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Guidelines and cost effectiveness for the long-term treatment of children with asthma.

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Abstract

The prevalence of certain chronic diseases is growing and new treatments become available. Therefore, in the future, the resources required to care for chronically ill patients may increase. If available budgets are limited, it is important to consider the efficiency of interventions to guarantee a maximum pay-off in terms of better health and quality of life within the given budget. An interesting question therefore is whether for specific diseases knowledge on cost effectiveness, epidemiology and the effects of interventions can be combined in a model to determine more efficient allocations of resources. The present report contains the first steps towards such a model of the long-term care for children with asthma. In particular, the report presents the following results: (1) a classification of existing interventions for the long-term care of asthmatic children, (2) a summary of “standard” care as presented in guidelines, and (3) a review of cost-effectiveness studies, summarising what is known about the costs and effects of interventions.

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Samenvatting

De zorg voor chronisch zieken doet een toenemend beroep op middelen binnen en buiten de gezondheidszorg. Als de beschikbare middelen beperkt zijn, dan is het belangrijk om aandacht aan het doelmatige gebruik van die middelen te besteden. Een doelmatige besteding moet er toe leiden dat voor een gegeven budget, de opbrengsten van de besteding van dit budget aan interventies in termen van verbeteringen in de gezondheid dan wel kwaliteit van leven van patiënten zo groot mogelijk zijn.

Voor chronische aandoeningen is de zorg vaak een complex geheel van veel verschillende soorten interventies. Bijvoorbeeld kan tertiaire preventie, met als doel dat de aandoening in de toekomst niet erger wordt, worden gecombineerd met een interventie om huidige symptomen te onderdrukken. Voor de verschillende interventies kunnen verschillende zorgverleners verantwoordelijk zijn. Dat betekent dat ook de kosten van uitvoering in eerste instantie door verschillende instituten of personen kunnen worden gedragen. Daardoor is er geen reden voor deze instituten om de budgettaire consequenties van interventies en hun effecten tegen elkaar af te wegen in een complete evaluatie van alle mogelijke interventies bij alle patiënten over het hele ziekteverloop. Vanuit een maatschappelijk perspectief kan juist zo een evaluatie belangrijke informatie geven over de meest doelmatige besteding van de beschikbare middelen.

Als eerste stap in de richting van een dergelijke evaluatie, geeft dit rapport een overzicht van beschikbare resultaten uit kosteneffectiviteitsstudies naar specifieke interventies voor de lange termijn behandeling van kinderen met astma. Studies van voldoende kwaliteit worden samengevat en hun resultaten zijn vergeleken met het advies in een viertal recente richtlijnen. Daartoe is eerst de zorg voor astmatische kinderen gestructureerd beschreven. Astma is gekozen als voorbeeld van een chronische ziekte, omdat bij kinderen astma een van de belangrijkste chronische aandoeningen is. De behandeling van astmapatiënten is onder te verdelen in diagnose, lange termijn behandeling en zorg bij acute aanvallen. De lange termijn behandeling bestaat weer uit diverse interventies, van allergeenmijdende maatregelen bij patiënten thuis tot symptoomonderdrukkende medicatie. Een goede diagnose en de juiste lange termijn behandeling zouden de frequentie en ernst van aanvallen moeten verminderen zodat minder acute zorg nodig is.

Veel richtlijnen onderscheiden drie categorieën van behandelingen bij de lange termijn behandeling van kinderen met astma, namelijk het vermijden van uitlokkende factoren, medicatie en voorlichting. De in de richtlijnen geadviseerde zorg bestaat uit een combinatie van interventies uit verschillende categorieën, bijvoorbeeld uit een behandeling met medicijnen, gecombineerd met maatregelen om allergenen te vermijden en het advies om met roken te stoppen en/of passief roken te vermijden. De richtlijnen geven advies over interventies in al deze categorieën, maar ze geven niet aan welke intensiteit van de diverse interventies het meest doelmatig zou zijn, dat wil zeggen, hoe een gegeven budget het best zou kunnen worden verdeeld over interventies uit de verschillende categorieën. Er kan samenhang zijn tussen de intensiteit waarmee een bepaalde interventie wordt uitgevoerd en de effecten van een interventie uit een andere categorie. Kosten gemaakt in de ene categorie interventies kunnen dan de noodzaak om kosten te maken in een andere categorie verminderen. Zo zouden bijvoorbeeld astmatici die allergisch zijn voor bepaalde stoffen, wellicht kunnen volstaan met lagere doses medicatie als ze de betreffende stoffen weten te vermijden.

In de richtlijnen ligt de nadruk vooral op effectiviteit van individuele behandelingen, zoals bewezen met behulp van gerandomiseerd klinisch onderzoek. Expliciete referenties aan

kosteneffectiviteit zijn schaars. Het advies in de richtlijnen is op het niveau van groepen medicijnen, of algemene interventies, maar geeft geen details welke stof, dan wel specifieke interventie het meest gewenst is (het advies is bijvoorbeeld om inhalatiecorticosteroiden voor te schrijven, niet om één specifiek inhalatiecorticosteroid voor te schrijven).

Kosteneffectiviteitsstudies gaan, in tegenstelling tot richtlijnen, juist vaak over één interventie, en vergelijken bijvoorbeeld twee typen medicijnen. Bovendien zijn ze vaak gedetailleerder en beoordelen specifieke interventies (bijvoorbeeld wordt één specifieke langwerkende bronchusverwijder, salmeterol, vergeleken met één specifieke kortwerkende bronchusverwijder, salbutamol).

Resultaten uit kosteneffectiviteitsonderzoek kunnen op twee niveaus van detail bijdragen aan de richtlijnen. Ten eerste kunnen vergelijkingen tussen alternatieve varianten van een behandeling worden gebruikt om algemene adviezen in de richtlijnen aan te scherpen tot een advies voor de meest kosteneffectieve specifieke interventie. Ten tweede kunnen resultaten uit kosteneffectiviteitsonderzoek misschien worden gebruikt om keuzes te maken over de intensiteit waarmee behandelingen uit verschillende categorieën worden uitgevoerd. Dat laatste vereist in ieder geval dat kosteneffectiviteitsstudies expliciete gegevens over kosten en effecten van de bestudeerde interventies bevatten. Verder zal informatie over de samenstelling van de populatie patiënten nodig zijn, omdat zij van elkaar kunnen verschillen in ernst van hun aandoening, en keuzes daarvan afhankelijk zullen zijn. Er kunnen niet alleen categorieën interventies worden onderscheiden maar ook groepen patiënten. Tenslotte treden mogelijk 'synergie' effecten op tussen behandelingen uit verschillende categorieën. Een interessant onderwerp voor onderzoek is dan om na te gaan in hoeverre het mogelijk is informatie over voorkomen van de ziekte te combineren met informatie over kosten en effecten van behandelingen en zo de beste verdeling te bepalen van een gegeven budget voor een bepaalde ziekte. Dit rapport levert een aantal bouwstenen voor de beantwoording van deze vraagstelling in de vorm van gestructureerde indelingen van interventies en kosteneffectiviteitsstudies naar de lange termijn zorg voor kinderen met astma, een samenvatting van de 'standaard' zorg, zoals te vinden in enkele recente richtlijnen en een overzicht van de resultaten van kosteneffectiviteitsstudies.

Het rapport is opgedeeld in zes paragrafen. Na de inleiding geeft paragraaf 2 een inventarisatie en categorisatie van mogelijke interventies. In paragraaf 3 volgt een samenvatting van het advies in vier richtlijnen voor de lange termijn zorg bij kinderen met astma. Omdat het onderzoek vooral over de Nederlandse situatie gaat, beperkt de vergelijking zich tot twee Nederlandse, een Amerikaanse en een Britse richtlijn. Paragraaf 4 geeft een overzicht van kosteneffectiviteitsstudies. In paragraaf 5 worden de resultaten samengevat en de richtlijnen vergeleken met resultaten uit kosteneffectiviteitsstudies. Tenslotte is paragraaf 6 een puntsgewijze opsomming van de belangrijkste conclusies uit paragraaf 5. Uit de vergelijking tussen richtlijnen en kosteneffectiviteitsstudies volgt dat niet voor iedere categorie interventies voldoende gegevens beschikbaar zijn om conclusies te kunnen trekken over de kosteneffectiviteit. Wat betreft allergeenmijdende maatregelen bijvoorbeeld zijn eigenlijk geen gegevens over kosteneffectiviteit te vinden. Voor medicatie zijn wel vrij veel gegevens beschikbaar. Er lijkt weinig verschil te zijn tussen de adviezen in richtlijnen en de resultaten van kosteneffectiviteitsstudies wat betreft het gebruik van inhalatiecorticosteroiden en andere ontstekingsremmende medicatie. Kosteneffectiviteitsstudies naar langwerkende bronchusverwijders ontbreken echter, terwijl daarover in de richtlijnen wel advies wordt gegeven. Uit onderzoek naar zogeheten 'self-management' programma's blijken deze voor bepaalde groepen patiënten tot netto besparingen te kunnen leiden. In de Nederlandse richtlijnen wordt 'self-management' vooral bestemd voor de groep met ernstig astma. Dit is

ongeveer in overeenstemming met de besproken resultaten van kosteneffectiviteitsonderzoek. Echter, voor patienten met minder ernstig astma is onvoldoende bekend wat de kosteneffectiviteit van self-management programma's is.

Summary

In the future, the resources required to care for chronically ill patients may increase due to increasing prevalence and treatment options. If the available budgets are limited, it is important to consider the efficiency of interventions. An efficient allocation of resources to interventions should result in a maximum pay-off in terms of improved health and quality of life of patients from a given budget. Care for chronic diseases is often complex and consists of several simultaneous interventions that aim at different aspects of the disease. For instance, tertiary prevention to preclude worsening of the disease may be combined with interventions to suppress current symptoms. Different interventions are sometimes provided by different institutes or persons. By implication, the immediate cost consequences of the interventions are also born by different agents (institutes or persons). Hence, there is no incentive for these agents to find an allocation that is efficient from a societal perspective. In the present report, the effects and costs of interventions are considered over the whole course of disease and from the perspective of society.

The report provides a summary of what is known about the cost effectiveness of specific interventions in the long-term care for asthmatic children. We review available good quality studies and compare their results with the advice given in current guidelines. For this purpose, we describe the care for asthmatic children in a structured way. We have chosen to evaluate asthma because it is an important chronic disease among children. Its treatment consists of diagnosis, long-term care and emergency care. Long-term care encompasses interventions that aim at different aspects of the disease and range from allergen avoidance measures in patients' houses to symptoms-suppressing medication. A correct diagnosis and appropriate long-term care should reduce the need for emergency care.

For long-term treatment of asthmatic children, three categories of interventions can be distinguished, namely avoidance of triggers, medication and education. Optimal care as presented in guidelines combines medical and non-medical interventions, like inhaled medication, actions to avoid allergens in daily living and advice not to start (or to stop) smoking and to avoid passive smoking. The guidelines, however, give no information on how to allocate resources to categories of interventions. Costs made in one category may partly substitute costs made in another category. For instance, allergic asthmatics may be able to reduce their medication by taking sufficient action to avoid allergens.

Effectiveness of care, assessed in randomised clinical trials, is the main criterion for the guidelines. Direct references to costs are scarce. Furthermore, the guidelines are not specific in their advice at the level of individual treatments (for instance, they mention "inhaled corticosteroids", a general class of medication and not one specific steroid.).

In contrast to guidelines, cost-effectiveness studies mostly evaluate single interventions, for instance two types of medication. They often compare specific individual treatments (for example, salbutamol is compared to salmeterol).

Results from cost-effectiveness analyses may add to the advice in guidelines at two distinct points. First, general advices in the guidelines on specific interventions may be extended to include an explicit statement on the most cost-effective form of this intervention. That is, within a category of interventions, the most cost-effective specific treatment could be singled out. Second, cost-effectiveness results may help to determine the best allocation of a given resource budget over broad categories of interventions. For the latter, explicit data on costs and effects of the interventions are needed. This implies that only those cost-effectiveness studies can be used, which report on costs and effects separately. A cost-effectiveness ratio

only is not sufficient, because it does not inform on the amount of money that is needed for the intervention. Even a complete list of costs and effects for all interventions, moreover, is not sufficient to allocate resources. One reason is that different patients may need different combinations of interventions. That is, there are not only categories of interventions, but also groups of patients. Another reason is a possible 'synergy' effect: the costs and effects of one intervention may depend on what other interventions it is combined with.

As pointed out in the conclusions, an interesting subject for further research is whether knowledge about cost effectiveness, disease prevalence and the effects of interventions on severity can be combined in a model to determine the most efficient allocation of a given budget over categories of interventions and patient groups. The present report contains some of the components needed to build such a model. Results are: (1) a classification of interventions and cost-effectiveness studies of long-term care for asthmatic children, (2) a summary of 'standard' care as found in guidelines, and (3) a review of cost-effectiveness studies with the state of the art knowledge on costs and effects of interventions.

The report is divided into six sections. After the introduction in section 1, in section 2 interventions for asthma are categorised. Section 3 summarises and compares advices on long-term treatment laid down in four recent guidelines. Since the analysis is to apply to the Dutch situation, two recent Dutch guidelines were chosen, supplemented by an American and British guideline for comparison. Section 4 reviews cost-effectiveness studies. Section 5 is a summary of results and confronts the guidelines with results on cost effectiveness. Finally section 6 presents the most important conclusions.

From the comparison of cost-effectiveness studies with guidelines, it follows that there is not enough information on cost effectiveness to allow for conclusions on each category of interventions. Comparisons between allergen avoidance and other types of interventions require more knowledge on the costs and effects of allergen avoidance measures than is currently available. For medication, the advice in the guidelines and results from various cost-effectiveness studies seem to agree on the relative importance of anti-inflammatory therapy. For the use of long-acting bronchodilators, evidence of cost effectiveness is still lacking, while advice on this medication is included in guidelines. Studies on patient self-management programs provide evidence that, for some specific categories of patients, these interventions result in net cost savings. The Dutch guidelines only mention self-management as an option for severe asthmatics. This reflects more or less the available results from cost-effectiveness studies. However, for other groups of patients, cost-effectiveness results are not yet available.

1. Introduction

When available health care budgets are limited, the efficiency of medical interventions could be an important element for the optimal division of these budgets. An intervention is defined to be efficient when its costs are reasonable in view of its health effects (Ruwaard and Kramers 1997, part V, definition translated by the authors). Thus, the cheapest intervention is not necessarily the most efficient, since more expensive interventions may be more effective. Improvements in efficiency can be obtained in several ways. Obvious improvements are an increase in effectiveness at similar costs, and a reduction in costs at similar effectiveness. Efficiency also improves, however, if an increase in effectiveness is achieved at reasonably higher costs or if a decrease in costs results in acceptably lower effectiveness. (See also Drummond et al. 1997)

To stimulate effective medical care, an increasing number of medical guidelines and standards is published to advise those who provide medical care. The contents of these guidelines may be considered to reflect the 'standard' care as it was perceived at the time the guideline was formulated. Of course, guidelines may have different authors and target audience, with different perceptions of what entails 'standard' care. The guidelines' point of departure, which may be either consensus among specialists or evidence based, is another reason why the contents and definition of 'standard' care may differ between guidelines. While evidence based guidelines reflect the existing 'standard' and, strictly spoken, contain only interventions with proven effectiveness that has been reported in the literature, consensus based guidelines come closer to everyday medical reality and reflect 'best practice'. In the present report, it is assumed that recent guidelines are a good benchmark for the best care available. The aim of this study is to find out how knowledge about cost effectiveness relates to the advice in guidelines.

It is a relatively new phenomenon to pay attention to cost effectiveness in guidelines. This became for instance clear at the conference 'Scientific Basis of Health Services' in October 1997 and at the fifth Amsterdam Cochrane Colloquium. In the Netherlands, the Ministry of Health has initiated a special project to integrate cost effectiveness into guidelines in collaboration with all kind of organisations in the field.¹

Given the definition of efficiency above, the introduction of cost effective interventions will not always lead to cost reductions, in particular if under-treatment and under-diagnosis are part of medical practice. The application of guidelines based on effectiveness or consensus will neither guarantee a cost decrease. The health of the population may improve at increased costs.

This report is about long-term care for children with asthma. Asthma is chosen as an example, to study the possibilities for efficient budget allocation in chronic diseases. The report serves as a first step. It gathers information from guidelines and cost-effectiveness studies about what interventions are available and what is known about their effectiveness and efficiency. Furthermore, results from cost-effectiveness studies are confronted with the advice in guidelines to answer the question how knowledge about cost effectiveness might change guidelines.

The aim of this study is to examine the cost effectiveness of long-term care for children with asthma, as reflected in recent guidelines. An explicit goal is to cover the whole disease process, from secondary prevention (avoidance of trigger factors) through prophylactic

¹ The Dutch Association of General Practitioners (NHG), the institute of Medical Technology Assessment (iMTA, Rotterdam), the Dutch Cochrane Center, the CBO, RAND, WOK, and various professional associations of medical specialists ("Wetenschappelijke Verenigingen").

medication to treatment of symptoms. The report first summarises the current 'standard' care for asthma patients, as available to physicians in guidelines. This care is then confronted with results from cost-effectiveness studies.

Special to asthma is its episodic character and the possibility of (partial) remission. Other chronic diseases may also have an episodic character, or proceed more like a progressive disease or behave as a combination of both, with periodic exacerbation and partial recovery. The costs incurred in care for asthma patients make up a substantial part (about 2.5%) of the total costs of care for children aged 1 to 14 years (Polder et al. 1997).

To gather cost-effectiveness results, a search in the 'Medline', 'OHE' and 'Cochrane' databases was performed. In addition, various reviews gave useful information, among them an unpublished review by Schermer and van den Boom (1997). The chapter devoted to asthma and COPD in the Public Health Status and Forecasts (Ruwaard and Kramers 1997, part V, chapter 8) was based on this review.

For some interventions no cost-effectiveness studies were available. For these interventions, Cochrane reviews, if available, were used as a summary of results on clinical effectiveness. No separate searches for clinical trials were done. For details on the search strategy and selection of articles, see the separate section 'Literature search' at the end of the report. Since the study is about children with asthma, whose treatment differs from that of adults, studies with children as the study population were selected. However, if sufficient results were not available, some studies on adult populations were also included. If that was done, it is indicated.

Section 2 starts with a short description of asthma in children, followed by an overview of treatment possibilities for these patients. Section 3 contains a detailed comparison of four recent guidelines. In the concluding part of section 3, the most important differences between the guidelines as well as their common denominator are discussed. Section 4 reviews results from cost-effectiveness studies. In section 5 cost-effectiveness results are compared with guidelines. Section 6 contains a list of the report's main conclusions.

2. Care for children with asthma, a framework

2.1 Asthma in children

Asthma is defined as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role [...]. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.” (National Institutes of Health 1997, p3).

In the Netherlands, the prevalence rate of asthma for children aged 0-14 is about 20 for boys and 13 for girls (per 1000, standardised for the Dutch population, in 1994, based on general practitioner registrations). These children suffer from asthma in varying degrees of severity. Their treatment costs make up about 2.5% of the total health-care costs for this age group (Polder et al. 1997). For a more detailed analysis of the costs of care for asthma and COPD, see Rutten-van Mólken et al. (1998).

2.2 Elements of treatment

Medication is important for the treatment of asthma patients, but treatment is not confined to medication. It consists of a set of interventions, for diagnosis, for long-term treatment and for use in emergency procedures. Schermer and van den Boom (1997) identified 24 interventions for the prevention, cure and care of asthma and COPD currently used in the Netherlands. The reviewers did not include the interventions that are specific to diagnosis and to care for an acute exacerbation.

Interventions can be roughly divided into interventions for diagnosis, long-term care and emergency care. In most practice guidelines, all three aspects are addressed, although separate guidelines exist for emergency treatment. This report focuses on long-term treatment, that is, on interventions used in the day to day care for asthmatic children. It can be argued that emergency care is more or less a separate subject, since treatments differ and special guidelines exist. An increase in the budget available for diagnosis and long-term care or improvement of these treatment modalities may reduce the need for and hence the costs of acute treatment (Sullivan and Weiss 1993, Sullivan et al. 1996). The cost effectiveness of diagnostic tests depends on their sensitivity, specificity and predictive value. Guidelines often include a specific section on diagnostic issues. Space limitations are the main reason for leaving out results on diagnosis in this report. A correct diagnosis, obtained with the help of the right amount of tests, is important for efficient care. For asthma, under-diagnosis may be important and a proper diagnosis is sometimes difficult, especially in young children. It should therefore be kept in mind in the interpretation of the results that the diagnosis is assumed to be correct.

Long-term treatment interventions for asthma can be divided into three categories, namely interventions directed at the avoidance of trigger factors, interventions that involve the prescription of medication, and interventions related to patient education. Medication can be subdivided into anti-inflammatory treatment and symptom treatment.

Treatment as recommended in the guidelines consists of a combination of interventions from all three categories. A patient should receive help to avoid triggers, as well as long-term medication and education. Non-medication (trigger avoidance and education) and long-term

medication are not seen as mutually exclusive, but they are recommended in combination in the guidelines.

Guidelines usually confine themselves to advice on interventions that are directed at the patient. Guidelines do not, or hardly, address issues related to the organisation of the healthcare system or to interventions aiming at the general population.

To summarise, the following lists (Table 1, Table 2) group care for asthmatic children and name the various interventions in each group. These lists are based on information from the guidelines discussed below and on Schermer and van den Boom (1997). Table 1 gives some examples of interventions for several elements of asthma care. This table does not aim at completeness. In contrast, Table 2 gives a complete summary of interventions for long-term care. These are the topic of this report. Since it is meant to give an overview of existing interventions, not all the listed interventions are a part of the recommended treatments in the guidelines.

Table 1: Aspects of asthma care

<p>Interventions aimed at the general population</p> <ul style="list-style-type: none"> • Environmental regulation to reduce smog • Education to improve knowledge on asthma • Anti-smoking interventions
<p>Organisation of care</p> <ul style="list-style-type: none"> • Disease management programs • Education programs aimed at care givers • Guidelines • Type of provider: <ul style="list-style-type: none"> • Role of an asthma nurse • Outpatient versus inpatient care • General practitioner versus specialist • Role of physiotherapy
<p>Content of care</p> <ul style="list-style-type: none"> • Diagnosis • Care in case of an exacerbation (acute asthma) • Long-term care (see subdivision in Table 2)

Table 2: Further division of long-term care

Main categories of interventions
Avoidance of triggers Medication Education to patient and parents
Subdivision of each category
<p>1. Avoidance of triggers</p> <ul style="list-style-type: none"> • Smoke: active smoking (less relevant for young children), passive smoking • Vaccination: against influenza, other • Allergens (e.g. house-dust mite, pollen, animal dander, fungi) <ul style="list-style-type: none"> ▪ allergen immunotherapy ▪ mattress/pillow encasings ▪ acaricides and other chemicals ▪ adjusted cleaning ▪ adjustments in house (floor, ventilation) ▪ removal of pets ▪ adjustments at school, work • Other trigger factors (air pollution, fog, smells, etc.)
<p>2. Medication</p> <ul style="list-style-type: none"> • Anti-inflammatory treatment (prophylaxe) <ul style="list-style-type: none"> ▪ inhaled corticosteroids (beclomethasone, budesonide, fluticasone) ▪ oral steroids (prednisone, prednisolone) ▪ cromoglycic acid (cromolyn), nedocromil ▪ anti-histamines (ketotifen) • Symptom relief (bronchodilators, quick-relief medication) <ul style="list-style-type: none"> ▪ adrenergics (sympathicomimetics): short-acting beta2-agonists (inhaled or oral; fenoterol, rimiterol, salbutamol/albuterol, terbutaline, tetraquinol) ▪ adrenergics (sympaticomimetics): long-acting beta2-agonists (salmeterol, formoterol) ▪ other, less specific, adrenergics (efedrine, epinephrine, isoprenaline) ▪ (parasympatholytics), anticholinergics (ipratropium, deptropine) ▪ xanthines (theophylline) • Antibiotics
<p>3. Education of patients and their parents</p> <ul style="list-style-type: none"> • Education on correct use <ul style="list-style-type: none"> ▪ correct use of medication ▪ correct use of inhaler ▪ correct application of avoidance measures • Education aimed at compliance, with medication and/or trigger avoidance • Coping/psycho-social support programs • Self-management programs (often include education)

3. Guidelines

3.1 Description of guidelines

Four recent guidelines on asthma care are reviewed below. They are the American guidelines from the National Institute of Health (NIH), the British guidelines from the British Thoracic Society (BTS), the Dutch guidelines for general practitioners from the Dutch society of general practitioners, 'Nederlands Huisartsen Genootschap' (NHG), and the Dutch paediatric pneumonologists' guidelines, 'Richtlijnen van kinderlongartsen' (PP).² They were the result of a 'Medline' search. A description of the search strategy is given on page 55. The goal in selecting these guidelines was to cover Dutch guidelines and to use some representative foreign guidelines as comparison material. Guidelines differ considerably in the amount of details and background information they provide and hence also in length: the NIH-guideline is a book of more than 100 pages, while the paediatric pneumonologists' guideline covers six pages in a journal.

A structure comparable to that presented in Table 2 can be found in the NIH, the NHG and the pneumonologists' guidelines, and to some degree in the BTS guidelines.

All guidelines contain

- Advice for a proper diagnosis
- Advice on interventions to control asthma, that is, advice on long-term treatment:
 1. Interventions aimed at the avoidance of 'trigger' factors: viral infections, allergens, smoke or other irritants. Exposure to such factors may increase symptoms and worsen the underlying inflammation (see, for instance, NIH 1997). Interventions to avoid trigger factors are of a tertiary prevention type, since their aim is a reduction of the worsening of the disease by avoiding exacerbations and reducing the progress of inflammation in the lungs.
 2. Interventions with medications to reduce inflammation, so called prophylaxe, for example, treatment with inhaled corticosteroids. Interventions with medications that reduce symptoms, for example, treatment with bronchodilators.
 3. Education of patients and their parents on the proper use of medication, especially how to correctly use inhaled medication, on coping with their illness and sometimes on the adjustment of medication to their health state.
- Advice on interventions to be used for an acute exacerbation of asthma.

Treatment is intended to "Control symptoms, maintain lung function and allow normal life" (BTS), or the aim of treatment is that "Patients should obtain a near normal lung function, be able to normal activity levels, experience no symptoms and minimal or no adverse effects and exacerbations should be prevented" (NIH).

The following sections only discuss interventions for long-term care mentioned in the guidelines. Other interventions to improve the condition of asthmatics exist, some of these were mentioned in Table 1. The cost effectiveness of interventions aimed at changes in the organisation of care and the choice of care provider are discussed in section 4.5.

² References to these guidelines are: National Institutes of Health (1997), British Thoracic Society (1997), Dirksen et al. (1998) and Hoekstra (1997).

3.2 Comparison of guidelines: trigger avoidance

3.2.1 Introduction

Trigger avoidance is discussed in all four guidelines. It contains interventions related to allergy, to avoidance of non-specific irritants and non-smoking measures. Allergen-immunotherapy, which is a medical treatment that is related to allergen avoidance, is included in this section because it is also directed at the allergy component of asthma.

3.2.2 Interventions related to allergy

Atopy plays an important role in asthma in children: in a Finnish publication 80-90% of asthmatic children was reported to be allergic (Clinical and Experimental Allergy, 1996). For the Netherlands, allergy plays a role in 80% of asthmatic children (Dirksen et al. 1998). Hence, the majority of children with asthma is allergic to one or more agents. If a patient is sensitive to some allergen, the general advice in the guidelines is to avoid it as much as possible. However, not all asthma has an allergy component and not all allergic asthmatics have an allergy for the same agents. Of course, interventions to avoid certain allergens make sense only for those patients who are allergic to these allergens. Moreover, such interventions usually restrict patients in their behaviour (they should not have a cat in their house) or involve costs (for instance, the costs of special mattress encasings). Therefore, it is necessary to find out what agents a patient is allergic to. This explains why all guidelines advise some kind of allergy test in their diagnosis section. They differ in the type of test recommended and in the degree of detail. The four selected guidelines are compared for their recommendations on treatment related to the allergic component in asthma, that is, allergen avoidance and immunotherapy.

Allergen avoidance

All guidelines recommend physicians to advise their patients to avoid agents to which they are allergic as much as possible. Some moreover mention the preventive effect of allergen avoidance in young children with a high risk to develop asthma (those with a family history of atopy, eczema or rhinitis). It may be important to start allergen avoidance at a young age, to stop or prevent sensibilisation (See, for instance, Hoekstra 1997).

Avoidance measures mentioned in the guidelines include special bed covers, chemicals (acaricides) to kill house-dust mites, removal of pets, special cleaning regimes and covering the (bed) room floor with a hard surface.

The BTS explicitly recommends bed covers and removal of pets, but states that the effect of acaricides is unproven. The NHG advises to take no pets or remove them, to improve ventilation to reduce humidity, to use special mattress, cover and pillow encasings or to wash cover and pillow regularly at 60 degrees Celsius or more, to have a hard floor in the bedroom, and to clean the house with water twice or thrice a week. It says that the effect of additional vacuum cleaning is unproven. NHG also recommends that actions to be taken depend on the individual situation and on financial possibilities. The NIH guideline mentions removal of pets, use of mattress and possibly pillow encasings, weekly washing of sheets, blankets and pillow in hot water as essential actions. Other actions mentioned include reduction of indoor humidity, removal of bedroom carpets, removal of carpets on concrete, washing of stuffed toys, control of cockroaches, dehumidifiers and regular vacuuming of carpets. Use of chemical agents to kill mites is mentioned, but not recommended, since its effect is only small. The PP guideline includes reduction of indoor humidity, ventilation, and special encasings of mattress, pillow and cover.

In summary, mattress and pillow encasings and/or washing of bed-textile in hot water are recommended by all guidelines. Advice to reduce exposure to pets is also common. Opinions apparently differ on the usefulness of frequent vacuum cleaning. The NIH guideline contains the longest list of possible actions.

Allergen-immunotherapy

Allergen immunotherapy is treatment with low doses of a specific allergen over a long period of time to make the patient insensitive to that allergen. It lasts 3 to 5 years and has a risk of provoking exacerbations.

This therapy is mentioned in the NIH guideline only. It gives the following criteria for immunotherapy to be indicated: clear evidence of a relation between symptoms and exposure to unavoidable allergen, symptoms during major portion of the year, and difficulty to control symptoms with pharmacological management. It concludes that immunotherapy is not the first recommended treatment, since it lasts long, adverse reactions may occur and the therapy has therefore been received with different enthusiasm.

It may be concluded that allergen-immunotherapy is not a part of the standard treatment for asthmatic children. Reasons for this are the possible occurrence of serious adverse effects and the length of the treatment which implies high costs³ and requires a high degree of patient compliance. Immunotherapy may also be excluded from in the Dutch and British guidelines because of their target groups. General practitioners nor paediatric pneumonologists are the providers of immunotherapy.

3.2.3 Smoking related interventions

The evidence in the literature about active smoking as a possible risk factor for the development of asthma is mixed (Flodin et al. 1995). In asthma patients, smoking worsens symptoms and all guidelines advise to stop smoking. Interventions directed at active smoking are less relevant for children, although they may start to smoke at the early age of 12 or younger⁴. Interventions to reduce or prevent smoking are not discussed in this report.

With regard to passive smoking, all guidelines mention that smoking in the environment of asthmatic children is damaging. In the literature, evidence that the relative risk of maternal smoking for the incidence of asthma is slightly, but significantly larger than one, can be found (Zmirou, 1990). Based on a meta analysis of 14 cohort studies, DiFranza and Lew (1996) estimated the relative risk of parental smoking for the incidence of asthma to be 1.4. All guidelines advise parents of asthmatic children to stop smoking or at least to avoid smoking near the child.

3.2.4 Vaccination

Since viral infections can be an important trigger in children, vaccination against influenza is often recommended. The measure is advised in the PP and NHG guidelines for all children on inhaled corticosteroids, and the NIH guidelines recommends vaccination for patients with persistent asthma, but the BTS guidelines do not mention vaccination at all. Thus all guidelines except the BTS recommend vaccination for patients with moderate to severe asthma.

³ Here again a possible reference to costs and efficiency appears in the guidelines. However, most guidelines in this case do not mention these efficiency considerations explicitly.

⁴ About 5% of boys and 2% of girls aged 10-12 years were classified as regular smokers. That is, they had been smoking during the four weeks before they were surveyed. For these and other data on the prevalence of smoking in the Netherlands, see StiVoRo (1998).

3.2.5 Avoidance of other triggers

Many other trigger factors may exist for individual patients. Some common trigger factors for an asthma exacerbation are physical exercise (exercise induced asthma), emotional stress, and special weather circumstances like fog or cold air. Avoidance is clearly not always a feasible and desirable reaction. Physical exercise for instance is recommended in the guidelines. In case of exercise induced asthma, patients are advised to use an inhaled short-acting bronchodilator in advance.

3.3 Comparison of guidelines: medication

3.3.1 Introduction

Medication to control infection and symptoms is a major element in the long-term care for young asthma patients. There is reasonable agreement among the guidelines in their advice on medication. In each guideline, medical treatment advice is based on so called steps on the 'asthma-stairs', with increasing dosages of medication and severity of illness at each step. The borders between the steps, however, are not always clearly defined and their exact definition differs between guidelines. Furthermore, the BTS and NHG guidelines define severity operationally, through medication needed to stabilise a patient's condition, while the NIH and PP guidelines also give severity criteria based on the measurement of lung function and pre-treatment symptoms. The severity criteria are not consistently used; the NIH sometimes uses required medication to indicate the border between steps and the NHG uses symptom-based criteria.

The severity criteria based on medication are used below to distinguish severity steps, but for each step additional severity criteria based on symptoms are described. At each step, the differences between the guidelines are discussed. The NHG and PP guidelines distinguish three steps, versus the NIH four steps and the BTS five. The third and fourth step in the NIH and the last three steps in the BTS are discussed under step three.

3.3.2 Step 1: bronchodilators only

Definition

All guidelines distinguish a first step called mild intermittent asthma. Patients in this step need a bronchodilator on an 'as needed' basis to relieve symptoms, usually a short-acting beta2-agonist. They suffer from symptoms of asthma only intermittently.

Definition by symptoms

The NIH defines step one by symptoms no more than twice a week, brief exacerbations of varying intensity, asymptomatic between exacerbations and nighttime symptoms less than twice a month. It has the following lung-function criteria: FEV₁ or PEF larger than 80% of predicted value and PEF variability less than 20%. The NHG guideline is stricter and defines this step by symptoms no more than once a week, but the NHG does not include criteria based on nighttime symptoms or lung-function. The PP uses as criteria exacerbations less than once a month, regular periods without symptoms and PEF variability less than 20%. The BTS, as already mentioned, gives no symptom-based definition of severity steps.

Doses of medication

Dosages of beta2-agonist (for DPI or MDI⁵ with salbutamol (=albuterol)) given in the guidelines are:

- NHG: for children aged 4-7, 100-200 micrograms, 1 puff, with a maximum of four times a day. For children aged 7-12, 100-400 micrograms, 1 puff, at most four times a day.
- NIH: child dose (age unspecified) of 90 micrograms, 2 puffs, 'tid-qid prn' (that is, 2 to 4 times a day) by MDI or 200 micrograms by DPI, as needed.
- BTS: a dose as low as possible (not specified).
- PP: no doses mentioned.

Alternative treatments

As an alternative to beta2-agonists, the NIH-guideline mentions ipratropium, but prefers beta2-agonists. The NHG-guideline advocates beta2-agonists, because they act faster and have a stronger effect than ipratropium. The BTS and PP mention no alternative to beta2-agonists at this step.

Criteria to step up

A change to step two medication (which involves the use of inhaled corticosteroids or other prophylactic medication) is advised:

- In the NHG guidelines, if bronchodilators are needed more than twice a day during one to two weeks or if symptoms occur more than once a week.
- In the NIH guideline, if symptoms reoccur or bronchodilators are needed more than twice a week.
- In the BTS guideline, if bronchodilators are needed more than once a day.
- In the PP, if bronchodilators are used more than incidentally (is 2-3 times a week).

Conclusion

The guidelines differ in the criteria to step up as well as in the initial definition of the first step. Obviously there is some difference of opinion about the indication criteria for anti-inflammatory medication. The American guidelines prescribe anti-inflammatory medication rather quickly, while the NHG and British guidelines have criteria that are slightly more stringent. The Dutch PP guideline comes closer to the American guideline and indicates inhaled corticosteroids quickly, with the argument that lung function may be maintained if treatment starts early.

However, if patients are divided into steps according to symptoms, the American guidelines have more stringent criteria than the NHG, with more patients included in step one. This could explain why the American guidelines are quicker to advise a change to step two for patients included in step one.

3.3.3 Step 2: add prophylaxe

Definition

A second step of medication includes the regular use of prophylactic medication (anti-inflammatory medication) to reduce the underlying infection in the lungs of asthma patients in addition to the use of a bronchodilator. This step is called mild persistent (and sometimes moderate) asthma.

⁵ Dry Powder Inhalator or Metered Dose Inhalator, two different devices to inhale medication.

If control can be obtained at relatively low doses of anti-inflammatory medication, the NHG and BTS guidelines classify patients in this step.

Definition by symptoms

The NIH gives symptom and lung function severity criteria. These criteria are symptoms more than twice a week but less than daily, exacerbations that may affect activity, nightly symptoms more than twice a month, FEV₁ or PEF larger than 80% of predicted, and PEF variability from 20 to 30%.

In the NHG guidelines patients with symptoms more than once a week are classified in step two. The PP guideline classifies in step two patients with weekly to monthly exacerbations, regular symptoms and PEF variability of 20-30%.

Doses of medication

The prescribed daily dose of inhaled corticosteroids (in micrograms per day, for beclomethasone/budesonide, taken usually in two daily doses using MDI or DPI) is:

- NHG: 400 for children aged 4-7 and 7-12, taken in four or two separate doses, respectively.
- NIH: 100-200 for children of unspecified age.
- BTS: 200-800 for schoolchildren, half the dose for young schoolchildren.
- PP: 400-500 for children of all ages.

While for adults doses are more or less similar, the doses advised for children differ. The differences could reflect that the guidelines are not equally cautious of adverse effects at higher doses of corticosteroids in children.

Alternative treatments

All guidelines advise inhaled corticosteroids combined with bronchodilators on an as needed basis. As an alternative, cromolyn (or nedocromil) is advised, although with different enthusiasm. The NIH guidelines indicate that for children, cromolyn or nedocromil must be tried before corticosteroids are prescribed, with the argument that cromolyn (or nedocromil) is safer than inhaled corticosteroids. If it does not result in adequate reduction of symptoms, then inhaled corticosteroids are indicated. The NHG guidelines mention cromolyn as an alternative if inhaled corticosteroids cause adverse effects, for patients with allergic asthma. However, they argue that cromolyn has been proven ineffective in children younger than four years and that cromolyn is less effective than inhaled corticosteroids. The NHG says that nedocromil has not been shown to be more effective than cromolyn. BTS mentions cromolyn or nedocromil as an alternative, but recommends a change to inhaled steroids if control is not achieved. The PP is most radical and says that there is little room for other anti-inflammatory treatment than inhaled corticosteroids.

Another alternative mentioned in the NIH guidelines is theophylline. It is however not preferred, because it has a modest effect and is toxic in too large doses. According to the NIH, theophylline may be an option for patients who need tablet-form medication and when cheap medication is needed.⁶ The NHG discards theophylline, because of its small therapeutic range and because inhaled corticosteroids have been proven superior. Leukotriene modifiers, a new type of medicines, are not advised in the NHG because there is as yet not enough evidence of their effectiveness. The NIH mentions them as a possible alternative for patients with mild persistent asthma, but stresses that further study is needed. Other medications such as deproprine, ketotifen and acetylcysteine get the predicate "not recommended" in the NHG guidelines. Anti-biotics are only indicated in case of a proven

⁶ This is one of the few references to costs found in guidelines.

bacterial infection. Theophylline and ketotifen are discussed shortly in the PP, but not recommended.

Criteria to step up

A change to step three medication (a higher dose of inhaled corticosteroids and possibly additional medication) is indicated if:

- Control of asthma can't be achieved by a low dose of corticosteroids, compliance has been good and medication is inhaled in the right way, in the NHG.
- Short-acting bronchodilators are needed every day and control of symptoms is not achieved by a low dose of corticosteroids, in the NIH.
- The BTS is not clear on when change to step three is indicated, probably when control is not achieved in step two.
- Patients have exacerbations more than once a week, and daily use of beta-agonists and inhaled corticosteroids does not help to gain control, in the PP.

Conclusion

For this step, the only differences found between the guidelines concern alternatives to inhaled corticosteroids. The guidelines offer different advice on which alternatives to choose at what indication. The basic approach is rather similar.

3.3.4 Step 3: a higher dose of anti-inflammatory medication

Definition

This step is called severe persistent asthma in the NHG. The NIH distinguishes a fourth step of severe persistent asthma and calls step three moderately persistent. Step three in the NIH guidelines is characterised by higher doses of inhaled corticosteroids if necessary combined with other medication, dependent upon the patient's individual situation. The BTS distinguishes a fourth and fifth step. The PP guideline calls step three severe asthma and has no fourth step.

Definition by symptoms

The NIH symptom and lung-function criteria for step three are daily symptoms, exacerbations which may affect activity and may last days, exacerbations more than twice a week, nighttime symptoms more than once a week, FEV₁ or PEF between 60 and 80% of predicted value, and variation in PEF of more than 30%. The NHG gives no symptom criteria for this step. The PP mentions the following criteria: more than weekly exacerbations, daily symptoms and a PEF variability of more than 30%.

For step four, the NIH criteria are: continual symptoms, limited physical activity, frequent exacerbations, frequent nighttime symptoms, FEV₁ or PEF less than 60% of predicted value, and a PEF variability over 30%.

Reference

The Dutch guidelines recommend general practitioners to involve a specialist at this stage, and the NIH suggests involving a specialist at step three. NIH's step four is characterised by a regular use of systemic steroids and the recommendation to involve a specialist. BTS advise to refer children to a specialist when they use more than 800 micrograms budesonide or beclomethasone a day.

Doses of medication

The prescribed daily dose of inhaled corticosteroids is (in micrograms per day, for beclomethasone/budesonide, high and medium dose by DPI or MDI):

- NHG: exact dose not mentioned, but 400 microgram or higher.
- NIH: high more than 400, medium 200-400.
- BTS: high 800-2000, medium 200-800. Lower doses for young schoolchildren are not mentioned, but it is advised to refer children who need more than 800 microgram to a specialist.
- PP: no mention of dose.

At first sight, these dosages may seem different. In practice, however, differences may be less obvious. Since the NHG and NIH do not mention upper limits, the high doses in the BTS can also be prescribed under the NIH and NHG guidelines. Lower limits are similar. It seems that the British guidelines are less cautious than the NIH with regard to possible adverse effects of high doses of inhaled corticosteroids. The Dutch guideline directed at specialists (PP) does not specify doses. Dutch specialists also prescribe high doses of inhaled steroids. Sometimes young children need high doses due to inadequate inhalation techniques.⁷

Alternative treatments

The NHG and NIH guidelines present a low to medium dose of inhaled steroids combined with long-acting bronchodilators as an alternative to a medium to high doses of inhaled corticosteroids. The PP also includes the addition of long-acting beta-agonists as an option if inhaled corticosteroids have insufficient effect. However, it states that it has not been proven that this strategy is preferred to a high dose of inhaled steroids in children (as it is in adults). Other treatment options are not mentioned.

The NIH and BTS mention two more alternative treatments, that is, theophylline as a long-acting bronchodilator, and the combination of nedocromil (or cromolyn) with a medium dose of inhaled steroids. According to the NIH, these alternatives are not to be preferred.

Theophylline may have possible adverse effects and cromolyn has not been proven effective, compliance is problematic with three different medications, and total costs for a combination with inhaled steroids and beta2-agonists are high. The BTS says that either cromolyn or theophylline is an option for the small number of patients who experience side effects with high doses of inhaled steroids.

Criteria to 'step up'

If control is not obtained, medication should be adjusted on an individual basis. This may include oral steroids. The BTS guideline seems a bit more careful than the NIH guideline in prescribing oral steroids. For the BTS includes an additional step (step four) with advice on several alternative medications to try out before oral steroids are indicated. Thus, step four medication in the BTS is very similar to step three, but it involves a higher dose of inhaled steroids, which can be combined with one or more from a large range of medicines. These may be long acting beta2-agonists, possibly in tablet form, theophylline, inhaled ipratropium, a high dose of inhaled bronchodilators, cromolyn, or nedocromil. Step four medication in the NIH involves oral steroids together with long acting bronchodilators and a high dose of inhaled steroids.

The reason that these options are not mentioned in the NHG guidelines is probably that at this point treatment by a specialist seems more appropriate than treatment by a general practitioner. Step five in the BTS guideline is similar to step four in the NIH guideline.

⁷ We are grateful to Dr. E.E.M. van Essen-Zandvliet for information on this point.

Conclusion

For treatment of severe forms of asthma, all guidelines recommend high doses of inhaled steroids as the primary medication. They differ, however, in the alternatives to a high dose of inhaled steroids and in the indication criteria for prescribing oral steroids.

3.3.5 Adjustment of medication

An interesting difference between the guidelines concerns the advice on the adjustment of medication for an individual patient. There are two ways to do this: to start with high doses and to step down ‘the asthma stairs’ or to start with low doses and to step up. The NHG guideline advises to step up if control cannot be reached with medication of lower steps and once control has been obtained to adjust doses to the lowest possible dose. In contrast, the BTS, PP and NIH-guideline advise to start medication at relatively high doses, to gain control as soon as possible, and then to step down.

3.4 Comparison of guidelines: education

3.4.1 Introduction

Apart from education related to the allergic component of asthma (advice to avoid allergens and how to do this), all kind of patient education interventions exist. Examples are: education of patients to improve compliance, education about the correct use of medication, and self-management programs. Education programs for children are often combined with programs for their parents.

The most intensive program, lung rehabilitation, is not just an education program. It focuses on physical exercise to improve patients’ condition. This type of programs has mainly been developed for COPD patients. However, for children with severe asthma who experience important problems despite optimal treatment special inpatient treatment programs in the Dutch “Astmacentra” (specialised hospitals for asthma and COPD patients) exist. The NHG guidelines recommend these programs for these patient group, but only after a specialist has confirmed the indication. The PP guidelines do not mention them. The British and American guidelines pay little attention to this type of programs or the role of exercise. They include the recommendation for patients to do sports in order to improve their general condition. This recommendation can also be found in the Dutch guidelines. Exercise induced asthma and its treatment are discussed in all four guidelines.

3.4.2 Self-management

Self-management programs usually are a combination of education and ‘self-treatment’. The self-treatment element means that patients get guidance for the adjustment of their medication to changes in their symptoms. That is, self-management programs could be said to include education in a kind of ‘patient-guidelines’. Through a timely increase of medication at the start of an exacerbation, severe exacerbations may be prevented. Furthermore, patients may feel more in control of and responsible for their own treatment, which may improve compliance.

Since most education programs contain elements of self-management, it is sometimes difficult to make a clear distinction between education and self-treatment. There exist education programs that just inform patients on their illness, but that leave the responsibility to adjust medication entirely to the medical professional. An examples of such a ‘pure’

education program is found in evaluations of special asthma nurses in inner-city areas in the United States (Clark et al. 1986; GRASSIC 1994; Neri et al. 1996).

The BTS guideline pays special attention to education and self-management. Written self-treatment plans are recommended, especially for patients with step three and higher medication. As stated in the guideline, self-management programs have been proven to reduce morbidity and health costs, although it remains an area for further research. Open questions are the best form of self-treatment plans and the indication criteria for self-management. According to the BTS, plans should be symptom-based in young schoolchildren and may be PEF-based in older children and adults.

The NIH guideline is very elaborate on education (as it is in general) and includes it as the fourth component in its asthma management recommendations under the name "Education for a partnership in asthma care". Self-management and a written self-management plan based on PEF and symptoms are recommended for all patients.

The NHG guideline pays some attention to education and to self-management. Self-management is considered an option for those children and parents who can cope adequately with the disease and with medication. The guideline mentions that the usefulness of self-management programs for all patients has not been sufficiently proven, but that it may be useful for patients with severe asthma. The PP guideline stresses that the effect of self-management on morbidity is small, and that programs are still subject of research. This guideline does not give any recommendation related to self-management except the recommendation that children with severe and highly variable asthma should use a peak flow meter.

Conclusion

It is clear that the guidelines differ in their attitude towards self-management and in the assessment of the evidence on its effectiveness. The two Dutch guidelines are less favourable than the other two and focus on the lack of evidence, especially for children who are treated by their general practitioner⁸. One reason for a lack of convincing evidence may be that some trials used patients that were sub-optimally treated before the start of the self-management trial. In case of significant results, it is unclear whether the success is due to the self-management program, or to a better general treatment during the trial period. From 1991 onwards, a Dutch self-management program for children aged 8 to 13 years has been distributed (Colland, 1993). The distribution followed on the positive outcome of a trial among children treated for their asthma by paediatricians. Patients were selected because of their insufficient self-management capabilities and then asked for consent and randomized. The trial demonstrated that self-management was effective for patients with insufficient self-management capabilities, treated by a paediatrician. This trial is not mentioned in the guidelines. The distribution of the program seems to be out of line with the current, more cautious, advice given in the Dutch guidelines.⁹

3.5 Conclusion

To conclude the section on guidelines, first the differences found between the guidelines are summarised. Since these differences are relatively small, a common denominator advice can be deducted. Thus, based on points of similarity between the guidelines, a kind of standard treatment advice is formulated.

⁸ That is, the majority of less severe asthma patients.

⁹ The useful remarks on the subject of self-management by E.E.M. van Essen-Zandvliet and J. van der Palen are gratefully acknowledged.

The most important differences between the guidelines concern:

- The indication criteria for inhaled corticosteroids.
- The importance attached to cromolyn as an alternative anti-inflammatory treatment.
- The attention for old or very new medications like theophylline and leukotrienen.
- The degree of elaboration on interventions other than medication.

However, there is enough similarity among the guidelines to find a 'common denominator standard for asthma treatment', based on their recommendations and some (maybe rather arbitrary) choices. This 'common denominator treatment' is presented below. It involves trigger avoidance, medication, education, non-smoking advice to parents, and vaccination of patients with persistent asthma:

- Patients are tested on allergy. If a patient is allergic to house-dust-mite, mattress encasings are indicated. Pillow and bed cover should also be encased or washed weekly in hot water. Patients who are allergic to animal dander, are advised to keep no pets. Other interventions, such as ventilation, low humidity, a hard bedroom floor, special cleaning and removal of pets from schools and day-care centers are mentioned less commonly.
- Medication is adjusted to the severity of asthma, on the basis of steps.
 1. Step one is mild intermittent asthma. The treatment is a beta2-agonist 'as needed'. This step is characterised by symptom-free periods in between not too frequent exacerbations. Change to step two medication is indicated if bronchodilators are needed daily (more than 2-3 times a week).
 2. Step two is moderate asthma. The treatment consists of the daily use of inhaled corticosteroids and use of a beta2-agonist 'as needed'. The dose of steroids should be just high enough to keep the asthma under control and this is a relatively low dose. Change to step three is indicated if control of asthma is not obtained, that is, if bronchodilators are needed daily.
 3. Step three is moderate to severe asthma. The treatment is a higher dose of inhaled corticosteroids combined with a short acting beta2-agonist 'as needed'. The dose of inhaled steroids is as low as possible, but may vary depending on the needs of the patient. If control is not obtained, that is severe symptoms are experienced daily, with frequent exacerbations, the change to step four is indicated.
 4. Step four is severe asthma. The treatment indicated is the same as in step three plus a regular dose of oral steroids. The required dose should be adjusted to the individual patient.

At step two, cromolyn is a possible alternative, although cromolyn is not recommended as such by the two Dutch guidelines. At step three, a medium dose of inhaled corticosteroids combined with a long-acting beta2-agonist is an alternative.

- The right medication dose for an individual patient should be found through either a step down or step up approach. According to the majority of the guidelines, stepping down is to be preferred.
- Self-management programs are an option. Patients with severe asthma receive education on self-management. Other patients are educated on their disease. The opinion on self-management programs for these groups is mixed, so here a common denominator advice cannot be formulated.
- Patients who are in step two or higher are vaccinated for influenza.
- Parents are advised to avoid smoking in the child's environment as much as possible.
- The inhalation device of preference is an MDI for children up to 7 years of age and a DPI for older children.

4. Cost-effectiveness studies

4.1 Introduction

This section summarises results from cost-effectiveness studies for the interventions discussed above. Cost-effectiveness analyses of medical interventions were introduced in the Seventies. From then on it became more common to evaluate the cost effectiveness of new interventions. In several countries, an economic evaluation is mandatory for new medicines to be reimbursed by the state medical fund (for instance in Australia, Drummond et al. 1997). Thus, it is not difficult to find cost-effectiveness studies of relatively new interventions and especially of medication. It is much more difficult to find such studies of older medicines or non-medication interventions. By definition, an intervention that is not effective can not be cost effective either. It follows that cost-effectiveness studies are only useful for interventions that have been shown to be effective. This implies that effectiveness cannot be determined on the basis of a review of cost-effectiveness studies, as it would result in a bias towards effectiveness. See also the conclusions in section 4.4, where effectiveness studies show self-management to be less effective than might be concluded from cost-effectiveness studies. Cost-effectiveness studies in asthma care compare interventions at different levels of detail. An analysis could be highly specific and compare two medical agents with the same function (for instance fluticasone versus budesonide) or it could be more general and for instance compare allergen avoidance with doing nothing. We distinguish three types of cost-effectiveness analyses, two different types of analyses of interventions for long-term treatment and a third type of studies on other types of interventions.

These are:

1. Studies which compare treatments from different categories of long-term care or which compare a particular treatment with a placebo or doing nothing. Referring to Table 2, examples of such treatments are anti-smoking interventions, allergy avoidance and anti-inflammatory medication. Examples of comparisons are prophylaxe plus bronchodilators versus bronchodilator monotherapy, evaluations of education programs versus no such programs and evaluations of allergen immunotherapy versus placebo. Since they are from different categories, treatments can also be combined.
2. Studies which compare alternative variants of a particular treatment. Here a combination of the alternatives is less reasonable, since they belong to the same category. Examples of comparisons are cromolyn versus inhaled steroids, or high doses versus low doses of inhaled steroids. In turn, more detailed studies compare different variants of the same alternative. For instance, they compare different brands of inhaled steroids (fluticasone versus budesonide) or various types of metered dose inhalers.
3. Economic evaluations of interventions in the organisation of care. This involves analyses of the way asthma care is organised and treatment is provided in practice.

Studies of the first type and most studies of the second type provide useful information for the inclusion of cost-effectiveness considerations in guidelines for asthma care. Since the current guidelines do not give specific advice on the choice between different types of the same medication (for instance fluticasone or budesonide), some studies of the second type may seem too detailed to be of immediate use. Such detailed studies might be used to extend the guidelines with more specific advice on the most cost-effective variant of a specific treatment. Studies of the third type provide useful information for a more efficient asthma care. They are, however, more difficult to include in guidelines aiming at specific professional groups.

It is obvious that a larger increase in efficiency can be obtained if the differences between alternatives are large than if there are only small differences in costs and effects. However, since asthma medication is taken by a relatively large group of patients, even small differences may lead to substantial efficiency gains.¹⁰

In the following sections, cost-effectiveness studies of the first two types will be discussed for each of the three categories of long-term asthma care: trigger avoidance, medication and education. In section 4.5 studies of the third type, concerning the organisation of care, are discussed. Since guidelines for the treatment of children are the subject of this report, only where results on children are completely lacking, results from studies in adults are included. Studies on the choice of inhalation device are not discussed in this review.

Many studies, especially studies on self-management programs or organisational measures, report on the ratio of the costs of the intervention to the benefits in terms of costs saved through a reduction in other medical treatments, such as hospital and emergency care. They call it a cost-benefit ratio. Such a ratio provides only an incomplete measure of the cost effectiveness of a certain intervention. It fails to include effects on the health of patients that are not related to medical costs, for instance an increase in symptom-free days. Moreover, effects related to medical costs are only measured in terms of costs, not of health effects. Sometimes these studies are called cost-benefit studies. Given their incompleteness with regard to benefits, this is not quite correct.

Another drawback of the ratio mentioned above is that it can only be interpreted if the intervention is compared to "care as usual" (That is, the type of care that is most commonly provided for the patient group studied). Then, in a marginal cost-benefit ratio of this type, 'costs' are the additional costs related to the intervention, while 'benefits' are the reductions in other medical costs, if any. For other types of comparisons, or for average cost-benefit ratios, it is unclear what to include under costs and what under benefits. It seems to be an arbitrary choice whether to include certain cost-reductions due to an intervention in the benefits or, in the form of lower costs, in the costs. However, this choice affects the cost-benefit ratio. Finally, if both factors of the ratio are expressed in monetary units, net costs (or benefits) can be computed. Net costs do not change if a certain element is interpreted as a cost increase instead of a benefit decrease and should therefore be preferred to a ratio.

It is more informative to find an explanation of the methods used to compute a cost-effectiveness measure and to know the value costs and effects separately, than to get just a single, sometimes arbitrary, measure of cost effectiveness. If possible, the separate values of costs and benefits are given for the studies reviewed.

Some studies also report costs per additional symptom-free day or related measures. These studies are the only full cost-effectiveness studies, as they also provide information on the health effects of interventions. Cost-effectiveness results are given whenever these were found in the study. As will become clear, there is no uniformly applied outcome measure for health effects in asthma patients.

4.2 Avoidance of trigger factors

4.2.1 Allergen avoidance

Introduction

Asthma patients can be allergic to a variety of substances. Not all of them can be avoided easily. For cost-effectiveness studies, it is important to note that the costs of allergen

¹⁰ In the Netherlands, two of the 1997 top ten in medication (ranked according to total costs) were respiratory medicines prescribed for asthma and COPD (Foundation for Pharmaceutical Statistics, 1998).

avoidance are largely born by patients themselves and may or may not be covered by insurance. This is in contrast to most other interventions, where costs occur mainly in the medical sector and may or may not be passed on to patients.

In a review of clinical studies, Schermer and van den Boom (1997) mention that there seems to be proof for a positive effect of several interventions, based on a number of randomised controlled trials. Outcome studies, with results from medical practice, were not available. A recent Cochrane review (Hammarquist et al. 1998) finds that neither chemical or physical measures, nor combinations of the two have been proven effective. This conclusion is based on a meta analysis of 23 trials among in total 230 patients of all ages. Six of these studies assessed chemical methods, thirteen physical methods and four a combination. After a discussion of several reasons for the lack of effect, three potential explanations are put forward. First, the avoidance measures may not have worked and did not reduce mite allergen levels substantially. Second, reduced mite allergen levels may have no effect on asthma. Third, patients may not have been compliant with the avoidance measures. The authors conclude that it is unlikely for mite eradication to have no effect, because mite allergen is the allergen to which asthmatics are most frequently allergic and its acute effects are well established. Hence, the conclusion of this review is that the hypothesis has not been tested with sufficient rigour. According to the authors, the most plausible explanation for the lack of effect is that the tested interventions did not remove mite allergen sufficiently. They recommend for new studies a careful design including a sufficiently large sample size and monitoring of mite exposure.

Two trials with large numbers of children and a long period of follow up are currently undertaken in the Netherlands. One of them assesses the effectiveness of mattress encasings and the other the effectiveness of a combined program of allergen avoidance and a special diet. Both are targeted at children who are considered at risk for asthma because of parent characteristics. These studies differ from the studies included in the meta analysis. The studies in the meta analysis consider the effect of allergen avoidance on patients who already have asthma, while the two new trials assess the effect on the incidence of asthma as well as on the course of disease.

Compliance

Compliance can be a problem in allergen avoidance. Schermer and van den Boom (1997) refer to the results of a Dutch study among 222 adult asthma patients, allergic to house-dust mite, of whom only 0.9 % had mattress encasings, and 34% had changed the floor cover in the bedroom. Less than 20% of parents of asthmatic children had adapted the mattress to reduce allergen exposure.

Relevant comparisons

Studies on allergen avoidance usually involve the comparison of a specific intervention such as mattress encasings to no such a measure, keeping other asthma treatments constant. Cost-effectiveness studies on this issue are scarce. Schermer and van den Boom (1997) did not report any economic evaluations of allergen avoidance in the literature until mid 1996. A new search in 'Medline', 'OHE' and 'Online Contents' for more recent publications resulted in no relevant studies involving children. Since no studies were found, we also tried to look for studies among adult patients, with the same disappointing result.

Results

- A Cochrane review (Hammarquist et al. 1998) found that none of the allergen avoidance interventions included in its meta analysis can be considered effective. Therefore, these interventions can neither be cost effective.

- Westley et al. (1997) analysed the cost effectiveness of an allergy consultation for patients of all ages. The introduction of such a consultation for severe asthma patients led to a decrease in medical consumption. A problem with this study is that it is not clearly described what the consultation entailed (a combination of identification of triggers, individual avoidance plans and medication advice) nor what costs were involved. Hence, generalisation of its results is not possible.

Conclusion

No studies are available about the cost effectiveness of allergen avoidance. From the results in Hammarquist et al. (1998) it follows that there is insufficient evidence that chemical, physical or combined measures are effective. The reviewers conclude that the most plausible explanation for the lack of evidence in their meta analysis is that mite exposure was not effectively reduced in the trials. They recommend larger studies with mite exposure monitoring and a careful design.

If interventions are not effective, they can neither be cost effective. Cost-effectiveness studies only make sense, when the effectiveness of allergen avoidance measures has been proven.

In practice, compliance is a problem. Given the current advice in the guidelines, the compliance to avoidance measures among Dutch asthmatic patients is rather low (See Schermer and van den Boom (1997) and the references therein.).

4.2.2 Allergen-immunotherapy

Good cost-effectiveness studies on allergen-immunotherapy for asthma patients were not found. Hence, the cost effectiveness of immunotherapy is uncertain. A Cochrane review (Abramson et al. 1998) summarises the results of studies on the efficacy of the therapy. It includes a meta-analysis of 54 randomised-controlled trials among patients of all ages. The conclusion is that immunotherapy leads to a significant overall improvement in asthma symptom scores. According to the reviewers, the studies were insufficient on the following points: the effectiveness of immunotherapy in comparison with other therapies, the difference in effectiveness among patients who were during the immunotherapy treated with inhaled corticosteroids versus among those who were not and the cost effectiveness of immunotherapy. It can be concluded that cost-effectiveness studies of this intervention would be useful.

4.2.3 Vaccination

Vaccination is an intervention used to avoid the effects of exposure to influenza and other viruses. Viral infections are an important trigger factor for exacerbations, especially in children.

Cost-effectiveness studies on vaccination of asthma patients could not be found, even if studies among adult asthma patients were included.

- Neijens et al. (1997) set out to gather data on the degree of vaccination among children with lung diseases in the Netherlands. Telephone interviews revealed that 56% of lung patients (for a broad category of lung diseases) were vaccinated. This percentage is increasing over time and concerns patients of all ages. No specific data for children could be found.
- A Cochrane study (Cates, Jefferson and Al 1998) reviews nine randomised trials of influenza vaccination for asthma patients. The trials involved different patient groups, adults or children, with varying severity of asthma. Three trials were targeted at children. The conclusion of the review is that there is little evidence that supports influenza vaccination in asthmatic patients. The proportion of patients with the risk of influenza in

one season may be small and many other viruses exist that can cause an exacerbation. This may explain why there was so little evidence of a protective effect of influenza vaccination in the trials. The authors recommend randomised controlled trials with a large number of patients to further assess the effectiveness of influenza vaccination.

4.3 Medication

4.3.1 Relevant comparisons

Relatively many comparisons of the cost effectiveness of different types of medication were found in the literature. Therefore, we mostly limited ourselves to studies among children. However, as section 4.3.3 shows, some studies involving other patient groups were also included. This was done if the type of comparison considered by the studies was interesting and no comparable studies could be found with children as the patient group. The conclusions in section 3.5 on guidelines indicate that the following comparisons, in order of increasing detail, seem particularly interesting. First, analyses should be considered about the border between steps of treatment. That is, analyses of the comparison of treatment with a bronchodilator versus no medication (step 1 versus nothing) as well as the comparison of step 2 treatment to step 1 treatment. In theory, similar studies could be set up for step 3 and higher treatments, but these have not been found. The comparison of step 1 with step 2 involves either the comparison of bronchodilators plus placebo with bronchodilators and inhaled steroids or the comparison of cromolyn with placebo treatment. These studies compare two interventions from different categories (as they were listed in Table 2), and therefore they belong to the first type of cost-effectiveness studies discussed earlier. Second, interesting analyses are comparisons of alternative medicines for a single step, namely, the comparison of cromolyn and inhaled steroids, long- and short-acting bronchodilators, and inhaled steroids only versus theophylline and steroids. These belong to the second type of cost-effectiveness studies, since they compare alternatives for a particular intervention. The third type of studies involves the relative cost effectiveness of the various types or brands of one specific medication. Examples are the comparison of several short-acting bronchodilators or inhaled corticosteroids, the comparison of cromolyn and nedocromil, and the comparison of inhalation devices.

4.3.2 First type of cost-effectiveness studies, treatment steps

- A Dutch cost-effectiveness study (Rutten-van Mólken et al. 1993) compares the daily use of inhaled corticosteroids plus a beta2-agonist to the daily use of a beta2-agonist only for children aged 7 to 16. That is, it compares a step 1 with a step 2 treatment. A number of marginal cost-effectiveness ratios are given for several outcome measures. A conservative estimate of the additional costs of inhaled corticosteroids are 7,20 Dutch Guilder per additional symptom-free day (in 1989 prices). Per patient year, the intervention results in 38 extra symptom-free days. With a less conservative estimate of costs, the addition of inhaled corticosteroids is dominant, because the additional drug costs of Dutch Guilder 480,- are more than compensated by a reduction in other costs of Dutch Guilder 670,- per patient.
- A British study compares inhaled corticosteroids (budesonide) to a placebo in children aged 1 to 3 years with severe asthma (Connett et al. 1993). Other medication was a bronchodilator (terbutaline) as needed. The follow-up period was 6 months. Costs per patient year are significantly lower and the amount of symptom-free days significantly higher in the budesonide group than in the placebo group, namely 1398 versus 1891

pounds and 195 versus 117 days. There are no additional costs per additional symptom-free day, but only benefits, both in terms of money and in terms of health effects. Costs in this study include indirect costs for parents' absence from work and children's' absence from playgroup. They were measured in 1991 and 1992. If only direct, medical, costs are taken into account, costs are 1114 versus 1414 pounds.

- A retrospective Swedish study (Gerdtham et al. 1996) analyses empirical data on the medical consumption of asthma patients of all ages. This study uses regression analysis to test the hypothesis that increased use of inhaled steroids leads to a decrease in the need for hospital care for asthmatics. Dependent variable is hospital days, independent variables are defined daily doses (DDD's)¹¹ of inhaled corticosteroids, use of bronchodilators as a proxy for prevalence, and general bed days in hospital as a proxy for general developments in hospital care. A significant correlation was found between inhaled steroids and hospital bed-days. Assuming that there is also a causal relation, this leads to the ratio of 1 additional DDD per year per 1000 persons causing 1.49 less hospital bed days per year per 1000 persons. Using Swedish costs (in prices of 1991), treatment costs for inhaled steroids of 2620 Swedish Crones per 1000 persons reduced hospital costs with 3940 Swedish Crones per 1000 persons. The net costs of the introduction of inhaled steroids are therefore -1.314 Swedish Crones per person, with only costs of inhaled steroids and hospital costs taken into account.

4.3.3 Second type of cost-effectiveness studies, alternative medications for treatment of patients in a given step

This type of studies is often carried out in combination with new drug trials. This may explain why most of them have rather short follow-up periods and involve adult patients. Shorter follow-up periods may be sufficient to establish the effectiveness in terms of certain clinical end-points. It can be expected that new medication is first applied to adults before being considered for application in children.

- Peters and Faulds (1995) give an overview of quality of life measures for asthma and the effect of salmeterol on quality of life and costs. One of the cost-effectiveness studies, discussed in the overview, found that the cost effectiveness of salmeterol compared to salbutamol varies with the outcome measure. This study was based on a 7.5 months trial conducted in the UK, among patients of unspecified age. The original reference was only available as an abstract (Hall et al. 1992). Peters reports mean total costs (that is costs of study drugs relief medication and consultation of primary and secondary care) per symptom-free patient of 405 and 523 English Pounds for salbutamol and salmeterol, respectively. However, if costs per patient with an improvement in morning PEFr were computed, salbutamol costs 1350 and salmeterol 876 Pounds. Incremental cost-effectiveness ratios for salmeterol compared to salbutamol reported are 736 Pounds per symptom-free patient in the last week and 648 Pounds per patient with improved morning PEFr. Since there is only an abstract of the original study, it is difficult to check its quality which renders the results less useful. For instance, it is unclear in what year prices were measured. The same holds for another study referred to in Peters. Moreover, the summary of that study does not allow clear interpretation of results. Therefore, its results are not reported here.
- Booth et al. (1996) compare the cost effectiveness of 80 mgs cromolyn per day with that of 100 mcgs corticosteroids (fluticasone) in UK children aged 4 to 12 years with

¹¹ For adults, one defined daily dose of inhaled steroids equals 800 mcg budesonide or beclomethasone and 600 mcg fluticasone per day (See WHO Collaborating Centre for drugs statistics, 1997).

moderate asthma. It is found that inhaled steroids are more cost effective, since they are cheaper and result in more successfully treated patients. This study has a rather short follow-up period of 8 weeks. Reported costs include only the study drug and the medication used for reduction of symptoms (salbutamol, to be taken as needed). Average medication costs per patient during those 8 weeks are (in 1995 English Pounds) 18.06 and 32.40 for inhaled steroids and cromolyn, respectively, including the costs of a bronchodilator. The inhaled steroid group used on average 41 doses of this bronchodilator, while the cromolyn group used 58 doses. As an outcome measure, the proportion of successfully treated patients is used, that is the proportion of patients with a symptom score below a given limit in the last three study weeks. Successful treatment proportions were between 70 and 80 percent and between 43 and 65 percent. Therefore, inhaled steroids are both cheaper and more effective.

4.3.4 Conclusion

It is a pity that the study on cromolyn has a short follow-up time. Given the difference between guidelines, its results in case of longer follow-up time would be interesting. At the moment, there are too few results to allow a conclusion about cromolyn as an alternative to inhaled steroids.

A comparison of long-acting bronchodilators combined with a moderate dose of inhaled steroids versus high doses of inhaled steroids is missing. Clinical trials are available, both for adults and for children. Our choice was, however, to include only systematic reviews of clinical trials, so that these will not be discussed here. No cost-effectiveness results for children were found.

Sufficient results exist to conclude that a combination of inhaled bronchodilators and inhaled steroids is more cost effective than a combination of inhaled bronchodilators and placebo for the indicated patients (See Rutten-van Mólken et al. 1993, Connett et al. 1993 and Gerdtham et al. 1996). This confirms what is said about inhaled steroids in most guidelines, though Connett's results apply to a different patient group, namely children aged 1-3 years.

4.4 Education and self-management

4.4.1 Relevant comparisons

Several cost-effectiveness studies on education and self-management programs for asthmatics exist. Since non-compliance as well as underuse of medication due to a wrong inhalation technique may be important factors in asthma, such programs, which aim to improve patients' knowledge and compliance, are potentially cost-effective interventions. According to one literature review, nonadherence among asthmatic patients of all ages varied from 30% to 70% (Bender et al. 1997). This study also mentions a review of 10 paediatric asthma adherence studies, which found that medication adherence averaged 48%.

In education and self-management, it is important to distinguish between programs directed at adults and at children. Cost-effectiveness analyses mostly compare care as usual with and without a self-management program. It is hard to think of a placebo-controlled design for this case, so that the control is a care-as-usual program. (One study has a program of lectures rather than a more elaborate small-group education program as the control).

Part of most programs is the optimisation of medication with the aid of a physician before the self-management program starts. Strictly speaking, such programs contain two different but entangled interventions, optimisation of medication and the self-management program. For the assessment of the contribution of each of them, the effect of better medication should be evaluated separately. In section 3.4, education was divided into self-management programs

and 'pure' education programs. These could be compared in their cost effectiveness. The relative cost effectiveness of programs of varying content and length is also interesting. Such studies should help to identify the most cost-effective self-management or education program. This also points to a complicating factor in establishing the cost effectiveness of education programs. Often, the program is a mix of several interventions. This implies that it is difficult to find out what elements are responsible for what favourable effects and what elements can be dispensed with. Finally, one study evaluates a lung rehabilitation like program with exercise and education (Weinstein 1996).

4.4.2 Reviews of clinical trials

Schermer and van den Boom (1997) discuss a number of trials and reviews of trials on education programs for children. They find mixed evidence on self-management. Furthermore, they point to a number of problems that self-management programs might have to deal with in the Netherlands: Indication criteria are not clear. There may be insufficient resources to implement the programs, especially in some regions. Medical professionals do not always comply with the program (they often fail to provide patients with the complete program). Finally, adolescents may be hard to reach. The conclusion in Schermer and van den Boom is that some gain in health can be obtained for children with severe asthma. Consultation of the Cochrane database resulted in three reviews on self-management. One was a review of self-management and teaching programs related to the morbidity of paediatric asthma (Bernard-Bonnin et al. 1995). It reviews studies until 1991. The other two reviews contain more recent studies, but apply to adults. They contain self-management and more limited education programs, respectively (Gibson et al. 1997; Gibson et al. 1998). The reviews find a significant effect of rather elaborate self-management programs and no significant effect of restricted education programs without elements of self-management or regular review. A fourth recent review (Van der Palen et al. 1998) compared 15 studies of self-management programs for adults that included self-treatment guidelines. It found that the available evidence on effectiveness is far from complete.

4.4.3 Cost-effectiveness analyses

We found sufficient studies among children for our review. Most studies compare the costs of medical consumption with and without a self-management program. Together with the costs of the program this allows the computation of a kind of "cost-benefit" ratio, where only the benefits in terms of reduced medical consumption are taken into account. More complete cost-effectiveness studies, that also take non-monetary effects on health into account were not found for children.

- The study by Clark et al. (1986) compares education with no education. The intervention studied consisted of 6 hours of group-education for parents and children aged 4 to 17 years. The patients were children visiting an asthma clinic. Significant effects were found only for those who were admitted to hospital the year before. For this specific patient group, the net costs of the intervention were minus \$16000, (costs of \$1600 and savings of \$17500, in "before 1986" US Dollars¹²) on the assumption that the costs per patient to provide education would not change if only this group was addressed. For the whole study group, net costs were positive, since the intervention did not have a significant effect on health-care use. Medication, the costs of which may change with a self-management program, was not measured.

¹² The exact year is not mentioned.

- Lewis et al. (1984) compare two modes of education for children, aged 7-12, and their parents. The experimental group received 5 hours of education in small groups, while the control group received 4.5 hours of education in a large group lecture. The experimental group obtained significantly better results than the control group for effects on 'trouble with asthma', in self-reported compliance, in number of emergency room visits and in number of days in hospital. For some other effect measures, results did not differ significantly between experimental and control group. The authors report a comparison of the costs of treatment (in "before 1984" US Dollars⁸) in the experimental group before and after the intervention. They only include costs of emergency room visits, hospitalisations and the education program. For all 48 children in the experimental group the program costs were \$6000. The reduction in hospital days and emergency room visits saved \$14550. Hence net costs (compared to care as usual in the period before) were - \$8550, or -\$178 per patient. Given the quantities reported, the costs of the control treatment would amount to \$1194 per patient, while the costs for the experimental treatment would be \$714 per patient. A comparison between these numbers is difficult since the patient groups are not comparable as regards the number of days in hospital and emergency room visits at baseline. The control group had less visits and days in hospital. Therefore, the control group might have been less ill. That may lead to the conclusion that the control group would have had fewer days in hospital anyway, which reinforces the conclusion that the experimental program is more cost effective. However, instead of having had less days in hospital anyway, the control group, being less ill, could have had less room for improvement. If that was the case, the differences between the groups weaken the results. This may explain why the authors present the results of a before-after comparison of the experimental group. However, effects on office visits are not reported, while medication use was not measured.
- Ronchetti et al. (1997) compare four and eight weeks versions of two different programs and a control 'care as usual'. Patients are children aged 6-14 years. They conclude that there is hardly any difference in effectiveness between the two programs and between the versions of different length. The only significant difference between the long and the short program was that the long program led to a significant reduction of emergency hospitalisations compared to the control group, and the short program did not. For the long program, a rough estimate of a cost-benefit ratio, is given, that is 1:5. A full cost-effectiveness analysis of the trials is not yet available.
- Weinstein et al. (1996) evaluate a "*special inpatient rehabilitation program*" for children with severe asthma (age 0.5-19 years). It is a before/after comparison of costs and outcomes. The intervention consisted of education, exercise training, a visit at home to check the environment, psychological assessment and treatment. The result can be summarised by costs of intervention of \$24600 to be compared to total discounted cost savings in medical consumption of \$29605 over four year, in 1992 US Dollars, discounted at 3%. That is, net costs were -\$5005 per patient. More detailed results on changes in the volume of medical consumption are given as well.

4.4.4 Conclusion

While reviews of clinical trials find mixed evidence of effectiveness, cost-effectiveness studies are more positive. In a review of five such studies, Schermer and van den Boom (1997) found that the savings on medical consumption are higher than the additional costs of a program. The five studies reviewed are the two summarised above plus another three older

studies (Fireman et al. 1981; McNabb et al. 1985; Rakos et al. 1985). All latter three involved relatively small sample sizes. The results from the clinical trials and cost-effectiveness studies seem contradictory, because an ineffective program cannot be cost effective. This may be explained by a diversity of trials reviewed, combined with a small amount of studies with results on cost effectiveness. Probably, cost-effectiveness studies as an addition to clinical trials are only started once clinical effectiveness has been demonstrated. This causes a bias towards more optimistic results of cost-effectiveness studies.

All the studies reviewed above were targeted at children and sometimes at their parents as well. The ages of the children differed between 4 and 17, but all covered the range from 7-12 years.

Evidently, it is important that the intervention is directed at the right target group and correctly executed. Clark's (1986) results imply that education is more cost effective for severely ill patients. The program evaluated in Weinstein (1996) had net cost savings and was targeted at severely ill patients.

Studies often have 'care as usual' as a control program and compare it with one education program of a given length and content. It remains unclear how much or what kind of education is most cost effective. Ronchetti et al. (1997) concluded that there was almost no difference in effectiveness between four and eight week programs, except for the number of emergency hospitalisations. Since hospitalisations are rather costly, the most cost-effective length of a program is still unclear.

4.5 Other interventions

There are also many treatment programs that combine an element of education with various other elements, such as additional diagnoses and consultations, or care from a specialist rather than a generalist. Since these programs are often specific and specially designed for a given situation, there is little information about them in guidelines. Another reason for this absence is the guidelines' target group. Guidelines usually address specific groups of medical professionals. They are not intended to guide the choice between medical professionals. An exception is the information on the organisation of care for asthma patients, the role of asthma nurses, and the choice between specialist and general practitioner in the BTS and PP guidelines. The NHG guidelines have a special attachment, which describes the "Transmural agreement" (Geijer, et al. 1998). This agreement describes a labour division between general practitioners and specialists in the care for asthmatic children. In this way, unnecessary specialist care may decrease and communication may improve. The agreement is an example of the many different interventions belonging to the category of "other interventions". Some other examples are:

- Advice on the choice between medical professions (allergist or generalist)
- 'Screening and targeting'-programs (active search to identify groups that should get special attention)
- Education programs for medical professionals to stimulate the correct prescription of medication.
- Asthma nurses

A problem with cost-effectiveness studies on these interventions is that the interventions are highly specific and consist of a number of entangled interventions. Therefore, it is hard to find out what part of the program contributed to what kind of effects or costs. Results on integrated care, a multidisciplinary approach to care for asthma patients and other interventions aimed at a better co-operation between care providers are also discussed in Schermer and van den Boom (1997). We tried to find studies with children as their patient group. However, some studies with broader patient groups were also included.

4.5.1 Studies on the choice between medical professions

- Bartter and Pratter (1996) carried out a literature review on the organisation of asthma care in the US, in particular on *expert versus generalist* care for patients of all ages. Based on a review of eight studies published between 1977 and 1993, they conclude that expert care has a positive impact on outcome and on the overall cost of care. Costs were only measured in two studies. One of them recorded only the costs of office visits. Therefore, information on costs seems too scarce to allow for the conclusion that expert care is more cost-effective than generalist care.
- Nyman et al. (1997) compare care by *allergists versus non-allergists* for asthmatic children (age 0-21). The authors performed a retrospective analysis of medical claims and tested for a systematic difference between both types of physicians in tests ordered, total costs, and 'management-breakdowns' (an emergency room visit or hospitalisation). In their regression analysis they controlled for severity by including several variables that reflect the use of certain medication, age, and gender. Results show that allergists are significantly more likely to order certain tests, that their patients have significantly more costs, and that allergists' patients are significantly less likely to be hospitalised. According to the authors, these results suggest that in the US, allergist care is more cost-effective, since fewer hospitalisations occur at comparable total costs of care. However, the results should be interpreted with caution, since effectiveness is only measured in terms of emergency room visits and hospitalisations and the coefficient for emergency room visits is not significant.
- Greineder et al. (1995) evaluates an asthma outreach program, with an *asthma-nurse* who provides additional care, mainly education, compared to care as usual (provided by a paediatrician). The study was located in the US and refers to an inner-city population of children (age 1-17) with severe asthma, identified as likely to benefit from the program. Patients served as their own controls in a before/after analysis of medical consumption. The nurse worked on average 8 hours per week at a cost of \$11 115 per year in salary. The program led to a reduction in the total number of emergency room visits and hospitalisations per year of 57 and 30, respectively. This was valued at \$87315. Thus the program led to a reduction in net costs (in 1993 prices), given that, according to the authors, changes in other elements of medical consumption (such as office visits) were small and would not affect the result. Given the special patient group, results cannot be generalised without caution.

4.5.2 Studies on 'screening and targeting'

- Bryce et al. (1995) and McCowan et al. (1997) evaluate the effects of a so-called facilitator in the UK. The facilitator systematically screened around ten thousand general practitioners' patient records for asthma symptoms and marked the records of possible asthma patients in the intervention group. The patients screened were between 1 and 15 years of age. Support (in the form of equipment and information) was given to general practitioners. Thus the intervention can be summarised as *general practitioner support*. Comparison of intervention and control group one year after the intervention points to significant differences. Three years after the intervention, care in both groups was no longer significantly different. For both groups total costs of care decreased over time, but the decrease was larger for the intervention group. However, the intervention group had more hospital admissions during the year before intervention. As the authors remark, that complicates interpretation of the results, because hospital costs are relatively large and caused by a small number of patients. To control for this, they remove the difference in

hospital costs in the pre-intervention year. Then, the additional costs of the one time intervention (the facilitator's salary) equal the extrapolated additional cost reduction of about £16000 over three years. One facilitator working a year is needed to screen 50000 records (which should result in circa 16000 potential asthma patients and hence save £16000). That is, the net costs of such a one time screening program are zero if the follow-up period is three years. Costs are in 1991 English Pounds. However, this conclusion should be carefully interpreted. First, information on the absolute costs of the intervention is lacking. Second, differences in hospital costs in the year before intervention trouble the results. Third, the care consumption in the third year is not significantly different between the groups.

- Munroe et al. (1997) compare screening followed by additional care and education by *pharmacists* with no intervention. The study is an analysis of medical claims over two years and compares an intervention with a control group. Only medical costs are compared. Patients are adults and have one to four diseases, one of which is asthma. The number of claims is used as a proxy for severity and charges in 1994 are used as a proxy for the costs of medical consumption. Then, the costs of the intervention (\$27 per patient per month) are more than covered by the savings in medical consumption, adjusted for severity (\$293 per patient per month). Prescription costs reported for asthma were on average \$114 in the intervention and \$86 in the control group per patient per month. For the asthma patients, intervention costs were higher after screening, which points to 'underuse' of medication in asthma patients.

4.5.3 Conclusion

It is hard to draw any general conclusions, since the interventions vary and aim at different patient groups. Most of the referenced studies were conducted in the United States, where costs and organisation of care are quite different from the Dutch situation.

The results from Bryce et al. (1995) and McCowan et al. (1997) on systematic screening and education of care providers are interesting. They point to the importance of continuity. After four years, the effects of their one time intervention had disappeared. It is also interesting that Munroe et al. (1997) find that an increase in medication costs can be cost-effective, which points to 'underuse' of medication. This is confirmed in a study by Naish et al. (1995) which compares the prescriptions of London general practices. This is not a cost effectiveness study and therefore not mentioned above, but the authors found that practices that were most compliant with guidelines had the highest medication costs.

4.6 Compliance

Compliance and misuse of medication is an important issue in asthma treatment. Estimates of the number of compliant patients vary as was briefly discussed in section 4.4.1 above. A Cochrane review of interventions among patients of all ages to improve adherence with medication in general (Haynes et al. 1998) concludes that a meta-analysis is not possible since the interventions differ too much. It is often hard to single out the effect of improved compliance from interventions with other elements, like education. The review mentions one compliance study on asthma, which is an evaluation of a self-management program in adults. The incorrect use of inhalation devices also results in a medication use that is too low, even if patients are compliant with their medication.

The compliance of medical professionals is another interesting issue. A Dutch study found that nurses, physicians or home-care providers are not always compliant with self-management programs and do not finish the program (see also section 4.4). Some other

studies analysed the compliance of medical professionals with guidelines. From a survey under 400 general practitioners in the US (Wolff et al. 1998), 44% of respondents reported that they used any guidelines. Only 27% knew how to find guidelines on a certain subject. Guidelines on asthma had been seen by 55% of respondents. A Dutch study (Jans, 1999) evaluated care for the adult asthma and COPD patients of 16 general practitioners that paid special attention to good asthma management by way of education on guidelines, feedback and peer review. Compliance to the guidelines was checked for 12 different items, like the number of consultation per year, adjustment of medication for patients with unsatisfactory pulmonary condition and referral to a chest physician. For 9 items, the degree of compliance was below 70%.

Cost-effectiveness studies of specific interventions (other than self-management programs) to improve compliance of asthmatic children or studies of interventions to improve compliance of professionals that care for asthmatic children have not been found.

4.7 Summary of cost-effectiveness studies

Most cost-effectiveness results are available on medication and on education and self-management. Even there however, all relevant choices have not been analysed. Hence, a lot of work remains to be done on the cost effectiveness of interventions for asthma in children. For interventions related to the avoidance of trigger factors, even the evidence on effectiveness is incomplete. Since it is not useful to analyse the cost effectiveness of an intervention that is not effective, it is not surprising that cost-effectiveness studies of allergen avoidance measures could not be found.

5. Summary of results and discussion

5.1 Guidelines

From the four recent guidelines reviewed in this report, a common denominator advice on long-term care can be abstracted. Although the individual guidelines differ from each other, these differences are not so large that such a common treatment advice cannot be formulated. The common denominator advice of the guidelines is described in section 3.5.

Some differences are found in advice on anti-inflammatory treatment. The American guideline is more hesitant than the other guidelines in prescribing large doses of inhaled corticosteroids. The two Dutch guidelines give less importance to cromolyn as an alternative to inhaled corticosteroids. Another difference is the consideration of other, either old or new types of medication as a possible alternative to the advised medical treatment. The Dutch guideline for general practitioners for instance is much more explicit than the British guideline in its statement that theophylline is not recommended.

Finally, the attention given to other, non-medication, interventions differs among the guidelines. This also has to do with the length of the guidelines, which varies considerably, from a few pages in a summary style, to an exhaustive discussion of all aspects of asthma care. Such differences in style and target group of the guidelines imply that some caution is required when conclusions are drawn about missing elements in some guidelines. For example, the Dutch guideline directed at general practitioners does not mention oral steroids as a long-term treatment. That is to be expected, since these patients will usually be under treatment of a specialist.

Guidelines usually address a specific professional group, for instance general practitioners. Furthermore, they confine themselves to advice on standard asthma care and discuss interventions that are directed at the patient. In other words, guidelines only discuss what we called 'the content of care' for asthmatics. Other elements of asthma care exist, including interventions that can be important when the cost effectiveness of care for children with asthma is considered, but that cannot be found in the guidelines. Guidelines do not, or hardly, consider issues related to the organisation of the health-care system. An example of such an organisational issue is the choice between alternative medical professions, for example, general practitioner care versus specialist care¹³. Interventions aimed at a broader group than asthma patients, such as regulations to reduce air pollution, are neither discussed in the guidelines.

5.2 Cost-effectiveness studies

Cost-effectiveness studies on interventions for asthmatic children mostly study interventions with medication or self-management programs. On medication, cost-effectiveness studies imply that an inhaled steroid combined with a bronchodilator is a more cost-effective treatment than a placebo plus a bronchodilator (See Rutten-van Mólken et al. 1993, Connett et al. 1993, and Gerdtham et al. 1996). Current guidelines are in agreement with these results. Sufficient studies that compare cromolyn to inhaled steroids are missing, which is a pity, given the disagreement among guidelines on this point. Guidelines advise long-acting bronchodilators for some patients. Cost-effectiveness results on this medication were not found. Given that this medication is rather expensive and therefore may have substantial budgetary consequences, such studies could give useful information for a guideline advice

¹³ In the Netherlands, there is a special addendum to the General practitioner's guideline with advice on the division of care between general practitioner and specialist (See Geijer et al. 1998).

that considers cost effectiveness. As to self-management, the number of complete and recent studies in children is still small. Combined with a low level of evidence about effectiveness, this may explain the caution in the Dutch guidelines. It remains unclear how much of what kind of education is most cost effective for what patient group.

An extensive program, similar to lung rehabilitation, for severe asthmatic children led to net cost savings in the US (Weinstein 1996).

Other studies assess special programs, like an asthma nurse who pays special attention to patient education. These programs may include changes in the organisation of care. Many special programs have the disadvantage that they consist of a number of interventions, and it is hard to find out what part of the program resulted in which effects. Furthermore, the programs are often tailored to a specific situation and target group. Finally, cost-effectiveness studies on interventions for allergen avoidance could not be found.

The analyses of self-management programs often concentrate on the effects of the program on other costs of treatment and on effects measured in terms of health outcomes. When a program results in decreases in the costs of emergency treatment, it is, of course, possible to conclude that the health effects are positive. When moreover total costs decrease, it follows that the program falls into the group of interventions that result in both cost-savings and health improvements and are always cost-effective. However, programs with net cost increases may also be efficient, if their positive effects on health are found worth the additional costs.

5.3 Discussion

Guidelines seem mainly based on effectiveness, not on cost effectiveness. Since effectiveness is a prerequisite for cost effectiveness and the guidelines tend to recommend only measures with a proven effectiveness, a minimum requirement for cost effectiveness is included indirectly. Nevertheless, one may say that cost effectiveness is not really used as a criterion in the guidelines. It is very rare that guidelines mention costs and cost effectiveness is not explicitly used as an argument to recommend certain interventions. The guidelines do not advise a specific type of most interventions, but rather mention all available variations. For the choice between interventions from different categories, guidelines focus on effectiveness. Non-medical, preventive interventions and medical interventions are recommended in combination and the advice is to combine the optimal intervention of both types.

There are two ways in which cost-effectiveness studies may add to guidelines. First, general recommendations in guidelines may be further specified. Using cost-effectiveness studies, the most cost-effective alternative could be advised, for instance, the most cost-effective type of inhaled corticosteroid. Possible exceptions when other variants may be better should be mentioned.

Second, cost effectiveness could be used to aid decision making on the most appropriate combination of interventions from different treatment categories. That is, cost effectiveness could help to decide how much effort should be put into allergen avoidance, combined with how much medication and how many self-management programs. When resources are limited, one may ask what division of resource use over the various categories of interventions is most efficient. Such a division may imply less than the optimal intervention in one of the categories, if the budget is rather low.

Cost-effectiveness studies exist that enable contributions to the first goal, further specification of advice. The second goal, to find the most efficient combination of interventions from various categories of treatment is much more ambitious. Given the results from cost-effectiveness studies currently available, one may only hope to meet it partially.

For allergen avoidance, too little is known from cost-effectiveness studies to state anything with certainty. The cost-effectiveness studies currently available are not sufficient to make the guidelines more specific. Anti-inflammatory medicines and bronchodilators are recommended in combination in the guidelines, and an optimal anti-inflammatory therapy is a pre-requisite to determine optimal symptom-reduction treatment. There seems to be little need for cost-effectiveness studies to add precision to the guidelines on the optimal division of resources between the two treatments. For all guidelines recommend to use bronchodilators on an as needed basis added to optimal anti-inflammatory therapy. They give rather explicit instruction on how to adapt the dose of anti-inflammatory medication such that patients receive the lowest dose that keeps their asthma under control. Hence it is not probable that a change towards more anti-inflammatory therapy would result in savings on bronchodilator-use. The opposite, less stress on anti-inflammatory therapy combined with more bronchodilators to alleviate symptoms does not seem to be a sensible option. Hence, for these two types of medication, no gains in efficiency can be expected from a change in the guidelines, because they recommend the most efficient choice already. This conclusion is confirmed by the results in the available cost-effectiveness analyses: they imply similar advice as that given in the guidelines. Long-acting bronchodilators are another, newer, medication. Guidelines include them in their advice for the treatment of severe patients. Clinical trials could be found on the combination of a low dose of inhaled corticosteroids with a long-acting bronchodilator versus a high dose of corticosteroids. However no systematic review of the trials or cost-effectiveness studies are available on this issue. This is a pity, since long-acting bronchodilators are rather costly, so that their inclusion in standard treatment is only cost-effective if they are quite effective.

For the choice between education and other treatments, or the choice on the optimal amount of education to provide, several cost-effectiveness studies are available. The guidelines differ in emphasis at this point. Therefore, results on cost effectiveness might be used to find out what is an efficient amount of resources to spend on education for various patient groups. Patient-compliance may be a problem in practice, especially for anti-inflammatory therapy, since its results are only visible in the long run and it has no immediate effect. Improvement of patient compliance is one of the goals of self-management programs. An interesting question is how the cost effectiveness of programs to improve patient compliance compare with programs directed at compliance of medical professionals, for instance, the dissemination of guidelines. Since economic evaluations of the latter are not yet available, that is not possible.

To conclude, cost-effectiveness results are lacking or scarce on a number of issues, and therefore, it cannot be expected that guidelines account for cost effectiveness for these issues. However, at some points, namely medication with inhaled steroids and intensive education and training programs for severe asthmatic patients, sufficient information is available and could be included in the guidelines.

Since the review focuses on long-term care, studies on interventions related to diagnosis and emergency care have been ignored. The choice of inhalation devices has been mentioned only briefly. If a given budget for the care of asthmatic children should be allocated optimally, of course these categories of interventions should be included. Hence, the summaries and reviews in this report are only part of what would be needed to formulate a model for budget allocation. Even more so, since not only cost-effectiveness results and guideline advices are needed but also information on prevalence of the disease, the distribution of patients over severity classes and the effect of interventions on health.

6. Conclusion

To finish the report, a short summary of its results is given below. These points were discussed more elaborately in section 5.

- Although the individual guidelines differ from each other, these differences are not so large that a common treatment advice cannot be formulated. The common denominator advice of the guidelines is described in section 3.5.
- Guidelines seem mainly based on effectiveness, not on cost effectiveness. It is very rare that guidelines mention costs, and cost effectiveness is not explicitly used as an argument to recommend certain interventions. The guidelines do not advise a specific type of intervention, but rather mention all available variations.
- There are two ways in which cost-effectiveness studies may add to guidelines.
- Cost-effectiveness studies exist that enable contributions to the first goal, further specification of advice.
- The second goal, to find the most efficient combination of interventions from various categories of treatment, is much more ambitious. Given the results from cost-effectiveness studies currently available, one may only hope to meet it partially.
- Cost-effectiveness studies on interventions for asthmatic children mostly study interventions with medication.
- On medication, cost-effectiveness studies imply that an inhaled steroid combined with a bronchodilator is a more cost-effective treatment than placebo plus a bronchodilator (See Rutten-van Mólken et al. 1993, Connett et al. 1993 and Gerdtham et al. 1996). Current guidelines are in agreement with these results.
- Guidelines advise long-acting bronchodilators for some patients. Cost-effectiveness results on this medication were not found. Given that this medication is quite expensive, such studies would be useful to improve the evidence for the guideline advice.
- The number of complete and recent studies on self-management in children is still small.

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Appendix 1 Literature

The study is based on literature searches: one for recent guidelines and several to find literature on the cost effectiveness of asthma interventions.

The aim of the search for guidelines was to find a useful, small, set of recent guidelines, not to provide a complete overview of all available guidelines. To find recent guidelines on asthma and COPD, Medline was searched in March 1998 with the mesh terms 'asthma' or 'COPD' and 'publication type=guideline'. This resulted in 84 references. Guidelines were considered for inclusion in this study if they were concerned with long-term care for asthma patients aged 20 years or less. Thus, guidelines on COPD and those solely concentrating on care for acute asthma were excluded. Guidelines that did not pay attention to children specifically were also excluded. Another selection criterion was a date of appearance from the last three years. Finally, we wanted to include some Dutch guidelines. Therefore, we did a quick search in current contents with Dutch keywords and found the two recent Dutch guidelines mentioned below.

Four guidelines were selected: the American guidelines from the National Institute of Health (1997), the British guidelines from the British Thoracic Society (1997), the Dutch guidelines for general practitioners from the Dutch society of general practitioners, 'Nederlands Huisartsen Genootschap', NHG (Dirksen et al. 1997), and the Dutch guidelines of paediatric pulmonologists, 'richtlijnen van kinderlongartsen' (Hoekstra 1997).

The databases Medline, OHE, and EconLit were searched to find cost-effectiveness studies on interventions by asthma, if possible with children as the patient group. Studies from 1996 onwards were considered. For earlier studies, the review by Schermer and van den Boom (1997) was consulted, which covered literature until about June 1996.

Medline was searched on the mesh terms 'asthma' and 'costs-and-costs-analysis'. This resulted for the past two years in 65 references. These were considered for relevant references. Furthermore, the same search strategy as applied in Schermer and van den Boom was used to see if any additional references resulted. In total 119 different references resulted. Furthermore, Medline was searched for those separate interventions for which we had few references. These searches used 'Costs-and-costs-analysis' as a mesh combined with a mesh term for the intervention. Such a search was done for the following interventions: 'immunotherapy', 'cromolyn-sodium', 'ipratropium', 'ketotifen', 'theophylline' and avoidance (for the latter, 'asthma-prevention and control' and 'hypersensitivity-prevention and control' were used as mesh terms). This resulted in only a few relevant studies. In addition, the keywords 'acaricide', 'mattress' and 'house-dust-mite' in combination with the mesh terms 'asthma' and 'cost-and-cost-analysis' resulted in a few relevant references only. These searches covered the years 1996, 1997 and 1998 until June.

The OHE-database was searched using 'asthma' in keywords and limiting references to years later than 1996. A database of economic literature, EconLit, was searched to see if any additional cost-effectiveness studies appeared in economic journals not covered by the OHE. The keyword used was 'asthma'. This resulted in 16 additional references, which were checked for relevance.

All references contained in Schermer and van den Boom were excluded, as well as studies that considered acute asthma. Studies with adult subjects were not considered in case sufficient alternatives with young subjects were available.

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