The Clinical Epidemiology of Allergic Contact Dermatitis

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ABSTRACT:

Background:

Allergic contact dermatitis (ACD) is a common dermatologic diagnosis affecting over 13 million patients annually in the United States. Despite its prevalence, limited research has been conducted regarding its clinical epidemiology. The development of contact dermatitis can vary based on genetics, environmental exposures, and co-morbidities such as atopic dermatitis (AD). This project examined the relationship of sex, race, age, and socioeconomic status with the risk of developing allergic contact dermatitis. A secondary goal of this project was to determine the predictors of and relevant allergens in ACD among patients with AD.

Materials:

We performed a retrospective chart review of 395 adults who were patch-tested at the Northwestern Medicine patch-testing clinic from 2014-2017. Patients were patch-tested with the North American Contact Dermatitis Group (NACDG) standard series and a supplemental allergen series. Demographic data such as sex, age, race, insurance, birthplace, and zip code (as a surrogate for income) were collected. Chi square tests and multivariable logistic regression models were used to estimate adjusted odds ratio and 95% confidence intervals.

Results:

There were no associations between sex, age, race, insurance, birthplace and the development of ACD. However, individuals estimated to be making less than the median income had an increased risk of developing allergic contact dermatitis (adjusted odds ratio [95% confidence interval] (3.50 [1.36-9.02]). AD patients (n=97) had

significantly higher rates of positive patch test reactions to ingredients in their personal care products or topical medicaments, including lanolin (P=0.03), quaternium-15 (P=0.04), fragrance mix I (P=0.008), cinnamal (P=0.02), neomycin (P=0.02), bacitracin (P=0.04), chlorhexidine (P=0.04), and budesonide (P=0.01).

Conclusions:

Low income was the only demographic factor found to be associated with the development of ACD. Patients with AD did not have higher rates of positive patch test reactions overall. However, they had higher rates of positive patch test reactions to multiple ingredients in their personal care products and topical steroid and antibiotic medicaments. Future research is needed to understand the risk factors associated with ACD to better predict and prevent this burdensome disease.

BACKGROUND:

Allergic contact dermatitis (ACD) is a delayed hypersensitivity skin reaction that develops after repeated or prolonged exposure to a chemical allergen. According to the American Academy of Dermatology, over 13 million individuals suffer from contact dermatitis, costing more than 700 million dollars in opportunity costs and 1.5 billion dollars in total medical costs (1). Contact dermatitis is diagnosed via patch testing, and the prevalence of ACD can vary based on genetic and environmental factors. The purpose of this project is to determine how various demographic factors impact the risk of developing ACD. A secondary aim of this project is to determine the association of ACD and atopic dermatitis (AD), a co-morbidity that costs the U.S. healthcare system over $75 billion (2).

Currently, there is limited information on the epidemiology of allergic contact dermatitis. Much of the present literature examines ACD to particular allergens, but few studies have sought to understand how sex, race, and age influence ACD, and to our knowledge, no studies have looked at how income, insurance, and birthplace affect the development of ACD. One Spanish study assessed the association between sex, age, type of referral, and occupation with ACD, and found female sex to be the only independent risk factor in their sample (3). Understanding how demographics impact contact dermatitis can allow for practitioners to be aware of clinical patterns and promote more culturally competent care. In addition, identification of the risk factors of ACD can lead to future prevention strategies for this common, burdensome dermatologic condition.

In addition, ACD has been implicated as a common co-morbidity in patients with atopic dermatitis (AD), yet the interplay of these two conditions requires further understanding. AD, commonly referred to as eczema, is a chronic, pruritic inflammatory skin condition. It usually begins in childhood and often extends into adulthood, causing significant burden and a decrease in quality of life for individuals throughout their lifespans (4).

The exact incidence of contact dermatitis among those with AD is unknown (5). In the past, it was believed that AD did not confer any increased risk for the development of ACD, and that it may even be protective. In 1976, Rogge and Hanifin showed 6 out of 7 patients with AD did not react to the allergen dinitrochlorobenzene (DNCB) after repeated exposures (6). Another study by Uehara and Sawai patch tested 150 AD patients, and found that those with severe AD were less likely to have positive responses to DNCB than those with moderate and mild AD (7).

However, more recent studies have hypothesized that AD, with its associated skin-barrier disruption, cutaneous and systemic immune dysregulation, and frequent application of emollients and medicaments, may predispose those affected towards developing ACD (8). Malajian and Belsito conducted patch testing in 2305 patients using the North American Contact Dermatitis Group standard screening studies. In their study, patients with AD were significantly more likely than patients without AD to have at least 1 positive patch test reaction and develop contact hypersensitivity to metal allergens (9). Another study conducted in Copenhagen examined questionnaire and clinical data from 3202 adults, finding that contact sensitization to at least one allergen, but not nickel nor thimerosal, was significantly associated with AD (10).

Given these recent studies highlighting ACD in AD patients, the present study additionally sought to determine the predictors of and relevant allergens in allergic contact dermatitis among patients with atopic dermatitis.

METHODS

Study Design

We performed a retrospective chart review of 395 adults (age ≥18 years), who were patch-tested at the Northwestern Medicine patch-testing clinic from 2014-2017. Patients were patch-tested with the North American Contact Dermatitis Group (NACDG) standard series and a supplemental allergen series. Data on patient demographics (sex, age, race, zip code, insurance, and birthplace) and patch testing results were extracted from the clinical database. The study was approved by the institutional review board of the Northwestern University and informed consent was waived.

Interpretation of patch tests

Patients were evaluated with a medical history and skin examination by a dermatologist prior to patch testing. Patches were applied to patient's upper back and removed after 48 hours. Patches were initially evaluated at 48 hours, and again at 72 hours when final patch test results, including any delayed reactions, were recorded. All reactions were graded as either negative or positive. Negative reactions included irritant responses. Positive reactions were further classified as +, ++, +++. One physician interpreted all patch test results, including the clinical relevance of all positive reactions. Relevance was established by patient history such as known or likely exposures, or improvement with allergen avoidance.

Assessment of AD

AD was diagnosed using the Hanifin and Rajka criteria (11). Major criteria included pruritus, typical morphology and distribution, chronic/relapsing dermatitis, and personal or family history of atopy (allergic rhinitis, asthma, AD). Minor criteria included xerosis, ichthyosis, palmar hyperlinearity, keratosis pilaris, age of AD onset, nipple dermatitis, cheilitis, Dennie-Morgan infraorbital folds, facial pallor/erythema, conjunctivitis and eyelid dermatitis, pityriasis alba, dermatitis of the anterior neck folds, history of cutaneous infections, clinical course worsened by environmental or emotional factors, pruritus when sweating.

Data processing and statistical methods

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute, Cary, NC). All demographic data were analyzed as binary variables: sex (male/female), age (younger than 40/40 and older), race (Caucasian/non-Caucasian), insurance (private insurance/non-private insurance), and birthplace (in/outside United States). Zip codes were used to correlate median household incomes for each indivdual using the 2016 American Community Survey. Income was analyzed as either above/below the median income of $50,500. Chi-square tests of association and multivariable logistic regression were used to determine the association between these demographics and a diagnosis of allergic contact dermatitis. Chi-square tests of association were also used to compare AD and all standard and supplemental series contact allergens. Cross-reactors were identified using the American Contact Dermatitis Society (ACDS) Contact Allergens Management Program (CAMP) database. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated. A two-sided P

value of .05 or less was taken to indicate statistical significance for all hypothesis tests. All analyses were performed using complete case analysis.

RESULTS:

Patient Characteristics

The total cohort consisted of 395 adults, 297 women (78.0%) and 283 Caucasians (71.6%). The mean age ± standard deviation at enrollment was 46.1 ± 15.6 years. 392 of these had data on ACD. Table 1 summarizes the demographic distribution between those with and without ACD.

Demographics and ACD

Chi-square tests of association showed no relationship between sex, age, race, insurance, birthplace, income and the development of ACD. However, with multivariable logistic regression adjusting for these demographics, those estimated to be making less than the median income (<$50,500) had an increased risk of developing allergic contact dermatitis (adjusted odds ratio [95% confidence interval] (3.50[1.36-9.02]).

Patch test results in AD patients

Ninety-seven patients (24.6%) of the cohort were diagnosed with AD, which included 73 women (76.0%) and 60 Caucasians (61.9%), with mean age ± standard deviation at enrollment 41.6 ± 16.4 years. Patients with AD were less likely to be Caucasian and more likely to be born in the United States. Table 2 summarizes demographic information among AD and non-AD patients.

Patients with AD compared to those without AD had similar proportions of any positive (+, ++ or +++: 72 [74.2%] vs. 197 [66.1%]; Chi-square, P=0.1362), stronger (++, +++: 30 [30.9%] vs. 75 [25.2%]; P=0.2647) and irritant (49 [50.5%] vs. 149 [50.0%];

P=0.9297) patch test reactions. However, AD patients had significantly higher rates of positive patch test reactions to ingredients in their personal care products or medicaments, including fragrance mix II (P=0.0084), lanolin (P=0.0288), neomycin (P=0.0030), quaternium-15 (P=0.0433), bacitracin (P=0.0425), cinnamal (P=0.0157), budesonide (P=0.0130), and chlorhexidine (P=0.0433). Tables 3 and 4 summarize the patch test results among AD vs non-AD patients for the NACDG standard and supplemental allergen series. Relevance was established in >90% of patients with positive reactions to one of these allergens.

Of these allergens, positive patch test reactions to quaternium-15, fragrance mix II, and chlorhexidine were more common in females with AD (P<0.05), whereas a reaction to neomycin was more common in males with AD (P<0.05). Caucasians with AD had significantly more positive reactions to neomycin, lanolin, quaternium-15, chlorhexidine than non-Caucasians (P<0.05), while non-Caucasians with AD had more reactions to bacitracin. Those age 40 and older with AD had more positive reactions to fragrance mix II and chlorhexidine than those younger than 40 (P<0.05). However, patients younger than 40 with AD had more positive reactions to neomycin (P<0.05).

Polysensitization in AD patients

A total of 110 (21.4%) patients were polysensitized (≥3 positive patch test reactions). The rate of polysensitization in AD patients was significantly higher than the rate in non-AD patients (23[20.4%] vs. 38[9.5%]; P=0.0119). There were no significant differences in sex, age, race, and birthplace between poly- and non-polysensitized patients [Table 5]. As an additional analysis, all patients with polysensitization were corrected for cross-reactors. With this modification, the number of patients with true polysensitization

decreased to 73, continuing to uphold a significantly higher rate in AD vs non-AD patients (29[29.9%] vs. 44[14.8%]; P=0.0035).

DISCUSSION:

Our study investigated the role of demographics in ACD. As far as we are aware, this is the first study to explore the relationship between income and contact dermatitis. We found a significant association between those making less than the median household income salary and the development of ACD. This may be due to different environmental exposures that result in increased sensitization. This study also found that birthplace and insurance does not affect the rate of ACD. No association was found between ACD and race, similar to results from previous studies. Deleo et al. investigated the association of race/ethnicity on patch test results from 1992-1998 and 1998-2006. In both studies, patch test data from 9,624 and 19,457 patients, respectively, were analyzed from the North American Contact Dermatitis Group. His team found that there was no overall difference in the proportions of Caucasians and African Americans that had ACD. Despite this, there were particular allergens to which Caucasians and African Americans had significantly different rates of positive patch test reactions (12,13). Similarly, we found that Caucasians with AD were more likely to have reactions to neomycin, lanolin, quaternium-15, chlorhexidine, while non-Caucasians with AD had more reactions to bacitracin.

Other studies have found that there is an increase in positive patch test reactions with increasing age (14,15). Specifically, Warshaw et al. showed that older individuals (>65 years old) had more positive patch test reactions than children (<18 years old), but had similar rates as younger adults (19-64 years old). Since our study was limited to

only adults, no change in the rate of patch test positive allergens was detected between those younger than 40 and 40 and older. In addition, although sex had no association with ACD, our analyses showed that females with AD were significantly more likely than males to react to patch test allergens found in topical agents. Lever and Forsyth also recognized this female predisposition for contact sensitization among AD patients (16).

Conflicting results have been reported on whether or not AD increases the risk of developing ACD. Our study found that patients with AD did not have a significantly increased risk for positive patch test reactions compared to patients without AD. These results have been seen in other studies. A recent systematic review and meta-analysis published in 2017 analyzed data from 74 articles and found no statistical difference in contact sensitization between AD and controls in their pooled analysis (17). Nedorost and Babineau examined patch test data from 1149 patients and also saw no overall difference in number of patch test reactions among AD vs. non-AD patients, but they did comment on a trend of increased numbers of patch test reactions to tixocortol pivalate and propylene glycol, allergens seen in topical treatments, in AD patients (18).

Similarly, our study found that when compared to non-AD patients, patients with AD had significantly higher rates of patch test reactions to ingredients in their personal care products or topical medicaments. Analogous patterns have been seen in children. Jacob et al. conducted a retrospective chart review of 1142 children across the United States, and saw different reaction profiles in those with and without AD. Children with AD were more likely to have positive reactions to cocamidopropyl betaine, lanolin, tixocortol pivalate, which are all allergens commonly found in emollients and medicaments (19). Another study patch tested 641 children with AD for seven

ingredients found in common topical treatments. 6.2% of subjects tested positive to at least one of the ingredients, with the most common allergen being the emollient currently being used by the individual. Risk factors significantly associated with contact sensitization to their AD treatment included AD onset before 6 years of age, IgE-mediated sensitization, and moderate to severe AD (20). This notion that moderate to severe AD results in a higher rate of contact allergy has also been seen in other studies (21).

Polysensitization has become an important concept in the clinical epidemiology of ACD. Recently, there has been a greater emphasis on identifying risk factors that predispose individuals to becoming sensitized to multiple allergens. Our study found a significantly increased likelihood of polysensitization among AD patients, even when corrected for cross-reactors. There results have been replicated in other studies. Carlsen et al. conducted a questionnaire case-control study of 562 polysensitized (defined as having three or greater positive reactions) and 1124 single/double-sensitized individuals. Their study concluded that people with AD were significantly associated with polysensitization, representing 45.1% of the polysensitized cohort (22). In our study, no specific demographic pattern was found among AD patients who were polysensitized. Despite the significant association between AD and polysensitization, there was no statistical difference in the overall number of +, ++, +++ reactions among AD vs. non-AD patients.

Due to the complex relationship between ACD and AD, the overlap in morphology, and common disease location sites, diagnosing ACD in individuals with AD becomes difficult. During the 2016 annual meeting of the American Contact Dermatitis

Society (ACDS), experts in the fields of AD and ACD created consensus recommendations regarding when to patch test in AD patients and which patch tests to include (23). They concluded atopic dermatitis patients should receive patch testing in situations where their dermatitis worsens or fails to improve with topical therapy. In addition, patch testing should be initiated in patients with atypical or changing distribution of dermatitis, adult or adolescent onset AD, or severe dermatitis prior to starting systemic immunosuppressants. Owen at al. recommend that patch testing include expanded screening for commonly encountered allergens found in topical therapies and the environment. An example would be the ACDS or NACDG core series (24). Furthermore, personal products, particularly current or past topical treatments, should be considered as possible culprits for dermatitis (25). Finally, caution should be taken when interpreting patch test results. As mentioned previously, patients with AD have a lower irritancy threshold, resulting in more irritant reactions and false positives (26). On the other hand, patients with severe AD may actually have diminished contact sensitivity, leading to false negatives (27).

Limitations

There are several strengths of this study such as the use of both the NACDG standard and supplement series, and the analysis of patch test data based off strength of reaction and polysensitization. However, one limitation is that all patch testing was performed in an academic dermatologic setting and results may not be generalizable to all patients with ACD or AD. Due to the retrospective nature of the study, income had to be estimated using patients' zip code information. Additionally, the analyses and results pertaining to AD were not categorized by AD severity. Our study also did not investigate

the past or current treatment regimens between AD patients with and without positive patch test results to determine if certain exposures made contact sensitization more likely.

CONCLUSIONS:

This study found low income to be the only significant demographic association with the allergic contact dermatitis. Additionally, this study examined the predictors of and relevant allergens in allergic contact dermatitis among patients with atopic dermatitis. Patients with AD did not have higher rates of positive patch test reactions overall. However, they had higher rates of positive patch test reactions to multiple ingredients in the personal care products and topical steroid and antibiotic medicaments. Further research is necessary to understand why some patients with AD experience this enhanced susceptibility while others do not.

This study has public health relevance at the practitioner and patient level. As mentioned previously, few studies have investigated the association of sex, age, race and contact dermatitis, and no studies have looked at the association of insurance, income, birthplace and allergic contact dermatitis. Although the data has been taken from a limited clinical cohort at Northwestern, the study can inform future population-based studies. More studies are needed to explore the mechanism of how socioeconomic status impacts contact dermatitis to allow for a better understanding of this common skin condition and what can be done to mitigate risk.

Furthermore, the first line treatments for dermatologists and primary care doctors treating AD are topical emollients and corticosteroids. When patients with atopic dermatitis present with recalcitrant lesions, doctors may suggest higher doses or

stronger medications, increasing the costs of the disease. However, chronic exposure to these medications may actually lead to allergic contact dermatitis and worsening of the rash, causing a vicious cycle. Awareness of this phenomenon may lead doctors to promptly provide patch testing when necessary and treat accordingly to prevent the cycle from continuing. This in turn may decrease the symptom and monetary burden of the condition on patients and society.

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Table 1: Baseline Cohort Characteristics			
	Allergic Contact Dermatitis		
	Negative (n = 79)	Positive (n =313)	
Characteristic	Freq (%)	Freq (%)	P-value
Age (years)*			
Younger than 40	24 (36.9%)	105 (38.9%)	
40 and older	41 (63.1%)	165 (61.1%)	0.7700
Sex*			
Female	58 (75.3%)	241 (79.8%)	
Male	19 (24.7%)	61 (20.2%)	0.3902
Race			
Caucasian	55 (69.6%)	223 (71.3%)	
Non-Caucasian	24 (30.46%)	90 (28.8%)	0.7762
Insurance*			
Private insurance	55 (73.3%)	242 (80.7%)	
Non-Private insurance	20 (6.7%)	58 (19.33%)	0.1617
Income*			
Less than $50,500	11 (13.9%)	70 (22.4%)	
$50,500 and greater	68 (86.1%)	243 (77.6%)	0.0978
Birth place*			
Born in US	51 (86.4%)	197 (82.1%)	
Born outside US	8 (13.6%)	43 (19.9%)	0.4253

Chi-squares tests of association between demographics and allergic contact dermatitis with associated p-values.
*16% data missing for age, 4% missing data on sex, 1% missing data for race, 5% data missing data for insurance, 24% data missing data for birthplace

Table 2: Baseline Cohort Characteristics			
	Atopic Dermatitis		
	Negative (n = 298)	Positive (n = 97)	
Characteristic	**Freq (%)**	**Freq (%)**	**P-value**
Age (years)*			
Mean ± STD	47.6 ± 15.0	41.6 ± 16.4	N/A
Sex*			
Female	224 (78.6%)	73 (76.0%)	
Male	61 (21.4%)	23 (24.0%)	0.6015
Race			
Caucasian	223 (74.8%)	60 (61.9%)	
Non-Caucasian	75 (25.2%)	37 (38.1%)	**0.0138**
Birthplace*			
Born in US	176 (80.0%)	73 (90.1%)	
Born outside US	44 (20.0%)	8 (9.9%)	**0.0394**

Chi-squares tests of association between demographics and atopic dermatitis with associated p-values.
*4% of patient data missing for sex, 12% of patient data missing for age, 23.8% of patient data missing for birthplace.

Table 3: Association Between Atopic Dermatitis and NACDG standard allergens (pos ≥ 1+)			
	Atopic Dermatitis		
	Negative (n = 298)	Positive (n = 97)	
Allergen	Freq (%)	Freq (%)	P-value
Benzocaine, 5.0% pet			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
2-Mercaptobenzothiazole, 1.0% pet			
Negative	295 (99.0%)	97 (100%)	
Positive	3 (1.0%)	0 (0%)	0.3212
Colophonium, (Rosin) 20.0% pet			
Negative	297 (99.7%)	96 (99.0%)	
Positive	1 (0.3%)	1 (1.0%)	0.4020
4-Phenylenediamine base, 1.0% pet			
Negative	283 (95.0%)	96 (99.0%)	
Positive	15 (5.0%)	1 (1.0%)	0.0824
Dimethylaminopropylamine, (DMAPA) 1.0% aq			
Negative	290 (97.3%)	96 (99.0%)	
Positive	8 (2.7%)	1 (1.0%)	0.3431
Fragrance Mix II, 14.0% pet			
Negative	294 (98.7%)	91 (93.8%)	
Positive	4 (1.3%)	6 (6.2%)	**0.0084**
Lanolin alcohol (Amerchol L101), 50% pet			
Negative	294 (98.7%)	92 (94.8%)	
Positive	4 (1.3%)	5 (5.2%)	**0.0288**
Carba Mix, 3.0% pet.			
Negative	289 (97.0%)	95 (98.0%)	
Positive	9 (3.0%)	2 (2.0%)	0.6183
Neomycin Sulfate, 20.0% pet			
Negative	293 (98.3%)	91 (93.8%)	
Positive	5 (1.7%)	6 (6.2%)	**0.0030**
Thiuram Mix, 1.0% pet			
Negative	296 (99.3%)	95 (98.0%)	
Positive	2 (0.7%)	2 (2.0%)	0.2347
Formaldehyde, 1.0% aq.			
Negative	283 (95.0%)	95 (98.0%)	
Positive	15 (5.0%)	2 (2.0%)	0.2103
Ethylenediamine Dihydrochloride, 1.0% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678

Bisphenol A epoxyn resin , 1.0% pet.			
Negative	295 (99.0%)	97 (100%)	
Positive	3 (1.0%)	0 (0%)	0.3212
Quaternium-15, 2.0% pet.			
Negative	295 (99.0%)	93 (95.9%)	
Positive	3 (1.0%)	4 (4.1%)	**0.0433**
Ethylhexylglycarin, 5% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Black Rubber Mix, pet 0.6%			
Negative	295 (99.0%)	95 (97.9%)	
Positive	3 (1.0%)	2 (2.1%)	0.4194
Potassium Dichromate, 0.25% pet.			
Negative	289 (97.0%)	91 (93,8%)	
Positive	9 (3.0%)	6 (6.2%)	0.1566
Myroxylon Pareirae Resin (Balsam of Peru), 25.0% pet.			
Negative	259 (86.9%)	86 (88.7%)	
Positive	39 (13.1%)	11 (11.3%)	0.6531
Nickel Sulfate Hexahydrate , 25% pet.			
Negative	252 (84.6%)	85 (87.6%)	
Positive	46 (15.4%)	12 (12.4%)	0.4588
Diazolidinyl Urea (Germall II), 1.0% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
DMDM Hydantoin (Germall 115) 1.0% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Imidazolldinyl Urea 2.0% pet.			
Negative	295 (99.0%)	96 (99.0%)	
Positive	3 (1.0%)	1 (1.0%)	0.9835
Bacitracin, 20.0% pet.			
Negative	290 (97.3%)	90 (92.8%)	
Positive	8 (2.7%)	7 (7.2%)	**0.0425**
Mixed Dialkyl Thioureas, 1.0% pet.			
Negative	295 (99.0%)	97 (100%)	
Positive	3 (1.0%)	0 (0%)	0.3212
Methylchloroisothiasolinone/methylisothiasolinone, 0.01% aq.			
Negative	280 (94.0%)	90 (92.8%)	
Positive	18 (6.0%)	7 (7.2%)	0.6794
Paraben Mix, 12.0% pet.			

Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
Cinnamal (Cinnamic Aldehyde) 1.0% pet.			
Negative	296 (99.3%)	93 (95.9%)	
Positive	2 (0.7%)	4 (4.1%)	**0.0157**
Fragrance Mix I 8.0% pet.			
Negative	275 (92,3%)	90 (92.8%)	
Positive	23 (7.7%)	7 (7.2%)	0.8713
Amidoamine (Stearamidopropyl Dimethylamine), 0.1% aq.			
Negative	297 (99.7%)	96 (99.0%)	
Positive	1 (0.3%)	1 (1.0%)	0.4020
2-Bromo-2-Nitropropane-1,3-diol (Bronopol), 0.5% pet.:			
Negative	295 (99.0%)	96 (99.0%)	
Positive	3 (1.0%)	1 (1.0%)	0.9835
Sesquiterpenelactone Mix, 0.1% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
2-Hydroxyethyl Methacrylate, 2.0% pet.			
Negative	292 (98.0%)	96 (99.0%)	
Positive	6 (2.0%)	1 (1.0%)	0.5241
Propylene Glycol , 30.0% aq.			
Negative	291 (97.7%)	92 (94.9%)	
Positive	7 (2.3%)	5 (5.1%)	0.1620
Benzophenone-3 (Oxybenzone or 2-hydroxy-4-Methoxy- benzophenone), 10% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Chloroxylenol (4-Chloro-3.5-xyleno), 1.0% pet.			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
Parthenolide, 0.1% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Methylisothiazolinone, 0.2% aq.			
Negative	270 (90.6%)	92 (94.9%)	
Positive	28 (9.4%)	5 (5.1%)	0.1898
Desoximetasone, 1.0% pet.			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
Methyldibromo Glutaronitrile/Phenoxyethanol, (MDBGN/PE) (Euxyl K400), 2.0% pet.			
Negative	289 (97.0%)	93 (95.9%)	0.5967

Positive	9 (3.0%)	4 (4.1%)	
Diphenylguanidine, 1% pet.			
Negative	288 (96.6%)	93 (95.9%)	
Positive	10 (3.4%)	4 (4.1%)	0.7223
Tocopherol (DL-o- Tochopherol), 100.0%			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Iodopropynyl Butylcarbamate, 0.5% pet.			
Negative	281 (94.3%)	91 (93.8%)	
Positive	17 (5.7%)	6 (6.2%)	0.8606
Ethyl Acrylate, 0.1% pet.			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
Benzophenone-4 (Suliasobenzone), 10% pet.			
Negative	292 (98.0%)	96 (99.0%)	
Positive	6 (2.0%)	1 (1.0%)	0.5241
Tosylamide/ Formaldehyde resin, 10.0% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Methyl metacrylate, 2.0% pet.			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
Cobalt (II) Chloride Hexahydrate, 1.0% pet.			
Negative	288 (96.6%)	94 (96.9%)	
Positive	10 (3.4%)	3 (3.1%)	0.8997
Tixocortol-21-pivalate, 1.0% pet.			
Negative	295 (99.0%)	94 (96.9%)	
Positive	3 (1.0%)	3 (3.1%)	0.1446
Budesonide, 0.1% pet.			
Negative	298 (100%)	95 (97.9%)	
Positive	0 (0%)	2 (2.1%)	**0.0130**
Hydrocortisone-17-butyrate, 1% pet.			
Negative	298 (100%)	96 (99.0%)	
Positive	0 (0%)	1 (1.0%)	0.0793
Disperse blue mix 124/106, 1.0% pet.			
Negative	296 (99.3%)	96 (99.0%)	
Positive	2 (0.7%)	1 (1.0%)	0.7230
Propolis, 10.0% pet.			
Negative	292 (98.0%)	94 (97.0%)	
Positive	6 (2.0%)	3 (3.1%)	0.5361

Lidocaine-HCI, 15.0% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
Propylene glycol, 100%			
Negative	291 (97.7%)	92 (94.9%)	
Positive	7 (2.3%)	5 (5.1%)	0.1620
Clobetasol-17-propionate, 1.0% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Cocamidopropyl betaine, 1.0 aq.			
Negative	292 (98.0%)	97 (100%)	
Positive	6 (2.0%)	0 (0%)	0.1591
Formaldehyde, 2% aq.*			
Negative	96 (100%)	23 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Oleamidopropyl dimethylamine 0.1% aq.			
Negative	288 (96.6%)	97 (100%)	
Positive	10 (3.4%)	0 (0%)	0.0676
Ethyl 2-cyanoacrylate, 10.0% pet.			
Negative	297 (99.7%)	95 (97.9%)	
Positive	1 (0.3%)	2 (2.1%)	0.0889
Cocamide DEA (Coconut diethanolamide) 0.5% pet.			
Negative	292 (98.0%)	97 (100%)	
Positive	6 (2.0%)	0 (0%)	0.1591
Compositae mix, 6.0% pet.			
Negative	295 (98.0%)	97 (100%)	
Positive	3 (2.0%)	0 (0%)	0.3212
Glutaral, 1.0% pet.			
Negative	295 (98.0%)	96 (99.0%)	
Positive	3 (2.0%)	1 (1.0%)	0.9835
Melaleuca Altemifolla, (tea tree leaf oil), oxidized, 5.0% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
Cananga Odorata Flower oil (yiang-yiang oil), 2.0% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Carvone, 5.0% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Lavandula Angustifolla oil. (lavander oil) 2.0% pet.			

Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Decyl glucoaide, 5.0% pet.			
Negative	295 (99.0%)	94 (96.9%)	
Positive	3 (1.0%)	3 (3.1%)	N/A
Jasminum Officinale oil (jasminum grandiflorum), 2.0% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Mantha Piperita oil (peppermint oil), 2.0% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
Hexylene Glycol 10%*			
Negative	84 (100%)	25 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Caster Oil*			
Negative	84 (100%)	24 (96.0%)	
Positive	0 (0%)	1 (4.0%)	0.0655

Chi-squares tests of association between standard allergens and atopic dermatitis with associated p-values.
*70% of patient data was missing for formaldehyde 2%, and 72% of patient data missing for hexylene glycol and caster oil.

Table 4: Association Between Atopic Dermatitis and NACDG supplemental allergens (pos ≥ 1+)			
	Atopic Dermatits		
	Negative (n = 298)	Positive (n = 97)	
Allergen	Freq (%)	Freq (%)	P-value
Benzoyl Peroxide, 1% pet.			
Negative	292 (98.0%)	96 (99.0%)	
Positive	6 (2.0%)	1 (1.0%)	0.5241
Diamino Diphenyl methane 2.0 pet.			
Negative	294 (98.7%)	96 (99.0%)	
Positive	4 (1.3%)	1 (1.0%)	0.8117
Padimate			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Betamethasone 17 Valerate 0.12% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Dichlorophene 1% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Lichen Acid Mix 0.3%			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Chlorhexidive Digluconate 0.5% aq.			
Negative	297 (99.7%)	93 (95.9%)	
Positive	1 (0.3%)	4 (4.1%)	**0.0037**
Disperse Yellow 9 pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	3 (0.7%)	0 (0%)	0.4186
Hydroquinone 1% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Benzalkonium Chloride			
Negative	296 (99.3%)	95 (98.0%)	
Positive	2 (0.7%)	2 (2.0%)	0.2347
1.3 Diphenylguanide 1%			
Negative	288 (96.6%)	93 (95.9%)	
Positive	10 (3.4%)	4 (4.1%)	0.7223
Eugenol 1% pet.			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678

Hydrocortisone 1% alc.			
Negative	298 (100%)	96 (99.0%)	
Positive	0 (0%)	1 (1.0%)	0.0793
Gold Sodiumthiosulfate*			
Negative	267 (92.4%)	87 (93.6%)	
Positive	22 (7.6%)	6 (6.5%)	0.7087
Octyl Methoxycinnamate 7.5% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Urea Formaldehyde			
Negative	295 (99.0%)	96 (99.0%)	
Positive	3 (1.0%)	1 (1.0%)	0.9835
Dust Mite			
Negative	183 (61.4%)	68 (70.1%)	
Positive	115 (38.6%)	29 (29.9%)	0.1223
Dimethylaminopropylamine 1% pet.			
Negative	290 (97.3%)	96 (99.0%)	
Positive	8 (2.7%)	1 (1.0%)	0.3431
Methylene-Gamma Butyro Lactone (Peruvian Lily) 0.01% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Sodium Lauryl Sulfate pet.			
Negative	291 (97.7%)	93 (95.9%)	
Positive	7 (2.3%)	4 (4.1%)	0.3562
Melamine Formaldehyde 7% pet.			
Negative	294 (98.7%)	95 (97.9%)	
Positive	4 (1.3%)	2 (2.1%)	0.6148
Ethylene Urea 1%			
Negative	297 (99.7%)	97 (100%)	
Positive	1 (0.3%)	0 (0%)	0.5678
Propyl Gallate 0.5% pet.			
Negative	295 (99.0%)	95 (97.9%)	
Positive	3 (1.0%)	2 (2.1%)	0.4194
Octyl Gallate 0.25% pet.			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Primin 0.1% pet.			
Negative	298 (100%)	96 (99.0%)	
Positive	0 (0%)	1 (1.0%)	0.0793
Palladium Chloride 1% pet.			

Negative	279 (93.6%)	93 (95.9%)	
Positive	19 (6.4%)	4 (4.1%)	0.4107
Triclosan			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Desoxymethasone 0.25 oint (topicort)			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Disperse Red 17 1% pet.			
Negative	298 (100%)	97 (100%)	
Positive	0 (0%)	0 (0%)	N/A
Propylene Glycol 100%			
Negative	296 (99.3%)	97 (100%)	
Positive	2 (0.7%)	0 (0%)	0.4186
Gentamycin			
Negative	293 (98.3%)	96 (99.0%)	
Positive	5 (1.7%)	1 (1.0%)	0.6509
Thimerosal			
Negative	272 (91.3%)	85 (87.6%)	
Positive	26 (8.7%)	12 (12.4%)	0.2901
Lanolin			
Negative	294 (98.7%)	92 (94.9%)	
Positive	4 (1.3%)	5 (5.1%)	**0.0288**
Budesonide 0.01% pet.			
Negative	298 (100%)	95 (97.9%)	
Positive	0 (0%)	2 (2.1%)	**0.0130**
Tobramycin eye drops			
Negative	297 (99.7%)	96 (99.0%)	
Positive	1 (0.3%)	1 (1.0%)	0.4020

Chi-squares tests of association between extended allergens and atopic dermatitis with associated p-values.
*3% of patient data missing for gold

Table 5: Demographic Patterns among patients with polysenstization			
	Atopic Dermatitis		
	Negative (n = 59)	Positive (n = 32)	
Characteristic	Freq (%)	Freq (%)	P-value
Age*			
Younger than 40	16 (29.6%)	9 (32.1%)	
40 and Older	38 (70.4%)	19 (67.9%)	0.8147
Sex*			
Female	38 (66.7%)	21 (67.7%)	
Male	19 (33.3%)	10 (32.3%)	0.9184
Race			
Caucasian	43 (72.9%)	19 (59.4%)	
Non-Caucasian	16 (27.1%)	13 (40.6%)	0.1867
Birth place*			
Born in US	36 (80.0%)	24 (92.3%)	
Born outside US	9 (20.0%)	2 (7.8%)	0.1673

Chi-squares tests of association between demographics and polysensitized individuals with and without atopic dermatitis.
*10% of patient data missing for age, 3% of patient data missing for sex, 22% of patient data missing for birthplace