



Indoor allergen exposure and asthma outcomes

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Purpose of review

The aim of the present review is to discuss updates on research regarding the relationship between indoor allergen exposure and childhood asthma with a focus on clinical effects, locations of exposure, and novel treatments.

Recent findings

Recent data continue to demonstrate that early life sensitization to indoor allergens is a predictor of asthma development later in life. Furthermore, avoidance of exposure to these allergens continues to be important especially given that the vast majority of children with asthma are sensitized to at least one indoor allergen. New research suggests that mouse allergen, more so than cockroach allergen, may be the most relevant urban allergen. Recent evidence reminds us that children are exposed to clinically important levels of indoor allergens in locations away from their home, such as schools and daycare centers. Exposure to increased levels of indoor mold in childhood has been associated with asthma development and exacerbation of current asthma; however, emerging evidence suggests that early exposure to higher fungal diversity may actually be protective for asthma development. Novel treatments have been developed that target TH2 pathways thus decreasing asthmatic responses to allergens. These therapies show promise for the treatment of severe allergic asthma refractory to avoidance strategies and standard therapies.

Summary

Understanding the relationship between indoor allergens and asthma outcomes is a constantly evolving study of timing, location, and amount of exposure.

Keywords

allergens, asthma, dust mites, molds, mouse

INTRODUCTION

Exposure to aeroallergens is an important factor in the pathogenesis and control of allergic diseases, including asthma. Indoor allergens are of particular importance and principally include house dust mites, pets such as dogs and cats, pests such as cockroaches and rodents, and molds. The relative importance of these different allergens varies based on different environmental factors depending on geographic, climatic, socioeconomic, and housing conditions. The measurement of indoor allergen levels in dust and air samples has allowed for the determination of risk levels associated with the development of sensitization and symptomology. In the present review, we summarize recent data regarding indoor allergen exposures and the associations with asthma morbidity. This review will focus on the most common indoor allergens including allergens from dust mites, cats, dogs, mice, cockroaches, and molds. A specific focus has been placed on intriguing recent findings including new methods to measure indoor allergens, inner-city exposures, and allergen exposures in schools or

daycare centers. In addition, new treatments that effectively disrupt the association between indoor allergen exposure and asthma symptoms will be presented. This review will not discuss exposures to indoor air pollutants or microbial products that are important, but beyond the scope of this topic.

OVERVIEW AND EPIDEMIOLOGY

Studies indicate that more than 80% of school age children with asthma are sensitized to at least one indoor allergen and that allergic sensitization is a strong predictor of disease persistence in later life [1–3]. In fact, in a cohort of children hospitalized for

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Curr Opin Pediatr 2016, 28:000–000

DOI:10.1097/MOP.0000000000000421

KEY POINTS

- Indoor allergen sensitization is common in young children with asthma, and this sensitization is a predictor of asthma persistence later in life.
- Cockroach allergen has traditionally been considered the primary inner-city indoor allergen; however, recent data suggest that mouse allergen may be the most relevant urban allergen exposure.
- In addition to home exposures, children are exposed to a wide variety of clinically relevant allergens in schools and daycare centers.
- In general, exposure to mold in homes and schools has been associated with asthma development and exacerbation of current asthma; however, emerging evidence suggests that early exposure to higher fungal diversity may actually be protective for asthma development.
- In recent years, novel therapies targeting TH2 pathways that have been successful in decreasing asthmatic responses to allergens show promise for the treatment of severe allergic asthma refractory to avoidance strategies and standard therapies.

asthma, 91% were found to be sensitized to at least one indoor allergen [4]. Bjerg *et al.* [5] have shown that, while pollen sensitization is strongly associated with the development of rhinitis, indoor allergen sensitization was more associated with asthma. The timing of sensitization is also an important factor as a recent study demonstrated that aeroallergen sensitization at younger ages was associated with an increased risk of asthma in later childhood [6].

NEW WAYS TO MEASURE INDOOR ALLERGEN EXPOSURE AND TO IDENTIFY ALLERGEN SENSITIZATION

Indoor allergens are typically measured in dust samples that are collected by either vacuuming settled dust or gathering airborne dust from filtered air within a room. Samples may be collected from multiple sites within a home. After collection, fine dust can then be extracted and tested for quantification of individual allergens. Typical dust sampling has relied on spot checks at a certain time point of vacuuming, which measures exposure levels in that exact location. Tovey *et al.* [7] recently developed a novel method to measure dust mite exposures in individuals over 24-h periods and found that exposures fluctuate over time and beds may not always be the main site of exposure as general considered.

Although home sampling is feasible in the clinical research community, there have not been easy-to-use methods for patients or parents to measure the allergen levels in their homes by themselves. Winn *et al.* [8] evaluated the use of an in-home test kit that allowed parents of dust mite allergic children the ability to easily and quickly quantify the level of dust mites within the home. This study demonstrated that dust mite levels in the 'testing' homes were significantly reduced over time compared with control homes that only received education [8]. The authors speculate that immediate knowledge of dust mite levels motivated the parents to more thoroughly perform dust mite avoidance strategies. Future studies are needed to further evaluate the utility and role of patient-directed or parent-directed home allergen measurements in the care of asthma and allergies.

As healthcare trends toward precision medicine where therapies are tailored toward an individual's exact need, allergic sensitization testing is also heading in this direction. In keeping with this idea of more focused treatments, Chen *et al.* [9] demonstrated the clinical utility of latent class analysis to identify patterns of allergic sensitization among children. Analyzing these patterns of allergic sensitization revealed additional associations with asthma than the evaluation of a single allergen or total immunoglobulin E [9]. Identifying patterns of polysensitization may be useful in treatment decisions and prognosis discussion. For example, it was shown that sensitization to cockroach actually reduced the symptom scores in participants with concomitant dust mite and pollen sensitization [10]. Future studies may continue this trend by viewing the whole sensitization profile in a subject instead of focusing on single allergen results.

THE KEY INNER-CITY ALLERGEN: COCKROACH VERSUS MOUSE

Indoor allergen exposure in inner-city areas has been of particular interest given that children living in urban areas have increased asthma severity, decreased asthma control, and greater healthcare use [11]. In the late 1990s, Rosenstreich *et al.* [12] found cockroach allergen to be highly detectable in inner-city homes. Furthermore, this study demonstrated that children with asthma who were sensitized and exposed to high levels of cockroach allergen had increased asthma morbidity [12]. This landmark study led to cockroach allergen being deemed the important indoor allergen in urban areas; however, mouse allergen has been gaining recognition in recent years [13]. Mouse allergen has been discovered to be prevalent in inner-city homes [14] with home exposure associated with

increased asthma morbidity [15]. Outside the home, a study of urban schools found mouse allergen to be the primary school-based allergen, not cockroach allergen [16]. In support of this, Ahluwalia *et al.* [17] reported that mouse and not cockroach allergen was the major allergen of relevance in inner-city Baltimore. In a city with high levels of both mouse and cockroach allergens, mouse allergen was more strongly and consistently associated with worse asthma outcomes including acute care visits, decreased spirometry, and bronchodilator reversibility [17]. Supporting these results, a more recent study of urban Baltimore and Boston found that sensitization to mouse allergen, but not cockroach, was an independent risk factor for rhinitis in inner-city children with asthma [18]. Although allergen reduction tactics in the inner city often focus on mouse and cockroach allergens, recent results have led to the suggestion that community-based asthma intervention strategies should prioritize reducing mouse allergen exposure [17]. Admittedly, the predominance and clinical importance of mouse versus cockroach allergens in a particular urban area depends on a variety of factors including weather and building conditions. It is expected that future studies will continue to focus not only on identifying the important inner-city allergen, but also efforts to eliminate exposures and improve asthma outcomes.

AWAY FROM HOME: EXPOSURE TO INDOOR ALLERGENS IN OTHER CHILDHOOD SETTINGS, SUCH AS SCHOOL AND DAYCARE CENTERS

Early studies on indoor allergen exposures and asthma outcomes focused on the home environment. Although parents can do their best to reduce or eliminate allergen exposures in the home, children spend a large portion of the day in schools or daycare centers. In recent years, the exposure to indoor allergens has been studied in these locations outside the home. Cat and dog allergens seem to be particularly ubiquitous in society because of the easy transfer of these pet allergens. This has been confirmed by data demonstrating that clinically relevant levels of pet allergens are found in homes without these animals [19]. Furthermore, a recent study of teenagers found that a large majority of cat-sensitized individuals did not live in a home with a cat [20[¶]], suggesting that sensitization occurs because of exposures outside the home or due to allergens tracked into the home. For children, the main location for this possible outside exposure is the school setting. In support of this, Almquist *et al.* [21] found that cat allergen was transported into

schools and associated with worsening of asthma for students with cat allergy who were subjected to this indirect pet exposure.

Indoor allergen exposures in schools are not limited to allergens being tracked in from home, but are sometimes because of allergens intrinsic to the school settings. Permaul *et al.* [16] noted mouse allergen to be present in high levels in inner-city schools due to infestation within the schools and not passive transfer from students' homes [22]. For younger children, exposure to dust mites and molds in day care centers was associated with wheezing [23]. Likewise, researchers in Denmark found that high classroom dampness was associated with increased wheezing and decreased spirometry in exposed students [24]. Finally, mold exposure in school classrooms was shown to be significantly associated with current asthma symptoms and asthma symptoms that improved over holidays and weekends when the students were out of school [25^{¶¶}]. This pattern of symptomatology is analogous to workplace exposures and health outcomes for adults [26]. These findings have prompted suggestions that governmental health policies should consider environmental interventions in schools to improve childhood asthma. It is expected that future research will focus on intervention tactics in schools to reduce allergen exposures and improve students' respiratory symptoms. These interventions have been successful in homes [27] and now need to be trialed in the school setting.

MOLD EXPOSURE AND ASTHMA

Molds grow best in warm and moist environments within the home including basements, windows frames, and bathrooms. *Aspergillus* and *Penicillium* species are generally regarded as the predominant indoor molds, and *Alternaria* is important in both indoor and outdoor environments. Recent literature in this field has focused on the association of mold exposure in early childhood with the development of atopic conditions including asthma later in childhood. Sharpe *et al.* [28[¶]] recently discovered that reporting mildew odor in the home was associated with an increased risk of childhood asthma. Supporting this, a birth cohort study demonstrated that exposure to moisture damage and visible mold in early infancy were associated with asthma development [29]. More specific measurement of mold exposure yielded similar findings as Oluwole *et al.* [30] documented that mold levels in dust samples from both play area floors and bedroom mattresses were significantly associated with current asthma. In a meta-analysis, increased levels of *Penicillium*,

Aspergillus, *Cladosporium*, and *Alternaria* species were associated with increased exacerbation of current asthma symptoms in children [31].

New research has now focused on the diversity of mold exposures and the associated clinical outcomes because there is growing evidence that exposure to a wide diversity of mold species may actually be protective. For example, Tischer *et al.* [32²²] found that exposure to higher fungal diversity shortly after birth was associated with a decreased risk of developing wheezing and aeroallergen sensitization in later childhood. Future work should continue to evaluate the role of fungal diversity on the development of atopic conditions.

NEW TREATMENTS TO DISRUPT THE ALLERGEN-ASTHMA ASSOCIATION

Allergen avoidance is considered the first line of treatment for patients with indoor allergen sensitivities and asthma. In general practice, allergen avoidance should be tailored based on an individual's-specific allergen sensitivities and known environmental exposures. In research, most of the studies in which environmental controls have been effectively implemented a multifaceted approach. For example, Morgan *et al.* [27] demonstrated that a comprehensive environmental intervention in the home was able to reduce levels of indoor allergens and resulted in improved asthma outcomes in children. Certainly, future studies will continue to focus on efficient and cost-effective strategies to reduce allergen exposures in homes and locations outside the home. After allergen avoidance, the mainstays of initial medication therapy include antihistamines, corticosteroids, and leukotriene receptor antagonists.

In recent years, novel therapies targeting TH2 pathways have been successful in decreasing the asthmatic response to allergen triggers. These medications provide hope for the future for patients with allergies and asthma refractory to environmental avoidance strategies and standard medications. Most notably, Krug *et al.* [33²²] recently reported promising outcomes in individuals taking a DNase that is able to cleave and inactivate GATA3, an important transcription factor of the TH2 pathway. In patients with allergic asthma, treatment with this DNase was able to significantly attenuate both late and early asthmatic responses after allergen challenge [33²²]. Similar disruption of the allergen exposure and asthma pathway was seen after treatment with a monoclonal antibody against thymic stromal lymphopoietin, which is a cytokine thought to be important in initiating allergic inflammation

[34]. Other new therapeutic approaches targeting specific cytokines in the TH2 inflammatory pathway have shown promising results for improving asthma outcomes [35–37].

Finally, recent advances in dust mite allergen immunotherapy have shown promising results. Virchow *et al.* [38] evaluated individuals with dust mite allergy-related asthma and found that treatment with novel dust mite sublingual allergen immunotherapy, when compared with placebo, was shown to improve asthma control. A very important secondary finding in this study was that there were no differences in outcomes detected between polysensitized individuals and those monosensitized to dust mite, demonstrating the clinical efficacy of single allergen immunotherapy even in patients with sensitization to multiple allergens [38]. Zolkipli *et al.* [39²¹] used dust mite allergen oral immunotherapy prophylactically in high-risk, but not yet sensitized, infants less than 12 months of age and found that this early life treatment reduced the development of sensitization to any allergen. The use of single allergen immunotherapy is often the concern regarding oral immunotherapy; however, the targeting of treatment with dust mite allergen makes sense given that this is known to be the most frequent indoor allergen associated with asthma worldwide. In fact, recent laboratory data demonstrated that house dust mite exposure selectively increased the proliferation of bronchial smooth muscle in patients with severe asthma [40]. It is expected that future research will continue to develop oral immunotherapy with a particular focus on dust mites.

CONCLUSION

Exposure to indoor aeroallergens is an important factor in the pathogenesis and control of childhood asthma. Although previous research focused on allergen exposures in homes, emerging research is shifting toward the importance of allergen exposures in schools and daycare centers. Furthermore, new techniques are being developed to more easily and efficiently measure levels of allergen exposure. In urban areas, mouse allergen has become an important exposure and may replace cockroach allergen as the most relevant indoor allergen exposure. Studies continue to demonstrate the association between mold exposure in early childhood and asthma development and symptoms. Although avoidance strategies are always the first line of defense in the treatment of allergies and asthma, novel therapeutics are being developed for patients with severe asthma triggered by allergens.

Acknowledgements

None.

Financial support and sponsorship

This work was supported in part by grants K24AI106822, K23AI104780, U10HL109172, U10HL098102, and U01AI110397 from the National Institutes of Health. This work was also conducted in part by support from the American Lung Association/American Academy of Allergy, Asthma, and Immunology Respiratory Diseases Faculty Award, and Deborah Munroe Noonan Memorial Award. There was also support from Harvard Catalyst/The Harvard Clinical and Translational Science Center (NIH Award # 8UL1TR000170) and financial contributions from Harvard University and its affiliated academic health-care centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University, and its affiliated academic health-care centers, the National Center for Research Resources, or the National Institutes of Health CTSU PI (Nagler).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *New Engl J Med* 1990; 323:502–507.
2. Illi S, von Mutius E, Lau S, *et al.* Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; 368:763–770.
3. Eggleston PA, Rosenstreich D, Lynn H, *et al.* Relationship of indoor allergen exposure to skin test sensitivity in inner-city children with asthma. *J Allergy Clin Immunol* 1998; 102 (4 Pt 1):563–570.
4. Beck AF, Huang B, Kercsmar CM, *et al.* Allergen sensitization profiles in a population-based cohort of children hospitalized for asthma. *Ann Am Thorac Soc* 2015; 12:376–384.
5. Bjerg A, Ekerljung L, Eriksson J, *et al.* Increase in pollen sensitization in Swedish adults and protective effect of keeping animals in childhood. *Clin Exp Allergy* 2016.
6. Rubner FJ, Jackson DJ, Evans MD, *et al.* Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. *J Allergy Clin Immunol* 2016. This study demonstrated that aeroallergen sensitization at younger ages was associated with an increased risk of asthma in later childhood.
7. Tovey ER, Liu-Brennan D, Garden FL, *et al.* Time-based measurement of personal mite allergen bioaerosol exposure over 24 hour periods. *PLoS One* 2016; 11:e0153414.
8. Winn AK, Salo PM, Klein C, *et al.* Efficacy of an in-home test kit in reducing dust mite allergen levels: results of a randomized controlled pilot study. *J Asthma* 2016; 53:133–138.
9. Chen Q, Zhong X, Acosta L, *et al.* Allergic sensitization patterns identified through latent class analysis among children with and without asthma. *Ann Allergy Asthma Immunol* 2016; 116:212–218.
10. He W, Jimenez F, Martinez H, *et al.* Cockroach sensitization mitigates allergic rhinoconjunctivitis symptom severity in patients allergic to house dust mites and pollen. *J Allergy Clin Immunol* 2015; 136:658–666.
11. Szeffer SJ, Gergen PJ, Mitchell H, Morgan W. Achieving asthma control in the inner city: do the National Institutes of Health Asthma Guidelines really work? *J Allergy Clin Immunol* 2010; 125:521–526; quiz 7-8.
12. Rosenstreich DL, Eggleston P, Kattan M, *et al.* The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *New Engl J Med* 1997; 336:1356–1363.
13. Ownby DR. Will the real inner-city allergen please stand up? *J Allergy Clin Immunol* 2013; 132:836–837.
14. Phipatanakul W, Eggleston PA, Wright EC, Wood RA. Mouse allergen. I. The prevalence of mouse allergen in inner-city homes. The National Cooperative Inner-City Asthma Study. *J Allergy Clin Immunol* 2000; 106:1070–1074.
15. Phipatanakul W, Litonjua AA, Platts-Mills TA, *et al.* Sensitization to mouse allergen and asthma and asthma morbidity among women in Boston. *J Allergy Clin Immunol* 2007; 120:954–956.
16. Permaul P, Hoffman E, Fu C, *et al.* Allergens in urban schools and homes of children with asthma. *Pediatr Allergy Immunol* 2012; 23:543–549.
17. Ahluwalia SK, Peng RD, Breyse PN, *et al.* Mouse allergen is the major allergen of public health relevance in Baltimore City. *J Allergy Clin Immunol* 2013; 132:830–835; e1-2.
18. Sedaghat AR, Matsui EC, Baxi SN, *et al.* Mouse sensitivity is an independent risk factor for rhinitis in children with asthma. *J Allergy Clin Immunol Pract* 2016; 4:82–88; e1.
19. Arbes SJ Jr, Cohn RD, Yin M, *et al.* Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: results from the National Survey of Lead and Allergens in Housing. *J Allergy Clin Immunol* 2004; 114:111–117.
20. Perzanowski MS, Ronmark E, James HR, *et al.* Relevance of specific IgE antibody titer to the prevalence, severity and persistence of asthma among 19-year-olds in Northern Sweden. *J Allergy Clin Immunol* 2016; Article in Press. This study uncovered that a majority of cat-sensitized individuals did not live in a home with a cat indicating that sensitization to pets can occur without obvious exposure.
21. Almqvist C, Wickman M, Perfetti L, *et al.* Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001; 163 (3 Pt 1):694–698.
22. Permaul P, Sheehan WJ, Baxi SN, *et al.* Predictors of indoor exposure to mouse allergen in inner-city elementary schools. *Ann Allergy Asthma Immunol* 2013; 111:299–301; e1.
23. Carreiro-Martins P, Papoila AL, Caires I, *et al.* Effect of indoor air quality of day care centers in children with different predisposition for asthma. *Pediatr Allergy Immunol* 2016; 27:299–306.
24. Holst G, Host A, Doekes G, *et al.* Allergy and respiratory health effects of dampness and dampness-related agents in schools and homes: a cross-sectional study in Danish pupils. *Indoor Air* 2015.
25. Chen CH, Chao HJ, Chan CC, *et al.* Current asthma in schoolchildren is related to fungal spores in classrooms. *Chest* 2014; 146:123–134. This study in school children demonstrated that mold exposures within the school were associated with asthma symptoms that improved over holidays and week-ends. These results support the theory that school exposures in children are analogous to workplace exposures in adults.
26. Lim FL, Hashim Z, Than LT, *et al.* Asthma, airway symptoms and rhinitis in Office Workers in Malaysia: associations with house dust mite (HDM) allergy, cat allergy and levels of house dust mite allergens in office dust. *PLoS One* 2015; 10:e0124905.
27. Morgan WJ, Crain EF, Gruchalla RS, *et al.* Results of a home-based environmental intervention among urban children with asthma. *New Engl J Med* 2004; 351:1068–1080.
28. Sharpe RA, Thornton CR, Tyrrell J, *et al.* Variable risk of atopic disease due to indoor fungal exposure in NHANES. *Clin Exp Allergy* 2015; 45:1566–1578. This study presented results from a birth cohort where exposure to visible mold and water damage in early infancy were associated with asthma development.
29. Karvonen AM, Hyvarinen A, Korppi M, *et al.* Moisture damage and asthma: a birth cohort study. *Pediatrics* 2015; 135:e598–e606.
30. Oluwole O, Kirychuk SP, Lawson JA, *et al.* Indoor mold levels and current asthma among school-aged children in Saskatchewan, Canada. *Indoor Air* 2016; Apr 24.
31. Sharpe RA, Bearman N, Thornton CR, *et al.* Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. *J Allergy Clin Immunol* 2015; 135:110–122.
32. Tischer C, Weikl F, Probst AJ, *et al.* Urban dust microbiome: impact on later atopy and wheezing. *Environ Health Perspect* 2016. This study found that exposure to higher fungal diversity shortly after birth was associated with a decreased risk of developing wheezing and aeroallergen sensitization. These findings support the theory that an increased diversity of exposure may actually be protective against atopy development.
33. Krug N, Hohlfeld JM, Kirsten AM, *et al.* Allergen-induced asthmatic responses modified by a GATA3-specific DNzyme. *New Engl J Med* 2015; 372:1987–1995. This study was a randomized, double-blind, placebo-controlled trial, evaluating the effect of treatment with a novel DNA enzyme (DNzyme) that cleaves and inactivates GATA3, an important transcription factor of the TH2 pathway. The results demonstrated that treatment significantly attenuated both late and early asthmatic responses after allergen provocation.
34. Gauvreau GM, O'Byrne PM, Boulet LP, *et al.* Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *New Engl J Med* 2014; 370:2102–2110.

35. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *New Engl J Med* 2013; 368:2455–2466.
36. Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *New Engl J Med* 2009; 360:973–984.
37. Corren J, Lemanske RF, Hanania NA, *et al.* Lebrikizumab treatment in adults with asthma. *New Engl J Med* 2011; 365:1088–1098.
38. Virchow JC, Backer V, Kuna P, *et al.* Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016; 315:1715–1725.
39. Zolkipli Z, Roberts G, Cornelius V, *et al.* Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. *J Allergy Clin Immunol* 2015; 136:1541–1547; e1-11.
High-risk, but not yet sensitized, infants treated with dust mite allergen oral immunotherapy had reduced development of sensitization to any allergen.
40. Trian T, Allard B, Dupin I, *et al.* House dust mites induce proliferation of severe asthmatic smooth muscle cells via an epithelium-dependent pathway. *Am J Respir Crit Care Med* 2015; 191:538–546.