

## The international consensus report on the diagnosis and management of asthma

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*The international consensus report on the diagnosis and management of asthma.*  
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**ABSTRACT:** The selection of medication depends on asthma severity and current treatment. Because asthma is both dynamic and chronic, medication plans need to accommodate variability among, as well as within, individual patients over time. This flexibility is achieved by adopting a stepwise approach, that correlates pharmacological therapy with asthma severity according to clinical features, lung function, and medication requirements, and includes criteria for successful asthma control. An increase in number and frequency of medications is indicated when control cannot be achieved at the current step, and the patient is using the medication correctly. The aim is to accomplish the goals of therapy with the least possible medication. Once control has been achieved and sustained at any step, reduction in therapy can be considered, to identify the minimum therapy needed to maintain control. Patients and physicians together should develop a personalized management plan to help patients understand, monitor and control their asthma.

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Data from many countries suggest that asthma morbidity is increasing, and in some countries asthma mortality is also rising. The reasons for this increase in morbidity and mortality are not clearly understood. Medical communities in several countries have responded to this concern by convening panels of asthma specialists to develop guidelines on asthma detection and treatment, and to disseminate their panel reports. In 1992, the National Heart, Lung, and Blood Institute of the United States took the initiative of establishing a working group of 18 physicians and scientists, representing 11 nationalities, for two purposes: 1) to explore the possibility of developing an international consensus statement on the diagnosis and treatment of asthma; and 2) to identify areas for scientific study, to help resolve differences and uncertainties in our understanding of asthma and its treatment.

The international consensus was developed over the course of 1 yr of hard work and three meetings, and was subsequently reviewed by 12 consultants from eight countries. The final report was released in March 1992 [1], published in major scientific journals [2, 3], and translated into at least six different languages. It is impossible to review the whole content of the report in the available space, and this paper will be limited to the pharmacological treatment of chronic asthma.

### Medication for asthma

Medication for pharmacological therapy, which is used to reverse and prevent airflow obstruction, includes anti-inflammatory agents and bronchodilators (table 1). Anti-inflammatory agents may interrupt the development of

inflammation and have a prophylactic and suppressive action. Bronchodilators act principally to dilate the airways by relaxing bronchial smooth muscle. Although bronchodilators reverse and/or inhibit bronchoconstriction and related symptoms of acute asthma, they do not reverse bronchial inflammation and hyperresponsiveness.

Table 1. - Medications for asthma

| Mode of action    | Medications         |
|-------------------|---------------------|
| Anti-inflammatory | Corticosteroids     |
|                   | Sodium cromoglycate |
| Bronchodilator    | Nedocromil sodium   |
|                   | $\beta_2$ -agonists |
|                   | Methylxanthines     |
|                   | Anticholinergics    |

### Route of administration

Asthma is a disease of the airways and, therefore, treatment *via* inhalation is generally preferable to systemic or oral treatment. Aerosolized medications that are used to treat asthma are available as metered-dose inhalers (MDIs), and/or dry powder inhalers. For the patient who has difficulty using an MDI, a spacer device attached to the MDI makes it easier to use, and improves delivery of the medication to the lungs. Nebulized or "wet" aerosols, generated by an air compressor, are particularly useful for children under 5 yrs of age, and in the treatment of acute severe asthma. MDIs are often difficult for children to use correctly, and can, therefore, be recommended only when the prescription is accompanied by thorough

and repeated instruction. The use of spacer devices allows children as young as 2–3 yrs of age to use the MDI, after careful training. A device that combines a face mask with a spacer may also decrease the age at which MDIs can be used, although data evaluating this device are limited. A good inspiratory effort is required for the dry powder systems; the lower age limit for the devices will vary. In general, they are most suitable for children over 5 yrs of age. Nebulizers are of value to children under 2 yrs of age, older children who have difficulty with the MDI or dry powder techniques, and those prone to severe exacerbations.

### A stepwise approach to pharmacological therapy

The selection of pharmacological treatment is made on the basis of asthma severity, and the patient's current treatment. Because asthma is a dynamic as well as a chronic condition, medication plans need to accommodate variability among patients, as well as within individual patients over time. An approach to pharmacological therapy that correlates with classification of asthma severity permits this flexibility.

Control of asthma is defined as: 1) minimal (ideally no) chronic symptoms, including nocturnal symptoms; 2) minimal (infrequent) exacerbations; 3) minimal need for *p.r.n.*  $\beta_2$ -agonist, ideally none; 4) no limitations on activities, including exercise; 5) Peak expiratory flow (PEF) circadian variation  $<20\%$ ; 6) (near) normal PEF; and 7) minimal (or no) adverse effects from medicine.

Figure 1 illustrates a stepwise approach to therapy, in which the number and frequency of medications are increased with increasing asthma severity. Progression to the next step is indicated when control cannot be achieved at the current step and there is assurance that the patient is using the medication correctly. The aim is to accomplish the goals of therapy with the least possible medication. Thus, clinicians must judge whether to increase treatment in a gradual step-up manner, or to give maximum treatment at the outset, which may include a burst or cycle of oral corticosteroids, in order to achieve control of the patient's asthma. In either case, once control is sustained for several weeks or months, a reduction in therapy - a step down - can be carefully considered, and is needed to identify the minimum therapy required to maintain control.

The steps suggested in the following discussion are guidelines only; specific medication plans should be tailored by the physician in recognition of the individual patient's circumstances.

#### Step 1

A patient has mild, intermittent asthma if he or she has a pretreatment baseline PEF greater than 80% of the predicted or personal best value, and PEF variability less than 20%; if the patient experiences intermittent, brief exacerbations (episodes of cough, wheezing or dyspnoea) less than once or twice a week; is asymptomatic between exacerbations; and/or has nocturnal asthma symptoms less than twice a month.

This requires only a short-acting inhaled  $\beta_2$ -agonist taken as needed to relieve asthma symptoms. A short-acting inhaled  $\beta_2$ -agonist or sodium cromoglycate prior to exercise, or sodium cromoglycate prior to exposure to known antigen, may be taken prophylactically if appropriate. If the short-acting inhaled  $\beta_2$ -agonist is required more than three times a week, the patient should be moved to the next step of care, regardless of PEF measurements.

#### Step 2

Moderate asthma encompasses a wide range of asthma severity; thus, two steps of therapy are associated with moderate asthma. A patient has moderate asthma if their pretreatment, baseline PEF is 60–80% of that predicted or the personal best, and PEF variability is 20–30%; if the patient experiences exacerbations more than twice a week, and the exacerbations may affect sleep and activity levels; if the patient has chronic symptoms that require a short-acting inhaled  $\beta_2$ -agonist almost daily; and/or experiences nocturnal asthma symptoms more than twice a month.

The primary therapy is inhaled anti-inflammatory medication, taken on a daily basis: inhaled corticosteroids, or sodium cromoglycate or nedocromil sodium. Children are usually given an initial trial (4–6 weeks) of sodium cromoglycate. The suggested introductory dose of inhaled corticosteroids is 200–400  $\mu\text{g}\cdot\text{day}^{-1}$  of beclomethasone dipropionate (BDP), or the equivalent. An inhaled short-acting  $\beta_2$ -agonist should be available to take as needed to relieve symptoms, but should not be taken more than three to four times a day.

If symptoms persist, and the clinician is satisfied that the patient is using the inhaled medications correctly, the dose of inhaled corticosteroids should be increased to 400–800  $\mu\text{g}\cdot\text{day}^{-1}$  BDP, or the equivalent. If the patient's anti-inflammatory therapy was initiated with sodium cromoglycate or nedocromil sodium, inhaled corticosteroids should be introduced either instead of, or together with, nedocromil sodium or sodium cromoglycate, to allow an overlap period.

#### Step 3

If a patient's asthma is at the higher end of the moderate range and/or the asthma is not controlled by Step 2 therapy, an increase in therapy is necessary. The dose of inhaled corticosteroids may be increased to 800–1,000  $\mu\text{g}\cdot\text{day}^{-1}$  BDP, or the equivalent. A spacer device with the inhaler is recommended to reduce oropharyngeal side-effects and systemic absorption. Doses over 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  may be necessary to achieve control of the patient's asthma, but should be administered only under the supervision of an asthma specialist. Additional, long-acting bronchodilators may also be considered, particularly to control nocturnal symptoms. Oral sustained-release theophylline, oral  $\beta_2$ -agonist, or long-acting inhaled  $\beta_2$ -agonist may be added. Theophylline serum concentrations should be monitored, with a general therapeutic range of 5–15  $\mu\text{g}\cdot\text{ml}^{-1}$ .

**Step-up:** Progression to the next higher step is indicated when control cannot be achieved at the current step, and there is assurance that medication is used correctly. If  $PEF \leq 60\%$  predicted or personal best, consider a burst of oral corticosteroids and then proceed.

**Step-down:** Reduction in therapy is considered when the outcome for therapy has been achieved and sustained for several weeks or even months at the current step. Reduction in therapy is also needed to identify the minimum therapy required to maintain control.

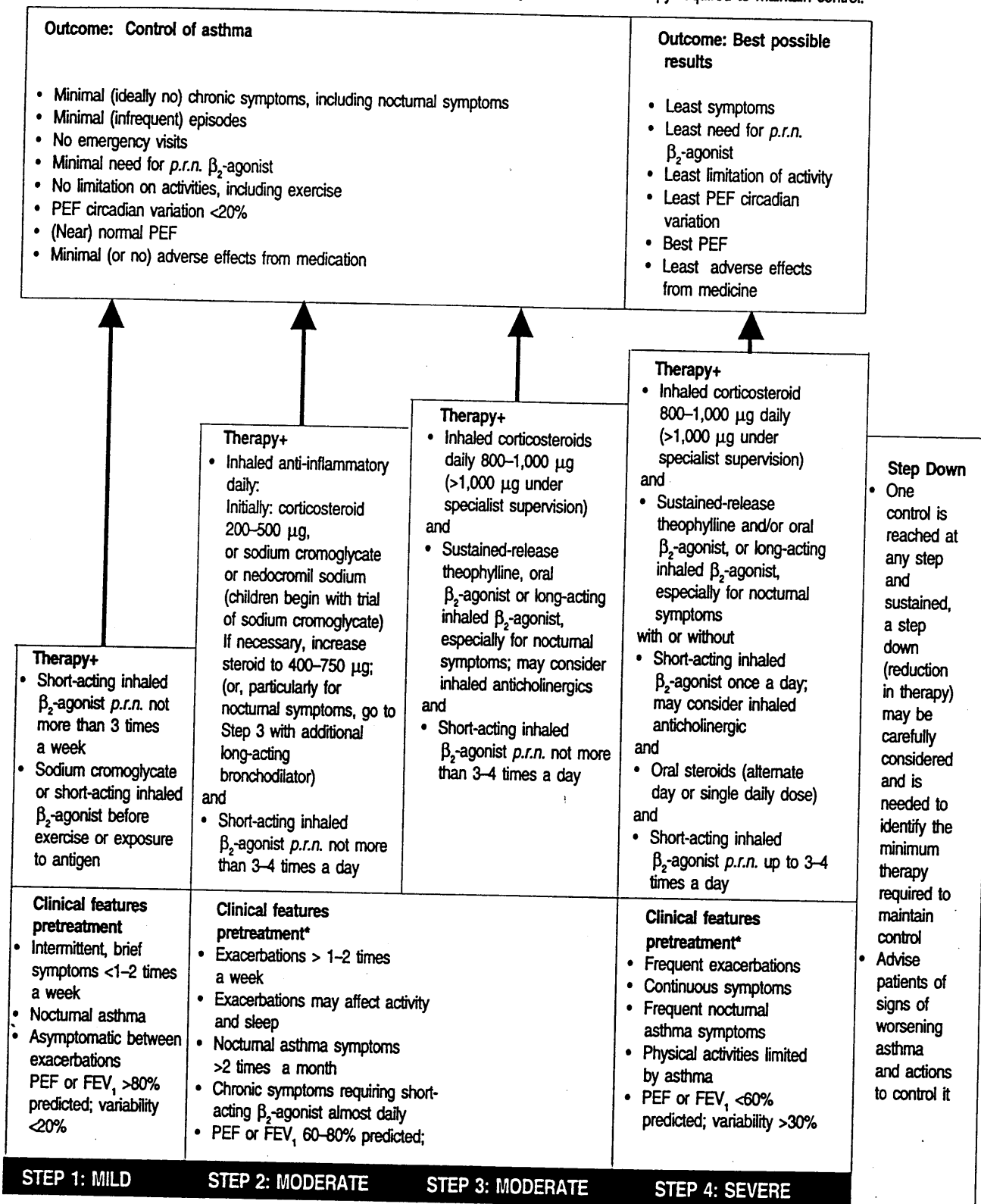


Fig. 1. — Chronic management of asthma: a stepwise approach to therapy. \*: One or more features may be present to assign a grade of severity; a patient should usually be assigned to the most severe grade in which any feature occurs; +: All therapy must include patient education about prevention (including environmental control where appropriate) as well as control of symptoms. PEF: peak expiratory flow;  $FEV_1$ : forced expiratory volume in one second.

The role of anticholinergics (ipratropium bromide) in chronic therapy is not well-established, but an introduction of anticholinergics may be considered as an alternative for patients who experience such adverse effects as tachycardia or tremor from inhaled  $\beta_2$ -agonists.

Inhaled short-acting  $\beta_2$ -agonists should be available to take as needed to relieve symptoms, but should not be taken more than three or four times a day.

#### Step 4

A patient has severe asthma if the pretreatment base-line PEF is less than 60% of the predicted or the personal best value, and PEF variability is greater than 30%; if he or she experiences highly variable, continuous symptoms and frequent nocturnal symptoms; has limited activities, and experiences severe exacerbations in spite of medication. Control of asthma, as defined earlier, may not be possible. In this more severe asthma, the goal of therapy becomes achievement of the best possible results, the least symptoms, the least need for  $\beta_2$ -agonist, the best flow rates, the least circadian variation, and the least side-effects from medication.

Therapy usually requires multiple daily medications. Primary therapy includes inhaled corticosteroids at higher doses (800–1,000  $\mu\text{g}\cdot\text{day}^{-1}$  or more BDP, or the equivalent). Doses over 1,000  $\mu\text{g}\cdot\text{day}^{-1}$  may be necessary, in combination with a long-acting bronchodilator. An inhaled short-acting  $\beta_2$ -agonist should be available as needed up to three to four times a day to relieve symptoms.

Oral corticosteroids, if needed in the long-term, should be used in the lowest possible dose (alternate or single daily doses after a 3–7 day burst). Persistent trials of high doses of inhaled corticosteroids (up to a maximum of 2,000  $\mu\text{g}\cdot\text{day}^{-1}$ ) administered with a spacer device should be made in an attempt to reduce oral corticosteroids. When patients are transferred from oral corticosteroids to high-dose inhaled corticosteroids, they should be monitored closely for evidence of adrenal insufficiency.

#### Special considerations for children

For children under 5 yrs of age, the PEF is either not attainable, or too dependent on fluctuating levels of attention and effort to be reliable. For younger children, the history, which should include assessment of the child's quality of life, and physical examination, although imperfect, are essential elements in decision-making. This can be enhanced by symptom reports kept by the patient on a diary card.

Underdiagnosis of asthma is a frequent problem, and it occurs most often in young children whose primary symptom is cough, or who wheeze only when they have respiratory infections and are dismissed as having bronchitis or pneumonia even though the signs and symptoms are more compatible with a diagnosis of asthma.

Viral upper respiratory tract infections are a common asthma trigger among children. Although there is no specific therapy, patients and parents need to be vigilant in adhering to the regular asthma medication treatment plans, and in being alert for early signs of an exacerbation, so

that asthma medication may be started or increased immediately. For those individuals who deteriorate rapidly every time they have a viral infection, it may be appropriate to institute a short course of oral corticosteroid therapy at the earliest sign of viral respiratory infection.

Recommended doses of medication for children differ from doses for adults. There is potential for concern about systemic absorption of high doses of inhaled corticosteroids and its possible effect on linear growth. Thus, when inhaled corticosteroids are added to treatment with sodium cromoglycate or nedocromil sodium in order to achieve control of asthma, an appropriate step-down to consider is gradually to reduce the inhaled corticosteroids and maintain control with the sodium cromoglycate or nedocromil sodium.

#### Asthma management zone

An asthma management zone system has been developed to help patients understand the chronic and variable nature of asthma, and to help them to monitor their disease, identify the earliest possible signs that the day-to-day control of asthma is deteriorating, and act quickly to regain control. The patient may initiate actions appropriate to each zone, according to a prearranged plan made with the physician.

The zones have been adapted to a traffic-light system, to make it easier for patients to use and remember. The zones suggested in the following discussion are guidelines only; specific zones should be tailored by the physician in recognition of individual patient's circumstances, especially since patterns of exacerbations vary markedly between patients, but often exacerbations follow a similar pattern in a particular patient. Furthermore, whereas the zones discussed below are presented as percentages of predicted PEF, in order to accommodate variations in patients' sizes and ages, the patient's understanding of the zones will be improved if their personal written treatment plan indicates the actual PEF values that correspond with the percentage range.

#### Green Zone

Green indicates all clear. Asthma is under control. PEF is usually 80–100% predicted or personal best, and usually has less than 20% variability. In this zone, there is no interruption of activities or sleep, and there are minimal (ideally no) symptoms. The specific medication to maintain this control of asthma in the Green Zone depends on the level of asthma severity. A stepwise approach to asthma therapy, discussed earlier, is used to identify the minimum medication required to maintain control; generally, the number and frequency of medications are increased with increasing severity of asthma.

#### Yellow Zone

Yellow signals caution. A PEF of 50–80% predicted or personal best, and with 20–30% variability, and/or

occurrence of asthma symptoms (nocturnal symptoms, decreased activity, coughing, wheezing, chest tightness with activity or at rest) while in the Yellow Zone indicates one of three things:

1. An acute exacerbation may be present, for which a temporary increase in medication, especially inhaled  $\beta_2$ -agonists and possibly oral corticosteroids, is indicated. Follow the medication plan developed with the physician.
2. A deterioration of asthma may be characterized by a gradual reduction in PEF that fails to have a sustained response to inhaled  $\beta_2$ -agonist, greater intolerance of daily activities or exercise, or the development of nocturnal symptoms. This indicates the need for further treatment to be arranged with the physician. A short burst of oral corticosteroids ( $30\text{--}60\text{ }\mu\text{g}\cdot\text{day}^{-1}$ , in single or divided doses) is recommended until PEF returns to its Green Zone value. The oral corticosteroids should then be ceased; this is often accomplished by gradually tapered doses. Alternatively, in selected cases (e.g. patients already on inhaled corticosteroids), the regular dose of inhaled corticosteroids may be doubled for 1 week, or until PEF and symptoms improve.
3. Frequent fluctuations into the Yellow Zone may indicate that the asthma is not sufficiently under control, and that the Green Zone therapy needs to be increased.

### Red Zone

Red signals a medical alert. PEF is below 50% of predicted or personal best. Asthma symptoms are present at rest, or interfere with activity. An inhaled  $\beta_2$ -agonist should be taken immediately. If PEF remains below 50%, despite the bronchodilator, immediate medical attention is required, preferably in a hospital-based emergency department. Therapy for the Red Zone emphasizes adequate dosage of inhaled  $\beta_2$ -agonist, which may require their frequent administration, and the early introduction of corticosteroids. Oxygen is also administered if the patient is hypoxaemic.

If the PEF improves after initial bronchodilator treatment, the Yellow Zone actions should be followed. Entry into the Red Zone may reflect a failure of the Green Zone therapy. After the exacerbation is controlled, the Green Zone therapy and patient adherence (to the medication plan and environmental control measures) should be reviewed, and adjusted accordingly.

### Directions for research

In developing the consensus statement on what constitutes an effective general approach to asthma therapy, the project participants discussed differences in opinions about specific treatment modalities. These differences reflect areas requiring scientific investigation, to improve our understanding of asthma and its treatment. The following areas were highlighted:

1. Although inflammation is a critical feature of asthma, direct measures of inflammation are difficult to accomplish. The link between PEF measurement and inflammation, and the link between inflammation and hyperresponsiveness, need more rigorous assessment and definition.

2. The recommended zones for therapy reflect expert opinion about what PEF ranges are appropriate. Sufficient data are lacking to establish precise zones for therapy. Studies are needed to identify more specifically what levels of PEF measures and PEF variability are required to achieve therapeutic objectives. Furthermore, it will be useful to investigate whether achieving maximal lung function is requisite for accomplishing other goals of therapy.

3. Recent studies have suggested that the chronic, regularly scheduled administration of short-acting inhaled  $\beta_2$ -agonists may be deleterious. Further studies will be important to clarify the role of short-acting inhaled  $\beta_2$ -agonists in regularly scheduled *versus* "as-needed" asthma therapy.

4. The roles of ipratropium bromide and other anticholinergic agents, theophylline and the new, long-acting inhaled  $\beta_2$ -agonists in the chronic care of asthma require further investigation relative to their efficacy and long-term adverse effects.

5. Comparative studies are recommended, that will evaluate both the effectiveness in achieving control of asthma and the long-term adverse effects of inhaled  $\beta_2$ -agonists, inhaled corticosteroids, and sodium cromoglycate or nedocromil sodium in children and adults. Parameters for assessing efficacy might include clinical, quality of life, and physiological assessments, as well as biopsy and bronchial lavage.

6. There is considerable debate over appropriate dosages for inhaled corticosteroids. Studies are needed to identify dose ranges (high, medium, and low doses) that define appropriate ranges for long-term administration, and to evaluate long-term adverse effects. More data are needed on the possible long-term adverse effects of higher doses of regularly scheduled inhaled corticosteroids, especially in children.

7. Investigations evaluating whether anti-inflammatory treatment of mild asthma can modify the course of the disease will also be important.

8. The use of immunotherapy continues to be an area of controversy. Further studies of the effectiveness and relative safety of specific immunotherapy treatment and newer forms of immunomodulation, particularly newer epitopes, are required.

The project participants also expressed the need to evaluate the efficacy of the International Asthma Project's recommended six part asthma management programme in accomplishing the stated goals of therapy, using the goals as outcome measures. This evaluation should include assessment of the epidemiological and socioeconomic impacts of the varying treatment recommendations. Such investigation is necessary to confirm the scientific opinions represented in the recommendations, and will provide a clearer understanding about how to improve the quality of life for asthma patients.

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### Discussion

**KOËTER:** Long-acting inhaled  $\beta_2$ -agonists were recently released onto the market in the Netherlands. Dr Beasley, can you speculate on the contribution or influence of these agents on asthma morbidity, and especially on asthma mortality? Secondly, what will be the place of these long-acting  $\beta_2$ -agonists in the management of mild asthmatic patients? Is there a role for these drugs here, or should they be used only for the more severe asthmatic patients?

**BEASLEY:** I think that we do not yet have sufficient information to know the exact place of salmeterol. We will need to wait until a number of good long-term studies are undertaken. When we evaluate salmeterol, we have to ask how its pharmacological properties compare with other  $\beta$ -agonists, in particular with isoprenaline forte and fenoterol, which have been incriminated in asthma mortality epidemics. In addition to the dose, relevant pharmacological properties include the efficacy, potency and selectivity. With regard to those properties, salmeterol is very similar to salbutamol, so I am reassured by that. There is some difference of opinion as to whether it may be marketed in too high a dose, and we are awaiting further data on that. As regards its long-term effects, we have not had sufficient studies. While we are trying to clarify this, we should follow the recommendations of the international consensus groups, which is to reserve it for the severe patients who are on optimal antiinflammatory treatment, but are still getting recurrent symptoms. It is, perhaps, logical then to give them a long-acting  $\beta$ -agonist, since *p.r.n.* use of a short-acting  $\beta$ -agonist would essentially involve regular use in any case.

**PAUWELS:** I can add a second argument for doing that, and it is an argument which has not been fully discussed today. There are two studies coming out now, a Finnish study by Laitinen and associates, and one by Pedersen in children. The Finnish study compared regular treatment with a bronchodilator *versus* regular treatment with an anti-inflammatory. After 2 yrs of treatment with a regular bronchodilator, baseline lung function was lower than in the people who received inhaled corticosteroids for that treatment period. They then switched the people on regular bronchodilators to inhaled corticosteroids, but observed that they were not able to reach the optimal level that they had in the steroid group. That means that probably in the long-term, by treating with bronchodilators alone, something is occurring that makes part of

the disease irreversible. The study by Soren Pedersen in children reached exactly the same conclusions. Since it has been shown for both formoterol and salmeterol that they really do not affect chronic inflammation in asthma, I would be very reluctant to recommend them as maintenance treatment on their own, without anti-inflammatory treatment, in mild-to-moderate asthma. This also fits with the international consensus recommendation that we still use them when we need a long-acting bronchodilator - and that means in moderate-to-severe asthma.

**OEI:** I have two questions for Dr Pauwels. You have told us about drugs to treat symptoms, but you do not mention strategies, such as house dust mite avoidance, which are included in the international consensus, and which are very important because they "treat" the symptoms preventatively and causatively. They may also enable us to reduce the drugs. Secondly, the international consensus concludes that the evidence for the role of immunotherapy in asthma is not convincing. But you have also written recently that there is a place for immunotherapy in certain situations, such as house dust mite and animal dander.

**PAUWELS:** I could not deal with all the aspects of the international report, which is a very large document, but I can briefly say that the management strategy plan includes six points and the first one is education of the patient, which is extremely important in achieving the goals for the management of asthma. The plan also includes control of triggers, both nonspecific triggers, such as cigarette smoke, and specific triggers such as house dust mite. There is evidence from around the world, and certainly in the Benelux countries, that house dust mite is an extremely important allergen in the pathogenesis of asthma. There are objective data showing that control of house dust mite decreased both the symptoms and the need for medication in asthma, so it is clearly an item that should be taken into consideration in the overall management of asthma. There are some specific measures that have proven efficacious in the control of house dust mite. With regard to immunotherapy, there are indeed a few clinical studies proving its efficacy in asthma where the allergen is clearly defined, including pollen and house dust mite. However, the number of allergens where efficacy has been proven without doubt is rather limited. Therefore, I agree with what you say and what is stated in the international report - that under special circumstances immunotherapy can be recommended.

**SCHOTSMAN:** Asthma is often triggered, especially in children, by viral infections of the upper respiratory tract. These viral infections are often complicated by bacterial infections. What is the role of antibiotics in the cure or even the prevention of bacterial infection? Many general practitioners are accustomed to administering antibiotics.

**PAUWELS:** This is specifically discussed in the report. Objective studies show that treatment with antibiotics in infectious exacerbations of asthma in children has a very limited role, and, in fact, has proven nonefficacious. So there is no reason why, except in a special case of complications, antibiotics should be prescribed systematically in acute exacerbations of asthma in children, or even in