Chapter one  Introduction

1.  PREFACE

In the first decades of the previous century, infectious diseases were responsible for a large part of morbidity and mortality. Nowadays, malignancies, cardiovasculair diseases and chronic disorders such as diabetes and hypertension are problems that the modern patient is most likely to face during his or her life. Allergic disorders such as rhinitis, asthma and AEDS (atopic eczema/dermatitis syndrome), although known to us since early history, have always been considered a bother rather than a burden.\(^1\) Only until recently, the impact on professional and educational life has been recognised. Due to allergic disease work and/or school days are missed.\(^2\) Studies to the quality of life by means of questionnaires have revealed that allergic patients experience their quality of life as diminished compared to healthy controls.\(^3,4\) Measurements to improve allergic symptoms, i.e. medication, lead to significant higher scores.\(^5,6\) A considerable amount of money is spent each year to alleviate allergic symptoms.\(^7,8\) In 2000 2339 euro per 1000 insured persons was spent on topical nasal medication, 19420 euro per 1000 insured persons on lung medication and 3001 euro per 1000 insured persons on systemic antihistaminics (costs for visits to general practioner, specialist and tests not included).\(^9\) Improvement of symptoms can also be achieved by avoidance of the responsible allergen. This might seem a cheap solution but in the case of house dust mite it really is rather expensive: the amount of money spent on the purchase of encasings for mattress, pillow and duvet to diminish exposition to mite allergen was estimated at 2,6 million euro in 2001 (Dutch Health Insurance Board, personal communication). Although the effect of medication on allergic diseases like asthma, AEDS and rhinitis is firmly established, the favourable effect of encasings still remains to be proven. Studies in asthmatic patients and patients with AEDS so far have shown results for and against the use of encasings. Studies with allergic rhinitis patients have not been performed yet. I n this thesis the effect of impermeable encasings on nasal symptoms and quality of life is studied.
2. ALLERGIC RHINITIS

2.1 General aspects

Rhinitis is a disease that can be caused by a variety of underlying disorders. According to the ARIA working group it can be classified as follows:

<table>
<thead>
<tr>
<th>Classification of rhinitis</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Polyps</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>Mechanical factors</td>
</tr>
<tr>
<td>Other infectious agents</td>
<td>Deviated septum</td>
</tr>
<tr>
<td>Allergic</td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>Foreign bodies</td>
</tr>
<tr>
<td>Persistent</td>
<td>Choanal atresia</td>
</tr>
<tr>
<td>Occupational</td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>Tumors</td>
</tr>
<tr>
<td>Persistent</td>
<td>Benign</td>
</tr>
<tr>
<td>Drug induced</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Granuloma</td>
</tr>
<tr>
<td>Other medication</td>
<td>M. Wegener</td>
</tr>
<tr>
<td>Hormonal</td>
<td></td>
</tr>
<tr>
<td>Atrophic</td>
<td>Malignant (midline destructive granuloma)</td>
</tr>
<tr>
<td>Emotional</td>
<td>Ciliary defects</td>
</tr>
<tr>
<td>Food</td>
<td>Cerebrospinal rhinorrhea</td>
</tr>
<tr>
<td>Gastro esophageal reflux</td>
<td></td>
</tr>
<tr>
<td>Irritants</td>
<td></td>
</tr>
<tr>
<td>NARES</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
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</tbody>
</table>

Other guidelines have been published by the International Rhinitis Management Working group, the Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis and by the German Task Force.

Allergic rhinitis is defined as a symptomatic disorder of the nose, induced after allergen exposure by an IgE mediated inflammation of the nasal membranes. It is characterised by nasal congestion, rhinorrhea, sneezing, itching and postnasal drip. Recently, the ARIA workshop stated in their executive report that allergic rhinitis should be considered a major chronic disorder due to its prevalence, its impact on quality of life, the economic burden, the reduced productivity at work and lost school days and its association with conjunctivitis, sinusitis and other comorbidities. Although the definition of allergic rhinitis seems quite clear, establishing the diagnosis is not always easy. The ARIA guidelines indicate that the diagnosis of allergic rhinitis is based on a combination of a thorough clinical history as well as diagnostic tests. However, both history and diagnostic tests have their pitfalls. In an extensive review, Gendo and Larson discuss the various studies to the diagnosis of allergic rhinitis. Taking medical history is - as expected - very important. Trigger questions in which provocation with specific allergens like pollen or animals are described, have a positive likelihood ratio up to 6.69 while the negative likelihood ratio varies from 0.09 to 0.81. Nevertheless, a positive answer does not guarantee an allergy just as a negative answer does not exclude it.
Skin tests are widely used because they are very informative, if performed by experienced health care professionals. A blood test like a RAST or Phadiatop can be a good alternative. Both, however, are hampered by the presence of false positive and false negative results. Another possibility would be to perform a nasal challenge test. This is mostly done in research settings and to a lesser extent in clinical practice i.e. to assess the diagnosis of occupational rhinitis. It is a time consuming test which requires a patient to stop all systemic and topical nasal medication for a considerable amount of time (nasal sprays have to be stopped 2 to 4 weeks before a test) and only one allergen can be tested at a time. Therefore, in the case of a patient with a suspected allergy for house dust mite, pollen and several animals, it would not be very practical. The ARIA advises to perform a nasal challenge test only in patients with a discrepancy between history and diagnostic tests, in the case of occupational rhinitis, in research settings, as a substitute for oral challenge with aspirin and finally, to test nasal hyperreactivity.

Pathophysiologicaly, allergic rhinitis can be defined as the interaction of allergen and specific IgE antibodies, bound on mast cells. As a result of this interaction, mast cells degranulate and biochemical mediators are released, leading to nasal symptoms as sneezing, nasal blockage, rhinorrhea and post nasal drip. This is followed in a number of cases by a recurrence of symptoms after several hours after the initial exposition and reaction, the so called late phase. Nasal priming and nasal hyperreactivity also have a major role in the symptom complex of allergic rhinitis; this will be discussed further on in the text.

2.2 Pathophysiology

As mentioned earlier, the allergic reaction is the consequence of exposition to allergen in a sensitised individual. The underlying mechanisms have not been fully elucidated as yet but we are relatively certain nowadays of a number of pathways.

When an allergen enters the nose of an allergic patient, it binds to allergen specific IgE bound to a mast cell. After cross linking, this leads to the release of several mediators, both preformed and stored such as histamine, tryptase and certain cytokines (TNFα, IL-4) or newly formed like the membrane derived leukotrienes (LTB4, C4, D4, E4), the prostaglandines (PGD2), bradykinine and PAF. The effects of the released substances are vasodilation, increased vascular permeability, mucus secretion and afferent nerve stimulation, resulting in what we know as the allergic nasal symptoms: blockage, rhinorrhea, itching and sneezing. This reaction takes place within minutes after exposition and subsides after a few hours. These mediators are also responsible for attracting a variety of cells - eosinophils (IL-5, LT-B4), basophils (IL-3, IL-5) and neutrophils (LTB4) - and upregulation of endothelial adhesion molecules like VCAM-1 by means of TNFα and IL-4. This facilitates adherence to and passage through the endothelium by eosinophils, basophils and lymphocytes, which carry the corresponding integrin VLA-4 on their surface. All cells migrate to the nasal mucosa and release their
products, e.g. histamine, leukotrienes and IL-5, thereby inducing a second period of nasal symptoms. Interestingly, only part of the allergic patients experience such a second period of nasal complaints, known as the late phase; so far, this phenomenon of selective appearance of the late response in only a part of the patient population can not be readily explained. Studies by de Graaf- in ’t Veld revealed that patients suffering from a late reaction can be identified by the higher secretion of albumin and tryptase in nasal fluid and by the more serious nasal complaints during the early reaction. This suggests that the late phase might be associated with the more severe cases of allergic rhinitis.

A second phenomenon is the priming effect: after exposition to an allergen patients develop increased sensitivity to this allergen and to other allergens. Otherwise stated, it takes less allergen to evoke nasal symptoms after the first provocation. Moreover, this is a temporary reaction. If a patient is not exposed for a few days, normal responsiveness is restored. Although the mechanism behind nasal priming is not clear, the influx of the various cells and/or the activated state might lead to a more potent reaction after rechallenge with allergen.

### Mast cell products and effects\(^7\)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td></td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Mucusproduction</td>
</tr>
<tr>
<td>Proteases (tryptase,</td>
<td>Mucusproduction</td>
</tr>
<tr>
<td>chemotryptase,</td>
<td>Generation of bradykinine</td>
</tr>
<tr>
<td>carboxypeptidase,</td>
<td></td>
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<tr>
<td>kininogenase)</td>
<td></td>
</tr>
<tr>
<td>Leukotrienes (B4, C4, D4,</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td>E4)</td>
<td>Mucusproduction</td>
</tr>
<tr>
<td>PGD2</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td>IL-3</td>
<td>Chemoattraction basophils</td>
</tr>
<tr>
<td>IL-4</td>
<td>Increased IgE formation by B-cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>Increased eosinophil proliferation</td>
</tr>
<tr>
<td></td>
<td>Increased eosinophil differentiation</td>
</tr>
<tr>
<td></td>
<td>Chemoattraction eosinophils &amp; basophils</td>
</tr>
<tr>
<td>TNF α</td>
<td>Stimulation inflammatory cascade</td>
</tr>
<tr>
<td></td>
<td>Upregulation leukocyte adhesion molecules on endothelium</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Increased proliferation of granulocytes</td>
</tr>
<tr>
<td>PAF</td>
<td>Chemoattraction eosinophils &amp; neutrophils</td>
</tr>
<tr>
<td></td>
<td>Increased vascular permeability</td>
</tr>
</tbody>
</table>

Furthermore, patients with allergic rhinitis develop nasal symptoms after exposition to so called aspecific stimuli like fog or cigarette smoke. This reaction is known as nasal hyperreactivity. Why this reaction develops is still not clear. Theories about possible mechanisms include increased sensitivity of the sensory nerve endings, change in nerve transmission, damage of the epithelial barrier, pro inflammatory mediator release and influx of inflammatory cells. Nasal hyperreactivity can be
prevented by treatment with topical corticosteroids, suggesting a role by inflammatory cells.\textsuperscript{14,19-24}

2.3 Pharmacological treatment and immunotherapy

Pharmacological treatment can be divided in systemic and topical treatment. Systemic treatment in allergic disease usually indicates the use of oral medication: antihistaminics or oral corticosteroids. Nowadays, the need for oral steroids is minimal compared to the sixties and seventies of the last century. The major drawback of the first antihistaminics was drowsiness. This is seen far less in the antihistaminics of the second and third generation. Their effectiveness has been demonstrated in several quality of life studies.\textsuperscript{26-32} Topical treatment is a second possibility in the treatment of nasal rhinitis. Nasal steroid sprays are very effective in relieving symptoms and according to several studies, are preferrable to oral antihistamines because of their superior effect on nasal blockage.\textsuperscript{33-36}\textsuperscript{37,38} Other topical nasal treatment include antihistamine sprays and cromones. Antihistamine sprays are effective but not as effective as nasal corticosteroids.\textsuperscript{39-41} Cromones are still widely used in pregnant
A recent development is the use of anti-leukotrienes. Leukotrienes are important mediators in the nasal allergic reaction; it was assumed that anti-leukotrienes could be an important addition to the therapeutic arsenal. Although there are only a few clinical trials yet, the first results are promising.42,43 Immunotherapy can be an option for patients with serious complaints. After a period of weekly injections with increasing concentrations of purified allergen, patients are injected monthly for up to 5 years. Patients with an allergy for pollen, grass, birch, ragweed, parietaria, and house dust mite show clinical improvement and need less medication.44-52 It is however a time consuming treatment with potential serious adverse reactions and thus should only be used by experienced physicians.

3. Epidemiology

The prevalence of allergic rhinitis is high in Western societies. In a Swiss population of children and adolescents an overall prevalence of 12.2% for hay fever and 9.3 for asthma was reported by Braun–Fährlander. Specific IgE for outdoor allergens – timothy grass, birch, mugwort - was shown in 29.5% of the children, and for indoor allergens – house dust mite, dog, cat - in 20.1% of the children.55 In the Odense study the lifetime prevalence of AD in a group of adolescents aged 12 to 16 years was 21.3% (girls 25.7% vs. boys 17.0%); the lifetime prevalence of inhalant allergy was estimated as 17.7% (6.9% allergic asthma, 15.7% allergic rhinitis).56 Schäfer found a positive skin prick test for house dust mite in 5.0 to 13.6%, birch 1.4 to 12.3% and for grass 10.7 to 16.1% in pre school age children in various parts of Germany.57 Canadian figures in 3371 consecutive patients of all ages with asthma, rhinitis or both indicate that after cat (76.5%) and dog (63%) sensitisation, house dust mite sensitisation is most important (54.2%), followed by grass (51.9%), tree (47.2%) and ragweed (44.9%) pollen.58 A Dutch study in 2496 randomly selected patients age 20 - 70 years, showed that IgE to house dust mite was most prevalent (23.8% in men, 19.3% in women), followed by timothy grass, birch and cat. The ECRHS study in subjects 20 to 44 years old, showed an identical picture: all subjects were tested for house dust mite, timothy grass pollen, cat and cladosporium plus a local allergen – birch in northern Europe, parietaria judaica in southern Europe and ragweed in the United States, New Zealand and Australia. House dust mite sensitisation was most prevalent, followed by grass pollen.59 Studies from the Southern part of Europe also show a high prevalence of atopic disorders: Garcia – Gonzales et al report in a group of 18 year old students, interviewed by an allergist, a percentage of 19.9% as suffering of rhinitis, 4.1% allergic rhinitis and asthma, 3.1% allergic asthma and 0.8% AEDS.60 In Maltese adolescents (13-15 years old) who took part in the ISAAC study 47.4% reported current rhinitis, 16% current wheezing and 7.7% of current skin disease suggestive for eczema. The percentages for doctor's diagnosed asthma, rhinitis and AEDS were respectively 11.1, 32.3 and 8.8%.61
A recent report by Olivieri showed a prevalence of allergic rhinitis of 15.9% in the adult Italian population. In Asia atopic disease is close to meeting Western European figures in some countries. Leung et al report 44% allergic rhinitis, 12% allergic asthma and 3.6% AEDS in Hong Kong adolescents, aged 13 and 14; for the age of 6 and 7 years the percentages are 35.1, 9.2 and 4.2 respectively, as described in the article of Lau. The reported overall prevalence of perennial rhinitis in Korea was 1.14.

Compared to a few decades ago, the numbers of patients suffering from allergic complaints are rising. Butland compared a group of British adolescents born in 1958 and 1970 at the age of 16. Atopic rhinitis in the first group had a current prevalence of 12% whereas 23.3% of the adolescents born in 1970 were reported having allergic rhinitis. AEDS rose from 3.1% to 6.4% in the same groups. von Mutius et al showed that the prevalence of allergic rhinitis rose from 2.3% in 1991 to 5.1% in 1995 in Leipzig school children. Most children had a positive skin test for grass pollen (9.1% in 1991 and 11.5% in 1995), birch pollen (8.4% in 1991 and 14.2% in 1995), mite allergen (4.6% in 1991 and 8.1% in 1995) and hazel pollen (3.8% in 1991 and 6.7% in 1995). Overall, positive skin prick tests increased from 19.3% in 1991 to 26.6% in 1995.

The reason for the increasing numbers of allergic patients is unclear although several hypotheses have been put forward. Most attention in recent years has been paid to the hygiene hypothesis. Strachan was the first to suggest that the decrease in childhood infections was responsible for the increase in allergic complaints. The results of several studies imply that serological evidence of childhood infections are indeed inversely correlated with the presence of allergic complaints. Matricardi has shown first in Italian military men and more recent in the NHANES III study that the presence of allergic complaints was negatively associated with positive serology for HAV, HSV and toxoplasma gondii. Other studies have shown inverse relationships between allergic diseases and other bacterial, viral and protozoal diseases. Originally, this was thought to be the consequence of an imbalance of the Th1/Th2 system. Childhood infections would enhance the Th1 system thereby decreasing the chance of development of allergy, a Th2 disease. Accepting this theory however, it is hard to explain the rise in autoimmune diseases and the coexistence of a Th1 and Th2 disorder in the same patient. Secondly, it raises the question why helminth infections seem to protect people from developing allergic diseases since these infections are known to evoke both high IgE concentrations and a cytokine profile of a Th2 response. Yazdanbakhsh proposes that the presence of a strong anti-inflammatory regulatory network, characterised by high concentrations of IL-10 and other factors could help to prevent the cascade of events leading to allergic inflammation. Chronic helminthic infections are associated with high levels of IL-10, IgG4 and poor T-cell responses. Other chronic infectious diseases are also associated with immunosuppression and a lower prevalence of atopy. She suggests that a continuous burden of infections - viral, bacterial, protozoa, helminthic - is instrumental for the development of a strong, regulatory network (see picture) and that the absence of such a network with regulatory cells can lead to both autoimmune and allergic diseases.
Future research will learn us if this exciting new hypothesis can indeed explain the increase of both Th1 and Th2 diseases.

Education of the immune system by pathogens. Dendritic cells can develop into distinct subpopulations, depending on the nature of the signals they receive from the microenvironment, and the direct T cell differentiation into polarized subsets. Viruses, bacteria, and helminths carry distinct signature molecules that interact with dendritic cells to stimulate Th1-type and Th2-type immune responses. When uncontrolled, strong Th1 and Th2 responses lead to autoimmunity and allergy. High pathogen burden may either change the physiology of the microenvironment or result in the accumulation of novel signature molecules that together endow dendritic cells with the ability to induce regulatory T cells. Regulatory T cells produce suppressory cytokines and are part of an anti-inflammatory network that ensures that inflammatory T cells (both Th1 and Th2) and their downstream effectors are kept under control.

After Yazdanbakhsh M et al.

4. Environmental control

One of the major areas of research of the past decades in the field of allergology has been the avoidance of house dust mite allergen as a tool to improve symptoms. The initial idea that reduction of exposition could lead to improvement was based on the observation that a stay at high altitude, an environment low in house dust mite, reduced bronchial hyperreactivity in children with asthma. Subsequently, attempts were made to create the same conditions at lower altitudes. A study by Platts-Mills showed that a stay in a “allergen-free” hospital room improved airway reactivity and reduced the necessity for medication. Ideally, however, we should be able to create this allergen free environment with a patient at home. To achieve this, various studies were performed analysing the preferred living conditions of the house dust mite. Knowledge about the optimum temperature for mite development and preferred humidity has lead to general advice to patients about furnishing and cleaning of the house such as the avoidance of upholstered furniture, curtains, floor coverings and...
carpets and regular washing of the bedding at 60 °C. However, the execution of these measurements can meet with various problems such as lack of financial means to replace furniture or lack of adequate time to clean the house on a daily basis. Other, easier ways of obtaining a home low in mite allergen were developed such as the application of new bedding\textsuperscript{94}, the precipitator\textsuperscript{95}, the acaricides pirimiphos methyl\textsuperscript{96} and benzylbenzoate\textsuperscript{97}, the application of liquid nitrogen on bedding and carpet\textsuperscript{98}, impregnated sheets\textsuperscript{99}, steam treatment of the carpet\textsuperscript{100} and washing the beddings with eucalyptus oil.\textsuperscript{101} Not all measures attempted have been proven to be easy to execute. Acaricides and covers have become the major intervention measures in research. Both have certain advantages and disadvantages. Acaricides are easy to use but necessitates repeating the procedure several times a year to maintain reduction of the allergen.\textsuperscript{102-104} Moreover, spraying could become expensive and time consuming in the end and subsequently, only possible for a selection of the atopic population. Also, reports on their effectiveness in reduction of house dust mite allergen are contradictive.\textsuperscript{105-109} Bed covers, developed in the early seventies, are also a relatively easy way to reduce exposure to mite antigen. Evaluation of the studies dedicated to encasings is difficult. The materials that we use now are quite different to 30 years ago. The first studies in asthma patients for example used simple plastic or vinyl covers; these were open studies since no placebo could be made for these encasings.\textsuperscript{110 111 112 113 114} Other studies, that used modern covers, are hampered by the lack of a placebo cover, such as the studies of Ehnert and Marks.\textsuperscript{115 116} Carswell was the first to introduce placebo covers.\textsuperscript{117} In a group of 56 children with asthma he was able to show significant improvement of Der P1 exposure, FEV1, symptom score and medication use but not in PC20 or PEF. There was also a considerable effect on Der P1 in the placebo group, almost 50%, indicating that simple cotton covers can also reduce exposure although less than an active cover. A third problem is the different follow up periods of the various studies. Evaluation after 3 or 6 months may be attractive, but is attended with two major problems. Firstly, house dust mite allergen exposure changes with season. Measuring allergen in dust samples together with clinical measurements after three or six months introduces the problem that one can’t be sure whether improvement can be attributed to the encasings or to the seasonal reduction of house dust mite. Secondly, measuring after three or six months means that follow up measurements may be performed in a pollen season. If the study is controlled for pollen sensitisation, this would not have to be a problem but most studies do not control for pollen sensitisation or for pet sensitisation.\textsuperscript{118 119 120 121,122} Rijssenbeek performed two studies that fulfill all criterial mentioned above.\textsuperscript{123,124} She excluded patients with pet allergy and the pet at home and pollen patients were seen outside the season; she used good quality covers and had placebo covers for the control group. More importantly, she was able to detect a difference in mite exposure in the active and the placebo group which is not the case in the studies of Luczynska and Woodcock.\textsuperscript{125 126} However, the study population was small and had moderate to severe asthma which could explain the lack of results. In recent study, comprising 60 children, Halken showed a considerable reduction in the use of inhaled steroids after one year using bed covers.\textsuperscript{127} The children were not allowed to have any other clinical relevant allergy beside HDM allergy and exposure in the mattress to Der p1, f1 or m1
had to be equal or higher than 2000 ng/gram dust. One could object that the study population is a rather selective one but otherwise this is a very elegant and well performed study conducted in a double blind, placebo (cover) controlled way, fulfilling all other criteria mentioned above, in a large group of children.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Mite avoidance</th>
<th>Period of study</th>
<th>Placebo group</th>
<th>Results on mites and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarsfield</td>
<td>14 children</td>
<td>Plastic covers</td>
<td>6 weeks</td>
<td>No</td>
<td>Reduction symptom score, mite count</td>
</tr>
<tr>
<td>Burr</td>
<td>32 adults</td>
<td>Vacuum cleaning, plastic covers</td>
<td>6 weeks</td>
<td>Yes</td>
<td>No effect on PF, medication use</td>
</tr>
<tr>
<td>Murray</td>
<td>20 children</td>
<td>Vinyl covers</td>
<td>1 month</td>
<td>Yes</td>
<td>Improvement of wheezing, PF, medication use</td>
</tr>
<tr>
<td>Walsh</td>
<td>50 adults</td>
<td>Plastic covers</td>
<td>12 months</td>
<td>Yes</td>
<td>Improvement allergen exposure, lung function tests, symptom score in patients with RAST&gt;2</td>
</tr>
<tr>
<td>Gillies</td>
<td>26 children</td>
<td>Plastic covers</td>
<td>12 weeks</td>
<td>Yes</td>
<td>IgE significant lower in active group, no improvement lung tests, symptom score, medication use</td>
</tr>
<tr>
<td>Ehnert</td>
<td>24 children</td>
<td>Covers + acaricides/ placebo acaricides</td>
<td>12 months</td>
<td>Yes</td>
<td>Improvement PC20 in cover group</td>
</tr>
<tr>
<td>Marks</td>
<td>35 children + adults</td>
<td>Cover + acaricides or placebo acaricides</td>
<td>6 months</td>
<td>Yes</td>
<td>No effect on allergen exposure, symptoms, PF, lung function</td>
</tr>
<tr>
<td>Carswell</td>
<td>70 children</td>
<td>Polyurethane covers, acaricides or placebo for both</td>
<td>6 months</td>
<td>Yes</td>
<td>Improvement allergen exposure, symptoms, medication, lung function</td>
</tr>
<tr>
<td>Cloosterman</td>
<td>29 adults</td>
<td>Covers, acaricides or placebo for both</td>
<td>6 weeks</td>
<td>Yes</td>
<td>Improvement of PF, symptom score</td>
</tr>
<tr>
<td>Frederick</td>
<td>31 children</td>
<td>Active covers or placebo</td>
<td>3 months</td>
<td>Yes</td>
<td>Reduction of allergen, no effect on symptoms or lung function</td>
</tr>
<tr>
<td>Van der Heide</td>
<td>45 adults</td>
<td>Active air filter/ placebo filter + covers/ active filter + covers</td>
<td>6 months</td>
<td>Yes</td>
<td>Slight improvement in PC20 in group with active filter and covers</td>
</tr>
<tr>
<td>Van der Heide</td>
<td>59 adults</td>
<td>Covers/ acaricides/ placebo acaricides</td>
<td>12 months</td>
<td>Yes</td>
<td>Improvement in PC20 in cover and acaricide group</td>
</tr>
<tr>
<td>Cloosterman</td>
<td>157 adults</td>
<td>Covers and acaricides</td>
<td>20 weeks</td>
<td>Yes</td>
<td>Reduction allergen, no effect on lung function</td>
</tr>
<tr>
<td>Rijssenbeek</td>
<td>27 adults + children</td>
<td>Active covers or placebo</td>
<td>12 months</td>
<td>Yes</td>
<td>Reduction of allergen, no effect on PD20 histamine, no change in PD20 allergen in active group, significant worse in placebo group</td>
</tr>
<tr>
<td>Rijssenbeek</td>
<td>30 adults + children</td>
<td>Active covers or placebo</td>
<td></td>
<td></td>
<td>No difference in PD20 histamine, QoL, asthma symptom score, significant reduction of nasal symptom score</td>
</tr>
<tr>
<td>Luczynska</td>
<td>45 adults</td>
<td>Active covers or placebo</td>
<td>12 months</td>
<td>Yes</td>
<td>No effect on allergen, lung function</td>
</tr>
<tr>
<td>Halken</td>
<td>60 children</td>
<td>Active covers or placebo</td>
<td>12 months</td>
<td>Yes</td>
<td>Significant reduction of inhaled steroid use and mite allergen</td>
</tr>
<tr>
<td>Woodcock</td>
<td>1122 adults</td>
<td>Active covers or placebo</td>
<td>12 months</td>
<td>Yes</td>
<td>No effect on allergen exposure or lung function</td>
</tr>
</tbody>
</table>
The subject of mite avoidance has also been studied in atopic dermatitis although far less studies have been dedicated to the clinical effect of encasings. The same problems are encountered here as in asthma studies: no use of placebo covers (August, Roberts), short follow up period (Tan), small groups (Gutgesell).\textsuperscript{128-131} Holm showed an effect of covers in adult atopic dermatitis but this study included both HDM sensitised and non sensitised patients.\textsuperscript{132} The only study that has a sufficient follow up period and is performed in a double blind placebo controlled manner, outside pollen season and exclusion of pet allergic patients if the pet was at home is the study of Oosting.\textsuperscript{133} Although allergen exposure was reduced by a factor 2.5, he could not detect a difference in the extent or severity of the eczema.

The studies concerning mite avoidance in allergic rhinitis are scarce; Kniest and Bernstein demonstrated the efficacy of acaricides in allergic rhinitis, but Kniest used a matched pair design with only 10 patients in each group. Bernstein had a group of 32 children with rhinitis, asthma or both. Symptom scores were not disaggregated for asthma and rhinitis and the randomisation procedure is unclear. Moon used a vinyl cover that was wrapped around the mattress.\textsuperscript{97,134-136} No study so far has yet been performed with covers for mattress, pillow and duvet in a double blind, placebo controlled setting.

In conclusion we can say that 9 double blind, placebo controlled studies to encasings have been performed in asthma patients, 3 in atopic dermatitis and none in allergic rhinitis.\textsuperscript{117-120,123-127,130,131,133} Only one study in atopic dermatitis and three in asthma are adequately performed regarding influence of pollen and pets in the household.\textsuperscript{123,124,127,133} Bearing this in mind it is surprising that in the Netherlands the costs for purchasing these encasings are fully covered by the insurance companies. Since the costs for these mite impermeable encasings are high and the results of mite avoidance studies in asthma and eczema are not as clear cut as they once seemed to be, the need for a large trial in allergic rhinitis is obvious.

5. Rhinitis and comorbid associations

Although much attention had been paid to the (increasing) prevalence of rhinitis, asthma and AEDS, less is known about the prevalence of rhinitis in asthma or AEDS patients and the consequences of comorbidity for quality of life in allergic patients. A review of comorbid associations of allergic rhinitis shows that the prevalence of allergic rhinitis in patients with asthma can be as high as 58\%.\textsuperscript{137} However, this is based on literature before 1990. A more recent article by Pariente reports a prevalence of asthma in 13.4\% of the patients with allergic rhinitis compared to 3.8\% in controls. These figures were based on a questionnaire in sent to 20000 households in France. The response rate was 84\%; 1367 patients were selected as having perennial rhinitis based on this questionnaire. Of these patients 1097 patients returned a complete, second questionnaire.\textsuperscript{138} A second study by Leynaert - part of the European Community Respiratory Health Survey - revealed a prevalence of
asthma in patients without rhinitis of 2% while in patient with rhinitis, 13.4% reported asthma. In the patients with asthma as much as 71% reported to be suffering from rhinitis. A recent review also by Leynaert of 4 other studies to comorbidity showed a prevalence of asthma in patients with rhinitis of 13.4 to 32.0 compared to 3.6 to 5.0 in patients without rhinitis. Although the figures are impressive, one should bear in mind that these studies are based on questionnaires, not all having performed skin and/or blood tests to confirm allergy, or a lung function test to assess asthma. More importantly, no figures are reported of the prevalence of atopic eczema in patients with allergic rhinitis and/or asthma and vice versa.

The effect of comorbidity on quality of life is also relatively unknown. Although many studies have been dedicated to allergic rhinitis and allergic asthma and their effect on quality of life, the majority has been done as a part of a study to the effect of medication with disease specific questionnaires. This makes it difficult not only to compare quality of life of allergic patients to that of the general population but also to compare the burden of asthma to that of allergic rhinitis. One way to compare these two groups would be to use an identical questionnaire in both sufferers from rhinitis and asthma. This implies that disease specific questionnaires would have to be exchanged for generic quality of life questionnaires, for example the SF-36, a questionnaire that is based on the short form of the Medical Outcome Study survey. A few studies have reported the results of the SF-36 questionnaire in the allergic population; Bousquet used this questionnaire in a study to quality of life in patients with perennial rhinitis. In his study population, the scores on all items were significantly lower than in the healthy controls. He had similar results in a patient group with asthma. In a recent study, Majani found that patients with seasonal allergic rhinitis had significant lower scores on SF-36 items than outside the pollen season. Leynaert was the first to investigate quality of life in patients with allergic rhinitis without asthma, allergic rhinitis with asthma and a healthy control group. Randomly selected patients, aged 20 to 44 years, were sent a self-administered questionnaire on asthma and asthma-like symptoms. Respondents were invited to the clinic for further testing including an interviewer-administered questionnaire and a lung function test. They were also asked to complete the SF-36 questionnaire. Their results show a group without airway complaints of 51%, 34% had allergic rhinitis without asthma, 9% had allergic rhinitis and asthma and only 2% had asthma without rhinitis. Since the number of patients with asthma without rhinitis was too small, this group was excluded from the analysis. Patients with asthma had a lower quality of life compared to patients without asthma as did patients with rhinitis compared to patients without rhinitis. Patients with allergic rhinitis and asthma had a lower score than patients with allergic rhinitis on items regarding physical functioning, general health and vitality. Item scores, comprising mental aspects of quality of life, were lower than controls in both patients with allergic rhinitis with and without asthma but no significant difference was found between these groups. This study was the first to show that the combination of asthma and rhinitis could lead to a lower quality of life than allergic rhinitis alone. The disadvantage of this study is that allergy tests were not performed; therefore the
The diagnosis of the allergic form of asthma and rhinitis is solely based on the information gathered by the self-administered questionnaire.

We may conclude that little is known about the prevalence of allergic rhinitis in patients with asthma and/or atopic dermatitis or the prevalence of asthma and/or atopic dermatitis in patients with allergic rhinitis. The studies performed are mostly based on questionnaires and lack information about sensitisation to the various allergens. Furthermore, the influence of comorbidity on quality of life to date has been underexposed. In addition, further studies assessing the prevalence of comorbidity and to the effect on quality of life are warranted.


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