Occasional review

Allergen avoidance in the treatment of asthma and atopic disorders

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The majority of asthmatic patients are atopic – that is, they have IgE mediated sensitivity to common inhalant allergens. Exposure and sensitisation to allergens from the house dust mite is established as an important risk factor for asthma in most parts of the world.[1–24] In addition, several recent studies have provided evidence of the importance of exposure to other indoor allergens, particularly those from cats, dogs, and cockroaches.[25–29] The rate of sensitisation to mites is directly related to exposure,[30] whilst conversion from sensitisation to non-sensitisation may occur in indoor environments with low allergen levels.[31]

The severity of asthma is also related to allergen exposure.[32–35] Objective indices of asthma severity such as bronchial hyperreactivity (BHR), forced expiratory volume in one second (FEV_1), and variability in peak expiratory flow rate (PEFR) in patients sensitised to dust mites correlate with the level of mite allergens in their beds.[32] Peat *et al* found a similar prevalence of sensitivity to mites in children living in areas with two different levels of exposure to mites but BHR was more severe in sensitised children living in the area with the highest mite levels.[1]

The relationship between exposure and asthma symptoms in sensitised individuals is complex, with some patients reacting to very low doses of allergen whilst in others the allergen level required to cause symptoms may be considerably higher.[36] Nonetheless, a pattern emerges in which asthma is usually more severe in those sensitised patients who are exposed to higher allergen levels.[32] Avoiding exposure is the logical way to treat asthma when the offending allergen can be identified and effective methods of avoidance have been devised.

Effective allergen avoidance is recognised by the British Thoracic Society as an integral part of the overall management of the sensitised asthmatic patient.[37]

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Allergen avoidance

The effectiveness of allergen reduction in the treatment of asthma was first suggested by studies in which patients were removed from their homes into a low allergen environment. Later, measures aimed at the reduction in allergen levels were attempted in patients' homes.

LESSONS FROM HIGH ALTITUDE STUDIES

The levels of mite allergen are dramatically reduced at high altitude (>1500 m) where humidity is too low to support mite populations. Mite sensitive asthmatic children had a progressive reduction in non-specific BHR when taken from their homes in Holland to the mite-free environment of Davos, Switzerland.[38 39] Similarly, a progressive reduction in asthma symptoms occurred in children admitted to the residential home at Misurina (altitude 1756 m).[40] Further studies from Misurina reported a significant decrease in mite allergen-induced basophil histamine release, mite-specific serum IgE level, and methacholine BHR with reversal of this trend after 15 days of allergen re-exposure at sea level.[41] Peroni *et al* found a significant reduction in total and mite-specific serum IgE and allergen-induced BHR after three and nine months at Misurina.[42] These results suggest that avoidance of mite allergen leads to a decrease in airway inflammation with consequent improvement in non-specific BHR and symptoms, and that re-exposure results in a rapid relapse. The high altitude studies were not controlled and there is a possibility that avoidance of other domestic factors such as exposure to pets or environmental tobacco smoke contributed to the observed improvement in asthma control. Nevertheless, mite avoidance is the most plausible reason for clinical success. These high altitude studies (table 1[38–48]) suggest that it is essential to achieve and maintain a major reduction in allergen levels and that, even with such a reduction in exposure, it may take many months for the effect on symptoms, medication use, pulmonary function, non-specific and specific BHR, and immunological parameters to become fully apparent.

An uncontrolled study of the effect of mite-free conditions at lower altitudes in which patients were admitted to the "allergen-free" environment of a hospital room (allergen level <0.2 μg Der p 1/g) did result in improved airway reactivity and reduced treatment requirements, but the benefits were transient.[49] Moving asthma patients into new "healthy homes" equipped with mechanical ventilation resulted in an increase in lung function and a decrease in medication use.[50]

All the studies reviewed in table 1 suggest that asthmatic subjects allergic to mites improve when moved from their homes into a low allergen environment. They also provide information on the duration of avoidance necessary. For example, studies of mite allergen

Table 1 High altitude studies

Author	*Location (altitude)*	*Study design (duration of stay)*	*Clinical outcome*
Kerrebijn[38] (Platts-Mills and Chapman[39])	Davos, Switzerland (1560 m)	House dust sensitive children (1 year)	Clinical improvement; reduction in BHR (histamine)
Morrison Smith[43]	Davos, Switzerland (1560 m) Font-Romeu, France	212 children (Davos) 37 children (Font-Romeu)	Improvement in symptoms and reduction in medication
Boner *et al*[40]	Misurina, Italy (1756 m)	14 mite allergic children (8 months)	Improvement of LF; reduction in BHR (exercise); reduction in medication
Piacentini *et al*[41]	Misurina, Italy (1756 m)	20 allergic children (80 days)	Drop in antigen-induced basophil histamine release; reduction in BHR (methacholine) and IgE
Boner *et al*[44]	Misurina, Italy (1756 m)	12 mite sensitive children (6+3 months; 3 months at home)	Change in serum ECP and EPX and total IgE during exposure (3 months summer holidays at home)
Simon *et al*[45]	Davos, Switzerland (1560 m)	17 mite sensitive children (5 weeks)	Decreased number of eosinophils and expression of T lymphocyte activation markers; LF improved
Peroni *et al*[42]	Misurina, Italy (1756 m)	Mite allergic children (9 months)	Decrease in total and specific IgE; reduction in BHR (exercise, histamine and allergen challenge)
Valeta *et al*[46]	Misurina, Italy (1756 m)	12 mite allergic children (3 months)	Decrease in PEF variability and improvement in BHR; after 3 weeks at homes PEF and BHR worsened
van Velzen *et al*[47]	Davos, Switzerland (1560 m)	16 allergic children (1 month)	Reduction in BHR (AMP challenge); improvement in PEF variability; reduction in eosinophils
Piacentini *et al*[48]	Misurina, Italy (1756 m)	16 mite sensitive children (3 months)	Reduction in BHR (methacholine); decrease in the percentage of sputum eosinophils

LF = lung function; BHR = bronchial hyperreactivity; PEF = peak expiratory flow.

avoidance in patients' homes have to be sufficiently long – if BHR is the primary outcome probably six months to a year is required.

Allergen avoidance in homes: practical measures

The real challenge facing practising physicians is to create a low allergen environment in patients' homes. Although not easy, it is possible to achieve substantial reductions in allergen exposure. Effective control strategies should be tailored to individual allergens, flexible to suit individual needs and cost effective. Many different avoidance measures for mite allergens have been tested with some widely exaggerated claims, and only a few have been subjected to controlled trials. It is important to make a clear distinction between those measures that have been only tested in the laboratory, those tested in field trials, and those tested in clinical trials.

DISTRIBUTION AND AERODYNAMIC PROPERTIES OF INDOOR ALLERGENS: RELEVANCE TO AVOIDANCE

Knowledge of the sources and aerodynamics of allergen-carrying particles is essential for the design of successful strategies to reduce personal exposure. Allergens from mites, cats, dogs, and cockroaches have different aerodynamic properties (table 2).[51–58] Mite and cockroach allergens can be detected in the air in significant amounts only after vigorous disturbance[51–54] and are contained within relatively large particles (>10 μm diameter).[55 56] In contrast, airborne cat and dog allergens are readily measured in houses with pets (and in a quarter of the homes without pets), and approximately 25% of airborne Fel d 1 and Can f 1 is associated with small particles (<5 μm diameter).[56–58] This underlies the difference in the clinical presentation of the disease. Mite and cockroach sensitive asthmatics are usually unaware of the relationship between allergen exposure at home and asthma symptoms (exposure is low grade and chronic). The large particles, however, may contain a large quantity of allergen and even small numbers may cause a significant inflammatory response when impacted in the airways. In contrast, patients allergic to cats or dogs often develop symptoms within minutes of entering a home with a pet due to the inhalation of large amounts of airborne allergen on small particles which can penetrate deep into the respiratory tract inducing acute asthma.[57 58] Application of this information is important and implies, for example, that air filtration units have no place in mite or cockroach avoidance but may be useful in removing cat and dog allergens from the air.

It is important to know where patients receive most of their exposure. The bed is the most important source of mite allergens and lowering exposure in the bedroom is the primary target of avoidance. In contrast, it is likely that most exposure to allergens of domestic pets occurs in the living room area and this must be taken into account when planning avoidance strategies.

Table 2 Differences in the aerodynamic properties between house dust mite and cockroach and pet allergens

Allergen	*Particle size*	*Airborne level*	
		Undisturbed	*Disturbed*
Mite: Group 1 Group 2	Large particles >10 μm	Undetectable with conventional assays (<0.2 ng/m^3 for mite allergens, <0.02 ng/m^3 for cockroach)	Detectable after vigorous disturbance
Cockroach: Bla g 1 Bla g 2			
		Homes with animal	*Homes without animal*
Cat: Fel d 1	Large particles >5 μm (~75%)	Detectable in all homes. Levels 4–5 times higher with animal in the room	Detectable in about one third of the homes without artificial disturbance
Dog: Can f 1	Small particles <5 μm (~25%)		

CONTROL OF HOUSE DUST MITES AND MITE ALLERGENS

Bed and bedding

Covers: the most effective and probably most important avoidance measure is to cover the mattress, pillows, and duvet with covers that are impermeable to mite allergens. These covers were initially made of plastic and uncomfortable to sleep on, but the development

of water vapour permeable fabrics which are both impermeable to mite allergens and comfortable have considerably increased compliance. Allergen levels are dramatically reduced after the introduction of covers[59] which should be robust, easily fitted, and easily cleaned as their effectiveness is reduced if they are damaged. Mite allergen can accumulate on the covers, possibly by circulation from the carpet,[60] and it is important that covers are wiped at each change of bedding.

Washing: all exposed bedding should be washed at 55°C as this is the temperature that kills mites in the bedding.[61] The cold cycle of laundry washing reduces allergen levels but most of the mites survive.[61] Additives for the detergents providing a concentration of 0.03% benzyl benzoate, or dilute solutions of essential oils in normal and low temperature washing, provide alternative methods of mite control.[62 63]

Feather versus synthetic pillows: asthmatic patients are often told to avoid using feather pillows and to replace them with those filled with synthetic materials. This has been challenged recently, first with the finding that synthetic pillows were a risk factor for severe asthma[64] and then with the report that polyester filled pillows contained more mite allergens than those filled with feathers.[65]

Carpets and upholstered furniture

Carpets are an important microhabitat for mite colonisation and a possible source of allergen from which beds can be reinfested.[66] Ideally, fitted carpets should be replaced with polished wood or vinyl flooring. Exposure of carpets to direct strong sunlight for at least three hours kills mites and this simple and effective treatment may be used in loosely fitted carpets in certain climatic areas.[67] Steam cleaning may be used as a method of killing mites and reducing allergen levels in carpets.[68 69]

Acaricides: a number of different chemicals that kill mites (acaricides) have been identified and have been shown to be effective under laboratory conditions.[70] However, data on whether these chemicals can be successfully applied to carpets and upholstered furniture are still conflicting. Le Mao *et al* reported that long term mite avoidance can be maintained by twice yearly treatments with benzyl benzoate,[71] but other studies could not confirm this.[72 73] The method of application of the benzyl benzoate moist powder on carpets is very important.[74] When carpets were treated for four hours only a very modest effect was observed, whilst allowing the powder to remain on the carpet for 12–18 hours with repeated brushing followed by vigorous vacuum cleaning reduced the concentration of mite allergens one month later. Allergen levels rebounded after two months, suggesting that repeated application every 2–3 months is necessary to control mite allergen levels.[74] Thus, the main problem of chemical treatment is not its ability to kill mites but the means of getting the chemicals to penetrate deep into carpets and soft furnishings, the persistence of mite allergen until recolonisation occurs, and the nuisance of frequent reapplications. Acaricides are ineffective on mattresses and upholstered furniture.[72–74]

Liquid nitrogen: mites can be killed by freezing with liquid nitrogen.[75] The technique can only be carried out by a trained operator which limits its use, especially since treatment needs to be repeated regularly. When used, both acaricides and liquid nitrogen should be combined with intensive vacuum cleaning following administration.[76]

Tannic acid: the protein denaturing properties of tannic acid are well recognised and it has been recommended for the reduction of indoor allergen levels in house dust. Woodfolk *et al* confirmed the allergen denaturing properties of tannic acid but also showed that high levels of proteins in dust – for example, cat allergen in a home with a cat – blocked its effects.[77] This suggests that $\geq 1\%$ tannic acid solution could reduce mite allergen levels, but only with aggressive vacuum cleaning being carried out before the treatment and in homes without pets. Products which combine both an acaricide and tannic acid have been shown to reduce skin test reactivity of the extracts prepared from dust taken from the patient's house and to have a temporary effect on mites and mite allergens.[78–80]

Vacuum cleaning: intensive vacuum cleaning may remove large amounts of dust from carpets, reducing the size of allergen reservoir.[76] However, some vacuum cleaners (with inadequate exhaust filtration) may increase airborne Der p 1 levels during use.[81 82] These results suggest that atopic asthmatic patients should use HEPA-filter vacuum cleaners with double thickness vacuum cleaner bags, although the benefits have not been established in a clinical trial. Ducted systems offer similar advantages.

Humidity control

High levels of humidity in the microhabitats are essential for mite population growth and reducing humidity may be an effective method of control. However, detailed models of the humidity profile of domestic microclimates in relation to humans in bed, for example, are not yet available. Reduction of central humidity alone may be ineffective in reducing humidity in mite microhabitats such as in the middle of a mattress. Central mechanical ventilation heat recovery (MVHR) units have been suggested as a means of reducing the numbers of mites in homes by reducing indoor humidity and several studies from Scandinavia have reported successful control of house dust mites within domestic dwellings.[83–85] However, MVHR units have failed to reduce indoor humidity sufficiently and to decrease mite allergens in the UK.[86] Increased ventilation is more likely to be applicable in climates with cold dry winters where the incoming air is of a sufficiently low humidity to retard mite growth and houses are very "tight" and energy efficient.[87] Similarly, a dehumidifier placed centrally in the house failed to affect allergen levels in a mild humid climate like the UK with relatively poorly insulated houses.[88] It is important to devise allergen avoidance measures that are not only

Table 3 Measures for reducing house dust mite allergen exposure

(1)	Encase mattress, pillow and quilt in impermeable covers
(2)	Wash all bedding in the hot cycle (55–60°C) weekly
(3)	Replace carpets with linoleum or wood flooring
(4)	If carpets cannot be removed, treat with acaricides and/or tannic acid
(5)	Minimise upholstered furniture/replace with leather furniture
(6)	Keep dust accumulating objects in closed cupboards
(7)	Use a vacuum cleaner with integral HEPA filter and double thickness bags
(8)	Replace curtains with blinds or easily washable (hot cycle) curtains
(9)	Hot wash/freeze soft toys

allergen-specific but also specific to a particular geographical area with housing and climatic conditions being taken into account.

Air filtration and ionisers

Due to the aerodynamic characteristics of mite allergens it makes little sense to use air filtration units and ionisers as the only way of reducing personal exposure.

Conclusions: house dust mite avoidance measures

A large number of proprietary mite allergen control products are currently available on the market with claims of clinical efficacy that have not been adequately tested. Mites live in different sites throughout the house and it is unlikely that a single measure can solve the problem of exposure. An integrated approach including barrier methods, dust removal and removal of mite microhabitats is needed if a comprehensive reduction in mite allergen exposure is to be achieved (table 3). Even in the same geographical area there is a marked difference in mite allergen levels between houses, and the design of houses has a profound effect on mite allergen levels. These issues need to be addressed in designing and building "low allergen houses".

PET ALLERGEN AVOIDANCE

Up to 60% of asthmatic patients show IgE mediated hypersensitivity to cat and/or dog allergen and up to one third of these sensitised individuals live in a home with a pet. In some parts of the world complete avoidance of pet allergens can be extremely difficult as sensitised patients can be exposed to pet allergens not only in homes with pets, but also in those without pets and in public buildings and public transport.[57 89–94]

Breed, sex and castration

The major cat allergen Fel d 1 is produced primarily in the sebaceous glands and in the basal squamous epithelial cells of the skin[95 96] with very high levels reported in cat anal secretions.[97] Fel d 1 production is under hormonal control[98] and the castration of male cats results in a 3–5 fold reduction of Fel d 1 concentration in skin washing with testosterone treatment restoring the Fel d 1 levels to pre-castration values.[99] It has recently been suggested that Fel d 1 production is higher in male than in female cats,[100] but the observed gender differences in Fel d 1 secretion are too low to suggest that patients allergic to cats could benefit by getting a female rather than a male cat or by castrating their male cats.

Another important question is whether one breed of cat (or dog) can produce more allergens or different allergens than any other? Since all domestic cats belong to the same species, it is unlikely that different breeds would produce breed-specific allergen molecules although there may be variation in the relative concentration of allergen produced by different breeds – for example, short hair and long hair.[101]

Removal of the animal from the home

The best way to reduce exposure to cat or dog allergen is to remove the animal from the home. Even after permanent removal of the animal it can take many months before reservoir allergen levels decrease.[102] Unfortunately, despite continued symptoms, many patients allergic to cats and/or dogs insist on keeping their pet. Asthma is often severe and difficult to control in pet sensitised asthmatics who continue to be exposed to the high allergen levels because they refuse to get rid of the family pet. Every effort should therefore be made to reduce exposure to pet allergens in homes where pets may coexist with a sensitised individual.

Control of airborne allergen levels with a pet in home

Airborne pet allergen levels increase by approximately fivefold when the pet is in the room, indicating that the immediate presence of a pet contributes to airborne allergen levels.[57] When it is not possible to remove the animal, the pet should be kept out of the bedroom and preferably outdoors or in a well ventilated area such as the kitchen.

Cat and dog washing: there is controversy on the effect of washing the cat on Fel d 1 levels.[103–105] A recent study showed no effect of washing in decreasing allergen shedding, but only two litres of water were used to wash a cat.[103] Other trials, however, have shown that large quantities of allergen can be removed from cats by immersion in tap water resulting in a decreased concentration of airborne allergen.[104 105] Washing dogs thoroughly in a bath using shampoo significantly reduces the levels of dog allergen in fur and dander samples.[106]

Air cleaners and vacuum cleaners: HEPA filter air cleaners can significantly reduce airborne concentrations of cat and dog allergens in homes with pets[106] and vacuum cleaners with built-in HEPA filters and double thickness vacuum cleaner bags remove allergen from dust reservoirs without leaking Fel d 1 and Can f 1.[107 108] As carpets may accumulate allergens up to a level 100 times that of polished floors, carpeting and soft furnishings should ideally be removed.[105]

Since getting rid of the family pet is rarely a viable option, we currently advise a set of measures listed in table 4 to patients who are allergic to cats or dogs and persist in keeping their pet. The clinical benefit afforded by the proposed avoidance measures has not yet been

Table 4 Measures for reducing cat/dog allergen exposure

(1)	Remove cat/dog from the home
If the pet cannot be removed:	
(1)	Keep the pet out of the main living areas and bedrooms
(2)	Install HEPA air cleaners in the main living areas and bedrooms
(3)	Have the pet washed twice a week
(4)	Thoroughly clean upholstered furniture/replace with leather furniture
(5)	Replace carpets with linoleum or wood flooring
(6)	Fit allergen-impermeable bedding covers
(7)	Use a vacuum cleaner with integral HEPA filter and double thickness bags

established. A recent study of cat owning patients allergic to cats with allergic rhinitis found that environmental control measures that were sufficient to reduce Fel d 1 levels by 91.4% over a 12 month period were associated with a significant improvement in clinical symptoms when used in combination with nasal steroids compared with medication alone.[109] This indicates that the best way to treat allergic disease is to combine environmental control and medication.

AVOIDANCE OF COCKROACH ALLERGENS

Sensitisation to cockroach allergens is an important risk factor for asthma in the USA where cockroach infestation is common in substandard housing apartment complexes.[23 24 27 29] Cockroaches have also been reported to be an important cause of asthma in the Far East (Taiwan, Japan) and there have been recent reports of cockroach-induced asthma in France.[28 55] In the colder climate of the UK cockroach allergens are not routinely used in the evaluation of allergic disease although there have been recent cases of cockroach infestation associated with asthma in the London Borough of Tower Hamlets (Dr C Luczynska, personal communication). In the USA cockroach asthma occurs primarily among lower socioeconomic groups and minority populations living in substandard housing. This patient population has the highest mortality and morbidity rates from asthma and is also the least compliant with any form of asthma treatment.

Both physical and chemical procedures are used to control cockroach populations in houses. Reducing access to food and water is critical so waste food should be removed and surface water should be contained by reducing leakage through faulty taps and pipework and reducing condensation by improved ventilation. Cockroach access should be restricted by caulking and sealing cracks and holes in the plasterwork and flooring. Several chemicals are marketed in the USA and elsewhere for controlling cockroach infestations including diazinon, chlorpyrifos, and boric acid. The most useful for patients with allergic disease are bait stations where the chemical is retained within a plastic housing. These stations may contain hydramethylnon (marketed as Combat) or avermectin (Avert). A paste formulation of hydramethylonon (Siege) is also marketed for use on cockroach runways and underneath counters etc.

Bait stations are generally effective in reducing cockroach levels for 2–3 months. The effect of cockroach control measures on allergen levels in houses has not been extensively studied, though a number of trials are underway. Cockroaches in apartment complexes are especially difficult to treat because of reinfestation from adjacent apartments. Asthma is the only disease unequivocally associated with cockroach infestation of houses and it is an important public health problem in towns and cities across the USA where housing conditions sustain large cockroach populations. Many patients are unaware that cockroaches may cause asthma so attempts to reduce cockroach allergen exposure must rely on improving patient education and concerted attempts by pest control companies and public health departments to reduce cockroach infestation.

Clinical trials of mite allergen avoidance in patients' homes

Having explored the science behind allergen avoidance strategies, the important question is whether allergen avoidance in homes by these techniques improves asthma control in sensitised patients. Trials of mite allergen avoidance in allergic diseases are reviewed in table 5. It is difficult to conduct a placebo-controlled trial in this area because the combination of skin weal and home visit is a potent stimulus for a change in behaviour resulting in increased cleaning, removal of mite habitats, and reduction in allergen levels. Virtually every controlled study has observed a significant reduction in mite allergen levels and sometimes improved clinical symptoms in both the control and active groups. A population study on an unselected group of asthmatic subjects with retrospective analysis of atopic status – for example, specific serum IgE determined from the "bank" of blood samples taken at the beginning of the study – would partially address this problem by "blinding" patients to their allergen sensitivities. As stressed previously, a successful trial would need to achieve and maintain a major reduction in allergen levels, be sufficiently long (probably not less than a year with a run in period of at least six weeks), and have adequate power.

There are conflicting data on the effectiveness of allergen avoidance carried out in houses, primarily because most of the studies have been small, poorly controlled, and have often used measures that we now realise do not reduce mite allergen exposure. Consequently, many fail to show clinical benefits. Thirty one studies of mite allergen avoidance in homes of asthmatic patients are listed in table 5,[73 110–139] seven of which used air cleaners, ionisers or precipitators[114 118 122 124 126 130 131] which is illogical due to the aerodynamics of mite allergens. Of the remaining 24, seven showed little or no effect of avoidance measures on mite/allergen levels,[73 112 116 123 129 132 133] three were uncontrolled,[110 115 125] one was not randomised,[117] one did not monitor the effects on mite/allergen levels,[111] one showed colonisation of bedding during the study,[113] one showed no difference in allergen levels between the two study groups at the end of the study,[128] and one used an

Table 5 Clinical studies of measures aimed at reduction in house dust mite allergen levels applied in homes of patients with asthma

Author	*Study design and duration*	*Avoidance measures*	*Effect on mites/allergen*	*Clinical outcome*
Sarsfield *et al*[110] (Leeds, UK)	Ch, As, MS; n = 14; UC; 3–12 months	Mattress encased (plastic covers); synthetic pillows; bedding washed weekly; dusting, vacuuming	Reduction in mite counts (from 80 to 2; p<0.01)	Improvement in symptom scores (9 to 1.89; p<0.05)
Burr *et al*[111] (Cardiff, UK)	Ad, As, MS; n = 32; crossover PC; 6 weeks	Mattress encased (plastic covers); vacuum cleaning of the bed; laundering of the bedding	Not monitored	No improvement in daily PEF reading or drug usage
Burr *et al*[112] (Cardiff, UK)	Ch, As, MS; n = 53; PC; 8 weeks	Mattress, carpets and upholstery vacuumed; blankets, sheets laundered; bedding washed; feather pillows, quilts replaced; soft toys removed	No difference in mite counts before and after treatment	Both active and control group improved, no difference between the groups
Burr *et al*[113] (Cardiff, UK)	Ch, As, MS; n = 21; crossover, C; 1 month + 1 month	New sleeping bags, pillows and blankets; mattress encased (plastic covers); carpets vacuumed	Colonisation occurred on new bedding after second study period	PEF variability lower during the treated period, but the difference NS; majority with higher PEF during the treated period (p<0.01)
Mitchell and Elliott[114] (Auckland, N. Zealand)	Ch, As, MS; n = 10; C, crossover; 8 weeks (4 + 4)	Electrostatic precipitator in the child's bedroom	Not monitored	Control vs active period; PEF: NS; medication use: NS
Korsgaard[115] (Aarhus, Denmark)	Ad, As and/or AR, HDS; n = 23; UC; 6 months	Mattress encased (plastic covers), n = 3; synthetic pillows, n = 22; bedroom carpet removed, n = 7; dusting, vacuuming	Not monitored in the study group over time	Beneficial effect reported by 15 patients, no change by 4
Korsgaard[116] (Aarhus, Denmark)	Ad, Ch, As, MS; n = 46; C; 12 weeks run in + 12 weeks intervention	Mattress vacuumed twice; synthetic pillows and quilts; bedding washed; bedroom carpet removed; bedroom aired + no plants	Difference between groups in BC (p<0.01) but not in LC or M	Improvement active vs control group: PEF: NS (both improved), symptoms: p<0.05, medication: NS
Murray and Ferguson[117] (Vancouver, Canada)	Ch, As, MS and/or HDS; n = 20; C; 1 month	Mattress, pillows encased (vinyl covers); toys, carpets and upholstery removed (bedroom); washing, dusting, vacuuming	Not monitored	Improvement active vs control group: symptoms (p<0.01), medication (p<0.5), PEF (p<0.05) and BHR (p<0.001)
Bowler *et al*[118] (Brisbane, Australia)	Ad, Ch, As, MS; n = 9; PC, crossover; 4 weeks (2 + 2)	Active period: mattress and pillow covered; washing, dusting, vacuuming; dust retardant and anti-static spray; active electrostatic filter of HEPA filter; placebo: inactivated air filter	Not monitored	Control vs active period: symptom scores: NS; PEF: NS
Walshaw and Evans[119] (Liverpool, UK)	Ad, As; n = 50; C; 1 year	Mattress, pillows encased (plastic covers); synthetic duvets; bedroom carpet, upholstery removed (n = 7); washing, dusting, vacuuming	Significant fall in mite counts in the active (p<0.001), but not in the control group	Improvement in MS As in active group: FEV_1/FVC (p<0.02), PEFR (p<0.05), BHR (PC_{20}) (p<0.01), medication (p<0.05), total IgE (p<0.05)
Gillies *et al*[120] (Leeds, UK)	Ch, As; n = 26; C; A – 12/52 avoidance, B 6/52 observation + 6/52 avoidance	Mattress, pillows encased (plastic covers); synthetic bedding; soft toys and pets excluded from bedroom; vacuuming	Mite counts: A – 40 (start), 1.2 (6/52), 0.8 (12/52); B – 22 (start), 10 (6/52), 2 (12/52)	Fall in total serum IgE in MS Ch (p<0.005); BHR, symptoms, medication use and PEF: NS
Dorward *et al*[121] (Glasgow, UK)	Ad, As, MS; n = 21; C; 8 weeks	Mattress and bedroom carpet treated with liquid nitrogen; washing, dusting, vacuuming; soft toys, plants and upholstery excluded from bedroom	Fall in number of intact mites in active group (p<0.01); no change in control	Active vs control: fall in the number of hours wheezing (p<0.05); reduction in BHR (p<0.02); total and specific IgE: NS
Verrall *et al*[122] (Hamilton, Ontario, Canada)	Ad, Ch, As, MS; n = 13; DB, crossover; 4 periods; 3/52 each	Laminar flow air cleaner device in the bedroom	Not monitored	No difference between the groups in the number of symptom-free days and symptom severity and PEFR
Reiser *et al*[123] (London, UK)	Ch, As, MS; n = 46; DB PC; 24 weeks	Mattress sprayed once every 2 weeks for 3 months with either Natamycin or placebo; mattress vacuumed	Small, NS trend to a fall in Der p 1 in both groups	No change in BHR, symptoms and LF
Reisman *et al*[124] (Buffalo, USA)	Ad, Ch, As, AR, MS; n = 32; DB PC, crossover; 8 weeks (4 + 4)	Active period: HEPA air cleaner; placebo period: placebo filter	Not monitored	Control vs active period: symptom and medication scores NS; last 2 weeks of each period: nasal congestion, discharge eye irritation (p<0.05); asthma symptoms NS
Morrow Brown and Merrett[125] (Derby, UK)	Ad and Ch, As and/or AR and/or AD, MS; n = 25; UC; 12 months	Acarosan foam on mattress and bedding and moist powder on carpets and soft furniture	Reduction in Der p 1 level	As (n = 12): 7 better, 5 no change; AR (n = 8): 6 improved 2 no change; AD (n = 5): 2 improved
Antonicelli *et al*[126] (Ancona, Italy)	Ad, Ch, As, MS; n = 9; PC, crossover; 16 weeks (8 + 8)	Active period: HEPA air cleaner; placebo period: placebo filter; routine house cleaning	No difference in reservoir levels of mite allergens between the periods; fall within both groups (p<0.05)	Control vs active period: AR symptoms: NS; LF: NS; PEF: NS; BHR (methacholine): NS
Ehnert *et al*[127] (Berlin, Germany)	Ch, As, MS; n = 24; DB PC; 12 months	A: mattress, pillow and quilt covered, carpets sprayed (3% tannic acid) 4 monthly; B: mattress and carpet treated with benzyl benzoate; C: placebo on mattress and carpet	Significant decrease in Der 1 in group A (p<0.005); no change in groups B and C	Significant increase in BHR (PC_{20}) in the encasing regimen group (A): within group p<0.01; no change in groups B and C: between groups p<0.05
Huss *et al*[128] (Washington, USA)	Ad, As, MS; n = 52; 12 weeks	Investigated the effect of supplementary computer instruction on adherence to mite avoidance measures	Significantly lower group 1 level in bedroom carpet in computer instructed group	No change in FEV_1; computer instructed group significantly less symptomatic by study weeks 9 and 10 (p = 0.033)
Dieterman *et al*[129] (Strasbourg, France)	Ad, Ch, As, MS; n = 26; DB PC; 12 months	Benzyl benzoate foam or placebo on mattress and upholstery; benzyl benzoate powder or placebo on carpets	No significant difference in Der 1 between the groups	Active vs placebo: clinical score, drug score, LF, PEF: NS
Warner *et al*[130] (London, UK)	Ch, As, MS; n = 20; DB PC crossover; 12 weeks (6 + 6)	Active period: active ionisers; placebo period: placebo ionisers	Active vs control period: airborne Der p 1 (p<0.0001)	Active vs control period: PEF: NS; symptom scores: NS (trend towards increased cough during active period); medication: NS
Warburton *et al*[131] (Manchester, UK)	Ad, As, MS; n = 12; crossover (active + passive period: 30 + 24 days)	Active period: HEPA air cleaner; passive period: no HEPA air cleaner	Airborne Der p 1 below detection limit in two thirds of samples	Active vs passive period: symptom scores: NS; LF: NS; BHR (histamine): NS; PEF: NS
Marks *et al*[132] (Sydney, Australia)	Ad, Ch, As; PC; 3 months run-in + 6 months treatment	Active tannic acid/acaricide to mattress, pillow, duvet, blankets, carpets and upholstery; mattress, pillow and quilt covered; placebo: inactive spray	At 2 weeks Der p 1 fell to 29% of baseline (p = 0.04 compared with placebo); 3 and 6 months: NS	Significant improvement in symptoms in both groups, but active vs placebo: NS; LF and BHR, active vs placebo: NS

contd

Table 5 contd

Author	*Study design and duration*	*Avoidance measures*	*Effect on mites/allergen*	*Clinical outcome*
Sette et al[133] (Verona, Italy)	Ch, As, MS; n=32	All homes: synthetic materials in the bedroom; daily vacuum cleaning and mopping; no feather pillows. Mattress treated with benzyl benzoate or placebo (n=24)	Assessed by Acarex test: no difference between 3 study group	No difference in BHR (PC_{20}) between 3 study groups; no change in serum IgE concentrations
Huss *et al*[73] (Washington, USA)	Ad, As; n=12; DB PC; 12 months	Benzyl benzoate powder (n=6) or placebo (n=6)	No change in mite allergen content in BC or LC	No difference in LF and PEF between the groups
Geller-Bernstein *et al*[134] (Rehovot, Israel)	Ch, As, AR, MS; n=32 (As n=31); C, DB	Acardust or placebo in bedrooms on day 0 and day 90; bedsheet changed every week, damp dusting daily; vacuuming weekly	Active: fall in Der f 1 from 10.05 to 4.15: control: fall in Der f 1 from 6.01 to 3.01	Significant improvement in severity of asthma; no difference in PEFR and wheeze
Carswell *et al*[135] (Bristol, UK)	Ch, As, MS; n=49; DB PC; 6 months	Benzyl benzoate powder or placebo on BC; benzyl benzoate foam or placebo on mattress, pillow and quilt; mattress, pillow and quilt covered (active or placebo); washing, dusting, vacuuming; soft toys excluded	M: 100% reduction in active vs 53% reduction in placebo ($p<0.001$); BC: active vs placebo : NS	Active vs placebo: PEF: NS; BHR (histamine): NS; LF (FEV_1): $p<0.05$; symptoms: $p<0.05$; medication use: $p<0.01$
Frederick *et al*[136] (Southampton, UK)	Ch, As, MS; n=31; single blind, crossover; run-in 2/52, treatment periods 3/12	Period 1: group 1: active covers, group 2: placebo covers (3/12); wash out 1/12; period 2: group 1: placebo covers, group 2: active covers (3/12)	Active vs placebo: significant reduction in Der p 1 in mattress, duvet and pillow ($p<0.0001$)	Active vs placebo: significantly lower levels of eosinophil peroxidase ($p=0.02$); within group: symptoms, FEV_1, BHR (PC_{20} histamine): NS
van der Heide *et al*[137] (Groningen, Holland)	Ad, As, MS; n=45; DB, randomised, 3 parallel group; 6 months	Group 1: active air cleaner; group 2: placebo air cleaner+mattress and pillow covers; group 3: active air cleaner+mattress and pillow covers	Significant reduction in Der p 1 with covers (groups 2 and 3) compared with group 1	Significant improvement in BHR (histamine) in group 3; trend to improvement in group 2
Halken *et al*[138] (Odense, Denmark)	Ch, As, MS; n=60; DB PC 12 months	Active group: semipermeable mattress and pillow covers; control group: cotton mattress and pillow covers	Active vs placebo: significant reduction in Der p 1 in mattress	Significant reduction in the dose of inhaled steroids, allergen specific BHR, morning PEFR and night asthma symptom score
van der Heide *et al*[139] (Groningen, Holland)	Ad, As, MS; n=59; DB PC randomised, 3 parallel group; 12 months	Group 1: Acarosan on mattresses and floors (n=21); group 2: placebo (n=19); group 3: mattress and pillow covers (n=19)	Significant reduction in Der p 1 with covers (group 3) compared with groups 1 and 2	Significant improvement in BHR (histamine) in groups 1 and 3

Ad=adults; Ch=children; As=asthma; MS=mite sensitive; HDS=house dust sensitive; AD=atopic dermatitis; AR=allergic rhinitis; P=placebo; DB=double-blind; C=controlled; UC=uncontrolled; BC=bedroom carpet; LC=living room carpet; M=mattress; NS=not significant; Der 1=Der p 1+Der f 1.

Table 6 House dust mite allergen avoidance in allergic rhinitis and atopic dermatitis

Author	*Study design and duration*	*Avoidance measures*	*Effect on mites/allergen*	*Clinical outcome*
Roberts[140] (Swansea, UK)	Ch, Ad, AD, MS; n=18; UC; 6 weeks	Mattress encased (plastic covers); regular vacuuming of bedding, bedroom carpets and curtains	Not monitored	Fifteen patients improved, three remained unchanged
August[141] (UK)	Ch, Ad, AD, MS; n=37; UC; 4–56 weeks	Mattress encased (plastic covers); regular vacuuming of mattress; carpets removed or vacuumed	Not monitored	19% complete remission, 41% almost clear, 27% better, 13% unchanged
Colleff *et al*[142] (Glasgow, UK)	Ad, Ch, AD, MS; n=20; PC; 12 weeks	NV=Natamycin spray and vacuuming (n=6); Nv=Natamycin spray and no vacuuming (n=4); nV=placebo and vacuuming (n=5); nv=placebo and no vacuuming (n=5)	Mite counts: 26% fall in NV ($p<0.01$), 50% fall in nV ($p<0.01$), 15% rise in Nv, 25% fall in nV (both NS)	Symptom scores: improvement rates 24% Nv, 20.4% nv, 8.4% NV and 0.7% nV. Fall in mite specific IgE: NV ($p<0.05$)
Kniest *et al*[143] (Utrecht, Holland)	Ch, Ad, AR; n=20; DB PC parallel group; 12 months	Benzyl benzoate or placebo on mattress, upholstery, soft toys and carpets at 0 and 6 months; intensive cleaning	Active vs control group: Acarex test ($p<0.05$)	Active vs control (matched pairs): symptom scores ($p<0.05$); physicians' assessment (NS); medication (NS); total IgE ($p<0.01$)
Howarth *et al*[144] (Southampton, UK)	Ad, AR, MS; n=35; DB PC; 6 weeks	Mattress, pillows and duvet covered in active or placebo covers	Active vs control group: significant reduction in Der p 1	Active vs control: improvement in sneezing ($p<0.02$), rhinorrhoea ($p<0.01$) and nasal blockage ($p<0.006$)
Sanda *et al*[145] (Nagoya, Japan)	Ad, AD; n=30: (3–4 weeks)	Patients hospitalised to clean room	Not monitored	Improvement in symptoms, long term remission, decrease in eosinophils and mite-specific IgG
Tan *et al*[146] (Liverpool, UK)	Ad, Ch, AD, MS; n=48; DB PC; 6 months	Active: mattress, pillow and quilt covered, carpets sprayed (benzyl benzoate+tannic acid), high filtration vacuum cleaner; control: placebo covers and spray, standard vacuum cleaner	Der p 1 in carpets: median reduction 91% active, 89% control mattress: insufficient dust (active)	Active vs control: change in eczema severity score ($p<0.01$) final eczema severity score ($p<0.01$); mean final area affected ($p<0.01$)

For definition of abbreviations see footnote to table 5.

acaricide without good evidence of the effect on mite allergens.[134]

The remaining nine studies showed a significant reduction in mite counts and/or mite allergen levels. In three of these the period of treatment was too short[120 121 136] but nonetheless showed some effect (fall in the number of hours of wheezing and some effect on BHR,[121] fall in total serum IgE,[120] reduction in the levels of eosinophil peroxidase[136]).

The final six controlled studies achieved both a significant reduction in mite/allergen levels and were sufficiently long to show an effect on outcomes.[119 127 135 137–139] All six studies showed evidence of clinical benefit such as a significant improvement in lung function, symptoms, and medication use but there was no effect on BHR (six month study, probably too short for this outcome),[135] a significant increase in BHR (PC_{20}) was reported after eight months,[127] improvement in pulmonary function, BHR, medication, and IgE was seen[119] and a reduction in the dose of inhaled steroid, reduction in non-specific BHR, and improvement in symptoms

and PEFR was found.[138] In a multiple regression analysis of the factors contributing to the improvement of BHR van der Heide *et al* concluded that the greatest improvement was found in patients who had the largest decrease in Der p 1 concentration in mattress dust.[137]

Allergen avoidance in the treatment of other atopic diseases

Allergen avoidance also improves disease control in other atopic disorders such as atopic dermatitis and allergic rhinitis. The relevant clinical trials[140–146] are reviewed in table 6.

Conclusions

Minimising the impact of identified environmental risk factors such as house dust mites, cats, and dogs is a first step in reducing the severity of asthma.[37] Although environmental control is difficult, it should be an integral part of the overall management of allergen sensitised patients. As a recommendation for future trials the Third International Workshop on Indoor Allergens and Asthma concluded: "There is an urgent need to develop adequately powered, randomised, controlled studies to investigate the potential benefits of low allergen domestic environments in patients with allergic disease. Such studies need to address compliance, cost effectiveness, be of adequate length (e.g. 12 months), and be tailored for different socioeconomic groups and age groups".[147] The 1995 revision of the British Thoracic Society asthma guidelines states: "Support for house dust mite avoidance measures reflects a change to the 1993 guidelines but further research into methodology and duration of action of these measures is needed".[37] If the benefits attributable to allergen avoidance were instead attributed to a new drug, that drug would be the subject of trials involving thousands of patients. It is unfortunate that the perceived lack of commercial benefit has discouraged large scale, population based trials. There remains an urgent need to develop a large scale trial of the widespread applicability of mite allergen avoidance and the effect on patient symptoms, exacerbation rate, use of medication, and overall health costs.

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