

WHAT IS MEANT BY CONTROL OF CHILDHOOD ASTHMA?

Asthma can now be controlled, but assessing control may not be that easy.

ROBIN J GREEN

Professor and Head: Department of Paediatrics and Child Health, University of Pretoria

Robin Green is Director of Paediatric Pulmonology and Intensive Care Services at Steve Biko Academic Hospital.

MAX KLEIN

Professor Emeritus, University of Cape Town and Honorary Professor, University of Pretoria

Max Klein was Head of the Division of Paediatric Pulmonology at Red Cross War Memorial Children's Hospital for many years, also serving as Director of the Paediatric Intensive Care Unit.

Correspondence to: robin.green@up.ac.za

Asthma is a problem throughout the world and its prevalence appears to be increasing. Its cause is unknown and therefore prevention is difficult. With the highly effective medications that are now available it is possible, in principle, to control asthma, enabling almost every asthmatic to achieve a life free of symptoms and exacerbations with normal lung function.¹ Many clinicians have found that it can be very difficult to corroborate that control has in fact been achieved.

Current national and international guidelines advise that at each visit a patient's asthma be categorised as uncontrolled, partially controlled, or controlled and that they be managed accordingly.² Categorisation of control relies heavily on patient-reported symptoms. But because asthmatics are known frequently to underestimate the severity of their condition,³ objective ways of corroborating patient histories and the physician's assessments are sought.

With the highly effective medications that are now available it is possible, in principle, to control asthma, enabling almost every asthmatic to achieve a life free of symptoms and exacerbations with normal lung function.

Asthma is characterised by variability, and each of the measurement modalities has known limitations. So it is perhaps not surprising that measuring a moving target like asthma with imperfect tools should be imperfect. But the degree of inconsistency between the various measures does not appear to have been recognised, with the result that the problem has been largely ignored and no solutions are offered.

Asthma control assessment has been put forward as a more valuable measure than assessment of asthma severity. However, even proponents of this system have noted weaknesses in this method.⁴

Asthma severity assessment has limited reproducibility among both generalists and specialists. It has not been validated clinically, especially in children, and asthma is a dynamic disease where severity changes over time. Although assessments of control may be desirable, they too fail to incorporate patient-specific goals of treatment and therefore the desired level of control is seldom reached.

Control assessments are not based on good clinical trials of the different assessment modalities. A close scrutiny of the literature, in respect of asthma control assessment in children, reveals many inconsistencies and recommendations based on, at best, weak scientific principles. In fact the GINA Guideline has made the point that 'A simplified scheme for recognizing controlled, partly controlled, and uncontrolled asthma in a given week is provided; ... This is a working scheme based on

current opinion and has not been validated.'² Unfortunately, however, this 'schema' for control has been taken up by many other guideline groups and written into fact. Such facts do not exist though, and every attempt should be made to test the validity of these claims. The latest NAEPP Asthma Guideline provides another solution for assessing control based on 'impairment' and 'risk'. Unfortunately this solution is not referenced and no judgement of its value can be made.¹

While the spirit of aiming for control is admirable, it may not be easy to assess with current measurements. This may be very important in claims that all asthmatics should be 'controlled'. This may in fact be more difficult to do and measure than is acknowledged, at least in children.

Let us review each method for assessing asthma control in turn.

Patient history and symptom recall

Since the mid-1990s information on a disassociation between asthma symptoms and patient perceptions of these symptoms has been known. An early study revealed that a proportion of asthmatic patients significantly underestimate disease severity and thereby may be at risk of increased mortality or morbidity.³ This information was highlighted succinctly in 2000 in the AIRE Study, where it was demonstrated that patient perception of asthma control did not match symptom severity – approximately 50% of patients reporting severe persistent symptoms also considered their asthma to be completely or well controlled.⁵ The paediatric data from this study were even more compelling, where the level of control was overestimated and 61% of parents of children with severe persistent asthma considered the asthma to be well controlled.⁶

Many reasons for this phenomenon have been defined in research settings and include poor patient knowledge of disease management,⁷ poor communication by physicians⁸ and undeclared nocturnal symptoms.⁹ In addition it is probable that failure to screen for adequate asthma control by physicians with continual passive reinforcement of sub-optimal control through doctor disinterest has fuelled this problem.

Asthma is characterised by variability, and each of the measurement modalities has known limitations.

We suggest that adequate consultation time spent with asthmatic patients uncovering both subjective and objective evidence of control and in addition focusing on issues that promote asthma control will serve to minimise this important problem.

The paediatric Childhood Asthma Control Test (cACT) aims to overcome some of the problems in history taking. It is now promoted as a validated measure and is widely used in clinical settings and

research studies. However, in the validation study itself the questionnaire only achieved a specificity of 74% and sensitivity of 68% against a specialist's rating of asthma control.¹⁰ In addition, studies utilising this test have failed to match test scores to other objective measures of asthma control.¹¹

While the spirit of aiming for control is admirable, it may not be easy to assess with current measurements.

Issues such as intra-patient differences over time are not adequately addressed. Questionnaire studies have the limitation of patient recall and require patients to be able to recognise asthma symptom severity, which many patients aren't able to do.

In a large study conducted in various countries, a standard questionnaire was administered to 7 786 adults and, through a proxy, to 3 153 children with asthma. Objective and subjective patient perception of asthma control and severity were assessed, including access to medical care, health care use, missed work or school, and medication use. The use of anti-inflammatory preventive medication, even in patients with severe persistent asthma, was low, ranging from 26% in Western Europe to 9% in Japan, as was the use of objective lung function testing. The correlation between self-perceived severity of asthma and objective assessment of severity on the basis of GINA criteria was consistently poor in all areas.¹²

Doctor assessments

There is clear evidence that the most significantly flawed area of assessment of asthma control is that involving doctor-directed assessment, either by questioning or examination. In fact there is a paucity of studies addressing this area. Most studies have to use proxy measures for elucidating the level of doctor assessments. Such measures include measures of medication use and lung function testing that has been performed. However, this is completely unsatisfactory as the real issue at stake is to know how doctors compare with objective tests in assessing asthma control. There is evidence that a standardised questionnaire by a doctor is better than conventional history taking. However, once again the gold standard by which these are measured is the stumbling block. In one study the authors use patient symptoms and peak expiratory flow rate (PEFR) over time to assess control.¹³

The authors of the GOAL Study¹⁴ devised the Asthma Control Questionnaire (ACQ). Using the ACQ to identify patients whose asthma is well controlled (i.e. minimal risk of being uncontrolled), a judicious cut-point is 0.75 (NPV=0.85). This means that

Table I. Gold standard criteria for defining patients with 'well-controlled' asthma¹⁴

<p>2 or more per week of:</p> <ul style="list-style-type: none"> • More than 2 days with symptom score >1 • Rescue β_2-agonist use on ≤ 2 days and ≤ 4 occasions • PEF $\geq 80\%$ predicted every day <p>And all of the following criteria:</p> <ul style="list-style-type: none"> • No night-time awakenings • No exacerbations (need for oral corticosteroids) • No emergency department visits or hospitalisations • No treatment-related adverse events enforcing a change in asthma therapy

if a patient has an ACQ score of 0.75 or less, there is an 85% chance that his/her asthma is well controlled (Table I).

If one is using the ACQ to identify patients whose asthma is not well controlled (i.e. minimal risk of being well controlled), a judicious cut-point is 1.50 (PPV=0.88). This means that if a patient has an ACQ score of 1.50 or greater, there is an 88% chance that his/her asthma is not well controlled. If the 6 point ACQ (without lung function) is used one gets a NPV=0.81 at 0.75 and PPV=0.87 at 1.5.

There is clear evidence that the most significantly flawed area of assessment of asthma control is that involving doctor-directed assessment, either by questioning or examination.

Most parents underestimated the severity of their children's asthma and reported good control with their global assessment. Parents frequently reported good control even when the children had daily asthma symptoms. Paediatricians should ask about specific asthma symptoms during patient encounters because a global question about asthma control will probably result in underestimations of asthma severity and control.¹⁵

Doctor assessment in assessing asthma control is an imprecise science and despite recommendations in asthma guidelines there is no clear evidence for which questions or combination of questions actually determine control.

Spirometry

Although objective lung function testing is always suggested as important in assessing asthma control, spirometry does not correlate well with asthma symptom history. Wildhaber *et al.* found no significant correlation between FEV₁ ($r=-0.22$, $p=0.34$), MEF 25 - 75 ($r=-0.27$, $p=0.06$) and patient symptoms.¹⁶ In the ACQ study mentioned above¹⁴ the PPV and NPV

for assessment using the various cut points do not change much if you leave out FEV₁. This suggests that spirometry is not much help in determining control.

Variability in lung function testing has been noted. 'Within-occasion variability' is noted more significantly for PEFR (coefficient of variability = 7%) and mid-expiratory flow rates (coefficient of variability = 11%) than for FEV₁ (coefficient of variability = 4%). 'Between-occasion variability' is however very significant for all spirometry measures. For FEV₁ this variance is 73%. This variance is attributed to the biological variability of airway resistance in asthma.¹⁷

Spirometry is a snap-shot of lung function, usually measured when airway inflammation is at its lowest in the mid-morning, and it has been suggested that change in spirometry or measures of airway hyper-responsiveness (AHR) are better predictors of asthma control. In a study by Guyatt *et al.* there was no correlation between FEV₁ and mean PEFR and an assessment of quality of life (Paediatric Asthma Quality of Life Questionnaire) but this study revealed that a closer correlation was seen in children 11 - 17 years old, suggesting that control assessment is most difficult in young children.¹⁸

It also appears that not all spirometric measures are equally useful. An important study of 4 - 18-year-old children has suggested that it might be possible to identify children for whom the PEFR is likely to give false-negative results. Thirty per cent of patients with a normal PEFR value had an abnormal FEV₁ or FEF_{25-75%}. As air trapping increased, the ability of a normal PEFR to predict normal FEV₁ and FEF_{25-75%} readings fell from 83% to 53%. The negative predictive value was significantly lower for patients with RV/TLC ratio >30 compared with patients with RV/TLC <30. Furthermore, poor predictive ability of PEFR is obtained when values 80% of predicted for age are considered normal.¹⁹

Nitric oxide (F_ENO)

F_ENO measurement by means of the NIOX MINO has been validated for successful use in children. The reliability coefficient for comparison of the larger NIOX and portable NIOX MINO was 0.97 when comparing the individual mean values of the two

devices. The mean of the intra-subject $F_{E}NO$ difference was 1.2 (-3.3, 0.8) ppb using the NIOX MINO.²⁰

What is less obvious from the literature is what $F_{E}NO$ measurements mean when compared with standard other measures of asthma control. There is clear evidence that $F_{E}NO$ is correlated with AHR and steroid response in asthmatic children.²¹ A study by Jones *et al.* has revealed that $F_{E}NO >15$ ppb has an 88% positive predictive value of loss of asthma control but the negative predictive value is low (25%). That means a low $F_{E}NO$ does not exclude the possibility of loss of asthma control.²² This fact seems to have been overlooked in determining the value of $F_{E}NO$ in routine screening for asthma control.

Although objective lung function testing is always suggested as important in assessing asthma control, spirometry does not correlate well with asthma symptom history.

Many previous studies of $F_{E}NO$ have documented poor correlation between $F_{E}NO$ and lung function testing.^{23,24} Studies of severe childhood asthma have hinted at a potential problem with use of $F_{E}NO$, namely that at least two subgroups of patients are identified: one with persistently raised nitro-oxide (NO) levels despite treatment with oral prednisolone, indicating ongoing steroid-insensitive inflammation, and another with normal levels of NO. Both subgroups included patients with persistent symptoms, which suggests that different patterns of difficult asthma in children exist.²⁵

It must be remembered then that while using $F_{E}NO$ to measure asthma control it may measure only some aspects of asthma and may not give a full story.

Conclusion

Failure to find agreement in many studies between asthma symptoms, spirometry and biomarkers may simply reflect the basic error in our understanding of asthma. This error stems from trying to lump a vast array of distinct disease phenotypes into a single

clinical entity. Asthma is a complex syndrome. Some correlations may exist between various parameters used in clinical assessment, but no single parameter can describe and assess all individuals. This is because we know that some asthmatic children are atopic, some not. Some children have overt nasal disease, some not. Some asthmatic children have significant airway inflammation while in some airway hyper-responsiveness drives symptoms. In some children poor symptom control has been ongoing for some time, while in some children drug therapy has been timeous and adequate. Multiple phenotypes may preclude finding one definitive test for control. Assessment of multiple parameters including physiological measures, symptoms, and activity limitation are necessary to categorise asthma clinical status accurately.²⁶

It may well transpire that until we define the individual asthmatic phenotype perfectly all 'lump sum' testing for control assessment will fail us. Hidden in these many studies may in fact be perfect correlation of individual markers for distinct asthma types. Until the day when we have a perfect test for assessing control we suggest that multiple individual patient and test-related factors need to be borne in mind when a test is used and a combination of tests may be more useful than one test.

However, our overriding concern is that measures for assessing asthma control may not tell us whether or not a patient is well controlled or at risk of asthma exacerbations and in addition, by using an imprecise schema for adjudicating 'control' we may be placing a burden on both patients and pharmaceuticals that may end up not matching up. In fact 'matching up' may be completely unobtainable in the real world.

It should also be obvious from this review that classification of the severity of asthma is an unhelpful concept. Since assessment of control is so difficult to make, classification of asthma severity is not useful.

With the recent publication of new asthma guidelines there is a certain degree of optimism that attempting to correct the deficiencies of asthma management of the past may finally be possible. Return to normal life is now the clear goal of asthma treatment. However, what is still unclear is how measurement of asthma control is most effectively performed. Each of the

conventional tools for doing this have both their proponents and detractors and evidence for and against reliability and validity. Despite the logical assumption that a doctor (especially one experienced with asthmatics) may have an inherent ability to judge asthma control, studies have shown that clinician assessment of asthma control without a specific objective tool performs poorly; hence the need to find a more sensitive marker of control.

There is no easy answer to the measurement of asthma control.

This review demonstrates that there is no easy answer to the measurement of asthma control. It seems likely that asthma control requires more than one end-point in assessment and no test (including $F_{E}NO$) is a 'dipsticks' test of asthma control. Individual patient and test-related factors need to be borne in mind when a test is used and a combination of tests is more useful than one test.

References available at www.cmej.org.za

IN A NUTSHELL

- Since asthma is such a common problem efforts are mounting to provide normal quality of life for sufferers.
- Recent asthma guidelines from around the world have suggested that control of asthma is both possible and desirable.
- However, the idea of asthma control places a burden of responsibility on doctors and parents that may or may not be easy to achieve.
- Many strategies of assessing asthma control have been suggested. Guidelines favour patient questionnaires and scores.
- However, spirometry and biomarkers have also been suggested.
- This review highlights the many weaknesses uncovered in each assessment parameter.
- The final message should be that control of asthma should still be aimed for.
- The sum of multiple measures of control is most important and where even one parameter stands alone in suggesting poor control this test should carry overriding consideration and the patient's asthma should be reviewed with an aim to improving control.