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Discordance between asthma control clinical, physiological and inflammatory parameters in mild asthma[☆]

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KEYWORDS

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Summary

Background: Discrepancies have been observed between clinical, physiological, and inflammatory asthma control criteria, mostly in asthmatic subjects using regular inhaled corticosteroids (ICS) treatment. This study compared the prevalence of discrepancies between these 3 control parameters in mild asthmatic subjects not taking ICS.

Methods: A retrospective analysis of demographic data and results from the Asthma Control Scoring System tool was performed in mild patients with asthma not taking ICS. The % score obtained for the clinical (symptoms), physiological (FEV₁), and inflammatory (sputum eosinophil percentage) criteria were compared. Discrepancy was defined as a >20% difference between any 2 scores.

Findings: Data from 213 subjects with mild asthma were analysed. Discrepancies between clinical and inflammatory scores were observed in 32% of subjects, whereas 31% showed discrepancies between physiological and inflammatory scores, and 20% between clinical and physiological scores. Sub-analysis of the discrepancy groups showed that respectively 88% and 89% of subjects had a higher clinical or physiological score than inflammatory score. Twenty-seven percent of subjects had residual airway inflammation despite adequate clinical control and optimal pulmonary function.

Interpretation: There are significant discrepancies between scores of subjective and objective asthma control criteria. Airway inflammation often persists in subjects with good clinical or physiological asthma control scores. The consequences of this persisting airway inflammation in mild patients remain to be further studied.

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Introduction

Asthma is a multi-faceted disease, characterised by symptoms, variable airflow obstruction, and lower airway inflammation. Current guidelines suggest that the main goal of asthma treatment should be an adequate control of the disease^{1,2} and a reduction in future risk of exacerbations.³ Until recently, asthma control was mostly defined according to subjective clinical features such as daytime and nighttime symptoms, rescue beta-2-agonist need, the ability to perform normal activities, absenteeism from work or school, and the severity and frequency of asthma exacerbations, and objective physiologic measures of expiratory flows.^{1,2} Measurement of airway inflammation is increasingly considered useful in the management of asthma and the most recent Canadian Asthma Consensus Report recommends that sputum eosinophil measurement be included, in addition to standard measures of asthma control, to guide adjustment of controller therapy in adults with moderate to severe asthma, in centres where this technique is available.⁴ We need however to better assess discrepancies between the 3 key components of asthma and determine what is the significance of those differences in regard to asthma management.

Discordance between clinical and physiological measures of asthma control have been previously studied.⁵ More recently, a lack of concordance between lower airway inflammation and clinical asthma control parameters or pulmonary function has also been described^{6–11} and residual eosinophilic airway inflammation has been associated with an increased risk of future asthma exacerbations in moderate/severe asthma.^{12,13} However, these studies have been performed mostly in subjects using inhaled corticosteroids (ICS).

Subjects with mild persistent asthma form the largest group of asthma patients¹⁴ and although they are well clinically controlled, they can experience asthma exacerbations.¹⁵

Despite no or few symptoms, lower airway inflammation may be present in these subjects.¹⁶ Still, the prevalence of these discrepancies and their impact on asthma control has not been determined in this population nor have potential long-term consequences of this feature been properly assessed.

The Asthma Control Scoring System (ACSS) is based on the asthma control criteria proposed by the Canadian Asthma Consensus Report,¹⁷ these criteria being relatively close to those proposed by the Global initiative for Asthma (GINA).² It is a validated tool, that showed adequate measurement properties, both as an evaluative and as a discriminative instrument.¹⁸ The ACSS is a composite score and it may therefore be useful to explore, quantitatively, discrepancies between the various manifestations of asthma and better define clinical phenotypes to help guide therapeutic decisions.

In this study, we looked at the prevalence and determinants of discrepancies between clinical, physiological, and inflammatory asthma control criteria, as reported by the ACSS, in mild asthmatic subjects not taking ICS.

Methods

Subjects and study design

This is an analysis of data from subjects presenting for initial assessment of asthma at the outpatient clinic of the Institut universitaire de cardiologie et de pneumologie de Québec or willing to take part to various studies on asthma pathophysiology and treatment, between 2003 and 2010 (Fig. 1). Data from subjects over 18 years old with a diagnosis of asthma, as defined by the Canadian Asthma Consensus Guidelines¹ for which the 4 clinical control parameters of the ACSS were documented, spirometry was performed (to provide a measure of FEV₁), and sputum induction with sufficient material for adequate analysis was

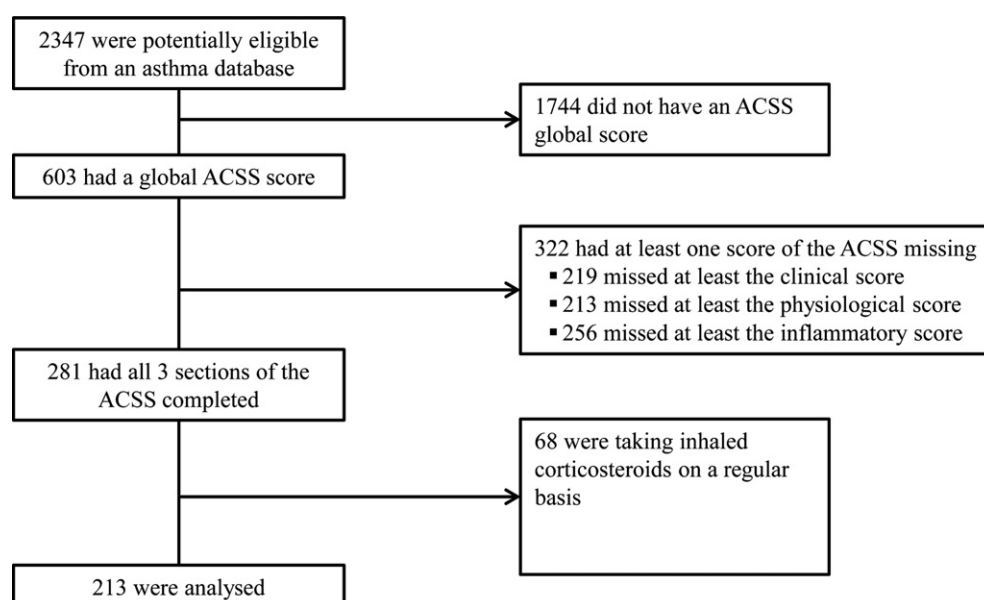


Figure 1 Visual representation of the number of patients who were screened and who completed the study.

obtained were considered. These subjects were not using ICS or any other bronchial anti-inflammatory treatment. The study was reviewed and approved by the local Institutional Ethics Committee (CER 20785).

Asthma Control Scoring System (ACSS)

Three types of parameters can be evaluated using the ACSS: clinical (diurnal symptoms, nocturnal symptoms, rescue beta-2-agonists use, activities), physiological (forced expiratory volume in one second (FEV₁) and/or peak expiratory flows (PEF), and/or PEF circadian variations) and, as an option, lower airway inflammation (induced sputum eosinophilia). The first section of the questionnaire (clinical parameters) is filled according to the patient's report, in reference to his/her last week experience, whereas the second and third sections are completed according to the results obtained from additional tests at the time of assessment. The three sections are quantified to obtain a total score of 100% each and a global score is determined using the mean score of the equally weighted sections filled (100% = very well controlled and 0% = not controlled at all). It should be remembered that high symptoms, low pulmonary function, and high eosinophil counts are resulting in a low score. For the purpose of this study, the 3 sections of the questionnaire had to be filled for a subject to be included and FEV₁ was used as the physiological parameter.

Spirometry

Spirometry was performed according to the recommendations of the American Thoracic Society.¹⁹ The best pre-bronchodilator FEV₁ of 3 reproducible values was recorded and percent predicted was used as the physiological parameter of the ACSS. Predicted values were obtained from Knudson.²⁰

Induced sputum

Sputum was induced using the method described by Pin et al.²¹ and modified by Pizzichini et al.²² A differential cell count, including eosinophils, neutrophils, macrophages, lymphocytes, and bronchial cells, was performed by an experienced technician (>10 years sputum cell counting experience).

Definitions

Discrepancy

Discrepancy was arbitrarily defined as a >20% difference between any 2 scores, corresponding to one subdivision of the ACSS which is based on the Canadian Asthma Guidelines.¹

Control

Controlled asthma was defined as an ACSS global score ≥80%, in keeping with the Canadian Guidelines recommendations.¹

Mild asthma

Subjects were included as mild asthmatics if they had very mild asthma, not requiring ICS regularly, or mild asthma that may have needed ICS treatment but that were not using them at the time of the initial evaluation.

Eosinophilic inflammation

Eosinophilic inflammation was defined as a sputum eosinophil count >2%.²³

Statistical analysis

Data were expressed as means ± SD or as numbers for categorical data. The analyses of categorical variables were performed using Chi-Square or Fisher's exact test. For continuous data, one-way ANOVA was fitted to compare groups with heterogeneous variances and, when applicable, the model was reduced to a one-way analysis with the same variance across groups. Reported *p*-values are based on this transformation. Posteriori comparisons were performed using the Tukey's comparison technique. The univariate normality assumptions were verified with the Shapiro–Wilk tests. The results were considered significant with *p*-values ≤0.05. All analyses were conducted using the statistical package SAS v9.2 (SAS Institute Inc, Cary, NC, U.S.A.).

Results

Subjects' characteristics

Data from 213 (122F/91M) mild asthmatic subjects not taking ICS were analysed. Clinical characteristics of the whole sample and subsamples are shown in Table 1. About one-third of subjects had discrepancies between clinical or physiological score and inflammatory score, whereas 20% had discrepancy between clinical and physiological scores. The various discrepancy groups did not differ in gender, mean age, duration of asthma, atopy, ACSS global score, FEV₁, or BMI.

Sub-analysis of the discrepancy groups showed that more subjects had a higher (better) clinical or physiological score than inflammatory score (60 (88%) vs 8 (12%) and 59 (89%) vs 7 (11%), respectively) (Fig. 2). Among subjects with a lower clinical score and a higher physiological or inflammatory score (considered as low perceivers), there were significantly more women than men (data not shown). There were no other significant differences in the characteristics of the subjects according to the higher score.

Since subjects could be in more than one discrepancy group, data were analysed according to the number of discrepancies (Table 2). Subjects did not differ in their clinical characteristics according to the number of discrepancies, except for the ACSS global score, which was significantly higher in subjects without discrepancy whereas subjects with 3 discrepancies had a significantly lower ACSS global score. Subjects having 2 discrepancies or more had significantly more eosinophils than subjects without discrepancy.

Table 1 Clinical characteristics of the total sample and subsamples.

	All subjects	Subjects without discrepancy	Mean diff > 20%			<i>p</i>
			<i>C</i> vs <i>I</i>	<i>P</i> vs <i>I</i>	<i>C</i> vs <i>P</i>	
<i>n</i> [%]	213	114 [53]	68 [32]	66 [31]	42 [20]	
Gender (F/M)	122/91	61/53	44/24	44/22	21/21	NS
Age (years) ^a	31 ± 10	31 ± 10	32 ± 10	32 ± 10	32 ± 9	NS
Duration of asthma (years) ^a	16 ± 10	16 ± 10	16 ± 11	16 ± 11	15 ± 9	NS
Atopy (yes/no)	189/213	101/12	63/3	59/5	35/5	NS
ACSS global score (%) ^a	82 ± 11	89 ± 8 ^b	74 ± 10	74 ± 10	74 ± 11	NS
Mean difference (%) ^a			46 ± 18	52 ± 16	34 ± 10	
FEV ₁ (% pred.) ^a	96 ± 16	98 ± 16	96 ± 15	96 ± 16	91 ± 18	NS
BMI (kg/m ²) ^a	26 ± 7	27 ± 8	28 ± 6	28 ± 6	28 ± 6	NS
Smoking (S/Ex/NS)	42/30/141	20/14/80	8/12/48	12/13/41	15/4/23	NS
Sputum eosinophils (%) ^a	4.0 ± 9.0	1.1 ± 2.8	8.9 ± 10.1	8.7 ± 10.0	6.3 ± 14.0	<0.0001 ^b
Sputum neutrophils (%) ^a	34.0 ± 23.0	33.8 ± 23.9	34.2 ± 20.9	32.0 ± 21.6	40.4 ± 23.1	NS

C: clinical score, *P*: physiological score, *I*: inflammatory score, F: female, M: male, FEV₁: forced expiratory volume in one second, BMI: body.

^a Mean ± SD.

^b Subjects without discrepancy vs all the other groups with discrepancy.

Relationship between asthma control and discrepancies

Data were analysed according to the level of control (Table 3). There were 145 (68%) subjects in the controlled group (ACSS global score ≥80%) and 68 (32%) subjects in the uncontrolled group (ACSS global score <80%). Particularly, 7 subjects showed total control, with an ACSS score of 100% (data not shown). There were significantly more subjects with discrepancies in the uncontrolled group than in the controlled group.

Interestingly, more than half of the subjects with an ACSS score <80% had a clinical score ≥80% and more than 60% had a physiological score ≥80%, whereas only about a third of these subjects had an inflammatory score ≥80%.

Clinical and physiological scores in relation to sputum eosinophils

When the mean clinical + physiological score was analysed according to sputum eosinophil percentages, 27% of subjects had inflammation (>2% eosinophils) even though their mean clinical + physiological score was ≥80% (Fig. 3).

Discussion

This study is, to our knowledge, the first to report the prevalence of discrepancies between clinical, physiological, and inflammatory asthma control criteria in mild asthmatic subjects not taking inhaled corticosteroids. The key messages of this analysis are that: 1) such discrepancies are common in mild asthma as reported in more severe asthma, 2) there are no specific subject characteristics which can help identify those with such discrepancies, and 3) the prevalence of residual airway inflammation despite good clinical control is high in this population. This brings 2 important questions to answer: 1) What are the long-term consequences of such unantagonised airway inflammation and 2) Should these results change our approach to mild asthma and lead to earlier introduction of anti-inflammatory agents, despite minimal symptoms and excellent airway function?

Using the ACSS, we found that a third of asthmatic subjects had discrepancies between inflammatory score and clinical or physiological scores. Among these, about 90% had a better clinical or physiological score than inflammatory score, suggesting that although control seems adequate according to symptoms or expiratory flows,

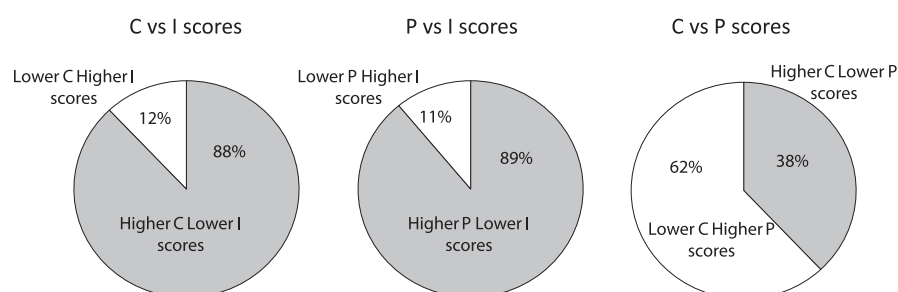


Figure 2 Discrepancy distribution according to the higher score. Among subjects that had >20% difference between 2 scores, this shows the percentage of subjects for which one score was higher in grey and subjects for which the other score was higher in white. C: Clinical score, P: Physiological score, I: Inflammatory score.

Table 2 Clinical characteristics of subjects according to the number of discrepancies.

	Number of discrepancies			
	0	1	2	3
<i>n</i> [%]	114 [53]	29 [14]	63 [30]	7 [3]
Gender (F/M)	61/53	16/13	39/24	5/2
Age (years) ^a	31 ± 10	30 ± 10	32 ± 10	29 ± 6
Duration of asthma (years) ^a	16 ± 10	16 ± 11	16 ± 11	15 ± 9
Atopy (yes/no)	101/12	25/3	57/5	6/0
ACSS global score (%) ^a	89 ± 8 ^b	78 ± 8	75 ± 10	63 ± 6 ^b
FEV ₁ (% pred.) ^a	98 ± 16	92 ± 16	95 ± 16	98 ± 23
BMI (kg/m ²) ^a	27 ± 8	27 ± 7	26 ± 6	25 ± 4
Smoking (S/Ex/NS)	20/14/80	11/3/15	9/13/41	2/0/5
Sputum eosinophils (%) ^a	1.1 ± 2.8	4.2 ± 13.7	7.5 ± 9.0 ^c	17.8 ± 14.3 ^b
Sputum neutrophils (%) ^a	33.8 ± 23.9	37.5 ± 23.8	33.5 ± 20.6	34.9 ± 28.4

F: female, M: male, FEV₁: forced expiratory volume in one second, BMI: body mass index, S: smokers, Ex: ex smokers, NS: non-smokers.

^a Mean ± SD.

^b $p < 0.003$ vs all the other groups.

^c $p < 0.0001$ vs 0 discrepancy.

underlying inflammation often persists. In addition, there are significantly more subjects showing discrepancies between the various asthma control parameters in a group of patients whose asthma was deemed uncontrolled according to the ACSS.

Table 3 Characteristics of subjects according to the level of asthma control as assessed by the ACSS.

Parameter	Global score ≥ 80%	Global score < 80%	<i>p</i>
<i>n</i>	145	68	
Gender (F/M)	86/59	35/33	NS
Age (years) ^a	31 ± 10	32 ± 9	NS
Duration of asthma (years) ^a	16 ± 10	16 ± 10	NS
FEV ₁ (% pred.) ^a	100 ± 14	87 ± 17	<0.0001
BMI (kg/m ²) ^a	27 ± 7	26 ± 5	NS
Smoking (S/Ex/NS)	20/20/105	22/9/37	0.005
ACSS global score (%) ^a	89 ± 6	69 ± 9	
Clinical score ≥ 80% (<i>n</i> [%])	131 [90%]	36 [53%]	<0.0001
Physiological score ≥ 80% (<i>n</i> [%])	142 [98%]	42 [62%]	<0.0001
Inflammatory score ≥ 80% (<i>n</i> [%])	118 [81%]	21 [31%]	<0.0001
>20% difference <i>C</i> vs <i>I</i> (<i>n</i> [%])	25 [17%]	43 [63%]	<0.0001
>20% difference <i>P</i> vs <i>I</i> (<i>n</i> [%])	27 [19%]	39 [57%]	<0.0001
>20% difference <i>C</i> vs <i>P</i> (<i>n</i> [%])	16 [11%]	26 [38%]	<0.0001
Sputum eosinophils (%) ^a	2 ± 7	8 ± 10	<0.0001
Sputum neutrophils (%) ^a	34 ± 25	35 ± 19	NS

C: clinical score, *P*: physiological score, *I*: inflammatory score, F: female, M: male, FEV₁: forced expiratory volume in one second, BMI: body mass index, S: smokers, Ex: ex smokers, NS: non-smokers.

^a Mean ± SD.

The relationships between clinical, physiological and, more recently, inflammatory asthma control parameters have been assessed in the global asthma population, particularly in moderate-to-severe asthmatics taking ICS as their regular medication.^{5–11} In this regard, Bora et al. found, following an analysis of data from 83 patients with asthma, that Asthma Control Test (ACT) scores did not show significant correlations with the airway inflammatory parameters.²⁴ Moreover, in a study exploring the analysis of induced sputum and asthma control status, as also determined by the ACT, Shiota et al. observed, in 101 patients with chronic asthma, that the asthma control score was not associated with airway eosinophilic or neutrophilic inflammation. However, the frequency of nocturnal symptoms was associated with sputum eosinophilia and the frequency of rescue SABA use was associated with sputum neutrophilia.¹⁰

As mild asthmatics represent the most important proportion of asthmatic patients¹⁴ they are a potential target for preventive strategies against disease progression. Discrepancies between asthma control parameters have been associated with an increased risk of asthma exacerbations in moderate to severe asthmatics.^{12,13} Although we do not know yet the involvement of such discrepancies and their possible role in asthma exacerbations in mild asthmatic subjects, identifying those showing discrepancies might be a first step in optimal management of the disease.

We found a high prevalence of subjects with no or few symptoms (high clinical score) or normal expiratory flows (high physiological score), but with high sputum eosinophil percentages (low inflammatory score). In addition, when eosinophil percentages were plotted against the mean percentage of clinical and physiological scores, almost one third of subjects showed increased eosinophil percentages (>2%) even though their level of control seemed adequate according to clinical and physiological scores (>80%). In mild asthmatic subjects not taking ICS, symptom perception is often inaccurate whether it is assessed by patients or physicians.²⁵ Since asthma is often mainly managed according to this parameter, failure to adequately

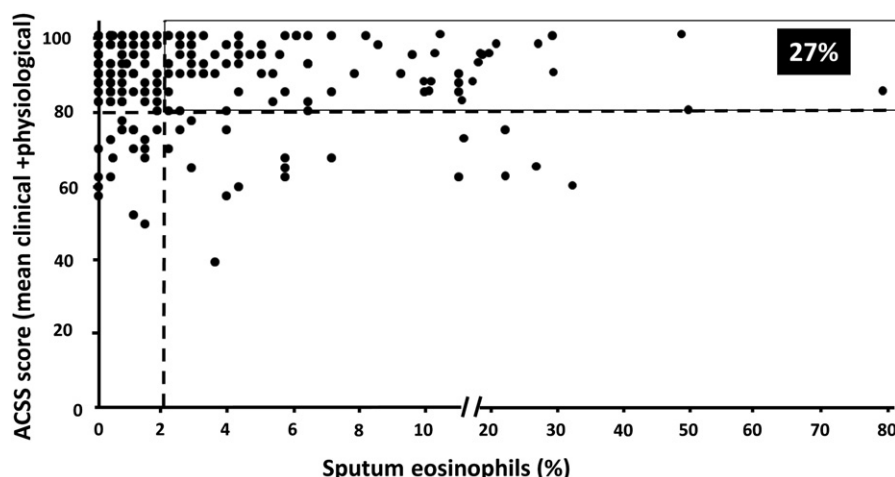


Figure 3 Percentage of sputum eosinophils in relation to the mean clinical + physiological score. Although clinical + physiological score is $\geq 80\%$, 27% of subjects still have more than 2% sputum eosinophils.

evaluate the asthmatic status may result in under-treatment for patients with a poor perception of symptoms, leading to potentially avoidable morbidity and mortality.²⁶ Studies on follow-up strategies have shown that sputum eosinophilia, exhaled nitric oxide, or airway responsiveness are more effective than symptom scores in reducing the number of exacerbations and hospital visits, particularly in moderate to severe asthma.^{27–29} In patients with mild persistent asthma, rates of severe asthma exacerbations, if untreated, are higher than expected, although the usefulness of sputum eosinophilia to guide therapy in this group of mild asthmatic subjects has not been demonstrated.

Although monitoring airway inflammation in steroid-naïve asthmatic patients does not seem to reduce asthma exacerbations, persistent eosinophilia has been associated with an accelerated decline in lung function and the development of fixed airway obstruction, possibly following airway remodelling.³⁰ It is possible that persistent untreated eosinophilia leads to progressive remodelling and chronic changes in airway function. We previously showed that patients with long standing mild steroid-naïve asthma had increased airway hyperresponsiveness compared to those with more recently diagnosed asthma, whereas they had the same degree of improvement in airway responsiveness after high-dose inhaled corticosteroids, suggesting permanent non-inflammatory changes in their airways.³¹ Furthermore, early intervention with budesonide has been shown to decrease the risk of severe asthma exacerbation and to improve asthma control in adults and children with mild persistent asthma.^{32,33} We know little about the long term effects of airway eosinophilia, as these patients do not usually have non-invasive measures of airway inflammation and are seen in primary care. Further research is therefore needed on this.

In the present study, ACSS global score was significantly higher in subjects without discrepancies and significantly lower in subjects with 3 discrepancies. Moreover, when data were analysed according to the level of asthma control, there were significantly more subjects with discrepancies in the uncontrolled group as compared to the

controlled one. This suggests that discrepancies between asthma control parameters have an impact on asthma control, but whether this represents a marker of future risk needs to be further determined in a longitudinal study, particularly in mild patients, even if those events are less frequent.

Our study had some limitations. First, the use of a percentage of predicted FEV₁ could have underestimated the level of control compared with the percentage of optimal individual FEV₁ since it does not take the component of fixed airflow obstruction in consideration. However, in our cohort of mild asthmatics, fixed airway obstruction was very uncommon; this may be more relevant in more severe patients.

The physiological measurement of the ACSS can either be FEV₁ or PEF. We chose to use the FEV₁ as it is more commonly measured in baseline assessment evaluation (either for a research project or in the clinic). Validation study of the ACSS showed good internal consistency for the physiologic section, suggesting that both FEV₁ and PEF can be used separately.¹⁸ Furthermore, comparison of the measurement properties of daily diary (using a modified diary version of the Asthma Control Questionnaire (ACQ)) vs the ACQ by Juniper et al. showed that there was no significant difference between group PEF daily measurements and single clinic FEV₁% predicted measurement.³⁴

The minimal clinically important difference of the ACSS has not been determined and discrepancy was therefore defined as a 20% difference between 2 scores. This corresponds to one subdivision of the ACSS which is based on the clinical status according to the Canadian Asthma Guidelines.¹ In addition, it is in keeping with the minimal clinically important difference in other validated asthma control tools.^{35,36}

Likewise, the cut-off value to separate controlled and uncontrolled subjects according to the ACSS global score has not been determined and an 80% score was chosen according to current control criteria. The various components corresponding to this score are based on the asthma control criteria as determined by the Asthma Consensus Report.¹

In conclusion, this study shows that discrepancies between clinical, physiological and inflammatory parameters of asthma control are frequent in mild asthmatic subjects not under ICS treatment. These discrepancies are highly prevalent in subjects with uncontrolled asthma. Although clinical or physiological scores seem adequate, underlying inflammation often persists. This stresses the need to assess the various components of asthma, as their evaluation may lead to a more appropriate asthma treatment, therefore potentially reducing asthma morbidity. The long-term effects of treating according to the various sets of parameters should be very instructive in this regard.

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Author contributions

Marie-Eve Boulay: contributed to acquisition of data, analysis and interpretation of data, and to preparation of the manuscript (literature search, figures, writing). Dr Louis-Philippe Boulet: is the guarantor of this study, contributed to its conception and design, and reviewed and approved the manuscript.

Conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this study.

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