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Canadian asthma consensus report, 1999

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Abstract

Objectives: To provide physicians with current guidelines for the diagnosis and optimal management of asthma in children and adults, including pregnant women and the elderly, in office, emergency department, hospital and clinic settings.

Options: The consensus group considered the roles of education, avoidance of provocative environmental and other factors, diverse pharmacotherapies, delivery devices and emergency and in-hospital management of asthma.

Outcomes: Provision of the best control of asthma by confirmation of the diagnosis using objective measures, rapid achievement and maintenance of control and regular follow-up.

Evidence: The key diagnostic and therapeutic recommendations are based on the 1995 Canadian guidelines and a critical review of the literature by small groups before a full meeting of the consensus group. Recommendations are graded according to 5 levels of evidence. Differences of opinion were resolved by consensus following discussion.

Values: Respirologists, immunoallergists, pediatricians and emergency and family physicians gave prime consideration to the achievement and maintenance of optimal control of asthma through avoidance of environmental inciters, education of patients and the lowest effective regime of pharmacotherapy to reduce morbidity and mortality.

Benefits, harms and costs: Adherence to the guidelines should be accompanied by significant reduction in patients' symptoms, reduced morbidity and mortality, fewer emergency and hospital admissions, fewer adverse side-effects from medications, better quality of life for patients and reduced costs.

Recommendations: Recommendations are included in each section of the report. In summary, after a diagnosis of asthma is made based on clinical evaluation, including demonstration of variable airflow obstruction, and contributing factors are identified, a treatment plan is established to obtain and maintain optimal asthma control. The main components of treatment are patient education, environmental control, pharmacotherapy tailored to the individual and regular follow-up.

Validation: The recommendations were distributed to the members of the Canadian Thoracic Society Asthma and Standards Committees, as well as members of the board of the Canadian Thoracic Society. In addition, collaborating groups representing the Canadian Association of Emergency Physicians, the Canadian College of Family Physicians, the Canadian Paediatric Society and the Canadian Society of Allergy and Immunology were asked to validate the recommendations. The recommendations were discussed at regional meetings throughout Canada. They were also compared with the recommendations of other similar groups in other countries.

Dissemination and implementation: An implementation committee has established a strategy for disseminating these guidelines to physicians, other health professionals and patients and for developing tools and means that will help integrate the recommendations into current asthma care. The plan is outlined in this report.

Sponsors: This is a joint report of the Canadian Thoracic Society, the Canadian Paediatric Society, the Canadian Society of Allergy and Clinical Immunology, the Canadian Association of Emergency Physicians and the Family Physician Asthma Group of Canada. It is sponsored by these organizations, as well as the Lung Association and the College of Family Physicians of Canada. It was supported by 3M Pharmaceuticals, Astra Pharma Inc., Boehringer Ingelheim Canada, Ltd., Glaxo Wellcome Canada Inc., Merck Frosst Canada Inc., Novartis Pharma Canada Inc and Zeneca Pharma Inc.

Special Supplement

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This article has been peer reviewed.

Summary of recommendations
Résumé des recommandations

The first Canadian guidelines on the best approach to management of asthma in children and adults in an ambulatory care setting were established in 1989 by a panel of Canadian and international specialists on asthma under the leadership of Dr. Frederick E. Hargreave.[1] In 1995, the Asthma Committee of the Canadian Thoracic Society organized a meeting to review the guidelines and incorporate the recent recommendations of the Canadian Association of Emergency Physicians on acute asthma[2] into the revised document.[3]

In light of recent research, a group of respirologists, pediatricians, immunoallergists, emergency and family physicians met at Niagara-on-the-Lake, Ont., from 28 to 31 May 1998, to review and revise the 1995 recommendations.[3]

All recognized the importance of adapting treatment to the individual and the situation at hand; however, we provide these evidence-based recommendations as a guide to clinicians. Recommendations are made for both adults and children. There may be some duplication of information across the various sections, but this will allow a more comprehensive reading of each section and emphasize the most important messages.

Goals

The goals of participants in the conference were to:

- review and discuss recent developments in the treatment of asthma
- review and revise the 1995 evidence-based Canadian guidelines[3] on asthma for children and adults
- develop strategies to implement the asthma guidelines at the regional level
- determine what key studies are required to increase the level of evidence supporting the recommendations.

Levels of evidence

Recommendations are based on a critical review of the scientific literature by small groups before the meeting and are categorized into 5 levels according to the strength of the supporting evidence (Table 1).[4]

These 5 levels do not describe the quality or credibility of the evidence; rather, they indicate its nature. In general, a randomized, controlled trial has the greatest credibility (level I evidence); however, it may have defects that diminish its value, and these should be noted. Evidence based on too few observations to give a statistically significant result is classified as level II. Generally, level III studies carry less credibility than level I or level II studies, but credibility is increased when consistent results are obtained from several level III studies carried out at different times and in different places.

Decisions must often be made in the absence of published evidence. In these situations, it is necessary to rely on the opinion of experts based on their knowledge and clinical experience. Distinction is made between the published opinion of authorities (level IV) and the opinion of those who have contributed to these guidelines (level V). Nevertheless, because of the exhaustive consensus-building process used in the preparation of these guidelines, this level V evidence has achieved a level of credibility that is at least equivalent to level IV evidence.

General principles of management of asthma

Asthma is characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and a variable degree of hyperresponsiveness of airways to endogenous or exogenous stimuli.

Inflammation and its resultant effects on airway structure are considered to be the main mechanisms leading to the development and maintenance of asthma; therefore, the main thrust of asthma therapy is to limit exposure to triggering factors and to reduce the inflammatory process using anti-inflammatory agents. If needed, therapies to maintain optimal airway calibre and to control symptoms may be added to ensure acceptable asthma control and to improve quality of life. This requires individual assessment of the need for therapeutic intervention and establishment of the risks and benefits of various therapeutic choices (environmental measures, education and pharmacotherapy).

Environmental control, particularly avoidance of relevant allergens and respiratory irritants, and proper patient education are essential to achieve adequate control of asthma. A list of the most common environmental measures is included in the section on environment.

Table 1: Levels of evidence[4]

Level I	Evidence is based on randomized controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.
Level II	Evidence is based on randomized controlled trials that are too small to provide level I evidence. They may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.
Level III	Evidence is based on nonrandomized controlled or cohort studies, case series, case–control studies or cross-sectional studies.
Level IV	Evidence is based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines.
Level V	Evidence is based on the opinions of those who have written and reviewed the guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers

Conference participants agreed to retain the concept of the asthma continuum adopted at the last Canadian Asthma Consensus Conference,[3] reflecting a dynamic therapeutic approach that allows drug therapy to be adapted to the severity of the underlying illness and facilitates adjustment of the intensity of therapy to the degree of control achieved.

They also agreed that the concept of "control" of asthma should be differentiated from "severity" of asthma.[5]

Criteria for asthma control

Although optimal control of asthma means the absence of respiratory symptoms and of the need for rescue bronchodilator, as well as normal pulmonary function, this is difficult to achieve in all patients with asthma. The participants preferred to base treatment needs on what they defined as *acceptable* asthma control, using clinical and physiologic parameters (Table 2). Such control is obtained through appropriate environmental measures, proper patient education and pharmacotherapy tailored to the individual. Control should be regularly assessed and treatment adjusted accordingly.

Assessment of the severity of asthma

The severity of asthma in a patient is judged by the frequency and duration of respiratory symptoms, the presence of persistent airflow limitation and the medication required to maintain control. When asthma is well controlled, one of the best ways to judge severity is to determine the level of treatment needed to maintain acceptable control (see Table 3 and the section on diagnosis and evaluation).

Signs of severe or poorly controlled asthma also include:

- the occurrence of a prior near-fatal episode (loss of consciousness, need for intubation), recent admission to hospital or a visit to the emergency department
- night-time symptoms
- limitation of daily activities
- need for an inhaled β_2-agonist several times a day or at night
- forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) below 60% of predicted values.

Each new treatment should be viewed as a therapeutic trial and its efficacy assessed by monitoring control according to the criteria described above. Furthermore, asthma severity is likely to vary over time; this is especially so in children, in whom asthma often decreases with age, and suggests the need to attempt to reduce medication when asthma ceases to be troublesome. Once control of asthma has been maintained for at least several months, an attempt should be made to reduce medication within the bounds of acceptable control.

Table 2: Indications of asthma control

Parameter	Frequency or value
Daytime symptoms	< 4 days/week
Night-time symptoms	< 1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school	None
Need for short-acting β_2-agonist	< 4 doses/week*
FEV_1 or PEF	> 85% of personal best, ideally 90%
PEF diurnal variation†	< 15% of diurnal variation

FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow obtained with a portable peak flow meter.
*May use 1 dose/day for prevention of exercise-induced symptoms.
†Diurnal variation is calculated by subtracting the lowest PEF from the highest and dividing by the highest PEF multiplied by 100.

Asthma management: a continuum

We propose the following algorithm for the management of asthma:

A. *When asthma is suspected from symptoms and clinical presentation, confirm diagnosis by objective measures of variable airflow obstruction and assess severity*
   - *Spirometry (the preferred method):* A 12% (preferably 15%) or greater improvement in FEV_1 (i.e., at least 180 mL) from the baseline 15 minutes after use of an inhaled short-acting β_2-agonist, a 20% (250 mL) or greater improvement after 10–14 days of ingested prednisone when symptoms are stable or 20% (250 mL) or greater "spontaneous variability" is considered significant.

Table 3: Levels of asthma severity based on treatment needed to obtain control

Asthma severity	Symptoms	Treatment required
Very mild	Mild–infrequent	None, or inhaled short-acting β_2-agonist rarely
Mild	Well-controlled	Short-acting β_2-agonist (occasionally) and low-dose inhaled glucocorticosteroid*
Moderate	Well-controlled	Short-acting β_2-agonist and low to moderate doses of inhaled glucocorticosteroid with or without additional therapy
Severe	Well-controlled	Short-acting β_2-agonist and high doses of inhaled glucocorticosteroid and additional therapy
Very severe	May be controlled or not well-controlled	Short-acting β_2-agonist and high doses of inhaled glucocorticosteroid and additional therapy and oral glucocorticosteroid

*See Table 1 on page S24.
Adapted from Cockfroft et al[5]

- *Serial measures of PEF:* > 20% change after administration of a bronchodilator or over time.
- *Methacholine challenge:* Provocative concentration of methacholine giving a 20% reduction in FEV_1 (PC_{20}) < 8 mg/mL (Juniper method[6]).

B. *Rapidly achieve best asthma control*
- If symptoms are infrequent and expiratory flows are normal, an inhaled short-acting β_2-agonist should be used on demand.
- If a rescue β_2-agonist is needed more than 3 times a week or if lung function is abnormal, an inhaled glucocorticosteroid equivalent to 400–1000 μg/d of beclomethasone dipropionate is the preferred next step (200 –1000 μg/d in children).
- If symptoms are frequent and expiratory flows are < 60% of predicted value, initial therapy with prednisone should be considered.

C. *Maintain acceptable asthma control* (Table 2 and Fig. 1)
- Determine minimal medication needs to keep best results, then write an action plan (Appendix).

D. *Ensure regular follow-up*
- Regularly review asthma control, medication needs and the action plan.
- Reassess environmental control and compliance with treatment.
- Assess the need for additional investigation, education or referral.

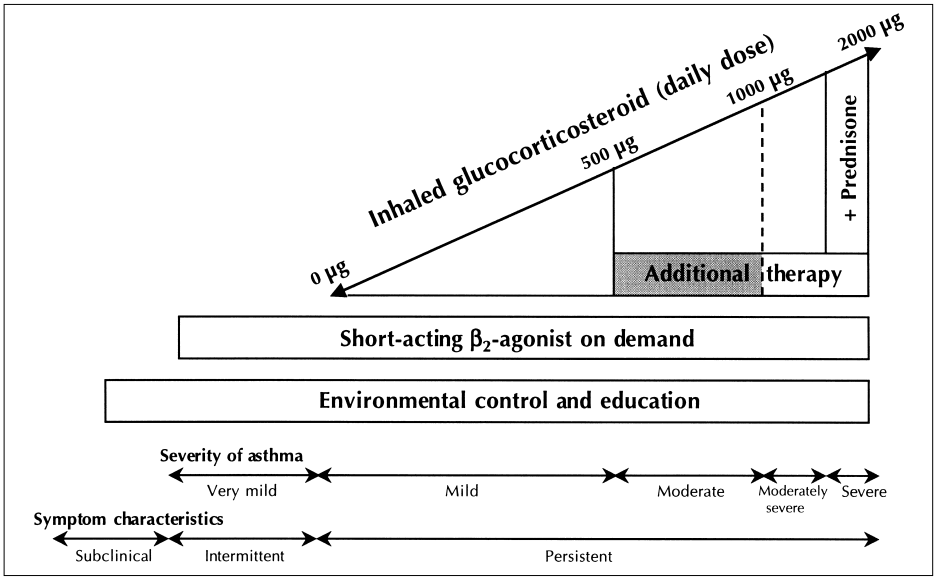

Fig. 1: Continuum of asthma management. Severity of asthma is ideally assessed by medication required to maintain asthma control. Environmental control and education should be instituted for all asthma patients. Very mild asthma is treated with short-acting β_2-agonists, taken as needed. If β_2-agonists are needed more than 3 times/week (excluding 1 dose/day before exercise), then inhaled glucocorticosteroids should be added at the minimum daily dose required to control the asthma. If asthma is not adequately controlled by moderate doses (500–1000 μg/d of beclomethasone or equivalent), additional therapy (including long-acting β_2-agonists, leukotriene antagonists or, less often, other medications) should be considered. Severe asthma may require additional treatment with prednisone.

General principles of drug therapy

Medications used to treat asthma are generally divided into 2 main categories: relievers and controllers.

Relievers are best represented by the inhaled short-acting β_2-agonists. These quick-acting bronchodilators are used to relieve acute intercurrent asthma symptoms, only on demand and at the minimum required dose and frequency. Inhaled ipratropium bromide is less effective, but is occasionally used as a reliever medication in patients intolerant of short-acting β_2-agonists.

Controllers (or preventers) include anti-inflammatory medications, such as inhaled (and oral) glucocorticosteroids, leukotriene-receptor antagonists, and anti-allergic or inhaled nonsteroidal agents, such as cromoglycate and nedocromil. These agents are generally taken regularly to control asthma and prevent exacerbations. Inhaled glucocorticosteroids are the most effective agents in this category.

The controller group also includes some bronchodilators that are taken regularly in addition to inhaled glucocorticosteroids to help achieve and maintain asthma control. These include the long-acting inhaled β_2-agonists salmeterol and formoterol, which are the first choice in this category, as well as theophylline and ipratropium. The β_2-agonists and ipratropium are considered of no significant benefit in reducing airway inflammation. There is some evidence that theophylline may have immunomodulatory effects, but the clinical significance of this remains to be demonstrated.

Asthma drugs are preferably inhaled, because this route minimizes systemic absorption and, thus, improves the ratio of the therapeutic benefit to the potential side-effects. The patient must have repeated instruction on how to use the inhaled medication. The recently developed oral leukotriene-receptor antagonists have good safety and tolerance profiles and are taken orally, which may help certain patients comply with treatment.

Asthma medications should be used at the minimum dose and frequency required to maintain acceptable asthma control; they should not be used as a substitute for proper control of the environment. Asthma medica-

tions are considered to be safe over many years when used appropriately.

The participants in the asthma consensus conference have reviewed the role of each category of medication. In the following sections they describe briefly the mode of action, pharmacologic and clinical profile, mode of administration and potential side-effects of these drugs.

Competing interests: The authors have received consultancy fees, travel assistance to attend meetings, speaker fees and honoraria from various manufacturers of asthma medications.

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Diagnosis and evaluation of asthma in adults

Recommendations

- Objective measurements are needed to confirm the diagnosis of asthma and to assess its severity in all symptomatic patients (level III) using:
  Spirometry: A 12% (preferably 15%) or greater (at least 180 mL) improvement in FEV_1 from the baseline 15 minutes after use of an inhaled short-acting β_2-agonist, a 20% (250 mL) improvement after 10–14 days of inhaled glucocorticosteroid or ingested prednisone when symptoms are stable or a 20% (250 mL) or greater "spontaneous variability" is considered significant (level IV).
  Peak expiratory flow (PEF): When spirometry and methacholine testing are unavailable, variable airflow obstruction (i.e., ideally 20% or greater diurnal variability) can be documented by home-measured PEF (level II), although this method is not as sensitive or reliable as FEV_1.
  Airway hyperresponsiveness: Measurement of airway responsiveness to methacholine in specialized pulmonary function laboratories may help to diagnose asthma (level III).
- Appropriate allergy assessment is warranted in patients with asthma (level III) and must be interpreted in light of the patient's history (level III).
- The primary measure of asthma severity in the treated patient should be the minimum therapy required to achieve acceptable control (level III).

Three main features must be considered in the diagnosis of asthma: symptoms, variable airflow obstruction and airway inflammation.[1–3] Airway inflammation is not yet readily tested in routine clinical practice and will not be considered further here. However, skin testing may be an adjunct to diagnosis and is discussed in this section.

Symptoms

Common symptoms of asthma include wheezing, chest tightness, dyspnea and cough. The characteristics of these symptoms, which are variable, often paroxysmal and provoked by allergic or nonallergic stimuli such as cold air and irritants, are useful in diagnosis. Nocturnal occurrence is common. Measuring the patient's response to a therapeutic trial may be helpful in diagnosis. Nonpulmonary symptoms that suggest a predisposition to allergy — rhinitis, conjunctivitis and eczema — are also common in, but not specific to, asthma patients. In patients with symptoms that are persistent or that do not respond to simple treatment, objective confirmation of variable airflow obstruction is required.[4]

Variable airflow obstruction

Objective measurements are needed to confirm the diagnosis of asthma in all patients and to assess its severity. Objective documentation of variable airflow obstruction can be obtained through measurement of FEV_1, PEF or hyperresponsiveness to methacholine inhalation challenge.

Forced expiratory volume in 1 second

Variable airflow obstruction can be illustrated by improvement in FEV_1 15 minutes after an inhaled β_2-agonist or after a 7- to 14-day course of inhaled glucocorticosteroid or ingested prednisone. A 12% or greater improvement in FEV_1 (i.e., at least 180 mL) from the baseline after administration of a β_2-agonist is considered significant[5] (i.e., outside the 95% confidence interval (CI) for repeatability in people without asthma). However, there are no data to confirm that a bronchodilator response outside this 95% CI is indicative of asthma, and some suggest basing diagnosis on a greater than 15% increase in FEV_1.[5]

Because there is greater variability in FEV_1 over a longer time interval (days or weeks v. minutes), longer-term changes in FEV_1, either without any specific therapeutic intervention or after glucocorticosteroids, must be greater than 20% (at least 250 mL). A trial of glucocorticosteroid involves maximizing the patient's response to a bronchodilator and obtaining a baseline FEV_1, then carrying out a follow-up measurement after a 2-week course of prednisone (taken at the rate of 30 to 40 mg/d) to determine significant response.[5]

Peak expiratory flow

Home measurement of PEF may also be used to document variable airflow obstruction.[6,7] Variable airflow obstruction is confirmed when the 95% CI of the mean percentage difference between the highest and lowest of 4 PEF values (morning and afternoon, before and after using a bronchodilator) is > 12%.[7] However, some recommend a 20% variability to confirm the diagnosis of asthma.[8] The importance of appropriate technique and the limitations of PEF are discussed further under "Home monitoring."

Airway hyperresponsiveness

In patients with normal airflow while resting, excessive

responsiveness to a bronchoconstrictor can be documented using a methacholine inhalation challenge.[8] This test should be done when symptoms are present or have occurred within a few days. Usually the test is available only in specialized centres, which may limit its utility. This test should be made available to primary care physicians who see most patients with mild asthma and where the measurement of responsiveness is most useful.[9] Tests for airway responsiveness may give normal results in patients with glucocorticosteroid-responsive cough due to eosinophilic bronchitis.[10]

Evaluation of asthma severity

There is no agreement about how best to assess overall asthma severity. Assessment of asthma severity before or without treatment usually takes into account 3 factors, including 2 considered in the diagnosis: symptoms, physiologic indicators of airway disease and asthma morbidity. Thus, some algorithm based on frequency and severity of symptoms (including the need for inhaled β_2-agonist rescue therapy), degree of airflow obstruction and indices of morbidity (admissions to hospital, need for intubation, emergency room visits, time away from work or school, etc.) can be used to classify asthma severity (Table 1).

Because asthma is controllable, the factors that define its severity before treatment become markers of its control in the treated patient. The amount of anti-inflammatory medication required to control symptoms is often added to the severity algorithm. However, a case has been made that the primary measure of asthma severity in the treated patient should be the minimum anti-inflammatory medication required to achieve ideal control (See Fig. 1, page S4).[11]

Table 1: Measures of asthma severity

Event or measurement	Severity of asthma		
	Mild	Moderate	Severe
FEV_1 or PEF; % of predicted	>80%	60–80%	<60%
Need for inhaled short-acting β_2-agonist	Every 8 or more h	Every 4–8 h	Every 2–4 h
Probability of			
Previous near fatal episode	0	0	+
Recent admission to hospital	0	0	+
Night-time symptoms	0 to +	+	+++
Limitation of daily activities	0 to +	+ to ++	+++

Note: FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow.

Diagnosis in children

The consensus group believes that, in children able to perform reproducible spirometry, the diagnosis can be established by the same method used for adults. When spirometry is not reproducible, for example in a young child, the diagnosis rests on careful and sometimes repeated history taking and physical examination. Some factors that are particularly useful in establishing a diagnosis in young patients are severe episodes of wheezing, wheezing after 1 year of age, more than 3 episodes of wheezing in a given year, a family history of asthma or atopy, a personal history of asthma or atopy, maternal smoking, clinical benefits from acute bronchodilator therapy, clinical evidence of improvement after anti-inflammatory treatment, chronic cough (especially nocturnal or associated with exercise) and wheezing when viral etiology is unlikely. The likelihood of a diagnosis of asthma increases with the number of these factors present (level V).

Suggestions for future research

- What will be the role of noninvasive markers of airway inflammation (e.g., expired nitric oxide, induced sputum and the quantification of its constituents) on the diagnosis and evaluation of asthma?
- Can the diagnosis of asthma be confirmed through noninvasive means in patients unable to perform reproducible spirometry (e.g., young children)?

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Provocative factors in asthma

Recommendations

- Increasing medication for asthma control should not be used as a substitute for avoidance of exposure to allergens and irritants (level III).
- Exposure to environmental tobacco smoke should be avoided (level III).
- Pregnant women and parents or caregivers of children with asthma should be particularly encouraged not to smoke (level II).
- There is insufficient information to recommend the use of residential air cleaners and humidifiers (level III).
- High concentrations of respiratory irritants should be avoided (level III).
- Occupational asthma should be suspected and investigated in all adults with new-onset asthma (level II).
- Once the diagnosis of occupational asthma has been confirmed, the patient should be removed from exposure to the causative substance (level III).
- In industries associated with a high risk of occupational asthma, the level of exposure in the workplace should be reduced and regularly monitored (level IV).

Aeroallergens

Aeroallergens are ubiquitous, although quantitative and qualitative differences depend on geographic location, climate, degree of urbanization and specific conditions in the home, school and workplace. Almost all adults appear to have T lymphocytes that are sensitized to at least some aeroallergens; thus, development of allergic disease may depend on quantitative differences in T cells.[1] Several lines of evidence link aeroallergens to asthma:[2]

- A total of 60% of adults and 80% of children with asthma have positive skin-prick tests for environmental allergens, and allergen-bronchial challenge tests are positive only in those with allergen-specific positive skin tests.
- Allergen sensitization is a risk factor for severe, acute asthma, especially if the patient is exposed to high concentrations of the specific allergen.
- In general, severity of symptoms and of bronchial responsiveness correlates with degree of sensitivity to allergens; in some patients, allergy does not play an important role.
- Symptoms, PEF and bronchial responsiveness usually improve when allergens to which the person is sensitized are avoided.

Aeroallergens, which are carried on inhalable particles, are proteins that vary in molecular weight from 14 to 78 kilodaltons. Outdoor allergens arise from pollen or mold spores; indoor allergen sources include several species of dust mites, cats, dogs and other mammals, cockroaches and indoor mold spores. The molecular structure and functional properties of common and important indoor allergens, based on the World Health Organization's nomenclature, have recently been summarized.[3] Recombinant allergens with immunoreactivity comparable to that of the natural allergens are being produced and evaluated for allergen standardization, for diagnostic testing and for immunotherapy with specific epitopes and naked DNA vaccines.

Infants are exposed and become sensitized to aeroallergens as well as food allergens in utero.[4,5] In people who are genetically predisposed to allergy, antenatal factors, including maternal and, thus, fetal exposure to allergens and materno–placento–fetal immunologic interactions are important in determining whether the predisposition results in allergic disease.[6] Exposure to low concentrations of indoor allergens in early childhood is associated with a low incidence of sensitization, but very low concentrations may be sufficient to sensitize children who are predisposed and have a family history of allergy, presumably after intrauterine priming.[7]

Aeroallergens as a risk factor for asthma

There are no reliable tests to detect which infants are at risk of developing allergic disease and asthma. A positive skin-prick test for egg protein, as a marker of specific immunoglobulin (Ig) E antibody, at 6 months of age in a group of high-risk children (i.e., with a family history of atopy) was associated with development of atopic dermatitis, wheezy illness and asthma by age 7 years[8] and was consistent with earlier studies.[9–11] In a community study[12] of 360 children, the cumulative incidence of newly diagnosed asthma from 6 to 11 years of age was 12%. Bronchial hyperresponsiveness to cold air at age 6 years was associated with a 2.6-fold increase in risk (95% CI 1.25–5.4). However, after adjusting for mild wheezing at age 6 years, which is associated with an increased risk of 7.5-fold (95% CI 3.6–15.0, $p < 0.001$), and for positive skin-test reaction to inhalant allergens at age 6 years, which is associated with an increased risk of 3.6-fold (95% CI 1.5–9.5, $p < 0.01$), the response to cold air was no longer a significant predictor. Therefore, hyperresponsiveness to cold air is associated with a subsequent diagnosis of asthma, but depends on the presence of atopy and prior mild wheezing.

Earlier studies, as indicated in the 1995 consensus statement,[13] identified exposure to household dust mites and indoor animals, especially cats, as risk factors for asthma. A recent 12-month study[14] of 476 children with asthma, aged 4–9 years, living in inner city communities in the United

States found that 36.8% of the children were allergic to cockroach allergen, 34.9% to dust-mite allergen and 22.7% to cat allergen. Analyses of dust showed that 50.2% of bedrooms contained high concentrations of cockroach allergen, 9.7% contained dust-mite allergen and 12.6% contained cat allergen. Adjusted rates of hospital admission were 0.37 a year for those who were allergic to and exposed to high concentrations of cockroach allergen compared with 0.11 for those allergic to other allergens ($p < 0.001$) and 2.56 unscheduled medical visits for asthma compared with 1.43 ($p < 0.001$). Those allergic to cockroach allergens experienced more days of wheezing, missed school days, night sleep loss and changes in activities than those allergic to dust-mite and cat allergens. This suggests that exposure to high concentrations of allergen in those allergic to a specific allergen is likely to enhance asthma morbidity.

In a higher socioeconomic group,[15] 135 of 1054 adolescents in 2 high schools were identified with asthma; 48 who were symptomatic and responded to histamine challenge and 123 controls were studied. Analysis of total IgE, dust-mite, cat and cockroach sensitization found only allergy to dust-mite allergen to be independently associated with asthma (odds ratio [OR] 6.6, $p < 0.0001$). Dust from 81% of the houses contained more than 2 μg/g of class-I allergen from 2 common species of dust mites, *Dermatophagoides pteronissinus* (Der P_1) and *D. farinae* (Der F_1); 40% contained cat allergens and 17% contained cockroach allergens. Asthma was not associated with race, socioeconomic status, smoking in the home, sensitization to outdoor allergens or indoor allergen concentration. When asthma is prevalent and high concentrations of dust-mite allergen are present, sensitization is the prime risk factor for symptomatic asthma. Nevertheless, the importance of the environment is dependent on the predominant exposures in that environment, which are influenced by cultural and geographic factors.

Seasonal changes in indoor allergen levels have been associated with changes in bronchial responsiveness.[16] In 32 people with asthma, who were allergic to dust mites, the provocative concentration of histamine giving a 20% fall in FEV_1 (PC_{20}) increased from 2.05 mg/mL in autumn to 4.51 mg/mL in spring ($p < 0.001$), indicating a reduction in airway responsiveness. In 11 control subjects, who were allergic but not sensitized to dust mites, there was no significant change (PC_{20} of 3.44 mg/mL in autumn and 4.52 mg/mL in spring). Increased bronchial responsiveness in autumn was associated with higher levels of Der P_1 in floor dust in homes.

Most indoor aeroallergens have been measured in terms of the amount per gram of dust, but, as they must be inhaled to have an effect, ambient airborne concentrations are likely to be much more important. In a recent placebo-controlled, double-blind study[17] using an allergen exposure chamber, 15 people with asthma, who were allergic to dust mites (as evidenced by both skin tests and conventional bronchial-inhalation challenge) were exposed to 1200 μg of the class-I allergen of a common dust mite and to a placebo. Symptoms, PEF and medication use were assessed before and after challenge: 12 reacted with symptoms and a median decrease in FEV_1 of 16.4% when exposed to allergen but not placebo; the other 3 had only minor symptoms during both active and placebo exposure and had no change in lung function. Late-phase reactions occurred in 1 person exposed to allergen, and in 3 given the conventional challenge. No healthy subjects reacted to any challenge. The authors concluded that asthma symptoms in allergic people were elicited by minor amounts of airborne allergen.

Another marker of the role of allergy in asthma is its association with acute asthma that is severe enough to require hospital admission. In a retrospective study involving 138 children aged 5–18 years seen consecutively in a specialized clinic,[18] admission to hospital was associated with age (OR 0.8), allergy to cockroach (OR 2.2) and cat (OR 2.9). Based on a stepwise, multiple logistic regression analysis, only cat allergen (OR 3.8), age (OR 0.8) and race (OR 3.2) were independent predictors. In a prospective, single-blind, randomized controlled study of house-dust avoidance measures in 23 children aged 5–18 years who had been admitted to hospital with acute severe asthma,[19] the 13 children in the experimental group had improved PEF at 3 and 6 months after intervention. The demographics and use of medication were the same in both the experimental and control groups. Improved PEF at 3 months was found in 6 of 7 children sensitized and exposed to dust-mite allergen when allergen concentrations in both bedding and bedroom floors fell. There was no difference in FEV_1. During the study, 4 of the children in the experimental group and 2 of the 10 in the control group were readmitted to hospital with episodes provoked by viral respiratory infections.

Exposure to high concentrations of outdoor allergens has been associated with provocation of severe acute asthma and asthma deaths in subjects allergic to specific allergens, most clearly *Alternaria* spores. Neither exposure to lower concentrations of allergen nor concomitant exposure to air pollutants has been consistently associated with symptoms.

Delfino and colleagues[20] assessed the effect of exposure to outdoor fungal spores and air pollutants on asthma symptoms, PEF and use of rescue medication in 22 subjects with asthma, aged 9–46 years, for 8 weeks during late spring and early summer using a random-effects longitudinal regression model controlled for autocorrelation and weather. Total fungal spore concentration was associated with a modest increase in symptom score (0.36), increased use of bronchodilator medication (0.33 puffs) and decreased evening peak flows (12 L/minute). There was also a modest association between concentration of particles with a diameter of 10 μm or less and increased use of rescue medication (0.15 puffs per 10 $\mu g/m^3$, $p < 0.02$). Ozone had no effect.

Every 2 weeks for 3 months, Hilterman and colleagues[21] followed 60 adults with intermittent to severe asthma to de-

termine, by nasal lavage, the effect of ambient air pollution or allergen exposure on inflammatory changes in the upper airways. Exposure to ambient ozone was associated with an increase in neutrophils (112% per 100 μg/m^3 increase in 8-h average ozone), eosinophils (176%), epithelial cells (55%), interleukin-8 (IL-8) (22%) and eosinophil cationic protein (ECP) (19%). Increases in mugwort-pollen counts (the major airborne pollen during the study period) were associated with increased eosinophils (107% per 100 pollen grains/m^3) and ECP (23%), but not neutrophils, epithelial cells or IL-8. This suggests that inflammation of airway mucosa is provoked by ambient ozone and ambient pollen exposure, but the type of inflammation is qualitatively different.

Respiratory infections

Viral respiratory infection is a well known provocative factor for episodes of asthma. As well, specific agents, including respiratory syncytial virus (RSV), adenovirus, mycoplasma and pertussis, can provoke episodes of wheezing illness and, in a few cases, prolonged bronchial hyperresponsiveness. Recent studies using polymerase chain reaction (PCR) have implicated human rhinoviruses (HRV) as important agents in all age groups, and 1 study using this technique suggested a high prevalence of chronic Chlamydia infection in asthmatic children.[22]

How viruses or other agents provoke asthma is not clear. There is evidence of increased IgE production during viral infection. A recent study[23] using a human B-cell culture system found that HRV-induced, double-stranded RNA activates an antiviral protein kinase that can induce Ig class switching to IgE, suggesting a mechanism for viral provocation of allergy and asthma. This is consistent with a study[24] of experimental HRV infection in asthmatic adults, which resulted in augmented eosinophilic inflammation (assessed in sputum) and enhanced bronchial responsiveness. In another controlled study[25] of experimental HRV infection in people with allergic rhinitis (but no asthma) and a nonallergic control group, there was a significant increase in bronchial responsiveness to histamine in the allergic group. Rhinovirus infection of cultured human tracheal epithelium, confirmed by PCR, resulted in increased expression (up-regulation) of messenger RNA for intercellular adhesion molecule-1 (ICAM-1) mRNA (the major HRV receptor on epithelial cells) and increased secretion of IL-1b, which itself up-regulates ICAM-1. Because ICAM-1 has important eosinophil attractant properties, this may be an important way in which the bronchial airway inflammatory response may be increased by HRV infection in asthma.[26]

RSV infection accompanying bronchiolitis is associated with persistent bronchial hyperresponsiveness in some children, but its role in causing asthma is unclear. Recent animal studies suggest that RSV infection in mice followed by aeroallergen exposure results in pulmonary inflammation with eosinophilic infiltration;[27] in guinea pigs, prior sensitization to allergen followed by infection with RSV results in much more severe mucosal damage.[28]

Viruses are of greatest importance in causing wheezing illness in children under the age of 3 years. Reports from several centres[29,30] now confirm that 20% or more of infants in this age group respond to viral infections with recurring wheezing, which resolves in later childhood. These infants have reduced lung function before the onset of viral infection, have apparently normal immune responses to viral infection and do not have risk factors for asthma (i.e., increased IgE levels, bronchial hyperresponsiveness or a family history of asthma). They may have narrower intrapulmonary airways than normal infants. A second group, about 10% of wheezy infants, also wheeze with virus infections, have some or all of the risk factors for asthma and have recurring wheeze (asthma) in later childhood.[31] There is a great need to develop tests that will accurately differentiate these 2 populations.

Occupational and irritant-induced asthma

Occupational asthma (OA), defined as asthma induced by exposure to a specific agent in the workplace,[32] is the most common occupational lung disease in developeds countries.[33–35] Occupational exposure has been estimated to cause 5%–15% of adult-onset asthma.[36–39] The prevalence of OA due to agents with high molecular weight is generally < 5%; prevalence due to low molecular weight agents is 5%–10%.[40] In 1 series, reactive airways dysfunction syndrome (RADS) or irritant-induced asthma accounted for 17% of 154 consecutive cases of OA.[41]

Many agents can cause OA. Those that cause immunologically mediated OA include a broad spectrum of protein-derived as well as natural and synthetic chemicals used in various workplaces. Extensive lists of causative agents and workplaces have been published and a computerized database is available.[42] These agents can be classified according to whether their pathogenic mechanism is immunologically mediated.

An occupational cause should be suspected for all new cases of asthma in adults. A detailed occupational history of past and current exposure to possible causal agents in the workplace, work processes and specific job duties should be obtained. Information can be requested from the work site, including material safety data sheets. Walk-through visits of the workplace may be necessary. Industrial hygiene data and employee health records can also be obtained.

Temporal associations are not sufficient to diagnose work-related asthma,[43] and objective tests are necessary to confirm the diagnosis. Workers with asthma symptoms should not be told to leave their job until the diagnosis is proven because part of the diagnostic work-up of OA may involve a trial return to the work site by the worker.

Challenge testing with the specific suspected agent has been used to confirm the work relationship.[44] These tests can be falsely negative if a wrong agent is used for testing or if the patient has been away from work for too long. Another method to confirm the work relationship is serial monitoring of PEF for a period at work and a similar period away from work.[45] Computerized peak-flow meters are helpful in overcoming some of the problems of PEF monitoring.[46] When the results of PEF monitoring suggest OA and specific inhalation challenges in the laboratory are not possible or negative, it is advisable to confirm OA by serial spirometry throughout a work shift[47] Combining PEF monitoring with serial assessments of nonallergic bronchial responsiveness can provide further objective evidence.

Identification of those with OA is important because progressive deterioration and permanent disability may occur if exposure continues after onset of symptoms.[48] Early removal from exposure may be associated with disappearance of symptoms and airway hyperresponsiveness.[48]

The ideal treatment is the permanent removal of patients with OA from exposure to the causal agent;[49,50] some workers who have continued in the same job after diagnosis have died.[51] Any patient with OA who remains in the same job should have respiratory protection and close medical follow-up. Worsening of asthma should lead to immediate removal from exposure.

Irritant-induced asthma is caused by single or multiple exposures to high concentrations of an irritant vapour, fume or smoke in previously normal people.[52] The term "reactive airways dysfunction syndrome" or RADS is used when the condition is caused by a single exposure.

A patient's pre-existing asthma may be aggravated by exposure to low levels of irritants, such as fumes, vapours or dust. However, the presence of asthma before being exposed to a sensitizing agent in the workplace does not preclude the development of true OA. People with asthma should not be exposed to concentrations of irritant higher than permissible (the airborne concentration to which nearly all workers may be exposed repeatedly without ill effects), although even this level may not be safe in those with airway hyperresponsiveness.

For further information, readers should consult the full text of the Canadian Thoracic Society Guidelines on occupational asthma.[53]

Indoor and outdoor respiratory irritants

Outdoor air pollution has been linked to acute exacerbations of asthma.[54] Currently, the air pollutants of most concern are inhalable particulates (diameter ≤ 10 μm [PM_{10}]), ground-level ozone, acid aerosol, sulfur dioxide and nitrogen dioxide. Of these, inhalable particulates appear to be the single greatest hazard. Recent studies have shown strong associations between ambient concentrations of inhalable particulates and emergency room visits,[55] admission to hospital and doctor visits for asthma.[56–58] An increase in respiratory symptoms and a decline in PEF have also been observed in asthmatic children following increases in particle concentration.[59–65]

The role of inhaled particulate pollution in exacerbating asthma is based on epidemiologic studies, as no human study using controlled exposure is available. However, such studies have shown that ozone increases airway responsiveness and inflammation, and sulfur dioxide causes transient bronchoconstriction in people with asthma. Observation of the association of inhaled particulates with a range of adverse effects in people with asthma in a variety of settings strengthens the argument for a causal effect.

In eastern Canada and the United States, increases in particulate concentration occur in association with increases in acid aerosol and ozone concentrations. Increased concentrations of that mixture of pollutants have also been associated with a greater number of admissions to hospital for asthma.[66] Although the adverse effects of particulates on people with asthma clearly do not depend on the presence of acid aerosols, increases in acid aerosol concentrations in some settings contribute independently to increased respiratory symptoms.[67]

Increases in ozone concentration have also been associated with more emergency room visits[66,68] and admissions to hospital for asthma, although ozone was present in combination with particulates and acid aerosols. Increases in ozone concentration have also been associated with worsening of asthma symptoms and decreased lung function in people with asthma independent of acid aerosols and particulates.[69]

Studies on humans using controlled exposure have demonstrated that people with asthma are much more susceptible than those without asthma to the bronchoconstricting effects of sulfur dioxide.[70–74] However, the effects of exposure to acid aerosol and nitrogen dioxide have been contradictory.[70–74] Ozone exposure causes predictable acute decreases in vital capacity under controlled conditions, but people with asthma are not more likely than healthy subjects to experience these effects. People with asthma exposed to ozone may experience more adverse effects following exposure to allergens.[75] A similar situation occurs with exposure to nitrogen dioxide.[76,77]

Indoors, the most important respiratory irritant is environmental tobacco smoke (ETS). Asthmatic children of smoking mothers have more severe asthma than those whose mothers are nonsmokers, [78] and when parents of an asthmatic child give up smoking, the child's condition improves.[79] Exposure to ETS is associated with increased frequency and severity of exacerbations of asthma[80] and the development of asthma in predisposed infants and young children.[81,82] The effects of ETS exposure may occur in utero.[83] In the Canadian climate, exposure to ETS represents an important risk to respiratory health.

Products of indoor combustion, such as nitrogen dioxide from gas stoves and wood smoke, may increase respiratory

symptoms in people with asthma,[84] but evidence for this is not conclusive. Formaldehyde and other volatile organic compounds detectable in indoor air are irritating to the eyes and the upper respiratory tract.

Preventing respiratory effects of irritants consists of reducing exposure. During periods of increased outdoor pollution, patients can minimize exposure by remaining indoors or reducing exercise outdoors. Reduction of indoor pollutants can be achieved by avoiding exposure to cigarette smoke, by ensuring adequate venting of gas stoves and ensuring that wood stoves are air tight. Pregnant and breastfeeding mothers should be encouraged to give up smoking. Smoking parents or caregivers of asthmatic children should also be encouraged to give up smoking. Various types of indoor air cleaners are available, but, although several have been shown to reduce levels of irritants significantly, health benefits have yet to be demonstrated consistently.[85,86] Human experimental studies have shown that bronchoconstriction resulting from controlled exposure to air pollutants in people with asthma can be prevented by use of an inhaled bronchodilator. Because continued exposure to respiratory irritants following the use of an inhaled bronchodilator will allow the inflammatory effects of irritant exposure to continue, preventing or reducing exposure should be the primary management approach.

Recent studies have focused on the relationship between air pollution and airway inflammation. For example, there is a greater influx of neutrophils and eosiniophils in the nasal mucosa of atopic people whose nasal mucosa are challenged by a specific allergen in the presence of ozone than in air.[21,87] People with asthma are also at higher risk of developing ozone-induced respiratory tract injury or inflammation characterized by increased neutrophils than people without asthma.[88,89] In addition, ozone exposure results in increased inflammation in the lower airways of allergic people with asthma, demonstrated by an increase in both neutrophils and eosinophils.[90] These results may explain the increased asthma morbidity associated with episodes of ozone pollution.

Pre-exposure to a number of air pollutants, alone or in combination, will result in increased bronchial responsiveness to specific allergen in allergic asthmatic patients. Pre-exposure to ozone has been shown to increase specific airway reactivity of asthmatic patients who are allergic to grass pollen,[75,91] although in at least one case these results could not be reproduced.[92] A similar outcome was obtained with pre-exposure to nitrogen dioxide alone[77,93] or mixed with sulfur dioxide.[76,94] These results may depend on the pre-exposure status of the patient with asthma, i.e., the presence of eosinophilic inflammation in the airway before exposure to the pollutant, which then enhances the inflammation with an influx of eosinophils and generation of pro-inflammatory chemokines.

There is now extensive evidence demonstrating adjuvant effects of air pollutants on the formation of specific IgE antibodies and cytokines in both animals and man. Experiments in rats showed that exposure to nitrogen oxide enhances immune responsiveness and the severity of pulmonary inflammation following antigen challenge.[95] This adjuvant effect of air pollution has been particularly well documented with diesel exhaust particle emissions, which have been shown to enhance specific IgE antibody production, increase cytokine production and increase the gene expression of Th_2 cytokines.[96] Several reports[97–102] have documented enhanced production of specific IgE antibody and cytokines in cultures of lymphoid cells from mice or rats pretreated with diesel exhaust particles, and in vivo animal studies[103–105] have demonstrated increased IgE-specific antibody production after intranasal pretreatment with diesel exhaust particles. These studies were extended to demonstrate that intratracheal immunization with antigen in the presence of diesel exhaust particles enhanced local IgE antibody production and also increased infiltration of eosinophils and the production of Th2 cytokines locally in the lungs compared with either antigen or diesel exhaust particles alone.[106–108] These results mimic the nature of inflammation in allergic asthma.

Saxon and collaborators[109–113] have demonstrated the relevance of the animal results to the problem in humans. In vitro studies[110,111] showed that diesel exhaust particles enhance IgE production by tonsillar B-cells in the presence of interleukin-4 (IL-4) and CD_{40} monoclonal antibody and alter the nature of the IgE produced. In vivo, 0.30 mg diesel exhaust particles in saline enhanced IgE production in the human upper respiratory mucosa; the particles had no effect on IgG, IgA, IgM, or albumin, although there was a small increase in IgG4.[109] Diesel exhaust was also shown to act as an adjuvant to ragweed allergen.[112] Nasal challenge with diesel exhaust particles also influences cytokine production: allergen plus diesel exhaust particles caused a significant increase in the expression of mRNA for Th_2 cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) with an inhibitory effect on IFN-gamma gene expression.[113]

The inflammatory and immunologic adjuvant effects of other forms of particulate pollution have not been examined extensively, although 2 studies have demonstrated inflammatory effects of fuel oil ash inhalation in animals.[114,115]

These various studies strongly suggest that air pollution can modulate or enhance airway inflammation associated with allergic and asthmatic diseases; however, no studies have demonstrated the effect of medications used to treat asthma. Management of the adverse effects of respiratory irritants on people with asthma consists primarily of preventing or reducing exposure. Exposure to outdoor pollutants may be reduced by remaining indoors, minimizing outdoor physical activity and breathing through the nose exposure. Reduction in indoor exposure can be achieved by avoiding cigarette smoke, assuring adequate venting of gas stoves and ensuring that wood stoves are air tight. Although some air cleaners can remove both particulate and gaseous indoor airborne pollutants, their effectiveness in preventing adverse effects in people with asthma is not

known. Finally, although bronchoconstriction resulting from controlled exposure to air pollutants in people with asthma can be averted by the use of inhaled bronchodilators, this is unlikely to prevent the inflammatory effects of the pollution and may aggravate them by masking symptoms. Preventing or reducing exposure should be the primary management approach.

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Asthma education and patient monitoring

Recommendations

- Asthma education is an essential component of asthma therapy (level I).
- The goal of asthma education is control of asthma via improved knowledge and change in behaviour (level III).
- Asthma education should not rely on written or videotaped material alone (level I).
- Asthma education is effective only in the presence of effective asthma therapy (level III).
- Education must be provided at each patient contact (level II).
- Good communication between health professionnals and coordination of their interventions is essential (level III).
- Patient self-monitoring may be effective using either measurement of PEF or monitoring of asthma symptoms (level I).
- Monitoring PEF may be useful in some patients, particularly those who are poor perceivers of airflow obstruction (level III).
- A written action plan for guided self-management, usually based on an evaluation of symptoms, must be provided for all patients (level II).
- Monitoring of pulmonary function in physicians' offices should be routine (level III).
- Patients with severe or poorly controlled asthma should be referred to an asthma expert (level II).

Patient education

Because asthma is a chronic but variable disease, patients and their families must be prepared to make lifestyle changes and adhere to drug therapy for long periods, even at times when symptoms are not evident. They must also be capable of making rapid decisions about symptom severity, self-medication and the need to seek medical advice. Many authorities consider education to be an integral component of asthma management.[1–3]

Although much information has been gathered on the role of education in asthma, efforts to evaluate the benefits of asthma education have been hampered by a lack of control groups and by the need for the concomitant use of inhaled glucocorticosteroids.[4–10] In addition, studies are often limited to evaluating the influence of education on the use of health services and knowledge.[4–7,11–17] Recently, many randomized, controlled trials with parallel groups have assessed the impact of asthma education on health care costs, patient well-being and environmental control.[8,11–37] Many have involved multiple interventions, including education, self-monitoring using PEF or symptoms, using programs of varying duration and intervals.[8,11–13,15,18–28,30–35]

Some studies and a recent meta-analysis suggest that many educational programs do not result in a significant reduction in asthma-related morbidity,[8,21–23,27,31–33,36–38] although benefits were observed in studies that included asthma patients with high morbidity, such as those who had been admitted to hospital or had visited the emergency room in the past.[11–13,28] The reasons offered for this limited success include suboptimal asthma management, short follow-up (1 year) and contamination of the control group.

A decrease in the number of admissions to hospital and visits to the emergency room has been documented, in specific subgroups of patients who are frequent users of health resources,[11,12,18–20,28,30,34,35] but other positive results have been less consistent.

A number of studies have tried to evaluate the impact of asthma education on patient well-being.[5–9,18–24,26–28,30–35] They suggest that, in addition of knowledge, patients gained such benefits as positive attitudes; greater family communication; increased physical activity and feelings of control; increased use of objective measures of airflow obstruction (e.g., PEF) to determine asthma severity; improved treatment compliance, self-management, inhaler technique, quality of life and pulmonary function; and reduced asthma severity, school absenteeism, emergency room visits, admissions to hospital, health care use and health care costs. However, improvements were not consistent across the studies and were sometimes short lived.

Reports of an improvement in environmental control in subjects sensitized to household dust mites after participation in an asthma education program[29] are promising, as they imply that, over time, the reduced exposure to allergen as a result of education may help to reduce airway responsiveness. Asthma education had no significant impact on patients sensitized to their domestic animals[39]; 1 year of reinforcement might not be long enough to persuade clients to give up a pet.

Strategies and methods

Education about asthma should be aimed at altering patients' behaviour rather than simply providing knowledge. The diverse range of educational strategies and methods used include individual teaching, small-group sessions, computer games, large-group lectures, checklists, video and audio tapes, workbooks and booklets, diaries, Internet web sites, problem-solving sessions and repeated audits. Published programs have been implemented in physicians' offices and administered by community agencies and hospitals in education centres. Community education programs should be coordinated with the treating physician.

Some programs are based, at least in part, on the PRECEDE model, which uses predisposing, reinforcing and enabling factors.[40] Predisposing factors include previous personal knowledge, attitudes, beliefs, values and perceptions. Reinforcing factors, which are essential to determine whether behaviours will persist, include positive and negative reinforcement by health providers and members of the patient's social network and self-reinforcement arising from reduced symptoms of asthma. Enabling factors are the resources available to change behaviour; they include skills possessed by the learners, financial resources and resources available to the educator. Understanding the causes of the patient's behaviour is important so that education can be modified accordingly. Recognizing past experiences with asthma enhances the patient's learning experience and increases its relevance.

Few studies have addressed the optimal method for educational intervention. There appear to be few differences in outcome between educational programs focused on individuals and those using small groups, although small-group teaching resulted in a slight decrease in frequency of exacerbations,[8,9,11,12–21,25,26,39] possibly because of the influence of peer support. In studies comparing group teaching with one-on-one counseling,[41–43] prospective assessment of asthma outcomes over 1 year was similar in the 2 groups. However, a retrospective analysis of asthma morbidity carried out 1 year later revealed a decrease in the use of health services by people who had taken part in small-group educational sessions.[27]

According to theory, interventions involving multiple educational methods may be most effective. Programs relying primarily on giving books or videotapes to asthma patients were successful only in improving knowledge.[15–17] Most programs that have focused on self-management skills, have been able to enhance other asthma outcomes.[11–14,18–22,24–29,31,32] It also seems clear that patients and their family should both be involved in the management of the disease. To build skills, the patients must be engaged interactively in the education program, rather than simply acting as passive recipients, and they must receive frequent feedback. Repetition of information is desirable because, without reinforcement, knowledge decreases over time. Development of problem-solving skills should help the patient adopt new behaviours.[37] Programs for children should be inviting and developmentally appropriate. An educational program's goals should be stated, and the program adjusted to the needs of the patient.

Components of an asthma education programs may include:

- information about airway inflammation and bronchospasm using figures to illustrate the concept; the rationale and methods for avoiding irritants and relevant allergens
- description of the rationale, correct use and side effects of preventive medications and bronchodilators
- demonstration and practice of inhaler technique and monitoring using symptoms or PEF meters
- description of criteria for control and steps to take when control deteriorates
- discussion of the action plan and an attempt to improve the patient's and family's understanding and willingness to implement the plan when it is needed[41]
- demonstration of techniques for successful communication with health care professionals
- emphasis on the need for regular follow-up
- discussion of intolerance to sulfites or acetylsalicylic acid
- specific information on food allergy
- discussion, when relevant, of conditions such as pregnancy.

Asthma education should begin in the physician's office[43] and must include a written action plan.[8,24,26,27,32] Asthma education is unlikely to be effective in the absence of effective asthma therapy.[21] An educational program may be carried out in brief segments to meet the constraints of a busy office and also keep from overwhelming the patient with information. Subsequent visits can verify and reinforce previous subjects and introduce new topics.

Teaching activities in the emergency department and hospital wards benefit from obvious relevance and the absence of travel or scheduling difficulties, but may suffer because the patient and family are too distressed to benefit from the efforts.[38] However, this may be the best place to start an educational intervention as a high proportion of patients fail to return for asthma education after their hospital stay or visit to an emergency department.[11,12] A particular educational opportunity may arise when patients in hospital are being observed to ensure that they are stable before discharge.[12] Education in the emergency department should focus on why the exacerbation occurred and the need for follow-up.

School-based programs may have a wide reach and can increase the school's sensitivity to issues concerning childhood asthma. However, this route has not been well studied. Programs that include assignments requiring parental involvement provide instruction for both child and parent.

Training for educators

Health care providers teaching patients with asthma should have the basic skills and knowledge necessary to transmit current principles of asthma self-management and to assess individual needs and the efficacy of the teaching.[44] Educational programs for asthma educators have been developed in various regions in Canada, and national certification for asthma educators is now available. This may standardize the information provided and improve the quality of asthma education.

Home monitoring

By modifying their therapy according to a written action plan based on home monitoring of disease severity, patients

can improve control of their asthma and avoid visits to acute care facilities.[32–34] Although PEF monitoring has been advocated as useful in detecting asthma exacerbations,[45–47] in most patients symptoms are a more sensitive measure and change earlier in the course of an exacerbation.[48–50] Most studies have shown that symptom-based and PEF-based actions plans had similar effects on asthma morbidity.[50]

Measurement of PEF may be useful in patients who have difficulty recognizing changes in their symptoms,[45–47] as evidenced by the lack of correlation between FEV_1 and symptoms, and by repeated exacerbations requiring urgent treatment while they are using a symptom-based action plan. PEF measurement may also be helpful in patients with very severe asthma[23] and to help some patients determine whether symptoms are due to reduced airflow. When PEF is used for asthma monitoring, the best of 3 values is the measure used.

Home PEF monitoring is not the best means of physiologic measurement because it tends to underestimate the degree of airflow obstruction.[51] PEF measurement requires instruments capable of rapid response, and correlation between PEF measured with a portable PEF meter and spirometers is poor.[51,52] PEF meters of the same brand may vary, and readings may change with extended use.[53] Significant errors occur in the reading range of many devices: some overreading in the middle flow range and underreading at high flow ranges. However, PEF meters are cost effective and easy to use in the home setting.

PEF devices must be checked regularly for accuracy and reproducibility of results.[53] Patients should be asked to bring their meter to clinic visits so that its readings can be compared with spirometry or an office PEF meter. This practice also allows the physician to check the patient's technique. The same device should be used for serial measurements.

Home PEF monitoring should be linked to an appropriate action plan. Patients should be taught about the importance of certain changes that suggest loss of asthma control: nocturnal symptoms; increase in β_2-agonist use; diminished response or decreased duration of response to β_2-agonists.[33] Adherence to action plans appears to be good in only a third of patients; many are reluctant to increase the dosage of inhaled glucocorticosteroids or make self-management decisions when asthma symptoms worsen.[54]

The roles of education (even a single session), PEF monitoring and action plans advocating patient-initiated changes in medication in achieving improved outcomes have not been studied separately. An action plan typically integrates level of symptoms or PEF and the need for changes in medication into a predetermined therapeutic regimen to prevent deteriorating asthma from developing into a more severe attack. Many plans recommend doubling the dose of inhaled glucocorticosteroid when augmented therapy is indicated and adding an oral glucocorticosteroid and contacting a physician when emergency therapy is indicated.

In most patients, the written action plan should be based on symptoms. Action plans based on the "stoplight" scheme are recommended: these specify the symptom severity or PEF range at which regular treatment should be continued (the "all clear" or "green" zone), augmented (the "caution" or "yellow" zone) and changed to an emergency plan (the "emergency" or "red" zone).

In terms of establishing these PEF ranges, Chang-Yeung[48] found that PEF dropped more than 30% from the baseline in only 27% of acute exacerbations in children, although decreases of at least 20% were observed in 51%. Malo[49] also found that PEF rarely falls below 70% of personal best during acute exacerbations. Therefore, although it could be recommended that 80% of personal best be used as the cut-off point for the yellow zone and 70% of personal best for the red zone, these values are higher than in previous consensus guidelines, and a 60% limit for initiating oral corticosteroids may be preferable in most instances.

Diary cards may be used to record symptoms, medication use or PEF, although PEF may influence subjective symptom assessment. Compliance problems are common in patients asked to keep long-term diary records. Using an electronic PEF meter with a memory and good compliance with PEF (defined as 50% of the measurements done) fell from 60% in the first 3 months to 30% at 1 year despite education and regular reinforcement.[54] Plans involving a greater number of self-care activities, such as PEF monitoring, may not be carried out in patients with more severe disease and poor self-care skills; further research into methods to convince such patients to adhere to an asthma management program is urgently needed.

Baseline morning and evening monitoring should be carried out over a number of weeks and continued regularly, with the frequency adjusted to the severity of the disease. Patients should be alerted to the significance of increased diurnal variation in PEF (greater than 20%). The best method of calculating diurnal variation in home monitoring is controversial. However, dividing the difference between the highest PEF and the lowest PEF during a 14-day period by the highest PEF during that period then multiplying by 100 is simple and satisfactory ([(highest PEF – lowest PEF) ÷ highest PEF] × 100). Diurnal variation should remain below 15% to 20%.

Monitoring in the physician's office

At each visit to the physician's office, the pattern and frequency of the patient's symptoms, especially those at night and with exercise, and β_2-agonist use should be documented. Use of the inhalation device should be observed.[55,56] Physical examination is much less reliable than spirometry for assessing the degree of airflow obstruction.[57] Physical findings and office testing represent point-in-time measurements, and greater weight should generally be placed on the history. Normal airflow does not exclude poorly controlled asthma.

History should be obtained from both patient and caregiver even in children under 11 years of age, as such information relates to quality of life and the child's perception of the impact of the illness. A history obtained from older children correlates well with physiologic measures and diary records.[58] The frequency of symptoms and exacerbations may be verified more precisely by inspecting the patient's symptom or PEF diary, recognizing that diaries are frequently falsified, particularly in children.[59] Use of electronic devices such as portable "electronic organizers," which automatically record the actual time records are made, may improve the accuracy of PEF and other diaries. PEF diaries should be inspected to assess PEF variability which correlates with airway hyperreactivity.

Objective assessment of airflow is important. Spirometry (for measurement of FEV_1 and FEV_1/forced vital capacity) is more reliable than PEF when carried out according to recommended standards. PEF can frequently result in underestimation of airway obstruction when compared to FEV_1.[60] A physician treating asthma should have access to a spirometer or have a PEF meter for office use, and testing should be done before and 10–15 minutes after an inhaled β_2-agonist. (This also allows the physician to observe how the patient uses the inhalation device.) Spirometers should be calibrated and maintained according to published standards.[61] Although reduced airflow usually reflects poorly controlled asthma, in some patients it may represent the best function possible.

Other means have been proposed to assess asthma control, but generally these are technically more difficult and not readily available. Assessment of nonallergic bronchial responsiveness (including exercise-induced bronchoconstriction in people who have symptoms primarily with exercise) may be useful in patients who, despite normal airflow, require excessive medication for symptom control and in those who fail to respond to therapy. It may help the physician correlate symptoms with abnormal airway function or to question the diagnosis or cause of the patient's symptoms (e.g., hyperventilation syndrome). In the future, sputum analysis (differential cell count, measurement of eosinophil cationic protein) may prove to be useful to assess airway inflammation and to manage and monitor asthma.[62] Other markers of inflammation, such as blood eosinophil count and blood total IgE concentration, as well as more invasive tests, such as endobronchial biopsies and bronchoalveolar lavage, are currently research tools only.

Follow-up

Regular follow-up is important to maintain good asthma control. Consistent follow-up by a primary health care provider is necessary to assess control of asthma, prescribe and adjust therapy and reinforce patients' knowledge about asthma and compliance with their therapy.[63] Convincing families to return for follow-up for nonacute care requires knowledge about the disease.[64] Patients with moderate or severe asthma have higher quality-of-life ratings, are more likely to receive anti-inflammatory therapy and are less likely to require acute care in an urgent-care centre, emergency department or hospital when assessed by a specialist, such as an allergist or respirologist.[65,66] Consideration should be given to referring patients with severe asthma and unacceptable asthma control to an allergist or respirologist. However, improvements in asthma control following referral to an asthma expert diminish in the absence of follow-up by the expert.[66]

Suggestions for future research

- Future research should focus on the relative importance of monitoring, education and written or electronic self-management plans — including patient-initiated adjustment of medication in response to changes in asthma severity detected by self-monitoring — in improving outcome.
- Randomized trials are needed to determine ideal PEF values for changing therapy and optimal changes in therapy when deterioration is occurring, particularly in children.
- The best method for determining PEF variability requires further study. Development of more reliable PEF meters or other devices for measuring airflow at home should be encouraged. Inexpensive electronic diaries linked to a device for measuring airflow that can be uploaded to a computer in the physician's office should be developed and evaluated.
- Further research is needed to improve self-monitoring techniques in disadvantaged groups.
- More research is needed to determine the most effective interventions and best programs and program duration for modifying behaviour, reducing morbidity and improving clinical outcome and quality of life. There is a need to compare small-group teaching with one-on-one counseling.
- Many computer education programs have been developed, although their usefulness remains to be established.
- Research is required to define the role of action plans and peak flow measurement.
- Research is urgently needed to identify effective methods of reaching disadvantaged groups, who are at increased risk of asthma mortality and who are less likely to take advantage of conventional education programs.
- More effective methods for changing particularly resistant behaviours, such as smoking in the home and keeping pets, also require elucidation.
- The impact of training programs for asthma educators must be assessed.

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Avoidance of environmental allergens

Recommendations

- Allergens to which a person is sensitized should be identified (level I).
- A systematic program to eliminate, or at least substantially reduce, allergen exposure in sensitized people should be undertaken (level II).
- Measures to control household dust mites can be effective in decreasing exposure and relieving asthma of patients sensitized to these allergens (level II).
- Humidity in the home, including the bedroom, should be kept below 50% (level II).
- Reduction of exposure to pet allergens cannot be effective without removing the pet from the home (level II).
- Compliance with avoidance measures must be reviewed repeatedly and its importance emphasized (level III).

Increased exposure to environmental allergens likely contributes to the increased prevalence and severity of asthma. Therefore, avoidance of environmental allergens is one of the primary goals of asthma management.[1,2] The association of IgE-mediated hypersensitivity to environmental allergens in asthma is well established; 60%–80% of both adults and children with asthma show hypersensitivity to environmental allergens, based on positive-immediate reaction to skin tests.[3–6] The production of specific IgE antibodies against environmental allergens is a strong risk factor for acute asthma and a significant risk factor for severe asthma exacerbations on exposure to high concentrations of allergen.[7–11] Severity of chronic asthma and airway hyperresponsiveness has also been correlated with degree of sensitivity to indoor allergens.[3,12–14]

Symptoms of asthma and objective measurements of airflow obstruction as well as airway hyperresponsiveness improve when patients avoid the environmental allergens to which they are allergic (Table 1).[15–21] This has been demonstrated most dramatically when sensitized patients with asthma have been moved to allergy-free mountain institutions.[21,22] When a cat is removed from a home, allergen concentrations decrease steadily over 6 months by 100- to 1000-fold.[23] Using impervious mattress, pillow and comforter cases and washing bedding weekly in hot water reduces mite allergen by 100- to 1000-fold within a month.[24] In a cockroach-infested urban dormitory, extermination followed by routine cleaning reduced cockroach allergen levels on the floor by 86%.[25] These and many other studies support the efficacy of measures to minimize indoor allergens in the management of people with asthma with demonstrated sensitivity to these allergens.

Adherence to measures of allergen avoidance remains problematic. Without formal education programs, almost no one installs mattress covers.[26,27] Adherence can be increased to 27% with repetitive clinic-based education and to 39% with the use of a computer-based educational program.[26] Removal of a favourite pet becomes even more difficult. Patients' compliance with avoidance measures is much lower than that with medications, primarily because of the relatively quicker clinical improvement after medications compared with avoidance measures. The importance of educating patients to the crucial role of minimizing allergen exposure cannot be overemphasized.

Suggestions for future research

- Studies are needed to define the duration of the effect of acaricides and liquid nitrogen in reducing household dust mites.
- Studies are needed to define the benefit of cockroach extermination to people with asthma who are sensitized to these allergens.
- Studies are needed to evaluate strategies to enhance compliance with measures to reduce allergen exposure.

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Table 1: Measures to minimize environmental factors contributing to asthma

• Avoid respiratory irritants, particularly tobacco smoke
• Minimize exposure to relevant allergens, particularly indoor allergens
Household dust mites
Maintain relative humidity below 50%
Encase mattress, boxspring (and possibly pillows) in mite and mite allergen impermeable covers
Launder bed linens in hot (55°C) water
Remove carpeting, where possible
Note: Air filters do not affect reservoir levels of household dust-mite allergen
Pet allergens
Removal of the pet from the home is the most effective approach
Exclude pet from the bedroom
Use HEPA room air cleaner
Use mattress and pillow covers
Remove carpeting
Vacuum upholstered furniture with a HEPA-filtered vacuum frequently
Washing the pet may temporarily reduce allergen load, but this must not be done by the allergic person

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Immunotherapy

Recommendations

- Immunotherapy is generally not recommended in the treatment of asthma (level IV).
- Immunotherapy should not be used in place of avoidance of environmental allergens (level III).
- Immunotherapy with clinically relevant allergens may be considered if disease activity is inadequately controlled by avoidance of the allergens and pharmacotherapy (level I).
- Immunotherapy should be avoided while asthma is poorly controlled (level III).
- Well-controlled asthma is not a contraindication for immunotherapy for allergic rhinoconjunctivitis or insect venom hypersensitivity (level III).
- Immunotherapy must be administered only by trained personnel in centres where there is medical supervision and resuscitative equipment (level III).

Efficacy

Despite numerous studies, the role of immunotherapy in the management of asthma remains controversial,[1,2] and interpretation of published reports varies considerably, presumably because of personal bias. It is reasonable to think that there will be more variability in responses to immunotherapy because of uncontrolled factors that differ for people receiving the same therapy: degree of allergen exposure and environmental control; other allergenic sensitivities not incorporated into the treatment; and nonallergenic triggers of asthma, such as infection or exposure to chemical sensitizers. The specificity of individual allergens in the treatment as well as the dose regimen employed may influence outcomes. Therefore, any large treatment group is likely to include both responders and nonresponders, and the investigator must use objective criteria to define those who benefit and those who do not. Variable responsiveness of individual patients likely accounts for the inconsistency in the literature.

Immunotherapy has been established as efficacious treatment for allergic rhinitis triggered by seasonal pollens, dust mites and animal allergens, although in the case of animal allergens, some authors still consider it controversial.[3–11] Controlled studies have demonstrated the efficacy of immunotherapy in asthma, and a meta-analysis[12] of 20 prospective studies concluded that allergen immunotherapy was effective in reducing the number of symptoms, the requirements for medication and airway hyperresponsiveness. Although the meta-analysis[12] focused on immunotherapy in adults, the same group of investigators is conducting an update of the systematic review of allergen-specific immunotherapy for asthma as part of the Cochrane collaboration.[13] In asthmatic adults allergic only to ragweed aeroallergen, Creticos and colleagues[14] found an improvement in the immunotherapy-treated group, in terms of peak expiratory flow (PEF) and medication use, during the first year compared with the control group, but these factors were similar for the 2 groups in the second year.

Recently, Sigman and Mazer[15] reviewed 1966–1994 reports on immunotherapy in the management of asthma in children, but meta-analysis was not possible because of the heterogeneity of the studies. Most studies showed some beneficial effects of immunotherapy, either improvement of asthmatic symptoms or a decrease of bronchial reactivity to specific antigens. Trials using household dust-mite immunotherapy provided the most consistent evidence of benefit; immunotherapy for grass pollens and cat dander was of some benefit, but the number of supporting studies was very small. Trials of immunotherapy for mould or dog dander were few and provided no convincing evidence of effectiveness. The heterogeneity and small numbers of studies precluded making firm recommendations for the use of immunotherapy in children with asthma.

A MEDLINE search of 1995–1998 reports of conventional immunotherapy and childhood asthma yielded 4 studies[16–19] with abstracts in English. Peroni and colleagues[16] conducted a double-blind, placebo-controlled trial of immunotherapy with a standardized extract of *Dermatophagoides pteronissinus* in 23 asthmatic children, aged 7–14 years, residing at high altitude. After 12 months, the 2 groups showed comparable improvement in clinical features and lung function, and diminution of nonspecific and specific bronchial hyperreactivity. The children treated with immunotherapy, but not those receiving placebo, had decreased sensitivity to *D. pteronissinus* on skin tests. The authors concluded that immunotherapy was beneficial, but the benefit of allergen avoidance derived from living at high altitude was even greater, resulting in the absence of difference between the treatment groups.

Costa and colleagues[17] studied 11 patients with asthma and household dust-mite allergy who received specific immunotherapy and inhaled glucocorticosteroids for 27 months, while 11 similar patients received inhaled glucocorticosteroids alone. Improvement in symptoms score, bronchodilator use and lung function was comparable in the 2 groups. The patients treated with immunotherapy and glucocorticosteroids experience faster improvement in bronchial hyperreactivity and PEF variability. After 18 months, patients in both groups stopped using inhaled glucocorticosteroids. This interruption was followed by impairment of all end points, which was more pronounced in the patients previously treated with glucocorticosteroids alone. The authors concluded that immunotherapy and inhaled glucocorticosteroids produced a faster improvement than glucocorticosteroids alone and led to a lower rate of relapse after interruption of therapy with inhaled glucocorticosteroids.

In a prospective 3-year study,[18] 300 children with asthma due to pollen or household dust-mites were randomly allocated to receive specific immunotherapy or not. Children receiving immunotherapy had significantly fewer days with asthma and drug use than those in the control group. In addition, the immunotherapy group had fewer asthma attacks and better quality of life than the control group.

Adkinson and colleagues[19] conducted the largest randomized controlled trial of immunotherapy in children with asthma; this is also the first study to assess polyvalent immunotherapy using a double-blinded, placebo-controlled protocol. In the trial, 121 children with moderate-to-severe perennial asthma received subcutaneous injections of either a mixture of up to 7 aeroallergen extracts or placebo for 18 months or longer. In the first phase of the trial, the children were evaluated and their treatment was optimized. The patients were sensitized to 2–7 of the 14 allergens tested. The children visited the clinic every 2 weeks, kept asthma diaries, were monitored by PEF measurement and received asthma education. Medication was adjusted to achieve the best control of symptoms with the least medication; 57 patients required regular glucocorticosteroid therapy.

After 1 year, immunotherapy or placebo treatment began. The management regimen established in the first phase was continued. Symptom scores, medication use and bronchial hyperresponsiveness declined in both treatment and control groups, but there were no significant differences between the groups. The 2 groups also did not differ in the number of days on which oral glucocorticosteroids were used. Complete remission (cessation of all drug therapy) was similar for the 2 groups — 7.5% in the treatment group and 8% in the control group. Skin-test reactivity to treatment allergens decreased substantially in the immunotherapy group.

In this study, immunotherapy did not provide additional benefit over close and careful management of asthma. This leads to speculation that immunotherapy may fulfill a role when optimal, comprehensive management of asthma, such as that provided to the study population, is not feasible.

Safety

Multiple factors must be considered before immunotherapy is employed, because the risk of adverse reactions to treatment, although low,[20,21] is significant and fatalities have occurred.[22,23] The Mayo Clinic[20] reported an incidence of reactions of 0.137% in 79 593 injections over 10 years: most were mild, all were responsive to treatment and there were no fatalities.

Immunotherapy should be restricted to patients in whom specific allergens are identified as playing a causative role in asthma and where the allergen cannot be avoided. Because of the increased risk of severe reactions, patients should not receive immunotherapy if they are taking a β-adrenergic antagonist (this medication is also contraindicated in the presence of asthma), if their asthma is not clinically stable or if they have an accompanying respiratory tract infection. Neither should immunotherapy be initiated nor the dosage increased during pregnancy. Patients must remain under medical supervision for a minimum of 20 minutes after injection of the allergen, longer in the case of high-risk patients.[24,25]

Suggestions for future research

- Studies are needed to determine the parameters characterizing responders to immunotherapy versus nonresponders.
- Evaluation of the safety and efficacy of novel immunotherapy preparations is required.

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Inhaled glucocorticosteroids in adults and children

Use of glucocorticosteroids in asthma

Recommendations

- Inhaled glucocorticosteroids offer the best option for the initial anti-inflammatory treatment of asthma (level I).
- The initial daily dose in adults is commonly in the range of 400–1000 μg of beclomethasone dipropionate or the equivalent (Table 1); higher doses of inhaled or the addition of oral or systemic glucocorticosteroid may be required if the asthma is more severe (level III).
- The initial daily dose of inhaled glucocorticosteroid in children should be 200–1000 μg of beclomethasone dipropionate or the equivalent; higher doses are rarely needed (level III).
- Early initiation of treatment with inhaled glucocorticosteroids in the natural history of the disease is associated with a better functional outcome (level III).
- Once best results are achieved, the dose should be reduced to determine the minimum required to maintain control (level III). This is especially true in children because they are more likely to have adverse effects but are also more likely to experience improvement or remission of their asthma (level III).
- Loss of control of asthma should be treated as early as possible to prevent exacerbation from becoming severe (level III). The dose of glucocorticosteroid required and the duration of the increase in dose depends on the severity of the exacerbation. Inhaled glucocorticosteroids must be added or increased 2- to 4-fold (level IV), or prednisone at the dose of 0.5 to 1.0 mg/kg a day (level I) must be added if the exacerbation is severe. This increased level of glucocorticosteroids must be maintained until the best results are achieved and for a minimum of 10–14 days (level III).

Inhaled glucocorticosteroids are the mainstay of asthma therapy and are clearly indicated in all but the mildest cases. They relieve persistent symptoms very effectively, improve lung function, decrease bronchial hyperresponsiveness and reduce morbidity caused by asthma.[1–6]

Initiation

The treatment of airway inflammation early in the course of asthma may prevent persistent asthma, reduce asthma severity and reduce the development of chronic airflow limitation.[7–9] Therefore, patients with variable airflow obstruction, airway hyperresponsiveness or sputum eosinophilia (with objective evidence of asthma) should be given a trial of regular treatment with an inhaled glucocorticosteroid to determine whether it is beneficial and to determine the best results obtainable from this treatment. The severity of asthma can be assessed reliably only after a trial of intensive therapy has been undertaken and the best results defined.[10]

The treatment of exacerbations of asthma early and effectively with inhaled glucocorticosteroids will prevent them from becoming severe, will reverse them as quickly as possible and should reduce mortality and morbidity.[2]

Dose

The optimum dose for initiating treatment with glucocorticosteroid in a patient who has not previously received this drug has not been studied. It is likely to vary depending on the severity of inflammation, the severity of airflow obstruction and other characteristics of the patient. Although a dose–response relation to inhaled glucocorticosteroids can be demonstrated,[11,12] most of the therapeutic benefit is obtained at total daily doses of 1000 μg or less of beclomethasone dipropionate, and, in most patients, only very small increases in benefit are achieved at higher doses.[5]

There is no advantage to starting at higher rather than lower doses. The consensus group agreed that, in general, an initial dose of inhaled glucocorticosteroids is 400–1000 μg a day of beclomethasone dipropionate, divided and inhaled via

Table 1: Proposed dose equivalencies for inhaled glucocorticosteroids

	Dose, μg/d		
Product	Low	Medium	High
BDP pMDI and spacer	≤ 500	501–1000	> 1000
BUD Turbuhaler*	≤ 400	401–800	> 800
FP pMDI and spacer	≤ 250	251–500	> 500
FP Diskus†	≤ 250	251–500	> 500
BDP pMDI (HFA)‡	≤ 250	251–500	> 500
BUD wet nebulization¶	≤ 1000	1001–2000	> 2000

Note: For children, the consensus group defined low dose as < 400 μg of BDP delivered via a pMDI attached to a spacer.
BDP = beclomethasone dipropionate; pMDI = pressurized metered-dose inhaler; BUD = budesonide; FP = fluticasone propionate; HFA = hydrofluoralkane (propellant).
*Budesonide Turbuhaler™ (Astra Pharma Inc., Mississauga, Ont.).
†Fluticasone propionate Diskus™ (Glaxo Wellcome Canada Inc., Mississauga, Ont.).
‡In solution with alcohol (QVAR®); other HFA inhalers may provide dose equivalencies similar to BDP delivered with a traditional pMDI.
¶Budesonide solution for wet nebulization (Astra Pharma Inc.).

a standard metered-dose inhaler (MDI). In children, an initial dose 200 μg of beclomethasone dipropionate a day using a spacer device in divided doses may be sufficient, especially if the disease is not severe and of short duration.

The additional dose of inhaled glucocorticosteroid needed to treat uncontrolled asthma in patients already receiving regular inhaled glucocorticosteroid treatment has not been examined. A 2- or 4-fold increase in the daily dose has been suggested, but this requires formal evaluation in a randomized controlled trial.

Duration

Benefits are usually observed within days or weeks, and most of the benefit is usually observed within 3 months of initiation of inhaled glucocorticosteroid. Once the best results have been achieved, the daily dose must be reduced at intervals of 2 weeks or longer (the exact interval needs to be studied) to identify the minimum dose needed to maintain this state. The ideal objective measurements for monitoring have not been determined.

The duration of glucocorticosteroid treatment is likely to vary with the cause of the uncontrolled asthma. For example, if the cause is exposure to allergen and this exposure has subsequently ceased, the need for treatment may be brief. However, in patients with persistent asthma, prolonged treatment is associated with progressive improvement in symptoms, PEF and methacholine PC_{20} (i.e., the provocative concentration of methacholine required to cause a 20% fall in FEV_1).[1–6] The duration of therapy required to reach maximum clinical benefit is not known and is highly variable[4,7,8] Whether the therapy can be successfully stopped is not known.[8] This is much more likely to be possible in children and in those with mild disease.

Suggestions for future research

- What is the optimum dose of inhaled glucocorticosteroid at which it is preferable to add a new class of medication rather than increase the dose?
- What is the duration of therapy required to obtain maximum benefit and what are its determinants?
- What is the long-term prognosis associated with intermittent as opposed to continuous use of inhaled glucocorticosteroids once the best results have been achieved?
- Can the onset of persistent asthma be prevented by early use of inhaled glucocorticosteroid in patients with bronchial hyperresponsiveness who are at high risk for clinical asthma?
- Is doubling the dose of inhaled glucocorticosteroid effective in managing acute non-life-threatening exacerbations of asthma?

Safety issues

Recommendations

- Inhaled glucocorticosteroids at the low and moderate doses generally required to control symptoms in asthma infrequently exhibit clinically important side-effects and provide the best risk–benefit profile (level I).
- Children who regularly require higher doses of inhaled corticosteroids (i.e., equivalent to 400 μg or more of beclomethasone dipropionate daily) should have their height measured regularly using a calibrated stadiometer (level IV). A change in growth velocity should lead to a reassessment of the therapy with emphasis on reducing glucocorticosteroid doses while maintaining adequate asthma control through environmental control and possibly the use of additional therapy.
- People who use inhaled glucocorticosteroids regularly should be encouraged to rinse and expectorate after inhalation to reduce oropharyngeal deposition and systemic absorption (level I).
- Physicians should frequently consider reducing the dose of inhaled glucocorticosteroid in patients who have achieved acceptable control of their asthma. Patients, whether children or adults, consistently requiring doses of more than 1000 μg/d of beclomethasone dipropionate or the equivalent to maintain acceptable control should be referred for specialized assessment (level IV).
- In patients with a personal or family history of glaucoma, intraocular pressures should ideally be measured within a few days of their commencing use of inhaled glucocorticosteroids, particularly if high doses are taken, and monitored at appropriate intervals (level IV).
- Patients using a pressurized inhaler should avoid depositing any of the aerosolized glucocorticosteroid in the eye. A dry powder inhaler or spacer may prevent such an occurrence (level IV).
- Bone densitometry is recommended in adult patients who require the equivalent of more than 1000 μg/d of beclomethasone dipropionate to maintain acceptable control or who have one or more risk factors for osteoporosis (level III).

Inhaled corticosteroid therapy for asthma is not devoid of adverse effects, but has a much better benefit-to-risk ratio than alternative treatments, such as prednisone, theophylline or short-acting β_2-agonist inhalants[2,12] At doses of up to 1000 μg/d, the adverse effects of inhaled glucocorti-

costeroids may be a nuisance, but are rarely associated with significant systemic effects.[13,14] For children the benefits and risks of inhaled corticosteroids have recently been reviewed.[15]

Pregnancy and lactation

Inhaled glucocorticosteroids are not contraindicated in pregnancy, but the use of the lowest dose consistent with achieving and maintaining optimal asthma control is recommended. There is no evidence demonstrating the deposition of inhaled corticosteroids in breast milk. Inhaled glucocorticosteroids can generally be continued during lactation.

Growth in children

Short-term growth as measured by knemometry (lower-leg growth) may be slowed with even low doses of inhaled glucocorticosteroids, but the effect on longer-term growth, if any, remains to be determined. Growth velocity has been found to be reduced in the intermediate term (6–12 months) with doses as low as 400 μg/d of beclomethasone dipropionate,[16] although possibly not at an equivalent dose of fluticasone.[17] No long-term randomized studies of adult stature in relation to inhaled glucocorticosteroid are available, but a retrospective cohort study did not find any effect on adult stature.[18]

Oropharyngeal candidiasis and dysphonia

Reducing the total daily dose, dose frequency and oropharyngeal deposition (by using a spacer and mouth rinse) all reduce the occurrence of candidiasis. Such local complications are unusual in children.[19] Antifungal therapy should be reserved for episodes of active thrush. In the case of dysphonia, reducing acute and chronic laryngeal stress may also be helpful.

Adrenocortical insufficiency

The total daily dose, cumulative inhaled glucocorticosteroid dose and combined oral and inhaled glucocorticosteroid therapy interact to increase the risk of adrenocortical suppression.[2,20] It is prudent to administer routinely a glucocorticoid supplement (100 mg hydrocortisone parenterally) if a patient receiving oral glucocorticosteroid therapy for more than 3 weeks in the previous 3 months suffers major trauma, surgery or a severe prostrating illness. The consensus group agreed that a blanket recommendation that all patients in such a situation, who are receiving more than 1000 μg/d of inhaled glucocorticosteroids, receive glucocorticosteroid supplementation is not justified in either children or adults. Acute adrenal insufficiency after discontinuation of inhaled glucocorticosteroids is seldom seen.

Ocular complications

Inhaled glucocorticosteroid therapy increases the risk of cataract formation in a dose-dependent fashion.[21] However, the benefits of inhaled glucocorticosteroid for asthma greatly outweigh this potential risk, especially in children for whom the risk of cataract appears very low.[22] Routine ophthalmologic surveillance for posterior subcapsular cataract is not warranted in patients treated with an inhaled glucocorticosteroid. Incipient glaucoma may be exacerbated by inhaled glucocorticosteroid therapy for asthma, even at a low dosage.[23] A case–control survey found an increased risk at doses greater than 1.5 mg/d of beclomethasone dipropionate or the equivalent.[24] Risk did not increase with the duration of inhaled glucocorticosteroid treatment or cotreatment with intra nasal glucocorticoid. Whether the magnitude of this risk is a function of individual patient susceptibility, the choice of drug, the type of delivery device used, the inhalation technique or cotreatment with nebulized β_2-agonist and anticholinergic bronchodilators is not known.[25]

Osteoporosis

According to expert opinion, an estrogen supplement should be provided in postmenopausal women treated with oral corticosteroids for prolonged periods unless a positive contraindication exists.[26,27] A dose-dependent osteoporotic effect of inhaled glucocorticosteroids has been demonstrated.[28,29] The effect is not usually clinically important at doses less than 1.2 mg/d of beclomethasone dipropionate or the equivalent but might be if additional risk factors for osteoporosis and fracture are also present (Table 2).[30]

Infection

Inhaled glucocorticosteroids should be avoided or used with due caution in asthmatic patients who may harbour a mycetoma or who have drug-resistant tuberculosis, atypical mycobacteria infection or immunosuppression. However, these are not absolute contraindications for the use of inhaled glucocorticosteroids. Isoniazid chemoprophylaxis is not routinely required in the presence of a positive delayed

Table 2: Clinical risk factors for osteoporosis[20]

Age > 60 years
Postmenopausal state without hormone replacement therapy
Male impotence or infertility
Previous fractures with minor trauma
Family history of fractures (parental)
Past or current chronic glucocorticoid therapy
Smoking
Alcoholism
Physical inactivity

skin reaction to purified protein derivative unless there are other specific indications such as a contact history with an active case of tuberculosis. Appropriate preventive action in patients exposed to varicella or measles while receiving inhaled or oral glucocorticoid therapy is recommended.

Minimizing risks

Environmental control measures should be promoted whenever prescribing any drug regimen for asthma. Mouth rinsing and expectoration after each dose can reduce systemic absorption up to 15%, although this is relevant only to inhaled glucocorticosteroids, such as beclomethasone dipropionate, that are only slightly inactivated by first-pass hepatic metabolism.[31] The use of a spacer with a pressurized MDI rather than an MDI alone may reduce the total available systemic dose in some circumstances, but spacers may either decrease or increase the systemic absorption of inhaled glucocorticosteroids relative to MDI alone, depending on their design and how the patient uses the devices.[32] Toogood and colleagues[14] found that, if a spacer reduces the systemic activity of an inhaled glucocorticosteroid, the most likely explanation (and the safest assumption) is that it is concomitantly reducing intrapulmonary delivery of the inhaled glucocorticosteroid.

Safety surveillance

There is a need for an automated surveillance system, possibly based on computer-monitored prescription, to document routinely each patient's inhaled and oral glucocorticosteroid use and to communicate this information to the responsible physician. Inhaled glucocorticosteroid should always be used in preference to an oral glucocorticoid, and the smallest effective dose should be used. The clinical benefits from the prolonged use of inhaled glucocorticosteroids should always be weighed against their potential side-effects. A continuing need for more than 1000 μg/d of beclomethasone dipropionate or the equivalent (with chlorofluorocarbon as a propellent) indicates a need for assessment by a specialist.

Skin thinning and bruising indicate chronic systemic glucocorticosteroid activity, but are generally not clinically important unless patients are using more than 1000 μg/d of beclomethasone dipropionate or the equivalent, especially with prednisone.[32] In selected patients, morning serum cortisol level may provide additional clinically useful safety surveillance information.

If a patient beginning regular inhaled glucocorticosteroid therapy is likely to need a maintenance dose above 1000 μg/d of beclomethasone dipropionate or the equivalent, it is prudent to assess and document the presence or absence of clinical risk factors for osteoporosis and to monitor bone density according to published guidelines.[26,27] This implies a baseline measurement by dual energy x-ray absorptiometry (DXA), follow-up measurements at appropriate intervals and, depending on the DXA results coupled with clinical considerations, the institution of appropriate drug therapy to correct or prevent bone loss. If DXA is not readily available, decisions about the need for preventative osteoporosis management must be based on the clinical risk factors summarized in Table 2.[20]

Routine screening for cataracts in patients taking inhaled glucocorticosteroids is not recommended as there is no evidence that early diagnosis favourably influences cataract treatment. Nevertheless, any patient who complains of impaired vision should be referred promptly to an eye specialist.[32]

Suggestions for future research

- What are the benefit-to-risk ratios of the various inhaled glucocorticosteroids delivered via the inhalation devices now available?
- What is the true risk of the various reported adverse effects of inhaled glucocorticosteroids in various subgroups such as children, the elderly and postmenopausal women?
- What is the risk of clinically relevant ocular complications at moderate to high doses of inhaled glucocorticosteroids?
- What are the risks and benefits of early treatment of osteoporosis in women on high-dose inhaled glucocorticosteroids?

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β_2-Agonists

Short-acting β_2-agonists

Recommendations

- Short-acting inhaled β_2-agonists are the drugs of choice in both children and adults for relief of acute symptoms and short-term prevention of exercise-induced bronchospasm (level I).
- When daily use of short-acting inhaled β_2-agonist is needed, a controller (anti-inflammatory) medication is required (level I).
- Regular controller (anti-inflammatory) medications should be used if short-acting β_2-agonists are used more than 3 times a week in addition to their once daily use to prevent exercise-induced symptoms (level IV).
- Patients who need a short-acting β_2-agonist several times a day require urgent reassessment with a view to increasing anti-inflammatory therapy (level III).

Short-acting β_2-agonists continue to be the drugs of choice for the relief of acute symptoms of asthma due to bronchospasm. They are most useful as rescue medication taken as needed. In Canada, the most widely used preparation is salbutamol, but other agents (terbutaline, fenoterol and metaproterenol) are also available. Salbutamol is also available in combination with ipratroprium bromide, an anticholinergic bronchodilator.

Short-acting β_2-agonists begin to act within a few minutes and cause maximum bronchodilation within 10–15 minutes. The duration of action varies with the agent, but airflow rates remain significantly elevated for 2–6 hours following inhalation. The degree of reversal of airflow obstruction achieved by inhaled β_2-agonists depends on the nature of the obstruction and intrinsic properties of the airway wall.

The immediate adverse effects of inhaled short-acting β_2-agonists are minimal, but include mild tremor and tachycardia. These systemic effects diminish with repeated use without loss of the bronchodilator effects. However, regular or frequent use of inhaled short-acting β_2- agonists may be associated with decreased control of asthma and increased airway responsiveness to direct and indirect provoking stimuli, including allergens (both early and late asthmatic reactions are increased), exercise and methacholine challenge.

Efficacy and safety

The widespread use of short-acting β_2-agonists over 50 years attests to their general efficacy and safety, but studies in the last 10 years have highlighted several important facts. First, there is no evidence that regular 4-times-a-day treatment with short-acting β_2-agonists benefits patients with any degree of asthma severity compared with the use of these agents only when needed for symptom relief.[1,2] Sec-

ond, the more potent β_2-agonists seem to have adverse effects when taken regularly; this is especially true of fenoterol, whose regular use is associated with increased morbidity and mortality due to increased severity of asthma.[3,4] Withdrawal of fenoterol has led to a rapid decline in both mortality and in hospital admissions, suggesting strongly that the adverse effects were related to increased severity rather than to cardiac toxicity.[5,6] Third, a study of regular versus as-needed salbutamol in people with mild asthma showed a consistent trend toward more symptoms, reduced lung function and increased airway responsiveness in the group treated regularly 4 times a day with salbutamol,[2] although for all outcomes except airway responsiveness, the differences were not statistically significant. More detailed mechanistic studies have shown that regular use of salbutamol may enhance early and late asthmatic reactions to allergen[7,8] and the degree of bronchial constriction resulting from standardized exercise challenge.[9] Numerous studies have confirmed that the regular use of short-acting β_2-agonists increases airway responsiveness to histamine or methacholine.[1,2,10–14]

The adverse effects of regularly inhaled short-acting β_2-agonist are not obviated by the concomitant use of inhaled glucocorticosteroid.[1] No beneficial anti-inflammatory effects have been firmly attributed to short-acting inhaled β_2-agonists; indeed, these agents may increase rather than decrease the cellular inflammatory response in asthma.[15,16]

When β_2-agonists are used as required for symptom relief, their frequency of use is a good marker of control of asthma. A pattern of escalating use of short-acting β_2-agonists is predictive of high risk of a major life-threatening episode of asthma.[17,18]

There is no evidence in humans to suggest that inhaled short-acting β_2-agonists increase serious cardiac arrhythmias or induce other cardiac abnormalities.[6] Although a hypokaliemic effect has been observed after inhaled β_2-agonists, this has generally been considered not clinically significant.

Long-acting β_2-agonists

Recommendations

- Inhaled long-acting β_2-agonists (salmeterol and formoterol) may be considered as an alternative to increased doses of inhaled glucocorticosteroids and should be used as an add-on therapy to moderate or higher doses of inhaled glucocorticosteroids to achieve control of persistent asthma symptoms (level I).
- Long-acting β_2-agonists are not recommended for relief of acute symptoms or for use in the absence of inhaled anti-inflammatory therapy (level II).

The long-acting β_2-agonists provide more sustained bronchodilation and, at least initially, provide prolonged protection from natural or laboratory challenges. They can be used as additional treatment in those whose asthma is not adequately controlled with anti-inflammatory medication. Long-acting β_2-agonists may reduce the number of exacerbations when added to inhaled glucocorticosteroids. Also, unlike the short-acting β_2-agonists, they do not seem to increase airway responsiveness or decrease control of asthma. However, long-acting β_2-agonist may mask deteriorating asthma especially if glucocorticosteroid or other anti-inflammatory therapy is withdrawn while symptoms are controlled with a long-acting β_2-agonist.

Efficacy and safety

In response to the concern that regular use of short-acting inhaled β_2-agonists may be associated with increased morbidity and mortality from the loss of control of asthma, careful pre- and post-marketing studies of salmeterol and formoterol have been undertaken to determine whether such risks occur with these agents. One post-marketing surveillance study of salmeterol[19] showed an odds ratio of 3.0 for death associated with use of salmeterol, but this was not statistically significant. Another prescription-event monitoring study[20] provided no evidence that the use of salmeterol is associated with excess mortality. Moreover, a large well-controlled study with formoterol,[21] with exacerbation as primary outcome, provided reassuring information that addition of formoterol to either low-dose or higher-dose inhaled glucocorticosteroid did not increase the frequency of mild or severe exacerbations of disease and was associated with improved control of symptoms and lung function.

The ability of these agents to induce sustained relaxation of smooth muscle in airways, preventing episodic or sustained shortening, particularly at night, is postulated to explain the observed clinical benefit.[22,23] The rationale for long-acting bronchodilator treatment is not only to provide prolonged symptom relief, but also to protect against challenges from allergens or exercise and other less-identifiable stimuli. Unfortunately, tachyphylaxis to bronchoprotection is readily demonstrated after only a few doses of salmeterol[24,25] and probably also occurs with formoterol.[26] Although both agents protect against exercise-induced asthma for 12 hours or more following a single dose,[27,28] the duration of protection following multiple doses is considerably shortened.[29,30] Even once-daily dosing with salmeterol has been associated with tachyphylaxis to its bronchoprotective effect against exercise-induced asthma in children treated with inhaled glucocorticosteroids.[31]

Formoterol is a full agonist at β-receptors, whereas salmeterol is a partial agonist with a different mechanism for prolonged duration of effect.[32–39] These pharmacologic dif-

ferences allow for a number of in vitro and in vivo differences between these two agents, including the possibility of a greater effect of formoterol when smooth muscle tone is markedly increased. In addition, formoterol induces bronchodilation more rapidly than salmeterol and the duration of its effect shows a more pronounced dose–response relation; however, these differences are of uncertain clinical relevance when the agents are used as suggested.

In a randomized crossover trial, a greater degree of inhaled glucocorticosteroid withdrawal could be achieved during salmeterol treatment before clinical features of an exacerbation were noted (increased symptoms and decreased lung function) despite increasing airway inflammation as judged by sputum eosinophilia.[40] Hence, salmeterol use can mask the development of increasing airway inflammation that, if salmeterol were not used, would increase symptoms and decrease lung function and draw attention earlier to the worsening inflammatory process.

Debate continues as to whether the use of long-acting β_2-agonist leads to subsensitivity to short-acting β_2-agonists needed for rescue therapy when symptoms are acute.[34,41] Experimental work suggests a lesser degree of response to short-acting β_2-agonists, but this may be due to improved baseline lung function, with less room for improvement with short-acting β_2-agonist.

Several studies have demonstrated that adding a long-acting β_2-agonist is preferable, in terms of controlling symptoms and lung function, to doubling or further increasing the dose of inhaled glucocorticosteroid in patients with persistent symptoms despite glucocorticosteroid and short-acting β_2-agonist therapy.[21,42–44] These studies address the increasing concern about adverse effects of high doses of glucocorticosteroids,[44,45] by suggesting that combination therapy with a moderate dose of inhaled glucocorticosteroid and long-acting β_2-agonist is preferable to high-dose inhaled glucocorticosteroid alone.

As with all forms of inhaled therapy, attention to the type of inhalation device and technique along with appropriate patient education and reinforcement is essential.[46]

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Leukotriene-receptor antagonists and related compounds

Recommendations

- Leukotriene-receptor antagonists (LTRAs) may be considered as an alternative to increased doses of inhaled glucocorticosteroids. LTRAs may be used as adjunct therapy to moderate or higher doses of inhaled glucocorticosteroids to achieve control of persistent asthma symptoms (level II).
- There is insufficient evidence to recommend LTRAs as first-line anti-inflammatory therapy in place of inhaled glucocorticosteroids; however, for patients who cannot or will not use inhaled glucocorticosteroids, LTRAs should be the primary treatment choice (level IV).

The cysteinyl leukotrienes C_4, D_4 and E_4 were originally described as slow-reacting substances of anaphylaxis.[1,2] These leukotrienes are produced through the action of 5-lipoxygenase on arachidonic acid, a fatty acid released from the phospholipid backbone of cell membranes following cellular stimulation.[3] Inflammatory cells known to be important in asthma, such as mast cells and eosinophils, are capable of producing and releasing leukotrienes. In adults with asthma, increased levels of cysteinyl leukotrienes have been observed following allergen challenge[4,5] and after exercise.[6] In children with asthma, increased levels of leukotrienes have been detected in urine after bronchoprovocation by exercise.[7] Following severe acute exacerbations of asthma in children, increased leukotriene levels have been found to persist for as long as 1 month.[8]

Leukotrienes appear to be important biochemical mediators in asthma. They can cause bronchoconstriction, mucous hypersecretion and increased airway vascular permeability resulting in airway wall edema.[9–11] Their action in human airway obstruction rests on the stimulation of specific receptors now termed cysteinyl leukotriene type 1 (CysLT1) receptors.[12]

The identification of the structure of the cysteinyl leukotrienes, C_4, D_4 and E_4, and their potential importance in the pathogenesis of asthma has led to development of several classes of drugs collectively known as the antileukotrienes. Some inhibit the synthesis of leukotrienes by effector cells of asthma, and it is theoretically possible to stop their production by inhibition of any of the enzymes in their biosynthetic pathway. However, the only enzyme that has been selectively inhibited is 5-lipoxygenase (5-LO).[13] (Zileuton, a 5-LO inhibitor, may not be marketed in Canada, because it must be administered 4 times daily and requires monitoring of liver enzymes.) It has also been possible to interrupt leukotriene formation by preventing the binding of arachidonic acid to the 5-LO activating protein.[14] Some pharmaceutical molecules are being investigated to modify the function of this protein, but none is available for clinical use.

A number of chemically distinct, specific, selective antagonists have been identified and used in studies of human asthma.[15–17] These compounds have been extremely important in establishing the central role of the cysteinyl leukotrienes in the pathogenesis of various manifestations of asthma, including exercise-induced bronchoconstriction,[6,18] allergen-induced bronchoconstriction[19–21] and aspirin-induced asthma.[22,23] They have also been evaluated as possible therapy for chronic persisting asthma. Zafirlukast and montelukast are CysLT1-receptor antagonists currently available for clinical use in Canada (Table 1). Montelukast may be used in the treatment of children with asthma as young as 6 years of age; zafirlukast may be used at age 12 years and over. Another antagonist, pranlukast, is not yet available in North America.

Efficacy in chronic persistent asthma

Adults

Clinical trials of up to 26 weeks duration have tested 4 antileukotrienes in patients with chronic persistent asthma.

In the earliest,[24] LY171883, a less potent CysLT1-receptor antagonist was shown to increase FEV_1) slightly but significantly (approximately 300 mL). Moreover, in patients who used inhaled β_2-agonists more frequently before randomized treatment began, this use decreased while their FEV_1 increased. In 2 other trials of 4–6 weeks' duration, the effectiveness of treatment with the 5-LO inhibitor, zileuton,[25] or the CysLT1-receptor antagonist, zafirlukast,[26] was compared with placebo. Patients receiving higher doses of either antileukotriene had a significantly greater increase in FEV_1 than did patients taking placebo; patients receiving lower doses of treatment had an intermediate increase in FEV_1. Chronic treatment with either antileukotriene was also associated with significant decreases in the use of asthma medication and in asthma symptoms and an increase in morning peak expiratory flow. Two short-term studies[27,28] comparing the CysLT1-antagonist montelukast with placebo over 1.5–12 weeks of treatment demonstrated a mean improvement of 14%–16% in FEV_1. These results indicate that, in patients with chronic persistent asthma, the leukotrienes mediate a clinically significant component of airway obstruction.

These findings have been confirmed and extended in 13-week and 26-week studies in patients with chronic persistent asthma in which the efficacy of treatment with zileuton was compared with that of placebo.[29,30] All patients were being treated only with inhaled β_2-agonists and had prebronchodilator FEV_1 levels that were about 60% of the predicted normal. Zileuton treatment was associated with an approximate 15% improvement in FEV_1, a decrease in asthma symptoms and reduced use of β_2-agonist. Also, in both trials over 2.5 times the number of patients receiving placebo treatment required glucocorticosteroid rescue treatment than did patients receiving high-dose zileuton treatment. There was no significant deterioration in the improvement in FEV_1 during the course of either study, thus showing that patients do not become tolerant of the effects of 5-LO inhibition. Studies using compounds that block the effects of leukotrienes (both LTRAs and 5-LO inhibitors) have shown that asthma control is improved in adults and in children older than 12 years of age.

There is some evidence that antileukotrienes may be even more effective in patients with severe asthma. Their effect added to the bronchodilation achieved even with high doses of inhaled β_2-agonists[31,32] suggests that they may have a place in the treatment of the severe bronchoconstriction associated with acute severe asthma, although this has not been evaluated in clinical studies. A clinical benefit of their addition has also been demonstrated in patients with poor asthma control, who are already taking high doses of inhaled glucocorticosteroids.[33] In one study,[34] the receptor antagonist pranlukast prevented asthma exacerbations in patients in whom the doses of inhaled glucocorticosteroids were reduced by half.

Two studies[22,23] that specifically assessed the role of antileukotrienes in patients with aspirin-sensitive asthma showed that these drugs effectively blocked the ASA-induced asthmatic responses.

In adults with exercise-induced bronchoconstriction, the regular use of inhaled β_2-agonists will reduce the ability of inhaled β_2-agonists to protect against exercise-induced bronchoconstriction.[35,36] Antileukotrienes were effective in this setting[6,18] without tolerance developing.

Table 1: Characteristics of the LTRAs, montelukast and zafirlukast

Characteristic	Montelukast	Zafirlukast
Effective in exercise-induced bronchoconstriction	Yes	Yes
Effective in allergen-induced asthma	Yes	Yes
Effective in ASA-sensitive asthma	Yes	Yes
Effective in persistent asthma	Yes	Yes
Dose frequency	Once daily	Twice daily
Food interactions	No	Yes
Drug interactions	Not significant	Yes
Comparison with inhaled corticosteroids*	No peer-reviewed publication	No peer-reviewed publication
Oral glucocorticosteroid-tapering effect	No peer-reviewed publication	No peer-reviewed publication

Note: LTRA = leukotriene-receptor antagonist; ASA = acetylsalicylic acid.
*Particularly in regard to changes in airway inflammation.

Children

There is little information about the use of cysteinyl LTRAs in the treatment of children with asthma. Most studies have been in adult populations, although many have included adolescents as young as 12 years of age. Only one study of chronic use of an LTRA in younger children has been published.[37] In it, the efficacy and safety of montelukast (in the form of a 5-mg chewable pill) were studied during an 8-week double-blind, placebo-controlled trial. The patients were 6–14 year old children with poorly controlled asthma (FEV_1 of 72% predicted); 35% regularly used inhaled glucocorticosteroids. Compared with placebo, the montelukast group showed a greater and sustained improvement in FEV_1 (8.2% versus 3.6%), a decrease in the use of β_2-agonist for symptom relief, and there was significant decrease in the percentage of days and patients with asthma exacerbations. An asthma-specific questionnaire[38] revealed significant overall improvement in quality of life and significant improvement in terms of symptoms, activity and emotions. These effects were seen in younger as well as older children, and equally in those receiving concomitant inhaled glucocorticosteroids compared with those with no regular anti-asthma medication on entry to the study.

In a 6-month open follow-up study of 121 of these pa-

tients[39] the effect of montelukast on FEV_1 was consistent and the increase in FEV_1 was not significantly different from that in a control group regularly treated with beclomethasone. Quality of life, as measured by the Asthma Specific Quality of Life Questionnaire, remained significantly improved throughout the 6-month open treatment and was also not significantly different from that of the beclomethasone control group.

A study of zafirlukast involving children over 12 years of age and adults[40] showed a significant increase in days without symptoms, fewer days on which β_2-agonists were required and fewer episodes of asthma per month in the treatment group versus the control group. There were also fewer health care contacts and fewer days of absence from school in children or work in adults.

The role of LTRAs in the treatment of exercise-induced bronchoconstriction in children has been investigated in 2 studies.[41,42] In patients 6–14 years of age, a crossover study demonstrated a significant decrease in exercise-induced bronchoconstriction 20–24 hours after taking a 5-mg chewable tablet of montelukast after 2 days of treatment.[41] Twenty to 24 hours after the second dose, montelukast decreased the area under the curve for FEV_1 following exercise bronchoprovocation by approximately 50% and significantly blunted the fall in peak FEV_1 (an18% fall versus 27% for the placebo group). In a study of the effect of zafirlukast on exercise-induced bronchoconstriction in children aged 6–14 years,[24] the maximum fall in FEV_1 from the baseline and the area under the curve for FEV_1 were significantly reduced 4 h after a single dose of 5, 20 or 40 mg of zafirlukast compared with placebo, but not after a 10-mg dose of zafirlukast. In this study of 39 patients, 20 patients received 5 and 20 mg zafirlukast and 19 received 10 and 40 mg zafirlukast. The peak fall in FEV_1 was 8%–10% for the zafirlukast groups compared with a 17% fall in the placebo group.

Safety

Because this entire class of drugs is new, patient exposure to these agents is limited. Nevertheless, a number of issues have emerged. In a safety study of over 3000 patients, about 4.5% receiving zileuton, but only 1.1% of those receiving placebo had reversible elevations in hepatic transaminases to more than 3 times the upper limit of the reference range. These elevations occur in the first 2–3 months after initiation of treatment; later, the incidence of increased hepatic transaminases falls to the levels observed in the control group.[29]

At the recommended doses of zafirlukast and montelukast, hepatotoxicity has not been identified as a problem. Both medications have a remarkable safety profile. Yet, a recent study identified a small group of patients with severe asthma who developed the clinical manifestations of eosinophilic vasculitis (Churg–Strauss syndrome) after being treated with zafirlukast (and more recently with montelukast) and stopping or reducing doses of oral glucocorticosteroids.[43] The authors have suggested that the disease was unmasked after glucocorticosteroid withdrawal.

Conclusions

Antileukotrienes constitute an important novel therapy for asthma. Current data indicate that inhibition of leukotriene synthesis or action has a beneficial effect in the treatment of both induced and spontaneously occurring asthma. There does not appear to be any indication for the use of antileukotrienes in patients with very mild, intermittent asthma, in whom infrequent use of inhaled β_2-agonists is adequate to control symptoms. However, for some patients with moderate and severe persistent asthma, it is clear that antileukotrienes will have a place in asthma consensus guidelines. These patients do not usually achieve optimum control of their asthma with low doses of inhaled glucocorticosteroids. The number of studies on the role of LTRAs in controlling symptoms and lung function compared with doubling or further increasing the dose of inhaled glucocorticosteroids in patients with persistent symptoms despite glucocorticosteroid and short-acting β_2-agonist therapy are fewer than for long-acting β_2-agonists; however, we believe LTRAs could be considered in the former situation.

In patients with mild asthma but persisting symptoms, in whom disease control is not achieved with infrequent β_2-agonist use, the current consensus guidelines on the management of asthma suggest that inhaled glucocorticosteroids are the most effective treatment. It is likely that the antileukotrienes will be effective in some patients with mild persistent asthma, suggesting that, in some situations, they may be used earlier. However, low doses of inhaled glucocorticosteroids, which are free of systemic unwanted effects, are very effective in this patient population; thus, antileukotrienes cannot be recommended (unless patients cannot or will not use inhaled corticosteroids) until studies comparing them with low doses of inhaled glucocorticosteroids have reported on their potential to control asthma and antagonize airway inflammation. If an antileukotriene is chosen as the next line of treatment, a therapeutic trial of 2–4 weeks will allow a decision to be made about the efficacy of the treatment. If the treatment is ineffective, it should not be continued beyond this time.

Suggestions for future research

- What is the comparative efficacy of antileukotrienes compared with low doses of inhaled corticosteroids (500 μg/d or less of beclomethasone dipropionate or its equivalent)?

- Is there a role for antileukotrienes as a first-line controller treatment in asthma (issues of potential adherence and ease of administration compared with benefits of inhaled glucocorticosteroids should be assessed in prospective studies)?
- For patients with asthma that is poorly controlled with moderate doses of an inhaled glucocorticosteroid (< 1000 μg/d), is the optimum strategy the addition of a long-acting inhaled β_2-agonist, the addition of an antileukotriene or an increase in the dose of inhaled glucocorticosteroids?
- What is the long-term effect of the earlier use of antileukotrienes on the natural history of asthma?
- What is the most effective antileukotriene?
- What is the effect of LTRAs on parameters of airway inflammation?
- What is the long-term effect on lung growth in children with asthma treated with LTRAs compared with regular treatment with inhaled glucocorticosteroids?

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Adjuvant therapy

Nonsteroidal inhaled anti-inflammatory agents (anti-allergic agents)

Recommendations

Disodium cromoglycate

- Disodium cromoglycate should not be added to an established regimen of inhaled or systemic glucocorticosteroids (level I).
- Disodium cromoglycate may be used as a less-effective alternative to short-acting β_2-agonist bronchodilators for the prevention of exertion-induced symptoms (level I).
- In children with mild symptoms, disodium cromoglycate may be an alternative to low-dose inhaled glucocorticosteroids when the patient is unwilling to take inhaled glucocorticosteroids (level I).

Nedocromil

- Nedocromil is a safe but modestly effective alternative to low-dose inhaled glucocorticosteroid in children older than 12 years and in adults with mild asthma where the fear of side-effects precludes the use of glucocorticosteroids (level I).
- Nedocromil may be considered as a less-effective alternative to short-acting β_2-agonist bronchodilators for the prevention of exertion-induced bronchospasm (level I).

Ketotifen

- Ketotifen is not recommended in first-line therapy for asthma (level II).

Disodium cromoglycate

There is excellent evidence that disodium cromoglycate (DSCG) therapy can reduce symptoms,[1,2] disability[3] and costly emergency room visits and admissions to hospital for asthma.[4] The associated improvement in pulmonary function is relatively small or nil[1–3,5–7] DSCG can prevent allergen-induced seasonal increases in airway responsiveness[8] and, under some circumstances, may correct perennial airway hyperresponsiveness.[7] However, it can neither augment nor sustain the improvement in airway responsiveness already achieved by inhaled glucocorticosteroids.[5]

DSCG approximates theophylline in terms of efficacy without its potential for toxicity.[3,7,9] DSCG (40 mg/d) may approximate beclomethasone (400 μg/d) in efficacy[10]; 60 mg/d of DSCG administered by nebulization has been shown to be equivalent to 600 μg/d of inhaled triamcinolone acetonide.[11] However, 80 mg/d of DSCG was inferior to 100 μg/d of fluticasone propionate over 1 year in asthmatic children aged 4–10 years.[12] In patients who are less than optimally responsive to low-dose inhaled glucocorticosteroids, adding DSCG achieves no gain in symptom control.[6,13–15] Also, DSCG does not facilitate the downward titration of the dose of beclomethasone in patients with persisting suppression of the hypothalamic–pituitary–adrenal axis resulting from high-dose inhaled glucocorticosteroid.[15] DSCG has not demonstrated a clinically useful degree of prednisone-sparing activity.[16] The addition of DSCG is less effective than the addition of salmeterol in adults with mild-to-moderate asthma regardless of whether inhaled glucocorticosteroids are taken.[17]

In Canada, the DSCG pressurized metered-dose inhaler contains 1 mg/puff and a minimum effective dose for DSCG is considered to be 10 mg 3–4 times daily.[18,19] Thus, only the nebulizer solution (20 mg/mL) for infants or the dry powder inhaler (20 mg/capsule) for older children or adults is likely to be effective.

Nedocromil sodium

There is excellent evidence that nedocromil can reduce asthma symptoms[20–24] and improve pulmonary function,[20,21,23] particularly when compared with β_2-agonist use alone.[24] However, airway hyperresponsiveness is not consistently lessened,[25,26] and the incidence of periodic exacerbations of asthma may remain unchanged.[22,27,28] Nedocromil is not a potent anti-inflammatory agent, and its regular use has little or no effect on markers of airway inflammation in people with asthma.[29] In patients with mild to moderate asthma, nedocromil may facilitate reduction in theophylline use by two-thirds[21] and, at a dose of 16 mg/d, may be as effective as theophylline as an add-on agent.[30] Comparisons with DSCG show more, less or equivalent efficacy.[31,32] Nedocromil may be substituted for 300–400 μg/d of beclomethasone[23,31,33] and as much as 600 μg/d in a few patients.[34] This effect is not consistently demonstrable.[25,35] Nedocromil at 16 mg/d may be effective as an add-on drug in patients with a less than optimum response to low-dose beclomethasone.[20,36–38] It is not effective as a substitute[34,39] or add-on drug[34] in patients whose asthma control is less than optimum on high-dose beclomethasone. Nedocromil's capacity to facilitate weaning a patient off prednisone is marginal at best, possibly allowing a reduction of up to 5 mg/d.[28,40] During the viral season, regular treatment with nedocromil sodium in children can significantly reduce asthma symptoms associated with respiratory infections.[41]

Ketotifen

Ketotifen is an orally active prophylactic agent for the management of asthma and allergic disorders.[42] In patients with mild asthma, compared with placebo, ketotifen can improve asthma symptoms and reduce the need for concomitant asthma drugs in 50%–70% of patients, but these effects may require 6–12 weeks of administration and the improvement in FEV_1 or PEF is slight.[42–44] Ketotifen appears to be less effective than DSCG in children with asthma.[45] In asthmatic children requiring moderate doses of inhaled glucocorticosteroids, the addition of ketotifen did not result in any significant glucocorticosteroid-sparing effect compared with placebo.[46]

Theophylline and its derivatives

Recommendations

- Theophylline should not be used as first-line therapy in children or adults with asthma (level I).
- In patients whose symptoms do not respond to moderate-dose inhaled glucocorticosteroids alone, the addition of theophylline may result in asthma control that is equivalent to increasing to high-dose inhaled glucocorticosteroids alone (level II).
- Theophylline may be useful in some children requiring high-dose inhaled glucocorticosteroids (level III).
- Because theophylline has a narrow therapeutic range and potential for severe side-effects, the dose must be titrated to minimize side-effects in patients starting the drug, especially if high doses are required (level III).

Theophylline has been used in the treatment of asthma for more than 50 years and, for a long time, was considered to be a first-line drug in the treatment of asthma. However, its popularity has declined in many industrialized countries, probably because theophylline has not been considered to be an anti-inflammatory agent and because it is not as good a bronchodilator as β_2-agonists. In recent years, theophylline has been relegated to third-line therapy, after β_2-agonists and, especially, inhaled glucocorticosteroids, which are now being used very early in the treatment of the condition.[47,48] Nevertheless, evidence is growing to indicate that theophylline has anti-asthmatic properties other than its bronchodilator action, including anti-inflammatory and immunoregulatory properties.[49–53] Therefore, further trials will be needed to clarify the role of theophylline in the treatment of asthma.[49,54] In this section, we review the place of theophylline in maintenance therapy for asthma, in light of new evidence and the most recent international recommendations.[48,55]

Theophylline is a modest bronchodilator, but its narrow therapeutic window and high incidence of side-effects limit its use. It has the advantage of being administered orally, which may enhance compliance; also, new long-acting (12-hour) and very long-acting (24-hour) formulations result in very good serum stability. The bronchodilator effect of theophylline is proportional to the serum concentration, but on a semilogarithmic base[56]; thus, improvement in FEV_1 is greater when serum levels increase from 28 to 55 μmol/L compared with the improvement observed when serum concentrations increase from 83 to 110 μmol/L; however, the risk of untoward side-effects is much higher in the latter case. In addition, theophylline is metabolized almost entirely by the liver and, therefore, its clearance is subject to several drug interactions (e.g., ciprofloxacin, erythromycin, cimetidine) and is influenced by various clinical conditions (fever, hepatitis, cirrhosis, cardiac failure).[57] Flow charts have been developed to assist in achieving therapeutic concentrations rapidly,[56] but required doses vary widely among patients and must be tailored to the individual by monitoring serum concentrations.

The main limitation to the use of theophylline is the frequency of adverse effects. The most common side-effects are headache, nausea and vomiting, abdominal discomfort, restlessness and insomnia. There may also be increased acid secretion, gastroesophageal reflux and diuresis. High serum concentrations may cause agitation, convulsions, tachyarrythmias, coma and death.[57]

Side-effects may be significantly reduced without compromising clinical benefit by aiming for serum concentrations of 28–55 μmol/L, rather than the previously recommended 55–110 μmol/L.[49] Some studies have suggested that theophylline could cause behavioural changes and learning difficulties in children,[58] but these findings have not been confirmed elsewhere.[59,60] Concomitant use of theophylline and the new leukotriene antagonists may lower the serum concentration of certain of the leukotriene antagonists, but not the theophylline concentration.

In chronic trials in children, theophylline was at least as effective as sodium cromoglycate, although it causes more side-effects.[7] Whereas Nassif and co-workers[61] showed some additive advantage of theophylline in glucocorticosteroid-dependent children, Tinkelman and colleagues[62] demonstrated that theophylline resulted in symptom control comparable to low-dose beclomethasone, but led to more bronchodilator use and more courses of systemic glucocorticosteroids. Side-effects were also observed significantly more frequently with theophylline. Thus, theophylline is not a first-line treatment.

For adults, theophylline appears to be inferior to inhaled glucocorticosteroids for primary therapy of asthma.[63,64] However, the addition of theophylline can improve symptom control in patients already taking high-dose inhaled glucocorticosteroids (e.g., 1000 μg/d or more of beclomethasone or its equivalent).[65] For some patients with

moderate asthma who are still symptomatic despite inhaled glucocorticosteroid therapy, the combination of moderate-dose inhaled glucocorticosteroid (e.g., budesonide, 400 μg twice daily) and theophylline at serum concentrations below the currently recommended therapeutic range may produce benefits similar to those with high-dose inhaled glucocorticosteroids (e.g., budesonide, 800 μg twice daily) alone.[66]

There may be a subgroup of asthmatic patients who particularly benefit from therapy with theophylline — those in whom effective asthmatic control is lost when theophylline is withdrawn and will not respond to increasing doses of glucocorticosteroids.[51,67] Theophylline is especially useful for control of asthma with nocturnal symptoms,[68–73] but, for those who are not taking inhaled glucocorticosteroids, nocturnal symptoms may be better controlled by the addition of an inhaled glucocorticosteroid than by the addition of theophylline twice daily without inhaled glucocorticosteroids.[74] However, long-acting β_2-agonists may afford better control of asthma with nocturnal symptoms[75–78] and also provide better continuous symptom control and reduce the need for rescue with short-acting β_2-agonists.[75–79]

Original trials of theophylline were based on measurement of acute bronchodilation and suggested that therapeutic concentrations ranged from 55 to 110 μmol/L (10 to 20 μg/mL), which placed patients at higher risk of side-effects because of the various clinical conditions that can affect theophylline metabolism. More recent trials examining the nonbronchodilator actions of theophylline suggest that doses producing lower serum concentrations have significant cellular and immunomodulatory effects.[49] The beneficial effects of theophylline on the cellular events associated with nocturnal asthma[52] and the clinical benefits seen at low serum concentrations of theophylline[66] may reflect these immunomodulating properties of theophylline.[49,53]

Theophylline is a nonspecific phosphodiesterase (PDE) inhibitor. However expanding knowledge of PDE isozymes indicates that PDE III is predominant in airway smooth-muscle relaxation whereas PDE IV appears to be important in inflammatory cells such as mast cells, eosinophils and T-lymphocytes.[80] Future clinical trials with more specific PDE antagonists will be important in redefining the role of these agents in asthma therapy.

Anticholinergic drugs

Recommendations

- Anticholinergic bronchodilators are not recommended as first-line agents. They may be used as relievers for patients who are unable to tolerate β_2-adrenergic bronchodilators (level III).

The most commonly used anticholinergic bronchodilators are quaternary derivatives. Their potency has been examined in stable ambulatory patients using MDIs.[81–83] Typically, ipratropium bromide or similar compounds cause bronchodilation more gradually than β_2-agonists, such as salbutamol, fenoterol or terbutaline. For example, ipratropium produces 50% of its bronchodilation in 3 minutes and 80% in 30 minutes, with maximal or peak effect evident only 1–2 hours after administration.[81,84] Compared with anticholinergics, the adrenergic compounds (β_2-agonists) cause greater bronchodilation in the first 2–3 hours following administration. Thus, quaternary anticholinergic agents are not first-line bronchodilator therapy for most patients with asthma.

The combination of anticholinergic and adrenergic therapy appears to produce greater bronchodilation than either agent used alone. In addition, an additive effect with theophylline has been documented.[83,85–88] The clinical relevance of these studies is uncertain now that the use of anti-inflammatory therapy is more widespread, but in acute asthma in both adults and children, there appears to be a clear role for combination therapy with ipratropium and β_2-agonists.[89,90]

The response of asthmatic patients to anticholinergic agents appears to be unrelated to their atopic status. However, Ullah and colleagues[87] have suggested that these agents are more useful in older patients.[87] Adrenergic receptor sensitivity declines with age, whereas the sensitivity of the cholinergic system appears to remain intact. This may make anticholinergics relatively more useful for older patients with asthma.

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Other drugs for severe asthma and unconventional therapies

Recommendations

- In chronic severe asthma that seems unresponsive to moderate doses of oral glucocorticosteroids, confounding issues should be assessed before increasing the dose of oral glucocorticosteroids or using other immunosuppressive agents (level I).
- Because of the associated clinical problems, patients with asthma who have a severe glucocorticosteroid dependence requiring further intervention should be referred to a specialized centre (level III).
- Potentially toxic immunosuppressive agents, such as methotrexate, cyclosporine and gold salts, should be reserved for patients with severe asthma who are dependent on long-term high-dose oral glucocorticosteroids and should be used only in specialized centres (level III).
- There is no objective evidence of any benefit, apart from placebo effect, from the more frequently used unconventional therapies such as acupuncture, chiropractic, homeopathy, naturopathy, osteopathy and herbal remedies (level I or III, depending on the therapy).

Oral glucocorticosteroids and glucocorticosteroid-resistant asthma

Glucocorticosteroids are the most effective anti-inflammatory drugs for the treatment of asthma. The primary mechanisms of action of these agents include interference with arachidonic acid metabolism, prevention of directed migration and activation of inflammatory cells and increased responsiveness of β-receptors in airway smooth muscle.[1] With the advent of highly potent inhaled glucocorticosteroids and other asthma therapies, long-term treatment with oral glucocorticosteroids is now seldom required to control asthma. Given the side-effects associated with both short- and long-term use of these agents, doses should be kept to the minimum necessary to achieve the desired level of asthma control.

The response to oral glucocorticosteroids may be quite variable. Patients with glucocorticosteroid-resistant asthma[2] have a baseline FEV_1 of less than 60% of the predicted value, a bronchodilator response of the FEV_1 greater than 30% of baseline and a change in FEV_1 in response to a 7-day course of oral glucocorticosteroids (20 mg of prednisone per day) of less than 15%. In contrast, responsive patients show an improvement in FEV_1 of greater that 30% at any time during the 7-day course of systemic glucocorticosteroid. In resistant patients, diurnal variability in PEF and a brisk bronchodilator response are common.[3] Resistant patients typically show little improvement in FEV_1 or PEF despite administration of high doses of systemic glucocorticosteroids for up to 2 weeks.[4,5]

No universally accepted definition of glucocorticosteroid-resistant asthma yet exists,[4] although Leung and Szefler[6] proposed that it be defined as failure to improve baseline morning prebronchodilator FEV_1 by >15% of the predicted value after at least 7–14 days of 40 mg oral prednisone or its equivalent (20 mg twice daily). The term "glucocorticosteroid-resistant asthma" is misleading as applied to most patients, because their glucocorticosteroid resistance is not absolute, but rather a shift of the dose–response curve to the right.

The third group, glucocorticosteroid-dependent patients, typically have severe asthma, require high doses of inhaled glucocorticosteroids and regular oral glucocorticosteroids (usually < 40 mg/day) to manage their symptoms.[1] Control of their asthma often deteriorates when their dose of oral glucocorticosteroid is reduced.[1]

Carmichael and colleagues[7] suggest that such features as longer duration of symptoms, morning fall in FEV_1, greater bronchial reactivity to methacholine and a positive family history may, to some extent, distinguish nonresponders from responders. Other mechanisms of glucocorticosteroid-resistant asthma have also been proposed.[8]

Patients should not be labeled as resistant to glucocorticosteroid until factors related to asthma care have been examined (Table 1). If conventional therapeutic options fail to achieve reasonable control, or if control is achieved only with high doses of systemic glucocorticosteroids, alternative therapies using nonsteroidal immunosuppressive agents may be considered in some patients.

Methotrexate

In low doses, methotrexate appears to inhibit the attraction of polymorphonuclear cells by leukotriene B_4 and interleukin-1.[9] A review by the working group for the Canadian Asthma Consensus Conference[8] on the role of methotrexate in chronic severe asthma described results of many randomized, placebo-controlled clinical trials. These suggested that use of methotrexate has a significant glucocorticosteroid-sparing effect, although some studies did not show additional improvements in pulmonary function.[8] More recently, a placebo-controlled, randomized, double-blind, parallel-group study[10] reported only marginal reduction in glucocorticosteroid use in 16 weeks of methotrexate treatment in 24 patients with severe asthma. Another 24-week, placebo-controlled, double-blind parallel-group study, which included a crossover arm at 12 weeks,[11] found that methotrexate (15 mg/week) resulted in a 38% reduction in oral glucocorticosteroid use and a 22% decrease in daily bronchodilator use but no improvement in lung function in 12 patients with severe asthma.

Table 1: Confounding factors to be checked before classifying a patient as glucocorticosteroid resistant or dependent

- Compliance with medication (e.g., enquire about filling of prescriptions at pharmacy)
- Proper use of devices
- Environmental control (e.g., avoiding smoking and environmental and occupational allergens)
- Treatment of concomitant conditions (e.g., sinusitis, gastroesophageal reflux)
- Exclusion of other conditions that may mimic asthma (e.g., vocal cord dysfunction, hyperventilation syndrome)
- Appropriateness of current therapy (e.g., inadequate doses of inhaled glucocorticosteroids)
- Concomitant use of adverse drugs (e.g., β-blockers, acetylsalicylic acid, etc.)

A recent meta-analysis[12] set out to determine whether treatment with low-dose methotrexate spares oral glucocorticosteroids in adults. It excluded studies that did not contain original data related to the primary question, had no controls or described patients younger than 18 years of age. The remaining 11 eligible studies all included an initial phase in which the baseline level of prednisone was reduced to the lowest possible dose. Methotrexate treatment resulted in a decrease in prednisone or prednisolone usage by an average of 4.37 mg/d or 23.7% of the initial dosage. The greatest effect was evident in patients whose glucocorticosteroid dose was reduced during the initial phase and in those who received treatment with methotrexate for 24 weeks.

Methotrexate in low doses (usually 5–25 mg weekly administered on a single day) has been used for the treatment of severe asthma for almost a decade with usually infrequent and minor side-effects. Increasing doses may be accompanied by an increase in side-effects, especially anorexia, diarrhea or nausea and vomiting. Other side-effects include leukopenia, which is unpredictable and can be life-threatening; hepatic fibrosis (risks factor being cirrhosis, alcoholism, obesity and diabetes); pulmonary toxicity (acute pneumonitis and insidious interstitial fibrosis); and opportunistic infections such as *Pneumocystis carinii* pneumonia, pulmonary cryptococcosis and nocardiosis.[13]

It is unclear why various investigators have obtained different results, but this may be related to the heterogeneity of study populations and the lack of consensus on what is meant by glucocorticosteroid-resistant and dependent asthma. At present, it is difficult to predict which patients will respond to methotrexate and further studies are required to define who is most likely to benefit. Methotrexate should be considered only in patients with severe asthma in whom optimal conventional therapy has failed to achieve adequate control and when there is concern about the side-effects of glucocorticosteroids.

Cyclosporine A

Cyclosporine is a potent nonselective anti-inflammatory agent that acts primarily by inhibiting transcription factors for cytokines derived from T lymphocytes.[14–16] Few well-controlled trials have examined the efficacy of cyclosporine in the treatment of chronic severe asthma. In an uncontrolled study,[17] 6 of 12 patients on cyclosporine (3 mg/kg daily) reduced their daily glucocorticosteroid dose and experienced an improvement in symptoms and PEF. In a 24-week double-blind, randomized, crossover trial in 30 patients[18] cyclosporine use (initial dose of 5 mg/kg daily, aiming at trough concentrations of 100–250 μg/L) was associated with a 12% increase in PEF and a 17.6% increase in FEV_1. This study was not designed to examine the glucocorticosteroid-sparing effect of cyclosporine.

In a double-blind, placebo-controlled, randomized, parallel-group study involving 34 glucocorticosteroid-dependent patients with asthma (mean oral prednisone dose, 16 mg/d),[15] cyclosporine use over 34 weeks was associated with a slight beneficial effect on some subjective indicators of asthma severity, but no improvements in pulmonary function and no difference in the final dose reduction of prednisone between the treatment groups. The authors suggested a limited place for cyclosporine use in the treatment of patients with asthma who are dependent on glucocorticosteroids.

More recently, a double-blind placebo-controlled study[19] in 39 patients who were dependent on glucocorticosteroid found that cyclosporine A (initial dose, 5 mg/kg daily) was associated with a 62% reduction in prednisolone use (from 10 to 3.5 mg) but only a 25% reduction (from 10 to 7.5 mg) with placebo ($p < 0.05$). The reduction in glucocorticosteroid dose was most pronounced during the last 12 weeks of the 36-week active treatment period. Patients receiving cyclosporine also exhibited a significant (9.4%) improvement in PEF.

Cyclosporine should be given in 2 doses, usually starting at 3 mg/kg a day (based on ideal body weight) and aiming at trough concentrations close to 150 mg/L; its administration requires close monitoring of blood pressure, renal function, white blood cell count and level of cyclosporine in the blood. Side-effects include hypertension, renal failure, hypertrichosis and paresthesia.

There is conflicting evidence concerning the value of cyclosporine in patients with asthma who are dependent on or resistant to glucocorticosteroid treatment. It is not known if there is a sustained clinical benefit after stopping cyclosporine treatment; indeed, this drug has many potential side-effects that may be more serious than those associated with prednisone.

Gold salts

Gold has been used to treat refractory rheumatoid arthritis for many years. It inhibits immunoglobulin E-mediated release of histamine and leukotriene C_4 from basophils and mast cells.[20] In the first double-blind, placebo-controlled study showing that gold was of some benefit in asthma,[21] 79 patients with asthma of variable severity, some of whom required glucocorticosteroids, were treated with gold salts or placebo for 30 weeks: 71% of those in the treated group improved compared with only 44% of the control group. A 22-week, double-blind study[22] compared intramuscular gold therapy with placebo in 9 asthmatic patients requiring high doses of prednisone. While on gold therapy, 5 of the patients reduced their need for glucocorticosteroid; 2 had to stop gold therapy because of severe proteinemia.

There is more convincing evidence that oral gold, auranofin, reduces the need for glucocorticosteroids in dependent asthmatic patients. In an open trial of severe glucocorticosteroid-dependent asthmatic patients, auranofin allowed reduction in oral glucocorticosteroids with improvement in methacholine-invoked bronchial responsiveness without deterioration of spirometric measures of lung function.[23] A double-blind, controlled study comparing auranofin (3 mg twice daily) with placebo[24] followed 28 asthmatic adult patients requiring at least 2.5 mg of prednisone daily (mean 7.6 ± 5.3 mg) for 26 weeks. Auranofin significantly reduced glucocorticosteroid use by 4 mg/d (versus 0.3 mg/d in the placebo group), asthma symptoms and exacerbations and improved FEV_1.

In a recent, large 6-month double-blind placebo-controlled multicentre study,[25] all patients were severely asthmatic, were taking low-dose inhaled glucocorticosteroids and required at least 10 mg of prednisone daily for at least 3 months. On the 157 people who completed the study, 82 were taking 3 mg auranofin twice daily. The primary efficacy end-point (i.e., a reduction of at least 50% of the oral glucocorticosteroid dose from baseline) was achieved in a significantly higher proportion of the auranofin group (41%) than the placebo group (27%). The glucocorticosteroid-sparing effect of auranofin was most pronounced in those requiring 10–19 mg of prednisone daily at baseline.

Oral gold is preferred to the parenteral formulation. Side-effects are frequent and include urticaria, stomatitis, leukopenia, thrombocytopenia and proteinuria. Therefore, close monitoring via complete blood counts and urine analyses is required. Although it can be concluded that 3 mg auranofin twice daily reduces the need for oral glucocorticosteroids in asthma, its exact role and risk–benefit ratio compared with oral glucocorticosteroids is still not well defined.

Intravenous immunoglobulin

Intravenous immunoglobulin is currently being evaluated for possible therapeutic benefit in many diseases including asthma. No double-blind controlled study is yet available, and 2 uncontrolled studies[26,27] in children showed conflicting results. In a recent open study,[28] intravenous immunoglobulin allowed a marked reduction in the dose of oral glucocorticosteroids in 2 glucocorticosteroid-insensitive asthmatic adults accompanied by improvements in FEV_1 and a decrease in the variability of PEF. With so little scientific evidence, it is impossible to recommend the use of intravenous immunoglobulin in the treatment of glucocorticosteroid-resistant asthma.

Other agents in severe asthma

Dapsone[29] and hydroxychloroquine[30] have been tested in small uncontrolled studies that may suggest a potential role in the treatment of severe glucocorticosteroid-dependent

patients with asthma. However, in a 2-month double-blind crossover study,[31] hydroxychloroquine was of no benefit in glucocorticosteroid-dependent asthma. There is little evidence to support the use of these drugs in severe asthma.

Unconventional therapies

Conventional medical management of asthma relies on control of the environment, a number of drugs and, occasionally, special techniques such as immunotherapy. Each approach is based on reasonable and sound science and many are associated with long-lasting success. However, the annals of asthma therapy are replete with alternative, unproven and mystic therapies, and reliance on drugs that are often progenitors of many of those still in favour today. These have always been popular and often have a long history of use. Recently, interest in their use has been growing. After interviewing 1539 adults, Eisenberg and colleagues[32] concluded that a third of adults in the United States use alternative, unconventional therapies, and 25% of those treated conventionally also use unconventional remedies. Information about the use of alternative therapies by asthmatic adults is unavailable, but some figures are available for Canadian asthmatic children. Spigelblatt and co-workers[33] found that 208 (11%) of 1911 children had previously consulted one or more unconventional practitioners. Chiropractic, homeopathy, naturopathy and acupuncture together accounted for 84% of use.

Only a limited number of well-controlled studies have addressed the value of unconventional therapies, the most popular of which are homeopathy, acupuncture, osteopathy, chiropractic, herbal medicines, hypnosis, yoga and Chinese, Japanese and Indian therapies. Ziment[34,35] has recently reviewed these therapies comprehensively. There is no objective evidence for any real benefit of these approaches.

Nevertheless, some patients will try these approaches and may even benefit. Most authors agree that they may indeed lead to an improvement in asthma control, but this is no different from a placebo effect; however, a placebo is more effective than no therapy in asthma.[35] Placebo responses occur in about a third of patients, but a much higher response is not infrequent and explains the positive results in some uncontrolled double-blind studies.

Physicians must show empathy toward patients who seek help from unconventional sources; however, they should explain the lack of scientific evidence and urge their patients not to stop their anti-asthma drugs, particularly anti-inflammatory drugs, in an uncontrolled way.

Homeopathy

In the only double-blind, parallel-group, placebo-controlled study[36] of the effect of homeopathy in asthma, 11 of 24 atopic asthmatic adults received homeopathic treatment for 4–8 weeks. More than two-thirds of the participants were taking inhaled glucocorticosteroids at baseline and did not modify their treatment. Although there was a significant improvement in the visual analog scale for symptoms in the treated group after the first week, there was no significant improvement in FEV_1 or histamine-provoked bronchial responsiveness. However, the effect seems very small, and a larger well-controlled study is needed to clarify homeopathy's role in the treatment of asthma.

Chiropractic

Although widely used in the treatment of asthma, specific chiropractic spinal manipulation was not effective in asthmatic adults in a recent double-blind, controlled study.[37]

Acupuncture

No good controlled study of the role of acupuncture in the treatment of asthma has shown an adequate response.[38] Fung and colleagues[39] found some mild protection against exercise-induced asthma in a placebo-controlled single-blind study.[39] In contrast, 2 well-controlled double-blind, crossover studies[40,41] failed to show any short- or long-term benefit of acupuncture over placebo in adults with asthma. Complications associated with acupuncture include transmission of disease (e.g., hepatitis B and C, HIV infection) and pneumothorax and local infections.

Hypnosis and relaxation techniques

It has long been recognized that relaxation techniques, including yoga, may improve the well-being of patients, and some open or single-blind studies have suggested a possible role for hypnosis, relaxation techniques or yoga in the treatment of asthma or in reducing bronchial hyperresponsiveness.[42] No well-controlled, double-blind randomized study has looked adequately at the role of such therapy.

Herbal medicine and Chinese, Japanese and Indian medicines

Although these approaches are popular in some countries, they have not been subjected to the scrutiny of a well-controlled, double-blind randomized study.

Suggestions for future research

- Research is needed to determine why some patients with asthma do not respond favourably to glucocorticosteroid therapy.

- Research is required to improve understanding of the interaction between airway remodeling, hyperresponsiveness and inflammation.
- Large, well-controlled trials are needed to evaluate the potential benefits of methotrexate in severe asthma. Further studies on the pharmacokinetics of low-dose methotrexate using different routes of administration may explain why some patients respond more positively than others.
- Given the significant side-effects associated with orally administered cyclosporine, the development of an inhaled formulation may prove beneficial; more studies are needed to determine the exact role of this drug.
- The place of auranofin in the treatment of glucocorticosteroid-dependent patients with asthma must be better defined, although there is good evidence that it has some glucocorticosteroid-sparing effects.
- Well-designed placebo-controlled studies are urgently needed to determine the role of unconventional therapies in the treatment of asthma, particularly homeopathy and acupuncture.

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Inhalation devices and propellants

Recommendations

- Inhaled drug delivery is recommended over oral or parenteral delivery for adrenergic bronchodilators and glucocorticosteroids (level I).
- The inhalation device that best fits the needs of the individual patient should be chosen (level III).
- With adequate teaching, adults and older children can use any of the commercially available hand-held inhalation devices. MDIs with spacers can be considered for all age groups, and specifically MDIs with valved spacer and face mask are advocated for young children and the elderly. Dry-powder inhalers can provide adequate drug delivery for most children by the time they reach age 5 years (level II).
- MDIs that use hydrofluoroalkane propellant are recommended over those using chlorofluorocarbons (level IV).
- Health care professionals must teach correct inhaler technique when devices are prescribed and dispensed (level I).
- Patients' method of using their inhalation device must be reassessed and reinforced periodically (level II).
- Asthma control should be reassessed when changing an aerosol device (level IV).
- Wet nebulizers for home use are rarely indicated in the management of asthma at any age (level III).
- A trial of wet nebulization in infants and children at home may be appropriate if an MDI with a spacer is not effective (level IV).
- When spacers are used, conversion from a mask to a mouthpiece is strongly encouraged as soon as the age and the cooperation of the child permit (level II).

Adults

Inhalation of bronchodilators and glucocorticosteroids results in faster onset of action with fewer systemic side-effects than taking the same drugs orally or parenterally.[1]

To be effective, an inhalation device must produce an aerosol of medication with a significant dose of particles in the so-called respirable range that enters the lower airways. Inhalation devices should also minimize local (oropharyngeal) and systemic side-effects of the drug and should be simple to use, portable, durable, unobtrusive and cost effective.[2] Because the efficacy and side-effects of inhaled medications are highly dependent on the device, drug and user, the response to a drug delivered from a specific inhaler may differ from the response to different drugs of the same class delivered by the same inhaler or the same drug delivered by a different device. Caregivers must be familiar with the characteristics of the devices they prescribe and dispense,[3] and they must ensure that their patients are able to use the prescribed devices properly.

Pressurized metered-dose inhalers

The pressurized metered-dose inhaler (pMDI) is the most widely used delivery system. As in other delivery systems, even when used correctly, only about 10%–20% of the nominal per puff dose reaches the targeted airways.[4] Fortunately, only a small amount of drug is needed to produce a useful clinical effect. There is general agreement on the technique for optimum use of the pMDI (Table 1).

The so-called "open-mouth" technique is most often recommended because it is believed that this method provides a space in which the aerosol cloud is "conditioned," that is, the velocity of the aerosol cloud slows and aerosol particle size decreases so that drug deposition in the distal airways is enhanced. However, many get good results from a pMDI using a "closed-mouth" technique, in which the inhaler mouthpiece is inserted in the mouth, as long as the tongue is not obstructing it.

Most recommendations suggest that patients should not exhale forcefully and completely to residual volume before inhaling from a pMDI for fear that bronchospasm may result in patients with marked airway irritability. However, for most patients, this is not a concern, and a slow complete exhalation to residual volume may be followed by slightly better drug delivery to the lung than incomplete exhalation. Another common recommendation is that at least 30 seconds elapse between pMDI actuations to allow recharging and reconditioning of the next dose. The clinical importance of this between-dose delay is not known but is likely minimal.

Approximately 40% of patients first assessed in a specialized respiratory care centre or pulmonary function laboratory will not use their pMDIs in the best manner.[5–7] Whether this is true of alternative inhalation devices is not clear. The most common difficulties are failure to coordinate actuation of the device with inhalation (the "aim-shoot-breathe"

Table 1: Recommended technique for using a pressurized metered-dose inhaler (pMDI)

- Shake the pMDI vigorously 3 or 4 times.
- Remove the cap.
- Place the mouthpiece 4 cm (2 fingers' width) in front of the widely open mouth.
- Following a slow, *relaxed* exhalation, start a *slow* inhalation.
- Depress the canister once during the first half of the inspiratory effort.
- Breath in slowly for about 5 seconds.
- Hold breath for up to 10 seconds or as long as possible.
- Repeat these manoeuvres for the number of puffs prescribed.

Note: Rinse mouth thoroughly after the use of inhaled glucocorticosteroids.

manoeuvre) and an involuntary cessation of inhalation when cold aerosol particles reach the soft palate. If inhaler technique can be improved and maintained, clinical improvement is likely. For some patients, this may require adding a spacer to the pMDI or switching to a breath-activated device such as a dry-powder inhaler (DPI). If technique with a pMDI is good, the patient is satisfied with the device and the disease is well controlled, little or no increase in clinical efficacy is gained by switching to a DPI or adding a spacer.[8]

Until recently, all pressurized aerosol inhalers used chlorofluorocarbon (CFC) propellants. These substances are now known to be damaging to stratospheric ozone levels and are being withdrawn from industrial, domestic and medical uses under an international agreement (the Montreal protocol).[9] In the next few years, CFC-containing inhalers will be withdrawn as alternatives, such as hydrofluoroalkane (HFA), become available.

HFA-driven inhalers are effective and safe, but caregivers must be aware of slight differences in characteristics between CFC and non-CFC driven inhalers.[10] For example, patients switching to a non-CFC inhaler must be warned to expect a different taste and a different aerosol sensation.[11] Alternative-propellant inhalers may also have deposition characteristics and, therefore, clinical efficacy that differs slightly from the comparable CFC inhaler.[12] Therefore, caregivers must treat the shift from CFC to non-CFC aerosol inhalers as they would any other change in inhaler format; that is, they must titrate the inhaler dose to the least amount of medication needed to achieve the desired clinical effect.

Metered-dose inhalers with spacers

The use of add-on "holding chambers" or "spacers" has increased recently. There are 2 reasons to consider using a spacer with a pMDI or DPI: inability to use the pMDI or DPI correctly; or persistent local oropharyngeal side-effects associated with inhaled glucocorticosteroids. The addition of a spacer to the pMDI can usually ensure aerosol delivery to the airways for most patients who are having difficulty.

Several types of spacers are available. Those with one-way valves can hold the aerosol discharged from the pMDI in suspension for 2–3 seconds, thereby easing coordination problems and permitting time for the patient to inhale slowly. It is possible to misuse a pMDI with a spacer and miss the dose, although the prevalence of this problem is not known. Common mistakes with the pMDI and spacer combination include inhaling from the spacer before actuating the pMDI and waiting too long after actuation before inhaling.[13] (See Table 2 for the recommended technique.) When multiple puffs from a pMDI are required, each dose should be inhaled separately from the pMDI and spacer combination because charging the spacer with multiple puffs is associated with reduced dosing to the airways compared with inhaling each puff separately.[13,14]

The use of a CFC-driven pMDI with spacer produces a clinical effect at least equivalent (and generally superior) to that of a correctly used pMDI alone. In some instances it may increase the amount of drug deposited in the airways, possibly because spacer devices act to condition the aerosol, slowing the jet of medication and allowing the propellant to evaporate. This influences particle size in favour of finer more respirable particles. Increased drug deposition is more likely when patients who have normal tidal volumes use a large-volume (e.g., 750 mL), valved spacer, although there is little evidence that such spacers offer any significant clinical advantage over smaller (e.g., 150 mL) valved spacer devices. However, when tidal volumes are very low (e.g., in children and the elderly), spacer volume may have an inverse relation to airway drug deposition due to dilution of the drug in larger spacers, coupled with low-volume inspirations. Whether this theoretical concern is clinically significant is not yet known.

As a cost-saving measure, caregivers or patients sometimes construct homemade holding chambers. Although devices made from recycled plastic containers or Styrofoam hot beverage cups may work, their delivery characteristics are untested and must be regarded as unreliable. If careful prescribing and monitoring of inhaled medication indicates that the patient is best served by a spacer, a commercially manufactured and validated device should be purchased; third-party reimbursement agencies such as insurance companies and provincial formularies ought to reimburse for these devices on the same basis as for the drugs they deliver.

By removing large aerosol particles that are not useful for therapy, spacer devices can reduce oropharyngeal deposition of glucocorticosteroid and, thus, help to reduce or prevent local oropharyngeal side-effects such as thrush and dysphonia. Rinsing the mouth after a dose of inhaled glucocorticosteroids can also significantly reduce the incidence of local side-effects, regardless of the inhalation device used.

Several potential problems with spacer devices have not been addressed adequately by clinical research and appropriate

Table 2: Accepted method for using a pMDI with a spacer

- Shake the pMDI and remove the cap.
- Remove the cap from the spacer, if it has one.
- Insert the pMDI into the spacer.
- Insert the spacer mouthpiece into the mouth.
- Following a relaxed exhalation, discharge the pMDI into the spacer once.
- Immediately after the canister is fired, breath in *slowly* and maximally from the spacer for about 4 seconds. A delay of 1–2 seconds between canister actuation and inhalation is acceptable, but not the best practice. For patients with a low tidal volume and inability to hold their breath, taking 2–3 tidal breaths in adults or 5–7 tidal breaths in children is an acceptable alternative. Relax and hold breath for up to 10 seconds or as long as possible.
- Repeat these manoeuvres for each puff prescribed.

Note: Rinse mouth thoroughly after use of inhaled glucocorticosteroids.

education of caregiver or patient. For example, the reduction in deposition of large particles in the oropharynx is often perceived by patients as a reduction in drug delivery and is apparently a reason for noncompliance with the device. Compliance with the caregiver's recommendation to use a spacer has never been quantified and the rate of compliance may be low.

Data suggest that caregivers have little knowledge of optimum spacer use and that this ignorance extends to matters of care and cleaning.[15] Holding chambers should be replaced when damaged or worn. This implies that the chambers should be inspected periodically by the caregiver — every 3–6 months seems reasonable. For plastic devices, an electrostatic charge may be present when the device is new, a problem that can be worsened by inappropriate cleaning, especially if the device is toweled dry. The electrostatic charge can cause aerosol medication to adhere to the sides of the spacer so that total drug delivery and, consequently, lung deposition are reduced.[16] In general, plastic holding chambers should be washed in a dilute solution of household detergent. The chamber should *not* be rinsed after washing and the device should be allowed to air dry without toweling. The thin film of detergent adhering to the walls of the chamber reduces electrostatic build-up.

Dry-powder inhalers

Various DPI devices are available. Currently, all are breath-actuated, effectively eliminating the coordination problem seen with the pMDI alone, and all are free of CFC and HFA propellants. For these and other reasons, the use of DPIs to deliver asthma medications is increasing.

Most adult patients find all DPIs easier to use than a pMDI alone, and switching from a pMDI to a DPI generally results in no loss of therapeutic control. There can be significant differences in lung deposition efficiencies among the various DPIs, but it is not clear whether these differences are clinically important, particularly for bronchodilators that ideally are taken as-needed using a sufficient number of inhalations to achieve clinical relief. Differences in lung and oropharyngeal deposition of inhaled glucocorticosteroids among DPIs may be clinically relevant.

The greatest single problem associated with all DPIs is inadequate inspiratory flow rate.[17] In some devices, the powdered medication may clump when the humidity is high, thus reducing effectiveness. Reduced efficacy will result if a patient exhales into the device before inhalation, as the dose will be expelled from the DPI. The next dose may also be affected by the added humidity of the patient's exhaled breath. Additives in some DPIs can cause cough and irritation. Some DPIs cause a slight sensation of drug entering the mouth (in contrast with the pMDI alone), causing some patients to feel that the device is malfunctioning.[18] Appropriate patient education is necessary.

The correct way to use a DPI is device specific (Table 3); some come preloaded with multiple doses, whereas others require manual loading of doses or dose packs. In contrast to the pMDI technique, a rapid rather than a slow inhalation is recommended for optimum airway deposition.

Bioequivalence and systemic side-effects of inhaled medications

Systemic bioavailability of inhaled medications is a complex issue. Although there appear to be minimal systemic side-effects when aerosol glucocorticosteroids are used in low doses, high doses of inhaled glucocorticosteroids (e.g., more than 1000 μg/d of beclomethasone, budesonide or equivalent) may create new problems. For example, most systemic side-effects from inhaled medications (e.g., adrenal suppression, altered bone metabolism) appear to be related to absorption via the bronchial circulation of the inhaled portion rather than the swallowed portion of the dose.[19,20] The potential for such side-effects is thus modulated, not only by the type of medication, but also be the efficiency of the delivery device used. Although the clinical implications of this phenomenon are not yet known, they could be of particular concern in postmenopausal women and in children in terms of the effects of inhaled glucocorticosteroids on bone metabolism and growth.

Wet nebulization

Wet nebulizers may be subdivided into jet and ultrasonic models and, as for pMDIs and DPIs, drug delivery from these devices also involves a complex interaction among the device, the drug formulation, the patient who inhales the drug and the patient's disease. Wet nebulizers are employed chiefly for the delivery of large bronchodilator doses during acute asthma attacks and, occasionally, for patients unable to use other inhalation devices. The output characteristics of various wet nebulizer systems vary greatly; drug deposition efficiencies can vary at least 10-fold depending such factors as the model of the nebulizer, the fill volume, the flow rate of the driving gas, whether mouthpiece or nose and mouth (mask) breathing is used and whether the nebulizer is operated continuously or intermittently.[21]

Several limitations and potential problems associated with

Table 3: Recommended technique for the use of a dry-powder inhaler (DPI)

- Remove any cap from the DPI.
- Load the unit dose according to the specific DPI device instructions.
- Perform a slow, relaxed exhalation, but do not exhale into the DPI.
- Insert the mouthpiece of the DPI into the mouth and form a tight seal with the lips.
- Inhale rapidly from the DPI.
- Relax and hold the breath for up to 10 seconds or as long as possible.
- Repeat these manoeuvres for each dose prescribed.

Note: Rinse the mouth thoroughly after the use of inhaled glucocorticosteroids.

the use of wet nebulizers should be noted. When the patient's airway disease is stable, the usual wet nebulizer delivery system deposits about 10% of the nominal dose in the lower airway. As the deposition efficiency of these devices when operated continuously depends on the patient's breathing pattern, the high inspiratory flow rates during an acute attack of asthma can reduce deposition dramatically. Many patients have difficulty maintaining nebulizers in clean working order. Wet nebulizers are much more expensive than any other delivery system, are not as portable and require more time to deliver a specific amount of drug compared with DPIs or pMDIs with or without spacers. Currently available ultrasonic devices are more portable, but are expensive. The many disadvantages of wet nebulizer therapy and the ability to achieve equal or better therapeutic effect with a variety of low-cost inhalers means that the wet nebulizer is rarely indicated for treatment of the ambulatory patient.[22]

Before nebulized medication is considered for maintenance management of asthma,

- The diagnosis of asthma should be reviewed and confirmed.
- The patient's inability to use alternative inhalation devices should be re-examined and confirmed.
- Optimum use of anti-inflammatory therapy should be confirmed.
- The patient's ability to operate the wet nebulizer correctly and to bear the expense of this therapy should be considered.

Following institution of home wet-nebulizer therapy,

- Improved control of asthma symptoms and objective measurements of lung function should be verified.
- The patient's ability to take care of the wet-nebulizer device, including cleaning and accurate drug dosing should be verified.

Inhalation therapy in the acute care setting

The Canadian Association of Emergency Physicians and the Canadian Thoracic Society have published guidelines for the use of various inhalation devices to treat acute asthma in the emergency department.[23–26]

Children

The type of medication, the delivery device, patient characteristics and the interaction of these factors all play a role in determining the quantity of medication delivered by inhalation to children with asthma. These variables make it difficult to study aerosol delivery in children. Studies in infants are scarce in part because of the difficulties related to their inability to cooperate and ethical considerations surrounding the need for invasive measurements, but also because of a lack of interest of sponsors in such studies. Nevertheless, age-specific recommendations can be made.

MDIs, spacers, DPIs and wet nebulizers can vary greatly in terms of particle distribution characteristics. The health care provider should know the pulmonary and systemic bioavailability of medication delivered by the device used by the patient. This is particularly important in considering the benefits and side-effects of inhaled glucocorticosteroids for various devices and ages.

Nebulizers

Although ultrasonic nebulizers are promising,[27] they tend to generate large particles with poor deposition characteristics[28] and are not recommended. With jet nebulizers, lung deposition increases with body size in infants,[29] but not in older children[29–31]; thus, dose must be corrected for body size after the age of 1 year.

In children, from 1% to 7% of the nominal dose in a nebulizer is deposited in the lungs, the larger proportion applying to adolescents.[32] This must be taken into account when prescribing for this age group. Increasing the relative humidity can significantly increase lung deposition.[33,34] Drying chambers can significantly increase the quantity of respirable particles available,[35] but they are cumbersome and not readily available. The wet nebulizer device is cumbersome and expensive, and, for the amount of medication delivered, the most costly of all methods of delivery.

Metered-dose inhalers

In MDIs, large droplets emanate from the valve mechanism, but particle size decreases as the propellant evaporates and the aerosol disperses. Deposition in the lung varies from 9% to 26% of the metered dose in adults[36–38]; deposition rates may be lower in children, whose technique may be less effective than that of adults.[39] Depending on the circumstances, breath-activated devices may result in more[40] or less[41] deposition than standard MDIs.

Spacers

A spacing device or "holding chamber" slows the velocity of the aerosol and allows more time for evaporation, which reduces particle size and, with a valve mechanism, improves coordination of delivery.[42] In the school-aged child, inhaling at tidal levels is at least as effective as a slow deep inspiration.[43] Holding the breath is not necessary.[42,43] However, the only study in infants using radiolabeling demonstrated a very low rate of deposition in the lungs — about 1% of the nominal dose.[44] In this study, 2 infants who were crying had the lowest deposition rates.

In adults, lung deposition rate generally doubles with the use of a spacer and gastrointestinal deposition of particles can be reduced from 81% to 17%.[45] This can dramatically improve the benefit and reduce the side-effects of in-

haled glucocorticosteroids, particularly those with a relatively high gastrointestinal bioavailability such as beclomethasone (about 20% bioavailable[46]). Even with the new HFA propellant, which markedly increases the pulmonary deposition of the medication, beclomethasone still has high rate of gastrointestinal absorption[46] and should not be inhaled without a spacer.

New spacers (e.g., Spacechamber™,[47] Optichamber™[48]) are being developed and tested, and are often associated with improved bioavailability of the medication. Currently, in Canada, the efficacy of a device does not have to be proven for it to be marketable; thus, it is imperative that the delivery characteristics of the chosen device are known by the health care provider.

Dry-powder inhalers

DPIs store medication as fine particle aggregates, either as a pure substance (e.g., budesonide) or with a carrier (e.g., fluticasone) that helps regulate the dose. Some multidose devices, such as the Diskus™, use separately sealed individual doses; in others, like the Turbuhaler™, doses are micronized from a reservoir. If this reservoir is exposed to humidity by being left open or stored in the bathroom, the efficacy of the medication will be reduced.[49]

The patient's inspiration provides the force that actuates the device, thus eliminating the need for good coordination required with MDIs. The rate of inspiratory flow is critical to delivery of the medication, although the efficiency of the Diskus™ appears to be relatively flow-independent over a wide range.[50] In one study,[51] 3- to 6-year-old children exhibited as much bronchodilatation using the Turbuhaler™ as those using an MDI. However, in another study,[52] younger children did not use the Turbuhaler™ as efficiently as older ones; this discrepancy was not seen when an MDI and spacer was used. Goren and colleagues[53] found that 79% of 4-year-old children, 92% of 5-year-old children and 100% of 6-year-old children benefited from the Turbuhaler™, although only 43%, 67% and 80%, respectively, used it correctly. Tilting the head backward, holding the breath for 10 seconds or inhaling from residual volume rather than functional residual capacity had no effect on efficacy of the Turbuhaler™.[54] A forceful and deep breath is required for optimum output from this device.[55]

Some DPIs, like the Turbuhaler™, deliver 20%–30% of the nominal dose in adults (about twice that of the MDI),[50,56] whereas the Diskhaler™ and Diskus™ appear to deliver 10%–15% of the nominal dose to the lungs.[37,57] In children, a dose reduction study of budesonide in a clinical setting[58] confirmed the 2:1 superiority of the Turbuhaler™ over the MDI. Although patients have criticized the Turbuhaler™'s high resistance to flow, this characteristic is probably the reason for the associated high bioavailability of the medication.[59]

A holding chamber, filled using a spring-loaded trigger, has been tested with a breath simulator using tidal volumes of 100 mL (equivalent to that of a 1- to 2-year-old child).[60] Of the resulting medication dose, 76% had a aerodynamic diameter <4.7 μm, making this a potentially extremely useful device for infants and young children.

Masks and mouthpieces

Nasal breathing can decrease lung deposition by up to 67%.[30] Therefore, inhalation via the oral route, preferably with a mouthpiece rather than a mask, is recommended when the child is old enough.

Propellants

MDI canisters contain propellants, surfactants and the medication, which may be in solution or suspension. These devices have been available for over 40 years, but are undergoing a revolutionary change in design with the conversion from CFC to HFA propellant under the Montreal Protocol.[61] The HFA-134a propellant operates at temperatures as low as –20°C,[62] which is important in Canada. In addition, alterations in the surfactant and valve mechanism are leading to more consistent dosing and a decrease in the tailing-off of the dose as the canister becomes almost empty.[63]

Beclomethasone is soluble in the new HFA formulation and has a higher fine-particle mass and bioavailability than in the CFC preparation.[64] However, it still has a high rate of gastrointestinal absorption[46] and probably should not be inhaled without a spacer. Salbutamol, which is suspended in the HFA formulation, has about the same bioavailability and efficacy as in the CFC preparation.[65,66] The problem of the lower availability of salbutamol after the container has been standing for over 1 hour, even with shaking,[67] has been rectified in the new canisters; the availability is now independent of the position in which the canister was stored.[63] Most of this technical information has not been peer reviewed.

Care of spacers

Electrostatic forces cause particles to adhere to the plastic walls of spacers, considerably lowering the amount of medication delivered to the lungs.[68,69] Using a metal spacer,[70] lining the plastic spacer with an antistatic spray[71] or simply washing it with soap and letting it drip dry[72,73] can dramatically improve particle delivery and respirable mass. In addition, the longer the medication remains in the electrostatic spacer, the lower the respirable mass.[14] Coating the spacer will also minimize this problem.[71] Particle half-life can be increased from 10 seconds to 30 seconds by using a coated spacer.[71]

Increasing the dead space between the spacer and the infant (mask, valving system) decreases bioavailability of the medication.[74] Bisgaard and colleagues[75] used an infant breath simulator to study 3 spacers that have different amounts of dead space, antistatic characteristics and vol-

umes. The total dose output from the spacer device ranged from 12% (Aerochamber™) to 20% (Babyhaler™) to 30% (nonelectrostatic device) of the total dose delivered.

Suggestions for future research

- National and international regulations governing inhalation devices must be established.
- DPIs that are spring-loaded, attached to holding chambers and breath-activated by infants should be available.
- Advances in ultrasonic and jet nebulization may make these techniques more useful.
- Dosimeters can greatly enhance the overall output of jet nebulizers by minimizing wastage in the expiratory phase. Perhaps direct targeting of molecules to specific receptors and liposomal formulations will greatly enhance the benefit–side-effect profile of medications.

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Asthma in the elderly

Recommendations

- A diagnosis of asthma should be more widely considered in elderly patients with dyspnea, wheezing or nocturnal cough (level III).
- Investigation to determine exposure to environmental and other asthma-inducing factors in elderly patients with recent-onset asthma should include a careful review of medications including self-prescribed ASA and other drugs with asthma-inducing potential (level II).
- Special care should be taken to allow elderly patients with asthma to choose an inhaler device with which they are comfortable and competent (level III).
- Measures should be taken to prevent osteoporosis in elderly patients with asthma who require prolonged treatment with oral corticosteroid (level I).
- Elderly patients with asthma require careful follow-up because they have an increased risk of exacerbations, which may be related to impaired perception of their disease severity (level II).

Epidemiology

Asthma may be first diagnosed at any age and is common in the elderly. A variety of population-based studies[1–3] have shown that the prevalence of asthma in the elderly is similar to that in other adult age groups, i.e., 4.5–8%. In one study,[4] 40% of the elderly population attending ambulatory care centres in hospitals or living in subsidized nursing homes and lodges had asthma, emphasizing that it may occur with and be mistaken for such disorders as cardiac failure and COPD; in those with long-standing asthma, the disease may be difficult to distinguish from COPD.[5]

Although in some elderly patients asthma may have been present earlier in life, in at least half it is recently acquired.[5] An incidence study[6] demonstrated a rate of newly diagnosed asthma of 0.1% a year in those over 65 years of age. Although atopy is considered to be less common in older adults, sensitization to cat allergen has been associated with late-onset asthma,[7] and allergy, often to household dust mites, was identified in 72% of elderly patients with late-onset asthma in Italy.[8] The use of replacement estrogen in women may increase the risk of late-onset asthma.[9]

Asthma in the elderly, more so than in younger populations, may be associated with the use of medications including ASA, nonsteroidal anti-inflammatory drugs (NSAIDs) and adrenergic-blocking agents, including topical preparations. There is also anecdotal evidence of the association of asthma with other agents.[10]

Elderly patients may have more severe asthma and may be more prone to exacerbations and the need for urgent treatment and hospital admission,[11] possibly because of underdiagnosis, undertreatment[1] or poor perception of symptoms.[12,13]

Diagnosis

As noted, asthma may be difficult to diagnose in the elderly because of misconceptions about its prevalence and

also because older patients may have diseases and disorders that mask the classic features of asthma. Spirometry before and after using a bronchodilator should be an essential investigation in an elderly patient with otherwise unexplained dyspnea, wheeze or cough. Although spirometry may be difficult to perform in the elderly, at least one report indicates that it is feasible even in confused patients.[4] Unfortunately, at least some elderly people with asthma will show airway obstruction without a response to β_2-agonist and, in some instances, this may reflect irreversible obstructive lung disease due to longstanding, unrecognized and untreated disease.[5]

Treatment

As in any age group, treatment must begin with the advice to avoid asthma-inducing agents. In the elderly patient with asthma, it is particularly important to take a careful medication history. Use of self-prescribed ASA has become common and may go unrecognized. ASA and NSAIDs are commonly prescribed in the elderly and may cause late-onset asthma. Oral and topical β-adrenergic blocking agents[14] and other anti-arrhythmic agents, including verapamil,[10] and others with acknowledged β-blocker potential can exacerbate or cause asthma in those who are predisposed to the disease.[15] Whenever possible, medications that might induce or aggravate asthma should be withdrawn. In other respects, the management of asthma in the elderly does not differ from that recommended for other age group, although particular care should be taken in the selection of and instruction in the use of inhaler devices.[16,17]

Attention should be paid to the prevention of osteoporosis in elderly patients who require oral glucocorticosteroid therapy. The use of estrogen replacement therapy in postmenopausal women who require oral glucocorticosteroids is generally recommended although this advice has been challenged in a report linking estrogen use to an increased risk of developing asthma.[8] Etidronate used cyclically with vitamin D and calcium supplementation has also been shown to improve bone density in older patients requiring prolonged oral corticosteroid therapy for asthma.[18]

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Asthma in pregnancy

Recommendations

- Avoidance of allergic and nonallergic triggering factors should be the first form of therapy for asthma during pregnancy (level III).
- The patient should be informed about the background risk of drugs in pregnancy in the general population. It should be made clear that, although relatively few medications have been proved harmful during pregnancy, no asthma or allergy medication can be considered to be proved safe (level II).
- Physicians should discuss with the patient the possible consequences for the mother and fetus of inadequately controlled asthma, including the impact on maternal and fetal morbidity and mortality (level II).
- Physicians should discuss medication choices and the rationale for the treatment plan; they should emphasize that the treatment program is considered to entail less risk than the uncontrolled illness that could result in its absence (level II).

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- Treatment should take the same stepped approach as in the nonpregnant patient and may include inhaled β_2-agonists, inhaled corticosteroids, ipratropium bromide, cromolyn and systemic glucocorticosteroids. Theophylline may increase nausea and reflux and is less desirable. There is significantly less information about the effects of the long-acting β_2-agonists and the leukotriene inhibitors, and there is less clinical experience with these drugs than with other classes of drugs. These drugs should be used only for patients whose asthma cannot be controlled using the more studied therapies (level II).
- The use of systemic glucocorticosteroids for severe asthma, especially for prolonged periods, may be associated with a greater risk of pre-eclampsia, antepartum or postpartum hemorrhage, low birth weight, preterm birth and hyperbilirubinemia (level II).
- Patients requiring systemic glucocorticosteroid therapy should be considered to be in a higher risk pregnancy (level II).
- Physicians should address all of the patient's questions and obtain and document the patient's concurrence with the therapeutic decisions (level IV).
- Physicians should monitor and support the patient and their health care providers with respect to asthma management during the pregnancy (level IV).

Asthma is present in 4%–7% of pregnant women and is the respiratory disorder most frequently complicating pregnancy.[1,2] The course of asthma during pregnancy is variable, and asthma control may remain unchanged, or become worse or improve and return the to the prepregnancy state within 3 months after parturition.[3,4] Overall, asthma control improves significantly in the last 4 weeks of pregnancy.[3]

Asthmatic pregnant women have been variably reported to have an increased risk of pregnancy-induced hypertension, pre-eclampsia, caesarian section, placenta previa and antepartum or postpartum hemorrhage.[2,5–7] Poorly controlled asthma may affect maternal comfort and safety and pregnancy outcome for both mother and child. However, data from well-designed studies have shown that treated asthmatic women have fewer adverse infant and maternal outcomes than those without therapy.[5,8,9] More severe asthma requiring systemic glucocorticosteroids may increase the risk of perinatal complications, including maternal pre-eclampsia, perinatal mortality, preterm births, low-birthweight infants and hyperbilirubinemia.[1,2,10] The relation between these pregnancy outcomes and the severity of asthma and asthma drug use by the mother is not always clear.

The pharmacologic management of asthma raises significant concerns about the risk of congenital malformation in the fetus. In the general population, there is a 2%–4% risk of major congenital malformations identified at birth; only 1% of these can be attributed specifically to medications.[1] The embryo is most susceptible during organ formation, from 4 to 10 weeks following the last menstrual period. Information regarding the effects of drugs administered during pregnancy comes from animal studies, human case reports and prospective cohort studies. Animal studies showing adverse effects are hard to extrapolate to humans due to dose and species effects. Most prospective cohort studies of asthma medications during pregnancy, even when available, suffer from low statistical power, and case–control studies may be biased by retrospective study design.[1]

For drugs with a longer history of usage, there tends to be more data to support a lack of adverse effects. Use of most common asthma medications (β_2-agonists, theophylline, cromolyn, inhaled glucocorticosteroids) during pregnancy has not been shown to be associated with increased perinatal risks including congenital malformations.[1,10] Oral glucocorticosteroids have been associated with pre-eclampsia in several studies.[2,10] Although no asthma medications can be considered proven safe for use during pregnancy, these drugs are used to prevent the potential direct and indirect consequences of uncontrolled asthma. The patient must be aware of the risks and benefits of appropriate asthma control and must give her informed consent to the therapeutic approach recommended during pregnancy.

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Management of patients with asthma in the emergency department and in hospital

Management in the emergency department

The management of exacerbations of asthma requires rapid access to facilities or personnel capable of delivering bronchodilators appropriately, defining the severity of the asthma episode objectively, ensuring appropriate monitoring of oxygen delivery and instituting safe referral and disposition. Bronchodilators should be titrated using clinical and objective measurements, and systemic glucocorticosteroids should be given to almost all patients who must seek treatment in the emergency department. In addition to relief of symptoms and objective improvement in measures of airflow, a detailed review of risk factors for severe asthma is needed and an educational intervention offered or arranged.

Patient assessment (all ages)

Recommendations

- A structured management plan should be used to treat patients with asthma in the emergency department (level III).
- The severity of airflow limitation should be determined objectively using spirometry (the preferred method), PEF measures or both, before and after bronchodilator therapy (level III), unless the patient is too young (< 6 years), uncooperative or moribund. These measurements should not postpone necessary treatment (level IV).
- The arterial oxygen saturation (S_aO_2) should be measured before and after treatment (level III).

The use of structured forms has been shown to improve documentation,[1,2] and patient outcomes are improved when physicians are given a brief educational program on asthma guidelines with a poster summary.[3,4]

Objective measurement of airflow (all patients more than 5 years of age)

Physicians' estimates of response to therapy are often inaccurate in acute asthma.[5] Failure of initial bronchodilator therapy to significantly improve the FEV_1 or PEF is predictive of a more prolonged attack course or the need for hospital admission.[6–11] The (S_aO_2) may correlate with PEF and, in some level III studies, correlates with the likelihood of admission.[12–19] Low (S_aO_2) may indicate a need for admission to hospital, but normal levels do not exclude severe asthma or the possibility of relapse. Measurement of (S_aO_2) may help to guide treatment in adult patients, but no studies have shown that arterial blood gases or (S_aO_2) predict outcome.

Drug therapy

Recommendations

- Supplemental oxygen should be used in treating patients with acute asthma to maintain (S_aO_2) > 94% (level IV).
- Short-acting β_2-agonists should be considered the primary class of medication for the management of exacerbations. It should be administered by inhalation and titrated using objective and clinical measures of airflow obstruction as guides (level I).
- The choice of delivery device (MDI with spacer, wet nebulization, dry-powder inhaler) will depend on the need for expedient treatment, availability of staff and the individual patient of any age (level I).
- The use of an MDI with a chamber (valved spacer device) is preferred over the use of a wet nebulizer for patients of all ages at all levels of severity (level I).
- All patients treated in the emergency department for an acute episode of asthma should be considered candidates for systemic glucocorticosteroid therapy (oral or intravenous) and receive it as soon as possible (level I).
- An anticholinergic drug should be added to β_2-agonist therapy for severe acute asthma and β-blocker-induced bronchospasm and may also help in cases of moderate acute asthma (level I).
- Aminophylline is not usually recommended for use as a bronchodilator in patients of any age during the first 4 hours of asthma management in the emergency department (level I).

Oxygen therapy will help normalize oxygen content while fixed airway obstruction related to airway inflammation and ventilation–perfusion mismatching resolve. This reduces the catecholamine response that can cause tachycardia and increased blood pressure.

Inhaled β_2-agonists produce the most rapid relief from acute bronchospasm with the fewest side-effects.[20–22] Before treatment with inhaled β_2-agonists (using a metered-dose inhaler [MDI] or wet nebulizer) does not preclude successful reversal of airflow limitation in the emergency department.[23]

Salbutamol is more effective and safer when inhaled than when taken intravenously.[20,24–32] Intravenous use of bronchodilators should be considered only if the response to the

inhaled drug is poor or if the patient is coughing excessively, is moribund or becomes so despite inhalation therapy.

The dosage of inhaled bronchodilators should be adjusted based on objective measures of airflow limitation and symptoms. It may be necessary to increase the dose to 1 puff every 30–60 seconds. There may not be a maximum dose, depending on the response to treatment, but some have suggested that 20–40 puffs may be required.[33,34] Sometimes continuous wet nebulizer treatment is indicated. Relief of bronchospasm with inhaled bronchodilators is best achieved if the principle of cumulative dosing is followed: sequential doses build on the therapeutic effects of previously administered doses.[35–37] Prehospital treatment with inhaled β_2-agonists (using an MDI or a wet nebulizer) does not preclude successful reversal of airflow obstruction in the emergency department.

Once a plateau is achieved (i.e., no further improvement noted after subsequent doses), continued administration of bronchodilators by any route is not likely to provide further clinical benefit and may result in toxic effects. Patients with severe asthma (i.e., FEV_1 or PEF < 40% of previous best or predicted value), who fail to improve by clinical or objective assessment, require more frequent administration of bronchodilators and continuous monitoring. The plateau must be defined in relation to attack severity and improvement in terms of a combination of clinical and objective measures (≥15% improvement in FEV_1 or PEF).

Three meta-analyses of level I studies in children[38] and adults[39,40] evaluating MDI and wet nebulization indicate that the use of an MDI with a chamber or spacer is associated with a more rapid onset of bronchodilation, shorter duration of emergency department treatment, fewer side-effects and greater patient preference.[38–41] More rapid and profound bronchodilation is achieved when sufficient doses are given with an MDI plus spacer device than when conventional doses are administered with a wet nebulizer.[42–44] This was true even in patients with the most severe airflow limitation (FEV_1 < 0.67 L).[42] The dry-powder inhaler (DPI) is at least as effective as an MDI or wet nebulization for acute asthma.[45,46]

In 2 meta-analyses of placebo-controlled trials,[47,48] glucocorticosteroids resulted in more rapid resolution of airflow limitation in admitted patients[49] and decreased relapse rate among those discharged from the emergency department. Systemic glucocorticosteroids should be given as soon as possible in all patients with moderate or severe asthma (i.e., FEV_1 or PEF < 60% of predicted value).

For patients in the emergency department or hospital, intravenous glucocorticosteroid therapy has no advantage over oral therapy in terms of rate of resolving airflow limitation.[47] The parenteral route is preferred if patients are unable to take medication orally (e.g., they are too breathless or are intubated) or if they are unable to absorb an oral dose readily (e.g., because of vomiting). The recommended oral dose is 40–60 mg of prednisone[47] or equivalent and the single intravenous dose is 125 mg solumedrol or 200 mg hydrocortisone.[50,51]

In 4 meta-analyses[52–55] of double-blind studies of therapy for acute asthma in adults and children, the combination of ipratropium bromide with a β_2-agonist was superior to a β_2-agonist alone in improving lung function. This combination was especially beneficial to patients with the most severe airflow limitation (i.e., FEV_1 < 1 L or PEF < 140 L/min): the mean increase in FEV_1 was 55.6% with the combination therapy, compared with 38.9% using a β_2-agonist alone.[56–61] In one study,[56] the combination of ipratropium bromide plus nebulized salbutamol not only produced greater bronchodilation but was also associated with fewer adverse effects (e.g., tachycardia and tremor) than larger doses of β_2-agonists alone. At least 4 level I studies[62–65] have reported no clinical benefit from adding anticholinergics. A systematic review of the use of anticholinergics in children[54,55] and a recent level I study[66] showed clear evidence of improvement in lung function and a 30% reduction in hospital admission rates in children with severe asthma. Studies of the treatment of mild to moderate asthma with single doses of ipratropium bromide have not shown any clinical benefit,[67] but lung function improvements in moderate asthma may warrant the use of this drug, particularly if it reduces both the need for frequent β_2-agonists and some of the related side-effects.

A meta-analysis of 13 level I studies of the use of aminophylline concluded that it does not provide a significant, additive bronchodilator effect compared with adequate doses of inhaled β_2-agonists in cases of acute asthma and appears to be associated with an increased risk of adverse effects.[68]

Management of refractory cases

Recommendations

- Epinephrine (intramuscular or intravenous), salbutamol (intravenous) and inhaled anesthetics are recommended as alternatives to conventional therapy in unresponsive cases of life-threatening asthma (level II).
- Intravenous magnesium sulfate (level I) and heliox (level III) may be useful in addition to usual therapy for refractory asthma.
- Ketamine and succinylcholine are recommended for rapid-sequence intubation in cases of life-threatening asthma (level I).
- Intubation should be performed by physicians experienced with this procedure (level IV).

Three randomized controlled trials[69–71] and a systematic review[72] showed additional benefit when magnesium was given to patients with severe asthma exacerbations who had not responded to standard β-agonist therapy. Two level I studies[73,74] that found no such benefit did not limit treatment to unresponsive cases. The safety of magnesium and the potential benefit justify its use in people with severe asthma who fail to

respond to titrated bronchodilators and glucocorticosteroids.

Parenteral bronchodilator therapy may be indicated when the inhaled route is not practical: for example, in patients who are coughing excessively, are too weak to inspire adequately or are moribund.

Intubated patients with asthma who do not respond to conventional bronchodilator therapy may benefit from an inhaled anesthetic agent with bronchodilating properties, such as ether,[75] halothane,[76–78] enflurane[79] or isoflurane.[80,81] Hypotension and cardiac dysrhythmias are associated with the use of these agents and are more likely to occur in hypoxemic patients.

The mode of ventilation for status asthmaticus may be a crucial factor in a successful outcome.[82–85] It is often difficult or nearly impossible to use ventilation because of the extreme hyperinflation associated with severe restrictive and obstructive defects. Ventilation strategies emphasize caution in attempts to reduce the partial pressure of carbon dioxide abruptly to normal levels.[83–85] It is advisable to use a controlled mechanical hypoventilation approach that accepts moderate to high degrees of hypercarbia until lung function improves, with occasional intravenous administration of bicarbonate to keep pH above 7.2.[83–85] The risk of barotrauma and volutrauma (shock) can be minimized with slow machine rates (6–8 breaths/min) allowing a low inspiration-to-expiration ratio and with low tidal volumes (6–8 mL/kg). With ventilation, patients may also require frequent suctioning of mucous secretions that are often seen in life-threatening attacks.

The efficacy of heliox has not been confirmed in a randomized controlled trial.[86,87] Benefit was reported in an observational study[86] and some believe that it has a role in refractory asthma.[87]

Ketamine is recommended as the agent of choice for intubation using a modified rapid-sequence intubation technique. It has a rapid response time, provides good levels of anesthesia and is a good bronchodilator (level IV evidence).[88–90] Pretreatment with benzodiazepines helps prevent the occasional reactions (hallucinogenic episodes) associated with ketamine.[91]

Immediately after administration of the sedative(s) (ketamine, benzodiazepine), paralysis should be induced with succinylcholine because it has the fastest response time and the shortest duration of action of drugs in its class. Paralysis following intubation should be maintained using vecuronium (0.15 mg/kg intravenously). Bag-and-mask ventilation does not precede intubation in a rapid-sequence intubation technique. It is difficult or even impossible to use bag-and-mask ventilation in cases of acute asthma because of severe hyperinflation. It may also cause harm by provoking gastric distension and an increased risk of aspiration. If there is a failure to successfully intubate, bag-and-valve-mask ventilation should be initiated while preparing for other airway interventions.

In children, pretreatment with atropine is recommended to prevent bradycardia that may occur with the use of succinylcholine.

Discharge treatment plan and follow-up care

Recommendations

- Consideration for discharge should be based on results of spirometry (percent of previous best, or percent of predicted or absolute value) and assessment of clinical risk factors for relapse (level III).
  - Patients with a pretreatment FEV_1 or PEF below 25% of previous best level or the predicted value (i.e., FEV_1 < 1.0 L or PEF < 100 L/min) usually require admission to hospital.
  - Patients with a post-treatment FEV_1 or PEF below 40% of previous best level or the predicted value (i.e., FEV_1 < 1.6 L or PEF < 200 L/min) usually require admission to hospital.
  - Patients with a post-treatment FEV_1 or PEF between 40% and 60% of previous best level or predicted value (i.e., FEV_1 = 1.6–2.1 L or PEF = 200–300 L/min) are possible candidates for discharge.
  - Patients with a post-treatment FEV_1 or PEF above 60% of previous best level or predicted value (i.e., FEV_1 > 2.1 L or PEF > 300 L/min) are likely candidates for discharge.
- Adults discharged from the emergency department who require glucocorticosteroid therapy should be given 30–60 mg/d of prednisone orally (or equivalent) for 7–14 days. No tapering is required over this period (level I). Children should receive 1–2 mg/kg a day of prednisone or equivalent (up to a maximum of 50 mg) for 3–5 days (level I).
- Inhaled glucocorticosteroids are an integral component of asthma therapy and should be prescribed for almost all patients at discharge, including those receiving oral glucocorticosteroids (level I).
- A treatment plan and clear instructions for follow-up should be given to patients discharged from the emergency department. Patients with high-risk factors, poor lung function or indications of chronic poor control should be referred to an asthma education clinic (level IV).

Spirometry and clinical assessment are used to establish risk of relapse. Important risk factors include admission to hospital or a visit to the emergency department in the previous 12 months, recent use of glucocorticosteroids, use of multiple categories of asthma medication, a previous severe or life-threatening asthma attack and the presence of psychosocial problems.[92–97] The most compelling evidence for using oral glucocorticosteroids comes from a Cochrane Collaboration review[48] showing that the pooled odds ratio for treatment with oral glucocorticosteroids after discharge is 0.35 (95% CI 0.17–0.78) or a 65% reduction in relapses.

Tapering doses of oral glucocorticosteroid has been popular in the past, but there is level I evidence that this is not necessary when duration of use is 15 days or less.[47,48,98] The recommended dose of inhaled glucocorticosteroid (beclomethasone or budesonide) at the time of discharge is 500–1000 μg/d, but this may depend on the dose and duration of oral glucocorticosteroid therapy (level IV). The more indicators of risk of asthma-related death or readmission to hospital in the patient's history the higher the recommended dose of inhaled glucocorticosteroids.[94,96,99]

Expert opinion indicates that high-dose inhaled glucocorticosteroid alone at discharge may be a reasonable choice in some cases after an asthma exacerbation. However, until further prospective trials confirm these findings, the use of oral and inhaled glucocorticosteroid at discharge is recommended.

Most experts believe that educating patients about asthma is the key to optimum disease control.[92,100–104] Whenever possible, emergency staff should develop brief written treatment plans with clear instructions for follow-up care and a review of drug-delivery techniques.

Management of acute asthma in hospital

Recommendations

- All patients admitted to hospital for acute asthma should be given systemic glucocorticosteroids, preferably by the oral route (level I).
- All patients should receive inhaled glucocorticosteroids in addition to systemic glucocorticoids (level IV).
- Bronchodilators should be administered by the inhaled route and their need should be determined using objective measurements. The choice of delivery device (MDI with spacer, wet nebulization, DPI) will depend on the need for expedient treatment, the availability of staff and patient selection (level I). Rapid onset, the possibility of titration, reduced cost, more effective use of hospital staff, better side-effect profile and increased opportunities for education all make MDIs or DPIs preferable to nebulization in all age groups (level I).
- Inhaled anticholinergics should be added to β_2-agonist therapy for 24–48 hours in cases of severe asthma and possibly moderate asthma (level I).
- Response to treatment and criteria for discharge should be based on serial pulmonary function studies and control of symptoms (level III).
- Patients with severe airflow obstruction (FEV_1 or PEF < 40% of previous best or predicted value following emergency treatment) or those who are hypercapnic, are unresponsive to treatment, deteriorating or have been intubated must have continuous care in the emergency department or a unit capable of frequent or continuous monitoring of oxygenation until their condition is stable or improved (level IV).
- Supplemental oxygen guided by oximetry to achieve $S_aO_2 > 94\%$ is recommended (level IV).
- Serial administration of arterial blood gases is recommended for critically ill patients and those with severe asthma if S_aO_2 is persistently low (< 90%) or if there is suspicion of hypercapnia (level IV).
- Patient education, including a formal written action plan for treatment after discharge, should occur during the hospital stay (level I).
- After discharge, patients should continue systemic glucocorticosteroids (30–60 mg/d for adults and 1–2 mg/kg daily for children) for at least 3–5 days for children and 7–10 days for adults (level I).
- Patients should continue to take inhaled glucocorticosteroids after discharge with adjustment of the dose according to the action plan or on the advice of a physician at a follow-up visit (level I).
- Follow-up arrangements with the primary care physician or asthma specialist must be made before discharge (level IV).
- Patients with severe disease (FEV_1 or PEF < 40% of previous best or predicted post-treatment value and/or frequent attacks) should be seen by a specialist during the hospital stay or as a follow-up after discharge (level IV).
- Patients who have achieved more than 70% of predicted or previous best pulmonary function, who have access to the required medication, whose inhaled drug delivery technique is confirmed to be adequate and who have a written action plan can be discharged from hospital (level IV).

Response to emergency treatment, clinical features that reflect the current attack and past disease severity, socioeconomic risk factors and pulmonary function tests are all used to determine the need for admission to hospital. Normally, patients over 5 years of age who achieve 60%–70% of predicted or previous best lung function (based on measures of PEF or FEV_1) will not require admission to hospital unless clinical factors indicating risk of relapse are significant. Important factors that define a patient at high risk for relapse include admission to hospital or a visit to the emergency department in the previous 12 months, recent use of systemic glucocorticosteroids, use of multiple categories of asthma medication, previous severe or life-threatening asthma attack, presence of psychosocial problems and the frequent, regular use of inhaled β_2-agonists.

The principles of inpatient management incorporate the spectrum of treatment options that are used in both acute

and long-term phases of asthma management. Opportunities exist to evaluate the need for education and to review barriers to compliance with treatment plans.

Systemic glucocorticoids are effective in reducing the duration and severity of asthma exacerbations.[47,48] Administration of glucocorticosteroids orally is preferred over the intravenous route, except when the patient is unable to absorb the medication due to dehydration or vomiting or in severely unresponsive patients who are critically ill. The question of administering inhaled glucocorticoids to patients in hospital has not been specifically addressed in a randomized controlled trial. As they are the mainstay of treatment in moderate and severe asthma, expert opinion indicates that early initiation of treatment or continuation of prescribed inhaled glucocorticoids reinforces the importance of the treatment.

Rapid onset of action, ability to titrate, reduced cost, more effective use of hospital staff and better side-effect profile all make MDIs or DPIs preferable to wet nebulization in all age groups.[105–107] The MDI with a spacer has been shown to be at least as effective or superior to wet nebulization in all age groups at all levels of severity, and the device is associated with fewer side-effects and greater patient acceptance.[38,41,108] Attempts to establish optimum level and frequency of dose in acute asthma have failed to reveal any clearly superior schedule of drug therapy.[40,42,109] Continuous or higher doses on a fixed schedule are associated with more side-effects[110] without clear superiority in terms of clinical outcome or pulmonary function. Following maximum bronchodilation, the schedule of therapy should be based on a combination of serial measurement of PEF, and any worsening of symptoms. Symptom-based treatment alone can lead to overuse of β-agonists. This can be prevented by confirming the association between PEF or FEV_1 and the patient's perception of the need for treatment.

Inpatient management with an MDI or DPI allows for dose titration, reinforcement of drug delivery technique, greater involvement of the patient in self-management and lower fixed and variable cost to hospitals.[105]

Respiratory therapy time is more efficiently spent carrying out objective measurements and educating patients than simply administering wet nebulization treatments.

Over the last 10 years, every published guideline on asthma management[33,34,101–103,111,112] has recommended the use of spirometry for accurate diagnosis and to aid in admission or discharge decisions, as both the perception of patients and physician assessment of airway obstruction have been shown to be poorly correlated with lung function.[113,114]

Unrecognized, persistently poor lung function can lead to unsafe treatment choices or inappropriate discharge plans. Continued treatment with high, fixed doses of bronchodilators after maximum bronchodilation or a return to normal lung function is an inefficient use of hospital staff and is likely to cause unnecessary side-effects. Titration of any medication is best achieved through serial objective measurements until the endpoint is reached. Relying on symptoms alone increases the risk of under- or over-treatment.

Increased pressure on Canadian facilities to use inpatient beds efficiently has led to the early discharge of patients with many types of problems. Patients with asthma should be discharged only if a safe level of relapse risk has been established using such objective criteria as pulmonary function tests.

In patients with severe asthma, PEF should be measured at any sign of deterioration and before and after administration of bronchodilators until their condition is stable. All patients admitted to hospital due to acute asthma should have daily pulmonary function tests to help establish parameters for safe discharge and drug doses.

The inability to predict rapid deterioration in acute asthma is described in case–control series for fatal and near-fatal asthma. Controlled trials to evaluate the question of management of patients on the hospital ward versus the intensive care unit are neither ethical nor necessary.

Intubated asthmatic patients clearly require admission to an intensive care unit for appropriate management. Controlled hypoventilation or permissive hypercapnia is recommended to avoid barotrauma in the intubated patient with asthma[83–85] Inhaled anesthetics,[75–81] ketamine,[88–90] magnesium sulfate,[69–72,115] intravenous β_2-agonists,[116] aminophylline[117,118] and heliox [86] are all considerations in the ventilated or severely unresponsive or deteriorating patient with asthma. Prospective blinded and unblinded trials have all confirmed some improvement in airway pressure or indices of oxygen delivery for all these agents. Consultation with a critical care or asthma specialist is strongly advised when using these types of agents, particularly if the patient is not responding.

The primary indicators of inadequate response to treatment are a persistent requirement for oxygen to maintain S_aO_2 > 94%, the need for frequent doses of titrated bronchodilators to control symptoms or a PEF of 40% or less of predicted value despite adequate doses of inhaled bronchodilators.

The monitoring of arterial blood gases is the most accurate way to confirm oxygen content, ventilatory insufficiency and metabolic derangements associated with inadequate oxygen delivery. The decision to intubate is based primarily on clinical status, but deterioration of arterial blood gases or failure to improve may provide another indicator of risk of deterioration or the need for management in the intensive care unit.

Initiation of asthma education should occur during the stay in hospital. Reduced admission rates, and less school and work absenteeism are expected benefits.[119–121]

Presumably, the patient with severe persistent asthma or frequent severe attacks has failed to improve due to lack of compliance with treatment, poor understanding of the condition or a brittle disease pattern. It has been suggested that asthma outcome may be better in patients seen by specialists.[122] Studies of the effectiveness of asthma education indicate that it increases patient satisfaction and reduces the need for admission to hospital and emergency department

visits, especially in patients with severe asthma or those who have frequent treatment failures.[119,123] Because education programs are usually organized and monitored by asthma specialists, it follows that their involvement in the follow-up of severe asthma is recommended.

The criteria for safe discharge from hospital are essentially the same as those for discharge from the emergency department. The main differences may relate to the fact that some people with asthma are admitted to hospital due to clinical risk factors or socioeconomic circumstances, rather than pulmonary function criteria.[33,96,97,123,124] The need to establish a clear action plan and ensure delivery of appropriate drug therapy is important for all patients with asthma, but patients in hospital are a particularly important group if admission is part of an ongoing pattern of poor disease control.[125]

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Implementation of the guidelines

Recommendations

- National guidelines should be adapted and implemented at a local level (level IV). This initiative could take the form of small-group problem-based workshops and case-based reviews, complemented by medical grand rounds. Workshops should focus on the practical day-to-day management issues, i.e., appropriate diagnosis, anti-inflammatory therapy, correct inhaler technique.
- The use of a stamp in asthma patients' charts has been shown to improve asthma care compared with no such intervention (level I).
- Key opinion leaders should be engaged to help promote asthma guidelines both as facilitators and as content experts for workshop programs (level IV).
- There is a need for further controlled trials to define more clearly the optimum strategies for guideline implementation and to evaluate the impact of asthma guidelines on the management of asthma, especially the effect on patient outcome. Ongoing audit and re-evaluation by various stakeholders, e.g., college of family physicians, government health groups, may be particularly important (level IV).
- A consortium of professional organizations, government, divisions of continuing medical education and industry should be encouraged to work together on implementing strategies to disseminate the recommendations. Industry, in particular, should be encouraged to collaborate in non-product-related programs that will make the best use of resources and prevent unnecessary duplication (level IV).

Asthma morbidity has been increasing[1] and, until recently, so has asthma mortality.[2,3] In addition, acute asthma has a disproportionate impact on overall health costs.[4] To overcome reported differences in asthma management, clinical practice guidelines (CPGs) have been established to define optimum care,[5] although they have not always received enthusiastic support.[6] Some authors deride CPGs as a "cookbook" approach to patient care[7]; others suggest that CPGs might lead to medicolegal problems; and some think the art of medicine may be at risk.[7] Despite these concerns, CPGs have evolved into a major component of health care.

Although CPG development is a challenging and demanding task,[5] their implementation has proved even more problematic.[8] Assessment of the national impact of asthma guidelines is difficult. After publication of the first Canadian asthma consensus statement in 1990,[9] rates of asthma mortality declined significantly through the early 1990s.[1] Prescribing data for the same period showed an increase in inhaled corticosteroids prescribed, but the number of units of β-agonists sold also continued to rise.[10]

Publication and even dissemination of guidelines does not ensure a change in physicians' practice. Investigators found that physicians' compliance with asthma guidelines was especially poor in terms of prescribing preventive medication and making routine objective measures of peak flow.[11] Direct mailing of recommendations did not alter the prescription of estrogen in menopause.[12] In Canada, a recent survey of a group of family practice physicians with a special interest in asthma revealed that only 47% of respondents were familiar with the 1995 guidelines (personal communication, Mervyn Dean, Family Practice Asthma Group, Corner Brook, Nfld.). It is likely that nonrespondents were even less aware of the 1995 guidelines. Thus, there is a need to do more to ensure a change in practice and, it is hoped, an improvement in the health of patients with asthma.

Despite the large volume of research on continuing medical education (CME) and interventions to improve professional practice,[13] few studies assess all outcomes, particularly changes in patient care.[14] Dodek and Ottoson[15] argue strongly that implementation of CPGs and CME are very similar: they both aim at improving patients' well-being by changing physicians' behaviour. Many factors that influence implementation of CPGs and the effectiveness of CME are also similar: e.g., changes in behaviour, implementing organization, the actors involved, etc. Thus, it appears reasonable to apply successful methodologies of CME to CPGs.

A number of implementation strategies have been suggested (Table 1),[16] and Grimshaw and colleagues[5] have outlined some key principles for implementing CPGs. There appears to be no "magic bullet" for improving the quality

Table 1: Effectiveness of strategies used to change practice[16]

Strategy	Acceptance/ use	Quality performance	Resource use	Outcome
Remuneration policy				
• criteria for payment	–	E	E	–
• amount of payment	–	–	–	–
• method of payment	–	E	E	–
Patient population				
• knowledge change	–	E	–	–
Administrative policy				
• computerized records	C	C	–	–
• restricted resources	–	E	E	–
• form change	–	–	E	–
Standards and feedback				
• standard specification	E	E	–	–
• chart audit	E	E	E	–
Practice aids				
• consultation	E	E	E	–
• algorithms	E	E	–	–
• chart reminder or protocols	E	E	E	–
• charting form	E	I	–	–

Note: E = effective; C = contradictory; I = ineffective; – = unknown.

of health care, but a wide range of interventions, if used appropriately, could lead to significant improvements in asthma management and outcomes[13] (Table 2). Multiple interventions appear to be more useful than single ones.[13,17] Traditional CME appears to be the least effective method for guideline implementation,[17] and despite successful implementation, an effect on patients' health[18] is not always guaranteed.

Local implementation of CPGs seems to work better than following externally formulated CPGs.[19] However, existing national CPGs may still serve as a template.[20] There is an important role for "academic detailing," in which key opinion leaders[13,14] are to be involved in the implementation strategy. In a randomized controlled trial of guidelines using a practice-based educational strategy,[21] a simple stamp on the patients' chart to remind the physician how to assess the patient was considered pivotal. Consensus conferences seem to influence at least the participants, who are capable and willing to change their initial recommendations when confronted with relevant data.[22] Opinion leaders have been shown to influence the behaviour of others particularly during "teachable moments."[23] Small-group learning in the form of case studies and workshops has been shown to be an effective way to teach and cause behavioural change.[14,24] In France, the use of fines to encourage adherence to CPGs has been suggested,[25] but such a policy entails high administrative costs.[26]

There is a need to study the various methods used in CME and apply appropriate ones in the implementation of CPGs. Also, randomized trials are needed to assess the effectiveness and cost of implementation strategies, in particular small-group, case-based learning. The latter is costly in terms of both time and money and may not reach enough people to be effective. Innovative strategies, such as educating the lay public, may have an effect, not only on the patient, but also on physician behaviour. In addition, there is a need to empower patients to control their disease, which can be achieved by providing a patient version of the guidelines.[27] It is important to evaluate methods used in the implementation of guidelines.[28,29]

Table 2: Strategies that influence the success of introduction of guidelines[24]

Probability of success	Development strategy	Dissemination strategy	Implementation strategy
High	Internal	Specific educational intervention	Patient-specific reminder at time of consultation
Above average	Intermediate	Continuing medical education	Patient-specific feedback
Below average	External, local	Mail to targeted groups	General feedback
Low	External, national	Publication in professional journal	General reminder of guidelines

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Controlled asthma

_____

Dose _____

_____

Dose _____

Take _____ *10 minutes before exercise*

WHEN NOT WELL

If your peak expiratory flow reading does not reach _____ following your medication for a 24-hour period.
Or
If you are getting a cold.
Or
If you are waking at night because of your asthma or have symptoms when you wake in the morning.
Or
If you require your bronchodilator (_____) frequently and are not getting the same effect.

Then

Increase your _____
Have extra _____
Other _____

Continue this treatment for 2 weeks.
See your doctor if _____

FOR A SEVERE ATTACK

If your peak expiratory flow reading does not reach _____.
If you have severe shortness of breath and can speak only in short sentences.
If you are having a severe attack of asthma and are frightened.
If you are needing your _____ more than 4 times hourly and are not gaining an effect.

Then

Take _____. Repeat if your symptoms do not improve.
Take _____ of prenisone.
Seek medical attention immediately by calling an ambulance.
Continue to use your _____ until help arrives.

Appendix: Example of a written action plan.