Rostrum

Asthma control versus asthma severity

Donald W. Cockcroft, MD, FRCP(C), and Veronica A. Swystun, BSc
Saskatoon, Saskatchewan, Canada

In performing clinical research in asthma, research groups encounter the task of describing study subjects according to the severity of their asthma. Asthma severity has traditionally been defined by using clinical features present only in the absence of therapy. With appropriate therapy, many of these defining features should be minimal or absent, and instead, define the lack of asthma control. Optimal asthma control is a realized standard that should be incorporated into any definition of severity. We believe that the traditional definition of asthma severity is in need of a restructuring that reflects current standards of management. It is no longer appropriate to confuse asthma severity with the degree of asthma control.

ASTHMA CONTROL

Asthma is controllable, and control is usually easily achieved. Current asthma consensus treatment guidelines stress establishing and achieving certain *goals of treatment*,[1-3] which define ideal asthma control. Symptoms should be absent or minimal with minimal or no requirement for "rescue" inhaled β_2-agonists. There should be no nighttime or early morning symptoms; lifestyle should be normal; morbidity should be absent; and expiratory flow rates should be either normal or near the patient's best. Thus there should be little resting bronchoconstriction and little response to bronchodilator. These goals are the same for all degrees of asthma severity. Control is achieved by standardized approach to therapy[1, 3] with patient education, environmental control, and adequate antiinflammatory medications, accompanied by an as-needed symptom reliever, usually an inhaled β_2-agonist. The need for inhaled β_2-agonist should be infrequent and is an important semi-objective feature identifying a lack of control.

Three reasons that patients with asthma may have suboptimal control include failure to follow asthma guidelines, existence of a nonresponsive, nonasthmatic condition, and very severe asthma. The most common reason for suboptimal control is failure to adhere to asthma treatment guidelines. Many practitioners may fail to recognize frequent symptoms as indicating poor control. This may be due to unfamiliarity with current guidelines or failure to identify frequent symptoms as an unnecessary problem. The patients themselves often do not adhere to recommendations by failing to follow environmental control, to take antiinflammatory medications, or to reduce or see the need to reduce the use of bronchodilators. Cost is an important factor contributing to patient noncompliance with inhaled antiinflammatory drugs because these are more expensive than bronchodilators. A second reason for suboptimal control of asthma is existence of a nonasthmatic condition, which will not respond to asthma medications. Some of these conditions may actually worsen with asthma therapy. Perhaps commonest are nonasthmatic airway diseases such as chronic obstructive pulmonary disease, bronchiolitis, and bronchiectasis. Once coexistent airway disease has been excluded, there are several other explanations for lack of control including regular or excessive use of inhaled β_2-agonist, which can worsen asthma control,[4] uncontrolled sinusitis, untreated gastroesophageal reflux, and psychogenic problems (psychogenic dyspnea, anxiety-hyperventilation, paradoxical vocal cord function, and factitious asthma). Finally, a small minority of patients with asthma cannot achieve adequate control despite appropriate and compliant application of asthma treatment guidelines. These patients with asthma warrant a meticulous search for exacerbating factors such as β_2-agonist overuse, sinusitis, gastro-

From Royal University Hospital/University of Saskatchewan, Department of Medicine/Division of Respiratory Medicine, Saskatoon.
Received for publication June 7, 1996; revised Aug. 2, 1996; accepted for publication Aug. 7, 1996.
Reprint requests: Donald W. Cockcroft, MD, FRCP(C), Royal University Hospital, Division of Respiratory Medicine, 103 Hospital Dr., Ellis Hall, Saskatoon, SK S7N 0W8 Canada.
J Allergy Clin Immunol 1996;98:1016-8.

0091-6749/96 $5.00 + 0 **1/1/77352**

TABLE I. Asthma severity in patients with well-controlled asthma

Asthma severity	Symptoms	Treatment requirements
Very mild	Mild - infrequent (synonym well controlled)	None or rare β-agonist
Mild	Well controlled	β_2-Agonist (occasional) ± low-dose* inhaled corticosteroids
Moderate	Well controlled	Moderate† to high‡ dose inhaled corticosteroid ± occasional ingested corticosteroid
Severe	Well controlled	High‡ to very high§ dose inhaled corticosteroid ± ingested corticosteroid
Very severe	Not well controlled	Very high§ dose inhaled + ingested corticosteroid ± additional therapies

Daily doses of inhaled corticosteroid (approximate equivalent doses) are indicated by symbols.
*Low dose: beclomethasone diproprionate ≤500 μg, fluticasone ≤250 μg, and budesonide ≤400 μg.
†Moderate dose: beclomethasone diproprionate, 500 to 1000 μg; fluticasone, 250 to 500 μg; and budesonide 400 to 800 μg.
‡High dose: beclomethasone diproprionate, 1000 to 2000 μg; fluticasone, 500 to 1000 μg; and budesonide, 800 to 1600 μg.
§Very high dose: fluticasone, 1000 to 2000 μg and budesonide, 1600-3200 μg.

esophageal reflux, and psychogenic problems. Once these have been excluded, such subjects have suboptimal control on the basis of existence of exceedingly severe asthma. Only in these patients is it appropriate to modify the goals of treatment because either they are not achievable or they are only achievable at the expense of unacceptably high doses of ingested corticosteroid.

ASTHMA SEVERITY

Asthma severity has been defined in various ways. This can include overall asthma severity, severity of an attack, or severity of airflow obstruction at one point in time. It is important to differentiate these. Traditionally, overall asthma severity has been defined by some combination of the following four features: symptoms, medication requirements, physiologic abnormalities (reduced flow rates), and morbidity.[1] It is evident that most of these criteria (symptoms, β_2-agonist requirements, morbidity, reduced flow rates) describe a lack of asthma control. The exception is the requirement for inhaled antiinflammatory therapy. The classification of severity described in Figure 1 of the International Guidelines[1] is often used to categorize patients for research studies. Two important features of this figure are often overlooked. The first is that the clinical and physiologic features are specified as being present *before treatment.* The second is the overlooked footnote, "Once the minimum medication required to maintain control of asthma has been identified, then this medication requirement reflects the overall severity of the condition."[1] It may be appropriate to use symptomatic and physiologic criteria to define severity of an attack or an exacerbation. However, it is not appropriate to use these markers of suboptimal control to define overall asthma severity.

THE PROBLEM

Asthma control (or lack thereof) is often inappropriately used to define asthma severity. It would appear that there is a common perception that *well-controlled* asthma is synonymous with *mild* asthma and that *poorly controlled* asthma is synonymous with *severe* asthma. Nothing could be further from the truth. Most of our patients with severe asthma have well-controlled asthma, thus meeting all the symptomatic and physiologic criteria for "mild asthma" except for antiinflammatory medication requirements. In contrast, patients with poorly controlled asthma having a moderate to severe exacerbation may be easy to treat with small amounts of inhaled corticosteroid and therefore have overall asthma severity that is fairly mild.

Failure to distinguish between asthma severity and asthma control has important implications. If we continue to regard asthma as a disease in which severity is characterized by symptoms and physiologic abnormalities, this will perpetuate the outdated concept that asthma is predominantly a bronchospastic disease and that symptoms, physiologic abnormalities, and β_2-agonist requirements are to be expected rather than prevented. Furthermore, patients with asthma may be miscategorized for clinical trials. Our experience is that patients with well-controlled asthma in bronchoprovocation studies have been referred to as mild, very mild, and on one occasion as *so-called asthmatics.* This has occurred even when the patients with

asthma had moderately severe disease on the basis of their requirements for inhaled corticosteroids. This is a major concern for entrance criteria into asthma drug studies. Historically, regulatory agencies and pharmaceutical companies have used entrance criteria for drug studies, which require that subjects demonstrate features that, by today's standards, indicate poor asthma control. For most studies, patients with asthma are required to have resting airflow obstruction (for example, FEV_1 <80% of predicted value), resting bronchoconstriction as defined by a positive bronchodilator response (usually >15% FEV_1 improvement after use of an inhaled β_2-agonist), and a certain degree of daytime and/or nighttime symptoms. Such entrance criteria may allow for measurable improvement of symptomatic and spirometric end points; however, patients meeting these criteria have suboptimal to poor asthma control. This poses a major ethical problem for asthma investigators. There are three ways to enroll significant numbers of patients who meet such entrance criteria. First, in patients with well-controlled asthma, the asthma can be destabilized by decreasing anti-inflammatory drugs. Second, one can exclusively enroll patients with asthma that fails to come under good control despite attempts to apply therapeutic guidelines. Third, one can enroll new patients not yet appropriately treated. None of these is acceptable. The first alternative is unethical, particularly if the planned investigation is placebo-controlled or of a long duration. The second, although ethical, will bias the study by selecting patients who are less likely to respond to (any) therapies. The third will have the opposite bias. In addition, patients whose asthma is poorly controlled and thus unstable often demonstrate much baseline variability, making the interpretation of test results difficult.

RECOMMENDATIONS

Asthma control and overall asthma severity should be distinguished. Asthma should be controlled by a standardized approach to therapy. Asthma severity should be defined by the minimum medication required to achieve adequate control[1-3] rather than by symptoms and abnormal lung function. An example of a proposed asthma severity classification is outlined in Table I. Asthma severity from very mild through mild, moderate, and severe is defined primarily by the (minimum) amount of inhaled corticosteroid required to achieve control. Only in patients with very severe asthma will we see a significant degree of suboptimal control.

These recommendations could be applied as follows: on entry to a clinical drug study, patients should have asthma that is well controlled. The therapeutic end point in such subjects would be the tapering of inhaled corticosteroids in a standardized step-down manner without reducing asthma control. We have espoused this idea for some time, but it has met with resistance from pharmaceutical companies, in part because federal regulatory agencies require symptomatic or physiologic endpoint criteria to classify asthma severity, to allow for measurable improvement, or both. The concept, however, is not new. Many years ago, we used this approach for the initial studies of inhaled corticosteroid.[5] Asthma control was achieved (by 1977 standards), and the minimum dose of ingested prednisone required for control was identified. In comparing beclomethasone dipropionate with placebo, prednisone was tapered and the end point was the amount of prednisone in milligrams that could be reduced while maintaining asthma control. Thus as early as 1977, we believed it inappropriate to look for improvements in symptoms or lung function in clinical asthma trials.

To comply with the present, *pretreatment* definition of asthma severity is to require a lack of asthma control. Because there are safe, effective therapies available for achieving asthma control, it is not ethical to enroll into drug studies patients whose asthma is poorly controlled. Asthma severity should be defined by minimum medication required to achieve control, as indicated by the International Guidelines.

We thank Jacquie Bramley for assisting in the preparation of this manuscript.

REFERENCES

1. US Department of Health and Human Services. International Consensus Report on Diagnosis and Treatment of Asthma. Bethesda: National Heart, Lung, and Blood Institute, 1992.
2. Kaliner M. Goals of asthma therapy. Ann Allergy Asthma Immunol 1995;75:169-72.
3. Ernst P, Fitzgerald JM, Spier S. Canadian Asthma Consensus Conference: summary of recommendations. Can Respir J 1996;3:89-100.
4. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336:1391-6.
5. Kerigan AT, Pugsley SO, Cockcroft DW, Hargreave FE. Substitution of inhaled beclomethasone dipropionate for oral prednisone in steroid-dependent asthmatics. Can Med Assoc J 1977;116:876-81.