Clinical Management Review

House Dust Mite Respiratory Allergy: An Overview of Current Therapeutic Strategies

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Although house dust mite (HDM) allergy is a major cause of respiratory allergic disease, specific diagnosis and effective treatment both present unresolved challenges. Guidelines for the treatment of allergic rhinitis and asthma are well supported in the literature, but specific evidence on the efficacy of pharmacotherapy treatment for known HDM-allergic patients is weaker. The standard diagnostic techniques—skin prick test and specific IgE testing—can be confounded by cross-reactivity. However, component-resolved diagnosis using purified and recombinant allergens can improve the accuracy of specific IgE testing, but availability is limited. Treatment options for HDM allergy are limited and include HDM avoidance, which is widely recommended as a strategy, although evidence for its efficacy is variable. Clinical efficacy of pharmacotherapy is well documented; however, symptom relief does not extend beyond the end of treatment. Finally, allergen immunotherapy has a poor but improving evidence base (notably on sublingual tablets) and its benefits last after treatment ends. This review identifies needs for deeper physician knowledge on the extent and impact of HDM allergy in respiratory disease, as well as further development and improved access to molecular allergy diagnosis. Furthermore, there is a need for the development of better-designed clinical trials to explore the utility of allergen-specific approaches, and uptake of data into guidance for physicians on more effective diagnosis and therapy of HDM respiratory allergy in practice. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

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House dust mite (HDM) allergy is strongly implicated in the pathogenesis of respiratory allergic disease,[1,2] and a large proportion of patients with allergic rhinitis (AR), allergic asthma (AA), or both are sensitized to HDM, predominantly *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.[3-6]

Disease management according to guidelines has traditionally focused on allergen avoidance and alleviation of symptoms by pharmacotherapy. However, accurate diagnosis of HDM sensitization is not easy in primary care, and symptomatic relief from pharmacotherapy ceases as soon as treatment ends. Allergen immunotherapy (AIT) has been shown to address the underlying allergic cause safely and effectively, with lasting effect after the end of treatment.[7] However, relevant guidelines are cautious in their recommendations to physicians owing to gaps in the evidence base, particularly heterogeneity of trial design, especially end points,[8] dosing, and duration of treatment.[9-16] Consequently, patients sensitized to HDM can experience delay in obtaining accurate diagnosis and effective, lasting treatment. These delays can be exacerbated by the low priority ascribed by

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Abbreviations used
AA- Allergic asthma
AIT- Allergen immunotherapy
AR- Allergic rhinitis
ARIA- Allergic Rhinitis and its Impact on Asthma
CRD- Component-resolved diagnosis
GINA- Global Initiative for Asthma
HDM- House dust mite
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
SPT- Skin prick test

patients and doctors and by the low number of allergy specialists in many countries.[17]

Until now, HDM allergy has been diagnosed by a clinical history of HDM exposure in combination with HDM sensitization[18] demonstrated by a combination of skin prick tests (SPTs) and specific IgE testing, with or without nasal challenge tests. Mite allergens (characterized in 24 groups according to their molecular profile and likely activity[3]) consist of body proteins and digestive enzymes within cells that have become detached from the gut wall and discharged within fecal pellets.[3] The recent availability of DNA sequences of allergens has enabled the preparation of purified, recombinant allergens and hypoallergenic allergen derivatives, which can be used for component-resolved diagnosis (CRD) to identify the individual molecules to which a patient is sensitized[19-21] and also for monitoring the progress of AIT.[22,23] This approach complements the information gained from SPT and IgE testing with nonpurified allergen extracts, and can distinguish between true polysensitization to multiple allergens and false-positive results resulting from cross-reactivity.[24,25]

The efficacy of HDM avoidance has been widely questioned.[26,27] Although an intuitive strategy, avoidance is not supported by robust evidence of efficacy, and some controversy has arisen over the impartiality of inclusion criteria in reviews. Despite this, avoidance is still widely recommended to reduce the severity of AR or AA symptoms in sensitized individuals, and may be effective as part of a holistic approach combining avoidance of tobacco smoke, improved education, and regular assessment.[29,30] The main impact of avoidance may be in babies with a familial genetic predisposition to asthma because intervention in childhood is effective in controlling asthma in atopic children.[31] In any case, the effectiveness of avoidance depends on specific allergen diagnosis.

Treatment of AR and AA by pharmacological agents has a solid evidence base of effective and safe treatment. However, many of the standard drugs have not been tested specifically in the context of HDM allergy and many HDM-allergic patients achieve only poor to moderate symptom control.[32] This evidence gap may be relevant in relation to less-than-adequate control or frequent recurrence of symptoms, given the potential for varying responses to different medications.[12]

Developments in immunotherapy are continuing to build on the successful demonstration of the safety and efficacy of both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in both reducing symptom burden and use of pharmacotherapeutic medication. Both SCIT and SLIT require treatment over several years, and SCIT must be given under medical supervision. Therefore, both SCIT and SLIT can suffer from low patient adherence, especially toward the end of treatment, and efforts to improve adherence would improve outcomes until such time as shorter treatment regimens may become available.[33]

SLIT has a superior safety profile to SCIT because it has a lesser risk of anaphylaxis, plus the advantage to patients of home administration and less commitment of time[33]; it also may prevent new sensitizations.[34] Evidence is now appearing on the efficacy, safety, and optimal dosing of SLIT tablets.[35,36] In addition to alleviating AR, the benefits extend to patients with mild to moderate HDM-induced AA[37] and enable reduced use of inhaled corticosteroids.[38]

Both specific diagnosis and effective, lasting treatment of HDM-induced respiratory disease present challenges. The greatest need in promoting more effective diagnosis is to increase awareness among primary care physicians of current techniques that can complement the information provided by SPT and IgE testing and increase referrals to allergists who have access to them. The most compelling need to improve treatment is generation of more robust clinical data on the effectiveness of avoidance and immunotherapy. Such data, which can contribute the most reliable foundation for more specific guidelines, depend on the conduct of randomized, double-blind, placebo-controlled trials.

METHODS

A series of pilot PubMed searches were used to identify the most appropriate key words, which were cross-referenced with MeSH terms. Search terms were then amalgamated into 2 groups specific to HDM allergy: disease or immunotherapy (Figure 1). The individual search terms used were asthma; allergic asthma; allergic rhinitis; respiratory allergic disease; allergic march; dust mite; pulmonol*, allerg*. The composite search terms used for disease were asthma + dust mite, allergic rhinitis + dust mite, respiratory allergic disease + dust mite, allergic march + dust mite, house dust mite allergy, and dust mite allergy. The composite search terms for immunotherapy were sublingual immunotherapy OR subcutaneous immunotherapy OR aller* immunotherapy tablet + asthma OR allergic rhinitis OR dust mite; immunotherapy + dust mite. A separate search was carried out for references to pharmacotherapy specific to HDM, using the term dust mite + relevant pharmacotherapy categories, and also dust mite + individual pharmacotherapies.

Information on the level of evidence relating to currently used pharmacological interventions for AR, AA, and HDM allergy with AR or AA was compiled from the Allergic Rhinitis and its Impact on Asthma (ARIA) and the Global Initiative for Asthma (GINA) guidelines and literature searches (Table I). A PubMed search was conducted for treatment of asthma/allergic rhinitis/dust mite, and filters applied for publication type (meta-analysis, clinical trial). PubMed and the Cochrane Library were searched for dust mite + pharmacotherapy interventions (categories and individual drugs).

Clinical aspects of the HDM allergy patient

Asthma and rhinitis have long been recognized as heterogenic diseases. In asthma particularly, a growing interest in symptomatic phenotypes may also extend to endotypes that reflect etiology.[39,40] Cluster analysis has helped refine such categories, paving the way for personalized medicine.[16,41] The clinical phenotypes of asthma and rhinitis relevant to allergy are encompassed in the term "respiratory allergic disease" and the concept of a united allergic airway reflects a shared underlying mechanism of pathogenesis.[42] HDM sensitization is a major cause of perennial AR and AA symptoms, and hence a major causative factor in respiratory allergic disease.

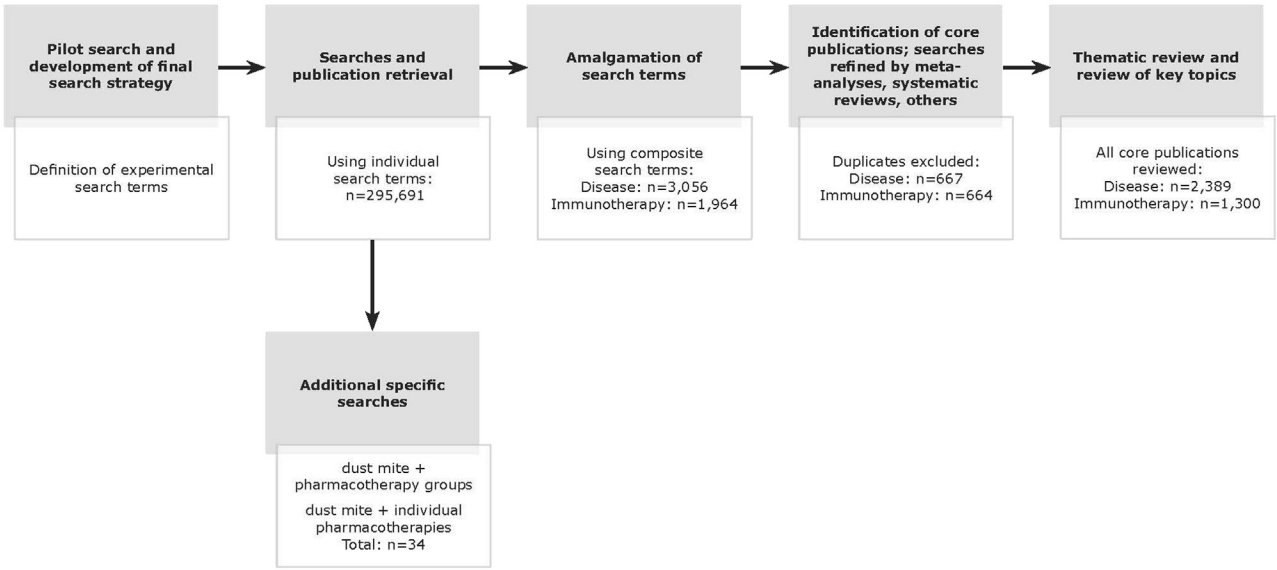

FIGURE 1. Search methodology. Methodology of individual and composite literature searches to identify literature relevant to AR and/or AA related to HDMs, and their treatment. Additional specific searches were conducted using asthma, allergic rhinitis, and dust mite, with interventions as associated keywords, and filters applied for publication type (meta-analysis, clinical trial) and age of publication up to 2013. Categories of evidence are based on Shekelle et al,[43] adapted by Cox et al.[44]

HDM allergy can have an impact on pulmonary function tests in patients who have already developed asthma. For example, the European Community Respiratory Health Survey (n = 12,687, 20.2% of whom had allergy to HDM) found an association between HDM allergy and lung function in HDM-sensitized patients with asthma. Specifically, FEV_1 was reduced by 119 mL in women and 112 mL in men when compared with patients with asthma who were not HDM-sensitized, and a lower FEV_1/forced vital capacity ratio was also observed (−1.95% and −2.48%, respectively).[45]

Exposure to HDM allergens in adults with asthma not previously sensitized to HDM increases asthma morbidity,[46,47] and those already sensitized have an increased severity of asthma.[48,49] A study conducted in 30 centers across 13 countries from Europe, Australia/New Zealand, and the United States found a strong association between sensitization to *D pteronyssinus* (adjusting for age, sex, smoking, passive smoking, parental history of asthma, and region) and asthma severity (1.61 [1.14-2.26]; $P < .002$).[50] Specifically, sensitization to HDM is a risk factor for recurrent asthma exacerbations.[51] Over time, patients with HDM sensitization are likely to experience concomitant rhinitis and asthma. In a general population study of 734 Danish adults without asthma symptoms who were examined on 2 occasions, 8 years apart, the risk of new asthma symptoms was many times higher in persons with AR at the beginning of the study than in those without (7.8 times for AR to pollens, 17.8 times for AR to animals, and 37.6 times for AR to mites) (Figure 2).[52] The highest risk was found for those with HDM-related AR.[52]

The comorbidity of AA and AR is likely to worsen each condition,[53] increasing the likelihood of patients reaching a "moderate-severe" state. This is consistent with the concept of "one airway," and it is also noteworthy that the severity of rhinitis parallels the severity of asthma, and vice versa.[54]

However, identifying a specific set of symptoms particular to HDM allergy is difficult because patients often have concomitant allergies. One possible avenue for future research is the degree to which allergies, and particularly HDM allergy, contribute to worsening the symptoms of asthma. For instance, a subgroup of 5% to 10% of the patients with mild to moderate asthma does not respond to mainstream controller medications, and AR is indicated as one of the major factors that can influence the effectiveness of asthma treatments in everyday clinical practice.[55] In this respect, sensitization to HDM may be a contributory factor to symptom severity.

In summary, HDM sensitization is a major causative factor in respiratory allergic disease that is implicated in both AR and AA. Comorbidity of HDM-related rhinitis and asthma can reduce lung function and increase the severity of asthma.

Issues affecting the patient pathway

Extent and impact of delayed diagnosis. Accurate diagnosis and appropriate treatment planning may be considerably delayed in HDM allergy,[32,56] and refining the initial diagnosis of rhinitis or asthma with the identification of relevant allergic sensitizations may help physicians to implement individualized strategies for treatment. Surprisingly, a survey of patients with respiratory disease from 10 European countries (n = 7004) found that an average of 33% (between 15% in Germany and 68% in the United Kingdom) had never received a diagnostic test for allergy, even though almost half of these (48%) had been seen by their family doctor.[57] Only 16% of the study population was treated with AIT; thus, treatment was limited to symptomatic medication for patients who had not undergone diagnostic testing for allergy.[57] A separate study of 411 adult patients from 6 European countries with clinically confirmed AR (from any cause) drawn from a random sample of 9646 (1600-1625 per country) found that 45% did not have a previous physician's diagnosis.[56]

A contributing factor may be low public awareness of HDM allergy as a treatable condition. For example, a quantitative study of patients' perceptions of HDM allergy in 4016 people from France, Italy, Germany, and Spain showed a significant gap between the

TABLE I. Levels of evidence for currently used pharmacological interventions for AR, AA, and HDM allergy with AR or AA

	Level of evidence		
Pharmacotherapy	**AR/rhinoconjunctivitis**	**Asthma**	**HDM respiratory allergy (AR or AA)**
Anticholinergics	1b	1a	NR
Antihistamines (second- generation H_1)			
Intranasal	1b	NR	NR
Ocular	1a 1b	NR	NR
Oral	1a	1a	1b[58-60]
Anti-IgE (omalizumab and others)	1b	1a/1b	1b[61-63]
β2-agonists			
Rapid-acting inhaled	NR	1b	1b[64]
Short-acting oral	NR	1b	NR
Long-acting inhaled	1b	1a	2b[65] LB[66,67]
Long-acting oral	1b	1a	NR
Decongestants			
Intranasal	1b	NR	1b[68,69]
Oral	1b	NR	NR
Corticosteroids			
Inhaled	1b	1a	1a[70]
Intranasal	1a	1a	2b[71]
Ocular	1a	NR	NR
Systemic	1b	1a	LB[72]
Leukotriene modifiers	1a	1a	1b[73]
Nedocromil sodium	NR	NR	2b[74]
Sodium cromoglycate	1b	1b	NR
Theophylline	NR	1a	LB[75]

Categories of evidence	
1a	Evidence from meta-analysis of randomized controlled trials
1b	Evidence from at least 1 randomized controlled trial
2a	Evidence from at least 1 controlled study without randomization
2b	Evidence from at least 1 other type of quasi-experimental study
3	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
4	Evidence from expert committee reports or opinions, clinical experience of respected authorities, or both
LB	Evidence from laboratory-based studies
NR	Not rated

Categories of evidence are based on Shekelle et al,[43] adapted by Cox et al.[44]

level of awareness of the symptoms of HDM allergy (57%), the proportion of participants with potential symptoms of HDM allergy (57%), and the actual proportion of participants diagnosed with HDM allergy (15%).[76] Many patients in this study felt that HDM allergy was "something you must accept and live with".[76] Similarly, an earlier study of 726 Danish patients with asthma and/or rhinitis found that 75% were allergic, and asthma was undiagnosed and untreated in 50% of all those with asthma and undertreated according to GINA guidelines in 76%. Rhinitis was undiagnosed in 32% of the patients, and 83% with moderate to severe rhinitis were undertreated.[77]

Delays in effective diagnosis and treatment for AR can affect the changing pathophysiology of the disease. Given the progressive nature of allergy, AR should be considered both a predictor of asthma[78,79] and a risk factor for asthma.[54,80] The presence of AR in 55.2% of the patients with asthma (95% CI, 54.4%-56.0%) indicates the level of comorbidity, and in addition, AR is associated with more severe asthma, more difficult to control asthma, and reduced quality of life.[54,80] However, the ARIA guidelines are not focused on investigating etiological factors. More acute clinician awareness of and adherence to ARIA guidelines, along with an evaluation of "disease control" parallel to that used in GINA,[81] might encourage physicians to respond with better management of symptom deterioration.[82]

A lack of resources often contributes to delayed diagnosis of allergy. A survey of 33 countries conducted by the World Allergy Organization Specialty and Training Council concluded that insufficient allergists were available. Patients with AA were more likely to see relatively poorly trained or allergy-naive system specialists, generalists, or primary care physicians.[17] Moreover, a survey of allergy management in primary care across European countries found that nonallergist pneumology or pulmonology specialists were more likely than allergists to receive referrals and that 20.6% of the practitioners in primary care had no access to allergy tests at all.[83] Also, in some countries, allergy is a specialist discipline, whereas in others it is considered a subspecialty or not a specialty at all.[84]

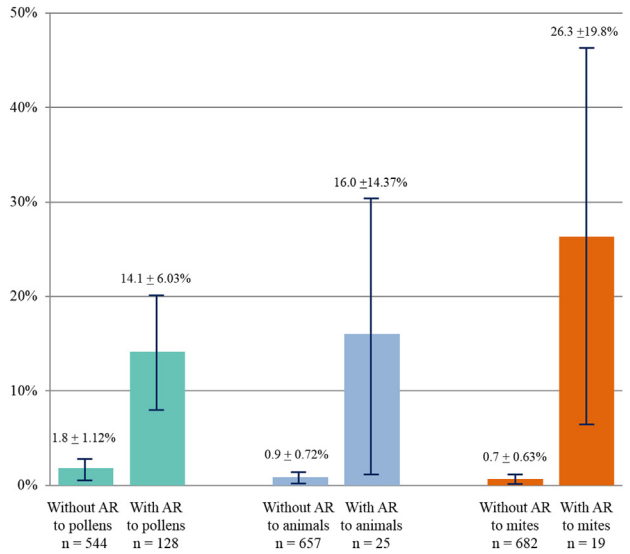

FIGURE 2. The risk of development of new asthma symptoms is high in AR. The highest risk of novel asthma symptoms in a general population of Danish adults was found for those with HDM-related AR.[52] The y-axis refers to the percentage of patients with AR related to sensitization to pollens, animals, or HDMs who developed asthma symptoms, grouped by the presence or absence of AR at the start of the study. 95% CIs are indicated.

Without a specific diagnosis, a significant proportion of patients do not use any medication, often because of concerns over cost,[32] whereas others self-treat using over-the-counter remedies.[85] A questionnaire-based patient survey found that up to two-thirds of people with respiratory, skin, or food allergies did not seek help until symptoms became intolerable,[32] but without medical help patients suffer sleep disturbance and cognitive impairment and are at risk of developing further sensitizations.[86] Notably, undertreatment is equally related to physicians: a direct comparison of the perception of AR symptoms in diagnostically confirmed patients by both patients and physicians found that physicians were likely to underrate the prevalence and severity of ocular symptoms and headache, cough, wheezing, and nocturnal waking and to underdiagnose asthma among patients with AR.[87] This underdiagnosis is surprising, considering the negative impact of AR on sleep,[88] concentration and productivity at work[89,90] or school,[91,92] fatigue and mood changes,[93] anxiety[94] and depression,[95] and overall quality of life.[89]

Accurate diagnosis of HDM allergy can be challenging, and large-scale patient surveys suggest that as many as 45% of the patients with confirmed HDM allergy had no previous diagnosis. More acute clinician awareness of, and adherence to, rhinitis guidelines, as well as an evaluation of "disease control" parallel to that used in GINA, might encourage physicians to respond with closer management of symptom deterioration.

Impact of nonadherence. The efficacy of conventional pharmacological interventions in rhinitis is currently undermined by poor adherence[96]; typically only 48.7% of the patients follow physicians' directions, with 34.3% adapting the prescription.[97] Adherence to prescribed treatment depends on complex relationships between efficacy, safety, onset of action, cost of medication, confidence in physician, and patient characteristics (psychosocial profile, socioeconomic status).[98] For example, a study of primary practice in Spain found that of the patients referred to allergy specialists, 86.2% had moderate to severe HDM-related disease (n = 519); however, good treatment control had previously been achieved by pharmacotherapy in only 43% of the cases.[99] Thus, support of the patients' education and subsequent improved adherence to the prescribed regimen may improve outcomes.[98]

Adherence to medication also plays a strong role in asthma management because patients may react to deterioration in symptom control by adjusting medication inappropriately.[100] Patient adherence is therefore an important factor in successful treatment of HDM-related respiratory disease because it can be almost half of the cases for both AR and AA.

Improving diagnostic procedures. Mite allergens, classified within allergen groups 1 to 24 according to their molecular structure and likely mode of action,[3] consist of body proteins and digestive enzymes contained within dissociated cells from the mite gut wall and retained within fecal pellets.[3] The 2 most dominant are cysteine protease (group 1) and lipid-binding protein capable of mimicking the Toll-like receptor 4 coreceptor MD-2 (group 2).[3] Another potent allergen group is the chitin-binding proteins group (group 23), typified by Der p 23. This group of proteins has been shown to elicit specific IgE reactivity in more than 70% of HDM-sensitive patients, and basophil activation even at less than one-tenth of the concentration of the major allergen, Der p 1.[101]

Group 1 cysteine proteases are variable in form and induce both species-specific and cross-reactive IgE antibodies, whereas group 2 allergens Der p 2, Der f 2, and Eur m 2 are highly cross-reactive between species.[102] Because of this, it is not possible to prove the sensitization of a patient to only 1 specific mite species. This presents diagnostic issues for the small percentage of sensitized individuals who are reactive to allergens from other groups but not to allergens from groups 1 or 2.[103]

To improve identification of HDM allergy, greater awareness of immunodiagnostic procedures is needed at the point of care. Two key diagnostic tools indicate HDM sensitization: either by direct *in vitro* measurement of HDM-specific IgE in serum or by indirect *in vivo* demonstration of HDM-specific IgE on cutaneous mast cells via an SPT. These 2 standard methods are now complemented to a limited extent by the development of CRD, which can identify critical allergens and enhance treatment.

Survey data report a wide variance in SPT although it is a core diagnostic tool.[104] Therefore, widespread acceptance of a standardized protocol with standardized allergen extracts is needed to improve accuracy.[23,105] However, multiallergenic screening of specific IgE is helpful in the case of multiple sensitizations to establish the relative impact of individual allergens, and may have a particular utility in general practice.[7] Variations between locations and methodology of allergen testing, concentration of solutions, and cross-reactivity may have an impact on the accuracy of either test results.

Both SPT and specific IgE testing show satisfactory qualitative, but not necessarily quantitative, agreement owing to a number of biological variables in SPT besides simple specific IgE concentrations. Standardization of the protocol for either test is clearly important, considering that batch-to-batch variations in the allergen content of extracts, lack or poor representation of allergens, poor immunogenicity of certain allergens, varying allergenic activities, presence of nonallergenic materials, and contamination may all affect test results.[106,107] Approaches used over the last 100 years to improve the quality of natural allergen extracts for immunotherapy

have included determination of protein content, assessment of biological activity, and antibody-based measurement of allergen content.[23]

Because of extensive interspecies cross-reactivity, testing for sensitivity to 1 HDM species (ie, Der p or Der f) is sufficient in most cases. Current commercially available HDM extracts contain variable amounts of major allergens Der p 1 (group 1) and Der p 2 (group 2), whereas other important allergens (eg, Der p 23) may be underrepresented or absent.[101] Consequently, some HDM-allergic individuals, particularly those without sensitization to group 1 and 2 HDM allergens, might remain undetected with the use of available HDM extracts.[101] Thus, molecular allergy diagnosis including all major HDM allergens, and/or improved HDM extracts, would be needed to close this diagnostic gap.

IgE for specific HDM allergens can also be detected by using an alternative molecular allergy diagnostic protocol from ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). So far, this approach does not carry any advantages compared with the use of HDM extracts because up to 97% of Der p−sensitized individuals can be diagnosed by a combination of Der p 1 and Der p 2.[103] However, proof of sensitization to group 1 and group 2 HDM allergens could be useful because most available HDM extracts are standardized on the basis of these major allergens. A microarray screening platform with 112 allergenic molecules from 51 allergen sources enables semiquantitative detection of specific IgE to nDer p 1, rDer p 2, and rDer p 10. This test includes additional major and minor HDM allergens, allowing the investigation of "molecular spreading" in HDM-allergic individuals. This observation, driving IgE-mediated sensitizations from a limited number of single allergens to a more complex IgE repertoire covering many major and minor HDM allergens, might be associated with more severe and/or lower airway disease. In the situation of a no clear-cut case history, conjunctival or nasal challenge tests with appropriate HDM extracts (Der p or Der f) may support the diagnosis of HDM sensitization and confirm its mucosal effect.

The use of CRD to measure the amount of specific IgE that binds to purified natural allergen components or recombinant cross-reactive allergen components can enable identification of the individual molecules to which a patient is sensitized.[19-21] This approach can add useful information to what is already known from SPT and specific IgE tests, considering that the critical allergen for treatment can be identified and the most appropriate treatment chosen. The availability of DNA sequences of allergens since 1988 has enabled preparation of purified, defined recombinant allergens and hypoallergenic allergen derivatives that can be used for CRD.[23] The technique can distinguish true polysensitization from the positive results from cross-reactive components, whereas SPT cannot.[24,25] This could have significant implications for therapy options because the multiallergen immunotherapy indicated by polysensitization could offer exposure to irrelevant allergens in the case of cross-reactivity. Treating the monosensitized patient with only the clinically relevant purified allergens has been suggested to offer a way to avoid new sensitizations.[21]

CRD can also be useful in monitoring the progress of AIT because IgE-mediated reactions decrease in line with a rise in the level of specific IgG_4 antibodies, in response to effective immunotherapy.[22] The immune response can be monitored and therapy adjusted, if necessary, which may improve compliance.[19]

In summary, extensive interspecies cross-reactivity makes it impossible to prove sensitization to a HDM species using SPT and IgE testing with unpurified extracts. Accuracy can be improved by CRD, which can identify the individual molecules to which a patient is sensitized and distinguish between true polysensitization and cross-reactivity. A further advantage is that CRD can also be used to monitor the course of AIT and to assess compliance. In addition, use of recombinant allergens in diagnostic tests can compensate for the variability of natural allergen extracts.

Treatment options. Following diagnosis, 3 therapeutic options are currently available for respiratory allergic disease caused by HDM allergy: (1) allergen avoidance, (2) pharmacological intervention, and (3) AIT. Allergen avoidance and AIT can be implemented only after the identification of the specific underlying allergy.

Effectiveness of avoidance measures

Avoidance strategies in HDM allergy are primarily based on encasing mattresses, domestic cleaning, and the use of acaricides. The theory is that by reducing or containing the mite population, exposure of the patient to mite allergens is also reduced, resulting in fewer symptoms. Although these measures are simple and intuitive, multiple factors affect mite prevalence, and mite reduction may not result in reduction of symptoms.[3,108-110] Treatment guidelines vary with regard to allergen avoidance, particularly in relation to asthma.[111] The ARIA guidelines conclude that there is no overall clinical benefit through avoidance measures to patients already suffering from HDM-related perennial AR and/or AA, although the impact of avoidance on the level of HDM exposure is uncertain.[26] The GINA guidelines acknowledge that measures should be implemented wherever possible to prevent the development of asthma and asthma symptoms and exacerbations. However, considering that mite allergens are environmental factors that trigger asthma symptoms, the GINA guidelines conclude that no single avoidance measure is likely to reduce exposure to mite allergens and an integrated approach to avoidance cannot be widely recommended.[112,113] Similarly, a 2015 Cochrane review has demonstrated a lack of clear evidence to inform clinical practice in the use of HDM reduction or avoidance measures in the treatment of atopic eczema. The authors recommended high-quality long-term trials of such measures.[114]

A Cochrane-based review of 54 randomized controlled trials explored the clinical impact of various allergen avoidance strategies for patients with asthma, diagnosed as sensitized to HDM allergens using allergen-specific IgE testing. In general, the quality of trials was poor, and even when using strict exclusion criteria to reduce the data sets for meta-analysis, no effect of control measures was found. The authors criticized current guidelines, suggesting that avoidance measures are not evidence-based and that the trials were highly selected and frequently nonrandomized.[27]

Data sets for HDM avoidance are less frequent for AR than for asthma, but a similar Cochrane review for AR identified 9 trials of suitable quality, with numbers too small for meta-analysis.[28] These studies investigated the use of impermeable bedding covers (4 trials), acaricides (2 trials), high-efficiency particulate air filters (2 trials), and a combination of approaches (1 trial). Acaricides proved to be the most promising intervention, with a borderline success rate, but again, no clear clinical advantages could be confirmed for any strategy.

The potential for bias in the application of inclusion criteria for such reviews has become a controversial topic in HDM allergy,[115] and some researchers have suggested that exclusion bias in the Cochrane reviews explains a "false-negative" finding in asthma, a criticism particularly relevant given the borderline findings for

efficacy.[116] Concerns have been raised in general regarding methodological bias in asthma meta-analyses[117] and reference bias in HDM allergy reviews.[118]

Until more conclusive data are available, allergen avoidance is still being widely used as a means to control symptoms in some patients.[115] It is likely to benefit children with asthma[29,119]; however, the poor quality of studies on AR means that they have failed to show conclusive evidence of the benefit of avoidance.[120] Also, adherence to avoidance strategies by patients has not always been perfect, with a probable impact on the success of the intervention.[28,121]

Home-based environmental intervention has been shown to be effective when combined with a holistic approach, including reduced allergen exposure, avoidance of tobacco smoke, improved education, and regular assessment.[29,30] However, it is important to distinguish between the impact of allergen avoidance in an already-sensitized population and in one in which nonsensitized individuals are at risk, where benefits in disease prevention have been observed by some researchers.[122]

To illustrate the inconsistency of results, a randomized study of the effects of a multifaceted intervention, including HDM avoidance during pregnancy and early life, resulted in increased risk of HDM sensitization, but better lung function in the intervention group at age 3 years.[123] In contrast, for tertiary prevention in particular, multifaceted avoidance strategies early in life are likely to show the greatest effect when used to modify and potentially prevent allergic progression.[124-127] A progressive intervention would identify infants with a genetic predisposition using familial asthma as a "genetic" proxy, then would recommend breast-feeding, allergen avoidance strategies, and timely use of appropriate medication to control early symptoms.[127,128] The target patient population is relevant here because intervention in childhood is effective in reducing the risk of poor asthma control among atopic, but not nonatopic, children.[31]

In general, evidence on the efficacy of avoidance is poor, and reduction in mite exposure does not necessarily reduce symptoms. No overall clinical benefit has been demonstrated from avoidance measures to patients already suffering from HDM-related perennial AR and/or asthma, but babies and children with a genetic predisposition to asthma may benefit from mite avoidance. Further investigation is needed on the diversity of sources of allergen exposure, the aerodynamic behavior of allergen particles, and the relationship between allergen exposure and clinical effect.[129]

Pharmacotherapy for HDM allergy

Treatment for AR and AA caused by HDM is guided by the ARIA[7] and GINA[111] guidelines and others.[12,120] Symptoms can be effectively controlled by pharmacotherapy products, which have a long-standing and strong evidence base for both rhinitis and asthma, and are rightly considered the cornerstone of disease management. First-line treatment for rhinitis is by oral or intranasal second-generation antihistamines and nasal corticosteroids, with other useful add-on options including oral leukotriene antagonists and antihistamine eyedrops,[7] whereas asthma treatment is a stepwise progression through inhaled corticosteroids, long-acting β_2-agonists, leukotriene modifiers, theophylline, and anti-IgE.[112] The evidence base for key treatment interventions demonstrates a clear division between the strata of diagnosis between symptom-led (rhinitis, asthma) or phenotype/endotype-led (in this case, allergy caused by HDM) (Table I).

Many pharmacological treatments for AR have been evaluated, but not all current drugs have been specifically researched in cases in which HDM allergy is the underlying cause and many patients achieve only poor or moderate control.[32] We need more evidence relating to specific treatment of HDM-related conditions. This gap in the evidence base is not relevant in cases in which symptoms are well managed using conventional treatments. It may, however, be relevant given the heterogeneity of asthma and rhinitis, and the potential for specific subsets of patients with asthma (in this case, HDM allergy) to respond differently to different medications.[12] In cases in which symptom control by pharmacotherapy is poor, more complete understanding of the relationship between asthma and the various phenotypes of allergic disease[3,130] could enable a more effective choice of pharmacotherapeutic agent.

Regardless of the treatment choice, it should take into account the severity, frequency of (re-)occurrence, and duration of symptoms, as well as less-than-effective control and the potential for patient aversion to long-term pharmacotherapy.[12]

In summary, the symptoms of both AR and AA can be effectively controlled by the available pharmacotherapeutic agents. However, many have not been tested specifically in the case of HDM-related conditions and a broader evidence base is needed.

AIT: Targeting the natural history of HDM allergy

AIT is the only current medical treatment that can modify the natural history of respiratory allergic disease. The efficacy in reducing symptom burden and medication use has been shown for both subcutaneous and sublingual AIT (SCIT and SLIT, respectively). SLIT has an improved safety profile, combined with the advantage of home administration and less commitment of the patient's time.[33] Few direct head-to-head studies have explored the relative safety and efficacy of these 2 approaches, so current practice relies on indirect comparison of outcomes. The evidence base for SLIT contains more placebo-controlled, dose-dependent, large-number trials.[9] Following calls for more robust AIT studies, evidence is now appearing from double-blind placebo-controlled studies on the efficacy, safety, and optimal dosing of sublingual tablets.[35,36] The benefits extend to patients with mild to moderate HDM-induced AA[37] and enable reduced use of inhaled corticosteroids.[37]

Historic concerns over safety due to systemic reactions with SCIT may have caused hesitation regarding its widespread use. When considering the relevance of these cases today, there are 2 key considerations: how the management of AIT has evolved over the years, and the relative safety profile of the allergen products used for specific preparations.

The second consideration, allergen product safety, must take into account class-specific and drug-specific differences. A dramatically lower systemic reaction rate has been observed for SLIT relative to SCIT (even in the latter, though, the percentage of systemic reactions per injection is low; ~0.2%).[131] HDM-allergic patients treated with HDM SLIT tablets for 1 year also showed no sign of IgE neosensitization to vaccine allergens.[132] After 1 year of treatment, IgE and IgG_4 titers specific for HDM increased by a factor of 1.5 and 4, respectively, but preexisting IgE levels to purified group 1, 2, and 10 allergens were unaffected.[132] Regarding HDM allergy, comprehensive systematic reviews suggest a reliable safety profile in SLIT.[9,133] It has been suggested that future generations of AIT will use the molecular modification of allergen proteins (hopefully including HDM allergen proteins) to reduce allergenicity and/or increase immunogenicity.[134]

Figure 3, *A* and *B*, summarizes existing clinical efficacy data from meta-analyses of SCIT and SLIT in AR and AA. Each data set first considers AIT across a series of allergens and then extracts a subset of data specific to HDM allergy.

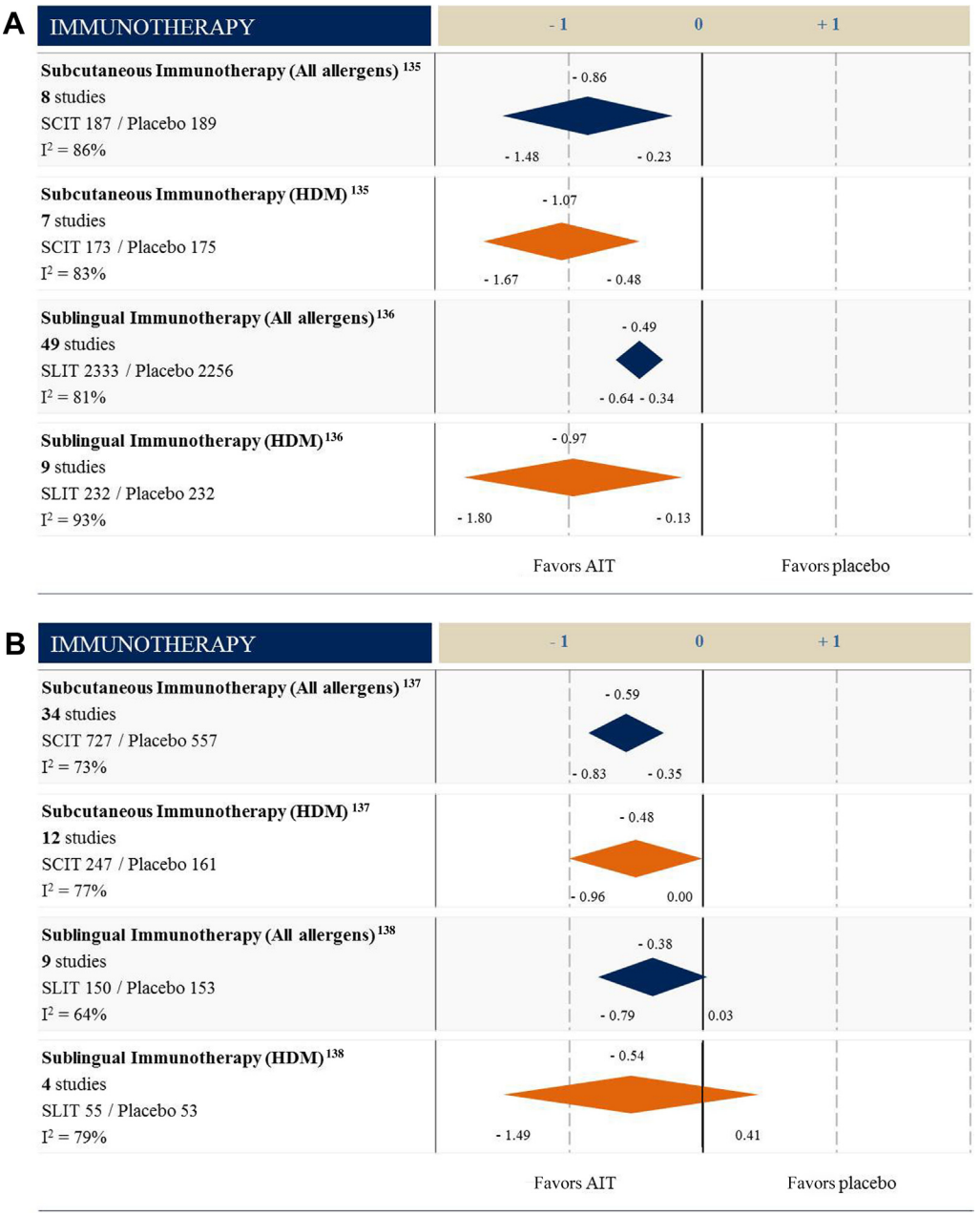

FIGURE 3. A, A summary of efficacy data for AIT in AR.[135,136] Forest plot to indicate the reported efficacy for SCIT and SLIT in AR related to HDM and to all reported allergens. The pooled estimates are mean difference between active and placebo in total symptom scores. **B**, A summary of efficacy data for AIT in AA.[137,138] Forest plot to indicate the reported efficacy for SCIT and SLIT in AA related to HDM and to all reported allergens. The pooled estimates are mean difference between active and placebo in total symptom scores.

In AR, 8 studies (n = 187 active/189 placebo) were found for SCIT, with a significant advantage found in favor of AIT ($P = .007$), and within the HDM allergy subset, 7 studies (n = 173 active/175 placebo) also showed a significant advantage ($P = .0004$).[135] For the use of SLIT in AR, 49 studies (n = 2333 active/2256 placebo) found an advantage for AIT for all allergens ($P < .00001$) and 9 studies (n = 232 active/232 placebo) found an advantage for the HDM allergy subset ($P = .02$).[136]

For AA, 34 studies (n = 727 active/557 placebo) reported a significant effect for SCIT applied to all allergens ($P < .00001$) and 12 studies (n = 247 active/161 placebo) found marginal significance for the HDM allergy population ($P = .048$).[137] Finally, data for the use of SLIT in AA were pooled from 9 studies (n = 150 active/153 placebo) and found no significance ($P = .07$), and only 4 studies were available for HDM allergy patients (n= 55 active/53 placebo), again finding no significance relative to placebo ($P = .27$).[138] It should be noted that the last study was compiled using minimal data, and it contradicts more recent systematic reviews finding advantages for SLIT.[133]

Allergen-specific strategies may have a role in altering the progression of respiratory allergic disease and enabling the long-term

prevention of asthma in children with HDM allergy.[139] Meta-analyses of SLIT in children have historically yielded mixed findings, with some systematic reviews showing contradictory results in both AA and AR.[140,141] As throughout HDM allergy investigations, trials have been of low quality, perhaps explaining these conflicting results.[142] The most recent findings suggest that there is now high-quality evidence in the pediatric population for using AIT for medication reduction while maintaining symptom control in AA. However, there is only low-moderate quality evidence on its impact in AR: some trials showed improvement in nasal symptom scores and/or medication scores, but a placebo was not always included.[143] The best evidence to recommend SLIT in children with AR is low to moderate level of evidence for the prevention of asthma development. More large randomized trials are needed, especially with HDM SLIT in children.[143]

The high clinical and methodological heterogeneity in studies of AIT in HDM allergy creates difficulties in extracting information for systematic reviews and prevents pooling for meta-analyses.[9,133,144,145] Potential diversity in products may also confound trial findings; a greater definition of allergen extract, quality, batch-to-batch stability, and concentration may be needed to strengthen trial validity.[9,146] These limitations partly explain the substantial gaps in our knowledge relating to the application of AIT for HDM allergy. For example, the only data available to ascertain optimal dosing strategies for SLIT are insufficient, compromising future guideline development,[133] although in SCIT, a maintenance dose in the range of 5 to 20 μg of major inhaled allergens has been shown to be effective.[11] A review of the 9 studies published in 2013 and 2014 on the use of SCIT and SLIT in the treatment of both AR and AA[36] confirmed their safety and efficacy and concluded that optimal clinically effective doses will be established for SLIT tablets under development in large, randomized, placebo-controlled trials for treatment of HDM allergy. Even so, this review criticized the dosing guidance offered for effective SLIT liquid because it was not directly usable by physicians.[36]

One clear potential advantage of AIT is its ability to maintain efficacy beyond treatment discontinuation, and so another area for exploration is the duration of treatment needed to induce a lasting effect. A study of patients with respiratory allergy who were monosensitized to mites and treated with SLIT or drug therapy for 3, 4, or 5 years followed their clinical condition for 15 years, finding that 4 years was the optimal duration.[147]

Polysensitization is more prevalent in patients with moderate to severe respiratory allergies in the United States, where multiallergen treatment is predominant, and Europe, where single-allergen treatment targeting the predominant allergen is preferred.[24] Large-scale, double-blind, placebo-controlled trials of grass pollen sublingual tablets have shown that polysensitized patients gained as much improvement as monosensitized patients.[24] However, data relating to HDM are less robust, although confirming that the symptoms of HDM-sensitized patients improved with HDM SLIT regardless of whether they were monosensitized to HDM or polysensitized to other additional unrelated allergens.[148,149] Several authors have pointed out that additional research is needed on simultaneous therapy with more than 2 allergens to determine whether single-allergen and multiallergen immunotherapy elicit distinct responses in monosensitized and polysensitized patients, and have called for more robust data to validate the use of multiallergen immunotherapy in polysensitized patients in practice.[24,150]

Although SCIT and SLIT have both been shown to be effective in reducing symptoms of HDM-induced AR and AA, and in reducing use of pharmacotherapy, many studies are limited by their high heterogeneity in design and definition of allergen extract, quality, batch-to-batch stability, and concentration. Recent double-blind placebo-controlled studies on SLIT tablets have shown benefits for patients with AR and/or mild to moderate HDM-induced AA. Future research should also include the elucidation of disease-modifying factors that confound or support AIT, the recommended time for therapy initiation, and the subsets of HDM allergy patients most responsive to AIT. Unlike much of the existing literature, future trials should use standardized outcome measures, definitions, and parameters.

CONCLUSIONS

HDM allergy plays a critical role in AR and AA, but delays on the part of patients in seeking treatment and on the part of physicians in achieving accurate diagnosis, coupled with lack of access to specialist allergy diagnosis, contribute to reduced treatment effectiveness.

Despite the range of effective pharmaceutical products available to treat respiratory allergic disease, intermittent self-medication or poor patient adherence to prescribed treatment may result in poor control of symptoms, and the benefits end when treatment stops. Although strong evidence supports pharmacological treatment of rhinitis and asthma in general, direct evidence of pharmacological impact on HDM allergy–related conditions is heterogeneous and weaker. The option of AIT is not widespread, possibly underused in clinical practice, and dependent on specific identification of HDM allergy. Allergen avoidance, like AIT, depends on identifying HDM as the cause of the immune response.

Accurate diagnosis—not only of the species of dust mite but preferably the allergen group—is one of the major limiting factors in the provision of adequate treatment for HDM-related respiratory disease. In addition to the clinical problems mentioned, the diagnostic techniques of SPT and specific IgE testing can be hampered by cross-reactivity and made more complicated by polysensitization. The increasing use of CRD has strong potential to complement these 2 standard techniques and the use of recombinant allergens can compensate for the variability of natural allergen extracts. Together these techniques can identify the individual molecules to which a patient is sensitized and can distinguish between true polysensitization and cross-reactivity. CRD can also be used to monitor the course of AIT and to assess compliance. However, the techniques may be available only to those individuals whose condition is particularly complex and who are lucky enough to be in specialist care.

Although avoidance of HDM is widely recommended as a strategy, evidence for its efficacy is variable and the ARIA and GINA guidelines conclude that no single avoidance measure is likely to reduce exposure to mite allergens, and even an integrated approach to avoidance cannot be widely recommended. Again, poor patient compliance can limit the effectiveness of avoidance tactics, and measuring compliance in a domestic setting over a long period of time is extremely challenging. Avoidance studies suffer from heterogeneity in clinical trial design, end point definition, and validated outcomes. The strongest evidence suggests that the main benefit of avoidance may be in the case of targeted multiple avoidance measures to avoid the development of asthma in atopic children.

Well-designed meta-analyses indicate that SCIT and SLIT are both effective in reducing symptoms of HDM-induced AR and

AA and in reducing the use of pharmacotherapy. AIT modifies the course of disease, and its benefits last after treatment ends. Recent randomized, double-blind, placebo-controlled trials are contributing robust evidence on the safety and efficacy of sublingual tablets. Future trials should address historic shortcomings in design to provide an improved evidence base that can enable refinement of the guidelines to offer more complete guidance on allergen-specific strategies.

We believe that this review has identified a need for deeper knowledge among physicians on the extent and impact of HDM allergy in respiratory disease, as well as for further development and standardization of access to molecular allergy diagnosis. Furthermore, the development of robust better-designed clinical trials to explore the utility of allergy-specific approaches, and uptake of resulting data into guidance for physicians on more effective diagnosis and therapy of HDM respiratory allergy in practice, is critical.

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