

Severity, control, and responsiveness in asthma

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Guidelines for asthma management have proposed that initial treatment should be based on assessment of asthma severity. The treatments proposed for different degrees of asthma severity are essentially estimates of the intensity of treatment needed to achieve asthma control. Responsiveness to treatment is heterogeneous, however, even among asthmatic patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing asthma control and adjusting treatment accordingly. Application of a guidelines-based approach to asthma management thus requires general agreement on what is meant by *severity, control, and responsiveness* and requires further an awareness of asthma as causing symptoms and functional impairment in the present and also as causing risk of adverse events in the future. (*J Allergy Clin Immunol* 2006;117:544-8.)

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TERMS AND DEFINITIONS

The *severity* of a disease is usually considered a function of the inherent intensity of the disease process. The term *control* is used to describe the degree to which the signs, symptoms, and laboratory abnormalities of a disease are minimized by therapeutic intervention. The *responsiveness* of a disease refers to the degree to which it shows a positive or favorable reaction to an intervention. Responsiveness thus refers to the ease with which adequate control is achieved by therapy. In general, the more severe the disease, the less responsive it is to treatment. Some have even proposed that asthma severity can be defined by the minimal amount of medication required to achieve control.¹⁻³ All of these features of a disease—its severity, its control, and its responsiveness to treatment—are more

easily assessed when the disease's effect is only to interfere with current comfort or function because these can usually be appraised through direct focused questions. When the disease does not impair current comfort or function but presents a risk of future morbidity or death, assessment of severity, control, and responsiveness is more difficult. They must be assessed through some measure, preferably quantitative, in which deviation from normal has been shown through clinical studies to be related to the risk of adverse events in the future. When a disease causes discomfort and impairment in the present and also increases the risk of morbidity or death in the future, as asthma does, it cannot be assumed that a treatment that reduces current discomfort-impairment necessarily reduces risks in the future.

DIMENSIONS OF CONTROL

Current impairment-discomfort

An example of a disorder in which the most important effect is discomfort-impairment in the present is pain, which can be equally severe whether from a progressive disorder likely to result in death (eg, bone metastases from lung or breast cancer) or from a disorder in which its importance is often limited to the pain itself (eg, trigeminal neuralgia). In assessing the severity of pain, definitive information is ultimately reported by the patient to the provider. The answer to the question, "Is my pain severe?" is, in the end, "You tell me." We do not leave it at that, of course, because patients have different thresholds for reporting pain, and we have learned to ask questions as prompts, such as whether pain is causing weeping or interferes with the ability to concentrate or sleep.⁴ The assessment of pain control is identical. The same questions are asked to determine whether pain has responded to treatment, and treatment is adjusted until the pain is tolerable or absent.

Assessment of the current symptoms and functional impairment caused by asthma is analogous, in that the final authority is the patient. Again, this does not mean that patients should be counted on to spontaneously volunteer the information. Random-dialing telephone surveys of asthmatic patients around the world have consistently shown that when asked specifically about daytime and nighttime symptoms, inability to exercise or pursue sports, and loss of time from work or school, asthma is causing important suffering and impairment, even in patients who rate the overall control of their disease as satisfactory and their treatment as the best that can be provided.^{5,6} That this could be determined by simply asking asthmatic patients focused questions in a brief telephone interview not only

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means that the information is obtainable but also that the providers caring for them might not know which questions to ask or do not have the time to ask them. Simple and easily administered questionnaires have now been developed and validated to enable rapid assessment of current asthma control, including the Asthma Control Test,⁷ the Asthma Control Questionnaire,⁸ the Asthma Therapy Evaluation Questionnaire control index,⁹ and others. Along these lines, spirometry might be thought of as a prompt. Asthma specialists commonly report finding a severely reduced FEV₁ in some patients who report few or no symptoms. After a trial of treatment, some of these patients return to report dramatic improvement in symptoms and functional capacity, acknowledging their previous impairment only in retrospect. These patients might say they simply had not known how impaired they were. Others say they had mistakenly attributed their symptoms and limitations to aging, obesity, or lack of fitness, which they did not regard as conditions worth reporting to a physician.

Future risk

An example of a disease that causes few or no symptoms in the present but is known to present a risk of morbidity or death in the future is hypertension. Hypertension is usually asymptomatic when detected but is associated with a heightened risk of stroke and congestive heart failure in the future.¹⁰ Assessment of the severity of this disorder is reported by the provider to the patient. The question, "Is my hypertension severe?," requires an answer based on knowledge of the risks of adverse outcomes associated with different degrees of blood pressure increase. For hypertension, the objective markers of severity and control have been well validated.¹¹ Not only have increases of systolic and diastolic blood pressure been shown to be related to the risk of stroke and heart failure, but treatment-induced reductions in blood pressure (ie, control) have been shown to reduce those risks.¹² For asthma, unfortunately, we know of no single marker of disease that allows a direct estimate of the risk of future morbidity and of responsiveness to treatment. Further reflection on hypertension also points out the distinction between treatments that reduce symptoms and those that reduce the risks of future morbidity or death. For a patient with hypertensive headache, an analgesic might relieve headache but will do nothing to alter the risk of future stroke. This points out an important feature of responsiveness. A good response in one domain (eg, current symptoms) does not necessarily imply a good response in another (eg, future risk). The facts of inhaled β -agonist treatment illustrate this for asthma. No treatment is more effective for acute relief of symptoms, but frequent use of a β -agonist is associated with a heightened risk of severe asthmatic attacks in the future.^{13,14}

VARIATION OVER TIME

The challenge to the assessment and monitoring of asthma derives from asthma causing both discomfort-

impairment in the present and an increase in risk of morbidity-death in the future. It is helpful to recognize the distinction between these 2 domains explicitly. It is additionally necessary to recognize that the severity of asthma is not fixed. The symptoms and airway inflammation of asthma vary over time,¹⁵ so that control needs to be assessed on an ongoing basis. The purpose of the initial assessment of asthma severity is to estimate the intensity of treatment likely to be needed to improve symptoms and function and to reduce risk (ie, to obtain control). The purpose of monitoring thereafter is to determine whether the treatment is indeed sufficient or whether additional therapy is necessary to achieve or maintain control.¹⁶

Variations over time in asthma symptoms, sleep interruption, and functional impairment limit the value of most asthma control questionnaires because they generally focus on the previous 4 weeks or so as the period of most accurate recall. It has been shown that assessment of short-term symptom burden underestimates the long-term functional burden of asthma, and therefore questions should also be asked about the overall or global effect of the disease.⁶ Perhaps the long-term functional effect of the disease would be best captured by serial application of a standard questionnaire over time.

Assessing the risk of future impairment is more difficult, especially when the different forms of risk are considered. The most obvious and probably most important future impairment is from asthma exacerbations. These account for asthma death and for distress, loss of time at work or school, and much of the cost of asthma care.¹⁷ Another future risk of asthma that is attracting increasing attention is progressive loss of pulmonary function. The existence of this risk has been established by the findings that severe and irreversible airflow obstruction is often found in lifetime nonsmokers whose only identifiable risk factor is asthma,¹⁸ that asthmatic nonsmokers have an accelerated rate of loss of pulmonary function,¹⁹ and that bronchial biopsy specimens from asthmatic patients show remodeling of all the tissue elements of the airway wall.²⁰ The final future risk to be considered here is progression of asthma severity, requiring more potent, intensive, expensive, or toxic therapies to obtain or maintain control.

Of these future risks, the one we are currently best able to assess is that of asthma exacerbations. The strongest predictor of this risk is probably the history of previous exacerbations requiring emergency department or hospital care, especially in the past year.²¹⁻²³ Severe symptoms, nocturnal awakenings, and frequent use of rescue therapy, which would all be captured in assessment of asthma severity-control in the present, also indicate an increase in the risk of exacerbations in the future.²⁴ This is not true, however, for all patients. Some with few symptoms for long periods are prone to sudden and severe attacks,²⁵⁻²⁷ and some treatments, like monotherapy with a long-acting inhaled β -agonist, control current symptoms but do not reduce the risk of exacerbations.²⁸ This accounts for the interest in identifying possible markers of risk of exacerbations and is an additional reason for performing

spirometry. Reductions in FEV₁ have been shown to be related to the risk of exacerbations over the following year.^{2,29} Measurement of nonspecific bronchial reactivity, as to methacholine or adenosine, has also been proposed as a way of estimating the risk of exacerbations provoked by irritants and other triggers encountered in the environment.³⁰ One study has indeed shown that adjustment of corticosteroid therapy to reduce bronchial reactivity was more effective than standard, guidelines-based therapy in reducing the rate of exacerbations.³¹

Measuring some marker of airway inflammation is an appealing approach to assessing future risk.³²⁻³⁴ Lymphocytic and eosinophilic inflammation is regarded as fundamental to asthma's pathogenesis, and the intensity of inflammation is thought to be at least a partial determinant of asthma severity.³⁵ This accounts for the interest in noninvasive markers of inflammation, such as eosinophil numbers in induced sputum³⁶ and the fractional concentration of nitric oxide in exhaled air.³⁷ It is certainly true that regular use of an inhaled corticosteroid, an anti-inflammatory treatment, reduces the rate of exacerbations in patients with moderate or severe asthma.³⁸ It is also true that in comparison with treatment based on the then-current guidelines, adjusting the dose of inhaled corticosteroid based on numbers of sputum eosinophils³⁹ or on levels of exhaled nitric oxide⁴⁰ can reduce the frequency of exacerbations or the dose of inhaled corticosteroid required. But the evidence that inhaled corticosteroid treatment also prevents progressive loss of pulmonary function is equivocal. A 5-year study of asthmatic children found regular treatment with inhaled budesonide to be significantly better than placebo in preventing exacerbations but no different in its effects on postbronchodilator FEV₁.⁴¹ Finally, no prospective study has yet shown that early treatment with an inhaled corticosteroid or any other controller medication prevents the progression of asthma to a more severe form.

RESPONSIVENESS

These considerations of the dimensions of asthma severity and control bring us to discussion of what is meant by *responsiveness*. As stated above, responsiveness refers to the ease with which control is achieved with a therapeutic intervention, but it is clear that severity and control need to be considered in both the domains of current symptomatic impairment and of future risk. It is also clear that responsiveness in one domain does not necessarily imply responsiveness in the other.⁴² As noted previously, substitution of a long-acting β -agonist for an inhaled corticosteroid maintains control of symptoms and function but does not maintain the reduction in risk of exacerbations.²⁸

COMPOSITE MEASURE OF ASSESSMENT

Because asthma severity and control must be assessed in the domains of current symptoms–impairment and future

risk, and because the elements of severity and control within the 2 domains do not correlate perfectly with each other, a composite measure seems necessary.^{2,33,43} The approach to assessment and monitoring has thus evolved to assess the different components discretely. Questionnaires include specific questions about daytime symptoms, nocturnal awakenings, exercise tolerance, time lost from work or school, and health care use. The markers assessed include measures of airflow obstruction (peak flow, FEV₁, and the average rate of exhalation of the middle 50% of forced vital capacity),^{29,44,45} of bronchial reactivity (as to methacholine, exercise, adenosine, or mannitol),⁴⁶ and of systemic or bronchial inflammation (blood or sputum eosinophil numbers or fractional concentration of nitric oxide in exhaled air).^{34,40,47} These tools for assessing asthma severity and control are promising, but the elements necessary for the composite measure to be precise, efficient, comprehensive, and easily applied are not yet completely defined. Once a composite measure is developed, its application after initiating or changing therapy will permit easy and complete assessment of responsiveness to treatment.

BENEFITS OF ACHIEVING CONTROL

The value of the repeated application of a simple tool for assessing asthma control was illustrated by a large international study of whether guideline-defined asthma control could be achieved.⁴⁸ Asthma control was defined in terms of the goals of therapy, as listed in the 1997 National Asthma Education and Prevention Program Guidelines⁴⁹ and the 1998 Global Initiative for Asthma guidelines.⁵⁰ *Total control* was defined by the absence of symptoms, nocturnal awakenings, and need for rescue medications; by a peak flow of greater than 80% of predicted value; and by the absence of exacerbations, emergency department visits, and adverse events for 7 of 8 consecutive weeks. All patients had uncontrolled asthma on study entry. They were treated with a low dose of an inhaled corticosteroid with or without a long-acting β -agonist and were reassessed every 12 weeks. If total control was not achieved, the dose of inhaled corticosteroid was increased stepwise to the maximum approved dose. By the end of the year, total control (ie, the absence of any sign or symptom of asthma) was achieved in 30% of the patients. A slightly lower but still high standard of control (“well-controlled” asthma) was achieved in 60%. An important finding of this study is that by aiming at achieving total asthma control and by adjusting therapy to achieve it, marked reductions in the rate of severe exacerbations and marked improvements in quality of life were achieved.

SUMMARY

For the goals of asthma management to be achieved, it is not enough to assess asthma severity at a single point in time. The initial assessment of severity simply provides

an estimate of the treatment likely to be needed to achieve the goals of therapy, which are to minimize both current discomfort and the risk of future impairment. Determining whether these goals are achieved (ie, whether the disease has responded to the treatment) requires assessment of asthma control. This requires assessment both of current symptoms and functional impairment and of future risk. Simple methods for assessing current discomfort and impairment are available. Less well-validated methods for assessing future risk are also available, and others are under development. Whatever methods are used for assessing control, they need to be applied repeatedly because both the inherent intensity of asthma and the presence of external factors that aggravate asthma might vary.⁴³ Significant fluctuations in asthma control occur even in patients with previously well-controlled asthma.⁵¹ Full assessment of responsiveness to therapy thus requires repeated assessment of asthma control over time.

REFERENCES

- 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;115:1049-55.
- Fuhlbrigge AL. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. *Curr Opin Pulm Med* 2004;10:1-6.
- Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996;98:1016-8.
- Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129-38.
- Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40-7.
- 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;166:1044-9.
- 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;113:59-65.
- 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;14:902-7.
- 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;160:1647-52.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
- Phillips RA, Weinberg JM. Hypertension 2005: an evidence-based approach to diagnosis and treatment—an American perspective. *Exp Rev Cardiovasc Ther* 2005;3:691-704.
- Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
- Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled corticosteroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887-91.
- O'Byrne PM. Daily inhaled corticosteroid treatment should be prescribed for mild persistent asthma. *Am J Respir Crit Care Med* 2005;172:410-2.
- Bateman ED. Measuring asthma control. *Curr Opin Allergy Clin Immunol* 2001;1:211-6.
- Sullivan SD, Weiss KB, Lynn H, Mitchell H, Kattan M, Gergen PJ, et al. The cost-effectiveness of an inner-city asthma intervention for children. *J Allergy Clin Immunol* 2002;110:576-81.
- Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow obstruction. *Thorax* 1984;39:131-6.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
- Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE, et al. Quality of life in asthma. Internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* 1994;149:371-5.
- Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55:566-73.
- Cowie RL, Underwood MF, Revitt SG, Field SK. Predicting emergency department utilization in adults with asthma: a cohort study. *J Asthma* 2001;38:179-84.
- Belesis Y, Dixon S, Thomsen A, Duffy B, Rawlinson W, Henry R, et al. Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol* 2004;37:201-9.
- Strunk RC, Sternberg AL, Bacharier LB, Szefer SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol* 2002;110:395-403.
- Ayres JG, Miles JF, Barnes PJ. Brittle asthma. *Thorax* 1998;53:315-21.
- Rodrigo GJ, Rodrigo C. Rapid-onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. *Chest* 2000;118:1547-52.
- Barr RG, Woodruff PG, Clark S, Camargo CA. Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up. Multicenter Airway Research Collaboration (MARC) investigators. *Eur Respir J* 2000;15:266-73.
- Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Sorkness CA, et al. Long-acting β_2 -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
- Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107:61-7.
- Prieto L, Bruno L, Gutierrez V, Uixera S, Perez-Frances C, Lanuza A, et al. Airway responsiveness to adenosine 5'-monophosphate and exhaled nitric oxide measurements: predictive value as markers for reducing the dose of inhaled corticosteroids in asthmatic subjects. *Chest* 2003;124:1325-33.
- Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159:1043-51.
- Gibson PG, Henry RL, Thomas P. Noninvasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. *Eur Respir J* 2000;16:1008-15.
- Boulet LP, Boulet V, Milot J. How should we quantify asthma control? A proposal. *Chest* 2002;122:2217-23.
- Harkins MS, Fiato KL, Iwamoto GK. Exhaled nitric oxide predicts asthma exacerbation. *J Asthma* 2004;41:471-6.
- Bartoli ML, Bacci E, Carnevali S, Cianchetti S, Dente FL, Di Franco A, et al. Clinical assessment of asthma severity partially corresponds to sputum eosinophilic airway inflammation. *Respir Med* 2004;98:184-93.
- Pavord ID, Sterk PJ, Hargreave FE, Kips JC, Inman MD, Louis R, et al. Clinical applications of assessment of airway inflammation using induced sputum. *Eur Respir J Suppl* 2002;37:40s-3s.
- Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001;164:738-43.
- Barnes PJ. Efficacy of inhaled corticosteroids in asthma. *J Allergy Clin Immunol* 1998;102:531-8.

39. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
40. 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;352:2163-73.
41. CAMP. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054-63.
42. Stempel DA, Fuhlbrigge AL. Defining the responder in asthma therapy. *J Allergy Clin Immunol* 2005;115:466-9.
43. Vollmer WM. Assessment of asthma control and severity. *Ann Allergy Asthma Immunol* 2004;93:409-13; quiz 414-6, 492.
44. Nishiyama O, Kato K, Kume H, Ito Y, Suzuki R, Yamaki K. Asthma health status: influence of disease severity categorized by peak expiratory flow. *J Asthma* 2003;40:281-7.
45. Timonen KL, Schwartz J, Nielsen J, Brunekreef B. Associations between markers of respiratory morbidity in European children. *Eur Respir J* 2002;19:479-86.
46. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;163:406-12.
47. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110:685-92.
48. 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;170:836-44.
49. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma. Bethesda (MD): National Institutes of Health/National Heart, Lung, and blood Institute, National of Health; 1997.
50. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda (MD): National Institutes of Health/National Heart, Lung, and blood Institute, National of Health; 1998. National Institutes of Health publication no. 02.3659.
51. Stempel DA, McLaughlin TP, Stanford RH, Fuhlbrigge AL. Patterns of asthma control: a 3-year analysis of patient claims. *J Allergy Clin Immunol* 2005;115:935-9.