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Assessment of asthma control: The SERENA study

Antonio Corrado [a,*], Teresa Renda [a], Guido Polese [b], Andrea Rossi [c] on behalf of SERENA (Studio ossERvazionalE per il monitoraggio dell'asma non coNtrollAto)/AIPO Study Group [1]

[a] Respiratory Intensive Care Unit and Thoracic Physiopathology, University and General Hospital Careggi, Firenze, Italy
[b] Pulmonary Unit, Rehabilitation Department, ULSS 20, Verona, Italy
[c] Pulmonary Unit, University and General Hospital, Verona, Italy

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Summary
Background: several studies suggest that many asthmatic subjects have uncontrolled asthma. The control of asthma is now considered the major goal of therapy.
Objectives: to ascertain the level of asthma control, by Asthma Control Test (ACT), in "real-life" clinical practice and the potential risk factors for uncontrolled disease in patients treated with inhaled corticosteroids (ICS) and long-acting beta-adrenergic agonists (LABA).
Methods: SERENA is a multi-centre, cross-sectional, 6-month observational, non-interventional study carried out in 16 Pulmonary Units in Italy. Asthmatic outpatients aged over 18, undergoing treatment with ICS at medium–high daily doses associated with LABA, were enrolled. The patients were divided in 3 subgroups according to the level of asthma control by ACT score (25:controlled; 20–24:partly controlled; <20: uncontrolled).
Results: Out of a total of 548 patients, 396 met the inclusion criteria. Only 9.1% of patients had asthma controlled, while partly controlled and uncontrolled asthma accounted for 39.6% and 51.3% respectively. The mean age was 54.5 ± 15.8 and the mean duration of asthma was 16.1 ± 14.1 years. There were more females than males (63% vs 37%) and females had highest prevalence of uncontrolled asthma (63.1%). The mean values of FEV_1% predicted were lower in the uncontrolled group ($p < 0.001$). The percentage of patients with at least 1 exacerbation, unscheduled visit and/or admissions was lower in controlled (22.2%, 8.3%, 8.3%) than in partly controlled (50%, 38.6%, 9.2%) and uncontrolled (83.2%, 66.2%, 27.8%) groups

* Corresponding author. Respiratory Intensive Care Unit, Thoracic Physiopathology Laboratory, AOU Careggi, Florence, Italy. Tel./fax: +39 0557946559.
E-mail addresses: corradoa@aou-careggi.toscana.it, antonio.corrado@aiporicerche.it (A. Corrado).
[1] The members of the SERENA/AIPO Study Group are listed in the Appendix section.

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($p < 0.0001$). The multivariate ordinal logistic regression analysis identified female sex, FEV_1 and exacerbations as the strongest independent factors associated with the uncontrolled disease.

Conclusion: This study highlights the importance in clinical practice of a periodic assessment by a validated asthma control instrument and exacerbations/health care contacts during previous year. Clinicians should be aware that a significant proportion of patients can have uncontrolled asthma, despite regular pharmacological treatment.

Introduction

The International Guidelines for the diagnosis and management of asthma have been available since 1995 [1,2]. Despite the almost annual publication of GINA Guidelines, the health initiatives undertaken and the asthma control campaigns, the control of asthma remains a crucial problem. Several clinical studies suggest that the asthma of many subjects is still uncontrolled and that asthma morbidity remains high while the disease seems to be far from an optimal control [3—6] although effective and safe treatments, such as inhaled corticosteroids (ICS) and long-acting beta-adrenergic agonists (LABA) are widely available [6]. It has been recommended that an effective and safe treatment must be graded on the basis of a periodic assessment of asthma control which represents the major goal of therapy [2,7]. The assessment of asthma control should include the control of the clinical manifestations and the control of the expected future risk to the patients such as exacerbations, losing lung function over time and side effects of treatment. It has been shown, in a randomized controlled study [8], that combining ICS with LABA was more effective than ICS alone in achieving the control of asthma. Recently the Asthma Control Test (ACT) has been developed and introduced in clinical practice [9—12] for the assessment of the control of asthma. The test has shown a good diagnostic accuracy for controlled and not well controlled asthma but a poor diagnostic accuracy for the assessment of uncontrolled asthma [13]. At the moment there are limited data on reliable cut points for identification of uncontrolled disease. Up to now all the studies published, which have tried to identify a relationship between ACT score and predictors of asthma instability in adult [14,15], did not include a population with sustained and homogeneous combined inhaled pharmacological treatment according to GINA guidelines.

The aim of the present study was to assess, in "real-life" clinical practice in Italy, the level of asthma control by ACT and the potential risk factors for uncontrolled disease in patients undergoing regular treatment with medium—high doses of ICS in association with LABA.

Methods

This observational, cross-sectional, non-interventional multicenter study was promoted by the Italian Association of Hospital Pulmonologists (AIPO: Associazione Italiana Pneumologi Ospedalieri) and was carried out from the 4th February 2010 to 11th April 2011 in outpatient clinics of 16 Italian Pulmonary Units. The protocol was approved by the local ethics committees of all the participating centres. All patients provided their written informed consent to participate in the study. All asthmatic patients ≥18 years-old of both genders, according to GINA guidelines [1,2], and on regular treatment with LABA plus ICS at medium/high daily doses (beclomethasone dipropionate — HFA >250—500/>500—1000 mcg or estimated equipotent daily doses of other ICS for adults) attending the outpatient clinic of each centre were considered eligible for the study and registered in the electronic database developed by AIPO. In each unit, one or more specialists filled out an electronic Case Report Form (e-CRF) with clinical information on patients with a confirmed diagnosis of Asthma. The e-CRF required the following basic information: demographic data, history of smoking, year in which asthma was first diagnosed, type of asthma according to the allergometric tests, spirometric data Forced Expiratory Volume in one second (FEV_1) and FEV_1/Forced Vital Capacity (FEV_1/FVC) measured in the last three months, symptoms reported by the patient at the time of the visit and referred to the last 4 weeks, current pharmacotherapy, number of exacerbations, number of visits to the emergency room or unscheduled visits in the preceding year. Presence and type of co-morbidities (cardiovascular, diabetes, obesity, dyslipidemia, gastro-oesophageal reflux, rhinitis, nasal polyposis, obstructive sleep apnoea — OSA, chronic renal failure, osteoporosis and depression) were also registered. The level of asthma control of each patient was assessed by means of the Asthma Control Test (ACT) questionnaire [9]. The total score ranges from 5 to 25 points. On the basis of the points scored, we divided the patients in three subgroups (controlled, ACT = 25; partly controlled, ACT = 24—20; and uncontrolled, ACT<20). The choice of these cut-off values was made a priori before the analysis of data on clinical consideration taking into account that 25 points scored represents a patient with asthma totally free of symptoms and a complete control of the disease. All the e-CRFs were sent on-line to the central database of the AIPO Study Centre for data processing and analysis that was blind with regard to the patient's identity.

All centres were asked to recruit consecutively within 6 months the patients who had attended their units and complied with the following inclusion criteria:

- aged >18;
- clinical diagnosis of asthma according to the GINA guideline version existing at the time of the study [1] and in treatment with long-acting bronchodilators

(LABA) plus Inhaled corticosteroids (ICS) at medium/high daily doses [1,2].

The Exclusion Criteria were as follows:

- clinical features suggesting emphysema or chronic bronchitis;
- refusal to participate;
- other de-compensated organ failures;
- known neoplastic diseases;
- severe psychiatric disorders;
- participation in an asthma-related research study within the previous 3 months.

All medical treatments were within normal clinical practice, the decision to prescribe any treatment was completely independent from the decision to include the patient in the study.

Data analysis

Results were given as means (SD) for normally distributed data, as medians with the Interquartile range (IQR) for non-normally distributed variables, and as percentages for categorical variables. The Student test was used for the comparison between means having first checked the assumption of equality of variances by the F test. The analysis of variance (ANOVA) for repeated measurements was used to test the difference between the means of several subgroups of a variable (multiple testing) having first checked the assumption of equality of variances by relying on the Bartlett test or the Bonferroni test for multiple comparisons when needed. When the assumption of equality of variances was violated, the Kruskall–Wallis test was used. Bivariate analyses were conducted with the chi-square test or the exact Fisher test (for categorical variables) and the two tailed *t*-tests. A multinomial regression model was fitted to the data by using asthma control (controlled, partly controlled, and uncontrolled) as dependent variable to identify the factors associated with asthma control. Multivariate associations of potential determinants with asthma control were expressed by relative risk ratios (using controlled asthma as the reference category) and their 95% CI. All the variables considered for the univariate analysis were included in the multinomial regression model. For all tests a p value of ≤ 0.05 was considered statistically significant. Analyses were performed by R 2.15.2 and Med-Calc (version 11.0.0.0).

Results

Of the 16 Units involved in the study, 5 withdrew after initial acceptance for technical reasons such as limited internal organization or lack of time. The final data were collected in 11 units. From the 4th February 2010 to 11th April 2011, 548 patients were enrolled but only 396 were included in the analysis because the ACT score was lacking in 26 patients while in 126 patients the inclusion criteria were violated regarding the doses of ICS. The median number of cases contributed by units was 22, range (1–175), and the interquartile range (IQR) was 8 and 33.

Characteristics of the patient population

Table 1 shows the characteristics of patients divided into the three subgroups according to the ACT score. Among the 396 patients: 36 (9.1%) had controlled asthma whereas 157 (39.6%) and 203 (51.3%) had partly controlled and uncontrolled asthma, respectively. The distribution of patients in the three subgroups was statistically different ($P < 0.0001$) with the highest percentage in the uncontrolled group. As reported in Table 1, patients with uncontrolled asthma were older than the other two groups. A higher proportion of females than males was found in the uncontrolled asthma group. By contrast, there was a greater prevalence of males in the partly and controlled asthma groups, respectively. Only 31 of 396 patients were current smokers, and the majority of them presented an uncontrolled asthma. The Body Mass Index was not different in the three subgroups of patients. The duration of asthma from the first diagnosis was longer and statistically significant in patients with uncontrolled asthma. Spirometry was available in 380/396 patients (95.9%). The mean values of FEV_1% predicted differed significantly across the groups of patients with different ACT scores, with the lower value in the uncontrolled asthma group ($P < 0.001$).

Co-morbidities

As reported in Table 1, 62.1% of patients were suffering from at least one co-morbidity. The rate of co-morbidities differed significantly across the three subgroups from 9.8% in controlled to 39.0% and 51.2% in partly and uncontrolled asthma respectively ($p < 0.0001$). Cardiovascular disorders (30,1%) and rhinitis/nasal polyposis (28.0%) were the most representative co-morbidities. Systemic hypertension alone represented the 23.5% of all co-morbidities. Obesity was present in 17.2% of patients, metabolic disorders (diabetes and dyslipidemia) in 15.6%, gastro-oesophageal reflux in 13.1%, obstructive sleep apnoea (OSA) in 2.78%, osteoporosis in 2.53%, chronic renal failure (CRF) in 0.25% and depression in 1.8% of all patients. The distribution of the co-morbidities according to the control of asthma by ACT is reported in Table 2. With the exception of OSA, CRF and depression the percentage of each co-morbidity was higher and statistically significant in uncontrolled asthma. Out of the 246 patients with co-morbidities, 104 presented one co-morbidity and 140 had two or more co-morbidities. The rate of distribution according to the ACT is reported in Table 2.

Pharmacological treatment

All patients recruited were treated with LABA plus medium/high daily doses of ICS. Table 3 illustrates the type of drugs used by the 396 patients and according to the ACT scores. ICS/LABA was used alone in 344 patients (86.9%), in association with systemic corticosteroids per os in 34 (8.6%), and regularly associated with short acting beta agonists (SABA) in 18 (4.5%). SABA as needed were used in 36.7% of patients exclusively with partly and uncontrolled asthma.

As reported in Table 3, the use of systemic corticosteroids per os associated to ICS/LABA was detected mainly in patients with uncontrolled asthma, whereas SABA as

Table 1 Characteristics of the patients according to the control of asthma by ACT.

Characteristics	All patients ($N = 396$)	ACT = 25 ($N = 36$) 9.1%	ACT = 24—20 ($N = 157$) 39.6%	ACT <20 ($N = 203$) 51.3%	*p* Value <0.0001°
Age, years, Mean (SD)	54.5 (15.8)	52.7 (13.6)	52.3 (15.7)	56.5 (16.0)	0.036*
Male sex, % (n° pts)	37.1 (147)	12.2 (18)	56.5 (83)	31.3 (46)	<0.0001°°
Female sex, % (n° pts)	62.9 (249)	7.2 (18)	29.7 (74)	63.1 (157)	
Smoking					
Yes, % (n° pts)	26.5 (105)	6.7 (7)	48.6 (51)	44.8 (47)	0.092°°°
No, % (n° pts)	73.5 (291)	10 (29)	36.4 (106)	53.6 (156)	
Current smoker, % (n° pts)	7.8 (31)	3.2 (1)	35.5 (11)	61.3 (19)	0.050#
Ex smoker, % (n° pts)	18.7 (74)	8.1 (6)	54.0 (40)	37.8 (28)	
No smoker, % (n° pts)	73.5 (291)	9.97 (29)	36.4 (106)	53.6 (156)	
BMI (kg/m^2), Mean (SD)	27 (4,9)	28.1 (5.4)	26.7 (4.9)	26.7 (4.8)	0.318**
Years from the first diagnosis, Mean (SD)	16.1 (14.1)	14.6 (13.3)	13.85 (14.7)	18.05 (14.45)	0.015***
FEV_1% pred, Mean (SD) in 380 patients	80.7 (16.8)	92.1 (11.6)	84.4 (15.3)	75.7 (17.0)	0.0001§
FEV_1/FVC in 380 patients	70.9 (13.9)	70.6 (13.4)	71.5 (12.8)	70.4 (14.7)	0.7400§§
Presence of at least 1 co-morbidity, % (n° pts)					
Yes	62.1 (246)	9.8 (24)	39.0 (96)	51.2 (126)	<0.840###
No	37.9 (150)	8.0 (12)	40.7 (61)	51.3 (77)	

° Pearson Chi-square 112,742; *ANOVA, One-way analysis of variance, F-ratio 3359; °° Pearson Chi-square 37,420, Chi-square trend 29,366; °°°° Fisher's exact test; # Pearson Chi-square 15,742; # Fisher's exact test; **ANOVA, One-way analysis of variance, F-ratio 1.149; ***ANOVA, One-way analysis of variance, F-ratio 4.271; §Kruskall—Wallis equality of populations rank test Chi-square 41,442 on 380 pts (patients: 34 ACT = 25; 153 ACT 20—24; 193 ACT<20); §§ ANOVA, One-way analysis of variance, F-ratio 0,30; ### Fisher's exact test.

needed were used exclusively in partly and uncontrolled asthma. The type and the daily dosages of drugs used were reported in Supporting information.

Exacerbations, admission to ED and unscheduled visits

Exacerbations

As shown in Table 3 the majority of patients, 253 (64.5%), reported at least one exacerbation during the previous year of the study. The rate of distribution of exacerbations through the subgroups of patients increased in a statistically significant way from 22.2% in controlled to 50.0% and 83.2% in partly and uncontrolled asthma respectively. This trend was statistically significant ($P < 0.0001$).

Admission to the emergency department

The majority of patients 315 (81.4%) did not experience an admission to the emergency department (ED) because of the exacerbation of asthma. Among the 72 (18.6%) patients

Table 2 Co-morbidities according to ACT.

Co-morbidities	Number of patients with co-morbidities	ACT = 25	ACT = 24—20	ACT <20	*p* Value
Panel A. Distribution of co-morbidities according to the ACT					
Cardiovascular disorders % (n° pts)	108@	10.1 (11)	30.5 (33)	59.2 (64)	<0.0001*
Rhinitis/nasal polyposis % (n° pts)	111	11.7 (13)	48.6 (54)	39.6 (44)	<0.0001°
Obesity % (n° pts)	68	10.3 (7)	36.7 (25)	52.9 (36)	0.001^
Metabolic disorders % (n° pts)	55#	7.3 (4)	27.3 (15)	65.5 (36)	<0.0001§
Gastro-esophageal reflux % (n° pts)	52	1.9 (1)	36.5 (19)	61.5 (32)	<0.0001&
Obstructive Sleep Apnoea — OSA % (n° pts)	11	18.2 (2)	63.6 (7)	18.2 (2)	0.1030**
Osteoporosis % (n° pts)	10	10 (1)	20 (2)	70 (7)	0.045°°
Depression % (n° pts)	7	0 (0)	28.6 (2)	71.4 (5)	0.4497^^
Chronic renal failure % (n° pts)	1	0	100 (1)	0	ND§§
Panel B. Distribution of patients with one or ≥2 co-morbidities according to the ACT					
1 Co-morbidity % (n° pts)	106	12.3 (13)	43.4 (46)	44.4 (47)	<0.0001*
≥2 Co-morbidities % (n° pts)	140	7.9 (11)	35.7 (50)	56.4 (79)	<0.0001°

Panel A: @11 patients had 2 co-morbidities associated for a total of 119 co-morbidities (cardiovascular co-morbidities per patient: 1.1018519); #7 patients had 2 co-morbidities associated for a total of 62 co-morbidities (metabolic co-morbidities per patient: 1.1272727); *Chi-square = 39.389; °chi-square = 24.703; ^Chi-square = 18.912; § chi-square = 28.836; & chi-square = 27.962; **Chi-square = 4.545; °°Chi-square = 6.200; ^Chi-square = 0.571; §§Chi-square = Not Detectable.
Panel B: *Chi-square = 21.189; °Chi-square = 49.900.

Table 3 Pharmacological treatment, exacerbations, admission to ED and unscheduled visits of the patients according to the control of asthma by ACT.

Treatment	All patients ($N = 396$)	ACT = 25 ($N = 36$)	ACT = 24–20 ($N = 157$)	ACT < 20 ($N = 203$)	*p* Value
ICS/LABA, % (n° pts)	86.9 (344)	10.2 (35)	40.70 (140)	49.13 (169)	0.0138[a]
ICS/LABA + CS per os, % (n° pts)	8.6 (34)	2.94 (1)	20.60 (7)	76.50 (26)	
ICS/LABA + SABA, % (n° pts)	4.5 (18)	0.0 (0)	55.55 (10)	44.44 (8)	

Exacerbation	All patients ($N = 392$)	ACT = 25 ($N = 36$)	ACT = 24–20 ($N = 154$)	ACT < 20 ($N = 202$)	*p* Value
0, % (n° pts)	35.5 (139)	77.8 (28)	50.0 (77)	16.83 (34)	<0.0001[b]
≥1, % (n° pts)	64.5 (253)	22.2 (8)	50.0 (77)	83.17 (168)	

Admission to ED	All patients ($N = 387$)	ACT = 25 ($N = 36$)	ACT = 24–20 ($N = 153$)	ACT < 20 ($N = 198$)	*p* Value
0, % (n° pts)	81.4 (315)	91.67 (33)	90.85 (139)	72.22 (143)	0.0001[c]
≥1, % (n° pts)	18.6 (72)	8.33 (3)	9.15 (14)	27.78 (55)	

Unscheduled visits	All patients ($N = 387$)	ACT = 25 ($N = 36$)	ACT = 20–24 ($N = 153$)	ACT < 20 ($N = 198$)	*p* Value
0, % (n° pts)	50.1 (194)	91.67 (33)	61.4 (94)	33.8 (67)	<0.0001[d]
≥1, % (n° pts)	49.9 (193)	8.33 (3)	38.6 (59)	66.2 (131)	

[a] Pearson Chi-square: 12.538.
[b] Pearson Chi-square: 73.05; Chi-square trend 72.809.
[c] Fisher's exact test.
[d] Pearson Chi square: 72.0919.

admitted to the ED the frequency of admission was higher in those with an uncontrolled asthma, Table 3.

Unscheduled visits

This information was missing in 9 patients. Fifty percent (193/387) of patients reported one or more unscheduled visits during the previous year and the need for unscheduled visits increased significantly when the control of symptoms according to ACT Score was poorest. Table 3.

A univariate ordinal logistic regression analysis of all patients using the ACT classification as dependent variable and gender, age, weight, height, years of asthma from the first diagnosis, smoking habit, FEV_1, pharmacological treatment, exacerbation of asthma, admission to the ED, and unscheduled visits as independent variables is reported in Table S1. Table 4 reports the multivariate ordinal logistic regression in 371 patients with asthma using the ACT classification as dependent variable and as independent variables all those included in the univariate analysis. Only the variables reported in the table were retained in model using a stepwise method and with a significance level for removal from the model of 0.2. Female sex, exacerbation and FEV_1 were the most predictive of lack of asthma control. The estimated odds in female vs males was 3.2. This means that females have a 3.2 times higher risk than males of having uncontrolled or less controlled asthma. Exacerbations contributed significantly to the lack of control of asthma with odds of 3.28. Patients with higher values of FEV_1 showed a better control of asthma, the odds of patients with a point FEV_1 higher was 0.96 times than those who didn't show a point increase in FEV_1.

Table 4 Multivariate ordinal logistic regression in 371 patients with asthma using ACT classification as dependent variable.

Variables	Odds ratio	Std. error	*p*	95% Confidence interval
Gender (Female vs Male)	0.3147952	0.0934723	0.0001	0.1759059–0.5633468
Unscheduled visits	1.607771	0.532789	0.152	0.8397495–3.078211
Height	0.978418	0.0146306	0.145	0.9501587–1.007518
Exacerbations	3.287085	1.132074	0.0001	1.673619–6.456026
Pharmacological treatment				
LABA/ICS + CS per os	1.867688	0.8680571	0.179	0.7510797–4.644325
FEV_1	0.9636538	0.0076904	0.0001	0.9486981–0.9788453

Variables included in the model: gender, age (as continuous variable), weight (Kg), height (cm), pharmacological treatment, year from the first diagnosis, FEV_1, admission to ED, unscheduled visits, exacerbations, presence of at least one co-morbidity, smoking habit. The variables included in the table were retained in model with stepwise multivariate ordinal logistic regression, with significance level for removal from the model of 0.2.

Fig. 1 shows the distribution of asthmatic patients treated with medium or high doses of ICS alone and medium/high doses of ICS with oral steroids (OS) according to the level of asthma control. The patients treated with high doses of ICS without OS presented a risk 1.72 times higher than those treated with medium doses of ICS without OS for partly or uncontrolled asthma; OR 1.72, (95% CI 1.1716—2.5216), $p = 0.0056$. The patients treated with medium/high doses of ICS with OS presented a risk 2.80 times higher than those treated with medium/high doses of ICS without OS for partly or uncontrolled asthma; OR 2.80 (95%CI 1.3671—5.7529), $p = 0.0049$.

Discussion

The data of our study show that the control of asthma is far from being achieved in real life. Our data extend and support previous observation showing that only a minority of asthmatic patients attains the control of asthma [4,5,16]. In our study, only 9.1% of patients had their asthma under control while a partly controlled and uncontrolled asthma accounted for 39.6% and 51.3% of patients respectively. Our analysis included only patients (396 out of 548) with a longstanding diagnosis of asthma and who were treated with medium/high doses of ICS associated to LABA. Our data shows that female sex, an age older than fifty, the years of asthma from the first diagnosis, treatment with ICS/LABA + CS per os, FEV_1, unscheduled visits, exacerbations, admission to the emergency department were each individually associated with an increased risk of uncontrolled disease. The multivariate analysis which encompasses all these factors showed that gender, exacerbations and FEV_1 were the strongest independent factors associated with uncontrolled asthma.

Several controlled studies in the last decade have shown that the control of asthma can be obtained in a large proportion of patients using inhaled steroids alone or in combination with long-acting β2-agonists [8,17,18]. Controlled Clinical Trials, however, do not always reflect real-life conditions, and epidemiological studies in the general population clearly show that asthma is far from being adequately controlled [3—5,11,19]. The rate of uncontrolled asthma reported in several studies [5,10,11,15,20—23] ranges from 49 to 69%. These results are consistent with the percentage of 51.3% reported in our study. However it must be pointed out that all previous studies, in which ACT was used for the assessment of asthma control in adults, included a heterogeneous population with regard to the therapeutic regimen. ICS/LABA were used in different percentages from 49.9% [14] to 55% [4] or it was not reported [15,24]. In our survey we found, despite a maximal treatment with high doses of inhaled corticosteroids associated to LABA, a high rate of uncontrolled asthma. When oral corticosteroids were added to the inhaled association the rate of uncontrol was higher. This finding is in keeping with that reported in other studies [25,26]. Sullivan et al. [25], using the asthma therapy assessment questionnaire (ATEQ) to evaluate the risk of subsequent asthma-related health care events in adult asthma patients, found that patients with three or four control problems were at significantly greater risk for oral steroids burst (RR 2.9) vs patients with no control problem. Gold et al. [26] reported that uncontrolled asthma was associated to use of oral steroids (OR, 2.5) compared with patients with controlled asthma. In a recent post hoc analysis of five large clinical trials [27] the need of oral steroids treatment was included in the definition of severe asthma exacerbations.

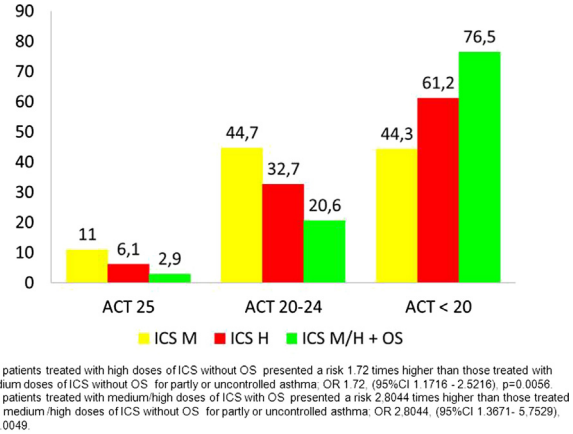

Figure 1 Percentage of distribution of asthmatic patients treated with medium or high doses of Inhaled Corticosteroids alone plus LABA or medium/high doses of ICS plus LABA and oral steroids according to ACT classification.

Smoking is reported [2,28] as a factor associated to a limited control of asthma. In our survey we found that a history of post-tobacco smoking was associated with reduced asthma control ($p = 0.040$, OR 0.4208). It has been reported [29] an increased risk of asthma higher in ex-smokers (OR 1.49) than in current smokers (OR 1.33) compared to non-smokers. The lighter effect in current smokers was hypothesized as due to a behavioural change as a response to beginning symptoms. Recently the impact of smoking on asthma has been evaluated in a large population-based international study [30]; the authors reported the highest mean of symptom score in ex-smokers.

Asthma is often associated with various co-morbidities, which may influence the asthma control and the response to treatment [31]. We found that the rate of the most representative co-morbidities such as Cardiovascular disorders, Rhinitis/nasal polyposis, obesity, metabolic disorders, gastro-oesophageal reflux and osteoporosis was higher in patients with uncontrolled asthma. Furthermore when we look at the association of more co-morbidities in a single patient we found that patients with ≥2 co-morbidities presented the highest rate of uncontrolled asthma. However, the weight of the presence of co-morbidities in the multivariate analysis was weak. Peters et al. [4], on the contrary, reported that chronic sinusitis, high blood pressure and gastro-oesophageal reflux were strongly related to uncontrolled asthma in a multivariate analysis. This discrepancy may be due in our opinion to the different sample of patients (396 vs 1811). Identification and treatment of co-morbidities is now recognized as an integral part of core management of asthma particularly in the more severe forms of the disease, even-though the effect of treating co-morbidities on asthma severity and long-term clinical outcomes needs to be further investigated [31].

Achieving adequate asthma control and minimizing future risk of exacerbations are the primary goals in the management of the disease. The prediction of exacerbation by means of clinical tool is a crucial aspect for the correct management of asthma.

It has been reported that validated asthma control questionnaire ACQ-5 [32], full composite ACQ7 [33] and ATAQ [25] are associated with future risk of asthma exacerbations and the risk of subsequent severe asthma-related health care events. Bateman et al. [32] in a retrospective pooled analysis of 5 studies classified the patients in two groups by their baseline ACQ-5 score. The patients with a baseline ACQ-5 score $\geq$1.5 vs those with a score $<$0.5 had a significantly higher exacerbation rate over 12 month period. Meltzer et al. [33] reported that each 1 point increase in ACQ was associated with a 50% increased risk of exacerbation for the following two week period.

Ko et al. [14] reported that in adult asthmatic patients a single measurement of ACT was useful for prediction of exacerbation and changes in treatment decision. Stanford et al. [15], employing ACT and C-ACT, found a positive relationship between uncontrolled asthma and exacerbations only in children. In our study we found that exacerbation was a strong predictor of uncontrolled asthma in adult asthmatic patients treated with moderate to high doses of ICS/LABA. Why our asthmatic patients, treated following international guidelines, have such a high percentage of either partly or uncontrolled disease? The explanation may lay on the hypothesis formulated by Bateman et al. [32] in their retrospective pooled analysis of 5 studies in which they reported that the achievement of current control in around 40% of the patients included in the analysis reflects the relatively refractory nature of their asthma and the limitations of the treatment used.

We acknowledge that our study has several limitations. The first is that in filling out the e-CRF, the pulmonary specialist might have been a different doctor from the caring physician. Furthermore, we did not record whether the pharmacological prescription originated from a pulmonologist, another specialist (geriatrist, internist, etc.) or a general practitioner. The second, as previously mentioned, was the fact that we did not ascertain whether the patients were actually taking the prescribed medications, there is no effective and accurate manner in which to measure true asthma medication adherence and we do not know if patients received a written management plan. Finally, the population of this study was not the result of an epidemiological design, but only represented patients who referred to the clinic of the units participating in the study.

Pulmonary function testing and a current asthma symptom alone might not accurately reflect the level of asthma severity and control [4,34,35]. Our findings support the need for a more global regular assessment of asthma severity and control, including asthma-related health care use and medication use. Moreover, a formal asthma control assessment (such as ACT) should be conducted at each clinical visit to improve the likelihood of achieving asthma control. Finally clinicians should be aware that a significant proportion of patients have an uncontrolled disease despite treatment in accordance with the established guidelines.

Appendix A. SERENA/AIPO Study Group

Marcobruni Nadia UO Broncopneumologia, Servizio Ambulatoriale, AO Spedali Civili di Brescia; **Bertini Stefania** Terapia Intensiva Pneumologica e Fisiopatologia Toracica, AOU Careggi, Firenze; **Ligia Giovanni Paolo** UO Pneumologia IV, Ospedale R. Binaghi, Cagliari; **Brunori Marco** UOC Fisiopatologia e Riabilitazione Respiratoria, Policlinico Umberto I°, Univ. La Sapienza, Roma; **Greco Pietro** UO Pneumologia, Ospedale S. Barbara — ASL Carbonia, Iglesias (CI); **Valente Salvatore** UO Pneumologia e Fisiopatologia Respiratoria, Policlinico Univ. A. Gemelli, Roma; **Negrin Rolando** UO Pneumologia, Ospedale S. Bortolo, Vicenza; **Ugolini Marcello** UO Pneumologia, AO S. Salvatore, Pesaro; **Cilenti Vincenzo** Servizio di Fisiopatologia Respiratoria, Istituto Regina Elena — Polo Oncologico, Roma; **Scavalli Patrizia** Servizio Fisiopatologia Respiratoria e Allergologia, Ospedale S.G. Decollato Andosilla, Civita Castellana (VT); **Romano Antonino** UO Allergologia, Complesso Integrato Columbus, Roma.

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.08.019

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