, and the relevant data are summarized in this text. Asthma symptoms are heterogeneous and are often specific for a patient, but the relation between symptoms and inflammation has never been investigated during specific studies. However, numerous studies on inflammation in asthma make it possible to assess indirectly this relationship. An asthma exacerbation is an important event because of its potentially serious nature and the cost due to hospitalization and professional absenteeism. The relation between inflammation and exacerbations is well established. A change in therapeutic strategy based on

symptoms or on the objective evaluation of inflammation has made it possible to reduce the number of severe exacerbations. The verbal description of symptoms by patients depends on their perception and governs the rapidity and coherency of therapeutic management. The perception of the asthma symptoms is variable, multifactorial and potentially associated with bronchial inflammation. Symptoms, exacerbations and perception are directly or indirectly related to inflammation. Therapeutic strategy may legitimately be based on the analysis of symptoms to prevent exacerbations by an early reduction in inflammation. However, interventions for each patient should be considered by integrating their symptoms with the patient's own perception of these symptoms.

Are symptoms a reflection of inflammation?

The main symptoms taken into account to characterize asthmatic disease are dyspnoea, sometimes associated

with 'respiratory discomfort', cough and wheezing (2, 3). These symptoms are sometimes quantified by using a qualitative score (absent, mild, moderate, severe) or a visual analogue scale (VAS) (4). Other symptoms such as chest tightness, sputum (5, 6) and specific exercise-related symptoms (7) are analysed more inconsistently. Composite scores are usually proposed including the incidence of symptoms, their day and/or nighttime occurrence and sometimes their repercussions on daily life. However, there is considerable heterogeneity in these different evaluations, and few studies have made it possible to validate these symptomatic scores (8). Moreover, in many studies, the evaluation of symptoms is integrated in a more global analysis of control, which takes into account drug consumption, the occurrence of exacerbations and changes in respiratory function.

No specific studies have been conducted in asthma to establish a causal relationship between bronchial inflammation and symptoms. However, there are mainly cross-sectional or longitudinal studies analysing inflammatory cells in the sputum, in particular eosinophils and the fraction of exhaled NO (FeNO). Certain studies compare these inflammatory markers with the severity and/or control of asthma and sometimes include a symptom score as primary or secondary outcome variable. Other studies have evaluated the general effect of a treatment or therapeutic strategy. A few studies have also investigated tissue inflammation with bronchial biopsies and more recently, exhaled breath condensates and their relation to symptoms.

Relation between symptoms and inflammation

In the asthmatic child, most of the studies performed to determine the relation between airway inflammation and symptoms used FeNO. Other inflammatory markers whether these are determined by invasive (bronchoalveolar lavage, bronchial biopsies) or noninvasive methods (exhaled breath condensate, blood parameters) have been relatively little studied up until now from this point of view. Different studies make it possible to evaluate the relation between inflammation and asthma symptoms in adults. They include the evaluation of sputum eosinophil counts, but few studies were specifically designed to answer this question (Table 1).

Relation between symptoms and inflammation assessed by sputum induction. Among ten studies allowing the analysis of this relation, half shows a relation between sputum eosinophilia on one hand and asthma symptoms on the other (3, 7, 9–11). This relation was either a qualitative relation (higher inflammation in the symptomatic group compared to the nonsymptomatic group), or a quantitative relation (positive correlation between inflammation and a symptom score) (3, 7, 9–11). Ryttilä et al. (7) found that the increase in sputum eosinophilia was higher in nonasthmatic subjects with respiratory symptoms than in healthy subjects, although it was lower than in uncontrolled asthmatic patients. In addition, other inflammatory sputum parameters (LTE4, ECP, RANTES levels and reduction in eosinophil apoptosis) were also associated with symptoms (9, 11). Two longitudinal studies provided indirect evidence during the response to treatment by inhaled corticosteroids (2, 5), and showed a reduction in sputum eosinophils concomitant with the improvement in symptoms, after treatment by inhaled corticosteroids (2, 5).

However, three other studies failed to show a significant relation between inflammation and symptoms. Two of these studies showed no correlation between sputum eosinophilia and a symptoms score, and a study analysing the effect of systemic corticosteroids on inflammation failed to show a relationship between the fall in the number of sputum eosinophils and symptoms (12, 13). In the study of Lemièrre et al. (12), the primary objective was the comparison of inflammation by different methods (induced sputum, FeNO, biopsies) in moderate-to-severe asthma. This study showed that infiltration of the bronchial mucosa by either eosinophils or neutrophils, analysed from biopsies, was not correlated with asthma symptoms of whatever severity. Interestingly, tissue eosinophilic inflammation was not correlated with sputum eosinophils but with FeNO. However, the heterogeneity of these patients who were considered to be difficult asthmatics should be underlined. They were often treated by high doses of inhaled corticosteroids and their adherence to treatment was not really known.

Relation between symptoms and fraction of NO in exhaled air (FeNO). In the asthmatic child, ten of the thirteen studies found in the literature were cross-sectional and three longitudinal. These studies were very heterogeneous

Table 1. Relation between symptoms and inflammation

	Sputum eosinophilia	FeNO	Bronchial biopsies/ bronchiolo-aveolar lavage	Exhaled breath condensates	Blood parameters
Dyspnoea	+ (7)	N/A	N/A	N/A	+ (7)
Nocturnal symptoms	– (7)	+ (29)	N/A	+ (28)	N/A
Composite symptoms score	+++ (9)	++ (29)	– (12)	+ (28)	+ (9)
Quality-of-life questionnaire	N/A	N/A	N/A	N/A	N/A
Beta-2 agonist consumption	+ (5)	+ (30)	N/A	N/A	N/A

Value of different inflammatory markers in adults: +++ certain, ++ probable, + possible, – absent, N/A not available.

for the number of included children, the severity and control of asthma, the duration of symptom evaluation (2 weeks to 12 months) and outcome variables: night symptoms (14), ACQ questionnaire (15), Usherwood questionnaire (16), Paediatric Asthma Assessment (17), composite score (18), occurrence of recent symptoms (19, 20), presence of wheezing during the previous year (21) or weekly β_2 -adrenergic agonist consumption (14, 22, 23). Eight of these studies showed a correlation between exhaled NO and asthma control (14, 16, 17, 19, 20, 22–24). In these studies, exhaled NO was higher in the case of uncontrolled asthma or if there were recent symptoms. In the study of Artlich et al. (19), asthmatic children who were uncontrolled during the two last weeks had significantly higher exhaled NO levels than controls. Results published by Covar et al. (14) were derived from data of the CAMP study, which followed up children treated by budesonide, nedocromil or placebo for 4–6 years. FeNO measured at the end of the treatment was significantly higher in children who had nocturnal symptoms at least once weekly or who used β_2 -agonists at least once weekly. Four studies found no correlation between symptoms and exhaled NO (18, 21, 25, 26). Franklin et al. (21) found no relation between FeNO and the presence of wheezing, during the last 12 months in 155 children derived from a neonatal cohort. In a cross-sectional study in young children (4 years) derived from a cohort of 429 children at risk of atopy, Brussee et al. (25) found no relation between FeNO and the intermittent or persistent asthma phenotype. Lastly, no correlation was observed between FeNO and clinical asthma symptoms in a study derived from the CARE study that included 144 children aged from 6 to 17 years with the primary objective of comparing a treatment with inhaled corticosteroids and anti-leukotrienes (26). In the asthmatic child, only one of three prospective and longitudinal studies (17, 18, 22) was designed to evaluate the relation between asthma control and inflammatory markers (22), and the two others were carried out by *post hoc* analysis. Spergel (17) studied 30 children with persistent asthma and followed them up prospectively for 6 months by measuring FeNO and evaluating the asthma monthly using the Paediatric Asthma Assessment questionnaire. The authors found a correlation between FeNO and the symptom score ($r^2 = 0.4$, $P < 0.0001$). Fitzpatrick et al. (18) followed up 75 children with persistent asthma for 6 months. The FeNO was significantly higher and remained high in children with severe asthma compared to mild-to-moderate persistent asthma. However, there was no correlation between symptoms (evaluated by a composite score over the last 3 months) and exhaled NO. In the study of Fritsch et al. (22), 45 children with mild-to-moderate asthma were randomized for treatment adjustment according to clinical criteria and respiratory function tests or according to exhaled NO and then followed up every month for 6 months. The results showed a significant correlation between FeNO and β_2

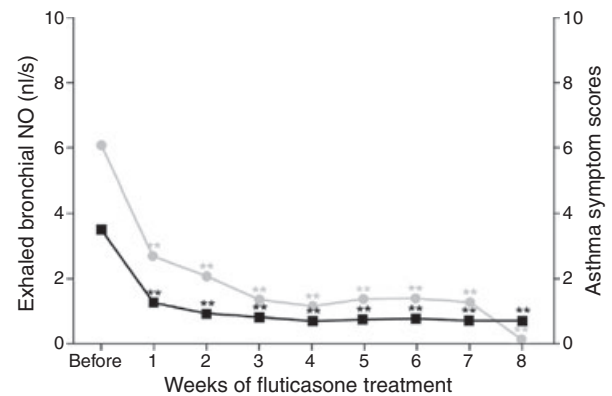


Figure 1. Asthma symptom score and exhaled bronchial nitric oxide (NO) in 16 patients with newly diagnosed asthma before and during 8 weeks of treatment with inhaled fluticasone (adapted from 29). ** $P < 0.01$, compared with baseline value before the treatment. (■) Bronchial NO flux (nl/s); (●) Asthma symptom score.

agonist consumption and asthma symptoms during the 2 weeks before measurement of FeNO. However, children whose follow-up was based on FeNO did not have a better clinical control of their asthma. Lastly, the study of Zacharasiewicz et al. (27) showed that it was possible to withdraw inhaled corticosteroid therapy in asthmatic children from measurements of FeNO.

In adults, six studies analyse the relations between symptoms and FeNO. Four of these studies demonstrated a decline in asthma symptoms after institution of anti-inflammatory treatment, and this was accompanied by a concomitant decrease in FeNO (2, 28–30). In these studies, the primary objective was to analyse a therapeutic effect or a management strategy and not to compare the 'symptoms' variable with FeNO. Nevertheless, the finding of parallel changes in these two variables suggests that there is a quantitative relation between symptoms and FeNO, as shown in the study of Lehtimäki et al. (29) (Fig. 1). This relation is however contradicted by two other negative studies (12, 31). Sandrini et al. (31) have investigated the effect of montelukast in asthma, although it was difficult to interpret these results as montelukast only had a slight anti-inflammatory effect, and there was no control group in the study.

Relation between symptoms and inflammation assessed by biopsies, exhaled breath condensate or systemic markers. Two studies carried out in children with severe asthma analysed the inflammatory infiltrate in bronchial biopsies. Payne et al. (32) carried out bronchial endoscopy after a test with corticosteroids in 31 children and found no correlation between either of the eosinophilic inflammations in bronchial biopsies. However, in children who correctly complied with treatment, eosinophils were higher in uncontrolled patients than in children whose asthma was controlled. In the study of de Blic et al. (33), carried

out in 28 children with severe asthma and persistent bronchial obstruction, the number of intraepithelial eosinophil and neutrophil polynuclear cells was significantly higher in uncontrolled children. Few studies have analysed exhaled breath condensates in the child. Ratnawati et al. (34) found no correlation between the nitrite/nitrate ratio and symptoms, evaluated by the incidence of nocturnal symptoms. Among 104 asthmatic children, Brunetti et al. (35) showed that the pH of the condensate was significantly lower in asthmatic children during an attack compared to children with stable asthma, and that the pH increased significantly after institution of corticosteroid treatment. The study of Kharitonov et al. (28) comparing FeNO and inflammatory markers in the exhaled condensate (nitrite, S-nitrosothiols, 8-isoprostane) showed a concomitant decline in symptoms and S-nitrosothiol concentration in exhaled breath condensate.

A single study (36) evaluated the changes in serum markers of inflammation in asthmatic children. In this study, 33 asthmatic children were randomized to continuation of treatment by inhaled corticosteroids or discontinuation of treatment. After discontinuation of corticosteroids, 71% of the children presented symptoms (and in 50% of cases had to use oral corticosteroids). Blood eosinophil counts and serum ECP and EPO levels were significantly higher in the children who became symptomatic.

Ryttilä et al. (7) compared systemic markers of eosinophil inflammation (blood eosinophil counts, serum eosinophil peroxidase concentration -EPO-) in symptomatic asthmatic and nonasthmatic subjects suffering from respiratory symptoms but with a significantly lower symptom score. Both asthmatic patients and nonasthmatic symptomatic subjects had a rise in these two systemic markers in comparison with healthy subjects, even if the level was significantly higher in asthmatic subjects (7).

To conclude, analysis of these studies shows that there is an unequivocal relation between asthma symptoms and inflammation. Most of the studies reported that uncontrolled asthmatics had more severe inflammation than controlled asthmatics. However, no studies have yet been specifically designed to answer these questions.

Asthma exacerbations: the ultimate consequence of inflammation

Exacerbations correspond to the clinical situation in which the relationship with inflammation is best documented. Treatment of exacerbations is based on the use of corticosteroids, with a high level of proof (level A) (1). Moreover, good asthma control by maintaining long-term inhaled corticosteroid therapy, even at low doses, currently remains the most important parameter determining the reduction in exacerbations, whatever their cause or seriousness is (37–40).

Definition of exacerbations

There is no unequivocal definition of an asthma exacerbation. The most recent GINA guidelines (1) defined exacerbations as episodes of a progressive increase in dyspnoea, cough, wheezing and/or chest tightness accompanied by a decline in Peak Expiratory Flow (PEF). Exacerbations are classified in four stages (mild, moderate, severe, or imminent respiratory arrest) according to symptoms, PEF and sometimes blood gas parameters. During clinical studies such as the FACET study, severe exacerbations are generally defined by the need for systemic corticosteroid therapy (decided by the investigator) or a 30% reduction in morning PEF below the baseline value for two consecutive days (41). Reviewing the 425 severe exacerbations of the study FACET, Tattersfield et al. (42) evaluated the clinical progression of symptoms, the need for emergency medication and the PEF 15 days around the day of diagnosis of the exacerbation. The increase in symptoms, the increased need for treatment and the decline in PEF changed in parallel culminating in an overt exacerbation.

Causes of exacerbations

Exacerbations have multiple causes. Infections, especially viral infections are important in the child, in particular rhinoviruses. Exposure to allergens (43) and irritants through pollution in or outside the home such as exposure to diesel particles is also involved (44, 45). The protective effect of inhaled corticosteroids seems to be the most important against allergens (46), and this protective effect is less clear against viruses or irritants (47–49). However, an experimental study in asthmatic adults infected by rhinoviruses showed that preventive treatment by inhaled corticosteroids began 2 weeks before the infection reduced the level of bronchial hyper-responsiveness and bronchial eosinophilia (50).

Relation between exacerbations and inflammatory cells (Table 2)

In adults, an increase in sputum eosinophils associated with increased ECP levels in supernatants was observed during exacerbations, with a reduction in eosinophils after institution of corticosteroids (51–54). When inhaled corticosteroids are reduced in controlled asthmatics, an experimental exacerbation eventually occurs. There is a parallel increase in bronchial hyper-responsiveness and eosinophil counts in the induced sputum (55–57). The existence of intraepithelial neutrophils and eosinophils in the severe asthmatic child is associated with the occurrence of frequent exacerbations (33). In the study by Norzila et al. (58), 38 children were investigated during asthma exacerbations by analysing the sputum during the acute phase and after 2 weeks. The number of

Table 2. Relation between asthma exacerbations and inflammation

	Sputum eosinophilia	FeNO	Bronchial biopsies/ bronchiolo-aveolar lavage	Exhaled breath condensates	Blood parameters
Changes during exacerbations	++ (66)	++ (20)	N/A	N/A	+
Predictor of an exacerbation	+++ (65)	+	N/A	N/A	–
Modified by treatment	+++ (54)	+++	N/A	N/A	N/A
Prevention strategy	+++ (4, 69)	++ (30)	N/A	N/A	N/A

Value of different inflammatory markers: +++ certain, ++ probable, + possible, – absent, N/A not available.

eosinophils, neutrophils and IL-5, IL-8, ECP and MPO levels was significantly higher during exacerbations, with a clear decline after 2 weeks of follow-up. The authors of this study (58) underlined that viral infection is the most frequently observed triggering factor in the child, and that viruses may directly activate macrophages and epithelial cells, promoting the secretion of IL-8 (59). In the mouse, with viral infection occurring in a background of inflammation, Th-2 can promote the synthesis of IL-5, a cytokine involved in the recruitment of eosinophils by CD8+ T-cells specific for the infecting virus. This shows that exacerbation results from a direct cause (infection) acting in a general inflammatory context (pro-eosinophilic or Th2) (60). An increased number of CD8+ T-lymphocytes was also found in the bronchi of subjects died of asthma compared to asthmatics who died of other causes (61). Eosinophilic and/or neutrophilic inflammation has been described during status asthmaticus (62, 63).

Both Th2 and also Th1 lymphocyte inflammation with production of IFN-gamma increases when asthma is poorly controlled (64). These findings may explain the frequent coexistence of eosinophils and neutrophils during exacerbations.

It has clearly been shown that sputum eosinophilia precedes the occurrence of an exacerbation (65). In the study of Pizzichini et al. (66) sputum eosinophil counts were raised several weeks before the increase in symptoms and reduction in FEV₁. Likewise, Castro et al. (67) showed that progressive withdrawal of inhaled corticosteroids led to an increase in bronchial eosinophilia and bronchial infiltration by T-cells (CD8+ or CD4+) associated with occurrence of an exacerbation.

Overall, these studies raise the question of the value of preventive treatment of exacerbations based on the follow-up of inflammation. In the study of Green et al., (4) 74 moderate-to-severe asthmatic patients were randomized in 2 groups and followed up for 1 year. The first group was treated according to British Thoracic Society (BTS) guidelines (68), which recommend that at each visit, inhaled corticosteroid therapy is increased or decreased according to changes in daytime or nighttime symptoms scores, use of emergency beta-2 agonists and changes in PEF. The second group was treated according to an algorithm establishing a threshold of bronchial eosinophilia of <3%. At the end of the study, adjust-

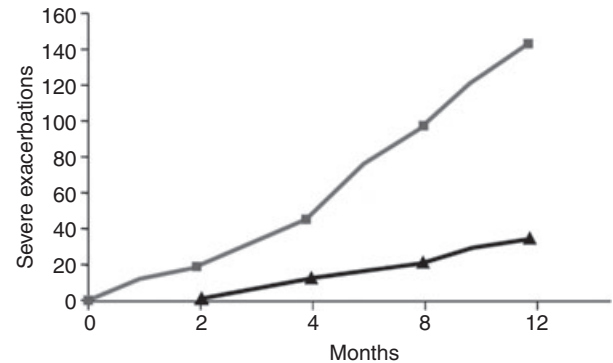


Figure 2. Cumulative asthma exacerbations (adapted from 4). (■) Control group; (▲) Sputum group.

ment of disease-modifying therapy according to the bronchial eosinophilia made it possible to reduce by 2/3 the number of exacerbations compared to adjustment according to BTS guidelines (39 and 109 exacerbations respectively) (4) (Fig. 2). There was also a significant reduction in the number of hospitalizations. It should be noted that respiratory function was equivalent in the two groups throughout the study, as was the mean dose per patient and per day of inhaled or oral corticosteroids (4). In a randomized, multicentre study over 2 years, 117 adults with a moderate-to-severe persistent asthma received a fixed-dose treatment based on symptoms and respiratory function, or a fixed-dose treatment adjusted according to sputum eosinophil counts (less than 2%) (69). Treatment adjustment according to the analysis of bronchial inflammation reduced the number of exacerbations associated with bronchial eosinophilia, and the severity of all the exacerbations. However, this strategy did not have any effect on the number of noneosinophilic exacerbations, which were the most frequent.

Relation between exacerbations and FeNO

In the child, the measurement of exhaled NO levels was studied as a potential predictor of asthma control and occurrence of exacerbations (70). Inhaled corticosteroid therapy in 40 controlled asthmatic children was stopped after a 2-week *run in* phase to confirm the control of their asthma. These children were followed up for 6 months by

measuring exhaled NO and FEV₁ at 1, 3 and 6 months. Loss of asthma control was defined as consumption of at least four doses of β_2 -agonists/week, a variation in PEF > 20% or the occurrence of an exacerbation more than once per month (70). This loss of control was observed in 9 (22%) of the 40 children. Measurements of exhaled NO during the weeks after discontinuation of inhaled corticoid therapy were significantly higher in uncontrolled children compared to children with controlled asthma (mean values of 35–40 ppb and 15 ppb respectively; $P = 0.01$). Sensitivity (71%) and specificity (93%) were best for NO values of 50 ppb. However, the interpretation of these results was made difficult by the variability of NO during the *run in* phase and the very wide variation in NO values during the follow-up. Systemic administration of glucocorticoids during severe exacerbations in the child leads to a reduction in exhaled NO (71).

The measurement of exhaled NO also makes it possible to adjust treatment by inhaled corticosteroids. In the study of Smith et al. (30), patients were randomized to two groups. The first group was treated according to the previous GINA recommendations (daily score based on symptoms, PEF and the use of emergency bronchodilators) and the second group was treated by measuring exhaled NO, the objective being to maintain it under 30 ppb. The primary outcome of the study, the number of exacerbations, was not significantly different between the two groups (0.49 episodes per patient and per year in the

NO group vs 0.9 in the GINA group) (Fig. 3). Moreover, no difference was observed for asthma control, use of oral corticosteroids, respiratory function and sputum eosinophilia. On the contrary, these results were obtained using a lower consumption of inhaled corticosteroids in the group with treatment adjusted by measuring NO compared to the group treated according to GINA recommendations (370 $\mu\text{g/day}$ and 641 $\mu\text{g/day}$ respectively) (30). The small number of exacerbations observed in this study is certainly explained by the severity of the asthma presented by these patients (mild asthma) and may explain the lack of statistical significance of the final result for patients followed-up according to the NO strategy. In a recent study, Shaw et al. (72) evaluated the efficacy of adjustment of inhaled corticoid therapy according to FeNO on exacerbations in 118 asthmatic subjects. Adjustment of inhaled corticosteroids according to FeNO did not make it possible to reduce significantly the incidence of exacerbations compared to adjustment according to BTS guidelines (72).

Asthma exacerbations are always associated with bronchial inflammation, and this is most often eosinophilic inflammation. This sputum eosinophilia may precede the worsening of symptoms and the decline in FEV₁ by several weeks. Adjustment of anti-inflammatory treatment by evaluating bronchial inflammation makes it possible to prevent the occurrence of asthma exacerbations.

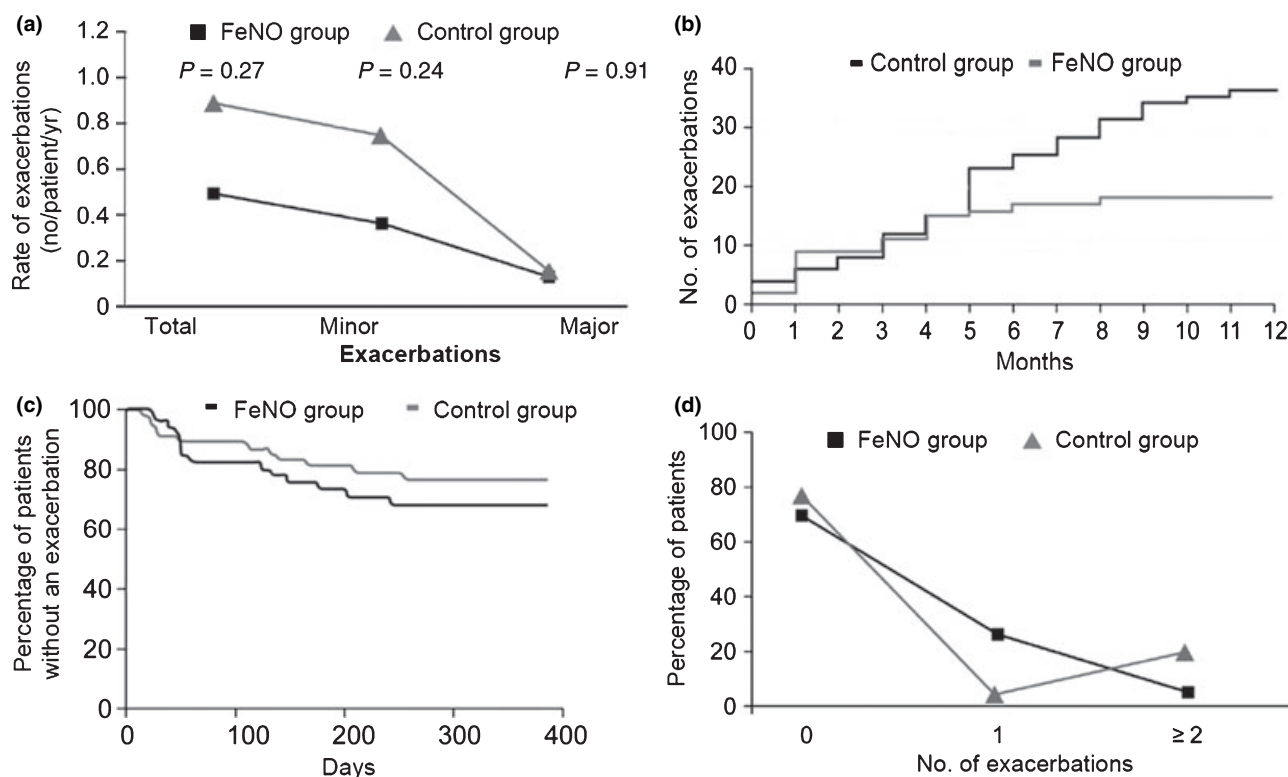


Figure 3. Rates of Exacerbations (adapted from 30).

Symptoms and exacerbations are the reality of asthmatic disease. However, their prevention and consequences for patients are mainly dependent on how they are perceived.

Impact of the perception of symptoms and its modulation by inflammation

Cough and dyspnoea are frequent symptoms in asthma and have a multifactorial origin (73). The exact mechanisms of asthmatic dyspnoea have not been completely elucidated. As asthma is a chronic inflammatory disease of the airways, persistent, local and systemic inflammations are probably involved in the development of symptoms. In asthma, symptoms are the result of a complex activation loop involving the stimulation of sensory nerve terminals, transmission and neuronal integration, interpretation by the cerebral cortex and finally recognition and verbal description by the patient (74). The relation between stimulus and perception may vary widely between individuals and in the same subject from one period to another because of external events (treatment for example) or the psychological background (anxiety, depression). As the verbal description of symptoms may vary according to circumstances, it constitutes a limit restricting communication between patients and doctors, both for children and adults. In asthma, the perception of symptoms is a major but very variable component. In a cohort of 113 controlled asthmatics, Magadle et al. (75) showed that 26% of patients had low perception of dyspnoea and of their bronchial obstruction. These patients used fewer short-acting β_2 -agonists although made significantly more emergency department visits. These patients with low perception of dyspnoea had a higher risk of near-fatal or fatal asthma compared to other asthmatics during the 2 years of prospective follow-up. The relation between perception and symptoms is not limited to a failure to perceive symptoms by certain patients. On the contrary, excessive perception may also exist or the wrong attribution of symptoms to asthma for a perception unrelated to it (74).

In the young child, the doctor-patient relation may be even more difficult to apprehend. Cognitive capacities and language skills rapidly progress in the child between 5 and 15 years, and respiratory perception scales have been developed specifically for the child (76). There are few data about the accuracy of perception of symptoms by children or their parents in asthma. In one study, a third of the episodes of worsening of asthma characterized by a decline in peak expiratory flow (PEF) below 80% of the optimal PEF was not recognized as such, by parents and children (77). In exercise-induced asthma, Panditi et al. (78) showed that the collection of information from parents was insufficient and that the collection of information

from children was essential for an accurate assessment of the incidence and severity of symptoms. In this study, there was a poor correlation between symptom scores in children and FEV₁ after exercise, and no correlation between the perception of symptoms by parents and respiratory function data. Lastly, when the exercise test was repeated, there was a poor reproducibility of the perception of variations in FEV₁ both by parents and children (78).

Mechanical factors involving respiratory muscles (79), pulmonary hyperinflation (80–82), temporal adaptation (83–85), bronchial hyper-responsiveness (83) and psychological (86), emotional and cognitive factors (87) may all affect the perception of dyspnoea in asthma. The stimulation of afferent pulmonary C-fibres triggers a certain number of cholinergic reflex responses inducing bronchoconstriction, hypersecretion and bronchial vasodilatation (88). Original studies carried out in the past (88, 89) or more recently (90–93) suggest that the activation of afferent C-fibre terminals may cause a sensation of dyspnoea, tachypnea and cough. Moy et al. (92) have suggested that information from pulmonary receptors rather than afferent feedback control from stimulation of chest wall receptors by hyperinflation may be important in giving rise to the sensation of breathlessness caused by minor bronchial obstruction. The stimulation of irritation receptors seems to increase this feeling of dyspnoea (73, 94).

Role of the eosinophilic inflammation

Eosinophils may release neurotoxins capable of injuring the afferent nerves involved in the perception of bradykinin-induced bronchoconstriction (95). Roisman et al. (95) observed a reduction in the perception of bradykinin-induced bronchoconstriction in asthmatics not treated by corticosteroids. The perception of bradykinin-induced dyspnoea was negatively correlated with the degree of eosinophilic inflammation of the bronchial mucosa. After a bronchial challenge test by inhalation of methacholine or hypertonic saline solution, In't Veen et al. (96) found that bronchoconstriction was less well perceived by patients suffering from severe asthma than by mild asthmatic patients. In severe asthmatics, the perception of bronchoconstriction was inversely correlated with the percentage of eosinophils in the sputum, whereas in mild asthmatics, the correlation was positive. Ottanelli et al. (97) confirmed that this relation may be positive or negative in treatment-naïve patients or patients already treated by inhaled corticosteroids, independently of baseline FEV₁, duration of disease history and, partly, PC20. The perception of dyspnoea was not different during the early bronchoconstrictive response to the allergen, induced by histamine or by exercise, but it was reduced during the late phase induced by the allergen (98). The late response is more often associated with eosinophil inflammation than the immediate response,

and this decline in the perception of the dyspnoea may therefore be related to inflammation.

Role of inflammatory mediators

Adenosine activates lung mastocytes causing their degranulation and the release of numerous inflammatory mediators, in particular histamine and prostaglandins, which may therefore stimulate C-fibre terminals (neurogenic inflammation) (99). The effects of prostaglandin E₂ (PGE₂) on this sensation of dyspnoea were investigated during exercise, in a group of healthy subjects (100, 101). Despite the absence of any change in respiratory resistances and pulmonary volume, inhaled PGE₂ significantly increased the sensation of dyspnoea compared to saline solution for the same level of work load, ventilation and oxygen uptake. These results suggest that afferent vagal activity plays a role in the sensation of dyspnoea during exercise. Ho et al. (100) showed in the rat that PGE₂ may potentiate the sensitivity of lung C-fibre terminals to capsaicin, a potent selective stimulant of lung C-fibres (90). The sensitivity of afferent lung C-fibres to mechanical stimuli, lung inflation and chemical stimuli is reinforced by PGE₂, causing an irritation of the airways, but PGE₂ does not modify the responses of lung receptors (slow or rapid-adapting receptors) to lung inflation (100). The methacholine challenge test in mild asthmatics is generally considered to activate directly bronchial smooth muscle, unlike inhalation of hypertonic salt solution or adenosine, which act indirectly by activating cellular (mastocytes) and/or neurogenic pathways (102) by inducing the release of mediators such as histamine, which secondarily activate the C-fibre nerve terminals and irritation receptors. In the study by Sont et al. (103), a hypertonic salt solution and methacholine caused different symptoms for similar changes to lung function parameters. The inhalation of hypertonic salt solution was accompanied by greater changes in Borg scores (VAS) than inhalation of methacholine. This suggests that the intensity of perception of airway obstruction partly depends on the mechanisms that cause this obstruction. In addition, these authors observed a significant relation between the severity of dyspnoea during the challenge test and the reduction in bronchodilatation induced by deep inspiration. For certain authors, this finding demonstrates the inflammation of the airways (104, 105). This study shows that potentially inflammatory cellular or neurogenic activation plays a role in the sensation of dyspnoea.

Clinical correlates

Perception in severe asthma attacks. Nosedá et al. (106) studied 25 subjects presenting severe asthma attacks including seven who received different doses of methylprednisolone. During the first day of the study, the initial

dyspnoea was modulated by different doses of corticosteroids. As the parallel changes in FEV₁ were very small, the changes in Borg scores had little relation to those of FEV₁. The reduction in dyspnoea could not be assigned to an improvement in FEV₁. The most obvious explanation was that the dyspnoea was improved by the reduction in airway inflammation induced by corticosteroids. However, Rosi et al. (54) could not confirm these results in 12 patients with severe asthma attacks. In this study, respiratory function, VAS scores, PEF values and the sputum cellular and biochemical profile (ECP) were evaluated before and after treatment by intravenous corticosteroids and a bronchodilator. FEV₁, PEF, VAS score and sputum eosinophils were all improved but not the neutrophilic inflammation. The improvement in dyspnoea (expressed by the fall in VAS score) was significantly correlated with the increase in FEV₁ but not with PEF or with the inflammation parameters measured in the sputum (54). The absence of any significant relation between airway inflammation parameters and the measurement of dyspnoea and their respective improvements may be explained by the fact that in severe asthma attacks, the clinical and functional measurements do not fully reflect the inflammatory response of the airways to anti-inflammatory treatment (53, 107). In particular, neutrophilic inflammation, which is often observed, is thought to be resistant to corticosteroids.

Perception in asthmatic smokers. The perception of dyspnoea is abnormal in COPD, but the situation seems to be different from that observed in asthma (108, 109). Ottanelli et al. (110) suggested that tobacco has an effect on abnormal perception associated with the sputum neutrophilia, which is often observed during persistent obstruction in severe asthma and smoker COPD (111–113). Asthmatic smokers or nonsmokers had variable perception without relationship with bronchial inflammation (114). The data of Ottanelli et al. (110) do not seem to show that neutrophils in the sputum have an important independent effect on the perception of bronchoconstriction by patients with permanent bronchial obstruction.

Other factors. Other factors may be involved in the perception of symptoms, such as rhinosinusitis, obesity, and associated cough, although the role of these factors has never really been investigated. Likewise, there are no specific data for patients with asthma that is diagnosed late, as a delay in diagnosis may be thought to lead to a reduction in the perception of symptoms.

Impact of anti-inflammatory treatment on dyspnoea in asthmatics

The perception of asthma symptoms was not modified by cromoglycate, whereas there was an increase in the perception of symptoms in certain subjects treated by

theophylline, contrasting with a clear improvement in their PEF (115). On the contrary, beclomethasone reduced the symptoms of asthma in most subjects, often without a perceptible improvement in PEF or spirometric data (115). These findings show that there is no direct and unequivocal correlation between perception and obstruction, and the treatments may reveal an uncoupling between the degree of perception and the severity of the obstruction (115).

Boulet et al. (116) evaluated the perception of dyspnoea during a methacholine challenge test, after short or long-term treatment by salmeterol, associated or not with inhaled corticosteroids. Salmeterol, after short or prolonged use, did not significantly modify the perception of bronchoconstriction. These authors (116) observed that the use of inhaled corticosteroids was associated with an improved perception of asthma symptoms, evaluated during the PC20. These results confirm the findings of Roisman et al. (95) that patients treated with inhaled corticosteroids had an increased perception of symptoms than corticosteroid-naïve patients for a given degree of eosinophil inflammation. Bijl-Hofland et al. (117) showed that compared with long-acting β_2 -agonists used alone, a combination of long-acting β_2 -agonists and inhaled corticosteroids had a positive effect on the perception of bronchial obstruction. A longitudinal Australian study (118) with administration of high doses of inhaled corticosteroids (budesonide) failed to show any difference between naïve or previously treated patients, in terms of variation in the Borg score during the reduction of FEV₁ induced by challenge tests. After 8 weeks of inhaled corticosteroid therapy, an improvement in the perception of dyspnoea was observed for a given reduction in FEV₁ (118). No variable, including the dose of corticosteroid therapy, baseline FEV₁, bronchial hyperresponsiveness, blood eosinophilia or serum levels of eosinophil cationic protein (ECP) predicted the changes in the perception of dyspnoea with inhaled corticosteroid therapy (118). The authors concluded that budesonide improved the perception of bronchial obstruction, but this effect was not related to the dose of corticosteroid therapy or changes in the markers of the circulating eosinophilia (118). These authors evaluated the changes in perception of bronchial obstruction after a reduction in inhaled corticosteroid therapy in 33 patients (57). The reduced perception of bronchial obstruction worsened during an exacerbation but was not correlated with eosinophil inflammation measured in the induced sputum for the patients in whom this data was available (57). The relation between perception of asthma symptoms and inhaled corticosteroid therapy is complex, as corticosteroids may reduce or increase the perceived symptoms depending on the setting. These differences in response raise the question of the characterization of asthmatic patients and a potential relation between the response to inhaled corticosteroid therapy and the patients' inflammatory phenotype.

Consequences for treatment strategy

The data discussed above show the complex relations between inflammation and the clinical and respiratory functional manifestations of asthma. These relations may have implications both for follow-up procedures and treatment strategies. The primary objective of asthma management is to reduce the incidence of exacerbations, in particular severe life-threatening exacerbations, and to relieve respiratory symptoms that cause a reduction in quality of life.

Implications for the treatment of exacerbations

During asthma exacerbations, systemic corticosteroids are able to improve rapidly symptoms and respiratory function. They also reduce the risk of relapse while reducing bronchial and systemic markers of inflammation. GINA 2006 guidelines (1) agree at the highest level of proof (level A) that systemic corticosteroid therapy must be used in all except the mildest asthma exacerbations (119, 120). Inhaled corticosteroid therapy also has a certain efficacy for the treatment of exacerbations. It was therefore shown that a combination of an inhaled corticosteroid with a rapid-acting bronchodilator (salbutamol) gave a better improvement in bronchodilatation than treatment by salbutamol alone (level B) (121). Moreover, prevention of relapses by inhaled corticosteroid therapy associated with prednisone was better than when prednisone was used alone (122).

Implications for follow-up strategy

Asthma follow-up is currently based on clinical and functional respiratory parameters according to the concept of disease 'control', using standardized questionnaires or not (1, 123–125). Several studies have integrated inflammatory markers with the criteria for monitoring the disease and the effect of treatments (126, 127). These markers may help (i) to anticipate or prevent loss of control by early adjustment of treatment and (ii) to safely reduce treatment pressure during satisfactory control to reach minimum effective treatment. The value of integrating inflammatory markers of bronchial responsiveness in follow-up was therefore investigated in randomized trials, in which the additional monitoring variables tested were bronchial responsiveness, eosinophil counts in the induced sputum and NO levels in the exhaled air. In the three cases, a strategy 'based on inflammation follow-up' was shown to be superior to the usual strategy in terms of number of exacerbations (for bronchial responsiveness and sputum eosinophils) or total dosing with systemic corticosteroids (for FeNO) (Figs 2 and 3). These results back up the hypothesis of a relationship between inflammation and clinical asthma symptoms.

However, despite these findings, the recommendations remain unchanged. This is because the variables measured cannot be routinely tested so that control based on clinical findings and respiratory function tests remains the fold standard for asthma follow-up.

Implications for treatment strategy

Inhaled corticosteroids remain the cornerstone of disease-modifying therapy for asthma (level of proof A) (1). They improve control and respiratory function and reduce the risk of exacerbation and death (1). If control is insufficient with corticosteroids alone, combination with a long-acting β_2 -adrenergic agonist (as a fixed-dose combination or separately) is more effective than doubling the doses of inhaled corticosteroid therapy or the addition of theophylline or an anti-leukotriene (1). In a recent randomized study enrolling 455 mild asthmatic patients, Papi et al. (128) showed that the use of a beclomethasone and salbutamol combination on-demand was as effective as the daily utilization of beclomethasone. Moreover, in 6 months, there were significantly fewer exacerbations in the group treated by the beclomethasone-salbutamol combination on-demand for a significantly lower cumulative dose of inhaled corticosteroids (128). Certain disease-modifying therapies also have a rapidity of action allowing their use to relieve symptoms. The study of the kinetics of exacerbations shows that they are generally preceded by symptoms, which gradually worsen over a few days. According to the hypothesis that these symptoms are the sign of an increase in inflammation subsequently resulting in an exacerbation, it should be possible to prevent exacerbations by increasing the doses of inhaled corticosteroids according to symptoms. This has led to the proposal of a strategy based on the use of a single treatment with the budesonide-formoterol combination both as maintenance and reliever therapy when symptoms occur. The GINA group experts have mentioned that this strategy gives 'a reduction in exacerbations and an improvement in asthma control in

adults and adolescents, with relatively low doses of treatment' (level A) (1).

Conclusion

Uncontrolled asthmatics generally have an increase in sputum eosinophils and of exhaled NO concentration, which generally falls during anti-inflammatory treatment. The association between respiratory symptoms and bronchial inflammation is not specific to asthma. Asthma exacerbations are always associated with bronchial inflammation and mostly with eosinophilic inflammation. Inhaled corticosteroids are the reference treatment to prevent exacerbations. Inflammatory markers and the clinical and functional signs of asthma generally change in parallel with the effect of treatments. In asthma, respiratory symptoms are the result of a series of complex processes: activation of sensory nerve terminals, neuronal transmission and integration, interpretation by the cerebral cortex, then recognition and verbal description by patients. Many factors and, in particular, smoking, emotional status or treatments can modify the perception of bronchial obstruction. Data suggest that the perception of bronchial obstruction may be related to the degree of eosinophilic inflammation and airway epithelial lesions. In most studies, inhaled corticosteroids improve the perception of obstruction. Several studies have shown that follow-up strategies based on sputum eosinophilia, exhaled NO or bronchial responsiveness are more effective in reducing the number of exacerbations than the usual strategies based on symptoms and respiratory function. They are not applicable in routine practice. The implications of this finding have conducted to propose for some patients, a combination of inhaled corticosteroid and bronchodilator for the treatment of symptoms, in addition to a maintenance treatment.

References

1. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2006 <http://www.ginasthma.com/Guidelineitem.asp?l1=2&l2=1&intId=60>.
2. Green RH, Brightling CE, McKenna S, Hargadon B, Neale N, Parker D et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. *Eur Respir J* 2006;**27**:1144–1151.
3. Louis R, Lau LC, Bron AO, Roldaan AC, Radermecker M, Djukanovic R. The relationship between airways inflammation and asthma severity. *Am J Respir Crit Care Med* 2000;**161**:9–16.
4. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**:1715–1721.
5. Bacci E, Cianchetti S, Bartoli M, Dente FL, Di Franco A, Vagaggini B et al. Low sputum eosinophils predict the lack of response to beclomethasone in symptomatic asthmatic patients. *Chest* 2006;**129**:565–572.
6. ten Brinke A, Zwiderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med* 2004;**170**:601–605.

7. Ryttilä P, Metso T, Heikkinen K, Saarelainen P, Helenius IJ, Haahtela T. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. *Eur Respir J* 2000;**16**:824–830.
8. Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. *Eur Respir J* 1997;**10**: 646–651.
9. Duncan CJ, Lawrie A, Blaylock MG, Douglas JG, Walsh GM. Reduced eosinophil apoptosis in induced sputum correlates with asthma severity. *Eur Respir J* 2003;**22**: 484–490.
10. Giannini D, Di Franco A, Cianchetti S, Bacci E, Dente FL, Vagaggini B et al. Analysis of induced sputum before and after withdrawal of treatment with inhaled corticosteroids in asthmatic patients. *Clin Exp Allergy* 2000;**30**:1777–1784.
11. Romagnoli M, Vachier I, Tarodo de la Fuente P, Meziane H, Chavis C, Bousquet J et al. Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002;**20**:1370–1377.
12. Lemièrre C, Ernst P, Olivenstein R, Yamauchi Y, Govindaraju K, Ludwig MS et al. Airway inflammation assessed by invasive and noninvasive means in severe asthma: eosinophilic and noneosinophilic phenotypes. *J Allergy Clin Immunol* 2006;**118**: 1033–1039.
13. Lemièrre C, Walker C, O'Shaughnessy D, Efthimiadis A, Hargreave FE, Sears MR. Differential cell counts in sputum in respiratory epidemiology: a pilot study. *Chest* 2001;**120**: 1107–1113.
14. Covar RA, Szeffler SJ, Martin RJ, Sundstrom DA, Silkoff PE, Murphy J et al. Relations between exhaled nitric oxide and measures of disease activity among children with mild-to-moderate asthma. *J Pediatr* 2003;**142**:469–475.
15. Rosias PP, Dompeling E, Dentener MA, Pennings HJ, Hendriks HJ, Van Iersel MP et al. Childhood asthma: exhaled markers of airway inflammation, asthma control score, and lung function tests. *Pediatr Pulmonol* 2004;**38**:107–114.
16. Leuppi JD, Downs SH, Downie SR, Marks GB, Salome CM. Exhaled nitric oxide levels in atopic children: relation to specific allergic sensitisation, AHR, and respiratory symptoms. *Thorax* 2002;**57**:518–523.
17. Spergel JM, Fogg MI, Boksaczanin-Knosala A. Correlation of exhaled nitric oxide, spirometry and asthma symptoms. *J Asthma* 2005;**42**:879–883.
18. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in school-age children: Atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol* 2006;**118**: 1218–1225.
19. Artlich A, Busch T, Lewandowski K, Jonas S, Gortner L, Falke KJ. Childhood asthma: exhaled nitric oxide in relation to clinical symptoms. *Eur Respir J* 1999;**13**: 1396–1401.
20. Mahut B, Delacourt C, Zerah-Lancner F, De Blic J, Harf A, Delclaux C. Increase in alveolar nitric oxide in the presence of symptoms in childhood asthma. *Chest* 2004;**125**: 1012–1018.
21. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;**58**: 1048–1052.
22. Fritsch M, Uxa S, Horak F Jr, Putschoegl B, Dehlink E, Szeffalusi Z et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006;**41**:855–862.
23. Paraskakis E, Brindicci C, Fleming L, Krol R, Kharitonov SA, Wilson NM et al. Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. *Am J Respir Crit Care Med* 2006;**174**:260–267.
24. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. *Pediatr Crit Care Med* 2004;**5**:48–52.
25. Brussee JE, Smit HA, Kerkhof M, Koopman LP, Wijga AH, Postma DS et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. *Eur Respir J* 2005;**25**: 455–461.
26. Strunk RC, Szeffler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;**112**:883–892.
27. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005;**171**:1077–1082.
28. Kharitonov SA, Donnelly LE, Montuschi P, Corradi M, Collins JV, Barnes PJ. Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. *Thorax* 2002;**57**:889–896.
29. Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Inhaled fluticasone decreases bronchial but not alveolar nitric oxide output in asthma. *Eur Respir J* 2001;**18**:635–639.
30. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;**352**:2163–2173.
31. Sandrini A, Ferreira IM, Gutierrez C, Jardim JR, Zamel N, Chapman KR. Effect of montelukast on exhaled nitric oxide and nonvolatile markers of inflammation in mild asthma. *Chest* 2003;**124**:1334–1340.
32. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001;**164**:1376–1381.
33. de Blic J, Tillie-Leblond I, Tonnel AB, Jaubert F, Scheinmann P, Gosset P. Difficult asthma in children: an analysis of airway inflammation. *J Allergy Clin Immunol* 2004;**113**:94–100.
34. Ratnawati R, Morton J, Henry RL, Thomas PS. Exhaled breath condensate nitrite/nitrate and pH in relation to pediatric asthma control and exhaled nitric oxide. *Pediatr Pulmonol* 2006;**41**:929–936.
35. Brunetti L, Francavilla R, Tesse R, Strippoli A, Polimeno L, Loforese A et al. Exhaled breath condensate pH measurement in children with asthma, allergic rhinitis and atopic dermatitis. *Pediatr Allergy Immunol* 2006;**17**: 422–427.
36. Lonnkvist K, Hellman C, Lundahl J, Hallden G, Hedlin G. Eosinophil markers in blood, serum, and urine for monitoring the clinical course in childhood asthma: impact of budesonide treatment and withdrawal. *J Allergy Clin Immunol* 2001;**107**: 812–817.

37. Powell H, Gibson P. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children (review). *Cochrane Database Syst Rev* 2003;**4**:CD004109.
38. Sin DD, Man SF. Low-dose inhaled corticosteroid therapy and risk of emergency department visits for asthma. *Arch Intern Med* 2002;**162**: 1591–1595.
39. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol* 2001;**107**:937–944.
40. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;**343**:332–336.
41. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;**337**:1405–1411.
42. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999;**160**:594–599.
43. Tillie-Leblond I, Godard P. Introduction for short texts from "La conference d'experts de la Societe de Pneumologie de Langue Francaise (SPLF) sur Asthme et Allergie". *Rev Mal Respir* 2007;**24**:221–222.
44. Murray CS, Poletti G, Keadze T, Morris J, Woodcock A, Johnston SL et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;**61**:376–382.
45. Johnston NW, Sears MR. Asthma exacerbations: epidemiology. *Thorax* 2006;**61**:722–728.
46. Subbarao P, Dorman SC, Rerecich T, Watson RM, Gauvreau GM, O'Byrne PM. Protection by budesonide and fluticasone on allergen-induced airway responses after discontinuation of therapy. *J Allergy Clin Immunol* 2005;**115**:745–750.
47. Friedlander SL, Busse WW. The role of rhinovirus in asthma exacerbations. *J Allergy Clin Immunol* 2005;**116**: 267–273.
48. Hashimoto K, Ishii Y, Uchida Y, Kimura T, Masuyama K, Morishima Y et al. Exposure to diesel exhaust exacerbates allergen-induced airway responses in guinea pigs. *Am J Respir Crit Care Med* 2001;**164**: 1957–1963.
49. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. *Lancet* 1999;**353**: 364–369.
50. Grunberg K, Sharon RF, Sont JK, In 't Veen JC, Van Schadewijk WA, De Klerk EP et al. Rhinovirus-induced airway inflammation in asthma: effect of treatment with inhaled corticosteroids before and during experimental infection. *Am J Respir Crit Care Med* 2001;**164**: 1816–1822.
51. Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Bacci E, Dente FL et al. Analysis of sputum cell counts during spontaneous moderate exacerbations of asthma in comparison to the stable phase. *J Asthma* 2003;**40**:155–162.
52. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;**95**:843–852.
53. Pizzichini MM, Pizzichini E, Clelland L, Efthimiadis A, Mahony J, Dolovich J et al. Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. *Am J Respir Crit Care Med* 1997;**155**: 1501–1508.
54. Rosi E, Lanini B, Ronchi MC, Romagnoli I, Stendardi L, Bianchi R et al. Dyspnea, respiratory function and sputum profile in asthmatic patients during exacerbations. *Respir Med* 2002;**96**:745–750.
55. Gibson PG, Woolley KL, Carty K, Murree-Allen K, Saltos N. Induced sputum eosinophil cationic protein (ECP) measurement in asthma and chronic obstructive airway disease (COAD). *Clin Exp Allergy* 1998;**28**: 1081–1088.
56. In't Veen JC, Smits HH, Hiemstra PS, Zwinderman AE, Sterk PJ, Bel EH. Lung function and sputum characteristics of patients with severe asthma during an induced exacerbation by double-blind steroid withdrawal. *Am J Respir Crit Care Med* 1999;**160**:93–99.
57. Salome CM, Leuppi JD, Freed R, Marks GB. Perception of airway narrowing during reduction of inhaled corticosteroids and asthma exacerbation. *Thorax* 2003;**58**:1042–1047.
58. Norzila MZ, Fakes K, Henry RL, Simpson J, Gibson PG. Interleukin-8 secretion and neutrophil recruitment accompanies induced sputum eosinophil activation in children with acute asthma. *Am J Respir Crit Care Med* 2000;**161**:769–774.
59. Corne JM, Holgate ST. Mechanisms of virus induced exacerbations of asthma. *Thorax* 1997;**52**:380–389.
60. Coyle AJ, Erard F, Bertrand C, Walti S, Pircher H, Le Gros G. Virus-specific CD8+ cells can switch to interleukin 5 production and induce airway eosinophilia. *J Exp Med* 1995;**181**:1229–1233.
61. O'Sullivan S, Cormican L, Faul JL, Ichinohe S, Johnston SL, Burke CM et al. Activated, cytotoxic CD8(+) T lymphocytes contribute to the pathology of asthma death. *Am J Respir Crit Care Med* 2001;**164**:560–564.
62. Azzawi M, Johnston PW, Majumdar S, Kay AB, Jeffery PK. T lymphocytes and activated eosinophils in airway mucosa in fatal asthma and cystic fibrosis. *Am Rev Respir Dis* 1992;**145**:1477–1482.
63. Tillie-Leblond I, Hammad H, Desurmont S, Pugin J, Wallaert B, Tonnel AB et al. CC chemokines and interleukin-5 in bronchial lavage fluid from patients with status asthmaticus. Potential implication in eosinophil recruitment. *Am J Respir Crit Care Med* 2000;**162**:586–592.
64. Boniface S, Koscher V, Mamessier E, El Biaze M, Dupuy P, Lorec AM et al. Assessment of T lymphocyte cytokine production in induced sputum from asthmatics: a flow cytometry study. *Clin Exp Allergy* 2003;**33**: 1238–1243.
65. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000;**161**:64–72.
66. Pizzichini MM, Pizzichini E, Clelland L, Efthimiadis A, Pavord I, Dolovich J et al. Prednisone-dependent asthma: inflammatory indices in induced sputum. *Eur Respir J* 1999;**13**:15–21.
67. Castro M, Bloch SR, Jenkinson MV, DeMartino S, Hamilos DL, Cochran RB et al. Asthma exacerbations after glucocorticoid withdrawal reflects T cell recruitment to the airway. *Am J Respir Crit Care Med* 2004;**169**:842–849.

68. British Thoracic Society, Scottish intercollegiate Guidelines Network. British guidelines on the management of asthma. A national clinical guideline. Revised edition November 2005. <http://www.enterpriseportal2.co.uk/filestore/bts/asthmaupdate-nov05.pdf>.
69. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;**27**:483–494.
70. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005;**60**:215–218.
71. Lanz MJ, Leung DY, White CW. Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticoids in children. *Ann Allergy Asthma Immunol* 1999;**82**:161–164.
72. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ et al. The Use of Exhaled Nitric Oxide to Guide Asthma Management: A Randomised Controlled Trial. *Am J Respir Crit Care Med* 2007;**176**: 231–237.
73. Manning HL, Schwartzstein RM. Pathophysiology of Dyspnea. *N Engl J Med* 1995;**333**:1547–1553.
74. Banzett RB, Dempsey JA, O'Donnell DE, Wamboldt MZ. Symptom perception and respiratory sensation in asthma. *Am J Respir Crit Care Med* 2000;**162**:1178–1182.
75. Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest* 2002;**121**:329–333.
76. Fritz GK, Yeung A, Wamboldt MZ, Spirito A, McQuaid EL, Klein R et al. Conceptual and methodologic issues in quantifying perceptual accuracy in childhood asthma. *J Pediatr Psychol* 1996;**21**:153–173.
77. Yoos HL, Kitzman H, McMullen A, Sidora K. Symptom perception in childhood asthma: how accurate are children and their parents? *J Asthma* 2003;**40**:27–39.
78. Panditi S, Silverman M. Perception of exercise induced asthma by children and their parents. *Arch Dis Child* 2003;**88**:807–811.
79. Killian KJ, Jones NL. Respiratory muscles and dyspnea. *Clin Chest Med* 1988;**9**:237–248.
80. Fessler HE, Brower RG, Permutt S. CPAP reduces inspiratory work more than dyspnea during hyperinflation with intrinsic PEEP. *Chest* 1995;**108**:432–440.
81. Loughed MD, Lam M, Forkert L, Webb KA, O'Donnell DE. Breathlessness during acute bronchoconstriction in asthma. Pathophysiologic mechanisms. *Am Rev Respir Dis* 1993;**148**:1452–1459.
82. Yan S. Sensation of inspiratory difficulty during inspiratory threshold and hyperinflationary loadings. Effect of inspiratory muscle strength. *Am J Respir Crit Care Med* 1999;**160**: 1544–1549.
83. Burdon JG, Juniper EF, Killian KJ, Hargreave FE, Campbell EJ. The perception of breathlessness in asthma. *Am Rev Respir Dis* 1982;**126**:825–828.
84. Ottanelli R, Rosi E, Romagnoli I, Ronchi MC, Lanini B, Grazzini M et al. Perception of bronchoconstriction and bronchial hyper-responsiveness in asthma. *Clin Sci (Lond)* 2000;**98**:681–687.
85. Rubinfeld AR, Pain MC. Conscious perception of bronchospasm as a protective phenomenon in asthma. *Chest* 1977;**72**:154–158.
86. Hudgel DW, Cooperson DM, Kinsman RA. Recognition of added resistive loads in asthma: the importance of behavioral styles. *Am Rev Respir Dis* 1982;**126**:121–125.
87. Peiffer C, Toumi M, Razzouk H, Marsac J, Lockhart A. Relationship between spontaneous dyspnoea and lability of airway obstruction in asthma. *Clin Sci (Lond)* 1992;**82**:717–724.
88. Coleridge JC, Coleridge HM. Afferent vagal C fibre innervation of the lungs and airways and its functional significance. *Rev Physiol Biochem Pharmacol* 1984;**99**:1–110.
89. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev* 1973;**53**:159–227.
90. Barnes PJ. Poorly perceived asthma. *Thorax* 1992;**47**:408–409.
91. Kelsen SG, Prestel TF, Cherniack NS, Chester EH, Deal EC Jr. Comparison of the respiratory responses to external resistive loading and bronchoconstriction. *J Clin Invest* 1981;**67**:1761–1768.
92. Moy ML, Woodrow Weiss J, Sparrow D, Israel E, Schwartzstein RM. Quality of dyspnea in bronchoconstriction differs from external resistive loads. *Am J Respir Crit Care Med* 2000;**162**:451–455.
93. Taguchi O, Kikuchi Y, Hida W, Iwase N, Satoh M, Chonan T et al. Effects of bronchoconstriction and external resistive loading on the sensation of dyspnea. *J Appl Physiol* 1991;**71**:2183–2190.
94. Lee LY, Morton RF. Pulmonary chemoreflex sensitivity is enhanced by prostaglandin E2 in anesthetized rats. *J Appl Physiol* 1995;**79**:1679–1686.
95. Roisman GL, Peiffer C, Lacronique JG, Le Cae A, Dusser DJ. Perception of bronchial obstruction in asthmatic patients. Relationship with bronchial eosinophilic inflammation and epithelial damage and effect of corticosteroid treatment. *J Clin Invest* 1995;**96**:12–21.
96. In't Veen JC, Smits HH, Ravensberg AJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998;**158**:1134–1141.
97. Ottanelli R, Rosi E, Romagnoli I, Grazzini M, Stendardi L, Duranti R et al. Do inhaled corticosteroids affect perception of dyspnea during bronchoconstriction in asthma? *Chest* 2001;**120**:770–777.
98. Turcotte H, Corbeil F, Boulet LP. Perception of breathlessness during bronchoconstriction induced by antigen, exercise, and histamine challenges. *Thorax* 1990;**45**:914–918.
99. Holgate ST, Church MK, Polosa R. Adenosine: a positive modulator of airway inflammation in asthma. *Ann N Y Acad Sci* 1991;**629**:227–236.
100. Ho CY, Gu Q, Hong JL, Lee LY. Prostaglandin E(2) enhances chemical and mechanical sensitivities of pulmonary C fibers in the rat. *Am J Respir Crit Care Med* 2000;**162**: 528–533.
101. Holtzman MJ, Zhang V, Hussain H, Roswit WT, Wilson JD. Prostaglandin H synthase and lipooxygenase gene families in the epithelial cell barrier. *Ann N Y Acad Sci* 1994;**744**:58–77.
102. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B et al. Indirect airway challenges. *Eur Respir J* 2003;**21**:1050–1068.
103. Sont JK, Booms P, Bel EH, Vandenbroucke JP, Sterk PJ. The severity of breathlessness during challenges with inhaled methacholine and hypertonic saline in atopic asthmatic subjects. The relationship with deep breath-induced bronchodilation. *Am J Respir Crit Care Med* 1995;**152**:38–44.

104. Pliss LB, Ingenito EP, Ingram RH Jr. Responsiveness, inflammation, and effects of deep breaths on obstruction in mild asthma. *J Appl Physiol* 1989;**66**:2298–2304.
105. Pliss LB, Ingenito EP, Ingram RH Jr, Pichurko B. Assessment of bronchoalveolar cell and mediator response to isocapnic hyperpnea in asthma. *Am Rev Respir Dis* 1990;**142**:73–78.
106. Nosedá A, De Bruyne I, De Maertelaer V, Yernault JC. Does an IV bolus of methylprednisolone relieve dyspnea in asthma exacerbations? *Chest* 2000;**118**:1530–1537.
107. Fahy JV, Boushey HA. Effect of low-dose beclomethasone dipropionate on asthma control and airway inflammation. *Eur Respir J* 1998;**11**:1240–1247.
108. Massasso DH, Salome CM, King GG, Seale JP, Woolcock AJ. Do subjects with asthma have greater perception of acute bronchoconstriction than smokers with airflow limitation? *Respirology* 1999;**4**:393–399.
109. Rutgers SR, ten Hacken NH, Koeter GH, Postma DS. Borg scores before and after challenge with adenosine 5'-monophosphate and methacholine in subjects with COPD and asthma. *Eur Respir J* 2000;**16**:486–490.
110. Ottanelli R, Rosi E, Ronchi MC, Grazzini M, Lanini B, Stendardi L et al. Perception of bronchoconstriction in smokers with airflow limitation. *Clin Sci (Lond)* 2001;**101**:515–522.
111. Keatings VM, Barnes PJ. Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma, and normal subjects. *Am J Respir Crit Care Med* 1997;**155**:449–453.
112. Ronchi MC, Piragino C, Rosi E, Amendola M, Duranti R, Scano G. Role of sputum differential cell count in detecting airway inflammation in patients with chronic bronchial asthma or COPD. *Thorax* 1996;**51**:1000–1004.
113. Thompson AB, Rennard SI. Assessment of airways inflammation in chronic bronchitis. *Eur Respir J* 1993;**6**:461–464.
114. Kleis S, Chanez P, Delvaux M, Louis R. Perception of dyspnea in mild smoking asthmatics. *Respir Med* 2007;**101**:1426–1430.
115. Higgs CM, Laszlo G. Influence of treatment with beclomethasone, cromoglycate and theophylline on perception of bronchoconstriction in patients with bronchial asthma. *Clin Sci (Lond)* 1996;**90**:227–234.
116. Boulet LP, Turcotte H, Cartier A, Milot J, Cote J, Malo JL et al. Influence of beclomethasone and salmeterol on the perception of methacholine-induced bronchoconstriction. *Chest* 1998;**114**:373–379.
117. Bijl-Hofland ID, Cloosterman SG, Folgering HT, van den Elshout FJ, van Weel C, van Schayck CP. Inhaled corticosteroids, combined with long-acting beta(2)-agonists, improve the perception of bronchoconstriction in asthma. *Am J Respir Crit Care Med* 2001;**164**:764–769.
118. Salome CM, Reddel HK, Ware SI, Roberts AM, Jenkins CR, Marks GB et al. Effect of budesonide on the perception of induced airway narrowing in subjects with asthma. *Am J Respir Crit Care Med* 2002;**165**:15–21.
119. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev*. 2001; 1:CD001740.
120. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev*. 2001; 1:CD002178.
121. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. *Am J Respir Crit Care Med* 1998;**157**:698–703.
122. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. *Jama* 1999;**281**:2119–2126.
123. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;**170**:836–844.
124. Juniper EF, Kline PA, Vanzielegheem 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**:483–489.
125. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;**113**:59–65.
126. Boulet LP, Boulet V, Milot J. How should we quantify asthma control? A proposal. *Chest* 2002;**122**:2217–2223.
127. LeBlanc A, Robichaud P, Lacasse Y, Boulet LP. Quantification of asthma control: validation of the Asthma Control Scoring System. *Allergy* 2007;**62**:120–125.
128. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;**356**:2040–2052.