Traditional and New Approaches to Asthma Monitoring

Christine A Sorkness PharmD

Once the diagnosis of asthma is established, monitoring must be implemented to achieve asthma control. Because of the variability of asthma, monitoring is a long-term commitment to effectively adjust treatment and assure that therapy goals are met. This paper reviews the definition of asthma control, including the dimensions of impairment and risk, and the 2007 National Asthma Education and Prevention Program's Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma, recommendations for periodic assessment and monitoring of effective control. New approaches to asthma monitoring, such as airway hyperresponsiveness, sputum eosinophils, exhaled nitric oxide, and pharmacogenetic measurements, will be critiqued. *Key words: asthma prevention, asthma control, asthma therapy, respiratory function tests, biological markers, questionnaires, genetic polymorphism*. [Respir Care 2008;53(5):593–599.

Introduction

Once an accurate asthma diagnosis is made and the asthma severity established to initiate therapy, the clinician must establish an effective approach to monitoring asthma in the individual patient. Treatment is focused on reducing asthma symptoms, functional limitations, impairment in quality of life, and the risk of adverse events associated with the disease or its management. Because of the variability of asthma, monitoring is a long-term commitment to adjust treatment to maintain control. This review will define asthma control, describe traditional strategies to monitor asthma control, and discuss new approaches to asthma monitoring.

Christine A Sorkness PharmD is affiliated with the School of Pharmacy, University of Wisconsin, Madison, Wisconsin.

Dr Sorkness has been a consultant and speaker for GlaxoSmithKline. She reports no other conflicts of interest in the content of this paper.

Dr Sorkness presented a version of this paper at the 41st RESPIRATORY CARE Journal Conference, "Meeting the Challenges of Asthma," held September 28–30, 2007, in Scottsdale, Arizona.

Correspondence: Christine A Sorkness PharmD, School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison WI 53705. E-mail: sorkness@wisc.edu.

Asthma Control and Goals of Therapy

Asthma control is the degree to which the manifestations of asthma are minimized and the goals of therapy are met. Poorly controlled asthma is associated with substantial disease burden,[1] greater health care utilization,[2] and lower quality of life.[3] The 2007 National Asthma Education and Prevention Program Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma (2007 NAEPP guidelines),[4] closely link the functions of asthma assessment and monitoring to the concepts of severity, control, and responsiveness. Severity is the intrinsic intensity of the disease process. It is most easily and directly measured in a patient who is not receiving long-term control therapy. Severity can also be measured once asthma control is achieved, by the step of care (ie, the amount of medication) required to maintain control. Control is defined as the degree to which the manifestations of asthma are minimized by therapeutic intervention and the goals of therapy are met. Responsiveness is the ease with which asthma control is achieved by therapy.

Asthma severity and control include the domains of current impairment and future risk.[4] Impairment is the frequency and intensity of symptoms and functional limitations the patient is currently experiencing or has recently experienced. Risk is the likelihood of asthma exacerbation, progressive decline in lung function (or, in children, reduced lung growth), or adverse effects from medication. The latter distinction, which is from the 2007 NAEPP guidelines, emphasizes the multifaceted nature of asthma, its variation over time, and the importance of considering separately asthma's current, ongoing effects on the current quality of life and functional capacity, and the future risk of adverse events. The 2 domains may respond differently to asthma treatment, and both require ongoing monitoring. Patients may have adequate control of symptoms and minimal functional impairment yet still be at substantial risk of exacerbation (often severe). The level of asthma control is the degree to which impairment and risk are minimized by therapeutic intervention (Table 1).[4]

Table 1. Goals of Asthma Therapy to Achieve Control

Reduce Impairment
Prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, in the night, or after exertion)
Require infrequent use ($\leq$ 2 d/wk) of short-acting β agonists for quick relief of symptoms
Maintain (near) "normal" pulmonary function
Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
Meet patient's and family's expectations of and satisfaction with asthma care
Reduce Risk
Prevent asthma exacerbations, emergency department visits, and hospitalizations
Prevent progressive loss of lung function. In children, prevent reduced lung growth
Provide optimal pharmacotherapy with minimal or no adverse effects

Table 2. Measures for Periodic Assessment* of Asthma Control

Signs and symptoms of asthma
Pulmonary function
Spirometry
Peak flow monitoring
Quality of life/functional status
History of asthma exacerbations
Adherence to pharmacotherapy and potential adverse effects
Patient-provider communication and patient satisfaction
Minimally invasive markers and pharmacogenetics (requires further evaluation)

*Recommended at 1–6-month intervals

Measurements for Periodic Assessment and Monitoring of Asthma Control

Periodic assessment and ongoing monitoring can determine whether the goals of asthma therapy are being achieved and asthma is controlled. The level of control (well controlled, not well controlled, or poorly controlled) will direct clinical actions as to maintenance or adjustment of therapy.

The 2007 NAEPP guidelines outline specific measures for periodic assessment and monitoring of control (Table 2)[4] and recommend that the frequency of monitoring visits is a matter of clinical judgment. In general, patients who have intermittent or mild persistent asthma that has been under control for at least 3 months should be evaluated by a clinician about every 6 months. Patients who have uncontrolled and/or severe persistent asthma and those who need additional supervision to help them follow their treatment plan need to be seen more frequently.[4]

Monitoring Signs and Symptoms of Asthma

Every patient with asthma should be taught to recognize symptom patterns that indicate inadequate asthma control. These symptoms should be assessed at each health care visit, with appropriate questions. At least 4 key symptom expressions should be included: (1) daytime asthma symptoms (including wheezing, cough, chest tightness, or shortness of breath), (2) nocturnal awakening from asthma symptoms, (3) frequency of use of short-acting β agonists for relief of symptoms, and (4) inability or difficulty performing normal activities (including exercise) because of asthma

Table 3. 2007 NAEPP Asthma Guidelines Recommended Frequencies for Spirometry

At the time of initial assessment
After treatment is initiated and symptoms and peak flow measurements have stabilized, to document attainment of (near) "normal" airway function
During a period of progressive or prolonged loss of asthma control
At least every 1–2 y to assess the maintenance of airway function Spirometry may be indicated more often than every 1–2 y, depending on the clinical severity and response to management.

NAEPP = National Asthma Education and Prevention Program
(From Reference 4)

Table 4. Additional 2007 NAEPP Asthma Guidelines Suggestions for FEV_1 Measurements

As a periodic (eg, yearly) check of the accuracy of the peak flow meter for patients who monitor peak flow
When more precision is desired in measuring lung function (eg, to assess drug response)
When peak flow measurement results are unreliable (eg, in some very young or elderly patients; if the patient has neuromuscular, orthopedic, or cognitive problems; or if technical artifact is suspected)

NAEPP = National Asthma Education and Prevention Program
(From Reference 4)

Table 5. 2007 NAEPP Asthma Guidelines Peak Flow Monitoring Recommendations

If PEF monitoring is performed, the written asthma action plan should use the patient's personal best measurement as the reference value.
Consider long-term daily PEF monitoring for patients who:
Have moderate or severe persistent asthma
Have a history of severe exacerbations
Poorly perceive airflow obstruction and worsening asthma
Prefer this method
Long-term daily PEF monitoring can help to:
Detect early changes in disease states that require treatment
Evaluate responses to therapy changes
Afford a quantitative impairment measure
PEF monitoring during exacerbations will help determine the severity of exacerbations and guide therapy decisions in the home, school, clinician's office, or emergency department.
Consider home PEF monitoring during asthma exacerbations in patients who have:
A history of severe exacerbations
Moderate or severe persistent asthma
Difficulty perceiving signs of worsening asthma

PEF = peak expiratory flow
NAEPP = National Asthma Education and Prevention Program
(From Reference 4)

symptoms. This detailed symptoms history should be based on a short (2–4-week) recall period. Symptom assessment for periods longer than 4 weeks should reflect more global symptom assessment, such as inquiring whether the patient's asthma has been better or worse since the last clinician visit, and query as to particular problems encountered during specific seasons or events.[4]

Monitoring Pulmonary Function: Spirometry

The 2007 NAEPP guidelines[4] recommend that it is important to assess pulmonary function periodically (Table 3), in addition to symptom assessment. Spirometry and peak flow measurements have been traditionally used. Low forced expiratory volume in the first second (FEV_1) is associated with a higher risk of severe asthma exacerbation.[5] Regular monitoring of pulmonary function is particularly important for (1) patients who do not perceive their symptoms until airflow obstruction is severe (referred to as "poor perceivers"), (2) individuals who have had a near-fatal asthma episode,[6] and (3) older patients, who are more likely to have poor perception.[7] These pulmonary function measures should be followed over the patient's lifetime to detect the potential for decline of lung function and rate of decline longitudinally.

Large-scale global asthma-control trials,[8] as well as traditional clinical drug efficacy studies, have successfully included spirometry. Lung function declines as adults age; adults with asthma have greater decline, on average, than those without asthma and who do not smoke. In children, lung function increases with age until it peaks at age 20. Children with asthma may have reduced lung growth, compared to children without asthma. Measurement of lung growth patterns over time have relied on post-bronchodilator FEV_1.[9] Reduced lung growth may reflect a progressive worsening of asthma control that warrants more aggressive treatment. Table 4 lists additional suggestions on FEV_1 monitoring from the 2007 NAEPP guidelines.[4]

Monitoring Pulmonary Function: Peak Expiratory Flow

The 2007 NAEPP guidelines stress that peak flow measurements are best used for ongoing asthma monitoring, not diagnosis.[4] Peak flow measurements, obtained with a handheld mechanical or electronic device, provide simple, quantitative, and reproducible assessments of the presence and severity of airflow obstruction. Because peak flow measurements are effort-dependent and technique-dependent, patients need initial instruction and demonstration, as well as ongoing reviews of technique. Table 5 lists the 2007 NAEPP guidelines recommendations for peak flow monitoring.[4]

Table 6. Instruments and Questions to Assess Generic and Asthma-Specific Quality of Life and Functional Status

Generic Quality-of-Life Instruments
Medical Outcomes Study 36-question short form[12]
Medical Outcomes Study 12-question short form[13]
Asthma-Specific Quality-of-Life Instruments
Mini Asthma Quality of Life Questionnaire[14]
Asthma Quality of Life Questionnaire[15]
Integrated Therapeutics Group Asthma Short Form[16]
Asthma Quality of Life for Children[17]
Questions for Patients
Since your last visit, how many days has your asthma caused you:
To miss work or school?
To reduce your activities?
To change your activity because of your child's asthma?
Since your last visit, have you had any unscheduled or emergency department visits or hospital stays?

The 2007 NAEPP guidelines indicate that studies have not clearly shown that action plans based on peak flow monitoring improve outcomes more than action plans based on symptom monitoring; either type of monitoring plan can be effective if taught and followed correctly.[4] Studies in both children[10] and older adults[11] with asthma support the 2007 NAEPP guidelines conclusions.

Monitoring Quality of Life and Functional Status

Periodic assessment of quality of life and related loss of physical function are recommended by the 2007 NAEPP guidelines,[4] in 4 domains: (1) work or school missed due to asthma, (2) reduction in usual activities at home, work, school, or recreational events, (3) sleep disturbances due to asthma, and (4) change in caregivers' activities due to a child's asthma. Generic and asthma-specific validated instruments (primarily suited for research studies) or simple questions (applicable for clinical settings) are recommended for ongoing monitoring (Table 6).[4,12–17]

In general, the impact of asthma is greater on the physical functioning component of quality of life than on mental functioning.[18,19] However, when loss of physical functioning in valued life activities occurs, a higher correlation with quality of life is found among adults who have asthma. Valued life activities are those that individuals find most meaningful or pleasurable, and loss of these is significantly associated with an increase in clinical asthma severity, the patient's perception of asthma severity, and decrease in general physical functioning.[20] Similarly, among adolescents who have asthma, quality of life correlates with shortness of breath during exercise.[21] In contrast, in younger children (mean age 9.3 ± 2.2 y) quality of life is more associated with the level of anxiety.[22]

The predictors of quality of life among people who have asthma may be related to the level of asthma severity. Lung function, however, is not an independent predictor of quality of life at any level of severity, whereas shortness of breath predicts quality of life at all levels of asthma severity.[23] Asthma symptom frequency is the most important determinant of the subjective experience of asthma and perception of quality of life.[24] Another important reason to monitor health-related quality of life is that it predicts health care utilization among patients who have asthma,[25] and for this reason may be a useful method of identifying patients who are at risk of exacerbation.

Table 7. Validated Asthma-Control Questionnaires

2007 NAEPP Asthma Guidelines Control Category	Questionnaire Score		
	ATAQ	ACQ	ACT
Well-controlled	0	≤0.75*	≥20
Not well-controlled	1–2	≥1.5	16–19
Very poorly controlled	3–4	NA	≤15

*ACQ scores of 0.76–1.4 are indeterminate regarding well-controlled asthma.
NAEPP = National Asthma Education and Prevention Program
ATAQ = Asthma Therapy Assessment Questionnaire[26]
ACQ = Asthma Control Questionnaire[27]
ACT = Asthma Control Test[28]
NA = data not available
(From Reference 4)

Asthma-Control Questionnaires to Monitor Asthma

Validated instruments for assessing and monitoring asthma control have been developed. Table 7 describes the 3 tools included in the 2007 NAEPP guidelines recommendations,[4,26-28] and the relationship of the scores to the asthma-control categories. These tools assess the impairment, not the risk domain.

Monitoring Asthma Control With Minimally Invasive Measurements

The 2007 NAEPP guidelines recommend some minimally invasive measurements (eg, airway hyperresponsiveness) for monitoring asthma control, but suggest that certain other measurements (sputum eosinophils and exhaled nitric oxide) require further evaluation to determine if they will be useful for routine clinical management.[4] Tools for using biomarkers to monitor asthma must be tested in both children and adults, because the disease presentation in these age groups may differ.

Airway Hyperresponsiveness

Airway responsiveness is measured by serially delivering doses of a provocative agent, such as methacholine, and calculating the provocative concentration that causes a

Table 8. Interpretation of Exhaled Nitric Oxide Values in Patients with Airway Disease

	Exhaled Nitric Oxide Concentration (ppb)*			
	Low	Normal	Intermediate	High
Adult	< 5	5–25	25–50	> 50 (or increase ≥ 60%)
Child <12 y	< 5	5–20	20–35	> 35 (or increase ≥ 60%)
Eosinophilic inflammation	Unlikely	Unlikely	Present, but mild	Substantial
Diagnosis factors	Consider: • Smoker In children also consider: • Cystic fibrosis • Primary ciliary dyskinesia • Chronic lung disease of prematurity	If symptomatic: • Review alternative diagnoses • If treated with inhaled corticosteroids, implies adherence; may consider dose-reduction	Interpretation based on clinical presentation If symptomatic and on inhaled corticosteroids, consider: • Infection • Allergen exposure • Add-on therapy or increase inhaled corticosteroid dose • Check adherence If asymptomatic and stable, no change in inhaled corticosteroid dose	Consider: • Atopic asthma if the history is appropriate • A positive response to a trial of inhaled corticosteroids or oral steroid is likely If symptomatic and on inhaled corticosteroids, consider: • Allergen exposure • Imminent exacerbation or relapse, depending on patient history • Steroid resistance • Poor adherence or inhaler technique • Inadequate inhaled corticosteroid dose If asymptomatic and stable on inhaled corticosteroids, no change in inhaled corticosteroid dose

*At 50 mL/s
(Adapted from Reference 35.)

20% decrease in FEV_1 (PC_{20}).[29] These bronchial-challenge procedures are time-consuming, expensive, and not yet definitive in their role in asthma management. Deykin et al[30] found PC_{20} unsuccessful in predicting exacerbations in patients weaned from inhaled corticosteroids. Sont et al[31] reported improved clinical control (reduced rate of mild exacerbations) and improved histopathologic outcomes (greater reduction in thickness of the subepithelial reticular layer) in a group of asthmatics whose inhaled corticosteroid dose was adjusted with a strategy guided by airway hyperresponsiveness. The airway-hyperresponsiveness-guided strategy resulted in a higher inhaled corticosteroid dose regimen than in the reference-strategy group.

Sputum Eosinophils

The intensity of eosinophilic inflammation can be measured by analyzing the cells and mediators in the sputum induced by inhalation of hypertonic saline.[32] This method has drawbacks, including difficulties in standardizing the process of inducing, preparing, and analyzing the samples, and the dedicated time of trained personnel required to do these tasks. However, there have been successes with this monitoring technique. Deykin et al[30] reported that sputum eosinophil count predicted responsiveness to starting and withdrawing inhaled corticosteroids. Green et al[33] found that adjusting inhaled corticosteroids to control sputum eosinophilia (as opposed to controlling symptoms, rescue inhaler use, nocturnal awakenings, and pulmonary function) significantly reduced both the cumulative dose of inhaled corticosteroid and the rate of asthma exacerbations.

Exhaled Nitric Oxide Concentration

An increase in exhaled nitric oxide concentration is reported to reflect the intensity of eosinophilic inflammation of the bronchial mucosa. Exhaled nitric oxide measurements are easy to perform and well-accepted by patients. These measurements distinguish individuals who do and do not have asthma, have documented repeatability, and have been correlated with other markers of asthma severity.[34] Guides to the interpretation of exhaled nitric oxide values in patients with airway disease have been published (Table 8).[35]

Studies have shown exhaled nitric oxide's ability to predict responsiveness to starting or withdrawing inhaled corticosteroids.[36] Smith et al[37] found that when inhaled corticosteroids were adjusted to control exhaled nitric oxide (as opposed to controlling the standard measures of asthma control), the cumulative dose of inhaled corticosteroid was reduced, with no worsening of the frequency of asthma exacerbations. However, there were no significant differences in other markers of asthma control, use of oral prednisone, or sputum eosinophil level. The Asthma Control Evaluation trial[38] will assess whether an exhaled-nitric-oxide-enhanced guideline-based approach to asthma management improves asthma outcomes, as compared to a guideline-based approach alone in inner-city adolescents and young adults with persistent asthma.

Pharmacogenetics in Managing Asthma

Pharmacogenetics is the study of the genetic causes of between-person variation in drug treatment response. Three genes have been identified that influence response to specific asthma medications (ALOX5 for leukotriene modifiers, β_2AR for short-acting β agonists, and CRHR1 for inhaled corticosteroids), but the 2007 NAEPP guidelines committee does not believe that the functional variants responsible for these associations have been definitively identified.[4] The existing studies conflict and are inconclusive. None of the reported genotypes, in isolation, clearly explains a sufficient amount of variation in the drug-response phenotype to warrant routine clinical testing at this time. Clinical trials are underway.

Summary

Ongoing monitoring of asthma control is essential to reduce impairment and risk. The 2007 NAEPP guidelines recommend periodic assessments of asthma signs and symptoms, pulmonary function, quality of life, and functional status. Validated asthma-control questionnaires are also now recommended. Minimally invasive tests and measurements, such as airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide, require more evaluation to determine if they will be useful for routine clinical management.

REFERENCES

1. Fuhlbrigge AL, Adams RJ, Guilbert TW, Grant E, Lozano P, Janson SL, et al. The burden of asthma in the United States: level and distribution are dependent on interpretation of the National Asthma Education and Prevention Program guidelines. Am J Respir Crit Care Med 2002;166(9):1044–1049.
2. Vollmer WM, Markson LE, O'Connor E, Frazier EA, Berger M, Buist AS. Association of asthma control with health care utilization: a prospective evaluation. Am J Respir Crit Care Med 2002;165(2):195–199.
3. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, et al. Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis. J Allergy Clin Immunol 2005;115(5):1049–1055.
4. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda MD: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. *Accessed February 12, 2008*.
5. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann RJ, Dockery DW, et al. FEV_1 is associated with risk of asthma attacks in a pediatric population. J Allergy Clin Immunol 2001;107(1):61–67.
6. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994;330(19):1329–1334.
7. Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. Thorax 1992;47(6):410–413.
8. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL Study. Am J Respir Crit Care Med 2004;170(8):836–844.
9. Covar RA, Spahn JD, Murphy JR, Szefler SJ; Childhood Asthma Management Program Research Group. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med 2004;170(3):234–241.
10. Wensley D, and Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. Am J Respir Crit Care Med 2004;170(6):606–612.
11. Buist AS, Vollmer WM, Wilson SR, Frazier EA, Hayward AD. A randomized clinical trial of peak flow versus symptom monitoring in older adults with asthma. Am J Respir Crit Care Med 2006;174(10):1077–1087.
12. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE. Jr, et al. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. Am J Respir Crit Care Med 1994;149(2 Pt 1):371–375.
13. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220–233.
14. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14(1):32–38.
15. Katz PP, Eisner MD, Henke J, Shiboski S, Yelin EH, Blanc PD. The Marks Asthma Quality of Life Questionnaire: further validation and examination of responsiveness to change. J Clin Epidemiol 1999;52(7):667–675. *Erratum in: J Clin Epidemiol. 2001;54(1):106–107.*
16. Bayliss MS, Espindle DM, Buchner D, Blaiss MS, Ware JE. A new tool for monitoring asthma outcomes: the ITG Asthma Short Form. Qual Life Res 2000;9(4):451–466.
17. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996;5(1):35–46.
18. Adams RJ, Wilson DH, Taylor AW, Daly A, Tursan d'Espaignet E, Dal Grande E, et al. Coexistent chronic conditions and asthma quality of life: a population-based study. Chest 2006;129(2):285–291.
19. Graham DM, Blaiss MS, Bayliss MS, Espindle DM, Ware JE Jr. Impact of changes in asthma severity on health-related quality of life in pediatric and adult asthma patients: results from the asthma outcomes monitoring system. Allergy Asthma Proc 2000;21(3):151–158.
20. Katz PP, Yelin EH, Eisner MD, Earnest G, Blanc PD. Performance of valued life activities reflected asthma-specific quality of life more than general physical function. J Clin Epidemiol 2004;57(3):259–267.

21. Hallstrand TS, Curtis JR, Aitken ML, Sullivan SD. Quality of life in adolescents with mild asthma. Pediatr Pulmonol 2003;36(6):536–543.
22. Annett RD, Bender BG, Lapidus J, Duhamel TR, Lincoln A. Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? J Pediatr 2001;139(6):854–861.
23. Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM. NHBLI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. Am J Respir Crit Care Med 2001;163(4):924–929.
24. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, et al. Relationship of validated psychometric tools to subsequent medical utilization for asthma. J Allergy Clin Immunol 2005;115(3):564–570.
25. Eisner MD, Ackerson LM, Chi F, Kalkbrenner A, Buchner D, Mendoza G, et al. Health-related quality of life and future health care utilization for asthma. Ann Allergy Asthma Immunol 2002;89(1):46–55.
26. Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, et al. Association of asthma control with health care utilization and quality of life. Am J Respir Crit Care Med 1999;160(5 Pt 1):1647–1652.
27. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902–907.
28. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113(1):59–65.
29. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing–1999. Am J Respir Crit Care Med 2000;161(1):309–329.
30. Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, et al. Sputism eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. J Allergy Clin Immunol 2005;115(4):720–727.
31. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. AMPUL Study Group. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. Am J Respir Care Med 1999;159(4 Pt 1):1043–1051.
32. Djukanović R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. Eur Respir J Suppl 2002;37:1S–2S.
33. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002;360(9347):1715–1721.
34. Sorkness CA, Lemanske RF Jr., Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Childhood Asthma Research and Education Network. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007;119(1):64–72. *Erratum in: J Allergy Clin Immunol. 200;120(2):285.*
35. Taylor DR, Pijnenburg MW, Smith AD, DeJongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. Thorax 2006;61(9):817–827.
36. Taylor DR. Nitric oxide as a clinical guide for asthma management (review). J Allergy Clin Immunol 2006;117(2):259–262.
37. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352(21):2163–2173.
38. Inner-City Asthma Consortium. Evaluation of an asthma treatment strategy based on exhaled nitric oxide measurements in adolescents: the Asthma Control and Evaluation (ACE) trial. http://clinicaltrials.gov. *Accessed March 20, 2008.*

Discussion

Colice: Where are we in estimating the risk of an exacerbation? What tools do we have? I'd love to see that included in the guidelines. I think there was a section in the Australian guidelines.[1] Does reversibility on inhaled steroids mean a higher risk of exacerbation? What about exhaled nitric oxide or sputum eosinophils?

1. Asthma management handbook 1998. National Asthma Counsel Australia. http://www.nationalasthma.org.au. *Accessed March 10, 2008.*

Sorkness: We did a pediatric asthma trial in which we purposefully did not use bronchodilator reversibility as an entry criterion, because we did not want to bias the study to the bronchodilator responders, because one of the study arms included a long-acting ß agonist.[1] So to qualify for this trial the patient had to have sufficient asthma symptoms, with either a positive PC_{20} or bronchodilator reversibility, but both were collected. Though these kids had an average FEV_1 of 94% of predicted at baseline, their average bronchodilator reversibility was 10%. They had a history of mild asthma. Then we compared bronchodilator reversibility at the beginning of the trial and at the end of the trial (just at 2 points in time). It was very interesting that the children who seemed to do better by predefined outcomes during the trial had less bronchodilator reversibility.

That doesn't surprise me. It agrees with my bias that the pre-bronchodilator FEV_1 was raised because of the inhaled steroids. Were they adherent to therapy prior? The shift in bronchodilator reversibility predicted a positive outcome. That study supports the European and Australian suggestion that if you lose your bronchodilator reversibility over time, you achieve better overall asthma control.

1. Inner-City Asthma Consortium. Evaluation of an asthma treatment strategy based on exhaled nitric oxide measurements in adolescents: the Asthma Control and Evaluation (ACE) trial. http://clinicaltrials.gov. *Accessed March 20, 2008.*

Myers: I'm intrigued by the exhaled nitric oxide data. I think we're struggling with how to use it in the clinical setting. Taking into consideration that 25 to 30 parts per billion exhaled nitric oxide is considered the normal range and above that is believed to indicate inflammation, most of the published studies have looked at a raw value in parts per billion and tried to correlate it to FEV_1. We look at percent change. In the patient with asthma whose exhaled nitric oxide is 160 parts per billion but it drops down to 80—

that may be as good as it gets; that's a 50% change. We've focused a lot of these clinical trials on the raw nitric oxide value, but do you think that maybe the percentchange is the better way to look at this?

Sorkness: I think you're right, Tim. Remember the kids in the ACE study had pretty high exhaled nitric oxide to begin with; they're atopic. During the course of this trial, these exhaled nitric oxide concentrations didn't go below 20 parts per billion; they stayed in that range. But what does that data mean? Is there a percentage of kids in whom the exhaled nitric oxide is just not going to drop, because of overwhelming inflammation? Should we be looking at the changes over time? Is there a subgroup that's particularly sensitive?

Children with high body mass index and high allergic sensitization might be a group with non-constitutive exhaled nitric oxide. I think this is a very small part of what we're going to learn about this. The "cut points" for exhaled nitric oxide are appealing to help predict how people respond to therapy, but I think we do need to focus on the changes in exhaled nitric oxide and other observations that help us. Carolyn, do you have any additions?

Kercsmar: No. You hit the nail on the head. The other thing particularly about this population is that they were extremely atopic and had extremely high degrees of allergic sensitization, along with elevated IgE [immunoglobin E] and very high exhaled nitric oxide values.

Where and how cut points get set is sometimes arbitrary. I don't think we know if we should just be trying to improve to the patient's best baseline or to achieve a preset cut point. This population may be unique, but reflective of a very important, large population of asthmatics that we need to address, regarding what is the best way to monitor severity and control. I think we may get some ideas from this trial.

Sorkness: I think one of the analogies might be what we call "near-normal FEV_1." Are we going to get to "near-normal exhaled nitric oxide"? I don't know.

Donohue: The exhaled nitric oxide approach seemed to help in obese people, in determining adherence, and also you mentioned a high IgE. One of the hardest things for us to assess clinically is the efficacy of the monoclonal antibodies to IgE used in the NAEPP treatment paradigm[1] in step 5. We can't use the IgE level because it's forming complexes and it goes up to 3.5 or 4 times. Have you studied the exhaled nitric oxide approach for looking at the utility of omalizumab?

1. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda MD: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. *Accessed March 10, 2008.*

Sorkness: The ICATA [Inner-City Anti-IgE Therapy for Asthma] trial, which is a clinical trial of omalizumab,[1] will address that question. We have, by the way, been criticized for the relevance of the ACE [Asthma Control and Evaluation] study:[2] why didn't we instead conduct a study of exhaled-nitric-oxide-driven therapy alone versus guideline-driven therapy? The reason was that it would not have been an ethical study in a vulnerable population, and clinicians want to know if measuring exhaled nitric oxide on top of good usual care makes a difference. We're going to do the same thing in the ICATA trial that we did in the ACE trial: take good usual care and determine whether adding anti-IgE therapy on top of that makes a long-term difference in an inner city population with asthma.

1. ICATA asthma mechanistic study. http://clinicaltrials.gov. *Accessed March 20, 2008.*
2. Inner-City Asthma Consortium. Evaluation of an asthma treatment strategy based on exhaled nitric oxide measurements in adolescents: the Asthma Control and Evaluation (ACE) trial. http://clinicaltrials.gov. *Accessed March 20, 2008.*

Diette: Do you think exhaled nitric oxide measurement can be used for monitoring adherence to therapy? Because exhaled nitric oxide can be a lot like wheeze, or exacerbations, or any other asthma outcome, in that-adherence is a mediator of that outcome. With an elevated measure (no matter where that is), you have to wonder if the patient was fully adherent but couldn't be any better controlled or, instead, is it a marker of poor adherence? And either way you still don't know what to do next; do you emphasize adherence or titrate the drug?

Sorkness: Your point is well taken. Exhaled nitric oxide *might* help assess adherence. Some of my colleagues have incorporated exhaled nitric oxide equipment in their clinics, but I think they're struggling with how to best use it. I've heard of clinical "*n*-of-1" studies. That is, they identify a patient who definitely has very poorly controlled asthma and his exhaled nitric oxide is very high, they put him on therapy and he's doing dynamite, and his exhaled nitric oxide level is basically tooting along, but then he comes back and he's lost asthma control and his exhaled nitric oxide is very very high. They use this information to raise the adherence issue, saying "Your asthma is pretty bad today and there's a lot of potential reasons for this. Is there some possibility that you have been doing so well that you stopped using your inhaled steroid?" If the patient asks, "How do you know that?" the answer is, "We've got this measurement here." It's just like any other tool a seasoned clinician uses. I don't know yet if it's cost-effective. We need a lot more information be-

fore we can say how strong a tool it can be for adherence monitoring.

Rubin:* Diurnal variability in pulmonary function has been associated with poor control and exacerbation risk. Is exhaled nitric oxide sufficiently sensitive to evaluate diurnal variability in that measurement as a measure of inadequate control of inflammation?

Sorkness: I know those studies have been done. My impression is that the Swedish investigators, who have done some great epidemiologic studies,[1] found a little bit of difference between day and night. It doesn't seem to be substantive. This suggests a lack of parallel with peak-flow variability. There doesn't seem to be a huge exhaled nitric oxide difference during the day. I think other variables are more important, such as smoking and ingestion of certain foods. I don't think extensive data are available from exhaled nitric oxide home monitoring, with a lot of repeat measures.

1. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Torén K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest 2006;130(5):1319–1325.

*Bruce K Rubin MD MEngr MBA FAARC, Department of Pediatrics, Wake Forest University School of Medicine, Winston Salem, North Carolina.

Rubin: The corollary would be, if there was such a difference, it would be important in these studies to note the time of day it was measured.

Sorkness: Right. Agreed.

Stoloff:* There were 2 papers in a recent issue of *American Journal of Respiratory and Critical Care Medicine*. One of them found no benefit from exhaled nitric oxide for managing asthma and predicting exacerbations in adults.[1] The other paper[2] was on the variables that determine exhaled nitric oxide, and it was astounding how many there were, including male/female, smoker/nonsmoker, weight, age, et cetera.

Those of us in primary care specialties are very concerned when a piece of equipment comes out that is not inexpensive and of unknown value. That's why in the final report,[3] when we looked at the work of the various committees, and at that data when combined with this, we had important concerns as to exactly—if you can't decide in the laboratory with well-funded studies where you put it in your menu of helping define control or evaluating patients—what are we going to do with patients in the real world?

*Stuart W Stoloff MD, Department of Family and Community Medicine, University of Nevada, Reno, Nevada, representing Monaghan/Trudell Medical.

1. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med 2007;176(3):231–237.
2. Travers J, Marsh S, Aldington S, Williams M, Shirtcliffe P, Pritchard A, et al. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. Am J Respir Crit Care Med 2007; 176(3):238–242.
3. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda MD: National Institutes of Health, National Asthma Education and Prevention Program; 2007. NIH Publication No. 08-4051. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. *Accessed March 10, 2008.*

Sorkness: Suggesting that it's not ready for prime time?

Stoloff: Not ready for prime time.

Enright: Do you have a sense of any unpublished data on the month-to-month reproducibility of exhaled nitric oxide in patients with stable asthma and the minimum clinically important difference?

Sorkness: I don't. Anna-Carin Olin, in Sweden, is doing an ongoing study with thousands of people, and looking at reproducibility.[1]

1. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Torén K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest 2006;130(5): 1319–1325.