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ORIGINAL RESEARCH

Seven Common Allergen Groups Causing Eyelid Dermatitis: Education and Avoidance Strategies

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Objective: Eyelid dermatitis is most commonly attributed to allergic response. This retrospective clinical study identifies common allergens with eyelid involvement and addresses a literary gap by providing a clear approach for effective management of periorbital allergic contact dermatitis (ACD) recurrence.

Methods: Charts of 215 patients diagnosed with periorbital dermatitis who were patch tested with Mayo Clinic Standard Series, Extended Standard Series, and personal products from 2013 to 2017 were examined. Positive reaction rates for patients with eyelid involvement were compared to those without. Findings were also compared to North American Contact Dermatitis Group (NACDG) 2013–2014 and Mayo Clinic Contact Dermatitis Group (MCCDG) 2011–2015 general patch test populations.

Results: The 215 patients showed more common allergy to shellac, benzalkonium chloride, acrylates, and surfactants than the NACDG and MCCDG study populations. Periorbital ACD allergen groups eliciting the highest positive reaction rates were, in descending order: metals, shellac, preservatives, topical antibiotics, fragrances, acrylates, and surfactants. Of the corticosteroids, only tixocortol pivalate (the screening agent for prednisolone and fluorometholone) and budesonide elicited positive reactions.

Conclusion: The top seven eyelid ACD allergen groups were identified. Avoidance of these allergens can be straightforward, with initial empiric counseling and free, online allergen avoidance programs. Patients who are unresponsive to avoidance should undergo patch testing.

Keywords: allergic contact dermatitis, periorbital skin, patch test, contact allergens, allergen avoidance program

Introduction

Allergic contact dermatitis (ACD) is a delayed type IV hypersensitivity reaction, peaking 24–48 hours after allergen presentation.[1] Acute ACD symptoms include vesicles or papules, macules, erythema, and periorbital swelling; chronic ACD symptoms include fissuring, lichenification, and scaling.[2,3] The differential diagnosis for ACD includes irritant contact dermatitis, seborrheic dermatitis, atopic dermatitis, phototoxic dermatitis, psoriasis, rosacea, urticaria, dermatomyositis, cutaneous T-cell lymphoma, blepharitis, and other infections.[4–7]

Particular susceptibility of the eyelids to ACD has been widely reported.[6–12] Multiple factors contribute to this observation: the eyelids constitute the thinnest skin on the body (0.55 mm), thus allowing for easier allergen penetration; their unprotected position on the body invites substantial cosmetic and environmental exposure, including frequent contact with allergens carried by the hands; and they

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function as a regular application site of many eye care medications and products.[7–9,11] In fact, the eyelids may manifest as the initial or singular site of ACD symptoms, even with allergen exposure occurring elsewhere on the body.[6,7,12] Consequently, ophthalmologists and optometrists are often the first providers to encounter patients with ACD.

Identification of ACD as the most frequent cause of eyelid dermatitis has been well established, especially in the dermatologic literature.[4,8,12–15] Eye care providers are quick to point to topical ophthalmic medications as potential ACD triggers. However, ACD is often misdiagnosed, or ophthalmologists and optometrists may be unsure of therapeutic options if patients fail to improve despite avoidance of ophthalmic medications.[3,16] When confronted with ACD, dermatologists often recommend patch testing, which traditionally involves the application of potential allergenic substances at dilute concentrations to the patient's skin via "patches," worn for 48 hours, with test interpretation at 96 hours.[2]

Patch testing, widely regarded as the gold standard for ACD diagnosis, is deemed a necessity in ACD treatment because accurate identification and proper avoidance of responsible allergen(s) offer a simple, effective cure.[17–19] Allergens in standard patch test series are recommended to have clinical relevance and/or positive reaction rates greater than 0.5–1.0%.[20] Citing patch test results, previous case series and reviews have highlighted allergens in such groups as preservatives, cosmetics, anti-inflammatory medications, anesthetics, and anti-glaucoma medications.[1,3]

Literary gaps exist, especially in ophthalmologic journals, on the causes of isolated periorbital ACD, and on modern clinical approaches to prevent ACD recurrence following allergen identification.[2,3,8,11,21,22] Moreover, if patch testing is unavailable, other strategies must be employed. This retrospective clinical study identifies ACD-related common allergens with eyelid involvement, compares current findings to previous reports, and advances the current literature by offering a straightforward, contemporary approach to identify patient products with and without common offending allergens for periorbital ACD management.

Methods

This retrospective study followed the ethical tenets of the Declaration of Helsinki and underwent Mayo Clinic Institutional Review Board (IRB) approval. The study was found to constitute minimal risk research, with an approved waiver of informed consent and adequate precautions taken to de-identify subjects' information and protect patient data confidentiality. From January 1, 2013 through December 31, 2017, 217 patients diagnosed with dermatitis involving the eyelids and 1975 patients with dermatitis not involving the eyelids were patch tested at Mayo Clinic, Arizona, to our Standard Series and Extended Standard Series (151 allergens). All patients were diagnosed with any of the following: asteatotic dermatitis, atopic dermatitis, allergic dermatitis, irritant dermatitis, dermatitis not otherwise specified, and/or seborrheic dermatitis.

Patch testing followed North American Contact Dermatitis Group (NACDG) standard guidelines (eg no oral or topical corticosteroid involvement; reactions graded on a standardized scale).[20] Patches were removed 48 hours after application to patients' upper backs. Reaction sites were evaluated, first immediately after patch removal, then again 92–108 hours after removal (as shown in Figure 1). The Mayo Clinic Standard Series included contact lens materials (eg methyl acrylates), antibiotics (eg neomycin),

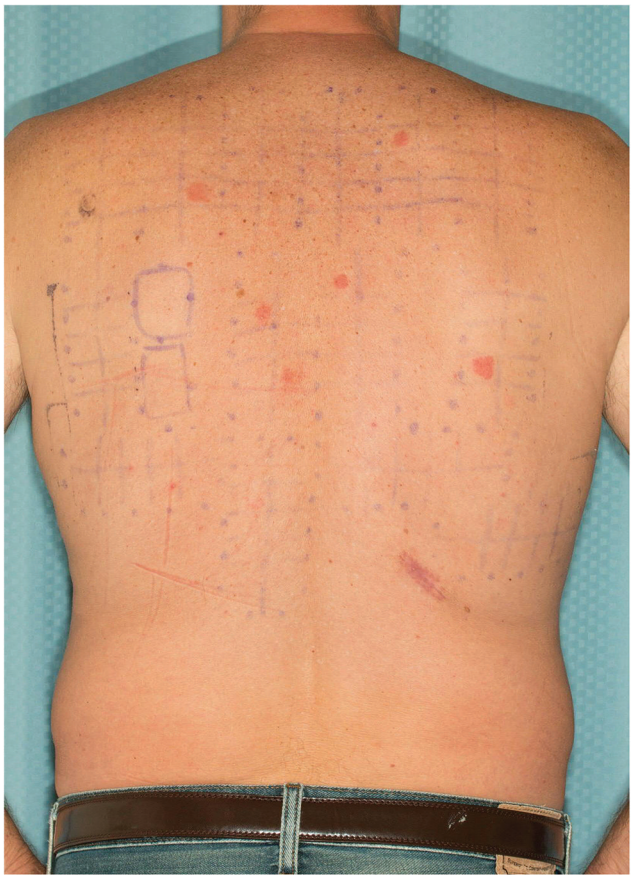

Figure 1 Patient showing positive reactions at several application sites of distinct allergens, following the removal of patches.

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anesthetics (eg benzocaine, lidocaine), and corticosteroids (eg hydrocortisone-17-butyrate, tixocortol pivalate, clobetasol-17-butyrate, triamcinolone, budesonide, desoximetasone), while the Mayo Clinic Extended Standard Series included such known allergens as thimerosal. (Of note for ophthalmologists, steroids in Group 1 [eg prednisolone, tixocortol pivalate, budesonide, loteprednol, fluorometholone, and difluprednate] and Group 2 are the most likely to cause contact allergy, while steroids in Group 3 [eg rimexolone, dexamethasone] are the least likely; Table 1 displays additional examples in each group.[23,24]) More importantly, the Mayo Clinic Standard Series includes several allergens frequently found in skincare products that are not included in the NACDG Standard Series, for potential clinical relevance in spite of relatively low positive reaction rates.[25]

Allergen test results were defined as follows based on day 5 readings: positive, if day 5 reaction grade = 2, 3 or 4; negative, if day 5 reaction grade = 0 or 1; or irritant, if reaction relevancy = I. Reaction grade was defined as follows: 0 = negative; 1 = macular erythema; 2 = weak (non-vesicular erythema, infiltration or papules); 3 = strong (edema or vesicles); 4 = extreme (bullous, ulcerative or spreading lesions).[20] Reaction relevancy was defined as follows: I = irritant; N = allergic, not relevant; P = allergic, formerly relevant; Q = allergic, questionably relevant; R = allergic, relevant.

Since two patients with eyelid involvement did not have reports of day 5 reaction results, a total of 215 patients with eyelid involvement were included in analysis. For these patients, reaction rates to their own products (365 patient products) were examined as well.

Table 1 Classification of Topical Corticosteroids Used in Ophthalmic Preparations

Group 1	Group 2	Group 3
Class A, D2 Plus Budesonide	Class B	Class C, D1
Testing agent: Tixocortol pivalate	Testing agent: Triamcinolone	Testing agent: Desoximetasone
Difluprednate (Durezol) Fludrocortisone acetate (Flarex) Fluorometholone (FML) Hydrocortisone acetate Prednisolone acetate (Pred Mild, Pred Forte, Blephamide) Prednisolone sodium phosphate	Triamcinolone	Clobetasol Dexamethasone (Maxidex) Dexamethasone sodium phosphate Rimexolone (Vexol)

Patient characteristics (basic demographic information, ie age, sex, race), results by allergen sorted by descending number of patients tested, and results by allergen sorted by descending positivity were recorded and examined.

Positive reaction rates for patients with eyelid involvement were compared to those for patients without eyelid involvement. Findings were also compared to general patch test patient populations as reported by the North American Contact Dermatitis Group (NACDG) on 4871 patients tested from 2013 to 2014, and to those reported by the Mayo Clinic Contact Dermatitis Group (MCCDG) Standard Series on 2582 patients tested from 2011 to 2015.

Results

Of the 215 patients with eyelid dermatitis (mean [SD] age, 53.1 [15.0] years) during the 4-year study period at Mayo Clinic in Arizona, 184 (85.6%) were female and 31 (14.4%) were male. These patients' reported racial demographics were as follows: 189 (92.2%) White, 5 (2.4%) Black, 4 (2.0%) Asian, 1 (0.5%) American Indian/Alaska Native, 6 (2.9%) Other, and 10 unknown. Given these demographics, we acknowledge that these results may not be completely applicable to patients with skin of color.

Of the Standard and Extended Standard Series, 74 allergens elicited positive reactions in these 215 patients with eyelid involvement. Table 2 displays the reaction rates for these 74 allergens (sorted by descending positivity in the patient population with eyelid involvement), alongside corresponding reactions rates for these allergens in the 1975 patients without eyelid involvement, and in the general patch test populations NACDG 2013–2014[26] and MCCDG 2011–2015.[20] Table 3 displays the 15 allergens eliciting the highest reaction rates in each of these four populations, ie Mayo Clinic 2013–2017 with eyelid involvement, Mayo Clinic 2013–2017 without eyelid involvement, NACDG 2013–2014,[26] and MCCDG 2011–2015[20] (sorted by descending positivity).

For the 215 patients with eyelid involvement, the highest reaction rates were elicited by the following allergen groups, starting with the highest rate of positivity: metals (eg, nickel in eyewear, gold in eye makeup); shellac (a tackifier that helps skincare products adhere to the skin); preservatives (eg, benzalkonium chloride [BAK] in skincare products, prescription and over-the-counter eye preparations); topical antibiotics (neomycin, bacitracin);

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Table 2 Reaction Rates for the 74 Allergens Eliciting Positive Reactions in Patients with Eyelid Dermatitis (Number of Positive Reactions/Number of Patients Tested), in Descending Order

Allergen	Eyelid Involvement					No Eyelid Involvement					Mayo Standard Series 2011–2015 (Positive Rxn Rate/ N of Patients)	NACDG Standard Series 2013–2014 (Table 6) (Positive Rxn Rate/N of Patients)
	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)		
Nickel (II) sulfate hexahydrate 2.5%	213	46 (21.6%)	167 (78.4%)	0	42/46 (91.3%)	1967	404 (20.5%)	1542 (78.4%)	21 (1.1%)	380/404 (94.1%)	23.0%/2565	20.1%/4850
Shellac 20% in alc[a]	110	18 (16.4%)	92 (83.6%)	0	17/18 (94.4%)	630	71 (11.3%)	551 (87.5%)	8 (1.3%)	70/71 (98.6%)		
Thimerosal 0.1%	142	19 (13.4%)	122 (85.9%)	1 (0.7%)	18/19 (94.7%)	744	84 (11.3%)	653 (87.8%)	7 (0.9%)	79/84 (94.0%)		
Cobalt (II) chloride hexahydrate 1%	214	23 (10.7%)	183 (85.5%)	8 (3.7%)	23/23 (100.0%)	1967	189 (9.6%)	1729 (87.9%)	49 (2.5%)	174/189 (92.1%)	12.4%/2569	7.4%/4859
Neomycin sulfate 20%	215	23 (10.7%)	190 (88.4%)	2 (0.9%)	22/23 (95.7%)	1972	183 (9.3%)	1776 (90.1%)	13 (0.7%)	174/183 (95.1%)	11.8%/2574	8.4%/4857
Gold (I) sodium thiosulfate dihydrate 0.5% in pet	141	15 (10.6%)	124 (87.9%)	2 (1.4%)	14/15 (93.3%)	746	66 (8.8%)	674 (90.3%)	6 (0.8%)	60/66 (90.9%)	15.9%/88	
Methylisothiazolinone 0.2% aq[a]	161	17 (10.6%)	143 (88.8%)	1 (0.6%)	17/17 (100.0%)	1562	246 (15.7%)	1300 (83.2%)	16 (1.0%)	245/246 (99.6%)	15.8%/964	
Myroxylon pereirae resin 25%	214	21 (9.8%)	187 (87.4%)	6 (2.8%)	21/21 (100.0%)	1972	246 (12.5%)	1697 (86.1%)	29 (1.5%)	243/246 (98.8%)	17.4%/2573	7.2%/4859
Bacitracin 20%	215	16 (7.4%)	198 (92.1%)	1 (0.5%)	15/16 (93.8%)	1972	139 (7.0%)	1822 (92.4%)	11 (0.6%)	131/139 (94.2%)	7.8%/2572	7.4%/4858
Potassium dichromate 0.25%	215	15 (7.0%)	199 (92.6%)	1 (0.5%)	15/15 (100.0%)	1970	147 (7.5%)	1792 (91.0%)	31 (1.6%)	141/147 (95.9%)	11.6%/2571	2.2%/4859
2-Hydroxyethyl methacrylate 2% (HEMA)	34	2 (5.9%)	32 (94.1%)	0	2/2 (100.0%)	283	12 (4.2%)	269 (95.1%)	2 (0.7%)	12/12 (100.0%)		
Benzalkonium chloride 0.1% aq	215	10 (4.7%)	203 (94.4%)	2 (0.9%)	10/10 (100.0%)	1969	127 (6.4%)	1825 (92.7%)	17 (0.9%)	121/127 (95.3%)		
MCI/MI 100 ppm aq	215	10 (4.7%)	204 (94.9%)	1 (0.5%)	10/10 (100.0%)	1974	143 (7.2%)	1822 (92.3%)	9 (0.5%)	143/143 (100.0%)	7.3%/2576	6.4%/4856
Propolis 10%	215	10 (4.7%)	203 (94.4%)	2 (0.9%)	10/10 (100.0%)	1975	59 (3.0%)	1902 (96.3%)	14 (0.7%)	55/59 (93.2%)	8.6%/2572	1.7%/4859
Hydroperoxides of linalool 1.0%	142	6 (4.2%)	135 (95.1%)	1 (0.7%)	6/6 (100.0%)	748	56 (7.5%)	689 (92.1%)	3 (0.4%)	56/56 (100.0%)		
Oleamidopropyl dimethylamine 0.1% aq	142	6 (4.2%)	133 (93.7%)	3 (2.1%)	6/6 (100.0%)	748	22 (2.9%)	721 (96.4%)	5 (0.7%)	21/22 (95.5%)		3.5%/4859
Amidoamine 0.1 aq	215	9 (4.2%)	206 (95.8%)	0	9/9 (100.0%)	1974	46 (2.3%)	1917 (97.1%)	11 (0.6%)	45/46 (97.8%)	3.7%/2515	1.2%/4859
Fragrance mix 8%[a]	215	7 (3.3%)	207 (96.3%)	1 (0.5%)	7/7 (100.0%)	1974	162 (8.2%)	1799 (91.1%)	13 (0.7%)	162/162 (100.0%)	12.0%/2575	11.9%/4858

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Methyl methacrylate 2%	215	7 (3.3%)	208 (96.7%)	0	7/7 (100.0%)	1975	27 (1.4%)	1937 (98.1%)	11 (0.6%)	27/27 (100.0%)	1.8%/2573	1.3%/4859
Thiuram mix 1%	215	7 (3.3%)	207 (96.3%)	1 (0.5%)	7/7 (100.0%)	1971	65 (3.3%)	1897 (96.2%)	9 (0.5%)	65/65 (100.0%)	3.8%/2573	3.1%/4859
Amerchol L101 (lanolin alcohol) 50%	159	5 (3.1%)	153 (96.2%)	1 (0.6%)	5/5 (100.0%)	1031	23 (2.2%)	1004 (97.4%)	4 (0.4%)	23/23 (100.0%)		5.4%4859
Methyldibromo glutaronitrile 0.5%[a]	161	5 (3.1%)	154 (95.7%)	2 (1.2%)	5/5 (100.0%)	1582	111 (7.0%)	1461 (92.4%)	10 (0.6%)	111/111 (100.0%)	7.4%/987	
Colophonium 20%	215	6 (2.8%)	208 (96.7%)	1 (0.5%)	6/6 (100.0%)	1972	64 (3.2%)	1891 (95.9%)	17 (0.9%)	64/64 (100.0%)	3.3%/2574	
Formaldehyde 1% aq	215	6 (2.8%)	209 (97.2%)	0	6/6 (100.0%)	1971	119 (6.0%)	1841 (93.4%)	11 (0.6%)	118/119 (99.2%)	7.2%/2572	5.6%/4858
Quaternium 15 1%	215	6 (2.8%)	209 (97.2%)	0	6/6 (100.0%)	1972	96 (4.9%)	1865 (94.6%)	11 (0.6%)	94/96 (97.9%)	5.7%/2573	
Resorcinol 1%	77	2 (2.6%)	75 (97.4%)	0	2/2 (100.0%)	728	7 (1.0%)	719 (98.8%)	2 (0.3%)	7/7 (100.0%)		
Ethylenediamine dihydrochloride 1%	215	5 (2.3%)	210 (97.7%)	0	5/5 (100.0%)	1972	36 (1.8%)	1927 (97.7%)	9 (0.5%)	36/36 (100.0%)	2.0%/2574	1.2%/4859
Hexahydro-1,3,5-tris (2-hydroxyethyl) triazine 1%	215	5 (2.3%)	210 (97.7%)	0	5/5 (100.0%)	1974	60 (3.0%)	1905 (96.5%)	9 (0.5%)	56/60 (93.3%)	3.8%/2573	
Lanolin alcohol 30%	215	5 (2.3%)	207 (96.3%)	3 (1.4%)	5/5 (100.0%)	1971	40 (2.0%)	1919 (97.4%)	12 (0.6%)	40/40 (100.0%)	2.8%/2572	
p-Phenylenediamine 1%	215	5 (2.3%)	208 (96.7%)	2 (0.9%)	5/5 (100.0%)	1970	103 (5.2%)	1858 (94.3%)	9 (0.5%)	102/103 (99.0%)	6.3%/2568	7.0%/4853
Dodecyl gallate 0.25%	140	3 (2.1%)	135 (96.4%)	2 (1.4%)	3/3 (100.0%)	748	38 (5.1%)	702 (93.9%)	8 (1.1%)	37/38 (97.4%)		
Propyl gallate 1%	140	3 (2.1%)	137 (97.9%)	0	3/3 (100.0%)	748	5 (0.7%)	743 (99.3%)	0	4/5 (80.0%)		
3-(Dimethylamino)-1-propylamine (DMAPA) 1% aq	159	3 (1.9%)	155 (97.5%)	1 (0.6%)	3/3 (100.0%)	1031	16 (1.6%)	1014 (98.4%)	1 (0.1%)	15/16 (93.8%)		1.8%/4858
Carba mix 3%[a]	215	4 (1.9%)	207 (96.3%)	4 (1.9%)	4/4 (100.0%)	1970	128 (6.5%)	1801 (91.4%)	41 (2.1%)	127/128 (99.2%)	9.6%/2573	4.8%/4859
Ethyl acrylate 0.1%	215	4 (1.9%)	211 (98.1%)	0	4/4 (100.0%)	1975	31 (1.6%)	1933 (97.9%)	11 (0.6%)	31/31 (100.0%)	1.8%/2573	1.1%/4859
Hydroperoxides of limonene 0.3%	140	2 (1.4%)	137 (97.9%)	1 (0.7%)	2/2 (100.0%)	748	17 (2.3%)	730 (97.6%)	1 (0.1%)	17/17 (100.0%)		
Methanamine 2%	142	2 (1.4%)	139 (97.9%)	1 (0.7%)	2/2 (100.0%)	748	8 (1.1%)	739 (98.8%)	1 (0.1%)	8/8 (100.0%)		
Phenyl salicylate 1%	142	2 (1.4%)	138 (97.2%)	2 (1.4%)	2/2 (100.0%)	747	6 (0.8%)	737 (98.7%)	4 (0.5%)	6/6 (100.0%)		
2-Bromo-2-nitropropane-1,3-diol 0.5%	215	3 (1.4%)	210 (97.7%)	2 (0.9%)	3/3 (100.0%)	1972	59 (3.0%)	1900 (96.3%)	13 (0.7%)	57/59 (96.6%)	3.5%/2571	2.1%/4859
Benzoic acid 5%	215	3 (1.4%)	212 (98.6%)	0	3/3 (100.0%)	1975	88 (4.5%)	1868 (94.6%)	19 (1.0%)	87/88 (98.9%)	8.8%/2574	
Black rubber mix 0.6%	215	3 (1.4%)	212 (98.6%)	0	2/3 (66.7%)	1971	20 (1.0%)	1949 (98.9%)	2 (0.1%)	20/20 (100.0%)	1.5%/2573	1.0%/4859
Composite mix II 5%	215	3 (1.4%)	212 (98.6%)	0	3/3 (100.0%)	1974	48 (2.4%)	1920 (97.3%)	6 (0.3%)	46/48 (95.8%)		
Glyceryl thioglycolate 1%	215	3 (1.4%)	211 (98.1%)	1 (0.5%)	2/3 (66.7%)	1974	50 (2.5%)	1911 (96.8%)	13 (0.7%)	44/50 (88.0%)	3.3%/2573	
Imidazolidinyl urea 2%	215	3 (1.4%)	211 (98.1%)	1 (0.5%)	3/3 (100.0%)	1972	25 (1.3%)	1934 (98.1%)	13 (0.7%)	24/25 (96.0%)	1.6%/2575	1.6%/4859
Tixocortol 21 pivalate 1%	215	3 (1.4%)	212 (98.6%)	0	3/3 (100.0%)	1972	42 (2.1%)	1924 (97.6%)	6 (0.3%)	41/42 (97.6%)	2.6%/2574	2.1%/4859
Benzophenone-4 10%	159	2 (1.3%)	157 (98.7%)	0	2/2 (100.0%)	1021	32 (3.1%)	987 (96.7%)	2 (0.2%)	31/32 (96.9%)		2.1%/4857

(*Continued*)

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Table 2 (Continued).

Allergen	Eyelid Involvement					No Eyelid Involvement					Mayo Standard Series 2011–2015 (Positive Rxn Rate/ N of Patients)	NACDG Standard Series 2013–2014 (Table 6) (Positive Rxn Rate/N of Patients)
	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)		
Phenylmercuric acetate 0.01% aq	90	1 (1.1%)	87 (96.7%)	2 (2.2%)	1/1 (100.0%)	453	4 (0.9%)	446 (98.5%)	3 (0.7%)	3/4 (75.0%)		
4-Tert-butylphenol formaldehyde resin 1%	215	2 (0.9%)	212 (98.6%)	1 (0.5%)	2/2 (100.0%)	1971	12 (0.6%)	1952 (99.0%)	7 (0.4%)	12/12 (100.0%)	1.0%/2573	1.0%/4859
Budesonide 0.01%	215	2 (0.9%)	211 (98.1%)	2 (0.9%)	1/2 (50.0%)	1973	17 (0.9%)	1951 (98.9%)	5 (0.3%)	17/17 (100.0%)	1.4%/2575	0.9%/4859
Disperse blue mix 106/124 1%	215	2 (0.9%)	213 (99.1%)	0	2/2 (100.0%)	1972	23 (1.2%)	1935 (98.1%)	14 (0.7%)	21/23 (91.3%)	3.2%/1687	1.0%/4859
Disperse orange #3 1%	215	2 (0.9%)	210 (97.7%)	3 (1.4%)	2/2 (100.0%)	1974	54 (2.7%)	1908 (96.7%)	12 (0.6%)	54/54 (100.0%)	3.0%/2573	
Fragrance mix II	215	2 (0.9%)	211 (98.1%)	2 (0.9%)	2/2 (100.0%)	1974	69 (3.5%)	1892 (95.8%)	13 (0.7%)	68/69 (98.6%)	5.2%/2572	5.7%/4859
Lidocaine 5%	215	2 (0.9%)	213 (99.1%)	0	2/2 (100.0%)	1974	11 (0.6%)	1948 (98.7%)	15 (0.8%)	10/11 (90.9%)	0.7%/2572	
Propylene glycol 20% in water	215	2 (0.9%)	212 (98.6%)	1 (0.5%)	2/2 (100.0%)	1975	48 (2.4%)	1919 (97.2%)	8 (0.4%)	47/48 (97.9%)	3.4%/2570	
Sodium benzoate 5%	140	1 (0.7%)	136 (97.1%)	3 (2.1%)	1/1 (100.0%)	748	12 (1.6%)	730 (97.6%)	6 (0.8%)	12/12 (100.0%)		
Rosa damascena extract 2%	141	1 (0.7%)	139 (98.6%)	1 (0.7%)	1/1 (100.0%)	745	3 (0.4%)	740 (99.3%)	2 (0.3%)	3/3 (100.0%)		
Benzyl salicylate 1%	142	1 (0.7%)	140 (98.6%)	1 (0.7%)	1/1 (100.0%)	748	1 (0.1%)	743 (99.3%)	4 (0.5%)	1/1 (100.0%)		
Ethyl cyanoacrylate 10%	142	1 (0.7%)	138 (97.2%)	3 (2.1%)	1/1 (100.0%)	748	10 (1.3%)	736 (98.4%)	2 (0.3%)	10/10 (100.0%)		0.4%/4859
Ethylhexyl dimethyl PABA 5%	142	1 (0.7%)	141 (99.3%)	0	1/1 (100.0%)	739	2 (0.3%)	736 (99.6%)	1 (0.1%)	2/2 (100.0%)		
Santalum album oil 2%	142	1 (0.7%)	140 (98.6%)	1 (0.7%)	1/1 (100.0%)	739	7 (0.9%)	731 (98.9%)	1 (0.1%)	7/7 (100.0%)		
Decyl glucoside 5%	159	1 (0.6%)	156 (98.1%)	2 (1.3%)	1/1 (100.0%)	1031	17 (1.6%)	1007 (97.7%)	7 (0.7%)	17/17 (100.0%)		1.7%/4859
Benzophenone-3 10%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1929	14 (0.7%)	1913 (99.2%)	2 (0.1%)	13/14 (92.9%)	0.9%/2539	0.6%/4859
BHT (2,6-ditert-butyl -4-cresol) 2%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1975	5 (0.3%)	1961 (99.3%)	9 (0.5%)	5/5 (100.0%)	0.3%/2574	
Cocamide DEA (coconut diethanolamide) 0.5%	215	1 (0.5%)	213 (99.1%)	1 (0.5%)	1/1 (100.0%)	1974	21 (1.1%)	1936 (98.1%)	17 (0.9%)	21/21 (100.0%)	1.7%/2574	0.9%/4859
Diazolidinyl urea 1%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1973	38 (1.9%)	1921 (97.4%)	14 (0.7%)	36/38 (94.7%)	2.0%/2576	2.0%/2576
DMDM hydantoin 1%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1975	21 (1.1%)	1940 (98.2%)	14 (0.7%)	21/21 (100.0%)	1.1%/2574	1.0%/4859
DMDM hydantoin 2% in aq	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1974	23 (1.2%)	1946 (98.6%)	5 (0.3%)	22/23 (95.7%)	1.7%/2573	
Iodopropynyl butylcarbamate 0.2%	215	1 (0.5%)	211 (98.1%)	3 (1.4%)	1/1 (100.0%)	1973	65 (3.3%)	1898 (96.2%)	10 (0.5%)	65/65 (100.0%)	6.4%/2555	

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Paraben mix 16%	215	1 (0.5%)	210 (97.7%)	4 (1.9%)	1/1 (100.0%)	1973	31 (1.6%)	1925 (97.6%)	17 (0.9%)	31/31 (100.0%)	2.8%/2576
Phenol formaldehyde resin 1%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1974	20 (1.0%)	1943 (98.4%)	11 (0.6%)	20/20 (100.0%)	1.5%/2573
Stearyl alcohol 30%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1975	7 (0.4%)	1961 (99.3%)	7 (0.4%)	7/7 (100.0%)	0.5%/2574
Tocopherol 100%	215	1 (0.5%)	213 (99.1%)	1 (0.5%)	1/1 (100.0%)	1975	10 (0.5%)	1960 (99.2%)	5 (0.3%)	9/10 (90.0%)	0.7%/2574
Toluenesulphonamide formaldehyde resin 10%	215	1 (0.5%)	214 (99.5%)	0	1/1 (100.0%)	1974	17 (0.9%)	1938 (98.2%)	19 (1.0%)	17/17 (100.0%)	0.7%/2573
Triethanolamine 2%	215	1 (0.5%)	213 (99.1%)	1 (0.5%)	1/1 (100.0%)	1975	10 (0.5%)	1955 (99.0%)	10 (0.5%)	10/10 (100.0%)	0.8%/2574
											0.6%/4859

Note: [a]Allergens with the greatest difference between those with eyelid involvement and without (3.9% difference or greater).

fragrances (in cosmetic and cleansing products); acrylates (in artificial/gel nails); and surfactants (eg in tear-free shampoos).

The Mayo Clinic Standard Series tests the following topical steroids: tixocortol pivalate, hydrocortisone-17-butyrate, budesonide, clobetasol-17-butyrate, triamcinolone, and desoximetasone. In the 215 patients with eyelid involvement, the corticosteroids eliciting positive reactions were budesonide and tixocortol pivalate (Group 1 corticosteroids). In the 1975 patients without eyelid involvement, the corticosteroids eliciting positive reactions were tixocortol pivalate, budesonide, hydrocortisone-17-butyrate, clobetasol-17-butyrate, and triamcinolone. As shown in Table 4, desoximetasone (a Group 3 corticosteroid) elicited no positive reactions in patients either with or without eyelid involvement.

Discussion

Allergic Contact Dermatitis with Eyelid Involvement

For ACD patients with eyelid dermatitis, the seven most common contact allergen groups were identified as follows (in descending order): metals; shellac; preservatives; topical antibiotics; fragrances; acrylates; and surfactants.

For a considerable number of allergens, reaction rates in patients with eyelid involvement were lower than those in patients without eyelid involvement and lower than those in general patch test populations, as shown in Table 2. For example, positive reaction rates to fragrance mix and to a broad palate of preservatives (eg iodopropynyl butylcarbamate) were lower in patients with eyelid involvement. These findings might call into question the commonly offered clinical explanation of the thin eyelid epithelium's particular susceptibility to ACD.[6–12] However, patients with eyelid involvement did show higher reaction rates to a few allergens, ie shellac, BAK, acrylates, and surfactants.

Of note, the relevance rates for patch test data shown in Table 2 are high in this study, reflecting a select population of patch test patients where the dermatologist's clinical index of suspicion for contact dermatitis was high.

Nonetheless, patients with eyelid dermatitis in this study were not necessarily diagnosed with dermatitis limited only to the eyelids. Future studies conducted on larger populations might limit diagnoses to eyelid skin involvement only.

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Table 3 Top 15 Allergens Eliciting the Highest Reaction Rates in the Following Four Populations: Mayo Clinic 2013–2017 with Eyelid Involvement, Mayo Clinic 2013–2017 without Eyelid Involvement, NACDG 2013–2014, and MCCDG 2011–2015 General Patch Test Populations (Sorted by Descending Positivity)

Rank	Mayo Clinic 2013–2017 with Eyelid Involvement	Mayo Clinic 2013–2017 without Eyelid Involvement	NACDG 2013–2014	MCCDG 2011–2015
1	Nickel (II) sulfate hexahydrate 2.5%	Nickel (II) sulfate hexahydrate 2.5%	Nickel sulfate, 2.5% pet	Gold sodium thiosulfate, 2%
2	Shellac 20% in alc.	Methylisothiazolinone 0.2% aq[a]	Fragrance mix I, 8% pet	Nickel sulfate hexahydrate, 2.5%
3	Thimerosal 0.1%	Myroxylon pereirae resin 25%	MI, 0.2% aq	Myroxylon pereirae resin, 25%
4	Cobalt (II) chloride hexahydrate 1%	Thimerosal 0.1%	Neomycin, 20% pet	Gold (I) sodium thiosulfate dehydrate, 0.5%
5	Neomycin sulfate 20%	Shellac 20% in alc[a]	Bacitracin, 20% pet	Methylisothiazolinone, 0.2% aqueous
6	Gold (I) sodium thiosulfate dihydrate 0.5% in pet	Cobalt (II) chloride hexahydrate 1%	Cobalt chloride, 1% pet	Benzalkonium chloride, 0.1% aqueous
7	Methylisothiazolinone 0.2% aq	Neomycin sulfate 20%	Myroxylon pereirae, 25% pet	Cobalt (II) chloride hexahydrate, 1%
8	Myroxylon pereirae resin 25%	Gold (I) sodium thiosulfate dihydrate 0.5% in pet	p-Phenylenediamine, 1% pet	Fragrance mix, 8%
9	Bacitracin 20%	Fragrance mix 8%[a, b]	Formaldehyde, 2% aq	Neomycin sulfate, 20%
10	Potassium dichromate 0.25%	Potassium dichromate 0.25%	MCI/MI, 0.01% aq	Potassium dichromate, 0.25%
11	2-Hydroxyethyl methacrylate 2% (HEMA)	Hydroperoxides of linalool 1.0%[b]	Fragrance mix II, 14% pet	Carba mix, 3%
12	Benzalkonium chloride 0.1% aq	MCI/MI 100 ppm aq	Formaldehyde, 1% aq	Benzoic acid, 5%
13	MCI/MI 100 ppm aq	Bacitracin 20%	Lanolin alcohol (Amerchol L 101), 50% pet	Propolis, 10%
14	Propolis 10%	Methyldibromo glutaronitrile 0.5%[a, b]	Carba mix, 3% pet	Methyldibromo glutaronitrile/ phenoxyethanol, 1.5%
15	Hydroperoxides of linalool 1.0%	Carba mix 3%[a, b]	Quaternium-15, 2% pet	Bacitracin, 20%

Notes: [a]Allergens with the greatest difference between those with eyelid involvement and without (3.9% difference or greater). [b]Allergens in the top 15 without eyelid involvement not found in the top 15 with eyelid involvement.

Allergic Contact Dermatitis without Eyelid Involvement

Upon comparison of the results from patients with eyelid involvement to those without (using Table 3), it is interesting to note that 11 of the 15 allergens with the highest positive reaction rates were the same across both groups. Since the first five groups (metals, preservatives, fragrances, shellac, and topical antibiotics) are also seen in the top seven groups for patients with eyelid involvement, avoidance of the top allergen groups for patients with eyelid dermatitis also affords promising benefits for the prevention of dermatitis on other areas of the body.

Topical Steroids

Topical corticosteroids, as shown in Table 1, can be classified into three groups according to Baeck and co-authors: Group 1 comprises non-methylated, most often non-halogenated molecules; Group 2 comprises halogenated molecules with a C_{16}/C_{17} cis ketal/diol structure; and Group 3 comprises halogenated and C_{16}-methylated molecules.[23,24] Group 1 steroids are the most common offenders in steroid-triggered allergic reactions, while Group 3 steroids are the least common.[24]

The only corticosteroids eliciting positive reactions in ACD patients with eyelid involvement were budesonide and tixocortol pivalate, which are both Group 1

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Table 4 The 25 Allergens That Did Not Elicit Positive Reactions in Mayo Clinic 2013–2017 Patients with Eyelid Involvement, But Did Elicit Positive Reactions in NACDG 2013–2014 and MCCDG 2011–2015 General Patch Test Populations (Sorted in Alphabetical Order)

Allergen	Eyelid Involvement					No Eyelid Involvement					Mayo Standard Series 2011–2015 (Positive Rxn Rate/N of Patients)	NACDG Standard Series 2013–2014 (Table 6) (Positive Rxn Rate/N of Patients)
	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)	Number of Patients Tested	Positive, n (%)	Negative, n (%)	Irritant, n (%)	Relevancy Among Those Testing Positive, n (%)		
2-Phenoxyethanol 1%	192	0	192 (100.0%)	0		1693	3 (0.2%)	1686 (99.6%)	4 (0.2%)	3/3 (100.0%)	0.5%/988	
Benzocaine 5%	215	0	215 (100.0%)	0		1973	30 (1.5%)	1937 (98.2%)	6 (0.3%)	27/30 (90.0%)	1.9%/2569	1.6%/4851
Cananga odorata oil 2%	88	0	87 (98.9%)	1 (1.1%)		414	6 (1.4%)	407 (98.3%)	1 (0.2%)	6/6 (100.0%)		1.2%/4859
Cetyl alcohol 5%	215	0	215 (100.0%)	0		1975	4 (0.2%)	1968 (99.6%)	3 (0.2%)	4/4 (100.0%)	0.3%/2574	
Chloroxylenol (PCMX) 1%	215	0	215 (100.0%)	0		1974	12 (0.6%)	1956 (99.1%)	6 (0.3%)	12/12 (100.0%)	0.8%/2573	0.5%/4859
Cinnamal (cinnamic aldehyde) 1%	215	0	214 (99.5%)	1 (0.5%)		1974	27 (1.4%)	1945 (98.5%)	2 (0.1%)	27/27 (100.0%)	1.9%/2571	4.2%/4858
Clobetasol-17-propionate 1%	215	0	215 (100.0%)	0		1973	7 (0.4%)	1964 (99.5%)	2 (0.1%)	7/7 (100.0%)	1.1%/2572	0.1%/4859
Cocamidopropyl betaine 1% aq	215	0	210 (97.7%)	5 (2.3%)		1973	50 (2.5%)	1904 (96.5%)	19 (1.0%)	49/50 (98.0%)	5.5%/2573	1.6%/4859
Desoximetasone 1%	68	0	68 (100.0%)	0		556	0	555 (99.8%)	1 (0.2%)			0.1%/4859
Dimethylol dihydroxyethylene urea 4.5% aq	215	0	214 (99.5%)	1 (0.5%)		1974	8 (0.4%)	1955 (99.0%)	11 (0.6%)	8/8 (100.0%)	0.5%/2573	
Epoxy resin, bisphenol A	215	0	215 (100.0%)	0		1972	19 (1.0%)	1941 (98.4%)	12 (0.6%)	19/19 (100.0%)	1.6%/2574	1.8%/4857
Ethyleneurea–melamine formaldehyde mix 5%	215	0	215 (100.0%)	0		1974	21 (1.1%)	1940 (98.3%)	13 (0.7%)	20/21 (95.2%)	1.3%/2573	
Ethylhexylglycerin 5%	11	0	11 (100.0%)	0		89	0	89 (100.0%)	0			0.2%/4859
Glutaral (glutaraldehyde) 0.2%	215	0	215 (100.0%)	0		1975	8 (0.4%)	1952 (98.8%)	15 (0.8%)	8/8 (100.0%)	0.8%/2574	
Hexylresorcinol 0.25%	193	0	192 (99.5%)	1 (0.5%)		1603	31 (1.9%)	1561 (97.4%)	11 (0.7%)	30/31 (96.8%)	3.3%/2573	
Lavandula angustifolia oil 2%	142	0	142 (100.0%)	0		747	13 (1.7%)	731 (97.9%)	3 (0.4%)	13/13 (100.0%)	0.3%/4859	
Mentha piperita oil (peppermint oil) 2%	140	0	139 (99.3%)	1 (0.7%)		748	9 (1.2%)	738 (98.7%)	1 (0.1%)	9/9 (100.0%)		0.6%/4859
Mercapto mix 1%	215	0	214 (99.5%)	1 (0.5%)		1971	7 (0.4%)	1957 (99.3%)	7 (0.4%)	7/7 (100.0%)	0.5%/2571	
Mercaptobenzothiazole 1%	215	0	214 (99.5%)	1 (0.5%)		1971	7 (0.4%)	1954 (99.1%)	10 (0.5%)	7/7 (100.0%)	0.7%/2573	0.5%/4859
Methyldibromo glutaronitrile/ phenoxyethanol 1%	54	0	53 (98.1%)	1 (1.9%)		391	10 (2.6%)	369 (94.4%)	12 (3.1%)	10/10 (100.0%)	6.2%/1121	
Mixed dialkyl thioureas 1%	215	0	214 (99.5%)	1 (0.5%)		1974	14 (0.7%)	1954 (99.0%)	6 (0.3%)	13/14 (92.9%)		1.0%/4859
Sodium-2-pyridinethiol-1-oxide 0.1% aq	90	0	90 (100.0%)	0		452	1 (0.2%)	451 (99.8%)	0	1/1 (100.0%)	0.9%/4859	0.9%/2539
Sorbic acid 2%	215	0	215 (100.0%)	0		1975	9 (0.5%)	1959 (99.2%)	7 (0.4%)	9/9 (100.0%)	0.6%/2573	
Sorbitan sesquioleate 20%	215	0	215 (100.0%)	0		1975	9 (0.5%)	1953 (98.9%)	13 (0.7%)	9/9 (100.0%)		0.7%/1689
Tea tree oil, oxidized 5%	215	0	215 (100.0%)	0		1973	48 (2.4%)	1916 (97.1%)	9 (0.5%)	47/48 (97.9%)	2.4%/1687	0.9%/4859
Triamcinolone acetonide 1%	214	0	214 (100.0%)	0		1966	1 (0.1%)	1961 (99.7%)	4 (0.2%)	1/1 (100.0%)	0.4%/2561	

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corticosteroids; meanwhile, the Group 3 corticosteroid desoximetasone elicited no positive reactions in ACD patients with or without eyelid involvement.

Although topical steroids did not appear in our top seven allergen groups, they remain of note in discussion, in light of their widespread use in ophthalmology and the literary gap on their paradoxical role as both potential ACD allergen and treatment for allergic conditions.[23] For patients with ACD involving the eyelids, a switch to Group 3 steroids may offer clinical benefit.

Topical steroids should not be overlooked in patch tests for eyelid dermatitis.[4,7]

Ocular Medications

Out of 365 patient products tested at Mayo Clinic from 2013 to 2017, only 12 elicited positive reaction rates, of which three were eye medications. Eye care providers often use a trial off of all eye medications to look for symptomatic improvement, or a unilateral trial of the suspected agent. Given that specific causal agents of patients' dermatitis within patient products (ie active versus inactive ingredients) cannot be ascertained, the ideal management of patients presenting with yet unexplained dermatitis involves patch testing of patients' own eye medications and close examination of ingredients to test true offenders not included in standard series.[13] For instance, BAK is still the most commonly used preservative in ophthalmic preparations, including tetracaine hydrochloride, timolol maleate solution, and brimonidine-timolol combination drops, and it may be the underlying culprit responsible for the positive reactions to these patient products seen in this study.

Metals

Given the relatively high reaction rates to nickel, cobalt, gold, and chrome found in this study, it is advisable to counsel patients with eyelid dermatitis to optimally avoid costume jewelry, nickel in eyewear (sunglasses or prescription glasses), gold- and chrome-containing cosmetics, nail lacquers, and some skin cleansers and moisturizers, facilitated by the use of an allergen avoidance database.

Nickel and Cobalt

Nickel has been found in certain makeup products (eg eye shadow, mascara), which may explain the greater incidence of reported nickel sensitivity in female patients.[4,9,27] Multiple studies across the past decade have found nickel to be among the most common contact allergens, if not the most common.[9,26,28] A few reports have noted ACD-inducing nickel found in eyelash curlers.[4,29] Therefore, avoidance of eyelash curlers may also be advisable, because of the potential allergenic composition of their metal frames. Additionally, cobalt exposure has been noted to correlate with nickel exposure.[4,27] Although nickel is generally not used in contemporary cosmetics, modified cobalt (eg cyanocobalamin and amine cobalt salt) is occasionally used in cosmetics and household products.

Gold

Sensitivity of many individuals to gold as a contact allergen has been well established in dermatologic literature (though not as widely reported in the ophthalmic literature), and the American Contact Dermatitis Society (ACDS) previously nicknamed it the "allergen of the year."[4,11,16,30] Indeed, in the NACDG 2003–2004 study, gold was the most common contact allergen responsible for causing dermatitis limited to the eyelids.[30] Skincare products known to contain gold include eye shadow, mascara, foundations, moisturizers, and eye masks. Outside of the presence of gold in these products or the occasional patient who develops a red rash under gold jewelry, the high rate of gold allergy is often of uncertain clinical significance. A one month trial off of gold jewelry is best reserved for patients with a history of a rash under gold jewelry.

Chrome

Lastly, the role of chrome in eyelid dermatitis has not been emphasized as a potential eyelid allergen and therefore represents an important finding in our study. Although potassium dichromate was not found in the top 15 contact allergens in the NACDG 2013–2014 study, it was found in those for the MCCDG 2011–2015 study.[20,26] Of note, 1422 skincare products active in the online allergen avoidance program SkinSAFE (out of 48,017 total products as of April 27, 2020) contain a version of chromates (eg chromium oxide green), used for green hue in numerous makeup products. Potassium dichromate is also used in many household products, eg glues, leather, and polishes.[20]

Shellac

Products that contain shellac or shellac wax (used as a tackifier in eye makeup products) include mascara, lipstick, and adhesive tooth whitening strips. Shellac, derived from lac beetle secretions, is included in neither the NACDG 2013–2014 Standard Series nor the ACDS 2017 allergen

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Table 5 Products on the Market Containing Thimerosal

Product Name	Manufacturer
Cortisporin Ophthalmic Suspension (RX) 7.5 mL	Monarch Pharmaceuticals
Neomycin Sulfate/Polymyxin B Sulfate/ Hydrocortisone Otic Suspension (RX) 10 mL	Sandoz
Neosporin Ophthalmic Solution Sterile (RX) 10 mL	Monarch Pharmaceuticals
Ocufen 0.03% Ophthalmic Solution (RX) 2.5 mL	Allergan
Poly-Pred Ophthalmic Suspension (RX) 5 mL	Allergan
Viroptic 1% Ophthalmic Solution (RX) 7.5 mL	Monarch Pharmaceuticals

Note: SkinSAFE database query on February 6, 2021.

panels.[31] Given its high reaction rate in our data (16.4%), shellac is important to note for eyelid dermatitis patients.

Preservatives

In the MCCDG 2011–2015 study, the 15 most common allergens included the preservatives methyldibromo glutaronitrile and BAK.[20] In this current study, BAK (found in skincare products, prescription and over-the-counter eye preparations) was also included in the 15 most common eyelid ACD allergens; meanwhile, methyldibromo glutaronitrile was included in those for ACD patients without eyelid involvement.

Thimerosal, known for inhibition of bacterial growth in ophthalmic solutions, has developed a reputation as a problematic contact allergen, noted as early as 1988.[9,32] It is now rarely used in vaccines, eye drop medications, or cleansing products for contact lenses; within the Environmental Working Group personal care product database as of April 27, 2020, only eight products included thimerosal, all of which were labeled "old formulation." Table 5 displays products on the market that contain thimerosal, according to the SkinSAFE database as of February 6, 2021.

Another preservative increasingly reported to elicit positive allergic reactions is methylisothiazolinone (MI), found in hair products, lotions, and shampoos.[9,13,20,26] In fact, both MI and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) ranked in the 15 most common contact allergens in this study, for populations both with and without eyelid involvement.

Manufacturers moving away from thimerosal and MI will often shift to BAK (or its derivatives), which also has emerging prevalence as a contact allergen, as seen in this study.[20] Like thimerosal, it has been employed in ophthalmic products for its antimicrobial properties.[8,20,32] BAK has been studied and described as "more toxic" than thimerosal, but its presence (or one of its cross-reactors) has been noted in a significant number of products, including many eye prescription and over-the-counter drops, cosmetics, hand sanitizers, deodorants, detergents, shampoos, and liquid soaps.[7,8,20]

Topical Antibiotics

Eye care providers are well aware of known allergic reactions to antibiotics neomycin and bacitracin, which are inexpensive and commonly used in eye medications. Use of these products should be avoided in patients with eyelid ACD.[4]

Fragrances

The fragrances in our top 15 most common contact allergens for eyelid dermatitis are (in order of descending positivity) Myroxylon pereirae resin, also known as balsam of Peru; propolis, also known as bee glue; and hydroperoxides of linalool (which imparts the aroma of lavender). Fragrances have a significant amount of cross-reactivity and are found in a wide variety of consumer products including soaps, shampoos, perfumes, and cosmetics (eg eye makeup).

Acrylates

Hydroxyethyl methacrylate (HEMA) was one acrylate in our 15 most common eyelid ACD allergens. Especially in recent years, HEMA has been noted as an allergen of rising prominence; the NACDG 2013–2014 study found a statistically significant increase in its positive reaction rate, compared to both its rate in the past two reporting periods and the pooled rate from the prior 6 years.[26] HEMA and other acrylates, as components of nail polish, artificial and gel nails, are known contributors to eyelid dermatitis (due to allergen transfer to the eyelid), sometimes also presenting with characteristic nailbed erythema representing periungual dermatitis.[4,8] Eliciting a history of artificial nail application and discussing discontinuation of this product as appropriate may be helpful for ACD patients.

Some acrylates, such as polymethyl methacrylate found in intraocular lenses and fluorosilicone acrylates in rigid contact lenses, are known to be well tolerated by the eye. For patients allergic to acrylates, it is important to clarify that although contact lenses are made of acrylates,

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they are made of "cured" (polymerized) acrylates, and therefore do not pose a risk of contact allergy.

Surfactants

Surfactants such as oleamidopropyl dimethylamine and amidoamine can be found in products such as tear-free, baby shampoos used for seborrheic blepharitis. Cocamidopropyl betaine, another surfactant, can be found in liquid soaps, shampoos, and eyelid hygiene products, which may be frequently used in ophthalmology clinics.[21,33] Although less well recognized, cocamide diethanolamine, derived from coconut oil with diethanolamine, has also been reported to cause eyelid dermatitis.[34] The role of these allergens in ACD has been well established in dermatologic journals since the 1980s, but not yet so in ophthalmologic journals.[21,33]

Eyelid ACD Management

Accurate identification and proper avoidance of problematic allergens offers the most straightforward, effective cure for eyelid ACD, as continued rubbing and itching can worsen symptoms.[1,2,17–19] Patch testing is widely regarded as the ACD gold standard, but is not always readily available.[17–19] Even without it, patients can be instructed to access free, online allergen avoidance programs to find safe products, such as SkinSAFE [www.SkinSafeProducts.com] and the Contact Allergen Management Program (CAMP) [www.ContactDerm.org]. Specifically, health care providers can enter the top seven allergen groups into CAMP (with ACDS member registration), or patients can browse SkinSAFE "EyelidSAFE" products, to choose products (both prescription and over-the-counter) free of these ACD triggers.

From an eye care provider's prescribing perspective, ophthalmic products can contain three common categories of allergens: preservatives, antibiotics, and topical steroids. Therefore, empiric common allergen avoidance therapy includes prescription of ophthalmic products 1) free of the preservative BAK; 2) free of aminoglycoside antibiotics (neomycin, gentamycin, tobramycin) and bacitracin; and 3) although less commonly a source for contact allergy, free of steroids such as prednisolone, loteprednol, and fluorometholone, with preference for dexamethasone or rimexolone. From a cutaneous therapy perspective, cold compresses, antihistamines, and topical corticosteroids (such as dexamethasone, given its low rate of allergy) can be employed to reduce patient discomfort and, in the case of topical corticosteroids, expedite resolution of acute inflammation.[1,4,6,16,35] When using topical ophthalmic or cutaneous eyelid corticosteroids, the lowest-dose, shortest course is recommended, given the potential for steroid addiction and side effects. Long-term use can result in eyelid skin atrophy, cataracts, glaucoma, tachyphylaxis, or even flaring erythema, so eye examinations and intraocular pressure monitoring are needed.[1,6,36] Local compounding pharmacies can make preservative-free dexamethasone and other ophthalmic medications to assist patients reacting to commercially prepared drops with BAK. If patients continue to flare upon tapering topical steroids, despite empiric top common allergen avoidance, chronic topical immunosuppressive options to be considered include steroid-sparing calcineurin inhibitors (eg tacrolimus and pimecrolimus) and the novel non-steroidal anti-inflammatory phosphodiesterase-4 inhibitor crisaborole.[37–39] For eyelids, tacrolimus is the calcineurin inhibitor of choice, as pimecrolimus is currently only available as a cream containing the moderately frequent contact allergen propylene glycol. Of note, crisaborole (Eucrisa) also contains propylene glycol. Additionally, if a patient requires chronic topical immunosuppression, patch testing should be considered.

Nonetheless, this study's findings and recommendations may be limited in the following ways: its retrospective nature precludes an evaluation for the efficacy of empiric avoidance of the top seven allergen groups; it does not address allergic conjunctivitis and dry eye syndrome (which can manifest as contact dermatitis); and its relatively small sample of 215 patients with periorbital dermatitis, patch tested at Mayo Clinic from 2013 to 2017, mostly comprised Caucasian and female patients, who are not fully representative of general patient populations. Finally, these top allergen groups discussed are not exhaustive, and are subject to change as products evolve and patients develop new sensitivities.

Conclusions

The top seven most common allergen groups involved in eyelid ACD are metals, shellac, preservatives (eg, BAK), topical antibiotics (eg, aminoglycosides and bacitracin), fragrances, acrylates, and surfactants (eg, cocamidopropyl betaine). This finding is in line with previous studies, which identify topical eye medications, cosmetics, hair products, preservatives, antibiotics, nail products, and facial skincare products as eyelid ACD triggers.[6–8,12,16,22]

Interpreting patient product labels with the most common contact allergens is not straightforward, primarily

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owing to the complexity of ingredient names, synonyms, or allergenic cross-reactors. Moreover, cosmetic product labeling does not require Food and Drug Administration (FDA) premarket approval; companies are responsible for ensuring compliance with all FDA labeling requirements. Online allergen avoidance programs save time that might otherwise be spent manually searching product labeling for specific allergen-free brands. These programs support patient empowerment and self-sufficiency on the journey to avoid common offending allergens and prevent ACD recurrence.

Ophthalmologists and optometrists are the first-line providers to evaluate and treat eyelid ACD. Sometimes patient use of a product over the entire body may manifest only as eyelid dermatitis. Understanding ACD diagnostic and treatment strategies is important for the improvement of patient outcomes. When simple product avoidance fails to alleviate ACD, patch testing to identify allergenic ingredients is recommended, in conjunction with online databases for safe products free of these problematic agents. For patients without access to patch testing, education about the top seven allergen groups and avoidance of products with these ingredients can be helpful. We acknowledge that empiric avoidance of all top common allergens may represent a clinical burden, and we therefore recommend avoidance only if clinical suspicion of contact dermatitis is high. Lastly, for patients suspected of allergy to the most commonly used topical steroid eye drops, providers should choose Group 3 steroids, such as dexamethasone or rimexolone, or even preservative-free compounded dexamethasone.

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