The Dutch College of General Practitioners (NHG) Practice Guideline
This NHG Practice Guideline is a translation of the Dutch guideline. It is specifically written for Dutch general practitioners in the Dutch environment. The advice which is given may therefore not be in accordance with the views of general practitioners in other countries.

NHG Practice Guideline 'Adult asthma: treatment'
This practice guideline and its scientific basis have been updated with respect to the previous version (published in NHG Practice Guidelines for the General Practitioner 1, 1999). The key messages are:

- A stepwise management plan is used in drug therapy.
- Before the current medication is increased or the next level of medication is started, the patient's compliance with the therapy, inhalation technique, and avoidance of asthma triggers should be checked.
- The general practitioner can attain treatment objectives for most patients by non-pharmacological means combined with a short-acting beta₂ sympathomimetic agent on an as-needed basis (Step 1) and/or a low or moderate dose of inhaled glucocorticoid (Step 2).
- The general practitioner is responsible for regular follow up of patients whose treatment objectives are reached with Step 2 medication.
- Referral usually takes place when there are problems in diagnosis or when there has been no improvement or insufficient improvement despite adequate treatment.

What's new:
- Cooperative agreements with the pulmonologist are described in detail in the 'Landelijke Transmurale Afspraak Astma bij volwassenen' [National Transmural Agreement on Adult Asthma].

INTRODUCTION
The NHG Practice Guideline 'Adult asthma: treatment' provides guidance for management of asthma in adults and in children aged 12 years and older. The diagnosis of asthma and COPD and the treatment of COPD are covered in the two other practice guidelines on asthma and COPD.¹ For the terminology used as well as background information, see the NHG Practice Guideline 'COPD and adult asthma: diagnosis'.

It is assumed that the diagnosis has been established in accordance with the guidelines in the NHG Practice Guideline 'COPD and adult asthma: diagnosis', and that the most important symptom of asthma has been confirmed: namely, reversibility of the bronchial obstruction.

The objectives of management are:
- few or no complaints, acceptable nocturnal sleep, normal or nearly normal daily activities
- the prevention or prompt treatment of exacerbations
- the attainment or maintenance of optimal pulmonary function
- all of this with as little inconvenience due to interventions as possible, i.e., medication at the lowest effective dose, the lowest frequency of administration, and with the fewest side effects

In addition to general measures, such as avoiding smoking and thorough cleaning when there is an allergy to house dust mites or other indoor allergens, management consists of providing information and drug therapy. A distinction is made between symptomatic treatment with bronchodilators and preventive treatment with anti-inflammatory agents. For intermittent asthma, the combination of general measures and symptomatic management with short-acting beta₂ sympathomimetic agents is sufficient. For mild persistent asthma or
a more serious form of asthma, treatment consists primarily of anti-inflammatory agents (preferably inhaled glucocorticoids), temporarily supplemented by a short-acting beta_2 sympathomimetic agent during exacerbations. If the treatment objectives are not attained with a moderate dose of inhaled glucocorticoid (budesonide or beclomethasone 400 μg twice daily or fluticasone 250 μg twice daily), the choice is between increasing the dose of inhaled glucocorticoid or adding a long-acting inhaled beta_2 sympathomimetic agent. Prior to this step, the diagnosis and management should be reviewed, and if in doubt, a pulmonologist should be consulted.

**MANAGEMENT GUIDELINES**

**Information and supervision**

The general practitioner should provide information on the following:

- **The nature of the condition.** Asthma is usually a very treatable condition. The symptoms can be triggered by allergens (especially from house dust mites and pets) and non-specific irritants (such as smoke or dust), or by exercise. Participating in sports is not a problem and is indeed recommended.
- **How the patient copes with the illness.** Discuss how asthma can interfere with functioning due to the fear of shortness of breath or embarrassment about using medication in the presence of others.²
- **The medication's purpose and effect.** Short-acting bronchodilators are used for occasional symptoms and anti-inflammatory agents are used for more frequent symptoms. It is essential to use the anti-inflammatory agent on a daily basis, adding the short-acting bronchodilator on an as-needed basis. A long-acting beta_2 sympathomimetic agent is to be used at a fixed dosage and preferably only as maintenance medication (in addition to the inhaled glucocorticoid).
- **Instruction in the inhalation technique.** Ask the patient to bring medications and inhalers to follow-ups in order to correct any errors in inhalation technique.³ Inhalation instruction can also be handled by a well-trained pharmacist's assistant, in consultation with the general practitioner. If the therapy is unsuccessful, check the patient's compliance and the possibility of incorrect use of the medications (too much, too little, use of inhaled glucocorticoid instead of bronchodilator for acute dyspnoea).⁴ Note that due to differences in particle size and/or the physical properties of inhalers, there may be different recommended doses for the same medication.
- **Self-treatment and self-monitoring.** When the patient is managing the disorder and medications well, an agreement can be made that he can start or increase the dose of short-acting bronchodilator in the event of an exacerbation, and can contact the surgery if he is unable to control the asthma adequately during the exacerbation. The benefit of self-monitoring programmes, using a peak flow meter at home, and instruction in self-treatment for all asthma patients has not yet been adequately studied. Self-treatment and self-monitoring may certainly be advisable, however, in certain patients with severe asthma.⁵

**Preconditions**

The care of patients with asthma and COPD can be partially delegated to a well-trained practice assistant or to a practice nurse who can perform some or all of the following tasks:

- providing information
- non-medicinal advice about such things as house-cleaning measures and smoking cessation
- lung function testing: teaching patients how to measure the peak flow at home, performing reversibility tests with the peak flow meter or spirometer, and performing
spirometry if COPD is suspected
- inhalation instruction
- scheduling and giving influenza vaccinations
- scheduling and participating in follow-ups

**Non-pharmacological therapy**

*Smoking* can result in more rapid deterioration of pulmonary function and shortening of life expectancy. In addition, smoking is a non-specific irritant that exacerbates asthma. Smoking cessation has been shown to delay further deterioration of pulmonary function. Advise patients to quit smoking and to avoid passive smoke inhalation to the greatest extent possible.6

Patients with asthma should be invited for an annual *influenza vaccination.*7

*Cleaning.* Studying the extent to which cleaning measures benefit the clinical picture is complicated. It is difficult to assess the effect of separate interventions, since there is a lack of methodologically good research with sufficient numbers of patients. When there is a proved allergy to house dust mites or other indoor allergens (such as from pets), consider the following, taking into account the patient's financial resources:8

- **bedroom:** introduce house dust allergen-proof covers for the mattress, pillows, and duvet, and install a smooth floor surface (easy to clean)
- **remainder of the house:** reduce dampness, modify house-cleaning routines (dust with a moist cloth 2-3 times a week)

There is no benefit from extra vacuum cleaning. Recommendations for avoiding non-specific irritants depend on the individual situation. There may be cases in which a primary care pulmonary nurse can come to the home, identify problems, and provide information and advice on cleaning. She also has a practical role in supervising patients with severe asthma who are very limited in daily activities. For practical advice, refer to the brochures of the Dutch Asthma Foundation.

If there are indications that the symptoms are worsening due to work-related factors, advise the patient to contact the *Occupational Health and Safety Department* about options for making adjustments in the work or changing jobs. If work-related factors are putting the patient's job or career track in jeopardy, referral to a pulmonologist is indicated.

**Drug therapy: general principles**

Medications used to treat asthma are most often administered by inhalation. Two different methods are used:9

- metered-dose aerosols
- dry powder inhalers

With metered-dose aerosols, neither the dose delivered nor the average particle size are dependent on the inspiratory force; rather, deposition in the lung is primarily determined by hand-lung coordination. The problem of coordination can be overcome by using a spacer or a 'breath-actuated' metered-dose aerosol. With dry powder inhalers, the dose delivered and the average particle size do depend on the inspiratory force, which therefore largely determines the deposition in the lung. Most types of dry power inhalers—with the exception of the multidose inhalers—are somewhat awkward to prepare for use. Deposition in the lung is greater with some of the dry powder inhalers (due to the physical properties of the device) and some metered-dose aerosols (due to a smaller particle size). Because of this, there may be different recommended doses for the same preparation, depending on the type of inhaler or metered-dose aerosol. The above properties and the patient's facility with the device should be taken into consideration when choosing the type of inhaler. In general, patients with adequate inspiratory force and adequate hand-lung coordination can use either a dry powder inhaler or a metered-dose aerosol. For older patients who
have inadequate inspiratory force and/or poor coordination, use of a metered-dose aerosol with a spacer is preferred. When prescribing multiple medications, the general practitioner should aim for consistency in the method of administration. Only in exceptional cases should oral therapy with beta₂ sympathomimetic agents or inhalation using an electric-powered jet nebulizer be considered.

The following inhalation instructions should be given:

- **Metered-dose aerosol**: Shake well before use, inhale slowly while spraying nebulizer, and hold the breath for at least five seconds.
- **Dry powder inhalation**: Inhale forcefully and deeply.
- **Spacer**: Shake the metered-dose aerosol well before use, spray one puff at a time, and inhale immediately after spraying in order to minimize deposition of medication on the spacer walls. Wash and air-dry plastic spacers regularly, to avoid deposition of medication on the spacer walls due to static electricity.

A distinction is made between:

- symptomatic treatment with bronchodilators
- preventive treatment with anti-inflammatory agents

There are three groups of bronchodilators: beta₂ sympathomimetic agents,¹⁰⁻¹³ anticholinergic agents,¹⁴ and theophyllines.¹⁵ These drugs reduce bronchial obstruction but have no anti-inflammatory effect. Maintenance treatment with a bronchodilator alone for moderately severe to severe asthma can result in more rapid deterioration of pulmonary function. In mild asthma, this risk is probably small.¹⁰ High doses of beta₂ sympathomimetic agents can cause side effects such as hand and finger tremors, headache, peripheral vasodilation, increased heart rate, and (with concomitant use of an inhaled glucocorticoid or theophylline) hypokalaemia. Ipratropium bromide is the only anticholinergic agent available for inhalation. It has almost no side effects, even at high doses. Due to their narrow therapeutic spectrum and the availability of good alternatives, theophyllines are not recommended for treatment of asthma in primary practice. There are two types of anti-inflammatory agents: glucocorticoids and cromoglycate or nedocromil.

Glucocorticoids are the most effective anti-inflammatory agents and are used to prevent or reduce hyperresponsiveness and allergic reactions.¹⁶ The most common local side effect is oropharyngeal candidiasis, which occurs in 5-13% of adults using these agents, but rinsing the mouth and spitting out the fluid after inhalation reduces the risk. The risk of systemic side effects increases at higher doses of inhaled glucocorticoids (1,600 µg budesonide or beclomethasone or 1,000 µg fluticasone per day). Cromoglycate and nedocromil are not as effective as inhaled glucocorticoids. Cromoglycate is more effective for allergic asthma and for exercise-induced asthma. The efficacy peaks only after several weeks.¹⁷ Nedocromil can be used for allergic and non-allergic asthma and exercise-induced asthma; it has no obvious value over the other older anti-inflammatory agents.¹⁸

Other medicinal options: Oral antihistamines did not appear to be sufficiently effective, while monoclonal antibodies to IgE have not been studied adequately. The role of antileukotrienes, such as montelukast, is still unclear, and no opinion has yet been formulated on the role of immunotherapy.¹⁹

Asthma and pregnancy. Little is known about the risks of asthma medication for the foetus. Short-acting beta₂ sympathomimetic agents, ipratropium bromide, cromoglycate, and
beclomethasone can usually be given during pregnancy (not enough is known about other inhaled glucocorticoids). Use of long-acting beta₂ sympathomimetic agents during pregnancy is not recommended. In acute severe asthma, prevention of hypoxemia outweighs the risks of systemic glucocorticoids for the foetus (possible elevated risk of cleft palate from use during the first trimester) and for the pregnant woman (elevated risk of pre-eclampsia).20

**Drug therapy: stepwise management**

Some asthma patients present with recurring long episodes of coughing ('bronchitis'), while others present with a more pronounced clinical picture of dyspnoea and wheezing. Two main categories have been defined for medicinal management:

- **Intermittent asthma** (symptoms once weekly or less) is treated with a short-acting bronchodilator (Step 1).  
- **Persistent asthma** (symptoms more than once weekly) may be mild, moderately severe, or severe. It is treated mainly with inhaled glucocorticoids (Step 2). Short-acting beta₂ sympathomimetic agents are reserved for exacerbations; they can be used temporarily together with long-acting beta₂ sympathomimetic agents.

For management of severe dyspnoea see the section: ‘Guidelines for acute severe dyspnoea’.

Before increasing the dose of medication, consider possible reasons why the treatment objective has not been reached:

- insufficient compliance  
- incorrect inhalation technique  
- insufficient avoidance of asthma triggers

Specifically, review the diagnosis and the treatment policy when moving from Step 2 to Step 3. When the treatment objective has been achieved for about 3 months, try to reduce the medication or to take one step back.

**Step 1. Intermittent asthma (symptoms not more than once weekly)**

If symptoms are infrequent (once weekly or less), start with a short-acting beta₂ sympathomimetic agent (see Table 1). Asthma patients above 60 years of age can be started on ipratropium bromide, if needed.14

For *exercise-induced asthma*, 1 or 2 puffs of a short-acting beta₂ sympathomimetic agent taken 10-15 minutes before exercising provides about 2 hours of protection.11

**Table 1. Short-acting bronchodilators**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>Powder inhaler</th>
<th>Metered-dose aerosol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>'as needed'</td>
<td>as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(up to 6 times</td>
<td>(up to 6 times daily)</td>
</tr>
<tr>
<td>Lower doses apply to some metered-dose aerosols or dry powder inhalers: consult the <em>Farmacotherapeutisch Kompas</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasionally/temporarily for:</td>
<td>Salbutamol*</td>
<td>100-400 µg, depending on the type of inhaler</td>
<td>200 µg</td>
</tr>
<tr>
<td></td>
<td>Terbutaline*</td>
<td>500 µg</td>
<td>250 µg</td>
</tr>
<tr>
<td></td>
<td>Fenoterol*</td>
<td>200 µg</td>
<td>200 µg</td>
</tr>
</tbody>
</table>
intermittent asthma (Step 1)  
exacerbations, as well as for  
continuous use of long-acting  
beta_2 sympathomimetic agents  
exercise-induced asthma

Occasionally for intermittent asthma  
at >60 years of age. (Step 1).  
Maintenance treatment for severe  
asthma (Step 4).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>Low dose</th>
<th>Moderate dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower doses apply to some metered-dose aerosols or dry powder inhalers: consult the Farmacotherapeutisch Kompas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance treatment for mild, moderately severe, or severe asthma (Steps 2-4)</td>
<td>Beclomethasone</td>
<td>200 µg twice daily</td>
<td>400 µg twice daily</td>
<td>800 µg twice daily</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>200 µg twice daily</td>
<td>400 µg twice daily</td>
<td>800 µg twice daily</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
<td>100 µg twice daily</td>
<td>250 µg twice daily</td>
<td>500 µg twice daily</td>
</tr>
</tbody>
</table>

Instead of an inhaled glucocorticoid for mild (allergic) asthma (Step 2), if necessary

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metered-dose aerosol, 5 mg 4 times daily 1 (twice daily 2)</th>
</tr>
</thead>
</table>

Ipratropium bromide #

* beta_2 sympathomimetic agents  
# anticholinergic agent

**Step 2. Mild persistent asthma (symptoms more than once weekly)**

Start 'new' patients with frequent symptoms (more than once weekly) on an inhaled glucocorticoid at a low to moderate dose (see Table 2).

For patients with intermittent asthma who need 2 or more inhalations of a bronchodilator daily for 2-4 weeks, changing to an inhaled glucocorticoid is advised.

Cromoglycate is a possible alternative in allergic asthma. If it has insufficient effect in 4-6 weeks, it can be replaced by an inhaled glucocorticoid. If after 3 months of treatment with a moderate dose of an inhaled glucocorticoid the complaints persist or the dose cannot be reduced, the reason should be investigated.

**Table 2. Inhaled glucocorticoids, cromoglycate**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>Low dose</th>
<th>Moderate dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance treatment for mild, moderately severe, or severe asthma (Steps 2-4)</td>
<td>Beclomethasone</td>
<td>200 µg twice daily</td>
<td>400 µg twice daily</td>
<td>800 µg twice daily</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>200 µg twice daily</td>
<td>400 µg twice daily</td>
<td>800 µg twice daily</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
<td>100 µg twice daily</td>
<td>250 µg twice daily</td>
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Instead of an inhaled glucocorticoid for mild (allergic) asthma (Step 2), if necessary

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<thead>
<tr>
<th>Medication</th>
<th>Metered-dose aerosol, 5 mg 4 times daily 1 (twice daily 2)</th>
</tr>
</thead>
</table>

**Step 3. Moderate persistent asthma (objective not reached despite 3 months on a moderate dose of inhaled glucocorticoid)**

Before moving to Step 3, the diagnosis and management should be reviewed, which may also take the form of a consultative referral. If the objective is not reached despite correct diagnosis and adequate treatment with a moderate dose of an inhaled glucocorticoid, moderate persistent asthma is present. There are two options:

- add a long-acting beta_2 sympathomimetic agent to the moderate dose of inhaled glucocorticoid (see Table 3), or
- change to a high-dose of the inhaled glucocorticoid (see Table 2).
Adding a long-acting beta$_2$ sympathomimetic agent to a moderate dose of inhaled glucocorticoid results in slightly more symptom-free days and nights than does a high dose of inhaled glucocorticoid.

**Table 3. Long-acting beta$_2$ sympathomimetic agents**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medication</th>
<th>Dose (maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower doses apply to some metered-dose aerosols or dry powder inhalers: consult the <em>Farmacotherapeutisch Kompas</em></td>
<td>Salmeterol</td>
<td>50 µg twice daily 1 (twice daily 2)</td>
</tr>
<tr>
<td>Maintenance treatment to supplement an inhaled glucocorticoid for moderately severe asthma (Steps 3 and 4)</td>
<td>Formoterol</td>
<td>6-12 µg twice daily 1 (twice daily 2)</td>
</tr>
</tbody>
</table>

**Step 4. Severe persistent asthma (objective not reached despite Step 3 medication)**

If the objective is not reached using one of the two medicinal options in Step 3, then severe persistent asthma is present. This is an indication for collaboration with a pulmonologist.

For patients with severe persistent asthma there are several options:

- combination of a high dose of inhaled glucocorticoid and a long-acting beta$_2$ sympathomimetic agent
- combination of a high dose of inhaled glucocorticoid and ipratropium bromide
- combination of a high dose of inhaled glucocorticoid, a long-acting beta$_2$ sympathomimetic agent, and ipratropium bromide
- maintenance treatment with an oral glucocorticoid

**Follow-up**

- Patients with intermittent asthma (occasional use of a bronchodilator) should be advised to come for a follow-up if their use of a bronchodilator increases, especially if it becomes daily.
- Patients with persistent asthma (maintenance treatment with anti-inflammatory agents) should have regular follow-ups, e.g., once every three months, until the treatment objective has been reached and/or the optimal medicinal management is clear. Thereafter, follow-ups can be made once or twice a year.
- At the follow-up:
  - Evaluate the complaints, nocturnal sleep, limitations experienced, and frequency of bronchodilator use.$^{21}$
  - Ask about the results of non-medicinal advice and avoidance of asthma triggers (house dust mites, pets, smoking).
  - Consider giving the patient a peak flow meter to record the peak flow at home or elsewhere, if there is uncertainty about effectiveness of the treatment or the significance of job-related or other provoking factors.
  - Note whether there are side effects of the medication. To reduce local or systemic side effects of inhaled glucocorticoids, lower the dose or choose a different preparation (some are just as effective at a lower dose) or a different inhalation form (spacer). For patients who use 7.5 mg or more of prednisone or prednisolone per day for more than 6 months, prevention of osteoporosis, among other things, must be considered; the pulmonologist is responsible for raising this issue.
  - Review the inhalation instructions.
  - Decide whether the medication can be reduced.
If the treatment objective is not being achieved, investigate the possible reasons. If necessary, change the medication and check the effect after 2 weeks, sooner if there is dyspnoea. If the treatment objective is achieved with the new medication, repeat the follow-up in 3 months.

If the treatment objective has been achieved in 3 months, try reducing the medication (reduce the dose of inhaled glucocorticoid by half or reduce the bronchodilator). Check the results after 2 weeks and, if satisfactory, continue for another 3 months. If the results are unsatisfactory, return to the previous dose.

Patients who are instructed how to treat an exacerbation should agree to contact the surgery if they are unable to bring an exacerbation under control.

The best method and frequency for monitoring pulmonary function is not yet certain. For patients on Step 3 medication, pulmonary function should be monitored by spirometry.

**Consultation or referral**

- Reconsider the diagnosis and treatment if after 3 months of daily use of 800 µg beclomethasone (or less by metered-dose aerosol with a small particle size) or 800 µg budesonide or 500 µg fluticasone, the dose cannot be reduced or the treatment objectives have not been achieved. This can also be handled by a diagnostic referral, if necessary. If the diagnosis of asthma is not in doubt but the response to treatment is unsatisfactory, the general practitioner can decide to give Step 3 medication (adding a long-acting beta_2_ sympathomimetic agent or doubling the dose of inhaled glucocorticoid). If Step 3 medication is needed for a longer period, the general practitioner should monitor the patient in accordance with the relevant conditions in the National Transmural Asthma Agreement.

- Referral to a pulmonologist should be considered if:
  - There is doubt about the diagnosis 'asthma' or there are persistent problems in achieving treatment objectives on Step 3 medication. The patient can be referred back if stability is achieved on Step 3 medication and the above-mentioned conditions have been met.
  - A patient with severe persistent asthma who continues to have great limitations despite optimal care can be referred to a pulmonologist to determine whether *pulmonary rehabilitation* is indicated—assuming that the diagnosis is correct and the therapy is adequate. A pulmonary rehabilitation programme includes optimizing the medicinal therapy, non-medicinal advice and inhalation instruction, guidance and support in smoking cessation, and improving general fitness and breathing technique. A combined approach (improving fitness, psychosocial support, attention to compliance, and inhalation technique) is preferred over any one intervention alone.
  - 'Work-related asthma' is suspected and factors at work seem to play such an important role that they could jeopardize the patient's job or career track.
  - There have been more than two exacerbations per year that have necessitated treatment with an oral glucocorticoid or hospital admission.

**Guidelines for acute severe dyspnoea**

An exacerbation is defined as a period of increased dyspnoea, sometimes with coughing or mucus production. In most cases it involves mild or moderately severe exacerbations without dyspnoea at rest or respiratory failure. Non-severe exacerbations can usually be treated by starting a short-acting beta_2_ sympathomimetic agent or increasing the dose. In a few patients, an exacerbation can lead to increased dyspnoea at rest or even to respiratory failure within a short time. The treatment of an exacerbation and the frequency of
follow-ups for it are determined by the severity of the current clinical picture and the effectiveness of therapy prescribed for previous exacerbations. The general practitioner:

- inspects the patient and examines the thorax
- looks into the cause of the exacerbation, to the extent possible (infection, discontinuation of the medication by the patient)
- determines whether there is another cause for worsening of the dyspnoea, apart from asthma

Criteria for acute severe dyspnoea are:

- dyspnoea or increased dyspnoea at rest, difficulty in speaking a full sentence, inability to lie flat
- respiratory rate >25/min (in very severe exacerbations the respiratory rate decreases again!)
- heart rate >110/min
- use of accessory respiratory muscles

Treat acute severe dyspnoea as follows: (see Table 4)

- Give a beta₂ sympathomimetic agent by spacer (4-10 puffs, spray one puff at a time and inhale 5 times), or subcutaneously if necessary (1 ml of 0.5 mg/ml), or via an electric-powered jet nebulizer (0.5-1 ml of 5 mg/ml). Wait with the patient for it to take effect. After several minutes repeat the inhalations of beta₂ sympathomimetic agents and, if there is insufficient improvement, give additional ipratropium bromide (2-4 puffs, one puff at a time). In less severe cases, a follow-up can be scheduled for a few hours later.
- If there is improvement, prescribe:
  - a course of oral steroids (It is advisable to carry a starting dose of prednisone or prednisolone tablets or a glucocorticoid for intravenous administration in the doctor's bag.)
  - instructions for bronchodilator use during the next 24 hours (e.g., a double dose or inhalation using a spacer)

- A follow-up should be scheduled for the following day, to:
  - evaluate the patient’s symptoms and limitations
  - examine the lungs
  - investigate the reason for the exacerbation, reviewing especially compliance, the inhalation technique, and exacerbating factors
  - adjust the management, if indicated

For a severe exacerbation the patient should be referred if:

- no improvement occurs within a half hour
- care options at home are inadequate
- previous exacerbations have always required hospitalization
- exhaustion leads to a decreased respiratory rate, reduced consciousness, a 'more placid' patient.

These are alarm signs for which emergency hospital admission is indicated.

Table 4. Drug therapy of acute severe dyspnoea

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage and administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta₂ sympathomimetic</td>
<td>metered-dose aerosol with spacer; 4-10 puffs of 200 µg (1 puff at a time in spacer)</td>
<td>Repeat inhalations after several minutes and if improvement is not adequate, give additional ipratropium bromide (2-4 puffs, one puff at a time).</td>
</tr>
</tbody>
</table>
agent, such as salbutamol

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Use</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>prednisolone</td>
<td>orally, 30 mg once daily for 7-10 days</td>
<td>Stop abruptly, but to prevent relapse, an adequate maintenance dose of inhaled glucocorticoid is needed.</td>
</tr>
</tbody>
</table>

**note 1**
The guidelines are based in part on other consensus texts.1-4 The guidelines are in keeping with other NHG practice guidelines on asthma and COPD.5-6


**note 2**
Fear and shame appear to be correlated with limitations in daily functioning and a risk of hospitalization.1-3


**note 3**
Approximately three-quarters of the patients make one or more mistakes using the inhaler.

Inhalation technique seems to improve with instruction.1,2

note 4
Compliance is moderate in asthma patients.\textsuperscript{1} A study in Dutch general practice revealed that only one-fourth of asthma patients took at least half of the prescribed daily dose of maintenance medication.\textsuperscript{2} In a more recent study, 82\% of the patients were found to use inhaled glucocorticoids as prescribed and an even higher percentage used beta\textsubscript{2}

sympathimimetic agents correctly.\textsuperscript{3}


note 5
Opinions are divided on the efficacy of self-monitoring programmes using a peak flow meter at home.\textsuperscript{1-5} In a six-month randomized prospective study in 70 asthma patients in an asthma outpatient clinic, self-monitoring using the peak flow meter in combination with a self-management programme resulted in fewer sick days, fewer exacerbations, and better lung function values.\textsuperscript{1} A study in 569 asthma patients found that self-monitoring by means of a peak flow meter at home did not result in lower morbidity or mortality.\textsuperscript{2} In a study in 801 patients, an extensive year-long patient education programme in a subgroup with severe asthma (n = 42) led to 50\% fewer hospital admissions than in a control group (n = 47).\textsuperscript{3-5} It has been recommended self-treatment advice (in writing and verbally) and a peak flow meter should be provided to adults with severe asthma, those with a variable pattern their asthma, and those who have been hospitalized for asthma.\textsuperscript{4} A review of the literature on self-management of asthma with inhaled glucocorticoids concluded that there is still insufficient evidence supporting the usefulness of self-management strategies with inhaled glucocorticoids, especially in general practice.\textsuperscript{6} In the absence of published scientific research on the follow-up policy, the recommendations for follow-ups in this guideline are based on consensus within the work group.


note 6
In 20-30\% of all cigarette smokers, pulmonary function decreases so rapidly that disability
or death can occur by about the age of 60 years.\textsuperscript{1,2} Smoking cessation reduces this rapid deterioration in pulmonary function. Smoking cessation at an early stage can even result in such diminished deterioration of FEV1 that the curve (at a lower level) is again parallel to that of non-smokers.\textsuperscript{3}

\textit{Nicotine replacement.} A meta-analysis of the effect of nicotine replacement on smoking cessation included 53 trials, with over 18,000 subjects, in 42 trials with chewing gum, 9 with patches, 1 with nasal spray, and 1 with inhalation.\textsuperscript{4} The probability of smoking cessation over 6-12 months was 19\% in the nicotine replacement groups compared with 10\% in the control groups (odds ratio 1.71, 95\% CI 1.56-1.87). In a study (n = 227) with a follow-up of more than 3 years, the final percentages of non-smokers were 50\% lower than after 1 year. The relative difference between treatment and placebo remained constant, abstinence after 1 year being 28\% with nicotine spray and 13\% with placebo, and abstinence after 3 years being 15\% with nicotine spray and 6\% with placebo.\textsuperscript{5}

In a placebo-controlled study (n = 237), use of nicotine patches for 5 months and nicotine nasal spray for 1 year was more effective than using nicotine patches alone: smoking abstinence after one year was 27\% compared with 11\%, and after six years it was 16\% compared with 9\%.\textsuperscript{6} Nicotine replacement therapy is also recommended in British guidelines for smoking cessation.\textsuperscript{7}

\textit{Antidepressants.} In a placebo-controlled study (n = 893), after 12 months, smoking abstinence in the group treated with the antidepressant bupropion for 9 weeks, with or without the addition of nicotine patches, was higher than for placebo: abstinence after 12 months was 15.6\% for the placebo (point prevalence), 16.4\% the for nicotine patch, 30.3\% for bupropion, and 35.5\% for bupropion plus nicotine patch. For continuous abstinence (not smoking for an entire year) the figures were lower in each case: 5.6\% for placebo, 9.8\% for the nicotine patch, 18.4\% for bupropion, and 22.5\% for the combination. The drop-out rate was 34.8\%. Since there was no intention-to-treat analysis, the absolute percentages are somewhat inflated. The study population was recruited via advertisements.\textsuperscript{8} In three other placebo-controlled studies with bupropion there was a positive abstinence percentage after 1 year (point prevalence).\textsuperscript{7} Only one of these three studies has been published fully.\textsuperscript{10} In one study abstinence after 6 months was 30\% in those receiving fluoxetine and 20\% in those receiving the placebo.\textsuperscript{9} There was also higher abstinence after 6 months in persons receiving nortriptyline than in those receiving a placebo.\textsuperscript{11}

\textit{Anxiolytics.} In two studies buspirone was no more effective than a placebo after 12 months, and in another study it was just as effective as a nicotine patch.\textsuperscript{9} Other studies have shown diazepam, meprobamate, and beta-blockers to be ineffective.

Conclusions:

- The simple advice to stop smoking results in 5\% stopping; a brief but methodical approach (the 'minimal intervention strategy') increases this to 10-20\%.\textsuperscript{10}
- All forms of nicotine replacement (chewing gum, nasal spray, inhalation, patch) double the rate of abstinence compared with a placebo (about 20\% after 1 year). This is by far the most extensively investigated therapy.
- There is some evidence that bupropion and other antidepressants such as nortriptyline and fluoxetine are effective, but as yet there are no data on their use and effectiveness in the usual general practice setting. There has been only one study comparing an antidepressant with the current standard treatment (nicotine replacement).
- Combinations of different types of nicotine replacement therapy (such as patches plus spray), or combination of nicotine replacement therapy with bupropion, result in
higher abstinence after 1 year. Over the long term, abstinence declines, but there is still a positive difference compared with a placebo.

- The preference of the work group is for advice to stop smoking, combined with the minimal intervention strategy. Nicotine replacement therapy is recommended for initial support.


**note 7**


**note 8**

Large numbers of house dust mites are found mainly in the bedroom, particularly on carpeted floors and upholstered furniture, in open cupboards, and in mattress and pillows.1-3 Many mites are also found on the scalp.4 A meta-analysis of placebo-controlled studies of the use of chemical measures (acaricides) and physical measures (vacuum cleaning, air filters, allergen-proof covers, etc.) included 23 rather small studies with an average follow-up of 19 weeks. Thirteen involved physical measures and four involved a
combination of chemical and physical measures. Five studies measured the effect of allergen-proof mattress and pillow covers, usually in combination with other measures. Outcome indicators were symptoms, subjective well-being, and pulmonary function measurements. Reduction of house dust mites occurred in six studies, not in 12, and was not specified in five. The method of randomization was not usually described. The difference between the treatment and placebo groups in the number of patients that improved was not significant (38/117 vs. 41/113, odds ratio 1.20, 95% CI 0.66-2.18). One possible explanation is that the measures taken did not result in adequate reduction of house dust mites (the areas of the head covered with hair may play a role, for this is a forgotten reservoir). In addition, patients with asthma are often susceptible to multiple irritants and allergens. The results of this meta-analysis conflict with a review article (which also included uncontrolled trials, however) that concluded that there is a small beneficial effect, while at the same time stating that there is an urgent need for adequately controlled trials with sufficient power and covering a longer period (12 months). In various responses to this meta-analysis it has been suggested that the negative results could be explained by insufficient reduction of allergens and the absence of a distinction between different populations. It was suggested that allergen reduction can be especially effective as an early intervention for individuals with the initial symptoms of asthma; the author of the meta-analysis responded that this hypothesis requires further study.

In a controlled study in the Netherlands in 157 patients with mild asthma (inhaled glucocorticoid not needed), the use of allergen-proof covers and spraying with acaricides in bedrooms and the living room was compared with the use of cotton covers and a placebo spray for 20 weeks. The concentration of house dust mites on the mattress decreased to just under 10% of the initial value. The use of acaricides did not significantly change the concentration of house dust mites on the floors, compared with use of a placebo. No effect on clinical parameters was found, possibly because follow-up was too short. In another 12-month partly-double-blind, placebo-controlled Dutch study in 59 adults with asthma and house dust mite allergy, using allergen-proof mattress and pillow covers appeared to cause a greater reduction in house dust mite allergens in mattress dust than did treating the mattress with acaricides. The hyperresponsiveness (PC20 histamine) in the 'cover' group decreased significantly after 6 and 12 months, but the change was minimal. It was not compared with placebo covers, the randomization method was not described, assignment of the covers was not at random, and there was no clinical outcome indicator. In a 6-month, double-blind trial involving 45 asthmatic adults with house dust mite allergy (50% also allergic to a pet and pollen), in three groups, the effect of air filters was compared with use of mattress and pillow covers in combination with either placebo air filters or active air filters. The reduction in house dust mite allergens in mattress dust was substantial in the 'cover' groups. In the active air filter group there was no reduction in house dust mites on the mattress. The three groups did not differ in the reduction of house dust mites on the bedroom or living room floors, perhaps because the placebo air filter apparently also collected dust, and the relatively heavy particles with dust mite allergen did not float in the air long enough after air turbulence. The hyperresponsiveness decreased markedly in the group using covers combined with active filters, and not in the other two groups. There was no clinical effectiveness indicator. An update of a report made for the Volksgezondheid Toekomst Verkenningen [Public Health Investigations for the Future] drew the following conclusions based on four reviews:

- Under controlled conditions, physical measures such as use of covers result in house dust mite reduction more often than does use of acaricides, even when the measures are taken by the patients themselves—although the percentage of successful
interventions is smaller in that case.

- The effect on clinical parameters is not as clear. In the majority of the studies in which allergen reduction was achieved under more controlled conditions (by professionals), clinical improvement was also seen. When professionals had less influence on the application of cleaning measures, the clinical results were very diffuse.

- A meta-analysis based on strict methodological criteria (reviews of identical interventions under identical control conditions) is still lacking.

Conclusion: The studies and reviews discussed have many methodological limitations. The quality of research was complicated by the fact that multiple allergens and non-allergic irritants were often significant factors. There were often combinations of interventions (physical and chemical measures) in various locations (bedclothes, furniture, floor coverings, bedrooms, and/or living rooms, etc.). The effect of allergen-proof covers on the reduction of house dust mites on the mattress has been well demonstrated, but such covers do not reduce house dust mites in other places, such as the bedroom floor. The effects of covers on clinical parameters (complaints, etc.) are much less clear. The efficacy of other measures (air filters, acaricides) on the reduction of house dust mites and clinical parameters has not been clearly demonstrated and there are objections to these measures (noise pollution from filters, resistance to the use of chemical agents). Based on these considerations, the cleaning recommendations made in the previous version of the practice guideline are being continued.

6. De Veth HC. Review: measures to control house dust mites are not effective in patients with asthma who are sensitive to mites. Evidence Based Medicine 1999;4:80.


note 9

Inhalation therapy can be administered with a dry powder inhaler or a metered-dose aerosol. With a dry powder inhaler, deposition in the lung depends primarily on the inspiratory force; lower force results in lower delivery and larger particle size, hence less deposition in the lung. With a metered-dose aerosol, deposition depends primarily on hand-lung coordination and the inspiratory force has no effect on either dosage delivery or average particle size. If deliberate inhalation is not feasible, a metered-dose aerosol with a spacer is preferred. If deliberate inhalation is feasible, the patient's inspiratory force and coordination determine the choice between a metered-dose aerosol (whether or not 'breath-actuated' or with a spacer) and a dry powder inhaler. A rare side effect of metered-dose aerosols is bronchoconstriction. Bronchoconstriction occurred after inhalation of a metered-dose aerosol in 1.5 percent of 11,000 patients, probably caused by one of the excipients. The recommendations for the use of a spacer are taken from an editorial. There are differences of opinion about the best way to inhale. The great variety of inhalers makes it difficult to choose the one most suited to the individual patient. Despite the known disadvantages, a metered-dose aerosol (whether or not 'breath-actuated' or with a spacer) remains a simpler and less expensive method of administration for many patients.


note 10

An association between the use of beta₂ sympathomimetic agents and increased mortality and morbidity from asthma, as reported in other countries, has not been observed in the Netherlands. Yet there are indications, also in Dutch studies, that pulmonary function deteriorates with continuous use of these agents, particularly if used as monotherapy. Other studies put this into perspective, however. In a randomized, cross-over study in 341 patients with moderately severe asthma treated with 200 µg salbutamol 4 times daily for 2 weeks or salbutamol on an as-needed basis for 2 weeks, peak flow values did not differ but regular administration of salbutamol was associated with fewer daytime and nocturnal complaints. Eighty-three patients with mild symptoms (27 with asthma and 56 with chronic bronchitis) were studied for 4 years, half being treated continuously at random with bronchodilators and the other half on an as-needed basis. No difference was found in peak flow variation or in the yearly deterioration of pulmonary function. In a placebo-controlled study in 983 asthma patients, 90% of whom were using inhaled glucocorticoids, the use of salbutamol 4 times daily for 12 months did not lead to more numerous exacerbations.
Conclusion: Beta₂ sympathomimetic agents are generally recommended as occasional symptomatic treatment for acute relief. If the patient continues to require the medication several times per day, treatment with an inhaled glucocorticoid is advised. The practice guideline follows these recommendations. The distinction between mild, moderate, and severe asthma is arbitrary. The recommendation of this practice guideline that treatment be changed to an inhaled glucocorticoid when beta₂ sympathomimetic agents are required daily for 2-4 weeks is based on consensus in the work group. The use of an inhaled glucocorticoid is also advised for a new patient in whom symptoms have been present daily for a long time.


note 11
In a 12-week, placebo-controlled study in 110 patients with exercise-induced asthma, montelukast (10 mg once daily) was more effective than a placebo. No drug tolerance was observed. No controlled trials comparing montelukast and short-acting beta₂ sympathomimetic agents have been reported. Two puffs of a short-acting beta₂ sympathomimetic agent 10-15 minutes before exercising provided over 2 hours of protection against exercise-induced asthma, and two puffs of salmeterol 10-15 minutes before exercising provided 10-12 hours of protection. With long-term use of salmeterol the duration of the protective effect decreases, however. Cromoglycate and nedocromil are effective for exercise-induced asthma, but beta₂ sympathomimetic agents are more
effective and are therefore preferred.\textsuperscript{2}


\textbf{note 12} \\
Regular use of beta\textsubscript{2} sympathomimetic agents has been observed to increase bronchial sensitivity to irritants; apart from that, the bronchodilatory effect is sustained.\textsuperscript{1} In this regard, there seems to be a clear difference between beta\textsubscript{2} sympathomimetic agents and ipratropium bromide.

In 13 stable patients with allergic asthma, the protective effect against bronchoconstriction decreased when the patient was exposed to allergens during 2 weeks of regular use of salbutamol (200 µg 4 times daily).\textsuperscript{2} The results of other studies are not all consistent with regard to the diminished protective effect of beta\textsubscript{2} sympathomimetic agents. There is little evidence of acquired tolerance to the direct bronchodilating effect of beta\textsubscript{2} sympathomimetic agents.

These observations support the policy of not prescribing long-term daily monotherapy with beta\textsubscript{2} sympathomimetic agents.


\textbf{note 13} \\
\textit{Long-acting versus short-acting beta\textsubscript{2} sympathomimetic agents.} Long-acting and short-acting beta\textsubscript{2} sympathomimetic agents were compared in several studies. In a 14-week, double-blind, controlled study on quality of life in 140 adult asthma patients, salmeterol was more effective than either a placebo or salbutamol.\textsuperscript{1} In another double-blind, randomized trial in 99 patients (age 44, FEV1 66% of the predicted value) for 12 weeks, formoterol (12 µg twice daily) was compared with salbutamol (200 µg 4 times daily). In patients on formoterol there was less additional use of short-acting beta\textsubscript{2} sympathomimetic agents and there was a higher morning peak flow. No significant differences were found in the other outcome indicators (FEV1, evening PEF, general opinions of patient and investigator, nocturnal sleep).\textsuperscript{2} In a third double-blind, randomized general practice study in 25,180 asthma patients, salmeterol (50 µg twice daily) was compared with salbutamol (200 µg 4 times daily). The most important outcome indicators were all of the severe complications and the drop-out rate. There was a lower drop-out rate for medical reasons in patients using salmeterol (2.9 vs. 3.8%, \(p = 0.0002\)). There was a slightly (but not significant) higher mortality in patients using salmeterol. Asthma was controlled better with salmeterol.\textsuperscript{3}

\textit{Doubling the dose of inhaled glucocorticoid versus adding a long-acting beta\textsubscript{2} sympathomimetic agent to a moderate dose of inhaled glucocorticoid.} A meta-analysis discussed the results of nine double-blind, randomized studies in which doubling the dose of inhaled glucocorticoid was compared with adding salmeterol to a moderate dose of inhaled glucocorticoid.\textsuperscript{4} The total population consisted of 3,685 patients who had symptoms despite use of inhaled glucocorticoids and in whom there was a more than
10-15% increase in the peak flow or FEV1 after inhalation of a short-acting \( \beta_2 \) sympathomimetic agent. In the salmeterol group there were about 2% fewer patients with an exacerbation, both the morning peak flow and FEV1 were somewhat higher after 3 months (22 l/min and 100 ml, respectively), and there was a small difference in the number of symptom-free nights (-5%) and days (-12%).

Adding formoterol to treatment with inhaled glucocorticoids has been studied less thoroughly. A study in 852 patients divided into four groups compared the effect on the number of exacerbations of adding formoterol or a placebo to a low dose (100 µg twice daily) and a high dose (400 µg twice daily) of budesonide.\(^5\) The greatest reduction in severe exacerbations occurred in the group receiving formoterol plus high doses of budesonide. High doses of budesonide reduced the number of severe exacerbations more than did adding formoterol to a low dose. For other effectiveness indicators, low-dose budesonide plus formoterol was somewhat better than high-dose budesonide plus the placebo. In another study, formoterol added to inhaled glucocorticoids in 125 patients with mild to moderately severe asthma apparently produced subjective and objective improvement compared with a placebo.\(^6\) However, this was not compared with doubling the dose of inhaled glucocorticoid.

One of the possible drawbacks of maintenance treatment on long-acting \( \beta_2 \) sympathomimetic agents is reduced sensitivity to short-acting \( \beta_2 \) sympathomimetic agents. This was studied in 17 asthma patients (FEV1 64% of the predicted value, age 34) for 8 weeks in a placebo-controlled, crossover study.\(^7\) A 2.5 to 4 times higher dose of salbutamol was needed in the salmeterol group to obtain the same bronchodilatory response as in the placebo group.\(^2\) A review of the literature on possible disadvantages of long-acting \( \beta_2 \) sympathomimetic agents found no signs of poorer control of asthma, accelerated deterioration of pulmonary function, or elevated bronchial hyperreactivity. There is no evidence of a link between long-acting \( \beta_2 \) sympathomimetic agents and higher mortality from asthma.\(^8\) In a 6-month, crossover study in 87 patients with mild or moderately severe asthma, the use of inhaled glucocorticoids was 17% lower in the group treated with salmeterol, yet pulmonary function improved.\(^9\)

Conclusion: Long-acting \( \beta_2 \) sympathomimetic agents have practical advantages (particularly for nocturnal symptoms) over short-acting \( \beta_2 \) sympathomimetic agents and are given in addition to inhaled glucocorticoids. In patients who continue to have symptoms on a moderate dose of inhaled glucocorticoid, adding a long-acting \( \beta_2 \) sympathomimetic agent is slightly more effective than doubling the dose of inhaled glucocorticoid. How the use of long-acting \( \beta_2 \) sympathomimetic agents affects the action and dose of short-acting \( \beta_2 \) sympathomimetic agents is not yet clear.

5. Pauwels RA, Löfdahl C-G, Postma DS, et al. Effect of inhaled formoterol and

note 14

Patients over the age of 60 who have characteristics of COPD respond better to ipratropium bromide.1-3

note 15

Xanthine derivatives produce bronchodilation through a mechanism that is not yet entirely understood. Due to individual variation in absorption and clearance, there is no fixed relation between the dose and serum concentration. Furthermore, the therapeutic and toxic doses are very close (narrow therapeutic spectrum) and side effects are fairly frequent.1 In recent years, there has been a minor reassessment of theophylline. In a 3-month, placebo-controlled study in 62 patients, adding theophylline (250-375 mg twice daily) to a moderate dose of budesonide (400 µg twice daily) proved to be more effective (on pulmonary function and beta₂ sympathomimetic use) than doubling the dose of inhaled glucocorticoid. Both treatments were well tolerated.2

note 16

Two review articles on the efficacy and safety of inhaled glucocorticoids for asthma concluded that their effect has been convincingly proved for bronchial hyperreactivity, pulmonary function, and symptoms, both in adults and in children. Side effects rarely occur at the usual doses (up to 400 µg in children and up to 800 µg in adults).1,2 There is, however, a highly individual sensitivity to suppression of endogenous cortisol production. Regular use of low-dose inhaled glucocorticoids for asthma is associated with a lower risk of death from asthma (in an epidemiological study in over 30,000 individuals, 77 of the 562 deaths were due to asthma).3 The frequency of administration is usually twice daily, but four times daily may be
preferable in severe asthma and once daily may be sufficient in mild asthma. A single dose of 1,000 µg beclometasone in the late afternoon or evening appeared to be just as effective as twice-daily administration of 500 µg. Various studies of the efficacy of monotherapy with bronchodilators compared with inhaled glucocorticoids in heterogeneous patient populations have confirmed the beneficial effect of inhaled glucocorticoids. Two of these studies (Haahtela et al.) were in patients with mild asthma (FEV1 84-88% of the predicted value) and they make a case for using an inhaled glucocorticoid as Step 1 for mild asthma. However, it is debatable whether the risks of long-term treatment with inhaled glucocorticoids offset the risk of more rapid deterioration of pulmonary function if mild asthma is treated with beta₂ sympathomimetic agents alone. Since this has not been adequately proved, there is at present no reason to change the usual therapeutic regimen.

A review concluded that the maximum effect of inhaled glucocorticoid (budesonide, beclometasone) is reached at a dose of 1,600 µg per day. There is no convincing difference between budesonide and beclometasone. In most cases a dose of 1,000 µg or less is sufficient if the patient inhales adequately. At doses of 1,600 µg or higher, the risk of local and systemic side effects increases. Adrenocortical suppression is unlikely at lower doses, although individual sensitivity varies widely. At doses above 800 µg, use of a large spacer is recommended because it reduces the risk of local side effects and improves deposition in the lung. An alternative is to divide the doses more widely over the day (e.g., 400 µg 4 times daily). In a cross-sectional study in 196 patients with mild asthma (FEV1 mean 93% of the predicted value), ages 20-40, who had been using inhaled glucocorticoids for an average of 6 years, a higher cumulative dose proved to be negatively correlated with bone density. Whether this ultimately results in an elevated risk of osteoporotic fractures at over 60 years of age is not known.

In four studies in adults and two in children, fluticasone proved to be twice as potent as budesonide dipropionate per unit body weight. Fluticasone has no clear advantages over budesonide or beclometasone, in either effectiveness or side effects. The risk of adrenocortical suppression increases at higher doses. This risk is most pronounced with fluticasone doses above 800 µg daily, and at therapeutically-equivalent doses it is definitely no less than with budesonide or beclometasone. Little is known about systemic side effects (osteoporosis, subcapsular cataract, 'bruising') of fluticasone. Not enough is known about the necessary duration of treatment with inhaled glucocorticoids. In view of the underlying pathophysiological mechanisms and the chronic nature of the disorder, treatment for at least 3 months appears to be indicated. The rule of thumb to 'start high and decrease slowly' seems to have no foundation for adults.


note 17
Cromoglycate prevents both early and late allergic reactions.¹ Two puffs 10-15 minutes before exercising is effective against exercise-induced asthma for slightly less than 2 hours; beta₂ sympathomimetic agents are more effective for exercise-induced asthma.²
There are no side effects.¹


note 18
One review article discussed placebo-controlled, double-blind studies and the role nedocromil plays in the treatment of asthma.¹ In patients treated with bronchodilators alone (n = 3,000), adding nedocromil had a beneficial effect compared with a placebo. In over 770 patients who were not satisfactorily stable on inhaled glucocorticoids, adding nedocromil (16 mg daily) produced improvement, but not in all parameters. Its effectiveness was greater in patients who used only bronchodilators than in those who used inhaled glucocorticoids as well. Three studies have compared nedocromil directly with inhaled glucocorticoids. In one study² beclomethasone was more effective and in the second³ there was no difference between nedocromil and inhaled glucocorticoids. In a
third study during 4-6 years in 1,041 asthmatic children, budesonide was more effective than nedocromil in decreasing hyperresponsiveness and controlling asthma. The question is whether there is an indication for nedocromil in addition to inhaled glucocorticoids and cromoglycate. The most significant objection is that while there is extensive documentation of the effectiveness of inhaled glucocorticoids, there is much less for nedocromil. In addition, extensive experience with inhaled glucocorticoids and cromoglycate has been acquired in daily practice.


note 19

Antileukotrienes. Leukotrienes are mediators of inflammation in the pathophysiology of asthma. Two categories of antileukotrienes for oral administration are licensed for use in several countries. In the Netherlands, as of the year 2000, montelukast is the only antileukotriene licensed for use in patients whose symptoms are not adequately controlled by inhaled glucocorticoids and as-needed short-acting beta_2 sympathomimetic agents. Its use is covered by medical insurance if a pulmonologist is the primary prescriber. In several studies in patients with mild or moderate persistent asthma, montelukast—usually as monotherapy—was more effective than a placebo (clinical picture, pulmonary function). There have been no good-quality studies comparing montelukast with the current reference therapy (montelukast monotherapy versus inhaled glucocorticoid monotherapy, montelukast added to inhaled glucocorticoid versus doubling the dose of inhaled glucocorticoid or versus long-acting beta_2 sympathomimetic agents). Zafirlukast has also been compared with placebo, primarily as monotherapy, but not with the current standard therapy. There was no difference in side effects among montelukast, zafirlukast, and placebo. In post-marketing surveillance, rare cases of a possible association with Churg-Strauss syndrome have been reported. In a study in 226 asthma patients on high doses of inhaled glucocorticoids, the dose of glucocorticoid could be reduced by 47% in those given montelukast, compared with 30% in those given a placebo (p = 0.046). A review article concluded that for mild persistent asthma either antileukotrienes or inhaled glucocorticoids can be chosen, weighing the greater efficacy of inhaled glucocorticoids against the higher expected compliance with use of antileukotrienes (because they are administered orally). Since good controlled studies comparing the latter with current standard therapy are lacking, the role of antileukotrienes such as montelukast and zafirlukast in the treatment of asthma is still unclear.

Monoclonal antibodies. The effect of intravenously-administered recombinant antibodies to IgE A was studied in a 20-week, placebo-controlled trial in 317 adults patients with allergic asthma who needed inhaled or oral glucocorticoids. Small differences were observed in the symptom scores and the reduction in oral steroid use. The treatment was well tolerated. Monoclonal anti-IgE may be an option for severe asthma that requires the use of an oral glucocorticoid.
Antibiotics. Another therapeutic option suggests a possible connection between Chlamydia pneumoniae and asthma. In an open, non-controlled study, 50 patients who had moderately severe asthma (FEV1 67.8% of the predicted value, age 48 years) with antibodies to Chlamydia pneumoniae were treated with doxycycline, azithromycin, or erythromycin for 3-6 weeks, and then followed for 6 months. Approximately half improved, of whom 7 became symptom-free. Since this was an open, non-controlled study, no further conclusions can be drawn.

Antihistamines. An oral antihistamine can be tried for the combination of allergic rhinitis and allergic asthma. The effect of 10 mg cetirizine given once daily was observed for 6 weeks during the pollen season in 93 patients in a double-blind, placebo-controlled study. Cetirizine was more effective than the placebo in reducing the complaints, but pulmonary function did not change in either group.

Immunotherapy. Based on 54 randomized, controlled studies, a systematic review by the Cochrane Collaboration on immunotherapy for asthma concluded that immunotherapy is effective (reduction in symptoms, asthma medication, and BHR, but no effect on pulmonary function). It is not clear whether immunotherapy is better than the standard medicinal therapy, whether mono-immunotherapy is better than a cocktail, or what is the optimal duration of therapy. Observation for 45 minutes after injection is necessary, ideally in a clinical setting. There is no consensus within the organization of pulmonologists about the role of immunotherapy for asthma. If necessary, the general practitioner can consult with a pulmonologist when he has questions about a possible indication in patients.

NO synthetase inhibitors. Nitrogen monoxide (NO) can damage lung tissue and reducing the concentration of NO relaxes the smooth muscles. Specific inhibitors of NO synthetase are potential future anti-asthma medications.


note 20

Pregnancies in asthmatic women are associated with an elevated risk of premature parturition, low birth weight, and pre-eclampsia. Possible explanations for this are hypoxia, other physiological effects of poorly-controlled asthma therapy, or side effects of the medication being used. There are indications that adequately treated asthma is associated with fewer perinatal complications. Oral glucocorticoid use is associated with pre-eclampsia and, in the first trimester, with an elevated risk of cleft palate. These risks must be weighed against the risk of hypoxia in the pregnant woman and foetus in the event of severe asthma. Treatment with beclometasone, short-acting beta<sub>2</sub> sympathomimetic agents, ipratropium bromide, or cromoglycate can be continued during pregnancy. Most of the data on inhaled glucocorticoids concern beclometasone. The patient information leaflets for budesonide and fluticasone state that not enough is known about their use during pregnancy; the least amount of practical experience is with fluticasone. No advice against use during pregnancy is provided with salmeterol, but the Pharmacotherapeutic Compass advises against taking salmeterol or formoterol during pregnancy, due to adverse effects on the embryo in animal studies.

Conclusion: Treatment with beclometasone, short-acting beta<sub>2</sub> sympathomimetic agents, ipratropium bromide, or cromoglycate can be continued during pregnancy. The potential risks of using oral glucocorticoids during pregnancy (pre-eclampsia, elevated risk of cleft palate in the first trimester) must be weighed against the risks of hypoxia in the mother and foetus due to asthma. Since recommendations on the use of salmeterol and formoterol are contradictory, their use during pregnancy is not advised at present.


note 21

In a study of 570 asthma patients in general practice, a revised version of an asthma severity index (wheezing at least once weekly, absence from school or work due to asthma, nocturnal wheezing attacks) was found to be accurately correlated with the peak flow measured during the consultation.


note 22

Van der Schans observed good results from postural drainage combined with certain breathing and coughing techniques. Others have not been convinced of the benefit of postural drainage. ‘Pursed lip breathing’—relaxed exhalation with the lips almost closed—was thought to help prevent airway collapse during exhalation. Patients have felt subjective relief, but the objective effect has not been determined conclusively.

Ambulant or clinical pulmonary rehabilitation is a useful approach for COPD. Even when there are severe limitations despite optimal care for asthma or asthma with persistent...
obstruction, this kind of combination of interventions (medical, nursing, and physiotherapeutic) seems useful.


note 23

A review article based on consensus guidelines, reviews, and empirical data on 1,400 patients with acute severe asthma in a casualty department stated that most asthma attacks are not life-threatening. In over 10% there was tachycardia (>120 beats/min) and in 20% the respiratory rate was 30/min or higher. Transpiration, use of accessory respiratory muscles, and major fluctuations in blood pressure are indications of severe bronchoconstriction. Cyanosis, reduced consciousness, gasping respiration, and silent chest occur in only 1% of cases. Objective indicators for emergency care are a peak flow or FEV1 of 35% of the predicted value or less. Recommendations for drug therapy are based on empirical data. Frequently-administered high doses of short-acting beta2 sympathomimetic agents are the preferred treatment: 10-12 puffs administered via a large spacer every 20 minutes for 1 hour. Nebulizers have no proved benefits. To promote recovery of somewhat longer duration, prednisone or prednisolone is often prescribed, but the benefits have not been adequately demonstrated in placebo-controlled trials. The effect can only be expected after 6-12 hours, regardless of whether administration is oral or intravenous. The usual doses vary greatly, from 30 to 40 mg prednisone or prednisolone per day in the Netherlands and England, to 200 mg prednisolone per day in the United States. If beta2 sympathomimetic agents do not provide adequate relief, adding ipratropium bromide can provide added bronchodilation. A meta-analysis of five studies revealed that adding ipratropium bromide reduced the number of hospital admissions (NNT 18 95% CI 11-17) and in patients with severe dyspnoea (FEV <35% of the predicted value), it had a clear effect on FEV1. An equivalent meta-analysis reached the same conclusion. Following the acute phase, attention is given to preventive medication: start an inhaled glucocorticoid or double the dose. In a double-blind, placebo-controlled study in 80 adults with asthma attacks (age 42 years, FEV1 36% of the predicted value) who were treated in the casualty department of a hospital, the use of a metered-dose aerosol with a spacer proved just as effective as a nebulizer. With 12 puffs of 100 µg salbutamol distributed over 3 inhalations in short succession, with an interval of 30 minutes between sessions, maximal bronchodilation was achieved in 90% of the patients in 1½ hours. Using a nebulizer, the dose required to achieve this was six times greater.

The British Thoracic Society recommends a dose of 2.0-5.0 mg (20-50 puffs, using a metered-dose aerosol).

In another study in 35 patients with asthma attacks (age 24, FEV1 37% of the predicted value), repeated administration of salbutamol (4 puffs of 90 µg) via a spacer was just as effective as 2.5 mg salbutamol via a nebulizer. The authors of a review article on the treatment of severe acute dyspnoea in asthma and COPD concluded that a spacer is an effective and practical alternative to a nebulizer.
A double-blind, randomized study compared two doses of methylprednisolone (1 and 6 mg per kg per day) in 47 patients with a severe acute asthma attack. The result (improvement in FEV1) was similar in the two groups. In a placebo-controlled, double-blind study in 44 patients with severe acute asthma attacks (age 28, PEF 22% of the predicted value, 130 l/min), who were treated with a beta2 sympathomimetic agent and glucocorticoids, there was no difference between the effect of albuterol or ipratropium bromide. A placebo-controlled, double-blind study in 35 patients admitted to hospital with an acute asthma attack revealed no rebound effect when prednisolone was tapered off after a course of 40 mg for 10 days. The results of another study were similar. There were no indications of adrenocortical insufficiency. A 10-day course is recommended because the maximum peak flow is reached on day 10. A prerequisite for not tapering off the dose of oral glucocorticoid is an adequate dose of inhaled glucocorticoid (average 900 µg budesonide daily). In patients not yet using glucocorticoids who came to a casualty department because of an asthma attack, those treated with high doses of an inhaled glucocorticoid (1,600 µg budesonide) in addition to an oral glucocorticoid had fewer exacerbations in the following 3 weeks than those who received the oral glucocorticoid and a placebo.

Conclusion: Frequent high doses of beta2 sympathomimetic agents (20-50 puffs of salbutamol administered via a spacer during 1 1/2 hours) is the preferred treatment for an acute severe asthma attack. Adding ipratropium bromide provides additional bronchodilation. Adding theophyllines has no proved benefit. The effect of a glucocorticoid can only be expected after 6-12 hours, regardless of how it is administered. A high-dose course of prednisolone does not have to be tapered off, provided that the patient uses adequate inhaled glucocorticoid. Thiazinamium is not recommended, in view of the fact that safe and effective alternatives are available. Antibiotics are not indicated for exacerbations.