

Review article

Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations

This review is the synthesis of a working group on mild asthma. Mild asthma includes intermittent and persistent mild asthma according to the Global Initiative for Asthma (GINA) classification, and affects between 50% and 75% of asthmatic patients. Mild asthma is more frequent, more symptomatic, and less well controlled in children than in adults. Cohort studies from childhood to adulthood show that asthma severity usually remains stable over time. Nevertheless, mild asthma can lead to severe exacerbations, with a frequency ranging from 0.12 to 0.77 per patient-year. Severe exacerbations in mild asthma represent 30–40% of asthma exacerbations requiring emergency consultation. In mild asthma, inflammation and structural remodelling are constant, of varying intensity, but nonspecific. Therapy with inhaled corticosteroids (ICS) decreases bronchial inflammation, but has only a slight effect on structural remodelling, and, when stopped, inflammation immediately recurs. Permanent low-dose ICS therapy is the reference treatment for persistent mild asthma. Effectiveness is to be reassessed at 3 months, and if it is insufficient the patient is no longer considered mildly asthmatic, and treatment has to be stepped up. As mild asthma is the most frequent form of the disease, diagnosis and management require physicians' particular attention.

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Mild asthma includes intermittent and mild persistent asthma according to the Global Initiative for Asthma (GINA) classification (1). It can be defined by the presence of symptoms for at least 12 months in the absence of continuous treatment with bronchodilators and without underlying bronchial obstruction, use of short-acting β_2 -agonist treatment (a few inhalations per week) and continuous low-dose inhaled corticosteroids (ICS) treat-

ment ($\leq 500 \mu\text{g/day}$ beclomethasone dipropionate – BDP – or equivalent), with no or rare episodes of exacerbation (≤ 1 per year) treated by a self-medication schedule or requiring special care but without hospitalization, and if possible without oral corticosteroid treatment.

This review is the synthesis of a working group of 11 lung specialists, four paediatricians, one pharmacologist, and one general practitioner (GP). The group was

Table 1. Results of the literature search (i.e. number of references about mild asthma)

Request	Limits	Request	Limits	Limits	Number of references
"Asthma"	- French or English - Humans	"Mild asthma" or "Intermittent asthma"	All adults: 19+ years	Publication categories: "Review" or "Meta-analysis" or "Randomized controlled trial" or "Clinical trial"	
Yes	Yes	No	No	No	51 338
Yes	Yes	Yes	No	No	853
Yes	Yes	Yes	Yes	No	591
Yes	Yes	Yes	No	Yes	370 (since 1985)
					222 (since 1997)
Yes	Yes	Yes	Yes	Yes	255 (since 1985)
					154 (since 1997)

convened to give an update on the state of knowledge concerning mild asthma. After validation of the definition of mild asthma, the members were divided into subgroups, each of which selected and reviewed the literature relating to their particular focus. The terms used for MEDLINE database searches were the following: asthma, humans, all adults: 19+ years of age, and review, meta-analysis, randomized controlled trial, or clinical trial. Only French and English articles were reviewed. Search results are presented in Table 1. Of the 51 338 references listed since 1997, 154 (0.3%) complied with the study criteria (meta-analysis, clinical trial, or randomized controlled trial on adult mild asthma), and 222 (0.4%) concerned both adults and children. The analysis of the literature data was then presented to the plenary group, and discussed and summarized at a meeting in Paris in November 2005. The conclusions of this working group on the epidemiology, type of bronchial inflammation, clinical consequences, and medical management of mild asthma are presented in the present article.

Epidemiology of mild asthma

Epidemiological data

No consensual epidemiological definition of asthma severity was found to exist. Although respiratory symptoms are the most frequently used criterion, the trend is to use a combined scoring approach that includes symptom frequency, respiratory function, treatment and treatment intensity, and impact on quality of life (2). In the main cohort studies, severity was estimated in terms of respiratory function and its evolution (3, 4). Several methodological approaches can be used to assess the prevalence of mild asthma. One such approach is based on symptom frequency assessed by standardized questionnaires (ISAAC-I and ISAAC-III studies) (5): number of wheezing episodes during the previous 12 months, with or without interruption of sleep or speech disturbance. A second approach combines different methods to calculate a global score. Severity can be evaluated according to the GINA guidelines (Table 2) (6–8), or by scoring clinical, functional, and treatment items (Table 3) (9, 10). These

two approaches differ notably with regard to the criterion of hospitalization (i.e. number of admissions) within the previous 12 months, which is not taken into account by the GINA classification. These quantitative scores remain to be validated in epidemiology. In addition, the severity-stage thresholds appear to be arbitrary: no consistent information could be found as to the distribution of the severity variable.

Although numerous epidemiological studies have assessed asthma prevalence in the general population, none has specifically focused on mild asthma. However, an estimate can be made from the studies presented in Table 4. In the Asthma Insights and Reality surveys (AIR) (8), asthma patients were classified according to the GINA criteria without taking account of therapeutic pressure (1): 41% of the 2803 patients included from Western Europe suffered from mild asthma (22% intermittent and 19% mild persistent asthma). The CREDES study (6) found different severity distributions according to age: 69% and 15% of asthmatic children under five had intermittent or mild persistent asthma, respectively, while the corresponding proportions of subjects over 70 were 24% and 38%. Taking all the studies together, the frequency of mild asthma ranged between 50% and 75%. Finally, the worldwide prevalence of mild asthma could be estimated at 3.3%.

Factors associated with the persistence of asthma and development of bronchial obstruction

The natural history of asthma can be analyzed on the basis of cohort studies of the long-term evolution of asthmatic populations, with screening for adverse events. The methodological limitations of such studies lie in treatment-impact not being taken into account in the assessment of severity. In the oldest cohort studies (11, 12), UK-born subjects were followed up at 7, 11, 16, 23, and 33 years of age. A small minority (5%) showed persistent asthma without remission since childhood, a third with total remission by 33 years of age, and a majority (60%) of intermediate cases with asthma persisting beyond childhood or recurring in adulthood. Even though no stratification according to severity was

Table 2. Combined assessment methods determining asthma severity according to the GINA (1)

	Liard et al. (7)	Credes (6)	Rabe et al. (8)
1st classification	Clinical and FEV ₁	Clinical stage	Clinical index
Intermittent	Symptoms <1 time a week Brief exacerbations Nocturnal symptoms <2 times a month Normal pulmonary function between attacks with FEV ₁ or PEF ≥80% FEV ₁ or PEF variability <20%	<3 attacks a month or <2 nocturnal breathing difficulties a month No FEV ₁	<2 diurnal breathing difficulties a week ≤ 1 exacerbation a week <2 nocturnal breathing difficulties a month No FEV ₁ Symptoms at exertion: ≤ 1 time a week Total symptoms: ≤ 2 times a week
Mild persistent	All the patients not included in the other categories and FEV ₁ or PEF ≥80% FEV ₁ or PEF variability <20%-30%	1–6 attacks a week (diurnal) or 2–4 attacks a month (nocturnal) No PFT	≥2 diurnal breathing difficulties a week ≥2 exacerbations a week ≥2 nocturnal breathing difficulties a month No PFT Symptoms at exertion: ≥2 times a week Total: 3–6 times a week
Moderate persistent	60%< FEV ₁ or PEF <80% FEV ₁ or PEF variability >30%, and daily symptoms or Nocturnal symptoms >1 time a week Exacerbations may affect activity and sleep	No PFT 1–2 attacks a day or 2–4 nocturnal symptoms a week	No PFT Every day (≤ 2 times a day) Exacerbations: every day ≥2 nocturnal symptoms a week Symptoms at exertion: every day Total: 7–20 times a week
Severe persistent	FEV ₁ or PEF ≤ 60%, FEV ₁ or PEF variability >30% or limitation of physical activities Frequent exacerbations Frequent nocturnal asthma symptom	No PFT Permanent diurnal breathing difficulty or Permanent (or quasi-permanent) nocturnal breathing difficulty	No PFT three times a day Every night/most of the nights Exacerbations: every day Symptoms at exertion: every day Total: 8–21 times a week
2nd classification	Treatment (4 classes)	Treatment (4 classes)	No classification
Stage 1	No systemic treatment	Treatment when needed	
Stage 2	ICS <800 µg/day	ICS ≤ 500 µg/day* or LABA or cromone	
Stage 3	ICS 800–2000 µg/day	ICS 500–1500 µg/day† or LABA	
Stage 4	ICS > 2000 µg/day or OCS	OCS or ICS ≥1500 µg/day‡	
Final classification	For each patient, the highest of the stages of the two classes	For each patient, the highest of the stages of the two classes	The occurrence of the diurnal or the nocturnal criterion

LABA, long-acting β_2 -agonists; OCS, oral corticosteroids; ICS, inhaled corticosteroids (beclomethasone dipropionate equivalent); PFT, pulmonary function test; FEV₁, forced expiratory volume for the first second; PEF, peak expiratory flow.

*≤ 250 µg/day for children <12.

†250 to 750 µg/day for children <12.

‡≥750 µg/day for children <12.

performed, smoking and atopic allergy were reported to be the two factors underlying persistence or re-emergence of bronchospastic symptoms. Persistent wheezing during childhood and adolescence was associated with bronchial obstruction at adulthood. The most recent cohort study (4), conducted in New Zealand, found that atopic allergy, persistent bronchial hyperreactivity up to 21 years of age, smoking, and being female were associated with persistence and recurrence of asthma. Children with obstructive ventilatory disorder continued to present obstruction as adults, whereas children with normal ventilatory function were very likely to be free of obstruction in adulthood. Severity was analyzed in an Australian cohort study (13): the least symptomatic cases of childhood asthma went on to become the mildest in adulthood. Aggravation was associated with the persistence of atopic clinical signs (eczema, hay fever, positive cutaneous tests) (14). In a cohort study in the US (3), where children were followed up from birth

to adolescence (i.e. 16 years of age), impact on ventilatory function was observed as of the first years of life. Thus, bronchial obstruction seems to show early onset in the natural history of asthma.

Asthma control and severe exacerbations in mild asthma

The clinical aspects of mild asthma can be approached in various ways: questionnaire surveys, assessment of the frequency of mild asthma among reported cases of exacerbation or acute severe asthma, or *via* the data of placebo limb to be found in clinical studies.

Asthma control in mild asthma

In the AIR study (8), 22% of the 2803 adult patients from Western Europe had intermittent asthma and 19% mild persistent asthma on the GINA criteria, although this

Table 3. Asthma severity scores

Author/population	Ronchetti et al. (9)/child (9-years old)	Zureik et al. (10)/adult
Asthma diagnosis	ATS criteria Questionnaire completed by the parents	Previous diagnosis of asthma and at least 1 attack (last 12 months) or treatment for asthma (last 12 months)
FEV ₁	Mild >80% (1) Moderate 70–80% (2) Severe <70% (3)	Mild >80% (1) Moderate 70–80% (2) Severe <70% (3)
Number of asthma attacks (last 12 months)	≤ 2 (1) 3–6 (2) >6 (3)	≤ 2 (1) 3–6 (2) >6 (3)
Hospitalizations (last 12 months)	0 (1) ≤ 2 (2) >2 (3)	0 (1) ≤ 2 (2) >2 (3)
Treatments	(1–3 weeks) 0–4 (1) 5–15 (2) >15 (3)	(last 12 months) OCS-ICS: yes (1) OCS-ICS: no (2)
Treatments for exacerbation (last 12 months)	0–2 (1) 3–6 (2) >6 (3)	Not applicable
Total score	5–15 5–7: mild 8–10: moderate 11–15: severe	4–11 4 or 5: mild 6: moderate ≥7: severe

Numbers in brackets correspond to the number of points given to each variable.

ATS, American Thoracic Society; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FEV₁, forced expiratory volume for the first second.

was without taking treatment pressure into account (1). Fifty-five percent of intermittent asthma patients claimed to be fully controlled, 36% well controlled, and 9% poorly controlled, compared with 21%, 56% and 23% respectively in case of persistent mild asthma patients. Only 30% of persistent mild asthma patients were under daily controller treatment. Several questionnaire surveys have assessed the impact of childhood mild asthma. In the Asthma in America (AIA) survey (15), 30% of mild asthma patients (i.e. 62% of the 721 children included in

this survey and assessed according to National Asthma Education and Prevention Program – NAEPP – criteria) were limited with respect to everyday life. In the AIR survey (16), 54% of the children presented intermittent asthma and 18% mild persistent asthma, and asthma control was insufficient in 8% and 25% of the children suffering from intermittent and mild persistent asthma, respectively. The study also highlighted parents' underestimation of severity: 12% of the children were in fact suffering from severe asthma, but the parents of only 2%

Table 4. Estimation of the prevalence of mild asthma

Reference	Asthma definition	Population	Frequency	Prevalence (over the whole population)
Credes (France) (6)	Asthma life, or CPAM table, or asthma treatment, or physiotherapist	Whole population $n = 16\,389$	Intermittent: 49% Mild persistent: 29% Moderate persistent: 11% Severe persistent: 10%	Intermittent: 2.9% Mild persistent: 1.7% Moderate persistent: 0.6% Severe persistent: 0.6%
Zureik et al. (International) (10)	Recent asthma 12 months ECRHS	Whole population $n = 17\,089$	Mild: 50% Moderate: 29% Severe: 21%	Mild: 3.3% Moderate: 1.9% Severe: 1.4%
Liard et al. (France) (7)	Asthma diagnosed by GP	Asthmatic patients Transversal study $n = 4362$ Age: 16–45	Intermittent: 13% Mild persistent: 26.6% Moderate persistent: 35.6% Severe persistent: 24.8%	
Rabe et al. AIRE Study (International) (8)	Current asthma diagnosed by GP (12 months or treatment)	Asthmatic patients Transversal study $n = 7786$ adults $n = 3153$ children	Intermittent: 22–54% Mild persistent: 12–20% Moderate persistent: 16–27% Severe persistent: 11–32%	

CPAM, Caisse Primaire d'Assurance Maladie (French national health insurance organization); ECRHS, European Community Respiratory Health Survey.

reported this as such. Stempel et al.'s (17) retrospective study found that, over a 3-year period, 73% of children underwent at least one episode of insufficient control. The Pediatric Asthma Care Patient Outcome Research Team (18), assessing medicine consumption in 638 children (66% intermittent asthma and 16% mild persistent asthma) and rating severity by scoring symptoms over the preceding 2 weeks, found 46% of the children poorly controlled and 37% of mild persistent asthma cases receiving treatment on an as-needed basis.

Severe exacerbation in mild asthma

The frequency of severe exacerbation in mild asthma can be assessed by surveys, placebo-group data from interventional studies, and hospital admission studies.

A Canadian survey (19) analyzed asthma severity from medical prescription data for 6661 mild asthma patients. The hospital admission rate for the preceding year was 3%. Evolution from mild to severe asthma was found in 3.3% of children and 2.9% of adults, over a 5-year observation period. A telephone survey of morbidity as a function of severity in 1788 asthma patients over 16 years of age (2/3 with mild asthma) (20) found that 3.6% of mild asthma patients had been hospitalized for exacerbation during the previous year and that respectively 16.1% and 28.4% of intermittent and mild persistent asthma patients had been to an emergency department during the same period. The National Health Interview Study (20) of 1788 patients from the US analyzed asthma severity as a function of diurnal and nocturnal symptoms over the previous 4 weeks, and of symptoms and exacerbation episodes over the 1-year period preceding the study; patients were classified according to NAEPP criteria (21), without taking treatment pressure into account. Forty-four percent of intermittent asthma patients had had diurnal or nocturnal symptoms over the previous 4 weeks, as against 20% of mild persistent asthma patients; 60% of intermittent asthma patients had had at least one exacerbation episode during the previous year as against 16% of mild persistent asthma patients,

with asthma impacting daily life for 11%, as against 19% for mild persistent asthma patients. Thirty-nine percent of patient classifications (based purely on patient reports) changed between 4-week and 1-year periods of interest. The reported frequency of exacerbation was extraordinarily high for mild asthma, but no precise definition of exacerbation was given and respiratory function was not assessed.

Three randomized studies dedicated to mild asthma – OPTIMA (22), START (23) and IMPACT (24) – provided longitudinal follow-up and placebo data enabling the frequency of severe exacerbation to be assessed. The 239 placebo-group patients of the OPTIMA study (22) showed a severe exacerbation rate of 0.77 per patient-year. In the START study (23), 198 (7.8%) of the 2548 placebo-group patients presented at least one severe asthma-linked event: event (defined as entailing hospital admission, death - not observed - or emergency treatment for exacerbation) during the study period. The mean number (mean $\pm$ standard deviation) of systemic corticosteroid treatments per patient and per year was 0.21 ± 0.53 in the placebo group. The IMPACT study (24) followed up 225 patients with mild persistent asthma for 1 year. Exacerbation (defined by resort to systemic corticotherapy) was remarkably low in the placebo group, at 0.13 episodes per patient-year; this may have been due to patients receiving inhaled or oral corticotherapy at inclusion, which would tend to affect evolution over the study period.

The study by Salmeron et al. (25) of 4087 emergency admissions for acute asthma found 30% of patients who could be considered mild asthma cases (less than one symptom per week over the three previous months), and 53% without ICS therapy. Mitchell et al. (26) defined three populations of asthmatic patients: near-fatal acute asthma, emergency admission for acute asthma, and outpatients; 37% of the 197 patients admitted to emergency department for acute asthma were considered to be suffering from mild asthma (Table 5). Finally, in a French study (27) of 169 emergency admissions for asthma, asthma was classified as intermittent in nearly 30% of cases and as mild persistent in 20%.

Table 5. Characteristics of three populations of asthma patients: patients with acute near-fatal asthma, patients consulting an emergency department for acute asthma, and asthmatic outpatients (Mitchell et al.) (26)

		Patients with acute near-fatal asthma (%; n = 45)	Patients consulting an emergency department for acute asthma (%; n = 197)	Asthmatic outpatients (%; n = 303)
Severity	Mild	0	37	54
	Moderate	47	47	40
	Severe	53*	15	5
Symptom frequency	0 or at exertion	29*	52	53
	1–2 times a week	38*	22	25
	≥ 3 times a week	33*	26	22

*Statistically significant ($P < 0.05$).

Certain studies (28, 29) have assessed the frequency of mild asthma in children presenting severe acute asthma or asthma-related death, reporting that between 7% and 34% of children coming to emergency consultation for asthma presented frequent episodic asthma, and between 37% and 43% infrequent episodic asthma according to the pediatric classification (30); these children would nowadays be considered as suffering from mild asthma (15). Likewise, Warman et al.'s (31) study of 219 children found 17% of intermittent and 23% of mild persistent asthma cases among emergency admissions. Over the 6-month period prior to admission, the mean number of exacerbations was 3.5 for children with intermittent asthma and 4.5 in case of mild persistent asthma (vs 9 in case of moderate or severe persistent asthma). Over the previous year, children with intermittent or mild persistent asthma had been hospitalized a mean 1.4 times for a mean 4.5 days, vs 1.7 hospitalizations for 8 days in case of moderate or severe persistent asthma. Exacerbation, however, was not defined – although probably a wide range of levels were included. An Australian study found that 33% of childhood deaths from asthma concerned asthma considered as mild (32), while, on the other hand, a more recent study of children presenting near-fatal acute asthma found only one in 30 to be a case of mild asthma (33).

Thus, the issue of severe exacerbation of mild asthma entailing hospital admission illustrates the problem of severity classification in relatively nonsymptomatic asthma. Certain severe exacerbations may be considered accidental and without long-term consequences in terms of evolution, while others represent aggravation and a change in severity status. The onset of severe exacerbation in a context deemed to be of mild asthma calls for vigilance and possibly revision of the severity rating.

Medico-economic aspects

Mild asthma entails direct (health-care consumption, including medicines) and indirect costs (loss of productivity). Intangible costs (disturbed educational and career plans, impaired quality of life) are difficult to estimate and

rarely studied (34). Analysis of the literature disclosed three complementary approaches – surveys of medical practice, observational studies, and intervention studies – all focusing on the benefits of ICS.

The French CREDES study (35) is an example of a practice survey. This was a survey of 3020 patients (10–44 years of age) who were selected from the National Insurance registers as having received coverage for at least one anti-asthma drug on five randomly chosen days in 1999. *A posteriori* severity-stage classification, taking into account symptoms as reported by questionnaire and anti-asthma treatments, estimated the percentages of intermittent and mild persistent asthma at 18% and 31%, respectively. Comparison of the direct costs (hospitalization, out-patient treatment, and medicines) of mild persistent and severe asthma found a ratio of 1–3.5. However, this cost analysis also reported that therapeutic management appeared insufficient in 25% of cases.

A retrospective observational study in France of more than 1000 asthma patients selected from a GP database analyzed the direct-cost impact of insufficient asthma control over a 15-day period, according to severity stage (36). Mild asthma was defined by the absence of ICS treatment. The direct costs associated with insufficient asthma control were approximately twice as high as good control. In a prospective study, Godard et al. (37) followed up more than 300 asthma patients between 16 and 44 years of age, classified according to (i) severity as rated by an expert group, (ii) therapeutic management, and (iii) estimated costs (logbook and quarterly telephone follow-up over one year). The mean direct cost ratio (asthma management costs, excluding hospitalization) between mild and severe persistent asthma was 1 : 4. Similar results have been reported in the US (38) and Italy (39).

The START intervention study enrolled more than 7000 mild asthma patients (5–66-years old), randomly allocated to ICS or placebo treatment groups over a 3-year period. Cost analysis, in the context of the American Public Health system (40), showed that the direct costs were higher for treated than for untreated patients. However, extrapolation of the data to seven other countries showed that an active treatment strategy for

Table 6. Interest of the methods of inflammation assessment

	Endobronchial biopsy	Bronchoalveolar lavage (BAL)	Induced sputum	Exhaled nitric oxide (eNO)	Exhaled breath condensates
Pathogenesis	+++	++	++	+	+
Inflammation	+++	+++	++	++	+
Bronchial remodelling	+++	+	+	0	0
Diagnosis	0	0	0	0	0
Follow-up of asthma control	0	0	++	++	0
Assessment of treatment efficacy	++	++	++	+++	0
Clinical use	0	0	0	++	0

0, no interest; +, minor interest; ++, medium interest; +++, major interest.

mild asthma not only was consistently more effective for patients, but it was also less expensive than no treatment under certain Public Health systems (Australia, Canada, and Sweden). These discrepancies can be attributed to the considerable differences in Public Health system and standard of living between the countries under study (41).

Nature of the airway inflammation in mild asthma

Studies of inflammation in mild asthma have used various methods over time and various inclusion criteria in terms of asthma severity, thus making meta-analysis hazardous. The oldest studies compared histopathologic characteristics of the airways of mild asthma patients and non-asthmatic subjects; asthma severity was not precisely defined, and patients were not taking ICS (42). More recent studies have compared mild and severe asthma patients (43), and it is nowadays uncommon to find asthma patients who have never been treated with corticosteroids. Such historical differences go some way to explaining the heterogeneity and variability of the literature data. Analysis of endoscopic bronchial biopsies can assess inflammation and bronchial remodelling in a given sample, shedding light on the role of histopathologic alterations in the functional and clinical profiles observed in mild asthma (44). Bronchoalveolar lavage liquid (BAL) analysis and less invasive methods, such as sputum cell analysis, provide further data (Table 6), while autopsies (45) and surgical (46) or transbronchial biopsies shed light on deep pulmonary involvement (47).

Alterations observed in mild asthma

Inflammation of the bronchial mucosa in mild asthma has been demonstrated by the increase in the number of inflammatory cells in biopsy, BAL and sputum samples (48). Bronchial biopsy found an increased number of inflammatory cells (mastocytes, eosinophils, and lymphocytes) in mild asthma patients compared with non-asthmatic subjects. Such cells showed activation criteria, and their mediators could be detected in the airways. Bronchopulmonary eosinophilia was found systematically, in particular in asthma patients having never received treatment (42), and persisted at a low grade even after ICS were prescribed (49). Results for the other inflammatory cells were variable, and nonspecific to mild asthma. In mild asthma, the number of CD4⁺T helper-cells and associated TH2 cytokines (IL-4, IL-5, IL-13) increased in the airways (50), but without specificity with respect to severe asthma. In mild asthma, no endobronchial infiltration due to neutrophils was reported (43); on the other hand, neutrophils were found in sputum, with no significant difference between normal subjects and asthmatic patients, regardless of the stage of severity (51). Bronchial inflammation in patients with mild asthma was

similar in atopic and non-atopic patients (52). In children, data are sparse; as in adults, eosinophils were not only found in all samples from asthmatic children, but also in samples from non-asthmatic atopic children (53, 54).

Airway wall remodelling includes changes in the bronchial epithelium which is observed in mild asthma (55). Damage mainly consists of the disappearance of the most superficial epithelial layer and the destruction of ciliated cells. Epithelial cell repair and activation would seem to differ between mild and severe asthma (56, 57). Basement membrane thickening affects the reticular lamina. This early characteristic of mild asthma observed on optical microscopy is due to acellular deposit of immunoglobulins, type I and III collagen, fibronectin, and tenascin (58). Sub-epithelial basement membrane thickness may increase with asthma severity (59), but this notion is controversial (60). Vascular changes induce sub-mucosal oedema and *in situ* airway recruitment of inflammatory cells. Vascular change has been reported in mild asthma (61), although sub-mucosal angiogenesis seems to be greater in severe asthma (62). Bronchial smooth muscle hyperplasia has been reported in mild asthma (63) with the thickening increasing with asthma severity (64). Moreover, the bronchial smooth muscle is abnormal and exhibits specific mastocyte infiltration (65). In children too, the basement membrane thickens (53, 54), even in very young patients and those with normal respiratory function. Doherty et al. (66) indirectly analyzed changes in the extracellular matrix by quantifying matrix metalloproteinases 9 and 8 (MMP9, and MMP8), and the tissue inhibitor of metalloproteinase-1 (TIMP1) in the BAL of controlled asthmatic children who had been symptom-free for at least 1 year. Even in remission, the asthmatic children showed lower MMP9/TIMP1 ratios than atopic children, indicating that airway remodelling persisted even in the absence of symptoms (66).

The relations between inflammation, airway remodelling, and assessment criteria for control and severity of asthma are as yet far from being clear. Most early studies focused on the relation between airway inflammation and bronchial hyperreactivity (67). Therapeutic studies of the efficacy of ICS in mild asthma gave variable results, probably because the margin of improvement in pulmonary function and bronchial hyperreactivity was small and difficult to demonstrate over a short period (68). The relationship between decreasing inflammation and improved bronchial hyperreactivity was established by Djukanovic (69). More recently, it was shown that low-dose ICS decreased eosinophilic inflammation and the concentrations of the mediators involved in airway remodelling in mild asthma (70). Reduced basement membrane thickness was reported in patients whose treatment was tuned to their bronchial hyperreactivity, although this decrease was obtained at the price of increased intake of ICS (71). Nevertheless, there are reasons for dissociating eosinophilic inflammation and bronchial hyperreactivity, in particular, according to

asthma severity. Patients with mild asthma are more liable to show improvement on both fronts under treatment with ICS, but the inflammation recurs on cessation of treatment (72).

Non-invasive exploration of inflammation

Measuring exhaled nitric oxide (eNO) is a simple non-invasive means of assessing airway inflammation. It is an immediate, sensitive and specific marker of eosinophilic airway inflammation, particularly well-adapted to asthma monitoring (73). eNO measurement has been shown to predict short-term response to corticosteroid therapy (74). Several studies have demonstrated dissociation between eosinophilic inflammation, symptom severity and respiratory function abnormalities in mild asthma (75, 76). In addition, it was suggested that, in reducing corticotherapy, a rise in eNO levels could be predictive of impaired asthma control (77), although this result has been questioned in a more recent study (78). Adjusting the dose of ICS by eNO feedback was shown to decrease the dose required for an optimal mild asthma control by 40% over 1 year; in addition, a significant decrease in the incidence of acute exacerbations was observed in subjects treated according to eNO monitoring (74). Zacharasiewicz et al. studied corticosteroid reduction in 40 children with asthma under control for 2 months (79), and identified the intensity of bronchial hyperreactivity, eNO level (>22 ppb), and percentage of eosinophils as predictors of future exacerbations. However, currently, eNO assay requires further validation in the diagnosis and monitoring of mild asthma before being applied in clinical practice.

Analyzing inflammatory markers in exhaled breath condensate is a method that remains to be standardized. Results are affected by the physical properties of each condenser, and the different collection systems may well differ significantly in terms of the particles they collect. Mediators of oxidative stress (e.g. 8-isoprostane, hydrogen peroxide), leukotrienes (cysteinyl-leukotriene and B4 leukotriene), and pH were the markers the most frequently assayed in exhaled breath condensates. No correlation has been found between forced expiratory volume for the first second (FEV₁), 8-isoprostane, and leukotrienes (80). Hydrogen peroxide levels correlated with other inflammatory markers (e.g. eosinophils, cationic protein) and clinical criteria (use of β_2 -agonist as rescue medication) (81). Exhaled breath condensates are easy to collect, but this method cannot yet be considered as a monitoring tool for asthma control.

Medical management of mild asthma

Mild asthma has been the subject of several international treatment recommendations (1, 82, 83), which, however, by focusing on moderate to severe asthma and introducing a new asthma classification taking account not only

of symptoms but also of on-going treatment, tend to put the spotlight on moderate to severe persistent asthma. This may be justified by the high morbi-mortality and costs associated with the most severe asthmas, but the risk is of giving a biased view of the management and prevalence of mild asthma, with consequent errors in therapeutic strategy.

Regardless of asthma severity, prolonged control of asthma is the goal of disease management. In addition, asthma control is recognized as a more relevant and useful tool than asthma severity to manage asthma patients, especially as many asthma patients are receiving or have received some asthma medication. This reflects an understanding that asthma severity involves not only the severity of the underlying disease but also its responsiveness to treatment, and that severity is not a fixed feature but may change over months or years (84).

Why must we treat mild persistent asthma?

The recommendations are unanimous in ruling out daily controller treatment for intermittent asthma, which is to be managed by as-needed reliever medication (rapid onset bronchodilator). On the other hand, in spite of the mild symptomatology and the difficulties to obtain compliance with regular treatment (24), there are a number of reasons for advocating permanent anti-inflammatory management in mild persistent asthma.

Firstly, ICS are effective against mild persistent asthma symptoms and reduce the severe exacerbation risk. The START study (23) sought to assess the interest of early ICS therapy (200 or 400 $\mu\text{g/day}$ budesonide) in patients with symptoms of mild persistent asthma for at least 2 years. This study was notable for its scale (7241 patients between 5 and 66 years of age; 2548 patients in the placebo group) and duration (3 years). During the study, 7.8% of the patients from the placebo group presented a severe adverse asthma-related event, *vs* 4.5% in the budesonide group. Treatment with budesonide also significantly reduced the use of oral corticotherapy over the 3-year period: 23% of the placebo group *vs* 15% of the budesonide group receiving at least one treatment with systemic corticosteroids. The mean number (mean $\pm$ standard deviation) of systemic corticosteroid treatments per patient-year was 0.21 ± 0.53 in the placebo group *vs* 0.12 ± 0.40 in the budesonide group. The inclusion criteria matched those of mild persistent asthma (symptoms experienced at least once a week but less than once a day), although respiratory function was not taken account of. Detailed analysis found 20.8% of placebo-group patients to show symptoms more than once daily, and that 40% of patients showed FEV₁ at less than 80% of predicted values prior to bronchodilation treatment. Cost-effectiveness analysis favored budesonide (40). The Childhood Asthma Management Program Research Group (CAMP) study (85), of 1041 children between five and 12 years of age, compared three

strategies (budesonide 400 µg/day, nedocromil, and placebo) over a four-to-six year period. At inclusion, asthma was rated mild to moderate, although the mean FEV₁ values (>90%) suggest rather a majority of mild persistent asthma cases. Budesonide administration improved control, with significant differences *vs* placebo on symptom score, β₂-mimetic use, oral corticotherapy, and number of emergency consultations. In the OPTIMA study (22), patients were randomly allocated to one of three groups (placebo, budesonide 200 µg/day, and budesonide 200 µg/day associated with formoterol) and followed up for 1 year. The severe exacerbation rate was 0.77 per patient-year in the placebo group, *vs* 0.29 and 0.34, respectively in the two treatment groups. Severe exacerbation was broadly defined as including resort to systemic corticosteroid therapy, hospital admission, emergency consultation, or morning peak expiratory flow (PEF) falling by >25% for two consecutive days. The percentage of days with symptoms was 29.4% in the placebo group *vs* 23.1% and 21.5% in the two treatment groups, and of nocturnal awakening due to asthma 7% *vs* 2.5% and 3.1%. Placebo- *vs* treatment-group differences were consistently significant. The main study limitation concerns the inclusion criteria: use of bronchodilator at least twice a week (without upper limit) with PEF variability ≥15% or PEF reversibility ≥12% following terbutaline intake. Bronchodilator use at inclusion was in fact almost one intake per day, suggesting a population of moderate persistent rather than mild asthma. Finally, the IMPACT study (24), of 225 adult mild persistent asthma patients, compared continuous treatment with inhaled budesonide at 400 µg/day, intermittent treatment with inhaled budesonide at 1600 µg/day for 10 days, oral corticotherapy at 0.5 mg/kg for 5 days, and intermittent treatment with zafirlukast at 40 mg/day, over a 1-year period. Significant improvement in symptom score and in number of symptom-free days was found with continuous budesonide treatment, while resort to oral corticotherapy did not differ between groups. Only continuous budesonide treatment significantly reduced inflammation parameters (eosinophil concentration in sputum and NO_e).

Secondly, ICS provide a functional benefit to mild asthma patients and can alter asthma evolution in children. The impact of early continuous anti-inflamma-

tory treatment on the bronchial remodelling involved in the development of airway obstruction remains controversial, although the two main prospective long-term treatment studies of mild childhood asthma indicate clinical and functional benefit with ICS. In the START study (23), FEV₁ measured after bronchodilatation treatment in patients receiving budesonide or placebo diminished over time, but significantly less in the budesonide group. In the CAMP study (85), budesonide administration was associated with a significant improvement in baseline FEV₁ and a limited reduction in the FEV₁/FVC (forced vital capacity) ratio. These studies may testify to the preventive action of ICS therapy on early childhood bronchial remodelling. In both studies, however, the difference between placebo and treatment groups was particularly marked at treatment onset and fell off thereafter over time. Longer term studies will be needed to assess the impact of ICS therapy on the functional evolution of asthma.

Thirdly, early ICS therapy entailed enhanced functional benefit. A non-randomized child study (86) found the FEV₁ pattern over a 3-year period to depend not simply on administration of ICS, but also on the time to initiation of treatment following asthma onset: at 3 years, mean FEV₁ was 89.6% in nontreated children, 96.2% in children starting ICS therapy more than 5 years after the onset of asthma, and 101% when treatment had been initiated less than 2 years after onset. In adults, Haahtela et al. (87) found a 2-year delay in initiating ICS therapy in mild asthma to be associated with a reduced functional benefit compared to initiation as of diagnosis.

What treatment objectives and what treatment in mild persistent asthma?

Asthma follow-up should focus on control, to be assessed at each consultation. Asthma control consists of an assessment of the illness over a period of a few (1–3) weeks, in terms of clinical and functional respiratory events and their consequences. Control is assessed in terms of three levels: uncontrolled, partly controlled, and controlled. Partly controlled asthma is the minimum to be sought for any patient, and consists of the fulfilment of all the criteria detailed in Table 7. Initial mild asthma

Table 7. Levels of asthma control in the GINA revision (2006) (1)

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue medication	None (twice or less/week)	More than twice/week	One in any week‡
Lung function (PEF or FEV ₁)*	Normal	<80% predicted of personal best (if known)	
Exacerbations	None	One or more/year†	

*Lung function is not a reliable test for children five years and younger.

†Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.

‡By definition, an exacerbation in any week makes that an uncontrolled asthma week.

treatment requires low-dose ICS, no dose-effect relation having been observed above 500 µg/day BDP equivalent in terms of any additional benefit in pulmonary function or symptoms (88). This dosage, optimal for mild persistent asthma according to the GINA, may prove insufficient for other bronchial inflammation response criteria, but higher doses bring no improvement in clinical response (88, 89). In mild persistent asthma, associating a long-acting β_2 -agonist to low-dose ICS provides no functional or symptomatic benefit and does not significantly reduce the risk of exacerbation compared with an equivalent ICS dose (22, 90), and is therefore not indicated in mild persistent asthma. In mild to moderate persistent asthma, antileukotrienes prove less effective than ICS therapy at doses of 400 µg/day BDP equivalent (91). Mild asthma studies have found antileukotrienes more effective than placebo and about as effective as low or moderate dose ICS, in terms of symptom score and quality of life, in particular in patients using only small amounts of β_2 -agonist as needed, with only a slight functional impact on their asthma, or with only slightly increased signs of allergy and bronchial inflammation (91, 92). Two studies reported better responses in children than adults (93, 94), but the likelihood of a response remains lower and the risk of exacerbation requiring oral corticotherapy greater under antileukotrienes than under ICS, especially in children (94, 95). Antileukotrienes cannot be seen as an alternative to ICS as first-line treatment for mild persistent asthma. In Europe, montelukast has not been approved as mild persistent asthma monotherapy.

What to do after prescribing first-line treatment?

Mild persistent asthma is a chronic disease requiring continuous treatment, and control can only be achieved in case of satisfactory compliance. Correct use of inhalers, awareness of the usefulness of measuring PEF, early recognition of exacerbation, and knowing what to do in case of it are integral parts of management, whatever the severity stage (1).

Two guidelines and the GINA 2006 recommend a management approach based on control: asthma control has to be regularly assessed and treatment adjusted accordingly (96). In mild asthma, reducing treatment intensity should only be considered following at least 3 months' control, in which case, the question arises as to the best practical means of reducing treatment intensity and the interest of aiming at withdrawal from medication. The GINA (1) recommends reducing the dose of ICS by 25% every 3 months.

Several studies have gone into the problem of withdrawal. In the study by Waalkens et al. (97), 28 children treated for 1 year with budesonide (200 µg three times a day) were randomized into two groups and followed up for 6 months. One group continued treatment for 6 months, while the other received a lower dose of ICS for 2 months, followed by 4 months on placebo. In the withdrawal

group, eight subjects were taken off the study due to aggravation, with five incidents of exacerbation requiring oral corticotherapy, vs zero such events in the group maintained on ICS therapy. Increased bronchodilator use, increased bronchial hyperreactivity, and reduced FEV₁ were also observed in the withdrawal group. In the study by Juniper et al. (98), 28 children treated for 1 year with budesonide (400 µg/day) were randomized between continuation of treatment and withdrawal. After 3 months, recurrence of clinical signs, reduced FEV₁, and increased bronchial hyperreactivity were observed in the withdrawal group. During the first year of the START study (23), 34% of placebo-group patients required supplementary corticosteroid treatment and 4% presented severe exacerbations, as against 20% and 2% respectively in the budesonide treatment group; in the third year, 50% of placebo-group patients required supplementary corticosteroid treatment and 6% presented severe exacerbations, as against 30% and 3%, respectively in the treatment group. Taken together, these three studies suggest that a daily controller treatment of ICS alleviates mild persistent asthma symptoms, but does not cure the pathology.

Should ICS therapy be continuous or intermittent?

Current recommendations may advocate daily anti-inflammatory treatment in persistent asthma, but it is clear that a good number of patients actually practice intermittent medication. Boushey et al. (99) compared the effectiveness of three strategies pursued over 1 year in persistent mild asthma patients: Group 1 received continuous budesonide (400 µg/day), Group 2 continuous zafirlukast (40 mg/day), and Group 3 followed an action plan geared to symptoms (budesonide at 1600 µg/day for 10 days, or prednisone at 0.5 mg/kg/day for 5 days, if needed). All three strategies improved morning PEF comparably and achieved comparable exacerbation rates, despite the fact that the Group 3 (intermittent) patients were taking short budesonide cures for no more than a mean 0.5 weeks per year. Nevertheless, the continuous budesonide treatment group showed greater improvement than the other groups on the other criteria (FEV₁ before use of bronchodilator, bronchial hyperreactivity, eosinophil concentration in sputum, NO_e, asthma control score, and number of symptom-free days). The authors concluded that mild persistent asthma could be treated by short cures of oral or inhaled corticosteroids. The study has been the subject of much discussion and cannot, in the present state of knowledge, be used to justify revising the recommendations. A longer study over several years and with a larger sample base will be needed to explore the clinical, functional and physiopathological differences between continuous and intermittent ICS therapy (in particular, examining irreversible FEV₁ loss with the intermittent approach), so as to identify those patients most likely to benefit from continuous ICS therapy.

Conclusions

Although there is no standard epidemiological definition of mild asthma, it may be taken as affecting between 50% and 75% of asthma patients. Cohort follow-ups from childhood to adulthood indicate that severity remains generally constant over the course of asthma. Absence of bronchial obstruction in childhood is associated with reduced functional impact in adulthood. Mild asthma can be associated with episodes of severe exacerbation. Hospital admission represents a specific risk factor that should lead to a reconsideration of severity.

In mild asthma, inflammation is a constant, but its cytological profile is nonspecific. Eosinophilic inflammation is persistent, but of variable intensity from patient to patient. Unlike in severe asthma, there is no endobronchial neutrophil infiltration. Bronchial remodelling is always present, but of varying severity. Non-invasive inflammation assessments (sputum eosinophilia and NOe) are yet to prove their specificity: the correlation with clinical and respiratory function data remains to be shown, and further studies will be needed for routine application. Inhaled corticosteroids therapy reduces bronchial inflammation, but has little impact on bronchial remodelling, and cessation is closely followed by recurrence.

Mild asthma is more frequent, more symptomatic, and less well controlled in children than in adults, with a risk

of severe complications and the need for emergency treatment. The frequency of severe exacerbation has been estimated to be between 0.12 and 0.77 episodes per patient-year. Between 30% and 40% of exacerbations requiring emergency care would seem to be in patients with mild asthma.

Mild persistent asthma needs treating, to reduce the risk of severe exacerbation and improve its evolution, which is especially possible when treatment is initiated early. Mild persistent asthma requires continuous anti-inflammatory treatment, for which low-dose ICS therapy ($\leq 500 \mu\text{g}$ BDP equivalent) is recommended as the initial controller treatment. Withdrawal from ICS therapy generally leads to rapid recurrence of symptoms, exacerbations, and reduced FEV₁, so that daily controller treatment must be maintained. In the absence of any large-scale long-term study of the clinical, functional and physiopathological differences between continuous and intermittent ICS therapy, the former is recommended. Associated long-acting β_2 -agonists or antileukotrienes are not recommended in first-line treatment. Asthma control is to be assessed at 3 months. Where control proves insufficient at 500 μg BDP equivalent despite good compliance, the patient should no longer be considered as suffering from mild asthma, and treatment should be stepped up until control is achieved. Reducing treatment doses (step-down) should not be considered until the patient has been controlled for at least 3 months.

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