



CME review

Mouse sensitization as an independent risk factor for asthma morbidity

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ARTICLE INFO

Article history:

Received September 1, 2011.

Received in revised form September 26, 2011.

Accepted for publication October 3, 2011.

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Release Date: March 1, 2012

Expiration Date: February 28, 2014

Estimated Time to Complete: 60 minutes

Target Audience: Physicians involved in providing patient care in the field of allergy/asthma/immunology

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At the conclusion of this activity, participants should be able to:

- Recognize the prevalence of mouse allergen exposure and sensitization, and identify the diagnostic methods for determining sensitization.
- Identify patients at highest risk for mouse allergen exposure and sensitization, and discuss the potential association with worsened asthma morbidity.

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Disclosure of Relevant Financial Relationships:

T.M. Moncrief, R.S. Kahn, A. Assa'ad and G.D. Marshall have nothing to disclose. No unapproved/investigative use of a product/device is discussed.

Recognition of Commercial Support: This activity has not received external commercial support.

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Introduction

Asthma continues to place a significant strain on the health care system due to rising lifetime prevalence, rate of attacks, and increase in health care use.¹ Genetic factors and personal and family history of atopy have been identified as risk factors for increased morbidity.^{2–4} Recently, research has focused on envi-

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Funding Sources: This work was supported by the 2008 Acorn Grant, American College of Allergy Asthma and Immunology Clinical Fellowship Award (Amal Assa'ad, MD, program director, and Terri Moncrief, MD, fellow-in-training).

ronmental exposures as potential catalysts in the complex interplay of the gene-by-environment interactions that produce the asthma phenotype.

In 1997, the National Cooperative Inner-City Asthma Study (NCICAS), a multicenter cohort of children with asthma, identified the combination of cockroach exposure and sensitization as a risk factor for hospitalization.⁵ This finding led to interest in other indoor exposures as potentially causing worsened asthma morbidity for inner-city children. Mouse allergen, first described as an occupational allergen in rodent handlers, has received heightened attention in recent years for its potential role in mediating inner-city asthma.⁶ Sensitization to mouse is measured by skin testing or measurement of specific IgE antibodies in the serum.⁶ Mouse allergen is ubiquitous, as evidenced by its detection in 95% of homes in the NCICAS cohort.⁷

The purpose of this systematic review is to identify insights in the recent literature evaluating the use of mouse sensitization as a potential biomarker for asthma morbidity, the proper technique to determine sensitization, the most appropriate population to screen, and the efficacy of mouse allergen eradication.

Methods

A systematic literature review was conducted using PubMed with the following search strategy: *mouse allergy* OR *mouse sensitization* AND *asthma morbidity*. The search was limited to human subjects. Primary articles and pertinent review articles were included. Studies focusing on rat allergen and experimental mouse models were excluded.

The primary search identified 180 articles, which was focused to 41 after a review of the titles to include data on mouse allergen exposure, sensitization, the relationship to asthma morbidity, and the effect of eradication. Abstracts were then reviewed and another 16 articles excluded based on these criteria. The remaining 25 articles were identified as relevant and reviewed. During the review process, 13 additional sources were identified through a backwards citation search. The final review included 38 articles.^{6–43} The articles were categorized for analysis by content, including (1) exposure to mouse allergen, (2) determination of sensitization, (3) association of exposure to sensitization, (4) association of exposure and sensitization to asthma morbidity, and (5) role of mouse allergen eradication.

Discussion

Exposure to mouse allergen

The major mouse allergen, *Mus musculus* 1 (Mus m 1), is a 16- to 19-kDa protein found in mouse urine and epithelial cells. Its particle size of 10 μm promotes deposition in the small airways on inhalation. Mouse allergen is detected in dust and measured at a lower limit of detection of 0.25 $\mu\text{g/g}$ of settled dust and 0.003 ng/m^3 of sampled air.^{8,9} Although most studies report the concentration of allergen in settled dust, Matsui et al⁸ documented a significant correlation between settled and airborne dust concentrations. Its presence is captured by enzyme-linked immunosorbent assay via a monoclonal antibody specific for the Mus m 1 or mouse urinary protein (MUP) allergens.

Mouse allergen is ubiquitous, detected in 99% of inner-city homes in the NCICAS cohort.⁷ The National Survey of Lead and Allergens in Housing attempted to collect indoor allergen data on a nationally representative sample of homes by recruiting participants from more than 800 homes across 75 locations. This study estimated an overall prevalence of detectable mouse allergen at 82%.⁹ Clinically significant Mus m 1 allergen exposure has been reported to be between 1 and 2 $\mu\text{g/g}$ but is most commonly defined as 1.6 $\mu\text{g/g}$ of dust.^{10–12} This amount is the median mouse allergen level found in the kitchens of a subset of low-income children with

asthma enrolled in the NCICAS cohort and was associated with greater odds of mouse sensitization (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.24–3.88; $P = .007$).¹³ Although the NCICAS cohort was the first attempt to define a clinically significant exposure, this work has not been replicated in populations at lower risk and may not be appropriately generalized.

Reported exposure to rodents is a reasonable estimate of true allergen load. In the NCICAS cohort, 49% of participants reported mouse infestation. Of those reporting infestation, 29% had corresponding visual evidence of rodents. Those participants who reported mouse infestation or had evidence of mouse excrement documented by trained study personnel were 5 times as likely to have detectable mouse allergen in household dust (OR, 5.01; $P = .0001$).⁷ Similarly, in a study of airborne and settled dust allergen levels in an inner-city, pediatric, predominantly African American cohort, participants with evidence of rodent infestation were 10 times as likely to have detectable mouse allergen (OR, 10.3; 95% CI, 1.2–88.8).⁸ Surveying more broadly in the United States, investigators have found that homes with self-reported mouse sightings were more than 3 times as likely to have high mouse allergen levels as homes with no reported sightings.¹¹ In a 2008 study, the positive predictive value of reported mouse exposure was reported as greater than 80%.¹² Self-report of mouse allergen exposure appears to be a potentially reliable demographic marker of patients at highest risk of significant exposure.

There are multiple determinants of mouse allergen load. Characteristics of the neighborhood, household, and housekeeping practices all influence the final concentration of mouse allergen. Mean Mus m 1 levels were found to be significantly lower in suburban neighborhoods compared with the city (0.009 vs 4.0 $\mu\text{g/g}$; $P < .001$). The same study reported a similar disparity in reported infestation, with 80% of city homes reporting infestation vs 5% of suburban homes.¹⁴ Older homes and those with families of lower income were also found to have significantly higher MUP concentrations than newer homes and those with residents of higher income.¹¹

Household characteristics have been implicated in determining mouse allergen levels. The NCICAS study found that homes with evidence of cockroach infestation were twice as likely to have detectable mouse allergen as well.⁵ Homes of children with asthma living in inner-city Baltimore, Maryland, with cracks or holes in the walls or ceiling were 5 times as likely to have detectable airborne mouse allergen as homes in better repair.⁸ The Healthy Public Housing Initiative in urban Boston, Massachusetts, correlated pet ownership, crowding, and prolonged occupancy (>2 years) with higher MUP concentration.¹⁵ The National Survey of Lead and Allergens in Housing identified both high-rise (>5 floors) and mobile homes as risk factors for high mouse allergen load (>1.6 $\mu\text{g/g}$) compared with single-family homes.¹¹ Unlike the findings of the Healthy Public Housing Initiative, presence of a cat in the home appears to be a protective factor in other studies. Chew et al¹⁰ describe a 0.3 odds of detectable mouse allergen in homes with a pet cat. This finding was replicated by a pooled analysis of 9 studies, which quoted odds of 0.2 of high mouse allergen in homes with a cat.¹⁶ Housekeeping practices have also been implicated. Those homes where the floors are mopped instead of vacuumed have 2 times the odds of a high allergen load.¹¹

Determination of sensitization

The criterion standard for diagnosis of mouse sensitization is an increase in nasal symptoms after intranasal challenge to mouse allergen; however, this is unrealistic to perform clinically. Sensitization is more commonly identified by skin prick testing (SPT) or intradermal testing (IDT) with commercially available extracts or measurement of mouse specific IgE antibodies in the serum. A study by Sharma et al¹⁷ compared the rates of positive nasal chal-

lenges in symptomatic laboratory rodent handlers with at least 1 positive diagnostic test result (SPT, IDT, or serum specific mouse IgE [mIgE] level measured by ImmunoCAP) to asymptomatic controls with negative diagnostic test results.

The authors found that a positive mIgE test result had a 47% sensitivity, 91% specificity, and positive likelihood ratio of 5.2 for predicting a positive nasal challenge result. A positive SPT result performed superiorly, with 67% sensitivity, 94% specificity, and a positive likelihood ratio of 11.2. IDT appears to be more useful for its negative predictive value, with 100% sensitivity, 65% specificity, and a positive likelihood ratio of 2.9. In summary, SPT is the superior test for detecting mouse sensitization in laboratory workers. One cannot rely on symptoms alone because only 31% of those workers describing symptoms had positive intranasal challenge results. The authors suggest that one should expect to detect 80% of mouse sensitized persons in the inner city with SPT, although these findings have not been replicated in an inner-city population.¹⁷ In addition, the studied population exhibited nasal and ocular symptoms, not lower respiratory tract manifestations. It may be inappropriate to extrapolate upper respiratory tract findings in sensitized rodent workers to lower respiratory tract morbidity in the asthma community. No study was identified that documents bronchial hyperresponsiveness after direct inhalation challenge in an asthmatic population.

Relationship of exposure to sensitization

Because daily activities have shifted from outdoors to indoors, sensitization to indoor allergens is becoming increasingly important. Eight studies investigated the relationship between exposure to mouse allergen and sensitization. Matsui and colleagues¹⁸ estimated that preschool children with asthma spend an average of approximately 2 hours per day outdoors. This translates to nearly 22 hours per day of potential exposure to indoor allergens. Children with asthma spend an estimated 1,000 hours per year inside classrooms, which may also be exposure risks. A study of Baltimore city schools detected Mus m 1 in 100% of schools surveyed, with the highest levels in the cafeterias and teacher's lounges. In the schools sampled, asthma prevalence was 3 times higher than the national average.¹⁹ These data suggest that sensitization in the community may be largely driven by exposure. In the NCICAS population, the children from homes with mouse allergen levels greater than the median in the kitchen (1.6 $\mu\text{g/g}$) had more than twice the odds of sensitization to mouse. In addition, those SPT positive to mouse pelt had 4 times the level of mouse allergen in their kitchens compared with SPT negative children.¹³ Matsui et al presented evidence in 2009 that mouse allergen exposure and sensitization rates are similarly disparate between inner-city and suburban homes as are asthma morbidity outcomes. Inner-city populations as a whole have demonstrated 100-fold higher mouse allergen levels than suburban homes and a higher percentage of sensitized residents (11%–46% vs 12%–13%).⁶

The relationship between mouse exposure and sensitization may be nonlinear. Sensitization is 4 times higher in populations exposed to 8 to 29 μg of mouse allergen per gram of dust compared with those unexposed. Sensitization rates cease to increase at the same rate at exposures of greater than 29 $\mu\text{g/g}$, suggesting a potential induction of tolerance at the highest concentrations. Although sensitization is highest at intermediate levels of allergen exposure, those exposed to the highest level have 1.5 greater odds of sensitization than those exposed to the lowest levels of allergen.²⁰ These data appear to support reducing allergen concentrations to the lowest possible levels.

The literature suggests that not only are time spent indoors, urban living, and age important, but geographic location and race may also be predictors of mouse exposure and sensitization. A multisite, cross-sectional study noted that levels of settled dust

mouse allergen in these sites were significantly lower than those levels reported in the Baltimore NCICAS cohort. In the same study, racial differences were seen. In Virginia, 12% of African American and Hispanic mothers were sensitized to mouse compared with just more than 3% of white mothers.²¹ This raises a potential mechanistic link between mouse allergen exposure and asthma morbidity in minority populations.

A more recent cross-sectional study compared a population from Bronx, New York, a borough known for increased asthma prevalence and morbidity, with populations from multiple locations throughout the country. In this study, Bronx families were nearly 6 times as likely to report mouse infestation as children from 7 other sites across the country. These children were also more than 4 times as likely to be SPT positive and exposed to indoor allergens, including mice.²² Similar to cockroach allergen, mouse exposure and sensitization may be linked to worsened asthma morbidity outcomes.

Relationship of exposure and sensitization to asthma morbidity

Finding a link between exposure and sensitization to mouse allergen and asthma morbidity may help direct interventions to modify risk. Unlike the findings related to cockroach, the NCICAS population exhibited no significant associations between exposure and sensitization to mouse allergen and asthma morbidity variables.¹³ Similar negative findings were published in a cross-sectional survey in New York City. Neither asthma prevalence nor morbidity outcomes were significantly correlated with mouse allergen levels.²³

Unlike the negative findings of the NCICAS cohort, mouse exposure has been associated with asthma morbidity in an atopic cohort. In a study by Salo et al,⁹ atopic individuals were noted to have nearly 2 times the odds of asthma symptoms and use of asthma medications in the past year and nearly 3 times the odds of wheeze in the preceding month if exposed to household dust MUP greater than 1.6 $\mu\text{g/g}$.⁹ Unlike the room-specific threshold documented in the NCICAS cohort, mouse allergen was quantified in this study by pooling dust from multiple locations within the home to create a "house index." In an inner-city Baltimore, pediatric, asthma population, children with positive mIgE test results who were exposed to greater than 0.5 $\mu\text{g/g}$ of Mus m 1 allergen had 70 times the odds of an asthma-related hospitalization (adjusted OR, 70.6; 95% CI, 5.5–909.6).¹⁸ This combination of high exposure and sensitization was also significantly associated with higher incidence of symptoms, use of rescue medications, and unscheduled health care use.

A critical question to answer is whether exposure or sensitization to mouse allergen in early life is linked to the development of asthma. The aforementioned study by Chew et al found that homes with MUP concentrations above a threshold of 1 $\mu\text{g/g}$ were associated with greater than twice the odds of having a resident with a diagnosis of asthma. A similar trend was found for daily mouse sightings and having a resident child with asthma, although this finding did not reach significance.²³ As part of the Home Allergens and Asthma Study, a prospective birth cohort in Baltimore, reported exposure to rodents was associated with nearly twice the odds of wheezing within the first year of life.²⁴ In a New York City birth cohort, children sensitized to MUP had nearly 5 times greater odds of early wheeze. The association held significance in an appropriate regression model. Sensitization in this cohort also exhibited a dose effect. The quantitatively higher mIgE concentration was more strongly associated with wheezing.²⁵ Similar evidence was collected in 2007, documenting twice the odds of physician-diagnosed asthma in adult women sensitized to mouse allergen in an all-female Boston cohort.²⁶ Similarly, children sensitized to mouse in a predominantly Hispanic population in New York were 3 times as likely to have an asthma diagnosis as children not sensitized.²⁷ Although inconclusive, the sum of these data suggest that exposure

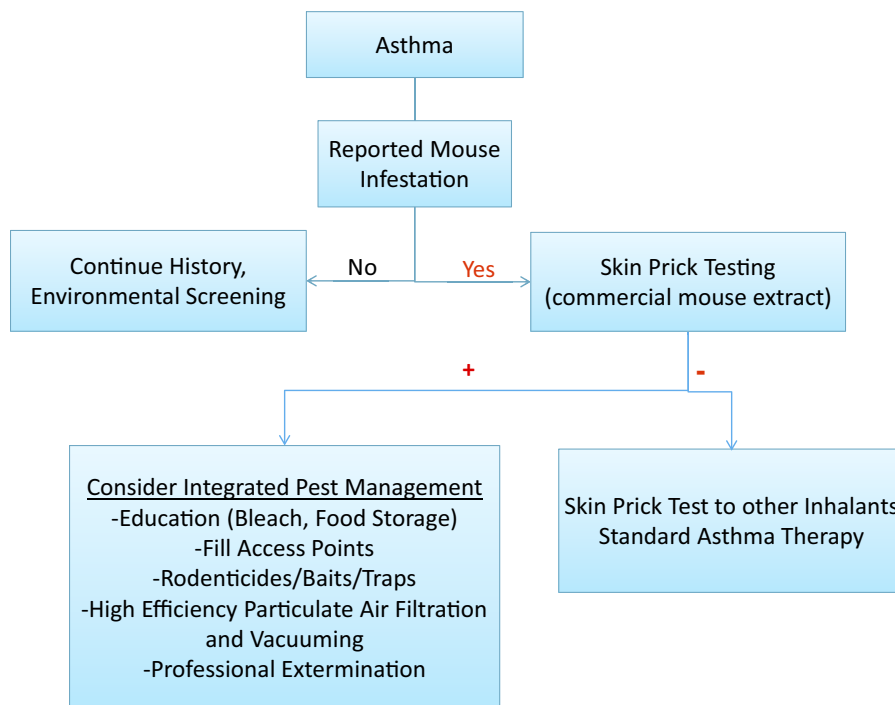


Fig 1. Proposed diagnostic algorithm and targeted therapy for inner-city pediatric patients with asthma at risk for highest morbidity.

and sensitization to mouse allergen during early childhood may contribute to the development of asthma.

Sensitization may be the critical link between exposure and asthma morbidity. An urban Boston cohort of women with asthma found 3 times the odds of asthma morbidity in those with serum IgE positive for *Mus m 1*. In this study, measures of morbidity included steroid use, emergency department visit, wheezing without a cold, and prolonged illness.²⁶ Similar to the findings in Boston, New York City children living in an area with high asthma prevalence who were sensitized to mouse were significantly more likely to have a diagnosis of asthma and unscheduled physician visits, emergency department visits, and hospitalizations.²⁷ An adult cohort in New York found a significant association between mouse sensitization and retrospective hospitalization but no association with quality of life, steroid use, intubation, or prospective emergency department visit.²⁸ One study also suggests a relationship between sensitization to mouse and severity of asthma.²⁹ The sum of these data is conflicting, with some reporting positive associations between mouse allergen exposure and asthma diagnosis and morbidity and some with opposite conclusions. In addition, it is unclear which measure of morbidity is most pertinent and varies among the studies. The literature does not support a conclusive link among mouse allergen exposure, sensitization, and asthma development or morbidity.

Effect of mouse allergen eradication

Understanding the relationship of the indoor environment to asthma development and morbidity helps target interventions to minimize exposures and their potential consequences. On the molecular level, Chen and Eggleston³⁰ described the effectiveness of household bleach at fragmenting mouse allergen and reduction of IgE binding, thereby rendering the protein unable to elicit an allergic response.³⁰ Significant reduction of mouse allergen and long-term maintenance of eradication is not as simple as cleaning with bleach, however. Integrated pest management (IPM) appears to be the most effective approach, incorporating several resources to eradicate indoor allergens. In addition to cleaning with household

bleach, IPM programs fill rodent access points; provide air filters; set traps, bait, and rodenticides; use professional extermination; and educate the families to remove food attractants from the home.³¹ Studies have documented successful reduction of mouse allergen levels with IPM.^{32,33} Notably, Phipatanakul et al³² performed a blinded randomized controlled trial of pediatric asthma patients living in Boston. Participants were both sensitized and exposed to mouse allergen and were randomized to IPM intervention or control arms. The intervention group had a 79% reduction in mouse allergen levels during the 5 months of the study, whereas the control group experienced a significant increase in mouse allergen load.³²

Eight articles were identified in this literature search that described targeted interventions to minimize mouse allergens. Two cross-sectional studies describe the lack of environmental control practices initiated by parents of children with asthma. An investigation of inner-city pediatric patients with asthma in Baltimore reported that children with asthma sensitized to mouse were not more likely to institute mouse controls than children with asthma who were not sensitized. Mouse control practices were significantly more likely if the patient or parent was sensitized to mouse and exhibited rhinitis symptoms than those who were not sensitized (78% vs 42%).^{29,34} These data suggest that parents fail to make similar associations between indoor exposures and asthma morbidity as they do between indoor exposures and rhinitis. Finkelstein and colleagues³⁵ suggest that the lack of control measures may be partly explained by failure of health care professionals to provide specific guidance. This cross-sectional study identified privately insured children with mild to moderate asthma all of whom have primary care physicians. Only 11% acknowledge receiving written instruction on trigger avoidance in the prior 6 months. Even so, having written information did not correlate with a change in exposure to common asthma triggers.³⁵ Clearly, physicians need to provide written educational materials to patients, but education alone does not seem to be effective.

The critical question is whether reduction of indoor mouse allergen exposure will reduce asthma morbidity. Four studies were

identified that attempted to answer this question. The most positive results were a reduction in daytime symptoms, school absences, night awakenings, and change of plans due to asthma symptoms after instituting IPM consisting of high-efficiency particulate air filtration of bedroom air and vacuumed surfaces, filling rodent access points, and educating the family about food containment practices.^{33,36} No study documented improvement in lung function or health care use after intensive interventions. One might argue that the lack of consistent improvement in symptoms, lung function, and health care use is a function of length of follow-up and maintenance of the interventions. Prospective studies of IPM with long-term follow-up have not been performed.

Study limitations and future directions

Our knowledge of the contribution of mouse allergen to inner-city asthma morbidity is evolving. Further investigation is needed, however. Most of the studies explored in this systematic review were cross-sectional, which does not offer the ability to infer causation. To determine a causal association between mouse allergen exposure, sensitization, and subsequent development of asthma and morbidity, one would need to follow up a cohort for many years. Investigating such a cohort would include making serial measurements of in-home mouse allergen, documenting the age at which sensitization first becomes detectable, making a firm diagnosis of asthma using spirometry, and documenting outcomes prospectively. It is also difficult to make an asthma diagnosis in the pediatric population before school age, but firm classification of asthma based on well-defined diagnostic criteria for these studies would be ideal. In addition, one's exposure to allergen may vary over time due to seasonal variation, change in housing condition and cleaning practices, and relocation. It is likely that allergen exposure at a single point is being inaccurately extrapolated to a person's exposure over time.

Finally, there is a significant risk of confounding in this population because sensitization to a single indoor allergen increases the likelihood of sensitization to other indoor allergens.²⁹ Exposure to other allergens, endotoxin, environmental tobacco smoke, or other pollutants may be the true indoor variables affecting asthma morbidity. Moreover, environmental exposures on a susceptible genetic background may explain a substantial portion of the risk. Socioeconomic status, parental mental health, differences in health care access, and health care use may be important mediating factors as well.

Conclusions

Current research has focused on the role of mouse allergen in asthma prevalence and morbidity in poor, inner-city, minority populations. Mouse allergen, a well-described sensitizer in the laboratory setting, is widespread in the community. The major allergen Mus m 1 is found at its highest levels in the kitchens of inner-city homes with the most impressive prevalence in urban Baltimore. It can be found in most inner-city and suburban homes, especially those in poor repair. Self-reported rodent infestation has overwhelmingly been identified as an acceptable proxy for quantitative measurement of allergen exposure, a fact of great importance to health care professionals. Interviewing families about the home environment may be a first screen to direct allergen testing in at-risk asthmatic patients.

The literature review identified inhalation challenge as the criterion standard for determining mouse allergen sensitization. Because this is clinically impractical, there are 3 other commonly used methods to detect sensitization. Of serum specific IgE testing to mouse allergen, SPT, and IDT, the sensitivity, specificity, and positive predictive value are strongest for SPT. Many of the studies in this review performed serum specific IgE testing, which may be more convenient in hospitalized patients and for large-scale, population-based research studies.

In studies of settled dust, mouse allergen levels greater than 1.6 $\mu\text{g/g}$ have been associated with higher rates of sensitization. Sensitization rates increase with exposure, but at the highest levels of exposure, the effect plateaus. In addition, multiple studies have found a relationship between exposure and sensitization to mouse allergen and asthma morbidity, but there have been negative findings as well, including in the NCICAS population. Intervention studies document success with reduction of indoor mouse allergen, but there is conflicting evidence on whether eradication reduces asthma morbidity. In summary, there appears to be a relationship between exposure to mouse allergen and subsequent sensitization. There is a theoretical but controversial link between sensitization and the development of asthma and asthma morbidity. The current literature does not overwhelmingly support symptomatic improvement with mouse allergen eradication but demonstrates the ability to decrease exposure in the short term. We propose a diagnostic algorithm that may be used to determine patients at highest risk for significant morbidity associated with mouse allergen exposure, assessment for sensitization, and subsequent intervention (Fig 1). Because the literature does not support universal implementation, we caution that this algorithm be used only for children with identifiable risk factors because interventions can be consuming of time and resources.

The development of the asthma phenotype is an intricate interplay of influences. In patients at the highest risk of poor outcome, screening for mouse exposure and sensitization may be a potentially modifiable piece of the puzzle.

Acknowledgments

We thank Mary R. Ward, PhD, external instructor in the Division of Epidemiology and Biostatistics at the University of Cincinnati, for the instruction in conducting and editing this review.

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