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Review Article

CLASSIFYING ASTHMA SEVERITY AND TREATMENT DETERMINANTS: NATIONAL GUIDELINES REVISITED

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ABSTRACT
Bronchial asthma is an inflammatory disease of the airways manifested physiologically by a widespread narrowing of the air passages. Being an inflammatory disease of the airways, the most effective treatment available for the management of bronchial asthma are anti-inflammatory agents such as corticosteroids. However, it is known that at higher dosage levels, even inhaled corticosteroids have harmful systemic side-effects. Hence, justification of use of high-dose of inhaled corticosteroids can only be made if patients with severe asthma can be accurately identified. For this precise reason, methods have been devised to categorize asthma severity through various National Asthma Management Guidelines. The present guidelines predominantly stress on symptoms and lung functions as the yardstick for determining the severity of asthma attacks and parameters determining airway inflammation have not yet been incorporated into them. However, these guidelines have proved to be fairly accurate in determining asthma severity and in guiding the treatment in these patients and all healthcare personnel are strongly advised to follow them. It is hoped that future guidelines may incorporate measures of inflammation as well, in order to further improve the diagnostic and treatment modalities in these patients.
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INTRODUCTION

Asthma is an inflammatory disease of the airways associated with intermittent episodes of bronchospasm.[1] Bronchodilators effectively relieve the bronchospasm and consequent symptoms but do not treat the underlying airway inflammation which is the mainstay in an underlying asthmatic attack. At present, corticosteroids are the most effective anti-inflammatory agents available for the treatment of bronchial asthma.

When given at low doses in the inhaled form, corticosteroids act as topical anti-inflammatory agents in the bronchial passages with minor risk of any significant systemic exposure.[2] Inhaled corticosteroids have been shown to have effectively reduced airway inflammation,[3] control asthma symptoms, decrease the frequency and severity of acute exacerbations, improve lung functions, reduce frequency of hospitalization[4] and consequently reduce both morbidity and mortality rates.[5] However, as higher doses of inhaled corticosteroids are used, the risks of systemic side effects have been known to increase.[6]

It has been observed that beneficial effects from higher doses of inhaled corticosteroids are significantly less than previously thought. One study indicated that maximal symptomatic and lung function improvements were found at low- to medium doses of inhaled fluticasone propionate.[7] Similar results were obtained while comparing increasing doses of inhaled fluticasone propionate and beclomethasone dipropionate.[8] Also, doubling the dose of inhaled corticosteroids during clinical deterioration does little to prevent an acute exacerbation.[9]

It has been observed that only those patients who are chronic asthmatics, resistant to most conventional therapies including oral and inhaled beta-agonists and who require chronically high doses of oral corticosteroids stand to benefit from very high doses of inhaled corticosteroids.[10,11] Also, systemic risks of long-term inhaled corticosteroids are substantially less than previously thought. Though inhaled corticosteroids are known to suppress the hypothalamic-pituitary-adrenal axis, it is rarely ever the cause of clinically perceived adrenal insufficiency.[12] Inhaled corticosteroids are also known to transiently decrease the growth velocity in prepubertal children. But this does not result in the diminution of the actual height attained.[13] Skin bruising is known to occur with long-term use of inhaled corticosteroids.[14] This occurs more commonly in the elderly and is primarily a cosmetic problem.

However, it needs to be remembered that long-term use of high doses of inhaled corticosteroids are associated with side effects such as osteopenia, myopathy, cataracts, growth retardation and Cushing's syndrome.[15,16]

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Hence it can be surmised that the benefit-to-risk profile of inhaled corticosteroids is clearly favourable at low-to-medium doses wherein considerable benefit is obtained with little risk of adverse systemic side effects. However, use of high doses of inhaled corticosteroids entails the risk of systemic side effects. Hence, the use of higher doses should be restricted to those carefully chosen clinical conditions in which the anticipated benefits can be justified. This can only be determined if patients with more severe asthma can be reliably identified.

Therefore, it is vitally important to categorize the severity of asthma attacks so that appropriate treatment modalities can be adopted.

CLASSIFYING ASTHMA SEVERITY

Classifying the severity of asthmatic attacks based on clinical features and convenient parameters such as peak flow rates, is believed to be an invaluable method in the management of bronchial asthma. Several methods for categorizing asthma severity have been devised in the United States of America, the United Kingdom, Australia and Canada and are routinely being used to follow and manage patients with bronchial asthma.

NAEPP Classification

The most widely accepted classification of asthma severity was that recommended by the National Heart, Lung and Blood Institute's (NHLBI) National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2. These guidelines placed major emphasis on diagnosis (including classification of asthma) and management, which included a stepped approach to asthma treatment. The NAEPP classification relies on an assessment of asthma symptoms and lung function at the time the patient is being evaluated and prior to commencement of treatment. Three variables are considered in classifying asthma severity, namely, daytime symptoms, nighttime symptoms, and lung function. 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 severe persistent daytime symptoms (placing him in the severe persistent category for this variable) but has nighttime symptoms less than twice per week and normal lung function (both in mild, intermittent category), the overall asthma categorization would be severe, persistent.

Recently, EPR 3 guidelines have been released which are essentially based on the 1997 EPR 2 guidelines as the framework. These guidelines are now organised around four essential components of asthma care, namely: assessment and monitoring, patient education, control of factors contributing to asthma severity and pharmacologic treatment.[17]

Table 1. NAEPP classification of asthma severity

Symptoms: Cough, Shortness of Breath, Wheezing or Chest Tightness.
Patients should be assigned to the most severe step in which ANY feature occurs:

Symptoms Severity	Days with Symptoms	Nights with Symptoms	PEFR FEV1	PEF Variability
Step 4 Severe Persistent	Continual	Frequent	≤ 60 %	> 30 %
Step 3 Moderate Persistent	Daily	> 1 / week	> 60% - < 80 %	< 30 %
Step 2 Mild Persistent	>2/ week, but< 1 / day	> 2 / month	≥ 80 %	20-30 %
Step 1 Mild Intermittent	≤ 2 / week	≤ 2 / month	≥ 80 %	< 20 %

Australian National Asthma Campaign Classification

This classification is developed based on the consensus of experts. By this method, asthma severity is assessed while the patient is clinically stable, at the same time taking into consideration a past history of either hospitalization or near-fatal asthma attacks.[18] 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 an 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 non-steroidal anti-inflammatory drugs, and immediate hypersensitivity to foods are termed 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.

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Table 2. Classification of asthma severity: method of Australian National Asthma Campaign[18]

Severity	Wheeze, tightness, cough, dyspnoea	Nighttime Symptoms	Symptoms on waking	Admission or emergency visits	Previous life-threatening attack	Short acting β-agonist use	FEV1	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 rate

The Global Initiative for Asthma Guidelines (GINA)

The Global Initiative for Asthma (GINA) guidelines are the combined efforts of NHLBI and the World Health Organisation (WHO). Although these recommendations are essentially similar to the NAEPP guidelines, there are subtle changes in language, including specific details within the stepped approach to asthma therapy. The guidelines were recently updated in 2008.[19] These latest updates are essentially based on research published and the impact of publications from July 1, 2007 through June 30, 2008.

Table 3. GINA classification of asthma severity by clinical features before treatment

	Symptoms /Day	Symptoms /Night	PEF or FEV1	PEF variability
STEP 1 Intermittent	< 1 time a week Asymptomatic and normal PEF between attacks	≤ 2 times a month	≥ 80%	< 20%
STEP 2 Mild Persistent	> 1 time a week but < 1 time a day Attacks may affect activity	>2 times a month	≥ 80%	20 - 30%
STEP 3 Moderate Persistent	Daily Attacks affect activity	> 1 time a week	60% - 80%	> 30%
STEP 4 Severe Persistent	Continuous Limited physical activity	Frequent	≤ 60%	> 30%

The presence of one of the features of severity is sufficient to place a patient in that category. Patients at any level of severity, even intermittent asthma, can have severe attacks.

The Global Initiative for Asthma released new guidelines for asthma management in the year 2000 which emphasized looking at asthma not only in terms of severity, but also in terms of response to treatment, which is equivalent to control. In addition, the new GINA guidelines used this approach with children under the age of 5, which was a major difference from the NAEPP guidelines. GINA recommended using the NAEPP classification of asthma only for research purposes. Instead they suggested these three asthma classifications which were more a variation in mindset than anything else:

- Controlled: At this level, there are no daytime or nighttime symptoms, no activity restrictions and infrequent need for quick relief medicines (no more than twice a week). Peak flow is normal and there are no asthma attacks.
- Partly controlled: At this level, daytime symptoms are occurring more than twice a week, sometimes at night and occasionally they limit activity. Quick relief medicines are needed more than twice a week. Peak flow rate is less than 80 percent of the personal best and asthma attacks occur at least once a year.
- Uncontrolled: Asthma is classified as uncontrolled if there are 3 or more of the features of partially controlled asthma at least 3 times a week and asthma attacks are occurring weekly.

***Asthma Severity:* (Updated guidelines 2008)**

GINA now reasons that classification of asthma by severity is useful when decisions are being made about management at the initial assessment of a patient. GINA therefore maintains that it is important to recognize that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment. Thus, asthma can present with severe symptoms and airflow obstruction and be classified as Severe Persistent on initial presentation, but respond fully to treatment and then be classified as Moderate Persistent asthma. In addition, severity is not an unvarying feature of an individual patient's asthma, but may change over months or years.

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Because of these considerations, the classification of asthma severity provided in table 3 above, which is based on expert opinion rather than evidence is not recommended as the basis for ongoing treatment decisions, but retains its value as a cross-sectional means of characterizing a group of patients with asthma who are not on inhaled glucocorticoid treatment, as in selecting patients for inclusion in an asthma study. Its main limitation is its poor value in predicting what treatment will be required and what a patients response to that treatment might be. Hence, a periodic assessment of asthma control has now been deemed more relevant and useful.[20]

Asthma control:

According to GINA, asthma control may be defined in various ways. The term control may indicate disease prevention, or even cure. However, in asthma, where neither of these are realistic options at present, it refers to control of the manifestations of disease. Ideally this should apply not only to clinical manifestations, but to laboratory markers of inflammation and pathophysiological features of the disease as well. There is evidence that reducing inflammation with controller therapy achieves clinical control, but because of the cost and / or general unavailability of tests such as endobronchial biopsy and measurement of sputum eosinophils and exhaled nitric oxide, it is recommended that treatment be aimed at controlling the clinical features of disease, including lung function abnormalities. Table 4 provides the characteristics of controlled, partly controlled and uncontrolled asthma.

Table : 4 Levels of asthma control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	**Three or more features of partly controlled asthma present in any week**
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week

Complete control of asthma is commonly achieved with treatment, the aim of which should be to achieve and maintain control for prolonged periods (21), with due regard to the safety of treatment, potential for adverse effects and the cost of treatment required to achieve this goal.

Validated measures for assessing clinical control of asthma are the Asthma Control Test (ACT) (http://www.asthmacontrol.com), the Childhood Asthma Control Test (C-ACT), the Asthma Control Questionnaire (ACQ) (http://www.qoltech.co.uk/Asthma1.htm), the Asthma Therapy Assessment Questionnaire (ATAQ) (http://www.ataqinstrument.com) and the Asthma Control Scoring System.

DISCUSSION

The above guidelines rely on asthma symptoms and lung function values for determining asthma severity. However there are significant issues involved in developing asthma severity categorization methods that incorporate symptoms and objective measures of lung function on the same scale. For instance, continual symptoms have the same significance as a FEV1 below 60% predicted. This apparently makes sense to the clinician but is difficult to support scientifically since numerous studies have shown that there is poor correlation between reporting of asthma symptoms and objective measures of lung function.[22,23]

Hence, patients cannot reliably predict changes in their lung function based on the symptoms they experience,[24] and physicians cannot accurately predict lung functions from examination of patients with asthma.

Another fundamental concern regarding the various guidelines is that they are based more on the concept of asthma control rather than asthma severity.[25] 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 recognized to be an inflammatory airway disease, severity categorization should also be based

on an assessment of airway inflammation. Nowadays, direct methods are available to assess airway inflammation. Induced sputum allows measurement of airway inflammatory cells and changes in sputum eosinophil counts may reflect deterioration in asthma control.[26] 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.[27] Exhaled levels of nitric oxide[28] and tests of bronchial hyperresponsiveness[29] may indirectly reflect airway inflammation.

Two studies have directly evaluated the added value of incorporating measures of airway inflammation into an approach for asthma management. One study[30] randomized asthma patients to a treatment strategy based on either asthma severity categorized only clinically 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.

The vital importance of categorizing asthma severity is very evident. Higher doses of inhaled corticosteroids can only be justified if patients with more severe asthma can be identified. National guidelines on asthma management have attempted to address this issue by proposing asthma severity categorization methods. However, despite serious efforts to disseminate these guidelines, database evaluations have shown that current asthma care around the world fails to adhere to recommendations of these guidelines.[31] This is a disturbing observation because underassessment of asthma severity results in ineffective treatment and an increase in morbidity and mortality in these patients.[32] Various studies have shown that, in spite of methodologic flaws, if patients are managed according to the recommended guidelines, it would significantly improve patient care.[33]

However, many investigators and clinicians have expressed concern that the current asthma management guidelines are symptom oriented and do not include measures of airway inflammation as a guide to the management of asthma. As studies of airway inflammatory responses progress, there is likely to be a place for the measure of airway inflammation in a future guideline. 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 consequent exacerbation of the asthma attacks. Incorporating measures such as methacholine challenge testing and sputum eosinophil counts into future guidelines would improve the assessment of the underlying airway inflammation and help to appropriately adjust anti-inflammatory therapy.

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Smokers who were told their "lung age" are more likely to quit smoking

Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ*. 2008; 336(7644):598-600.

In this randomised controlled trial, 561 current smokers (age >35) were offered spirometry. Participants in intervention group received their results in terms of "lung age" (the age of the average healthy individual who would perform similar to them on spirometry). Those in the control group received a raw figure for forced expiratory volume at one second (FEV1). Both groups were advised to quit and offered referral to local NHS smoking cessation services. The quite rate at 1 year (assessed by salivary cotinine testing) were 13.6% and 6.4% (difference 7.2%, P=0.005, 95% confidence interval 2.2% to 12.1%; number needed to treat 14).