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ORIGINAL ARTICLE

What lies beyond Asthma Control Test: suggestions for clinical practiceMarco Caminati, MD¹, Cristian Caimmi, MD², Annarita Dama, MD¹, Michele Schiappoli, MD¹, Giovanni Passalacqua, MD³, and Gianenrico Senna, MD¹¹Allergy Unit, Verona University and General Hospital, Verona, Italy, ²Rheumatology School of Specialization, University of Verona, Italy, and ³Department of Allergy and Respiratory Diseases, IRCCS San Martino Hospital, IST, University of Genoa, Italy**Abstract**

Background: Asthma Control Test (ACTTM) validity relies on Global Initiative for Asthma (GINA) definition of control. It includes neither reversibility nor inflammation assessment despite their importance as hallmark of asthma, partially unrelated to symptoms. Furthermore though rhinitis may affect the patient's perception of asthma control, its impact on ACT accuracy has not been systematically evaluated. **Objective:** To explore ACT validity according to a definition of control including: forced expiratory volume in 1 s (FEV₁) ≥ 80%, negative reversibility test, exhaled nitric oxide at a flow rate of 50 ml/s (Fe_{NO}) < 50 ppb. **Results:** 177 asthmatics referring to our Unit have been studied. ACT with cut-off score ≥ 20 showed a good positive predictive value (83.5%) but low sensitivity (47.8%), specificity (66.7%), and negative predictive value (26.5%). ROC curves analysis indicates that ACT in patients with mild intermittent rhinitis is more reliable (AUC: 0.714; *p* < 0.05) than in patients with nasal polyposis/chronic rhino-sinusitis (AUC: 0.176; *p* > 0.05). Considering asthma classification, the probability that ACT detects patients with uncontrolled asthma is significantly higher in moderate persistent asthma subgroup than in mild persistent asthma one (OR 5.464; IC 95%: 2.5–11.9; *p* < 0.05). **Conclusions:** As ACT mainly relies on patient's reported outcomes, it may not completely reflect the airways inflammation and airways obstruction. The presence and severity of rhinitis may affect ACT outcome. The awareness of the variables that could influence ACT evaluation is much more important in the primary care setting where ACT may often represent the only tool for asthma assessment.

Keywords

Asthma control, Asthma Control Test, asthma perception, exhaled nitric oxide, reversibility test, rhinitis, spirometry

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Published online xx Month xxxx**Introduction**

According to recent European epidemiological data, among treated asthmatic patients one out of two does not achieve a satisfactory control [1]. Asthma control still represents a matter of concern, as comorbidities and several other variables (patient habits, geographic and socio-economic setting, and psychological aspects) may influence both objective assessment and subjective control perception [2]. Moreover, to which extent the mechanisms of airflow limitation (reversible or not), airway inflammation, and bronchial hyper responsiveness (BHR) overlap still remains partly unclear [3]. For these reasons, asthma control assessment and follow-up of asthma control still represent a challenge in everyday practice, despite the current availability of numerous markers (functional parameters, clinical assessment tools, biomarkers of inflammation). A recent meta-analysis confirmed the validity of Asthma Control Test (ACTTM) in assessing controlled and not well-controlled asthma [4] on the basis of National Asthma Education and Prevention Programme (NAEPP) [5] and Global Initiative for Asthma (GINA) [6] guidelines. It should be noticed that

NAEPP and GINA definitions of control do include neither reversibility nor inflammation assessment, despite the increasing evidence of their importance as hallmark of asthma, partially unrelated to clinical outcomes [3,7]. Furthermore, epidemiological studies have shown that up to 90% of patients with asthma suffer from concomitant rhinitis and a common pathophysiological background has been demonstrated [8–10]. The presence of rhinitis heavily affects asthma control [8,11] and the treatment of nasal symptoms could lead to a better control of both diseases [8,9]. Some studies have provided evidence that rhinitis is associated with an incremental adverse impact on the disease-specific Quality of Life of patients with asthma [11,12]. However, to which extent rhinitis affects the patient's perception of asthma control and, consequently, ACT accuracy has not been systematically evaluated.

In the present study, we explored the ACT performance according to a definition of control including clinical and patient reported outcomes (ACT), as well as functional (FEV₁ and reversibility test) and inflammatory assessment tools. As an indirect marker of airways inflammation, the measurement of exhaled nitric oxide (Fe_{NO}) was performed. In addition we evaluated the impact of nasal comorbidity (allergic rhinitis, nasal polyps, and sinusitis) and asthma severity on ACT performance.

Materials and methods

A cross-sectional evaluation of asthma control among patients referring to our Asthma Outpatient Clinic for a follow-up visit was performed. The study received the local Institutional Review Board approval. A written informed consent was administered to each patient before the inclusion into the study. Clinical data of consenting, non-smokers adult patients who had been previously diagnosed with asthma, with or without rhinitis were considered for the analysis. Asthma diagnosis relied on positive reversibility test and/or methacholine bronchial challenge. In patients with moderate to severe persistent rhinitis, rhinoscopy had been performed in order to detect nasal polyps. Patients revealing poor adherence to asthma treatment at the time of evaluation, were excluded from the analysis. At the time of evaluation asthma control assessment included clinical (ACT), functional (FEV₁ and reversibility test), and inflammatory outcomes. All the subjects underwent baseline spirometry, followed by reversibility test (salbutamol 400 mcg). The pharmacological treatment was properly held prior to the lung function assessment. According to ATS/ERS guidelines [13], a FEV₁ increase greater than 12% and 200 mL was considered as the threshold for a positive reversibility test. FeNO was measured by chemiluminescence using a nitric oxide analyzer set at a flow rate of 50 ml/s (CLD 88 sp, ECO-Medics, Duernten, Switzerland). Patients were also asked to complete the ACT. In the presence of FEV₁ ≥ 80% of predicted, negative reversibility test, and FeNO < 50 ppb, the patient was classified as controlled. Concerning the last parameter, American Thoracic Society guidelines suggest FE_{NO} level > 50 ppb as the relevant cut-point for an inadequately controlled airway eosinophilia [7]. In accordance with published studies [4], an ACT score ≥ 20 was considered indicative for controlled or partly controlled asthma. Sensitivity, specificity, positive and negative predictive value of ACT in assessing asthma control was evaluated. 2 × 2 crosstab and Chi-square test were used to compare the proportion of true positive patients using ACT cut-off of 20 within those with uncontrolled asthma and between different asthma severity grading.

ACT performance in specific subgroups of patients (patients with mild intermittent rhinitis versus patients with rhinitis and polyposis) was also assessed by receiver operating characteristic (ROC) analysis. We considered the test as with low accuracy if AUC ≤ 0,7, medium accuracy if 0,7 < AUC ≤ 0,9, and high accuracy if 0,9 < AUC < 1 [14]. Statistical analysis was performed by means of SPSS 17.0 statistical software (SPSS Inc., Chicago, IL) [15].

Results

A total of 177 adult patients (76 females; 101 males; mean age: 36.8 years; standard deviation: 16.32) were considered for the analysis. Table 1 summarizes the main characteristics of the study population. At the time of evaluation, all the subjects were receiving pharmacological therapy for asthma. Ongoing drugs, doses and schedule corresponded with the treatment step suggested by GINA guidelines on the basis of asthma severity classification and level of control [6]. On one hand, ACT with the established cut-off score (20 points) showed a good positive predictive value (83.5%) in detecting non-controlled asthma, but displayed low sensitivity (47.8%), specificity (66.7%), and

Table 1. Main characteristics of the study population.

Total population – <i>n</i>	177
Age, years – mean (SD)	36.8 (16.3)
Sex, M/F – <i>n</i> (%)	101/76 (57/43)
FEV ₁ % – mean (SD)	86.4 (12.1)
FEV ₁ /FVC – median (IQR)	0.77 (0.10)

n, number of subjects; SD, Standard Deviation; IQR, in interquartile range; FVC, forced vital capacity.

negative predictive value (26.5%) for non-controlled asthma. On the other hand, significant differences emerged when evaluating the ACT performance in subgroups of patients with different asthma severity and rhinitis severity. As far as asthma grading is concerned, the probability that ACT detects patients with uncontrolled asthma (true positive cases) is significantly higher in moderate persistent asthma than in mild persistent asthma (OR 5.464; IC 95%: 2.5–11.9; *p* < 0.05). ROC analysis indicates a poor accuracy of AUC for both mild intermittent rhinitis (AUC: 0.714; *p* = 0.025) and rhinitis with nasal polyposis/chronic rhino-sinusitis (CRS) (AUC: 0.176; *p* > 0.05), despite in the first case it is higher suggesting that ACT was more reliable in patients with mild intermittent rhinitis (Figure 1).

Discussion

Lung function and symptoms assessment represent the core measure of asthma control. FEV₁ has a pivotal role, as it is a strong independent predictor of future risk and exacerbations [3,6]. However asthma is a multifaceted disease and the complex interplay among its components, airflow limitation, airway inflammation, and bronchial hyper responsiveness, still represents a major concern [3,16]. From a practical point of view, it implies that an accurate asthma control assessment should include both lung function and airways inflammation, together with clinical aspects and patient related outcomes [2,17]. On the contrary it may be impractical to perform a complete assessment at every asthma visit, especially if there is no access to pulmonary function labs. An easy tool that allows “at a glance” but accurate assessment of asthma control could be useful in daily clinical practice and even more in primary care setting, that often represents the first line approach of asthmatic patients. It has been demonstrated that ACT makes it quick and easy for clinical practitioners to detect if asthma is not well controlled [4]. In fact, relying on available data, it shows a clear-cut efficiency according to the GINA/NAEPP model of control [4]. It should be noticed that a marker of inflammation is not included in the GINA/NAEPP definition of asthma control, whereas airway inflammation is the hallmark of asthma [3,7] and it may not strictly correlate with symptoms and lung function outcomes [17]. In addition Asthma Control Test mainly relies on patient’s reported outcomes, which may not completely reflect the underlying airways inflammation and airways obstruction, in particular when the patient accepts his symptoms as the norm.

As far as functional parameters is concerned, recent evidences have suggested the role of bronchodilator response as a reliable measure of asthma control, as it can identify patients who have the potential for further functional improvement

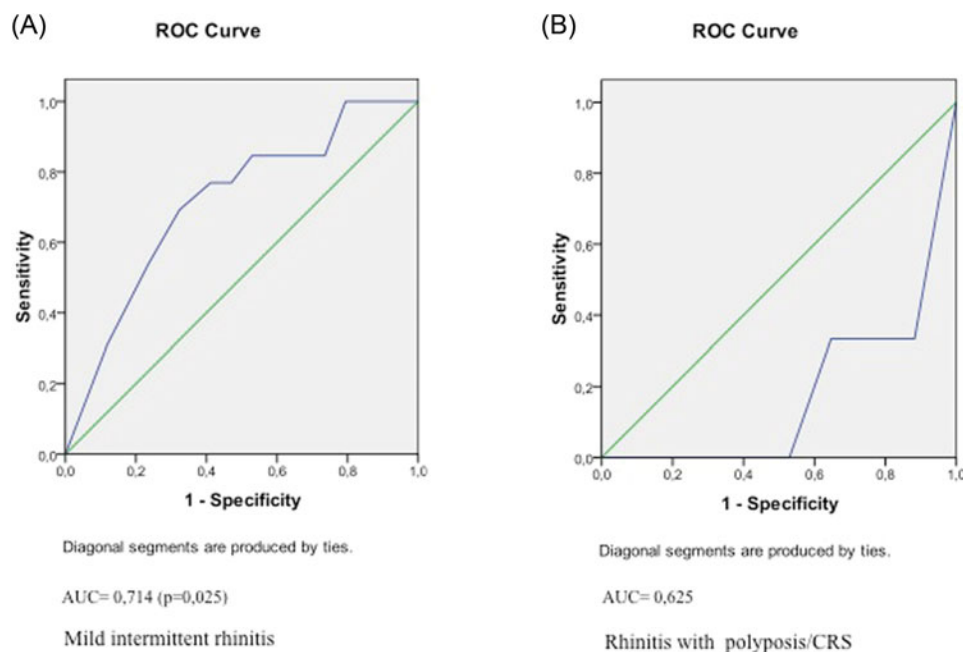


Figure 1. ROC analysis of ACT in specific subgroups of patients. (A) Patients with mild intermittent rhinitis. (B) Patients with rhinitis and polyposis/CRS. AUC, Area under the curve.

[18]. For these reasons, beside FEV_1 , which is widely considered to play a key role in asthma control, the model of control, we have proposed, relies also on airways inflammation and reversibility assessment [3,6]. In particular, we aimed at exploring whether the assessment of asthma based on ACT alone sufficiently reflects the underlying airways inflammation and airways obstruction (reversible or not). Excluding current smokers and non-adherent patients from the analysis, we ruled out two major confounders associated with poor asthma control [19], although it may certainly represent a source of bias. According to our findings, ACT performance may change depending on different definitions of asthma control, as its sensitivity and specificity drop down if functional parameters and airways inflammation assessment are included in asthma monitoring. In fact, our data suggest that, according to a definition of control based on FEV_1 , reversibility test and evaluation of airways inflammation, ACT is reliable in identifying uncontrolled asthmatic patients but its performance is not optimal in detecting controlled patients. In other words, in case of negative ACT ($ACT \geq 20$), we cannot exclude that our patient has a poorly controlled bronchial inflammation or a reversible bronchial obstruction. In addition, the probability that ACT detects patients with uncontrolled asthma is significantly higher in moderate persistent asthma than in mild persistent asthma. Thus we hypothesize that in patients with mild persistent asthma ACT may overestimate the level of asthma control. Other studies have consistently reported the discrepancy between patient asthma perception and real/objective control of the disease [20–22]. Although common practice usually ignores or underestimates such discrepancies [23], misperception of asthma has been linked to adverse asthma management outcomes, in terms of exacerbations, quality of life, and costs [24,25]. Some attempts have been made in order to preventively identify over- and under-perceivers. Many variables concur in determining patients' perceiver status, such as ethnicity, age, gender, and psychological aspects [24,25]; however, the problem has not been solved satisfactorily till now. According to

our results, it could be argued that the clinical features of the disease may also play a role, as the presence of mild and persistent asthmatic symptoms seems to lead the patients to accept his symptoms as the norm. Advances in classifying patients according to their ability to perceive their asthma status will probably help to achieve good asthma control in a larger number of patients [25]. It has been suggested that sharing with the patient a tailored asthma management plan, through the investigation of his own beliefs and personal treatment goals, may be a first step in this direction [24].

We also evaluated to which extent ACT performance is affected by the presence and severity of rhinitis, which is the most common asthma comorbidity, mainly involved in asthma control [8–10]. Coexisting rhinitis is associated with a more frequent use of asthma-related medications and health-care resources, as well with higher cost-of-illness [4,15]. Some epidemiological studies have suggested that treatment of AR is associated with a lower risk of emergency department visits and hospitalizations for asthma [8–10]. It has also been shown that rhinitis and asthma influence each other in terms of control and Health Related Quality of Life [12]. Furthermore, an incremental adverse impact on the disease-specific QOL of patients with asthma has been described [11]. To our knowledge, the potential role of rhinitis in affecting the patient's perception of asthma control and, consequently, ACT accuracy has not been systematically evaluated. Our observations suggest that ACT seems to be less reliable in patients with important nasal comorbidity (in terms of severe allergic rhinitis, nasal polyps, sinusitis), probably because of the role of nasal obstruction in asthma perception [8,11,12]. Further investigations are required to confirm this result and to determine whether appropriate treatment of rhinitis would efficiently improve ACT accuracy.

Questioning the well-known lung function and symptoms based model of asthma control assessment, as well as tearing down the validity of ACT in assessing controlled and not well-controlled asthma are out of the authors' aim. The main

objective of the present study is to underline that many variables, like rhinitis, may affect ACT outcome beyond subjective bronchial symptoms. The awareness of these variables is much more important in the primary care setting (General Practitioner, Pharmacists) where ACT may often represent the only tool for asthma control assessment.

A potential limitation of the study is the small sample size, as a larger study population would certainly increase the strength of our findings. We also evaluated our population cross-sectionally, and at the moment, we are not able to provide longitudinal data in order to repeatedly confirm our results. In addition, we are not able to provide any data about the potential correlation of an appropriate treatment of rhinitis and improvement of ACT accuracy in asthmatic patients with nasal comorbidity. However, our results highlight the potential impact of rhinitis on ACT accuracy that to our knowledge has not been systematically evaluated so far. Moreover, our findings underline the importance of an integrated approach, involving clinical aspects, assessment of comorbidities, functional parameters, and biomarkers of inflammation, in order to achieve the most accurate asthma control assessment and follow-up.

Conclusions

As Asthma Control Test mainly relies on patient's reported outcomes, it may not completely reflect the underlying airways inflammation and airways obstruction, in particular, when the patient accepts his symptoms as the norm. The presence and severity of rhinitis may affect ACT outcome, even independently of asthma control. The awareness of the variables that could influence ACT evaluation is likely to improve asthma control assessment and it is much more important in the primary care setting where ACT may often represent the only tool for asthma assessment.

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Declaration of interest

The authors report that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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