Categorizing Asthma Severity: An Overview of National Guidelines

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ABSTRACT

Asthma is an inflammatory disease of the airways associated with intermittent episodes of bronchospasm. Corticosteroids are the most effective anti-inflammatory class of medication currently available for the treatment of asthma. However, as higher doses of inhaled corticosteroids are used the risks of systemic exposure and side effects will correspondingly increase. Justification of the benefits from higher doses of inhaled corticosteroids can only be made if patients with more severe asthma can be identified. Methods to categorize asthma severity have been introduced in various national asthma management guidelines. Unfortunately, there are substantial conceptual and practical differences among these recommended approaches to asthma severity categorization. Furthermore, these recommended approaches suffer from a focus on features of asthma control, such as symptoms, short-acting beta-agonist use, and lung function rather than actual measures of asthma severity that would encompass markers of airway inflammation. Without the endpoints necessary to assess airway inflammation, current recommendations for asthma severity categorization may lead to systematic under dosing of appropriate anti-inflammatory therapy with subsequent perpetuation of the asthma exacerbation cycle.

INTRODUCTION

Asthma is an inflammatory disease of the airways associated with intermittent episodes of bronchospasm.¹ Bronchodilators can effectively relieve bronchospasm, but do not treat the underlying airway inflammation. Currently, corticosteroids are the most effective anti-inflammatory class of medication available for the treatment of asthma. When given in the inhaled form, especially at low doses, corticosteroids act as topical anti-inflammatory agents in the airways with little risk of systemic exposure.² Inhaled corticosteroids have been shown to effectively reduce airway inflammation,^{3,4} control asthma symptoms, improve lung function, decrease exacerbations,⁵ and reduce hospitalization⁶ and mortality rates^{7,8} from asthma. However, as higher doses of inhaled corticosteroids are used the risks of systemic exposure² and side effects will correspondingly increase⁹.

The benefits of higher doses of inhaled corticosteroids may be less substantial than previously thought. A recent meta-analysis indicated that maximal symptom

and lung function improvements were found at low-to-medium doses (table 1) of inhaled fluticasone propionate.¹⁰ Similar observations were made in a 24-week study comparing increasing doses of inhaled fluticasone propionate and beclomethasone dipropionate.¹¹ A study employing bronchial biopsies also failed to confirm enhanced *in vivo* anti-inflammatory benefits with very high doses of fluticasone propionate.¹² Doubling the dose of an inhaled corticosteroid during asthma deterioration, a common clinical approach, provides little benefit in preventing an exacerbation.¹³ It is only in highly select groups of patients with such severe asthma requiring chronic oral corticosteroids that very high doses of inhaled corticosteroids seem to provide additional benefits to improving lung function, symptom control, quality of life and the ability to reduce oral corticosteroids.^{14,15}

Similarly, the clinically relevant risks of systemic adverse effects from the long-term use of inhaled corticosteroids are less than generally perceived. Inhaled corticosteroids are known to suppress the hypothalamic-pituitary-adrenal axis, but are very rarely the cause of clinically recognizable adrenal insufficiency.¹⁶ Parents are concerned that inhaled corticosteroids might affect the growth of their children. Growth velocity does transiently decrease with initiation of inhaled corticosteroid treatment in prepubertal children, but this effect does not seem to result in diminution of actual height attained.^{17,18} The risk of developing either cataracts^{19,20} or osteoporosis²¹ is small. Skin bruising does occur with long-term use of inhaled corticosteroids, especially in the elderly, but this is primarily a cosmetic problem.^{22,23} Although these observations are reassuring, it must be acknowledged that long-term use of high doses of inhaled corticosteroids have been associated with such side effects as Cushing's syndrome, growth retardation, osteopenia, myopathy and cataracts.^{19,20,24}

The benefit versus risk profile of inhaled corticosteroids is clearly favorable at low-to-medium doses. Considerable benefit can be achieved with little risk of adverse systemic effects. Use of higher doses of inhaled corticosteroids should be restricted to those carefully defined clinical circumstances in which the anticipated benefits can be

justified against the risk of systemic side effects. Justification of the benefits from higher doses of inhaled corticosteroids can only be made if patients with more severe asthma can be identified.

METHODS OF CATEGORIZING
ASTHMA SEVERITY

There are three basic methods advocated by various national guidelines to categorize asthma severity. The first method, developed by a consensus panel convened through the US National Asthma Education and Prevention Program and presented as the Expert Panel Report 2, relies on an assessment of asthma symptoms and lung function at the time the patient is being evaluated prior to the initiation of treatment.²⁵ Three variables are considered in categorizing asthma severity: daytime symptoms, nighttime symptoms and lung function (table 2). Abnormalities within each of these three variables are graded into four separate categories of severity. Overall asthma severity is categorized according to the worst individual variable. For example, if a patient has frequent nighttime symptoms (placing them in the severe, persistent category for this variable) but has daytime symptoms less than twice per week and normal lung function (both in the mild, intermittent category), the overall asthma categorization is severe, persistent.

The National Asthma Campaign in Australia²⁶ advocates the second method. A description of the development of this method is not given, but presumably it was based on consensus of experts. This method stipulates that asthma severity should be assessed while the patient is clinically stable, but also adds that a history of either hospitalization or near-fatal asthma attacks should be taken into consideration in severity categorization (table 3). Like the method established in the Expert Panel Report 2, the worst individual categorization will determine overall asthma severity. An additional consideration to asthma severity categorization is the identification of the "high risk" patient. There is overlap between variables used to categorize asthma severity and characteristics of the "high risk" patient. However, other factors, such as poor compliance with treatment, denial of asthma as a personal medical problem, history of asthma initiated by aspirin or other nonsteroidal

Table 1. Comparative Daily Doses of Inhaled Corticosteroids²⁵

Drug	Low Dose†	Medium Dose†	High Dose†
Beclomethasone dipropionate	168 to 504	504 to 840	>840
Budesonide Turbuhaler	200 to 400	400 to 600	>600
Flunisolide	500 to 1000	1000 to 2000	>2000
Fluticasone propionate	88 to 264	264 to 660	>660
Triamcinolone acetonide	400 to 1000	1000 to 2000	>2000

† dosages listed in micrograms.

anti-inflammatory drugs, and immediate hypersensitivity to foods are included as high-risk characteristics. Identifying a high risk patient will not necessarily lead to changes in therapy, but does indicate the need for closer follow-up.

The British Guideline on the Management of Asthma²⁷ provides a third method for categorizing asthma severity. It emphasizes control of symptoms and maintenance of normal lung function, but specifies that symptom control should be based on individual assessment and that normal lung function and complete relief of symptoms may not always be possible. This approach differs from both the US and Australian methods as specific categories of asthma severity are not described, but rather steps are defined based on the need for medications to achieve individual asthma control. The British guidelines were developed through an evidence-based process, but no specific evidence is provided to support the recommended approach to determining

asthma severity. Similarly to the US approach, the British guidelines identify daytime symptoms, need for short-acting beta-agonists, exacerbations, physical activity limitations and lung function as the important endpoints of asthma management.

The Canadian guidelines for asthma care, developed through consensus of experts, include two separate methods for determining asthma severity.²⁸ The first recommended approach is similar in concept to the method advocated in the British guidelines. Physicians define acceptable asthma control based on daytime symptoms, nighttime symptoms, physical activity limits, exacerbations, absence from school or work, use of rescue short-acting beta-agonists, and lung function. Asthma severity is categorized through assessment of symptom control and need for medication (table 4). The second Canadian approach is similar to the Australian method. It combines features of lung function, symptom

Table 2. Classification of Asthma Severity: Method of Expert Panel Report 2²⁵

Severity	Symptoms	Nighttime Symptoms	Lung Function
Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV ₁ /PEF ≤60% PEF variability >30%
Moderate persistent	Daily symptoms Daily use of short-acting beta-agonist Exacerbations affect activity Exacerbations ≥2/week	>1/week	FEV ₁ /PEF >60% but <80% PEF variability >30%
Mild persistent	Symptoms >2/week but <1/day Exacerbations may affect activity	>2/month	FEV ₁ /PEF ≥80% PEF variability 20% to 30%
Mild intermittent	Symptoms ≤2/week Asymptomatic between exacerbations Exacerbations brief	≤2/month	FEV ₁ /PEF ≥80% PEF variability <20%

FEV₁ : forced expiratory volume in one second; PEF: peak expiratory flow

Table 3. Classification of Asthma Severity: Method of Australian National Asthma Campaign²⁶

Severity	Wheeze, tightness, cough, dyspnea	Nighttime symptoms	Symptoms on waking	Admission or emergency visits	Previous life threatening attack	Short-acting beta-agonist use	FEV ₁	PEF
Severe	Every day	>1/week	>1/week	Usually	May have a history	>3 to 4/day	<60%	<80%
Moderate	Most days	<1/week	<1/week	Usually not	Usually not	Most days	60% to 80%	80% to 90%
Mild	Occasional	Absent	Absent	Absent	Absent	<2/week	>80%	>90%

FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow

control, history of hospital admissions, and near-fatal asthma attacks to determine asthma severity (table 5).

There are conceptual differences among these approaches to severity categorization. The US approach, detailed in the Expert Panel Report 2, concentrates on current symptoms and lung function abnormalities, while the Australian method incorporates historical features. The Expert Panel Report 2 advises medication dosing according to pretreatment severity; the British guideline uses the reverse approach, inferring severity categorization from the amount of medication required to control symptoms and maximize lung function. There are also specific procedural differences among the guidelines. The Expert Panel Report 2 has four different severity categories and makes a fundamental distinction between persistent and intermittent asthma. The Australian approach uses only three severity categories: mild, moderate, and severe. In the British guideline, separate asthma severity categories are not specified, but five different steps of asthma treatment approaches are described. The Canadians use five separate severity categories, ranging from very mild to very severe, in one approach, that reflects the British method, and three separate categories in their other approach, similar to the Australian method. Each of the guidelines recommends using an assessment of daily symptoms, exacerbations, nighttime symptoms, and use of short-acting beta-agonists as an important basis for determining asthma severity. Although the recommended approaches use similar symptoms, they differ in how individual severity categories are distinguished based on these symptoms. For instance, in the Expert Panel Report 2 nighttime symptoms occurring more than once per week would be graded as moderate, persistent, while in the Australian approach nighttime symptoms occurring with that frequency would be considered indicative of severe

asthma. In one Canadian method the use of short-acting beta-agonists 3-6 times per day would indicate moderate severity; in the Australian recommendations use of short-acting beta-agonists with such a frequency would indicate severe asthma. Interestingly, there is good agreement among the guidelines on how severity categories are distinguished based upon objective criteria of lung function.

ASTHMA SEVERITY CATEGORIZATION METHODS IN CURRENT GUIDELINES – A CRITICAL ASSESSMENT

Concern has been expressed about the methods used to develop recommendations for severity categorization in these national guidelines.²⁹ One area of weakness is in the use of consensus to develop recommendations. Only the British method specifically states that it was evidence based, but no evidence was cited to support the general approach of implicitly defining asthma severity through the type of medications needed to achieve asthma control. Guidelines, especially those developed by specialty societies, have been criticized for not adhering to established methodologic standards for evaluating and synthesizing the scientific evidence.^{30,31} The original Expert Panel Report on diagnosis and management of asthma has been faulted for relying on the subjective judgment of the panel through consensus rather than supporting recommendations with clear scientific evidence.³² Unfortunately, the Expert Panel Report 2 used the same methods.

Implementation of these recommendations is another area of concern. If recommendations about severity categorization are to be used by health care providers, careful field-testing prior to dissemination for implementation is advisable to ensure that the guidelines can be properly understood. At the University of Iowa, researchers asked asthma specialists and

Table 4. Classification of Asthma Severity: Method of Canadian Consensus²⁸

Severity	Symptoms	Treatment
Very severe	May be controlled or not well controlled	Short-acting beta-agonist use High doses of inhaled corticosteroids Additional therapy Oral corticosteroids
Severe	Well controlled	Short-acting beta-agonist use High doses of inhaled corticosteroids Additional therapy
Moderate	Well controlled	Short-acting beta-agonist use Low-to-moderate doses of inhaled corticosteroids ± Additional therapy
Mild	Well controlled	Short-acting beta-agonist use occasionally Low doses of inhaled corticosteroids
Very mild	Mild-infrequent	Short-acting beta-agonist use rarely

Table 5. Classification of Asthma Severity: Method of Canadian Consensus²⁸

Severity	FEV ₁ /PEF	Short-acting beta-agonist use	Near-fatal episode	Hospital admission	Nighttime symptoms	Limitation of daily activities
Severe	<60%	Q 2 to 4 hr	+	+	+++	+++
Moderate	60% to 80%	Q 4 to 8 hr	–	–	+	+ / ++
Mild	>80%	<8 h	–	–	– / +	– / +

Symptom: not reported, – ; reported, + ; reported more often, ++ and +++
FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow

family medicine faculty to answer questions about the Expert Panel Report 2 method of asthma severity categorization.³³ Family medicine faculty answered 56% of the questions correctly; asthma specialists scored only 7% better, answering only 63% of the questions correctly. Recently, Baker and colleagues³⁴ found that pediatric allergists and pulmonologists demonstrated poor agreement in assessing asthma severity in a series of case vignettes, despite being provided the Expert Panel Report 2 methods. These observations suggest that considerable education will be required for health care providers to understand and effectively use recommended methods for asthma severity categorization in national guidelines.

Issue has been taken with the principle that grading of the worst individual category should determine overall asthma severity categorization. Two studies involving large numbers of patients evaluated how the Expert Panel Report 2 methods actually categorize asthma and found that the majority of patients were categorized as moderate-to-severe.^{35,36} This observation is contradictory to the prevailing belief that most patients actually have mild asthma.³⁷ Surprisingly, in one large study a single variable, nighttime symptoms, seemed to be the most important determinant of overall asthma severity categorization.³⁶ These observations raise two important issues: if one variable is playing a predominant role in determining severity categorization, it limits the value of an approach that emphasizes considering multiple factors, and an asthma severity categorization method that places most patients in only one or two categories may not have adequate discriminatory resolution.

The guidelines emphasize reliance on asthma symptoms and lung function for determining asthma severity. There are important methodologic issues involved in developing an asthma severity categorization method that incorporates symptoms and objective measures of lung function on the same scale. For example, the Expert Panel Report 2 includes the separate variables daytime symptoms and lung function on a scale ranging from mild, intermittent to severe, persistent asthma. Consequently, continual symptoms have the same significance as a FEV₁ (forced expiratory volume in one second) below 60% predicted. This intuitively makes sense to the clinician, but is difficult to support scientifically because numerous studies have shown that there is poor

correlation between reporting of asthma symptoms and objective measures of lung function.^{36,38,39} Other observations make it difficult to support scaling symptoms and lung function in the same way. Patients cannot reliably predict changes in their lung function based on the symptoms they experience⁴⁰ and physicians cannot accurately predict lung function from examinations of patients with asthma.⁴¹

Changes in symptoms are a poor indicator of impending changes in lung function.⁴² Symptom reporting may be affected by factors other than asthma itself. Women may report more symptoms and rely more heavily on use of short-acting beta-agonists than men with the same degree of airway obstruction.⁴³ Negative mood may be an important determinant of short-acting beta-agonist use and perception of asthma symptoms.⁴⁴ Most worrisome has been the repeated observation that both patients and physicians may substantially underestimate the severity of asthma, especially when they make this estimate based primarily on symptoms.^{45,46} Although the guidelines appropriately incorporate measures of lung function, as well as symptom assessment, they fail to take into account the unfortunate reality that most primary care providers do not routinely incorporate objective measures of lung function into their assessment of asthma.⁴⁷ Consequently, on a practical basis implementation of guideline recommended asthma severity categorization will not be possible until health care providers accept the value of spirometry and incorporate its use into their everyday practice.

A more fundamental and conceptual concern about the recommended approaches to asthma severity categorization is that these methods are based on the concept of asthma control rather than asthma severity.⁴⁸ Symptoms and lung function indicate how well the manifestations of the disease are controlled, but do not reflect the severity of the underlying inflammation. As asthma is accepted to be an inflammatory airway disease, severity categorization would be most reasonably based on an assessment of airway inflammation. Current guidelines provide insight into airway inflammation only indirectly, by integrating the dose of inhaled corticosteroids needed to provide control of symptoms. However, direct methods are available to assess airway inflammation. Induced sputum allows measurement

of airway inflammatory cells; changes in sputum eosinophil counts may reflect deterioration in asthma control.⁴⁹ Bronchoscopy is increasingly used for bronchoalveolar lavage to measure airway inflammatory cell counts and airway biopsy is used to directly evaluate airway remodeling and inflammation.⁵⁰ Exhaled levels of nitric oxide⁵¹ and tests of bronchial hyperresponsiveness⁵² may indirectly reflect airway inflammation.

The importance of airway inflammation as the measure of asthma severity is demonstrated by recent observations in patients at the extreme ends of the asthma spectrum, those with mild, intermittent asthma and those with very severe asthma. Mild, intermittent asthma, as defined in the Expert Panel Report 2, describes patients using short-acting beta-agonists infrequently for symptom control. Because these patients are categorized as having intermittent asthma and do not use inhaled corticosteroids, it is implied that on-going airway inflammation is not present. However, elevated exhaled nitric oxide levels and bronchial biopsy evidence of airway inflammation have been found in patients with mild, intermittent asthma.^{53,54} In a small group of young adults with a history of asthma but no clinical evidence of asthma for over one year, bronchial biopsy specimens have confirmed on-going evidence of airway inflammation.⁵⁵ Low dose exposure to allergens in a group of patients with mild asthma under controlled research conditions has been shown to worsen airway inflammation without significantly changing asthma symptoms.⁵⁶ These observations indicate that perhaps absent or minimal symptoms may not truly reflect disease activity. It has been noted that near-fatal and fatal episodes of asthma occur in patients with seemingly mild disease;⁵⁷ it is possible that in these patients an assessment of airway inflammation, rather than symptoms and lung function, would have indicated more severe disease. Bronchial biopsy studies have indicated that there may be two different types of inflammatory processes in adults with very severe asthma, a neutrophilic dominant and an eosinophilic dominant form.⁵⁸ This observation has been confirmed in studies using induced sputum.⁵⁹ In children with very severe asthma, bronchoscopic biopsy has actually shown extensive remodeling with little inflammation.⁶⁰ Clinically, patients with very severe asthma have fluctuations in symptoms and lung function despite aggressive treatment with inhaled and oral corticosteroids. The studies of airway inflammation suggest that their disease may not be corticosteroid responsive. Using dosage of inhaled corticosteroids as a surrogate marker of disease severity would not be appropriate in these patients.

Two studies have directly evaluated the added value of incorporating measures of airway inflammation into an approach for asthma management. Sont and colleagues⁶¹ randomized asthma patients to a treatment strategy based on either asthma severity categorized by the Expert Panel Report 2 alone or asthma severity categorization along with methacholine inhalation challenge studies as a measure of

bronchial hyperreactivity. Bronchial hyperreactivity was used in this study as an index of underlying airway inflammation. The patients treated according to measures of bronchial hyperreactivity received higher doses of inhaled corticosteroids, but had significantly fewer episodes of asthma exacerbation and significantly more effective control of airway inflammation as determined by bronchial biopsies. Green et al.⁶² randomized patients with asthma either to a management approach based on the British guidelines of symptom and lung function control or to another path incorporating use of induced sputum eosinophil counts. The group treated according to measures of airway inflammation had significantly fewer asthma exacerbations. These studies suggest that asthma would more effectively be controlled if severity were categorized using an index of airway inflammation, rather than solely through control of symptoms and lung function.

CONCLUSIONS

Asthma is a frustrating disease for both patients and health care providers. It is a common disease; approximately 7% of the US population currently suffers from asthma.⁶³ Patients with asthma often feel that their disease is not treated effectively. Surveys reveal that most asthma patients limit their activities because of respiratory symptoms and as a consequence, report dissatisfaction with their lifestyles.⁶⁴ Health care providers recognize that routine asthma care requires millions of office visits annually and that acute asthma problems prompt many additional emergency department visits.⁶³ Asthma still causes deaths, especially in high risk inner city populations.⁶³ Persistent asthma can cause deterioration in lung function over time, e.g., conversion from reversible airflow obstruction to irreversible airflow obstruction as seen in chronic obstructive pulmonary disease.^{65,66}

Frustration with asthma care is especially apparent now because patients and health care providers have multiple effective options for treatment. Despite remarkable advances in asthma pharmacotherapy, patients with asthma often adhere poorly to the recommended treatment regimens.⁶⁷ Poor adherence relates, in part, to difficulties asthma patients have in understanding that asthma is an inflammatory disease that requires long-term anti-inflammatory preventive measures. Poor adherence also is based on concerns about potential side effects of asthma medications. For example, patients report that they frequently do not use inhaled short-acting beta-agonists because of associated side effects.⁶⁸ Concerns by patients about the side effect profile of inhaled corticosteroids are even greater. Compounding the effects of patients' poor adherence to asthma treatment regimens has been the historic reluctance of American physicians to regularly prescribe inhaled corticosteroids for asthma.^{69,70} Recent trends suggest that treatment regimens for asthma are beginning to increase the inclusion of inhaled corticosteroids, but there is still a too frequent tendency to inappropriately rely on beta-agonists alone for asthma therapy.⁷¹ For both patients and health care providers,

education about appropriate pharmacotherapy is the key to better asthma care. The foundation of education regarding asthma pharmacotherapy is in understanding the balance between the benefits of inhaled corticosteroids and the potential risks.

There is clear rationale for categorizing asthma severity. Higher doses of inhaled corticosteroids can only be justified if patients with more severe asthma can be identified. National asthma management guidelines have attempted to address this issue by proposing asthma severity categorization methods. Unfortunately, despite extensive efforts to disseminate these guidelines, surveys and database evaluations consistently show that current asthma care around the world fails to adhere to the recommendations of these guidelines.⁷²⁻⁷⁴ These observations are disturbing because underassessment of asthma severity results in ineffective treatment and suboptimal outcomes.^{75,76} Even though the recommended approaches for asthma severity categorization suffer from various methodologic flaws, management of asthma patients according to these guidelines would still result in improved care.⁷⁷⁻⁸⁰ A more difficult issue concerns the inherent limitations of the current asthma severity categorization methods, especially the failure to include measures of airway inflammation. Without the endpoints necessary to assess airway inflammation, current recommendations for asthma severity categorization may lead to systematic under dosing of appropriate anti-inflammatory therapy with subsequent perpetuation of the asthma exacerbation cycle. Incorporation of measures such as methacholine challenge testing and sputum eosinophil counts into routine asthma care may improve the ability to assess the severity of underlying airway inflammation and to more appropriately adjust anti-inflammatory therapy.

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