

Predictors for the development of progressive severity in new-onset adult asthma

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Background: A proportion of patients with adult-onset asthma have severe disease. Risk factors for an increase in asthma severity are poorly known.

Objective: We sought to identify predictors for the development of severe asthma in adults.

Methods: A cohort of 200 adults with new-onset asthma was prospectively followed for 2 years. At baseline, patients underwent a comprehensive assessment of clinical, functional, and inflammatory parameters. After 2 years, change in asthma severity was assessed by using the Global Initiative for Asthma score (range, 1-4), which is based on asthma control (Asthma Control Questionnaire), lung function (FEV₁), and inhaled corticosteroid requirement. ANOVA and multiple regression equations were used in the analysis.

Results: One hundred twenty-eight patients completed 2 years of follow-up. Seventeen (13.3%) patients had an increase in asthma severity, whereas 53 (41.4%) patients had a decrease. A lower postbronchodilator FEV₁/forced vital capacity ratio and a higher number of cigarette pack years smoked at baseline were significantly associated with an increase in asthma severity at follow-up. Multiple regression equations showed that only the number of cigarette pack years smoked was independently associated with an increase in asthma severity, with an odds ratio of 1.4 (95% CI, 1.02-1.91) for every 10 pack years smoked.

Conclusion: A history of cigarette smoking in patients with new-onset adult asthma predicts an increase in asthma severity during the first 2 years of the disease in a dose-dependent manner. (*J Allergy Clin Immunol* 2014;■■■:■■■-■■■.)

Key words: Adult-onset asthma, new-onset asthma, asthma severity, prospective follow-up study, predictors, smoking

Abbreviations used

ACQ: Asthma Control Questionnaire
AMC: Academic Medical Centre
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
GINA: Global Initiative for Asthma
OR: Odds ratio

Adult-onset asthma is a heterogeneous disease with a variable clinical course. Disease severity ranges from very mild to very severe.¹ The majority of these patients have mild or intermittent asthma^{1,2}; however, a proportion of patients had more severe asthma over time.¹ The characteristics of patients with severe adult-onset asthma have been well described in several cross-sectional studies. We previously reported that these patients are more often nonatopic and have persistent sputum eosinophilia, higher blood neutrophil counts, and more nasal polyps.³ Other authors also concluded that patients with the adult-onset asthma phenotype are less often atopic⁴ and have more sputum eosinophilia⁵ compared with patients with the childhood-onset asthma phenotype. Patients with adult-onset asthma also have respiratory tract infections⁴ more often, and many have persistent airflow limitation.^{4,5} In particular, nonatopic male patients with adult-onset asthma seem to be at risk for persistent airflow limitation,⁶ which is possibly related to persistent infection with *Chlamydomydia pneumoniae*.⁷ This suggests that severe adult-onset asthma is a distinct phenotype.³

The natural history of disease severity after the diagnosis of adult-onset asthma has never been prospectively evaluated, and predictors for the development of severe asthma are still unknown. Identification of patients at risk for severe asthma at disease onset might be important for early therapeutic intervention.⁸

In the present study we hypothesized that specific predictors for deterioration of adult-onset asthma can be identified at asthma onset. Therefore the aim of this study was to prospectively identify the predictors of increase in asthma severity in a cohort of patients with new-onset adult asthma.

METHODS

Patients and definitions

Two hundred patients with adult-onset asthma were recruited from the outpatient pulmonary clinics of an academic hospital (Academic Medical Centre [AMC], Amsterdam, The Netherlands) and 2 secondary care hospitals in The Netherlands, 1 in Amsterdam (St Lucas-Andreas Hospital) and 1 in Hoofddorp, a municipality 20 km from Amsterdam (Spaarnse Hospital). All the study measurements were conducted at the AMC. All patients had to have a recent (<1 year) diagnosis of asthma. Adult-onset asthma was defined as

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asthma with an onset at greater than 18 years of age. Asthma diagnosis was based on typical symptoms and reversibility in FEV₁ of greater than 12% of predicted value, a positive inhaled methacholine provocation test result (PC₂₀ <8 mg/mL), or both.⁹

Patients were excluded if they had a self-reported history of childhood asthma or other chronic respiratory diseases in childhood, frequent episodes of dyspnea as a child, or use of a bronchodilator or other asthma medication in childhood.

Current smoking and exsmoking were allowed. Patients with a smoking history of greater than 10 pack years were included only if they showed reversibility in FEV₁ of 12% or greater of predicted value and had a normal diffusion capacity (diffusing capacity of the lungs for carbon monoxide >80%).

The study was approved by the AMC Medical Ethics Board. All participants were informed and provided written informed consent. The study was registered in the Dutch trial register (NTR1846).

Study design

This study was part of the Adult-onset Asthma and Inflammatory Subphenotypes study (ADONIS-study), a longitudinal prospective cohort study in adults with new-onset asthma. At baseline, patients underwent comprehensive assessment of clinical symptoms, lung function, markers of inflammation (fraction of exhaled nitric oxide levels and blood and sputum eosinophil counts), and atopy and sinus computed tomographic scanning and nasal endoscopy. Thereafter, they were monitored by their own treating physician at regular intervals. After 2 years, patients were reassessed in our laboratory with regard to clinical symptoms, lung function, medication requirement, and markers of inflammation (fraction of exhaled nitric oxide levels and blood eosinophil counts).

Clinical measurements

A comprehensive history was taken, and physical examination was performed. In addition, patients completed self-reported questionnaires, including the Asthma Control Questionnaire (ACQ-6)¹⁰ and the Sino-Nasal Outcome Test.¹¹

Lung function measurements

Lung function measurements were performed in the lung function laboratory according to international recommendations with a spirometer (MasterScreen PFT; Jaeger, Care Fusion, Hoechst, Germany) that was calibrated daily and comprised FEV₁ and forced vital capacity (FVC).¹² Post-bronchodilator measurements were taken 10 to 15 minutes after inhalation of 400 µg of salbutamol.

Inflammatory parameters

Fraction of exhaled nitric oxide was measured with a portable rapid-response chemoluminescent analyzer (flow rate, 50 mL/s; NIOX System, Aerocrine, Sweden).¹³

Venous blood was collected, and white blood cells were counted. Total and specific IgE levels to common aeroallergens were measured by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden); atopy was defined as an IgE level of greater than 0.35 kU/L for at least 1 allergen.

Sputum induction was performed according to international standards.¹⁴ All patients underwent nebulization 3 times for 5 minutes with a 4.5% saline solution. Sputum processing was done according to the full sample method, and differential cell counts were analyzed on cytospin preparations.

Assessment of chronic rhinosinusitis and nasal polyposis

Chronic rhinosinusitis was diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps.¹⁵ In short, this diagnosis is based on symptoms assessed by using the Sino-Nasal Outcome Test questionnaire combined with sinus computed tomographic scan abnormalities (Lund-Mackay score >11),¹⁶ endoscopic signs of chronic rhinosinusitis/nasal polyps,¹⁵ or both.

Asthma severity score

Assessment of asthma severity was based on the Global Initiative for Asthma (GINA) 2002 guidelines.¹⁷ The GINA score is a composite score based on treatment and clinical measures.¹⁷⁻²⁰ Patients are divided into 4 asthma severity categories (ie, intermittent, mild persistent, moderate persistent, and severe persistent; score of 1-4, respectively; see [Methods](#) and [Fig E1](#) in this article's Online Repository at www.jacionline.org).

Three parameters (inhaled corticosteroid dose, FEV₁, and symptom score) for calculation of GINA severity scores were available in all patients at baseline. At follow-up, 20 (10%) patients were lacking FEV₁ data or an ACQ score because of lack of time or practical difficulties in completing study visits. By using the 2 available parameters, a "least GINA score" was calculated, corresponding to their mildest GINA classification (see [Fig E1](#)). This modified GINA score for these 20 patients was used for further analysis.

The difference in GINA scores at 2-year follow-up with respect to baseline scores was determined to assess the change in asthma severity. A negative number represented deterioration of asthma severity; zero represented no change, and a positive number represented improvement of asthma severity. Patients were divided into one of these 3 categories.

Statistical analysis

Comparison of baseline mean values between included patients and patients lost to follow-up were made by using the Student *t* test or Mann-Whitney rank sum test (for nonnormally distributed data). For nominal variables, the χ^2 test was used.

Differences in baseline variables among the 3 groups (deterioration, no change, and improvement) were compared by using 1-way ANOVA or the Kruskal-Wallis test (for nonnormally distributed data). Changes in the 3 groups over time were analyzed with a paired *t* test. Multinomial logistic regression (the "no change" group was used as reference) and binary logistic regression (the "no change" and "improvement" group together were used as reference) were performed. Because their results were similar, only binary logistic regression outcomes are reported. The significant predictor variables were used in a multivariate binary logistic regression model. Results are expressed as odds ratios (ORs).

SPSS software, version 20 (IBM SPSS, Chicago, Ill), was used for all statistical analyses. Statistical significance was set at a *P* value of less than .05.

RESULTS

Baseline characteristics

Among the 200 patients initially included in the study, 72 (36%) no longer participated after 2 years of follow-up. Most patients were lost to follow-up because of a lack of time (*n* = 33), comorbidities (*n* = 9), distance (*n* = 5), or language barrier (*n* = 1) or for unknown reasons (*n* = 24). Baseline characteristics of included patients and patients lost to follow-up are shown in [Table I](#). Included patients were more often male (*P* = .03), used higher doses of inhaled corticosteroids (*P* = .05), and were more often exsmokers or current smokers (*P* = .03) compared with patients lost to follow-up.

Asthma severity

Seventeen (13.3%) patients showed an increase in asthma severity (increase in GINA score), whereas 53 (41.4%) patients showed improvement (decrease in GINA score) after 2 years compared with baseline. Baseline characteristics of these groups are shown in [Table II](#). The patients whose asthma deteriorated used lower doses of inhaled corticosteroids, had milder asthma at baseline (*P* < .01), and had more pack years smoked (*P* = .02). These patients also tended to be current smokers more often (*P* = .078). There were no other significant differences in baseline characteristics, including lung function and inflammatory

TABLE I. Baseline characteristics of included patients and patients lost to follow-up (n = 200)

Covariate	Included (n = 128)	Lost to follow-up (n = 72)	P value
Age (y)	48 (15)	48 (15)	.925
Female sex (%)	50.8	66.7	.030
BMI (kg/m ²)	28.3 (5.2)	26.8 (5.4)	.062
Exsmoker or current smoker (%)	62.2	45.7	.026
Pack year	11 (14)	8 (14)	.205
Fluticasone equivalent (μg)	375 (250-500)	250 (0-500)	.049
ACQ score	1.29 (0.92)	1.39 (0.96)	.478
GINA score	3 (2-4)	3 (2-4)	.422
Atopy (%)	46.1	42.3	.602
CRS (%)	55.2	52.5	.736
Nasal polyposis (%)	19.2	20.3	.856
pb FEV ₁ (% predicted)	100 (17)	100 (17)	.975
pb FEV ₁ /FVC (% predicted)	95 (11)	96 (11)	.664
Exhaled NO (ppb)	20 (13-45)	22 (13-40)	.653
Total IgE (kU/L)	61 (26-199)	60 (26-239)	.872
Blood neutrophils (× 10 ⁹ /L)	3.8 (1.4)	3.7 (1.5)	.685
Blood eosinophils (× 10 ⁹ /L)	0.16 (0.09-0.25)	0.17 (0.11-0.29)	.255
Sputum neutrophils (%)	70.8 (48-85)	74.7 (54-83)	.474
Sputum eosinophils (%)	0.45 (0.1-2.6)	0.90 (0.28-4.3)	.367

Mean (SD) or median (interquartile range) values are shown. Significant *P* values are shown in boldface.

BMI, Body mass index; CRS, chronic rhinosinusitis; NO, nitric oxide; pb, postbronchodilator.

parameters. Table III presents the within-subject changes in the same variables after 2-year follow-up, showing a significant decrease in ACQ scores (*P* = .049) despite the increased inhaled corticosteroid dose (*P* < .001) in the deterioration group.

Predictors of increase in asthma severity

At first, univariate logistic regression with multiple variables was performed. Table IV shows that the FEV₁/FVC ratio and pack years smoked were significant predictors of an increase in asthma severity (increase in GINA score). An OR of 1.5 (95% CI, 1.10-2.02) was found for every 10 pack years a patient had smoked. When using a cutoff point of more than 20 pack years, an OR of 3.6 (95% CI, 1.22-10.76) was found. Having a lower FEV₁/FVC ratio at baseline was predictive for deterioration as well. Every 10% lower FEV₁/FVC ratio was associated with an OR of 1.6 (95% CI, 1.03-2.56). A cutoff point of an FEV₁/FVC ratio of less than 95% of the predicted value (mean of population) was associated with an OR of 3.9 (95% CI, 1.30-11.98).

The significant variables in univariate analysis were fitted into a logistic regression model to calculate adjusted ORs. This showed that the only independent predictor for deterioration of asthma severity was the number of pack years smoked with an OR of 1.4 (95% CI, 1.02-1.91) for every 10 pack years smoked. A low FEV₁/FVC ratio at baseline was no longer significantly associated with asthma deterioration (Table V).

DISCUSSION

This prospective cohort study shows that the only independent predictor for an increase in asthma severity within 2 years after diagnosis in adults with new-onset asthma is a positive smoking history. Even a limited number of pack years of cigarette smoking

is associated with increased risk for asthma deterioration, whereas inflammatory parameters, lung function, sex, body mass index, and sinonasal symptoms are not predictive for worsening of early asthma. These results suggest that previous smoking is the most important factor influencing asthma severity in patients with adult-onset asthma.

To our knowledge, this is the first prospective longitudinal cohort study that evaluated predictors for asthma deterioration in adults with new-onset asthma. One previous longitudinal study investigating risk factors of asthma severity was performed in a mixed population of patients with longstanding childhood- and adult-onset asthma.¹⁸ This study showed that patients with severe disease at baseline were at risk for severe disease 9 years later. Comparison of this study with our study is difficult because of the lack of assessment of longitudinal change in asthma severity in the latter study and differences in patient selection criteria. Our observation that smoking history predicts deterioration extends the findings by Polosa et al.²⁰ They retrospectively studied patients with allergic rhinitis who had asthma within a period of 10 years and found that patients with more severe asthma had more pack years smoked than those with milder asthma. Our results also extend the results from other longitudinal studies in mixed asthma populations looking at components of asthma severity, including asthma exacerbations and accelerated decrease in FEV₁.²¹⁻²⁵ These studies showed that recent exacerbation history was a strong predictor of future asthma exacerbations,²¹ whereas active smoking,^{22,25} high levels of exhaled nitric oxide,²³ and infiltration of CD8⁺ cells in the airway wall²⁴ were shown to be predictors of an accelerated decrease in FEV₁. All these results provide evidence that a positive smoking history in adult patients with new-onset asthma is a strong and dose-dependent predictor of an increase in asthma severity over the next 2 years.

The strength of our study is its prospective design with extensive baseline assessments to fully characterize the patients. Also, the study population is unique because all patients were recently given a diagnosis of adult-onset asthma. Smokers and exsmokers were purposely not excluded from participation in the study as long as they met the stringent diagnostic criteria for asthma. This is important because most asthma studies exclude smokers or subjects who have smoked for more than 10 pack years, although a large proportion (20% to 30%) of the actual population of asthmatic patients are current smokers.²⁶⁻²⁸ We avoided including patients with “pure” chronic obstructive pulmonary disease by excluding exsmokers or current smokers with persistent airflow limitation or reduced diffusion capacity but cannot exclude the inclusion of patients with overlap between these diseases.²⁹ Unfortunately, we did not reassess bronchodilator reversibility and diffusion capacity at the 2-year follow-up visit. Therefore we were not able to determine whether asthma in smokers might have evolved phenotypically into chronic obstructive pulmonary disease. However, there was a trend for a lower postbronchodilator FEV₁/FVC ratio in patients with increased asthma severity compared with those whose asthma had improved, suggesting the development of persistent airflow limitation.

We chose to use the GINA score for classifying asthma severity because it is a composite score of asthma control, lung function, and treatment.⁹ Thus asthma severity is assessed in a broad and realistic perspective, which is important, especially when evaluating changes in severity over time. In our opinion missing data

TABLE II. Baseline characteristics of patients included in the analysis (n = 128)

Covariate	Deterioration (n = 17)	No change (n = 58)	Improvement (n = 53)	P value
Age (y)	50 (13)	50 (16)	46 (14)	.375
Female sex (%)	41.2	48.3	56.6	.474
BMI (kg/m ²)	28.7 (4.4)	27.2 (4.5)	29.4 (5.8)	.086
Smoking status (%)				.078
Never smoker	35.3	32.8	45.3	
Exsmoker	47.1	55.2	50.9	
Current smoker	17.6	12.1	3.8	
Smoking history (pack years)	20 (21)	10 (13)	8 (12)	.014
Fluticasone equivalent (μg)	250 (62-250)	250 (0-500)	500 (250-500)	<.001
ACQ score	1.15 (0.77)	1.13 (0.98)	1.52 (0.86)	.066
GINA score	2 (2-3)	2.5 (2-3)	3 (3-4)	<.001
Atopy (%)	41.2	48.3	45.3	.865
CRS (%)	58.8	48.3	62.0	.341
Nasal polyposis (%)	23.5	20.7	16.0	.734
pb FEV ₁ (% predicted)	93 (18)	101 (18)	102 (16)	.145
pb FEV ₁ /FVC (% predicted)	90 (9)	96 (11)	97 (10)	.086
Exhaled NO (ppb)	17.4 (14-44)	19.6 (13-43)	22.2 (13-45)	.862
Total IgE (kU/L)	125 (19-497)	60 (25-170)	51 (27-168)	.285
Blood neutrophils (× 10 ⁹ /L)	4.2 (1.7)	3.8 (1.3)	3.7 (1.3)	.369
Blood eosinophils (× 10 ⁹ /L)	0.17 (0.07-0.21)	0.16 (0.09-0.25)	0.16 (0.09-0.29)	.800
Sputum neutrophils (%)	77.3 (59-89)	71 (48-84)	62.7 (47-80)	.302
Sputum eosinophils (%)	0.4 (0.1-1.3)	0.4 (0.1-2.3)	0.6 (0.2-6.2)	.426

Mean (SD) or median (interquartile range) values are shown. Significant *P* values are shown in boldface.

BMI, Body mass index; CRS, chronic rhinosinusitis; NO, nitric oxide; pb, postbronchodilator.

TABLE III. Longitudinal changes: comparison between baseline and 2 years

	Deterioration (n = 17)			No change (n = 58)			Improvement (n = 53)		
	Baseline	2 y	P value	Baseline	2 y	P value	Baseline	2 y	P value
BMI (kg/m ²)	28.7	28.9	.492	27.2	27.3	.716	29.4	29.7	.974
Fluticasone equivalent (μg)	250	500	<.001	250	250	.181	500	250	<.001
ACQ score	1.15	1.55	.049	1.13	1.05	.217	1.52	1.05	<.001
GINA score	2	4	<.001	2.5	2.5	.322	3	2	<.001
pb FEV ₁ (% predicted)	93	95	.302	101	103	.149	102	105	.007
pb FEV ₁ /FVC (% predicted)	90	87	.245	96	94	.084	97	96	.100
Exhaled NO (ppb)	17.4	25.6	.326	19.6	21.3	.106	22.2	23.0	.513
Blood neutrophils (× 10 ⁹ /L)	4.2	4.6	.256	3.8	3.7	.842	3.7	3.5	.363
Blood eosinophils (× 10 ⁹ /L)	0.17	0.15	.222	0.16	0.17	.350	0.16	0.17	.181

Significant *P* values are shown in boldface.

BMI, Body mass index; NO, nitric oxide; pb, postbronchodilator.

TABLE IV. ORs for factors potentially associated with a deterioration in GINA scores

Covariate	OR	95% CI
FEV ₁ /FVC ratio <95%	3.9	1.30-11.98
>20 pack years	3.6	1.22-10.76
Sputum neutrophils >64%	2.5	0.60-9.98
FEV ₁ /FVC ratio (per 10% lower)	1.6	1.03-2.56
BMI >30 kg/m ²	1.6	0.56-4.52
Every 10 pack years smoked	1.5	1.10-2.02
Nasal polyposis, yes	1.4	0.40-4.59
Age >50 y	1.3	0.48-3.68
CRS, yes	1.2	0.42-3.35
Atopy, yes	0.8	0.28-2.24
Female sex	0.6	0.23-1.80
Exhaled NO	0.6	0.19-1.79
Sputum eosinophils >2%	0.4	0.08-2.00

Univariate ORs with 95% CIs are shown. Significant ORs are shown in boldface.

BMI, Body mass index; CRS, chronic rhinosinusitis; NO, nitric oxide.

on ACQ scores or FEV₁ in a small proportion of our patients was not relevant because an accurate estimation of the severity score could still be made (see Fig E1).

Our results could have been biased by the rather large proportion of patients who were lost to follow-up. Patients who were lost to follow-up were more often nonsmoking women using lower doses of inhaled corticosteroids than the participants, suggesting that they had milder asthma and did not require regular follow-up. One might argue that the higher number of smokers among the participants compared with those who were lost to follow-up might have influenced our results. However, a small enrichment of the population with exsmokers or current smokers is not expected to affect the results of a logistic regression analysis.

The most likely explanation for the effect of smoking on asthma deterioration is persistent smoking-induced inflammatory pattern, which is glucocorticoid insensitive. Active smoking changes the type of airway inflammation to more mast cells and

TABLE V. Multivariate ORs for factors associated with a deterioration in GINA scores

Covariate	OR	95% CI
Ten pack years	1.4	1.02-1.91
FEV ₁ /FVC ratio (per 10% lower)	1.4	0.88-2.36
FEV ₁ /FVC ratio <95%	3.1	0.99-9.92
Ten pack years	1.4	1.01-1.89

ORs with 95% CIs are shown. Two models are selected with significant variables from Table IV.

neutrophils and less eosinophils.^{30,31} Exsmoking asthmatic patients are more frequently known to have neutrophilic airway inflammation,³¹ which is associated with glucocorticoid insensitivity. Smoking is also known to cause airway remodeling, with an increased epithelial wall thickness and more goblet cells in the bronchi, leading to more symptoms of dyspnea and sputum production. A longitudinal study with a follow-up period of 23 years showed that the protective effect of inhaled corticosteroids on lung function decrease was absent in patients who had smoked for more than 5 pack years.³² However, reduced beneficial effects of inhaled glucocorticoids caused by smoking were found in some, but not all, studies.^{33,34} The results of our study support the hypothesis that smoking, even for a short period of time, has persistent effects on corticosteroid sensitivity, leading to a rapid increase in asthma severity despite an increase in inhaled steroid doses shortly after asthma diagnosis.

The results from this study have a number of clinical implications. Clinicians should be alert for an increase in asthma severity in patients with new-onset adult asthma who have a history of smoking. These patients are prone to a more rapid increase in asthma severity, and therefore early therapeutic intervention is warranted. Because corticosteroids are less effective in smokers than in nonsmokers,³³ novel targeted therapeutic options might be more suitable for these patients.

In summary, we showed that smoking or having smoked in the past is an independent risk factor for increased asthma severity within 2 years after asthma diagnosis. The more pack years smoked, the higher the risk of increased asthma severity. Lung function, sinus disease, and type of airway inflammation at the time of asthma diagnosis are not associated with more severe asthma after 2 years. Because exsmokers or current smokers with new-onset asthma are at increased risk of severe asthma, these patients should be coached intensively to stop smoking and monitored closely and receive aggressive preventive therapy. Because inhaled corticosteroids are not very effective in these patients, novel targeted therapies need to be developed for this highly prevalent patient category.

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Clinical implications: Adults with new-onset asthma and a positive smoking history are at risk of severe disease and might be candidates for early targeted interventions.

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METHODS

Asthma severity score

Assessment of asthma severity was based on the GINA 2002 guidelines.^{E1} Classification follows 3 steps. The first step is to determine each patient's treatment category based on the daily dose of inhaled corticosteroids (low, medium, or high).^{E2} Second, symptom scores and FEV₁ data are assessed as follows: (1) intermittent symptoms or FEV₁ of greater than 80% of predicted value; (2) mild persistent symptoms or FEV₁ of greater than 80%; (3) moderate persistent symptoms or FEV₁ of 60% to 80%; and (4) severe persistent

symptoms or FEV₁ of less than 60%. The final step is to combine the clinical severity of step 2 with the medication dose of step 1 into an overall category (Fig E1).^{E1}

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Classification of Asthma Severity

symptoms & lung function	current treatment step		
	step 1 intermittent	step 2 mild persistent	step 3 mod. persistent
step 1: <i>intermittent</i> symptoms - FEV ₁ > 80%	intermittent	mild persistent	moderate persistent
step 2: <i>mild persistent</i> symptoms + FEV ₁ > 80%	mild persistent	moderate persistent	severe persistent
step 3: <i>mod. persistent</i> symptoms ++ FEV ₁ 60-80%	moderate persistent	severe persistent	severe persistent
step 4: <i>severe persistent</i> symptoms +++ FEV ₁ ≤ 60%	severe persistent	severe persistent	severe persistent

FIG E1. Asthma severity score according to the GINA guidelines (2002).^{E1} Categorization is based on a composite score of treatment with symptoms and lung function. The presence of 1 feature of severity is sufficient to place a patient in that category.