

The role of cockroach allergens in asthma

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Cockroach allergy has been recognized as an important cause of asthma. Cockroach asthma has been described as a more severe disease, associated with perennial symptoms and high levels of total IgE. Cockroaches produce several allergens that induce sensitization, and exposure to high levels of cockroach allergens in the home is a major risk factor for symptoms in sensitized individuals. Previously identified allergens from *Blattella germanica* and *Periplaneta americana*, the most important domiciliary species, include Bla g 2 (inactive aspartic protease), Bla g 4 (calycin), Bla g 5 (glutathione-S-transferase), Bla g 6 (troponin), the Group 1 cross-reactive allergens Bla g 1 and Per a 1, Per a 3 (arylphorin), and Per a 7 (tropomyosin). Strategies for decreasing environmental exposure to cockroach have been recently investigated. The results suggest that a sustained decrease in cockroach allergen levels is difficult to accomplish, even after successful extermination of cockroach populations. Cockroach allergens have been cloned and produced as recombinant proteins in high-level expression vectors. The use of recombinant cockroach allergens should allow mechanisms of cockroach-induced asthma to be investigated and may lead to the development of new approaches to asthma treatment in the future. *Curr Opin Pulm Med* 2001, 7:14–19 © 2001 Lippincott Williams & Wilkins, Inc.

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Cockroach allergy has been recognized as an important cause of asthma for over 30 years. Bernton and Brown were the first to report positive skin test results to cockroach in 44% of 755 allergy clinic patients in New York. In that study, isolated cockroach sensitivity was observed in 13% of the patients, who otherwise would have been considered nonatopics [1]. Subsequently, Mendoza and Snyder [2] and Schulaner [3] reported a high incidence of cockroach sensitivity in children in New York City, and showed a close association between cockroach sensitivity and low socioeconomic status of these patients. Bernton, McMahon, and Brown have performed bronchial challenges using cockroach extract and showed immediate responses in all ten patients studied [4]. Kang *et al.* [5] confirmed the causal relationship between cockroach allergy and asthma by showing early and late phase and dual bronchoconstriction after inhalation of cockroach extract by sensitized patients with asthma. Kang *et al.* also demonstrated that most patients had specific IgE to cockroach in their sera, and that patients with a positive challenge had a significant increase in peripheral blood eosinophils 24 to 48 hours after challenge [5]. These studies have clearly demonstrated that asthma caused by cockroach is antigen-specific and that it is similar to other types of atopic asthma.

The most common domiciliary species of cockroach are *Blattella germanica* (German cockroach) and *Periplaneta americana* (American cockroach). Although cockroach allergens are found throughout the home, including in beds, furniture, and carpets, allergen levels are highest in the kitchen [6]. It appears that cockroach allergens derive from several sources, including cockroach saliva, fecal material, secretions, cast skins, debris, and dead bodies. Significant amounts of allergen can be recovered by washing roaches, and from the frass that accumulates in jars where cockroaches are kept in the laboratory. Cockroach aeroallergen particles have similar properties to mite allergens, in that they are relatively large (> 10 µm diameter), are detectable mainly after disturbance, and are thought to fall rapidly [7,8]. In keeping with this, patients are usually not aware of their allergy to cockroaches and do not report symptoms of asthma on entering a house that is infested with roaches. Recently, intranasal and air samplers combined with a sensitive immunostaining system were used to investigate the behavior of cockroach-allergen-carrying particles. Bla g 1-carrying particles could be detected during quiet domestic activity or even under no disturbance, in the air and in nasal filters, in houses containing low levels

(geometric mean 1.5 U of Bla g 1/g of dust) of allergen in Australia [9•]. In agreement with previous studies, airborne particles containing cockroach allergen were associated with particles greater than 10 μm [9•].

Seasonal variation in cockroach infestation has been found in a study of six inner-city apartments in Blacksburg, Virginia, sampled monthly for a period of 1 year. In the kitchen, the number of cockroaches captured in sticky traps peaked in June, whereas the highest levels of allergen Bla g 2 did not peak until August. Allergen levels remained elevated several months after the drop in the number of cockroaches in the home [8].

Exposure to cockroach allergens and sensitization

It has been demonstrated that cockroach allergy is strongly linked to socioeconomic factors and that it occurs wherever living conditions sustain cockroach infestation [6,7,10]. Recently, enzyme-linked immunosorbent assays (ELISA) have been developed for assessing allergen exposure to cockroach allergens, including Bla g 1, Bla g 2, Per a 1 and Per a 3 [6], which provide a quantitative test for measuring allergen in house dust. Several studies have demonstrated that most patients sensitized to cockroach were exposed to high levels of cockroach allergens in their homes, and that cockroach allergy is an important risk factor for asthma-related emergency room visits and hospital admissions [6,11,12]. In addition, inner-city schools may be a significant source of exposure to cockroach allergen [13]. The National Cooperative Inner City Asthma Study has confirmed that sensitization and exposure to cockroach allergens are a major risk factor for severe asthma in children from large cities in the United States [14]. A clear relationship has also been demonstrated between current exposure to Bla g 1 and current sensitization to cockroach in children with asthma living in the inner-city environment [15]. These data have been confirmed in case control studies of school children in the United States, which showed that the degree of cockroach sensitization, as determined by skin prick test, was associated with increased exposure to cockroach allergen Bla g 2 [16•]. Based on these results, threshold levels of cockroach exposure have been proposed, above which susceptible individuals would be at an increased risk to develop sensitization or asthma symptoms. These levels have been established at 2 U/g and 8 U/g of allergen, respectively.

A recent prospective study in children born from asthmatic or allergic parents, living in metropolitan Boston, has demonstrated a significant association between exposure to cockroach allergens in the first 3 months of life and the development of repeated wheeze in the first

year [17••]. The presence of cockroach allergen in the family room and repeated wheeze continued to be significant after adjustments for socioeconomic factors such as income and race. In the same cohort, it has been reported that children exposed to Bla g 1 or Bla g 2 in the first 3 months of life developed lymphocyte-proliferative responses to Bla g 2 by the age of 2 [18••]. Exposure to greater than 2U/g Bla g 1 or Bla g 2 in the kitchen predicted increased lymphocyte proliferation. A less marked correlation has been found for exposure to high levels of Der f 1 (≤ 10 mg/g) in the family room and lymphocyte-proliferative responses to this mite allergen; no correlation was observed for levels of Fel d 1 and the respective Fel d 1-specific response [18••].

Epidemiology

The initial observations made by Bernton and Brown while they were working in New York showed that approximately 40% of their patients with asthma were sensitized to cockroach allergen [1]. In Chicago, Kang *et al.* identified up to 60% of cockroach-allergic patients among those with asthma [5]. A similar prevalence of cockroach sensitization has been found in several other North American cities, including Boston, Detroit, Washington DC, New Orleans, Atlanta, Louisville, Tampa, and Kansas City [6]. In Southeast San Diego, cockroach is a significant cause of IgE-mediated sensitization among Hispanic children with asthma. Most of these socioeconomically disadvantaged children were exposed to levels of cockroach allergens Bla g 1 and Bla g 2 that were above those reported as threshold levels for increased sensitization, particularly in dust recovered from bedroom carpet samples [19].

Emergency room (ER) asthma studies carried out in Charlottesville, Virginia, and Wilmington, Delaware, established that sensitization to cockroach allergens was an important risk factor for asthma-related admissions to the ER, for both adults and children. In each of the ER studies, the prevalence of IgE antibodies to cockroach allergens, ranging from 18 to 33%, was comparable to those to mite, cat, or pollen allergens [11,20,21].

Cockroaches have been reported to be an important cause of asthma in many regions of the world, including Taiwan, Japan, Thailand, and Singapore in the Pacific Rim, Costa Rica and Puerto Rico in Central America, India, South Africa, and more recently, Europe [6]. There have been few studies of the prevalence of cockroach allergy in Europe. In France, a prevalence of 24.5% has been found among clinic patients with asthma, rhinitis, or both, according to skin test reactions to *B. germanica* [22]. A recent study from Italy showed that only 12.7% of atopic children had positive skin tests to cockroach extracts, but this study included patients with asthma as well as with rhinitis, urticaria, and atopic

dermatitis [23]. In Brazil, 55% of children and young adults with asthma and/or rhinitis presented positive skin test results to cockroach allergens [24••]. The prevalence of positive skin test results was comparable to the prevalence previously found among low-income patients living in large cities in the United States.

Characteristics of cockroach asthma

Kang *et al.* [25], studying patients with asthma in urban Chicago, have identified distinctive characteristics of cockroach-allergic patients with asthma, compared to asthmatics sensitive to other allergens, particularly ragweed. These investigators have found high prevalence of allergy to cockroach (48%) and ragweed (45%) among patients with asthma. Cockroach sensitivity affected more female subjects, except in the age group below 15 years old. Cockroach-allergic patients had year-round symptoms of asthma, some of them presenting with winter exacerbations, requiring emergency room visits or hospitalization. In addition, they had longer duration of asthma, were sensitive to fewer other allergens besides cockroach, and showed a higher proportion of steroid dependency, suggesting more severe disease as compared to patients allergic to ragweed. Patients with cockroach allergy also had particularly high levels of serum IgE antibodies as compared to general asthmatics, and a higher prevalence of elevated total IgE as compared to ragweed-allergic patients.

Cockroach allergens

Molecular biology

Several allergens from both *B. germanica* and *P. americana* have been identified, cloned and sequenced [24••,26–34,35•] (Table 1).

The first cockroach allergens to be identified with immunochemistry were Bla g 1 and Bla g 2 [26,27]. Molecular cloning techniques determined the amino acid sequence of Bla g 2 and established that it is a 36-kDa aspartic protease, found in cockroach gut tissues, which may be involved in digestion [30]. Recent evidence revealed that Bla g 2 is an inactive aspartic proteinase

[36••]. Bla g 1 has an unusual structure consisting of a series of up to seven tandem repeats, each approximately 100 amino acid residues in length [34], including an allergen originally reported as Bla g bd90K [28], and has a structural homologue in *P. americana* (Per a 1) [35•]. These cross-reactive Group 1 cockroach allergens (Bla g 1 and Per a 1) show 30% homology to a mosquito (*Anopheles gambiae*) protein precursor ANG12 that is secreted only in the female insect after a blood meal. This suggests that these allergens may have a digestive function. Bla g 4 belongs to a super-family of ligand-binding protein (calycins or lipocalins) [31]. This family includes other important allergens such as mouse and rat urinary proteins; dog allergens Can f 1 and Can f 2, β -lactoglobulin from cow's milk, and bovine and equine allergens. The lipocalins are extracellular proteins that bind hydrophobic molecules with high affinity and selectivity. Three-dimensional models of the tertiary structure of Bla g 4 were obtained, and predicted a structure similar to other members of the calycin family [31]. Recombinant Bla g 4 expressed in bacteria or yeast has excellent allergenic activity [31,33]. Other *B. germanica* allergens include Bla g 5, which is a member of the GST-2 family of glutathione-S-transferases [32], and Bla g 6, a troponin. Bla g 5 shows 40 to 50% of homology to other insect GST's and 28% homology to the house dust mite GST allergen (Der p 8). These are enzymes involved in the detoxification of endogenous and xenobiotic toxic compounds, and in insects GST production is associated with resistance to insecticides. Allergens from *Periplaneta americana* reactive with sera from patients living in Taiwan have been reported, including Per a 3, an insect storage protein related to arylphorin [29].

Identification of tropomyosin as a major *P.americana* allergen

Use of sera from cockroach allergic asthmatic children to screen a *P. americana* cDNA library, a major cockroach allergen, which reacts with approximately 50% of sera from cockroach allergic patients, has been recently identified [24••]. This allergen shows high degree of sequence identity to tropomyosins from invertebrates,

Table 1. Immunochemical properties of cockroach allergens

Species	Allergen	Prevalence of IgE, ab, %	Molecular weight, kDa	Function
<i>Blattella germanica</i>	Bla g 1	30–50	20–25	Unknown
	Bla g 1 (Bd90K)*	77	90	Unknown
	Bla g 2	60	36	Aspartic protease
	Bla g 4	40–60	18	Lipocalin (calycin)
	Bla g 5	70	23	Glutathione-S-transferase
	Bla g 6	50	18	Troponin C
<i>Periplaneta americana</i>	Per a 1	~50	20–25	Unknown
	Per a 3	< 80	72	Arylphorin/hemocyanin
	Per a 7	50	33	Tropomyosin

*The Bla g 1 allergen shows 94% homology to the nucleotide sequence previously termed Bla g Bd90K [28]. Group I cockroach allergens (Bla g 1 and Per a 1) consist of a number of tandem amino acid repeats of approximately 100 amino acid residues [34,35].

particularly from mites (80% identity) and shrimp (82% identity), and has been designated as Per a 7, according to the World Health Organization/IUIS allergen nomenclature. Tropomyosins had been previously identified as important allergens in mites (*D. pteronyssinus* and *D. farinae* Der p 10 and Der f 10, respectively) and shrimp [37–41,42••]. Interestingly, a monoclonal antibody raised against *D. pteronyssinus* (mAb 1A6), shown previously to bind to shrimp tropomyosin, also recognized cockroach tropomyosin on immunofluorescence. Our results raise the possibility that tropomyosin may be the basis for cross-reactivity among mites, cockroach, and shrimp, and that the high degree of sequence identity has clinical significance. In keeping with this, van Ree *et al.*, working in the Netherlands, have shown the development of IgE to shrimp and snails in 3 of 17 patients receiving mite immunotherapy, accompanied by clinical symptoms of oral allergy syndrome upon shrimp ingestion for 2 of them. These authors demonstrated the presence of IgE to cross-reactive tropomyosin from mite, shrimp and snail, and positive skin prick test results to shrimp in the two patients who developed the oral allergy syndrome [43]. This study suggested that increased exposure of some patients to mite allergens (through immunotherapy) results in sensitization to cross-reactive seafood tropomyosins.

Allergenic importance of cockroach allergens

Recombinant (r) cockroach allergens have been produced in *E. coli* (Bla g 4, Bla g 5, Per a 1, Per a 3) or in the yeast *Pichia pastoris* (Per a 1, Bla g 2, Bla g 4, Per a 7). Serologic studies suggest that a cocktail of Bla g 1, Bla g 2, Bla g 4, and Bla g 5 would diagnose 95% of patients with cockroach allergy in the United States. Quantitative skin tests show that these allergens give positive reactions at concentrations as low as 10⁻⁶ µg/ml.

The prevalence of IgE ab to Per a 1 is 30 to 50%. Skin tests using natural Per a 3 gave positive reactions in 83% of cockroach allergic patients living in Taiwan. However, patients showed differences in reactivity to recombinant isoforms of Per a 7, from 26 to 94%. Analysis of reactivity to Per a 7 by plaque immunoassay and ELISA shows that approximately 50% of the cockroach allergic patients have IgE to this allergen. While further assessment of the allergenic reactivity of recombinant *P. americana* allergens is required, the current data demonstrate that Per a 1, Per a 3, and Per a 7 are important allergens that should be considered for research and clinical use.

Environmental control

Control of cockroach exposure has been considered difficult and this issue has been recently investigated in inner-city homes. A report from the National Cooperative Inner-City Asthma group showed that

intervention based on professional extermination using abamectin resulted in decrease in Bla g 1 levels in the kitchen, but only for a short time. The reduction achieved was to levels still above those considered as clinically significant [44••]. More recently, Eggleston *et al.* have studied the effect of professional extermination with 0.05% abamectin and house cleaning measures on cockroach infestation and allergen levels in inner-city homes in Baltimore. Although such measures resulted in cockroach population decrease and substantial reduction of allergen levels in some homes, levels at the end of the 8-month study period were still above 20 U Bla g 1/g in most homes [45••]. It remains to be established whether the achieved reduction of allergen levels is adequate to improve asthma symptoms in sensitized individuals. Similarly, Williams *et al.* have also reported successful cockroach extermination with hydramethylnon, however with persistence of elevated Bla g 1 and Bla g 2 levels up to 6 months following treatment [46]. The results of these studies demonstrate that the current pesticides, applied by professional pest control technicians, are effective. However, sustained removal of cockroach allergen from inner-city homes will be difficult to achieve. It is suggested that, to achieve effective control of allergen exposure in the household, cockroach extermination needs to be done in all rooms, not only in kitchens, and may need to be coupled with thorough cleaning measures (addressing reservoirs of allergen in carpets, rugs, and other sites) and efforts to prevent reinfestations.

Immunotherapy

Immunotherapy with cockroach extract has been reported to cause beneficial changes in immunologic and clinical parameters in one small study, performed in 1988 [47]. At present, cockroach immunotherapy is not considered to have proven efficacy. The indications for immunotherapy for patients with asthma remain controversial, but several placebo-controlled clinical trials have shown therapeutic benefits of specific immunotherapy for patients with asthma allergic to mites, animals, and pollens [48••]. Success in immunotherapy may be improved with the use of standardized extracts; the United States Food and Drug Administration is currently pursuing the development of standardized cockroach extracts.

The production of recombinant cockroach allergens will facilitate the development of improved forms of immunotherapy. Cocktails of recombinant allergens could be used in conventional immunotherapy protocols. Other novel strategies include the use of overlapping peptides, hypoallergenic variants of allergens generated by site-directed mutagenesis, and Th1 adjuvants [36••,48••]. It is expected that some of these new strategies could be incorporated to develop new forms of

immunotherapy for cockroach allergy, which would be effective for current disease or perhaps for prophylactic immunization.

Conclusions

It has been well established that asthma is an inflammatory disease and that it is associated with immediate hypersensitivity to perennial indoor allergens, rather than to those allergens that are predominantly outdoor and seasonal. Cockroach allergy is a major cause of asthma, particularly among inner-city patients and those living under conditions that maintain cockroach infestation in the home. Recent studies have shown that early exposure to cockroach allergens in children born to parents with asthma and allergies may contribute to the development of recurrent wheezing and asthma in early childhood. It has also been shown that exposure to cockroach allergens in early life is associated with increased lymphocyte-proliferative responses to cockroach allergens by the age of 2. Recommendations aimed at reducing exposure to cockroach allergens could be helpful for susceptible children. Results of recent studies showed that significant reduction in cockroach-allergen levels in homes is difficult to achieve, despite successful cockroach extermination. In addition, sensitization to cross-reactive allergens present in mites, foods, and parasites, particularly to tropomyosins, may contribute to disease. Several cockroach allergens have been cloned and are currently being produced as biologically active recombinant proteins. Progress on the molecular cloning of cockroach allergens may result in the development of novel forms of immunotherapy, which may benefit cockroach-allergic patients with asthma and could potentially be used as vaccines to prevent disease in the future.

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