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Asthma control in 2011

Optimising asthma treatment in adults. Part 1

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The aim of the management of patients with asthma is to optimise their asthma control. The assessment of patients' asthma symptoms and their lung function and addressing comorbidities (such as rhinosinusitis, sleep apnoea and obesity) and risk factors (such as allergen exposure and exercise) are discussed in the first part of this two-part article.

Key points

- **Asthma control – the extent to which the effects of the disease are reduced or removed by treatment – encompasses the concepts of current control and future risk.**
- **The emphasis on asthma control in clinical management differs from the earlier emphasis on asthma severity, which was defined in terms of clinical features before treatment.**
- **Asthma that is well controlled is characterised by infrequent daytime symptoms, no activity limitation, no nocturnal symptoms and normal lung function.**
- **When assessing asthma control, it is important to consider both patient symptoms and lung function measurement, as well as addressing comorbidities (such as rhinosinusitis, sleep apnoea and obesity) and risk factors (such as allergen exposure and exercise).**

Asthma is defined as a chronic inflammatory disorder associated with physiological abnormalities in the airways such as variable airflow limitation and airway hyper-responsiveness.[1] The underlying pathology and physiology leads to symptoms of episodic breathlessness, chest tightness, wheeze or cough. The disease manifestations are inherently variable over time. Hence, a patient might experience a long period of apparent disease quiescence and still suffer from exacerbations.

Asthma has gained increasing awareness over the past two decades. National and international guidelines have been developed to advocate best practice.[1,2] The reduction in asthma mortality in the past two decades is probably attributable to the widespread use of inhaled corticosteroids (ICS; beclomethasone, budesonide, ciclesonide and fluticasone) in adults.[3] Nevertheless, asthma prevalence has remained relatively stable and disease burden remains significant.[4] In addition to the effects on the patient, asthma contributes to a significant amount of absenteeism and loss of productivity in the workforce.[4]

Optimal asthma management remains a challenge despite the development of effective medications and practice guidelines. Inhaled medications are the cornerstone of its pharmacological treatment. Although short-acting β_2-agonists (SABAs; salbutamol and

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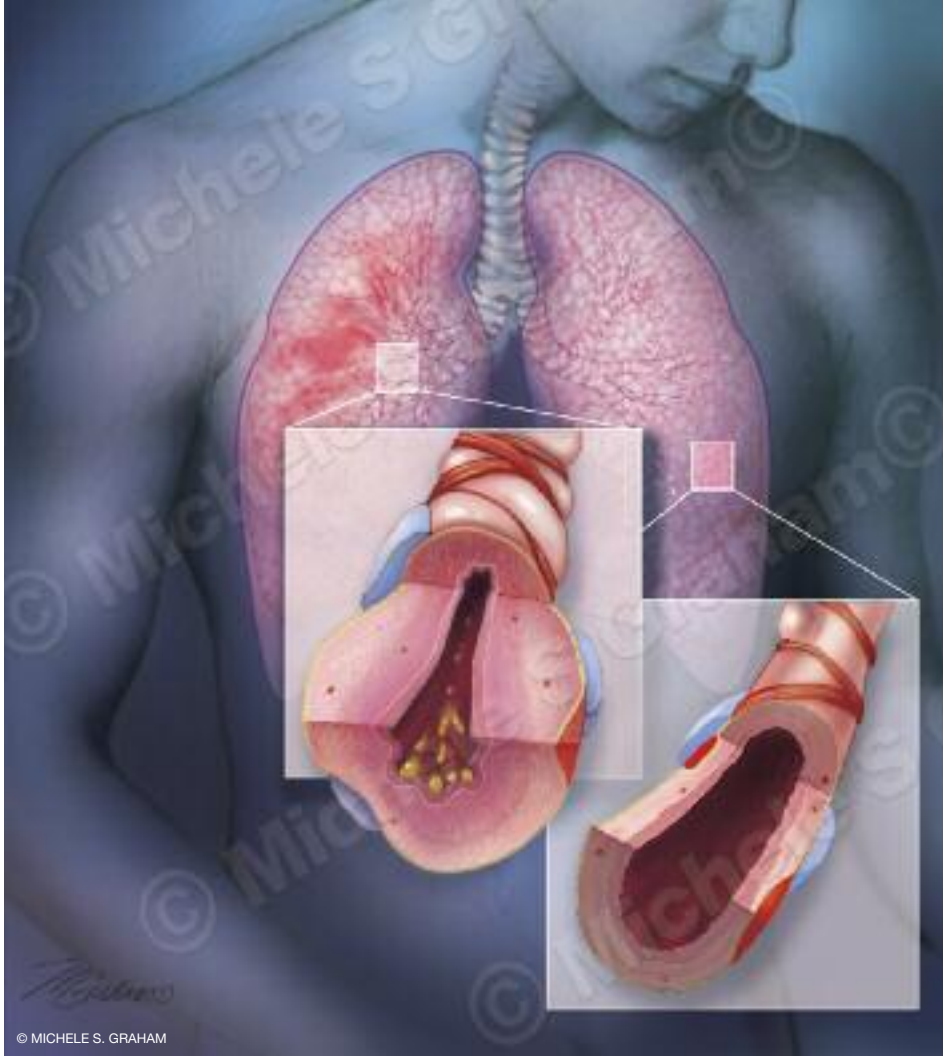
terbutaline) are effective at providing short-term symptomatic relief, their overuse is discouraged because they do not alter the underlying airway pathology or long-term clinical outcomes. ICS are effective at treating airway inflammation but not all asthma symptoms are due to inflammation, hence some patients continue to experience symptoms even after the airway inflammation has been adequately suppressed.[5,6] Long-acting β_2-agonists (LABAs; eformoterol and salmeterol) are effective bronchodilators and can improve patient symptoms when used in conjunction with ICS.[7] Long-acting β_2-agonist monotherapy, on the other hand, has been associated with increased asthma deaths and is not recommended.[8,9] Combination ICS/long-acting β_2-agonists products (budesonide/eformoterol and fluticasone/salmeterol) have become the most commonly prescribed asthma medications in Australia.[4] The real indication for combination inhalers, however, is likely to be significantly less than current prescriptions.

Optimal management of asthma requires accurate diagnosis, measurement of lung function, regular assessment of asthma control and assessment of comorbidities that are likely to impact on patient symptoms. Asthma control is defined as the extent to which the effects of the disease are reduced or removed by treatment, and encompasses the concepts of current control and future risk.[10] Accurate assessment of asthma control allows initiation of appropriate therapeutic options. More importantly, monitoring the response to treatment and reassessing asthma control at regular intervals allows the clinician to fine-tune the dose of medications to prevent overtreatment while minimising the risk of exacerbations.

Obesity is an increasingly common problem that has been associated with increased asthma prevalence and poorer asthma control.[11-13] Rhinosinusitis often coexists with asthma and significantly impacts on symptoms.[14,15] Other factors, such as adherence, are also pertinent to successful treatment. Although most patients can be managed in general practice, some benefit from referral to a respiratory specialist or a multidisciplinary tertiary centre.



Conventional conceptual illustration showing an asthmatic airway during an asthma exacerbation (left) and a nonasthmatic airway (right). The figure on page 20 illustrates in more detail the changes seen in the airways based on histological studies.

The assessment of patients' symptoms and their lung function and the addressing of comorbidities and risk factors are covered in this first part of a two-part article. The second part, to be published in the September issue of *Medicine Today*, continues the addressing of current control with discussion of optimal medication prescribing and use, and then addresses future risk with discussion of regular monitoring of asthma control and medication dose titration as clinically indicated to reduce the risks of asthma exacerbations, accelerated decline in lung function and medication side effects.

ASTHMA IN AUSTRALIA

In 2008, the Australian Centre for Asthma Monitoring (ACAM) authored an update of asthma statistics in Australia, which was published by the Australian Institute of Health and Welfare.[4] Overall, there has not been any significant decline in the prevalence of asthma in the Australian community. Consistent with international data, there is a slight female predominance among adult asthmatics. Most patients have mild or very mild disease.

TABLE 1. INHALED CORTICOSTEROID DAILY DOSE ACCORDING TO POTENCY CATEGORIES[2]

Dose level	Ciclesonide*	Beclomethasone dipropionate (HFA)†	Fluticasone propionate†	Budesonide†
Low	80 to 160 µg	100 to 200 µg	100 to 200 µg	200 to 400 µg
Medium	160 to 320 µg	200 to 400 µg	200 to 400 µg	400 to 800 µg
High	>320 µg	>400 µg	>400 µg	>800 µg

* Ex-actuator dose; † Ex-valve dose.
ABBREVIATION: HFA = Hydrofluoroalkane propellant.

Disappointingly, less than 10% of patients undergo lung function testing or possess an asthma action plan. Patients in rural areas are more likely to require hospital admission than their urban counterparts, although the reason for this is unclear. As expected, hospitalisation rates for adults peak during winter, given that most exacerbations are attributable to viral infections.[16]

The ACAM data provide a useful insight into prescribing practices in Australia.[4] Around 74% of ICS are prescribed as a ICS/long-acting β_2-agonist combination, usually in the most potent formulation although the majority of effect of ICS is seen at low doses. Table 1 lists the relative potency of different ICS formulations.[2] Reassuringly, since 2002 there has been a downward trend in the proportion of ICS supplied in the most

TABLE 2. LEVELS OF ASTHMA CONTROL[1]

A. *Assessment of current clinical control (preferably over four weeks)*

Characteristic	Controlled (all of the following)	Partly controlled (any measure present)	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice per week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less per week)	More than twice per week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

B. *Assessment of future risk (risk of exacerbations, instability, rapid decline in lung function, side effects)*

Features that are associated with increased risk of adverse events in the future include:
Poor clinical control, frequent exacerbations in past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.
† By definition, an exacerbation in any week makes that an uncontrolled asthma week.
‡ Without administration of bronchodilator; lung function is not a reliable test for children aged 5 years and younger.
ABBREVIATIONS: FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow.

SOURCE: *GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION, GLOBAL INITIATIVE FOR ASTHMA (GINA) – 2010 UPDATE.* GINA; 2010. © GINA.

Healthy airways
The airways are like tubes with a thin lining of healthy tissue surrounded by a band of radial muscle. The airways conduct air into and out of the air sacs where the exchange of oxygen and carbon dioxide occurs.

Airways in asthma – between attacks
The airway lining is swollen, inflamed and damaged in places. The muscle is thickened, 'twitchy' and contracts too easily.

Airways in asthma – during an attack
The muscle around the airway contracts, the lining becomes more swollen or inflamed, and more mucus is produced ('mucus plugs' in the airway). All of these things narrow the airway, causing wheezing, tightness, breathlessness and coughing.

Figure. Schematic representation of a healthy airway and an asthmatic airway during different phases of the disease.

potent formulation. Interestingly, only 28% of those patients using short-acting bronchodilators report using an ICS and less than 20% of adults are regular users of preventer medication. Hence, there is evidence of suboptimal control in a large proportion of patients with asthma in Australia, with concomitant evidence of overprescription in some instances. The low dispensing rate of ICS suggests that many patients may be using them intermittently.

ASTHMA CONTROL

Asthma control – the extent to which the effects of the disease are reduced or removed by treatment – encompasses the concepts of current control and future risk.[10] Asthma that is well controlled is characterised by infrequent daytime symptoms, no activity limitation, no nocturnal symptoms and normal lung function (Table 2).[1] Some patients can achieve well-controlled disease with relatively low doses of ICS, while others may require more intense therapy. Future risk refers to the risk of asthma exacerbations or accelerated decline in lung function, as well as risk of side effects from medications. This highlights the need for regular follow up and dose titration as clinically indicated.

The emphasis on asthma control in clinical management differs from the earlier emphasis on asthma severity, which was defined in terms of clinical features before treatment.[10] Confusion, however, was inevitable because these same features were also used to assess control once a patient was on treatment, and reassessment of the intrinsic severity of the disease would have required cessation of treatment. Thus, focusing on asthma control attempts to eliminate this confusion and highlights the importance of a patient-centred measure as a treatment outcome.

Engaging and educating the patient about the disease is important in achieving asthma control. The representation of the asthmatic airway during stable disease compared with a nonasthmatic airway provided in the Figure may be of help in educating patients about the changes that asthma causes, even in the absence of an exacerbation.

SUGGESTED STEPS TO OPTIMISE ASTHMA CONTROL

Confirm the diagnosis

The diagnosis of asthma should be based on symptoms and confirmed by objective lung function measurement given the heterogeneity in the manifestation of this syndrome. Patients often present with symptoms such as episodic breathlessness, chest tightness or wheeze. Typically, symptoms are variable in intensity during the day (worse at night or in the early morning) and between days (some days better than others). Symptoms also typically improve with inhalation of a short-acting β_2-agonist, although this feature in the history is not specific for asthma. Other features may include a history of childhood asthma, a family history of asthma, or coexisting allergic diseases such as rhinosinusitis and eczema.

The risk factors for adult-onset asthma are poorly defined. However, in longitudinal population studies, asymptomatic

hyper-responsiveness, lower lung function at baseline and smoking are among the risk factors.[17,18] Adult-onset asthma may sometimes appear to develop in previously healthy individuals following a respiratory tract infection.

Cough may be a predominant feature in some individuals but asthma is an unlikely cause for chronic cough in adults in the absence of other respiratory symptoms. Some patients with mucus hypersecretion may have a regular productive cough with yellow mucus. Copious amounts of sputum and green-coloured sputum are indications for further assessment and imaging to exclude other airway pathology such as bronchiectasis. Sinus disease may also result in significant postnasal drip with excess secretions pooling in the major airways (especially during sleep).

Patients with asthma are just as likely to smoke as those who do not have the condition; however, a history of smoking should always alert the clinician to the possibility of chronic obstructive pulmonary disease (COPD). Some patients, of course, may suffer from both conditions. The distinction between asthma and COPD is important because the therapeutic options are different in both stable disease and during disease exacerbations. Table 3 outlines the main differences between the two conditions and the common differential diagnoses of asthma are listed in the box on page 23. Thus, a detailed history to exclude other conditions and identify comorbidities is essential for the optimal control of asthma.

The clinical suspicion of asthma should always be confirmed by objective lung function tests. Evidence of variability in airway function should be measured by performing spirometry before and after inhalation of a short-acting bronchodilator. Patients may have reversibility even if the pre-bronchodilator forced expiratory volume in 1 second (FEV_1) is in the normal predicted range. Monitoring peak expiratory flow readings at home over a period of time is an alternative method to detect evidence of diurnal variability suggestive of asthma, but good technique is essential. A single peak flow measurement, on the other hand, provides limited information. Bronchial provocation tests measure the degree of airway hyper-responsiveness and can be useful for both diagnosis and monitoring of asthma (see below).

Although there is no gold standard diagnostic investigation for asthma, objective lung function measurement provides essential information for accurate diagnosis of the disease and serves as a baseline for future follow up.

TABLE 3. DIFFERENCES BETWEEN ASTHMA AND COPD

Characteristic	Asthma	COPD
Age of onset	Any age	Usually over 40 years
Breathlessness	Episodic	On exertion
Smoking	Sometimes	Common
Atopy	Often	Rare
Variable airflow limitation	Often	Sometimes
Airway hyper-responsiveness	Often	Sometimes (in severe disease)
Progression	Variable	Often
First-line treatment	ICS	Long-acting bronchodilator (anticholinergic or β_2-agonist)
Symptomatic response to ICS	Majority	Variable

ABBREVIATIONS: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid.

Assess asthma control at every visit

Symptoms

As mentioned above, asthmatic symptoms vary in character and intensity. Frequent daytime and any recent nocturnal symptoms may be a sign of suboptimal asthma control. Similarly, daily need for short-acting bronchodilators should result in a re-evaluation of the patient's asthma control and therapy.

Triggers for asthma include specific environmental situations such as exposure to allergens, respiratory tract infection, fumes, strong scents and exercise. Although some patients may experience symptoms after ingestion or inhalation of specific foods or preservatives (such as metabisulfites in wine), true food allergy resulting in worsening of asthma is rare in adults. Exercise-induced symptoms typically start after five to eight minutes of exercise and are particularly responsive to pretreatment with short-acting β_2-agonists.

Asthma control measures

Documenting specific variables such as 'symptom-free days' is often useful for comparison at future visits. Increasingly, composite measures that refer to several patient symptoms provide a 'score' that can, in turn, be used to describe a patient's level of asthma control.

Validated questionnaires such as the Asthma Control Questionnaire (ACQ) have been widely used in asthma research. The ACQ provides a composite score based on seven questions that relate to patient symptom intensity and

short-acting β_2-agonist use in the preceding week as well as the patient's pre-bronchodilator FEV_1.[19] A shorter version of this test can be used for patients taking a long-acting β_2-agonist. The Asthma Control Test (ACT; called Asthma Score in Australia) is a validated five-item instrument asking about symptoms in the preceding four weeks that patients can complete before attending for their clinical review.[20]

The degree of asthma control should be viewed as a continuum but categorising a patient's level of asthma control (such as 'controlled', 'partly controlled' and 'uncontrolled') allows for ease of communication between health professionals. In general, three categories are used although the terminology for such categories differs between guidelines with subtle differences in their definition (Table 2).

In primary practice, assessment of asthma control is inevitably based on asthma symptoms. Some measure of airway function is advocated as part of the assessment process; however, the physiological determinants of asthma control are largely unknown.

Role of lung function tests

Spirometry

Measuring lung function is central for the diagnosis and optimal monitoring of asthma. Performing spirometry allows for the calculation of FEV_1, FVC (forced vital capacity), the spirometric ratio FEV_1/FVC and, if performed before and after inhalation of a short-acting bronchodilator, the amount of acute bronchodilator reversibility. FEV_1 improves within two months of treatment with ICS whereas airway hyper-responsiveness continues to improve beyond one year of continuous anti-inflammatory treatment.[21]

The presence of airway reversibility on spirometry in a patient established on ICS might be an indication of suboptimal treatment. A single spirometric measurement, however, correlates only weakly with patient symptoms.[22] Hence, the combination of spirometry measurement together with the patient's symptom profile provides a more comprehensive assessment of disease status. Asthma symptoms may also persist despite normal spirometry; in these cases, referral for further lung function tests and specialist input would be indicated.

Complex lung function

Airway hyper-responsiveness is a physiological abnormality characteristic of asthma that can be measured in a laboratory using bronchial provocation tests. The degree of airway hyper-responsiveness is variable over time and the abnormality is responsive to ICS treatment.[21] The sensitivity and specificity of provocation tests depend on the population being studied (general population screening versus selecting those with respiratory symptoms). Thus, the test results must be interpreted in the clinical context. Airway hyper-responsiveness has prognostic significance in asthma and correlates with long-term morbidity.[23]

Provocation tests can be divided into 'direct' and 'indirect' tests depending on the stimulus used and its mechanism of action on the airway. Methacholine is a commonly used 'direct' challenge, so-called since it exerts its effects through stimulating the airway smooth muscle directly. 'Indirect' agents, such as inhaled mannitol and hypertonic saline, on the other hand, are thought to better reflect current symptoms because they exert their mode of action via inflammatory mediators in the airway.[24] Airway hyper-responsiveness to mannitol correlates with patient symptoms and quality of life measures, and improves with ICS treatment.[25,26] It is worse in patients with the eosinophilic inflammatory phenotype as opposed to the neutrophilic inflammatory phenotype.[27] However, changes in the inflammatory milieu in the airway do not always correspond with changes in airway hyper-responsiveness.[28,29]

DIFFERENTIAL DIAGNOSES OF ASTHMA

- Chronic obstructive pulmonary disease
- Rhinosinusitis
- Gastro-oesophageal reflux disease
- Sleep apnoea
- Bronchiectasis
- Vocal cord dysfunction
- Cardiac disease – congestive cardiac failure, mitral valve stenosis
- Hyperventilation syndrome

Inflammatory biomarkers can provide information about the underlying pathology and may consequently permit a more tailored treatment approach. The most studied biomarker is the sputum inflammatory cellular profile, but tests using this remain confined to tertiary and research centres because of the manpower and costs involved. Inflammatory phenotypes can be divided into eosinophilic or non-eosinophilic asthma based on the percentage of inflammatory cells seen in the sputum.[30] Eosinophilic asthma is more responsive to ICS treatment, with improvements in spirometry and airway hyper-responsiveness seen within eight weeks.[31,32] Non-eosinophilic asthma is more frequently reported in adult-onset asthma and its response to ICS is more variable.[33-35] The role of macrolide antibiotics in the treatment of non-eosinophilic asthma is currently being investigated.[36] Thus, monitoring inflammatory phenotype in a patient can influence prescribing practice as the response to treatment is somewhat dependent on that phenotype.

Measuring exhaled nitric oxide using simple hand-held devices may have a role in the clinical management of asthma. Fractional exhaled nitric oxide

(F_ENO), a nonspecific marker of airway inflammation, is elevated at diagnosis, reduces with ICS treatment and correlates with asthma control over time.[37-40] Although it has not proven to be superior to clinical monitoring in reducing exacerbations in clinical studies,[41] monitoring the trend of F_ENO in an individual patient might be clinically useful in optimising asthma control and titrating medication dose. Measuring IgE levels has a limited role in everyday asthma management but may be useful in the assessment of severe asthma cases.

Detailed lung function tests, including measurement of the degree of air trapping, the propensity for airway closure and the degree of ventilation inhomogeneity, have been associated with asthma severity, risk of exacerbations and poor asthma control.[42-46] They allow better understanding of the behaviour of the airway in asthma, are easy to perform and are increasingly being used in certain clinical situations such as monitoring lung function in children and in conditions such as cystic fibrosis.[47-49] However, most of these tests are currently confined to research situations.

Identify comorbidities risk factors and triggers

Comorbidities are common in patients with asthma and may impact on the expression of symptoms.

Rhinosinusitis

Untreated rhinosinusitis may result in recurrent infections and predispose to poor asthma control.[14] Patients with untreated rhinitis may suffer from nasal congestion, which could contribute to the sensation of breathlessness or increase bronchoconstriction due to reduction of nose-breathing.

Gastro-oesophageal reflux disease

Patients with gastro-oesophageal reflux disease (GORD) may experience chest tightness that could lead to symptom misperception and may be incorrectly attributed as asthma-related. Treatment of symptomatic GORD with proton pump inhibitors results in improvement in asthma quality-of-life measures, especially in patients experiencing nocturnal asthma symptoms; however, clinically-significant improvements in lung function are minimal.[50,51]

Vocal cord dysfunction

Vocal cord dysfunction is another condition that may coexist with asthma or lead to a false positive diagnosis of asthma.[52] Patients may experience breathlessness on inspiration and expiration. Other symptoms may include a choking sensation, throat tightness, voice hoarseness, stridor and wheeze. Symptoms typically respond poorly to β_2-agonists and patients often utilise more medical resources with repeated attendances for clinical review.[53] Some patients may present to emergency departments with such nonresponsive symptoms. Unnecessary escalation of ICS treatment should be avoided in such circumstances.

Vocal cord dysfunction may be difficult to diagnose between acute episodes and an upper airway assessment in a dedicated clinic with ENT and speech pathology input can be helpful.[54] Patients with vocal cord dysfunction benefit from interventions to relax the laryngeal muscles.[55-57]

Obesity and obstructive sleep apnoea

Obesity is associated with worse asthma control, and symptoms in obese asthmatics are also less responsive to ICS and LABA treatment.[12,58-60] Asthma is not systematically overdiagnosed in obese compared with nonobese individuals.[61] The mechanism linking obesity and poor asthma control remains poorly understood but obesity results in altered lung mechanics and this may predispose obese individuals to respiratory symptoms.[62] Hence the effects of obesity and asthma on the respiratory system may be additive.[63]

Obstructive sleep apnoea has also been associated with poor asthma control independent of obesity.[64] Again, the mechanism for this is unclear but mechanical factors in the upper or lower airways

resulting from breathing at low lung volumes during sleep may be important.

Smoking

Smoking is an important comorbidity that should be assessed in every patient with asthma. Smoking is associated with more severe symptoms, poorer asthma control and increased short-acting β_2-agonist use.[65,66] It is well known that smoking leads to accelerated lung function decline in the general population, but individuals with asthma who smoke seem to be particularly susceptible to this loss of lung function.[67-70]

Patients with asthma who smoke are usually excluded from most clinical trials, which makes it difficult to extrapolate trial results, and hence treatment, to this group of patients. Smoking reduces the effectiveness of inhaled and oral corticosteroids in patients with asthma.[71-74] Hence patients with asthma who smoke may require an increased dose of ICS for a similar benefit compared with nonsmoking patients. Efforts to help patients quit smoking are just as important as standard asthma treatment.[75]

Allergens

Measures to reduce the exposure of patients with asthma to common allergens such as house dust mite are costly and burdensome, and have limited effects on asthma control.[76] Such measures should only be recommended on an individual basis.

Sensitisation to cat allergen is associated with more severe asthma.[77] Patients with difficult-to-control asthma who are pet dander-sensitised should remove the pet from their environment. These patients, however, are often nonadherent to such a recommendation.[78]

Exercise

Although exercise is a common trigger for asthma symptoms, it should be empha - sised to patients that exercise is beneficial and should not be avoided. Regular preventer treatment, with use of inhaled short-acting β_2-agonists prior to exercise if necessary, can effectively prevent exercise-induced asthma.

SUMMARY

Asthma is common condition that continues to cause significant morbidity. Current asthma control should be assessed at every consultation as poor asthma control is a risk factor for future exacerbations, but many patients accept an ongoing level of symptoms and do not raise the issue with their doctor. Comorbidities and risk factors should be addressed to optimise asthma control. MT

REFERENCES

A list of references is available on request to the editorial office.

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REFERENCES

1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, GINA 2010. GINA; 2010. Available online at: www.ginasthma.org (accessed July 2011).
2. National Asthma Council Australia (NAC). Asthma management handbook 2006. Melbourne: National Asthma Council Australia; 2006. Available online at: www.nationalasthma.org.au (accessed July 2011).
3. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000; 343: 332-336.
4. Australian Centre for Asthma Monitoring. Asthma in Australia 2008. Australian Institute of Health and Welfare (AIHW) Asthma Series no. 3. Cat. no. ACM 14. Canberra: AIHW; 2008. Available online at: www.asthmamonitoring.org/AinA08_html/Index.htm (accessed July 2011).
5. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002; 360: 1715-1721.
6. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178: 218-224.
7. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL Study. Am J Respir Crit Care Med 2004; 170: 836-844.
8. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993; 306: 1034-1037.
9. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmaco - therapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129: 15-26.
10. Reddel HK, Taylor DR, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society Statement. Asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180: 59-99.
11. Ford ES, Mannino DM. Time trends in obesity among adults with asthma in the United States: findings from three national surveys. J Asthma 2005; 42: 91-95.
12. Lessard A, Turcotte H, Cormier Y, et al. Obesity and asthma: a specific phenotype? Chest 2008; 134: 317-323.
13. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med 2006; 100: 648-657.
14. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. Allergy 2008; 63: 292-298.
15. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. Chest 2006; 130: 429-435.
16. Busse WW, Lemanske Jr RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010; 376: 826-834.
17. Anto JM, Sunyer J, Basagana X, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. Allergy 2010; 65: 1021-1030.
18. Jamrozik E, Knuiman MW, James A, Divitini M, Musk AW. Risk factors for adult-onset asthma: a 14-year longitudinal study. Respirology 2009; 14: 814-821.
19. 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: 902-907.
20. Nathan RA, Sorkness CA, Kosinski M, et al.

Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004; 113: 59-65.
21. Reddel HK, Jenkins CR, Marks GB, et al. Optimal asthma control, starting with high doses of inhaled budesonide. Eur Respir J 2000; 16: 226-235.
22. Shingo S, Zhang J, Reiss TF. Correlation of airway obstruction and patient-reported endpoints in clinical studies. Eur Respir J 2001; 17: 220-224.
23. Xuan W, Peat JK, Toelle BG, Marks GB, Berry G, Woolcock AJ. Lung function growth and its relation to airway hyperresponsiveness and recent wheeze. Results from a longitudinal population study. Am J Respir Crit Care Med 2000; 161: 1820-1824.
24. Joos GF, O'Connor B, Anderson SD, et al. Indirect airway challenges. Eur Respir J 2003; 21: 1050-1068.
25. Brannan JD, Koskela H, Anderson SD, Chan HK. Budesonide reduces sensitivity and reactivity to inhaled mannitol in asthmatic subjects. Respirology 2002; 7: 37-44.
26. Porsbjerg C, Brannan JD, Anderson SD, Backer V. Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. Clin Exp Allergy 2008; 38: 43-50.
27. Porsbjerg C, Lund TK, Pedersen L, et al. Inflammatory subtypes in asthma are related to airway hyperresponsiveness to mannitol and exhaled NO. J Asthma 2009; 46: 606-612.
28. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000; 356: 2144-2148.
29. Hanxiang N, Jiong Y, Yanwei C, et al. Persistent airway inflammation and bronchial hyperresponsiveness in patients with totally controlled asthma. Int J Clin Pract 2008; 62: 599-605.
30. Hargreave FE. Induced sputum for the investigation of airway inflammation: evidence for its clinical application. Can Respir J 1999; 6: 169-174.
31. Pavord ID, Pizzichini MM, Pizzichini E, Hargreave FE. The use of induced sputum to investigate airway inflammation. Thorax 1997; 52: 498-501.
32. Berry M, Morgan A, Shaw DE, et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. Thorax 2007; 62: 1043-1049.
33. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002; 57: 875-879.
34. Bacci E, Cianchetti S, Bartoli M, et al. Low sputum eosinophils predict the lack of response to beclomethasone in symptomatic asthmatic patients. Chest 2006; 129: 565-572.
35. Godon P, Boulet LP, Malo JL, Cartier A, Lemiere C. Assessment and evaluation of symptomatic steroid-naive asthmatics without sputum eosinophilia and their response to inhaled corticosteroids. Eur Respir J 2002; 20: 1364-1369.
36. Simpson JL, Powell H, Boyle MJ, et al. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. Am J Respir Crit Care Med 2008; 177: 148-155.
37. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J 1993; 6: 1368-1370.
38. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996; 153: 454-457.
39. Jones SL, Kittelson J, Cowan JO, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 2001; 164: 738-743.
40. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J 2008; 31: 539-546.
41. Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev 2009; (4): CD006340.
42. Sorkness RL, Bleecker ER, Busse WW, et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol 2008; 104: 394-403.
43. Mahut B, Peiffer C, Bokov P, Beydon N, Delclaux C. Gas trapping is associated with severe exacerbation in asthmatic children. Respir Med 2010; 104: 1230-1233.
44. Gibbons WJ, Sharma A, Lougheed D, Macklem PT. Detection of excessive bronchoconstriction in asthma. Am J Respir Crit Care Med 1996; 153: 582-589.
45. in't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. Am J Respir Crit Care Med 2000; 161: 1902-1906.
46. Bourdin A, Paganin F, Préfaut C, Kieseler D, Godard P, Chanez P. Nitrogen washout slope in poorly controlled asthma. Allergy 2006; 61: 85-89.
47. Chapman DG, Berend N, King GG, Salome CM. Increased airway closure is a determinant of airway hyperresponsiveness. Eur Respir J 2008; 32: 1563-1569.
48. Downie SR, Salome CM, Verbanck S, et al. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. Thorax 2007; 62: 684-689.
49. Horsley A. Lung clearance index in the assessment of airways disease. Respir Med 2009; 103: 793-799.
50. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2006; 173: 1091-1097.
51. Kiljander TO, Junghard O, Beckman O, Lind T. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2010; 181: 1042-1048.
52. Parsons JP, Benninger C, Hawley MP, Philips G, Forrest LA, Mastronarde JG. Vocal cord dysfunction: beyond severe asthma. Respir Med 2010; 104: 504-509.
53. Mikita J, Parker J. High levels of medical utilization by ambulatory patients with vocal cord dysfunction as compared to age- and gender-matched asthmatics. Chest 2006; 129: 905-908.
54. Morris MJ, Christopher KL. Diagnostic criteria for the classification of vocal cord dysfunction. Chest 2010; 138: 1213-1223.
55. Mikita JA, Mikita CP. Vocal cord dysfunction. Allergy Asthma Proc 2006; 27: 411-414.
56. Seifert E, Kollbrunner J. Vocal cord dysfunction: dealing with aggressivity. Swiss Med Wkly 2007; 137(7-8): 127-129.
57. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. The relationship between chronic cough and paradoxical vocal fold movement: a review of the literature. J Voice 2006; 20: 466-480.
58. Farah CS, Kermode JA, Downie SR, et al. Obesity is a determinant of asthma control, independent of inflammation and lung mechanics. Chest 2011; Mar 17 [Epub ahead of print].
59. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007; 101: 2240-2247.
60. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006; 27: 495-503.
61. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults. CMAJ 2008; 179: 1121-1131.
62. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol 2010; 108: 206-211.
63. Nicolacakis K, Skowronski ME, Coreno AJ, et al. Observations on the physiological interactions between obesity and asthma. J Appl Physiol 2008; 105: 1533-1541.
64. Teodorescu M, Polomis DA, Hall SV, et al. Association of obstructive sleep apnea risk with asthma control in adults. Chest 2010; 138: 543-550.
65. Althuis MD, Sexton M, Prybylski D. Cigarette smoking and asthma symptom severity among adult asthmatics. J Asthma 1999; 36: 257-264.
66. Tønnesen P, Pisinger C, Hvidberg S, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res 2005; 7: 139-148.

67. Fletcher C, Peto R. The natural history of chronic airflow obstruction. BMJ 1977; 1(6077): 1645-1648.
68. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring Cohort. Am J Respir Crit Care Med 2009; 180: 3-10.
69. Apostol GG, Jacobs DR Jr, Tsai AW, et al. Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults Study. Am J Respir Crit Care Med 2002; 166: 166-172.
70. 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: 1194-1200.
71. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002; 57: 226-230.
72. Chaudhuri R, Livingston E, McMahon AD, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med 2006; 174: 127-133.
73. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med 2003; 168: 1308-1311.
74. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med 2007; 175: 783-790.
75. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. Eur Respir J 2004; 24: 822-833.
76. Wright GR, Howieson S, McSharry C, et al. Effect of improved home ventilation on asthma control and house dust mite allergen levels. Allergy 2009; 64: 1671-1680.
77. Cazzoletti L, Marcon A, Corsico A, et al. Asthma severity according to Global Initiative for Asthma and its determinants: an international study. Int Arch Allergy Immunol 2010; 151: 70-79.
78. Ling M, Long AA. Pet dander and difficult-to-control asthma: therapeutic options. Allergy Asthma Proc 2010; 31: 385-391.