

Letters

IDIOPATHIC ANAPHYLAXIS SUCCESSFULLY TREATED WITH OMALIZUMAB

Recently, successful anti-IgE therapy with omalizumab has been documented not only in patients with moderate-to-severe allergic asthma but also in patients with other immunologic conditions, including latex hypersensitivity,¹ peanut allergy,² urticaria and angioedema,^{3,4} and fire ant anaphylaxis,⁵ among others. The success of omalizumab in these disorders suggests that this novel molecule may be advantageous in other potentially immunologic phenomena such as idiopathic anaphylaxis. Accordingly, we report a case of successful omalizumab treatment for recurrent idiopathic anaphylaxis in a patient who was recalcitrant to other therapies.

Our patient, a 48-year-old man, presented with recurrent flushing, palpitations, urticaria, dyspnea, severe abdominal cramping, diarrhea, and hypotension since 1993. Although he was asymptomatic between events, these episodes occurred at least 6 times per year, frequently requiring emergent care with epinephrine, intravenous corticosteroids, and antihistamines. His medications, exercise patterns, and diet could not be temporally correlated with the episodes despite both retrospective and prospective diaries, but anaphylaxis appeared to occur during flare-ups of his chronic sinusitis.

A comprehensive evaluation revealed a history of controlled hypertension and the presence of allergic rhinitis and chronic sinusitis. Skin and radioallergen sorbent assay testing to multiple foods failed to demonstrate any suspect agents. Double-blinded preservative challenges to sodium benzoate, sodium metabisulfite, and parabens did not precipitate any reactions, and preservative-free diets were not helpful. Laboratory evaluation revealed normal levels of complement, C1 inhibitor assays, 5-HIAA, and catecholamines but an elevated serum IgE level of 1,821 IU/mL. Twenty-four-hour urine methyl histamine concentrations were normal between episodes but significantly increased (quadruple the upper limit of normal) after each event. The patient never had a rash to cause concern for urticaria pigmentosa, and multiple bone marrow biopsy specimens showed normal numbers of mast cells.

Daily antihistamines and treatment of his sinusitis did not resolve his symptoms. Long-term corticosteroid therapy decreased the frequency and severity of reactions but resulted in significant morbidities. Consequently, in October 2006, we initiated a therapeutic trial of 375 mg of omalizumab subcutaneously bimonthly, and, since then, he has not had further episodes of anaphylaxis. For several months after beginning omalizumab, he had occasional mild facial flushing, which has since resolved. He has been asymptomatic for more than 1 year.

Initially described in 1978 by Bacal et al,⁶ idiopathic anaphylaxis has since been classified into 2 broad categories—*idiopathic anaphylaxis-generalized* and *idiopathic anaphylaxis-angioedema*. The former describes a condition with episodic urticaria or angioedema associated with objective hypotension, syncopal events, stridor, voice changes, or apparent bronchoconstriction with or without gastrointestinal symptoms. The latter describes symptoms characterized by proximal airway obstruction manifested as laryngeal or pharyngeal edema and/or severe tongue swelling. Of all patients

diagnosed with anaphylaxis, 31.5% to 59% are attributed to idiopathic causes.⁷

Although the specific mechanisms of idiopathic anaphylaxis remain largely uncharacterized, our patient's response to omalizumab suggests a mechanism involving IgE. Without controls or crossover protocol, though, we cannot guarantee a cause-and-effect relationship, but because of the mechanisms of omalizumab (described below), it seems reasonable to attribute the remission to omalizumab therapy.

That omalizumab ameliorated his symptoms does not necessarily imply that he is responding to an as-yet-unidentified classic IgE antigen. We suggest that the molecule may be mediating its effects by reducing his elevated IgE level below a critical threshold or via other anti-inflammatory mechanisms. For example, Chang and Shiung⁸ postulate that omalizumab may not only decrease concentrations of serum IgE but may also serve as mast cell stabilizers by down-regulating the high-affinity IgE receptors on mast cells and basophils (FcεRI). Such down-regulation diminishes the density of FcεRI and may therefore "desensitize" mast cells and basophils by preventing the aggregation and cross-linking of the receptors. Furthermore, as FcεRI-bound IgE dissociates from the high-affinity receptors, omalizumab can quickly bind this free IgE, which further down-regulates both IgE and FcεRI.

Other possible anti-inflammatory mechanisms involve the down-regulation of FcεRI on dendritic cells, which may diminish antigenic presentation and the potential formation of IgE-anti-IgE immune complexes. Though these complexes cannot associate with FcεRI, they can bind antigens, thereby decreasing the concentration of antigens that may bind to mast cell and basophils receptors. Furthermore, a reduction of eosinophil numbers and IgE-expressing B lymphoblasts may also be attributable to the anti-inflammatory effects of omalizumab.⁸

In conclusion, our patient's significant clinical response to omalizumab therapy in the setting of idiopathic anaphylaxis suggests a novel anti-inflammatory or mast cell-stabilizing effect. His successful treatment, in addition to the responses reported in latex hypersensitivity, peanut allergy, urticaria and angioedema, and fire ant anaphylaxis, suggests the need for prospective studies to evaluate a broadened spectrum of the clinical indications and mechanisms of action of omalizumab.

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USE OF DILUTE SODIUM HYPOCHLORITE SPRAY AND HOME CLEANING TO REDUCE INDOOR ALLERGEN LEVELS AND IMPROVE ASTHMA HEALTH PARAMETERS

Environmental exposure control has been central to allergy practice. Environmental exposure is at least essential for allergen sensitization and triggers symptoms.¹ Home cleaning to reduce home occupant allergen exposure produces considerable improvement in the health of asthmatic patients.² Sodium hypochlorite, long part of cleaning practice, denatures allergenic material.^{3–6} Reports indicate families routinely using bleach have less allergic disease⁷ and improved quality of life for asthmatic children.⁸ The hypothesis of this study is that low-concentration hypochlorite-based cleaning practices reduce indoor allergen exposure and allergy and asthma symptoms; and, sodium hypochlorite–based sprays do not degrade pulmonary function in asthmatic individuals.

Dilute hypochlorite spray is available as Clorox Anywhere hard surface daily sanitizing spray (Clorox Company, Oakland, California). Monoclonal antibody–based immunoassays for Alt a 1, Der p 1, Fel d 1, and Can f 1 were purchased from Indoor Biotechnologies (Charlottesville, Virginia). Spirometry used a Renaissance II Spirometer (Puritan/Bennett, Carlsbad, California), and daily peak flow measurements used Tru-Zone peak flow meters (Monaghan Medical Corporation, Plattsburgh, New York). Vacuum samples were taken using an OmegaVac HEPA vacuum (Atrix International, Burnsville, Minnesota) equipped with high-efficiency dust collection bags (Midwest Filtration, Cincinnati, Ohio) by methods reported previously.⁸

Human subject work was approved by our pediatric institutional review board. The study was descriptive, applied, placebo-controlled, and single-blinded. Subject households served as their own control. The study was conducted during a 6-month period from June to December 2006. A 2-week period of placebo spray use preceded a 4-week period of active spray use. All families contained at least 1 asthmatic child and 1 asthmatic adult, and homes met criteria for cleaning habits and age or condition. Persons who reported sensitivity to bleach were excluded. Each family received education about home cleaning protocols, including use of dilute hypochlorite spray 2 to 3 times per week on upholstered furniture, bedding, carpets, and countertops. All unused spray was collected and new spray was delivered at every visit. Used bottles were weighed, and the amount of spray used was calculated.

Specific dust collections were taken before and after spraying. The area sampled before treatment was not sampled after treatment.

Sample locations were alternated to eliminate bias. At each 2-week visit families completed health questions on a 5-point Likert scale that evaluated medication use and morning and evening wheezing and asthma-related symptoms. After initial spirometry and dust collection, the home was treated using the assigned spray. Spray treatment was performed by a family member. Immediately after treatment, spirometry measurements were repeated. Data were analyzed using SPSS statistical software, version 13 (SPSS Inc, Chicago, Illinois).

In total, 32 families enrolled and 25 families completed the study. Spray use was estimated at 4,312 g or 5 to 6 bottles every 2 weeks. No statistically significant differences were seen before and after spirometry with no instance of declining spirometric results for any of the study participants. Peak flow readings had no statistically significant difference ($P = .97$ for morning readings and $P = .90$ for evening readings) between placebo and active spray use.

Health and Wellness Questionnaire data indicated that during spray use participants reported fewer colds, less coughing, less flu, less gastrointestinal distress, and less wheezing. Responses to the Likert scale questions (Table 1) indicated wheezing, breathing, stuffy nose, and sneezing were significantly improved after active spray was introduced. Improvements were statistically significant for 7 of the 12 questions.

Comparison dust allergen values collected before and after spray indicated a significant reduction in Fel d 1, Can f 1, and the sum of all allergens measured. After 1 month of spray use, Fel d 1 and Alt a 1 decreased more than 50%, and reduction in the sum of all allergens was significant. Reduction in total bacterial colonies was greater for hard surfaces than for soft surfaces (48% vs 20%), with statistically significant reduction in bacteria after spray use in total bacteria and methicillin-resistant *Staphylococcus aureus* and fecal coliforms for all surfaces.

Acceptance and use of the dilute sodium hypochlorite spray were good. No complaints were made concerning odor or irritation by any of the participants. No incidents of bleaching upholstery or carpet were

Table 1. Answers to Likert Scale Health Questions for Active (Use of Dilute Sodium Hypochlorite Spray) and Placebo (Sterile Deionized Water Spray) Groups^a

Question	Placebo, mean (SD) (n = 100)	Active, mean (SD) (n = 100)	P value
Evening			
Wheeze	1.90 (0.90)	1.50 (0.80)	.001 ^b
Cough	2.37 (1.26)	2.13 (1.18)	.17
Breathing trouble	2.04 (1.12)	1.74 (0.96)	.04 ^b
Controller medicine use	2.33 (1.44)	1.96 (1.42)	.07
Morning			
Wheeze	1.75 (0.88)	1.51 (0.81)	.046 ^b
Cough	2.22 (1.19)	2.06 (1.21)	.35
Breathing trouble	1.99 (0.94)	1.68 (0.93)	.02 ^b
Controller medicine use	2.21 (1.25)	1.89 (1.36)	.08
Stuffy nose	2.31 (1.27)	1.92 (1.22)	.03 ^b
Sneezing	2.59 (1.25)	1.88 (1.07)	<.001 ^b
Itchy eyes	2.25 (1.19)	1.63 (0.93)	<.001 ^b
Attention trouble	1.96 (1.20)	1.68 (1.08)	.08

^a Larger numbers indicate increased (more frequent) problems.

^b Statistically significant at a 95% confidence level.

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recorded. No deterioration in breathing parameters occurred during the time of the study. Allergen levels were consistently decreased shortly after spraying, with greatest reductions in those allergens with the highest levels (cat, dog, and *Alternaria*).

This work emphasizes the impact of cleaning on asthmatic trigger reduction in indoor environments. It suggests an association between indoor allergen reduction and improved symptom scores. Methods by which allergens are introduced into and removed from homes are not understood and poorly controlled.

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OCCUPATIONAL RESPIRATORY ALLERGY DUE TO *BOLETUS EDULIS* POWDER

Boletus edulis is a highly appreciated edible mushroom that belongs to the large phylum of Basidiomycota and to the class of Agaricomycetes. Commonly known as *king bolete* in English-speaking countries or *porcino* in Italy, it has many other common names throughout the world. We report a case of occupational asthma due to inhalation of dried *B edulis*.

A 37-year-old, nonsmoking man, in good general health and with no history of atopy, presented with recurrent asthma that had developed 2 years earlier, when he began to work in a pasta factory. Dyspnea and dry cough occurred at night and more rarely in the workplace for 2 to 3 weeks every 3 months. This peculiar symptom cyclicity was related to exposure to *B edulis* powder used for the production of porcini mushroom-flavored pasta. The patient never

had symptoms after ingestion of foods and denied eating mushrooms for more than 3 years.

Extracts were obtained from both the *B edulis* powder and the defrosted fresh mushroom, which were stored at 4°C overnight. Proteins were extracted by stirring for 2 hours at 4°C in phosphate-buffered saline (1:10 and 1:2.5 wt/vol for the powder and the fresh mushroom, respectively). Insoluble particles were removed by centrifugation at 15,000 rpm for 1 hour at 4°C. Protein concentration was determined using the Bradford method¹ and was 12.45 µg/µL for the lyophilized mushroom and 6.44 µg/µL for the fresh mushroom. Samples were electrophoresed according to Laemmli.² After staining with 0.1% Coomassie brilliant blue, the sodium dodecyl-sulfate–polyacrylamide gel electrophoresis profile of both extracts showed similar bands ranging from 17–18 kDa to 85–88 kDa. Proteins were electrophoretically transferred to a nitrocellulose membrane, which, after blocking, was incubated overnight at 4°C with 1:4 diluted patient serum. Bound specific IgE was detected by peroxidase-conjugated anti-human IgE antibodies from goat (1:10,000 in saturation buffer) using the enhanced chemiluminescence Western blotting kit. The extracts were stored at –20°C until required. Skin prick tests with diluted extracts of fresh and lyophilized *B edulis* were performed, using saline solution and histamine (10 mg/mL) as negative and positive controls, respectively. Positive reactions to extracts of fresh (at both 1:100 and 1:10 dilutions) and lyophilized (1:10,000, 1:1,000, 1:100, and 1:10) *B edulis* were observed. Immunoblotting with both extracts showed IgE reactivity in the patient's serum to the same bands at approximately 17, 55, and 88 kDa (Fig 1). The results of skin prick tests with food commercial extracts (including wheat) and other powders used in the pasta factory (eg, spinach, tomato, and paprika) were negative. Determinations of specific IgE to aeroallergens, including molds, and champignons yielded negative results. The patient underwent

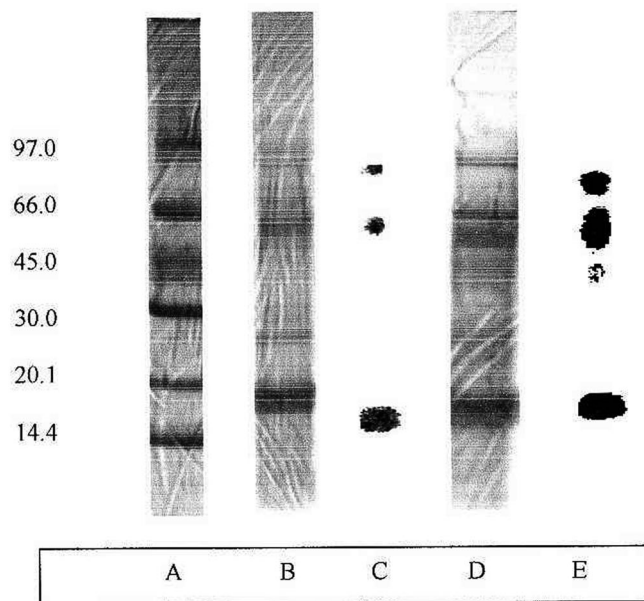


Figure 1. *Boletus edulis* protein identification. Lane A, Molecular weight markers. Lanes B and D, Defrosted fresh and lyophilized *B edulis*, respectively. Lanes C and E, Immunoblotting with the serum from a patient with asthma after inhalation of *B edulis* powder.

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bronchial testing during a symptom-free period. The results of basal spirometry were normal, whereas the results of methacholine bronchial challenge were positive. Specific inhalation challenge with *B edulis* powder at a concentration of 5 mg/m³ was performed in a challenge chamber according to standardized procedures.³ Serial forced expiratory volume in 1 second monitoring showed an immediate asthmatic response after 10 minutes, which still persisted 12 hours after the challenge.

Few reports are available on ingestive and inhalative allergy to *B edulis* in the literature,^{4–7} and, to the best of our knowledge, characterization of *B edulis* allergens using immunoblotting has been rarely performed,^{5,6} including only 1 patient with respiratory allergy. Although spores are thought to cause respiratory allergy, edible parts of the mushroom may contain various thermostable food allergens.^{5,6} Using fresh *B edulis* extract, Roncarolo et al⁵ described 2 thermostable IgE-binding bands at 26 and 39 kDa in the serum of a patient with allergic symptoms after ingestion of fresh raw or cooked dried *B edulis*, without any respiratory symptoms. In lyophilized *B edulis* extract, at least 4 water-soluble proteins were detected by Helbling et al,⁶ the most reactive at 55 and 80 kDa. The same authors found IgE binding to a 75-kDa digestion-stable protein in the serum of a patient with anaphylaxis after ingestion of *B edulis*, whereas no IgE response to this protein was detected in the serum of another patient with respiratory allergy and oral allergy syndrome to *B edulis*. In view of the immunoblotting findings observed in our patient, using the fresh and lyophilized *B edulis* extracts, we suggest that components at approximately 17, 55, and 88 kDa may be responsible for IgE-mediated respiratory allergy to *B edulis*.

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ANAPHYLAXIS CAUSED BY TANGERINE SEEDS BUT NOT TANGERINE FRUIT

Approximately 8% of children younger than 5 years experience food-induced allergic disorders.¹ Most food-induced allergic reactions are caused by peanuts, tree nuts, milk, eggs, seafood, and wheat. Occasionally, antigens from fruit can cause allergic reactions. We describe a 4½-year-old boy with anaphylaxis due to tangerine seeds but not to tangerine fruit.

A 4½-year-old boy was referred for evaluation of anaphylaxis. One year earlier, he had an anaphylactic reaction after ingesting pistachio nuts associated with lethargy, generalized urticaria, and facial swelling. Almonds induced a similar anaphylactic reaction previously. Treatment with oral diphenhydramine and intramuscular epinephrine helped reverse both episodes. Skin prick test (SPT) results were positive to cashew (4 × 5-mm wheal), which is in the same family as pistachio and almonds (5 × 5-mm wheal), but negative to peanut. The family was instructed to avoid all cashews, almonds, and pistachio nuts. His medical history was notable for well-controlled atopic dermatitis.

One month later, the patient developed anaphylaxis with generalized urticaria and wheezing 2 hours after ingesting a tangerine with seeds. Specifically, he chewed and then swallowed 1 tangerine seed. The reaction required treatment with diphenhydramine orally and aerosolized albuterol. The patient had previously tolerated ingestions of seedless tangerines.

The SPT was performed on the patient using fresh tangerine fruit extract, tangerine seed extract, histamine, and control. Tangerine fruit extract was made by crushing tangerine fruit pulp; tangerine seed extract was generated by crushing 1 tangerine seed in 3 mL of saline. To exclude the possibility of a nonspecific irritating action, the extracts were used to test a subject tolerant to tangerine, who did not react to either extract.

Results demonstrated a positive SPT response to extract of tangerine seed (20 × 10-mm wheal, wiped off within minutes due to severity of reaction) (Fig 1). The SPT response to histamine was positive (2 × 2-mm wheal), with negative results to the tangerine fruit itself and control. Because of the strong history and positive response to SPT, oral challenge to tangerine seed was not performed for the patient's safety.

We describe the first case of anaphylaxis due to sensitivity to tangerine seed but not to tangerine fruit. This conclusion is based on the clinical history elicited that previous oral ingestions of seedless tangerine fruit produced no allergic reactions and strong SPT reactivity to tangerine seed extract in our patient with no SPT reactivity to tangerine fruit extract. In contrast to allergic reactions to citrus fruit, allergic reactions and anaphylaxis to seeds, such as sesame, mustard, and poppy, are common and have been reported previously.^{2–4} The present patient, who was sensitive to several tree nuts and to tangerine seed but not to tangerine fruit, was likely responding to cross-reacting antigens in tangerine seeds and tree nuts. Cross-reactivity between seeds and tree nuts has been attributed to common allergenic structures in hazelnut, sesame seeds, and poppy seeds.² However, the full clinical spectrum is far from established.⁵

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Figure 1. Skin prick test responses in the patient. The right upper quadrant shows negative saline control; left upper quadrant, histamine; right lower quadrant, tangerine juice; left lower quadrant, tangerine seed extract.

Several cases of allergy to orange seed but not to orange fruit have been reported.⁶ In that study, patients tolerated orange juice but

could not tolerate orange seed, and the authors concluded that allergenic determinants in orange juice were weaker than those in orange seed.⁶ Many patients in that study were sensitive to other foods, such as walnut, hazelnut, sesame seed, and Chinese prickly ash seed, suggesting that the allergenic determinants in orange seed cross-reacted with those in nuts and seeds.⁶

In summary, because this child also had a history of anaphylaxis to almond and cashew, it is likely that he was sensitive to cross-reacting antigens in nuts and seeds. This, then, is the first report of a systemic reaction after ingestion of tangerine seeds but not tangerine fruit.

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