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Research Article

CONTROL IN BRONCHIAL ASTHMA DO WE ACHIEVE IT

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ABSTRACT
Asthma affects more than 5% of the world's population and indicators suggest that its prevalence continues to rise, particularly among children.[1] In spite of advanced methods in the detection and treatment of the condition, asthma remains the cause of significant morbidity and economic burden. Asthma guidelines indicate that the goal of treatment should be optimum asthma control. The terms control and severity are often used interchangeably in clinical practice and medical research but appear to be related only indirectly. It is possible for a patient to have severe asthma but good control if properly managed. On the other hand, there may be a patient with less severe asthma but poor control because of poor compliance and adherence to treatment is aimed at obtaining control. In a busy clinic practice with limited time and resources, there is need for a simple method for assessing asthma control with or without lung function testing. Various parameters are required for the assessment of the control and severity of the asthma like clinical symptoms, lung function tests, limitation of the activities, nocturnal symptoms and the need for the rescue treatment. Assessment of the control and severity are important for the better management of the disease. Here we have reviewed the various asthma control instruments that can be used for the evaluation of asthma control, so that they can be used appropriately in day-to-day assessment of these cases.

Key Words: *Bronchial Asthma, Control, Instruments, Act*

INTRODUCTION
Bronchial Asthma has been defined by GINA as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with the treatment (Bateman ED *et al.,* 2011).

Asthma is a problem worldwide, with an estimated 300 million affected individuals. Based on the application of the standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that global prevalence ranges from 1% to18% of the population of the different countries (Masoli M *et al.,* 2004). Asthma affects more than 5% of the world's population and indicators suggest that its prevalence continues to rise, particularly among children. In spite of advanced methods in the detection and treatment of the condition, asthma remains the cause of significant morbidity and economic burden (Nathan RA *et al.*, 2004). In the United States alone, asthma accounts for 2 million emergency visits a year and, with approximately 500,000 hospitalizations annually and is the third leading cause of preventable hospitalization. Asthma attacks interfere with daily activities, including attending school and going to work. Among those who reported at least one asthma attack in the previous year (Lara, 2010): Children 5-17 years of age missed 14.7 million school days due to asthma; adults 18 years of age and over who were currently employed missed 11.8 million work days due to asthma. Health care use for asthma includes outpatient visits to doctors' offices and hospital outpatient departments, visits to hospital emergency departments (EDs) and hospitalizations. The increase in the prevalence in the symptoms in Africa, Latin America and parts of the Asia indicates that the global burden of the asthma continues to rise. The WHO has estimated that 15 million DALYs are lost annually due to asthma,

representing 1% of the global disease burden. Annual worldwide deaths from asthma have been estimated to be 2.5 lakhs and mortality does not appear to correlate well with prevalence (Masoli *et al.*, 2004). The prevalence of a life-time diagnosis of bronchial asthma has also reported to be increased in all age groups in India. The incidence of new childhood bronchial asthma is also on the rise (Pal and Barua 2008).

The management of chronic diseases requires an approach to both the current manifestations and the long-term effects of disease. The focus of asthma management has shifted from treatment of an acute disease to that of long-term control and prevention of future risks. With improvements in controller therapy, it is now recognized that highly satisfactory levels of current control can be achieved and maintained for long periods. The goal of asthma management is to achieve and maintain control of the disease without side effects from the therapies used (BTS 2003). Large, multinational, community-based surveys of asthma have shown, however, that the majority of patients have an alarmingly high rate of symptoms and disruption of life from their disease, indicating that this goal is not being achieved (Rabe *et al.*, 1999). As a result, some have suggested that asthma control, as defined in guidelines, is unrealistic for the "vast majority" of patients. If this conclusion is correct, it is necessary to consider whether this shortcoming is caused by the refractory nature of the disease, limitations of current treatments, or a problem of treatment strategies, coupled with low physician and patient expectations and treatment compliance (Jones *et al.*, 2002). Surprisingly, most clinical studies assessing the efficacy of "controller" therapies in asthma do not address whether control was achieved but rather focus on improvements in individual end points obtained with fixed doses of treatment. Assessment of individual asthma end points alone, such as lung function, may overestimate the level of asthma control achieved (Bateman *et al.*, 2001). It is thus relevant to consider different strategies for maintaining control and to identify those that are most effective in reducing future risk (Figure 1).

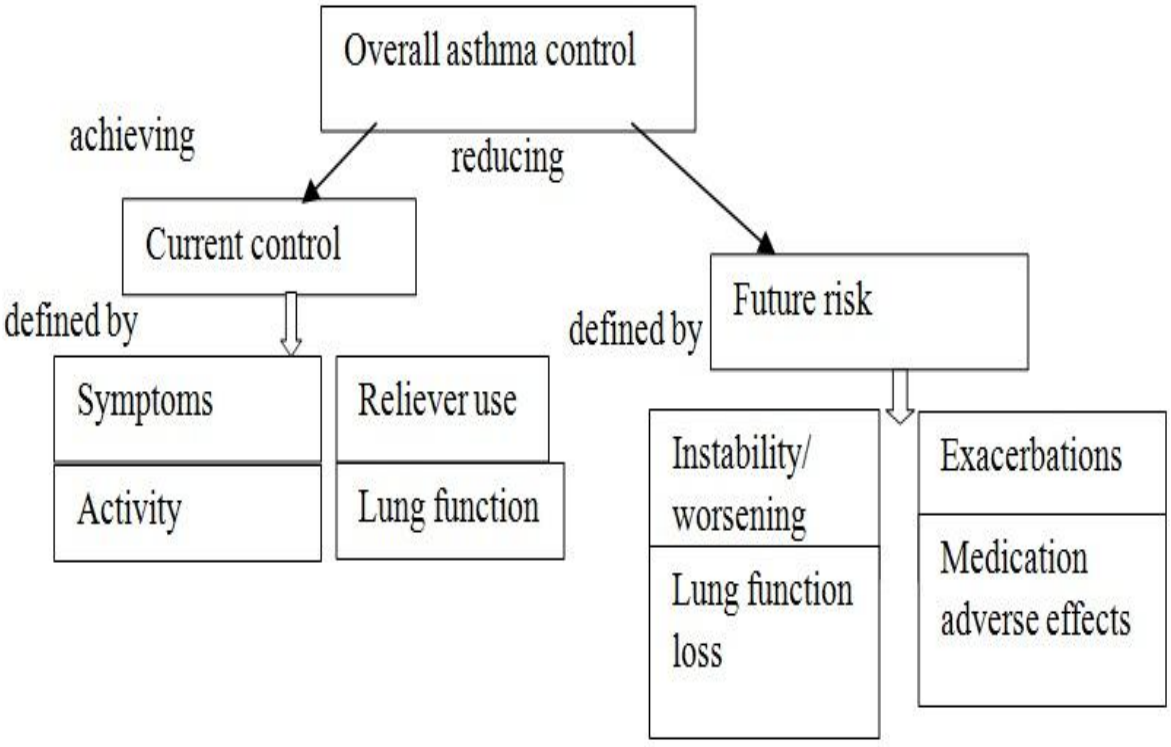

Figure 1: Principles of Asthma Control

The terms control and severity are often used interchangeably in clinical practice and medical research but appear to be related only indirectly. It is possible for a patient to have severe asthma but good control

if properly managed. On the other hand, there may be a patient with less severe asthma but poor control because of poor compliance and adherence to treatment is aimed at obtaining control. Various parameters are required for the assessment of the control and severity of the asthma like clinical symptoms, lung function tests, limitation of the activities, nocturnal symptoms and the need for the rescue treatment. Assessment of the control and severity are important for the better management of the disease. Lung function tests are also needed to assess the control and response to the treatment of the asthma.

MATERIALS AND METHODS

Asthma Control

It refers to the control of the manifestations of the disease. The aim of the treatment should be to achieve and maintain control for the prolonged periods (Beteman *et al.,* 2004). So, the assessment of the control means not only assessment of the clinical manifestation, but also the prediction of the future exacerbation. Good clinical control leads to reduced exacerbation. Global initiative for asthma control has classified asthma control into three levels (Bateman *et al.,* 2011) (Table 1).

Table 1: GINA classification according to the level of the control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/ week)	More than twice/week	Three or more features of partially controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	

The above classification has shown to correlate well with Asthma Control Test and with U.S. National Expert Panel Report 3 Guidelines (Ortiz 2009). Concepts of asthma severity and control are important in the evaluation of patients and their response to treatment but the terminology is not standardized and the terms are often used interchangeably.

Controlled asthma is characterized by (Chhabra 2008): Minimal or no symptoms during the day and at night; no asthma attacks and emergency visits to physicians or hospitals; minimal need for reliever medications; no limitations on physical activities and exercise; nearly normal lung function; and minimal or no side-effects from medication.

It must be emphasized that the state of control in asthma is not a permanent one. Asthma control is a target to be attained and maintained by constant adjustments of treatment (Chhabra, 2008). The term ‘‘severity’’ should be used to refer to the intensity of treatment required to control the patient’s asthma. This may be determined by the patient’s underlying phenotype. Measurement of patho-physiological markers may help to characterize the phenotype and provide additional information about future risk of adverse outcomes. NIH (USA) definition of asthma control is given in Table 2.

Table 2: National Institute of Health (NIH) definition of asthma control (GINA 1998)

	Goals of GINA/NIH	Totally Controlled Each Week All of	Well Controlled Each Week 2 or More of
Daytime symptoms	Minimal (ideally no)	None	<2 days with symptom score >1
Rescue _2-agonist use	Minimal (ideally no)	None	Use on < 2 days and< 4 occasions/wk
Morning PEFR	Near normal	>80% predicted every day	> 80% predicted every day

Symptom score: 1 was defined as "symptoms for one short period during the day."
Overall scale: 0 (none) – 5 (severe).

Poor control in bronchial asthma may be for because of several factors like co-existing allergic rhinitis, severe persistent disease, ongoing exposure to triggers (e.g. occupational asthma, pets, mite etc), inadequate assessment, inadequate treatment, ineffective delivery of treatment (e.g. poor inhaler technique), non-adherence to therapy, inadequate use of action plans, functional and psychological problems affecting willingness to use therapy and overreliance on complementary/ alternative treatment (Barnes *et al.,* 1996). Social, cultural and economic factors also have a role in modulating patient behaviour. In evaluating reasons for poor control, a physician must take into account all these factors.
There are many published but proprietary questionnaire instruments that might be useful in assessing asthma control. Asthma control composite score instrument is a single questionnaires (with or without physiologic measures) designed to (i) measure the multidimensional construct of asthma control (which comprises more than just asthma symptoms and frequency of SABA use) and (ii) produce a numeric score. Instruments could target adults, children, or both. Several standardized measures for assessing asthma control have been developed, such as Asthma Control Test, Asthma Control Questionnaire, Childhood – Asthma Control Test, Asthma Therapy Assessment Questionnaire and Asthma Control Scoring System (Liu *et al.,* 2007, Volmer *et al.,* 1999, Boulet *et al.,* 2002). There are 13 additional instruments for which at least 1 validation study was published in a peer-reviewed journal. These are summarized in Table 3. These measures are less used practically in clinical setting than in the research setting.
ACCI -Asthma Control and Communication Instrument; Breathmobile -Breathmobile Assessment of Asthma Control; CAN -Asthma Control in Children; cATAQ, ATAQ for Children and Adolescents; ACT –Asthma Control Test in adults and children; FSAS -Functional Severity of Asthma Scale; LASS -Lara Asthma Symptom Scale; PACT -Pediatric Asthma Control Tool; PEF -peak expiratory flow; RCP -Royal College of Physicians ''3 Questions''; SASCQ -Seattle Asthma Severity and Control Questionnaire; 30-Second - 30-Second Asthma Test. Asthma guidelines indicate that the goal of treatment should be optimum asthma control. In a busy clinic practice with limited time and resources, there is need for a simple method for assessing asthma control with or without lung function testing. The Asthma Control Questionnaire (ACQ), the Asthma Therapy Assessment Questionnaire (ATAQ) and the Asthma Control Test (ACT) have been studied, validated and used worldwide for assessment of the asthma control. With its high sensitivity, specificity and positive predictive value, asthma control test (ACT) can serve as an alternative diagnostic tool in assessing asthma severity even without an aid of a spirometer or a peak flow meter on an out-patient basis or as home based. ACT is one of such test which is a simple, economical, 5 item scored questionnaire, easy to administer (Mendoza *et al.,* 2007).*(i).The Asthma Control Questionnaire (ACQ):* ACQ was developed and validated by Juniper EF, et al **(**1999**).** It contains a total of seven items: 5 cover symptoms (nocturnal awakening, severity of morning

Table 3: Summary of the characteristics of asthma control score instruments

			Questionnaire Content						
Instrument	**No of questions**	**Recall window**	**Symptom frequency**	**Rescue therapy use**	**Sleep interference**	**Activity limitation**	**Exacerbations**	**Others**	**PFT variables**
ACCI	5	1 week	X	X	X	X	X		
ACQ	6	1 week	X	X	X	X			FEV_1
ACSS	8	1 week	X	X	X	X			FEV_1, PEFR
ACT	5	4 weeks	X	X	X	X		Self rating of control	
ATAQ	4	4 weeks		X	X	X		Self rating of control	
Breathmobile	7	4 weeks (3 items); 2 years (2 items)	X	X	X	X	X		
cACT	7	4 weeks	X	X	X	X		Self rating of control	
CAN	9	4 weeks	X		X	X			
30 second	5	1 week (3 items); 3 months (2 items)	X	X	X	X			
Asthma Quiz	6	1 week (4 items); 30 days (activity, exacerbations)	X	X	X	X	X		
cATAQ	7	4 weeks or 12 months	X	X	X	X		Parent rating of child's control	
FSAS	6	12 months	X	X	X	X			
LASS	8	4 weeks	X		X		X	Parent rating of child's control	
PACT	10	3 months	X	X	X	X	X		
RCP	3	1 week or 1 month	X		X	X			
SASCQ	5	4 weeks	X	X	X	X	X		
TRACK	5	4 weeks (3 items); 3 months (rescue medication); 12 months (exacerbations)	X	X	X	X	X		

asthma symptoms, need to limit activity, shortness of breath and wheezing), one is related to the use of beta agonists and the lung function measured as FEV1 % predicted is given a score. The experiences of the past seven days are recorded. The patients respond to each question using a 7-point scale. The items are equally weighted and the ACQ score is the mean of the seven items, ranging from 0 (well controlled) to 6 (extremely poorly controlled). The ACQ has strong measurement properties as an evaluative and a discriminative instrument and can be used in clinical trials and cross-sectional studies. While the

requirement for spirometry imposes a limitation as this may not be available especially at primary and secondary health care levels and further the patients may not be using ß2 agonist inhalers, the Juniper ACQ has been shown to perform equally well in a shortened 5-item version not requiring information on lung function and inhaler usage. The scoring may be considered cumbersome for the illiterate and the less well-educated (Chhabra 2008).

(ii).The Asthma Therapy Assessment Questionnaire (ATAQ): ATAQ is a disease management tool. The ATAQ instrument can be self administered. It has elements related to overall assessment of therapy and contains four questions related to control. The control domain highlights potential asthma management issues, such as patient self-reported asthma symptom control, missed daily activities, missed work and/or school, nocturnal awakenings and high use of quick-reliever medication. Additionally assessed for children are wheeze during the day when exercising and not exercising. For each completed survey, a score of 0 on the Control Domain indicates no control issues as measured by the instrument and the highest possible score indicates all possible control issues measured by the instrument. The Asthma Control Domain for adults ranges from 0 (no control problems) to 4 (4 control problems) and reflects the level of asthma control in the past four weeks. The Asthma Control Domain for children and adolescents ranges from 0 (no control problems) to 7 (7 control problems) and reflects asthma control in the past four weeks. While the ATAQ requires information on inhaler use, it does not require lung function testing and measures control over the previous four weeks and therefore is more vulnerable to problem of recall. Compared to ACQ and ACT, it has been used much less in published studies (Chhabra 2008).

(iii).The Asthma Control Test (ACT): ACT consists of five items: shortness of breath, patient rating of control, use of rescue medication, work/school limitations related to asthma and nocturnal asthma symptoms. Each of the five items is assessed on a 5-point scale and the response is summed to give scores ranging from 5 (poor control) to 25 (complete control). It has been shown to have reliable internal consistency, validity and responsiveness. It is easy to administer, easy to understand and can be easily applied in the clinic. The scoring system is simple and allows categorization into controlled and uncontrolled states. It does not require lung function data and thus can be applied at all levels of healthcare. However, it requires information on inhaler or nebulizer use, which would not be available in a substantial proportion of patients. The ACT evaluates the control over the previous four weeks. Problems in recall are therefore more likely with the ACT. Large scale studies are however lacking on its clinical utility (Schatz *et al.*, 2007).

ACT involves the following questionnaire (Jordan *et al.*, 2009):

1. In the past 4 weeks, how much of the time did your asthma keep you out from getting routine work done at, school or at home?

Score: 1 -All of the time; 2 -Most of the time; 3 -Some of the time; 4 -A little of the time; 5 -None of the time.

2. During the past 4 weeks, how often have you had shortness of breath?

Score: 1 -More than once a day; 2 -Once a day; 3 -3 to 6 times a week; 4 -Once or twice a week; 5 -Not at all.

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing and shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

Score: 1 -4 or more nights a week; 2 -2or 3 nights a week; 3 -Once a week; 4 -once or twice; 5 -Not at all.

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication?

Score: 1 -3 or more times per day; 2 -1 or 2 times per day; 3 -2 or 3 times per week; 4 -Once a week or less; 5 -Not at all.

5. How would you rate your asthma control during the past 4 weeks?

Score: 1 -Not controlled at all; 2 -Poorly controlled; 3 -Somewhat controlled; 4 -well controlled; 5 -Completely controlled.

The score of 19 or < 19 indicates poor control and score of > 19 indicates good control and < 15 indicates very poor control.

In a study done by Nathan *et al*., (2004), he described the development of the asthma control test (ACT), as a patient-based tool for identifying patients with poorly controlled asthma. Asthma guidelines indicate that the goal of treatment should be optimum asthma control. In a busy clinic practice with limited time and resources, there was a need for a simple method for assessing asthma control with or without lung function testing. A 22-item survey was administered to 471 patients with asthma in the offices of asthma specialists. The specialist's rating of asthma control after spirometry was also collected. Asthma specialists were blinded to the survey responses interviewed the patients and rated asthma control by asthma specialists on a five point scale ranging from not controlled at all to completely control. The patients were categorized into not controlled which was further categorized into (not controlled at all, poorly controlled or somewhat controlled) and controlled as (well controlled or completely controlled). Result of the stepwise logistic regression analysis of the study revealed that as a screening tool, the overall agreement between ACT and the specialist's rating ranged from 71% to 78% depending on the cut points used and the area under the receiver operating characteristic (ROC) curve was 0.77. A cut point of 19 demonstrated the highest area under the ROC curve. ACT was compared with the other measures like ATAQ (asthma treatment assessment questionnaire) and ACQ (asthma control questionnaire). The results reinforces the usefulness of a brief, easy to administer, patient-based index of asthma control (Nathan *et al.*, 2004).

In another study done by Xin *et al.*, (2009), the validity of the Asthma Control Test (ACT) for assessing clinical asthma control in Chinese patients in primary care settings was studied. Study involved 403 asthma patients from 15 primary care settings in China, who had completed the ACT, Asthma Control Questionnaire (ACQ) and spirometry testing. According to the rating of asthma control by asthma specialists in line with the GINA guidelines, patients were divided into uncontrolled, partly controlled and controlled groups to evaluate the reliability, empirical validity and screening accuracy of the ACT. The screening accuracy of the ACT and ACQ was analyzed comparatively and the asthma control levels rated by the patients and the specialists were also compared. The ACT score was found out to be reliable, valid and practicable for asthma control assessment in Chinese patients in the primary care setting. In another study done by Schatz *et al*., (2006), the reliability and validity of the ACT of asthmatic patients, who were not on follow up for asthma to the asthma specialist, were studied. In this study 313 patients were included. They completed the ACT and the Asthma Control Questionnaire (ACQ) at 2 physician visits (4-12 weeks apart). Pulmonary function was measured and asthma specialists rated the level of asthma control. They found that, ACT is a reliable, valid and responsive to changes in asthma control over time in patients new to the care of asthma specialists. A cutoff score of 19 or less identifies patients with poorly controlled asthma.

In another study, Mendoza *et al.*, (2007) compared the Asthma Control Test (ACT) and GINA classification, including FEV1, in assessing asthma severity and validated ACT as a screening tool for asthma severity. They included 86 patients of bronchial asthma. In this prospective cohort study involving adult asthmatic patients, the patients were classified based on their ACT scores into controlled asthma (ACT>19) and uncontrolled asthma (ACT < 19). They were then classified according to their GINA

guidelines depending upon FEV1 and peak expiratory flow rate (PEFR) values obtained by spirometry. Patients were classified as intermittent, mild persistent, moderate persistent and severe persistent. Correlation as well as measures of validity was obtained, with level of significance set at 0.05. ACT had 92.3% sensitivity and 90.5% specificity with AUC of 0.972. They concluded that with high sensitivity, specificity and positive predictive value, ACT can be used as an alternative diagnostic tool in assessing asthma severity even without an aid of a spirometer or a peak flow meter. An ACT score of at least 20 can classify patient as intermittent or controlled asthmatic while an ACT score <20 can classify the patient as in persistent or uncontrolled asthmatics.

In one recent multi-centric study by Thomas *et al.*, (2009) ACT was compared as a predictor of GINA-defined control of asthma among 2949 patients attending primary care physicians and specialists in France, Germany, Italy, Spain, UK and the USA. It was observed that an ACT score of <19 (not well-controlled asthma) correctly predicted GINA-defined partly controlled/uncontrolled asthma 94% of the time, while an ACT score of >20 predicted GINA-defined controlled asthma 51% of the time, with kappa statistic of 0.42, representing moderate agreement. In this multinational survey, the ACT was useful in predicting GINA-defined asthma control categories and was particularly useful in confirming patients whose asthma was not controlled according to the GINA classification. An ACT score of <19 correctly predicted GINA 'partly controlled' or 'uncontrolled' asthma 94% of the time overall and >93% of the time in each country. The area under the receiver operating characteristics curve for ACT score predicting GINA control was 0.84 (95% CI 0.82–0.85). An ACT score >20 predicted GINA-defined controlled asthma only in 51% of the time. This is largely because substantial numbers of patients with an ACT score >20 had GINA 'partly controlled' and a few GINA 'uncontrolled', asthma. Many of the discrepancies could be explained by either the timing of exacerbations or by variability in item content and grading between the ACT and GINA definitions. The study concluded that an ACT score <19 is useful for identifying patients with poorly controlled asthma as defined by GINA. In our study (Gaude and Patil 2012), it was observed that ACT correlated well with the criteria's as mentioned by GINA. The results also correlated with the severity of bronchial asthma as per GINA guidelines. A total of 103 patients of bronchial asthma were followed up for a total duration of 12 weeks. Asthma control was evaluated with ACT questionnaire and was correlated with GINA guidelines. It was observed that about 8% had ACT score of 5-14, 22% had score of 15-19 and 70% had score of 20-25. Majority of patients (64%) were having mild persistent asthma, 16.9% had moderate persistent and 18.8% of patients had severe persistent asthma. Out of 103 patients, 32% of patients were uncontrolled and 68% of patients were controlled according to ACT score. Out of controlled patients, 89.2% were having mild persistent and 5.4% of patients were in moderate and severe persistent category respectively. The sensitivity of the ACT test was as 85.7%, specificity was 96.8%, positive predictive value was 94.7% and negative predictive value was 90.9%. The p was calculated as < 0.05 each time. This showed that both the test was having agreement between each other. Thus, ACT can be used as a surrogate test in assessing asthma control and the severity, especially in places where spirometry and peak flow meter are not available. ACT is a simple, inexpensive tool that can be used especially in our country where financial resources are limited, disabling our patients to do the standard diagnostic test such as the spirometry. Further studies are needed to evaluate the benefits of the ACT over time in a real world setting. The ACT is easily and rapidly completed by patients and can serve as a useful tool in the clinic to assess asthma control, ideally in conjunction with a complete medical history and lung function testing.

Exhaled Nitric Oxide: Measurement of exhaled Nitric Oxide (FENO) is a quantitative measure of airway nitric oxide (NO), a gaseous mediator produced endogenously in cells by NO synthases. Exhaled NO is commonly regarded as an indirect marker for airway inflammation. NO is generally accepted as a marker of airway inflammation. Individuals who have asthma have been shown to exhale high levels of NO, which decreased in response to inhaled corticosteroids. The test is noninvasive, easy to perform in children and patients with severe airflow obstruction and has no risk to patients. FENO greater than 47 ppb suggests eosinophilic inflammation and corticosteroid-responsive asthma, but persistently high FENO in a patient with ongoing asthma symptoms may occur despite adequate anti-inflammatory treatment (Pijnenburg *et al.,* 2005). A clinically important decrease of FENO is defined as a change of 20% for values over 50 ppb (or a change of 10 ppb for values lower than 50 ppb) that occurs 2 to 6 weeks after initiation of corticosteroid therapy (Szefler *et al.,* 2002). Even though there is direct correlation between FENO and eosinophilic airway inflammation, the sensitivity and specificity of FENO for sputum eosinophila are only approximately 70% and the relationship between FENO and eosinophilia may occur independently of asthma control (Brightling *et al.,* 2003). But it can be used as one surrogate marker of asthma control. The cost of purchasing and maintaining equipment may be prohibitive for some studies. As less expensive and portable handheld devices are developed, this may be less of a limitation; however, these devices need further evaluation as clinical research tools (Szefler *et al.,* 2012).

RESULTS AND CONCLUSION

In conclusion, asthma control is important in day-to-day management of the bronchial asthma patients for the proper control of the inflammation and symptoms. Unless this is achieved, the lung functions will not return to as near normal as possible. ACT is one instrument which can be used in everyday practice to know the asthma control and this is a rapid tool which does not require spirometry and can be easily employed at the community level practice.

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