

Diagnosis and Prevalence of Lanolin Allergy

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Background: Current evaluation of suspected allergic contact dermatitis to lanolin includes patch testing to lanolin alcohol (30% in petrolatum). Using this method, the prevalence of lanolin allergy is low (1.8%–2.5%).

Objective: The objective of this study was to determine whether patch testing to a single lanolin derivative results in underdiagnosis compared with patch testing to 12 lanolin derivatives.

Methods: Patients were prospectively patch tested to (1) lanolin alcohol (30% in petrolatum) in our standard allergen series; (2) Amerchol L101 (50% in petrolatum) in our cosmetic series; and (3) 10 lanolin derivatives (using concentrations and vehicles recommended in the literature) in a supplemental series.

Results: Of 286 patients, the overall prevalence of positive reactions to lanolin in at least 1 of the 3 patch test series was 6.29% (95% confidence interval [CI], 3.48%–9.11%) ($n = 18$). The prevalence rates of lanolin allergy using the standard, cosmetic, and supplemental series were 1.05% (95% CI, 0%–2.23%), 3.85% (95% CI, 1.62%–6.07%), and 3.85% (95% CI, 1.62%–6.07%), respectively. Amerchol L101 was associated with increased reaction rates compared with the standard (odds ratio, 3.81; $P = 0.007$) and supplemental (odds ratio, 8.85; $P < 0.001$) series, whereas reaction rates were similar for the standard and supplemental series ($P = 0.78$).

Conclusions: Amerchol L101 and patients' own products should be added to a standard patch testing allergen series to adequately identify lanolin allergy.

LANOLIN IS a natural substance derived from the sebaceous glands of sheep.¹ Known for its emollient properties, lanolin is widely used in personal care products and as a vehicle for topical therapeutic agents. The role of lanolin and its derivatives in allergic contact dermatitis has been debated for many years.^{2–7}

Several factors affect the assessment of the frequency of lanolin sensitivity. Lanolin is a mixture of esters and polyesters of high-molecular-weight alcohols and acids,^{1,4,8,9} and its composition can vary on the basis of many factors, including sheep breed and habitat. In addition, several lanolin derivatives exist, each with a separate process of extraction and modification. Varying concentrations of lanolin, the vehicles used, and the age of products

used in patch testing also contribute to the difficulty in identifying the constituents responsible for allergy to lanolin.

Patch testing is the primary diagnostic tool used to identify allergens that cause allergic contact dermatitis. Previous studies suggest that the alcoholic fraction of lanolin may be responsible for allergy to lanolin.^{9–16} Thus, the current evaluation of patients suspected to have contact allergy in North America typically includes testing to lanolin alcohol (30% in petrolatum). The most recent and large studies performed by the North American Contact Dermatitis Group and the Mayo Clinic Contact Dermatitis Group show reaction rates of 2.5% and 1.8%, respectively, for lanolin alcohol (30% in petrolatum).^{17,18} However, the exact frequency of adverse reactions to lanolin in the general population is difficult to assess because most individuals with such reactions simply discontinue use of the suspected trigger and seldom consult physicians.¹⁹ In addition, proponents of lanolin as a relevant allergen suspect that contact allergy to lanolin is underdiagnosed because clinicians are not testing with the appropriate type or number of lanolin derivatives. Supported by recent literature,^{2,20,21} this hypothesis is part of the “lanolin paradox.”

Adapted from Fisher's²² “paraben paradox,” the lanolin paradox⁶ describes 4 characteristics of lanolin that contribute to the difficulty in determining its relevance as an allergen. First, lanolin-containing topical medicaments tend to be more sensitizing than lanolin-containing cosmetics. Second, patients with allergic contact dermatitis after applying lanolin-containing topical medicaments to

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damaged or ulcerated skin often can apply lanolin-containing cosmetics to normal or unaffected skin without difficulty. Third, false-negative patch test results often occur in lanolin-sensitive patients. Fourth, patch testing with a single lanolin-containing agent (lanolin alcohol [30% in petrolatum]) is an unreliable and inadequate method of detecting lanolin allergy.

To address the fourth lanolin paradox, we aimed to better define lanolin contact allergy reaction rates and optimal derivatives for patch testing by performing patch testing with 12 lanolin derivatives.

METHODS

Patients

After approval by the Mayo Clinic Institutional Review Board, we conducted a prospective study from January 1, 2009, through December 31, 2011, by recruiting patients referred for patch testing as part of their dermatologic care. Patients did not undergo patch testing if topical corticosteroids were applied to test sites, if immunosuppressive therapy (eg, oral corticosteroids) was administered, or if concurrent medical conditions could affect evaluation of patch test results.^{23,24} Information regarding patient characteristics and the results of patch testing were abstracted from the clinical database. Patients who denied research authorization were excluded from the analysis.

Patch Testing and Interpretation of Results

All patients in the study were patch tested to a minimum of the standard allergen series used at our institution (includes lanolin alcohol [30% in petrolatum]), hydrogenated lanolin Amerchol L101 (50% in petrolatum) included in the cosmetic allergen series used at our institution, and a supplemental series of 10 lanolin derivatives. Lanolin alcohol (30% in petrolatum) and Amerchol L101 (50% in petrolatum) were obtained from Chemotechnique (Vellinge, Sweden). Derivatives in the supplemental series were obtained from Estée Lauder (New York, NY); they were compounded in the Mayo Clinic Pharmacy (Scottsdale, AZ) and applied in concentrations and vehicles recommended in the literature.²⁵

The patch testing method was the same as previously described^{23,26} and was consistent with the previously reported method of the North American Contact Dermatitis Group.^{24,27,28} Testing was conducted with Finn chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Vennesla, Norway), and patches were applied to the patient's upper back and removed after 48 hours. Reactions were evaluated initially at 48 to 72 hours and again at 96 to 168 hours after patch application. Final patch test reading, interpretation of results, and assessment of relevancy were performed by the ordering physician (staff and supervised resident physicians). Patch-test reactions were interpreted with the following criteria: negative reaction, macular erythema, weak reaction (nonvesicular erythema, infiltration, and

possibly papules), strong reaction (edematous or vesicular lesions), extreme reaction (spreading, bullous, ulcerative lesions), and irritant reaction. Reactions were further interpreted as relevant or irrelevant on the basis of a history of either known contact with substances containing the allergen or a history of circumstances of likely contact with substances containing the allergen. Each reaction was recorded as follows: I, irritant; N, allergic, not relevant (no exposure to products that contain the allergen); Q, allergic, questionably relevant (current exposure to products likely to contain the allergen); P, allergic, formerly relevant (past exposure to products likely to contain the allergen); and R, allergic, relevant (use test or patch test with the product containing the allergen is positive, or ingredient verified in patient's product and use of that product is verified). For this study, a positive allergic patch test result was defined as a weak, strong, or extreme reaction at the last reading, or as a macular erythema reaction if the result was relevant after irritant reactions had been excluded. Past, questionable, and currently relevant reactions were included as positive.

Sample Size Calculation

Before patient recruitment, we determined that 300 subjects would provide 80% power to detect a difference of 3% between the proportion classified as allergic with the standard testing method (1%), and the proportion classified as allergic using 10 supplemental lanolin derivatives (4%), assuming that 4% of patients would have discordant results between the 2 methods. If the true proportion of subjects with lanolin allergy (using all testing concentrations) was 4%, we expected a 95% confidence interval (CI) of 1.8% to 6.2%.

Statistical Analysis

Patient data were entered into a clinical database. Patient characteristics were summarized by mean (SD) for continuous variables and by frequency and percentage for nominal variables. The reaction was considered a dichotomous variable (positive or negative). The percentage of positive reactions and corresponding 95% CIs were computed. Because each patient underwent multiple testing episodes, the assumption of independence of each record in logistic regression did not hold when examining factors associated with lanolin allergy and when comparing the positive reaction rates between the different series. Hence, generalized estimating equations with logit link were applied.

To evaluate risk factors associated with lanolin allergy, a univariate analysis was performed for the following potential risk factors: age (<40 or ≥40 years), asthma, race, and sex. Because we were comparing test results, the type of series was included. If a variable had a $P < 0.05$, it was included in the model selection procedure. Backward elimination was used to select the best set of risk factors. In the final model, the adjusted odds ratios (ORs), 95% CI, and P value were reported. $P < 0.05$ was considered statistically significant. For multiple comparisons of the different test series,

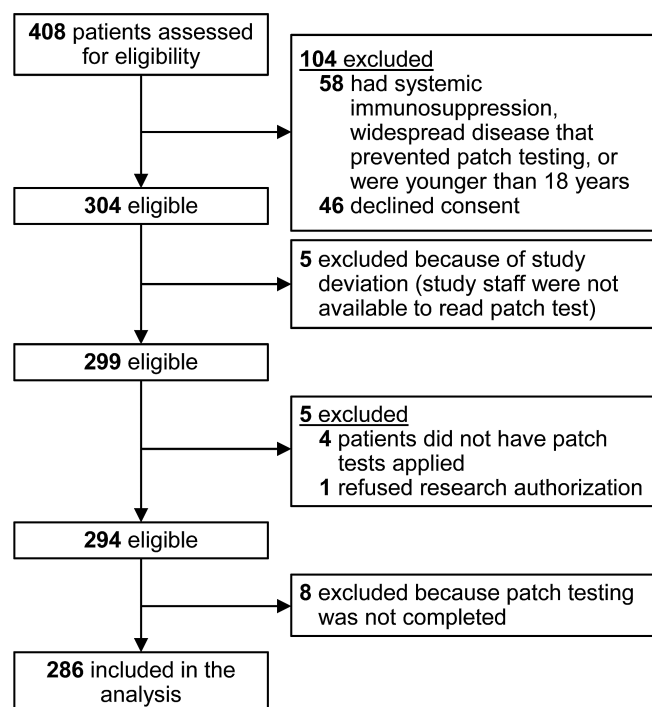


Figure 1. Patient accrual and analysis.

the significance level was adjusted to 0.017 so that the familywise type I error rate was 0.05. All analyses were performed with SAS 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Figure 1 depicts the process used to identify the 286 patients in our study. Patient characteristics are shown in Table 1.

The reaction rate for lanolin alcohol (30% in petrolatum) in the standard series was 1.05% (95% CI, 0%–2.23%). The reaction rate for Amerchol L101 (50% in petrolatum) was 3.85% (95% CI, 1.62%–6.07%). The overall reaction rate for the supplemental series (10 lanolin derivatives) was 3.85% (95% CI, 1.62%–6.07%). The overall prevalence of positivity to lanolin in the study population was 6.29% (95% CI, 3.48%–9.11%); that is, 18 patients had a positive reaction to at least 1 of the 3 patch test series (standard + cosmetic + supplemental series). Reaction rates for individual agents are shown in Table 2. The strength and relevance of positive reactions are shown in Table 3.

We noted discordant positivity to lanolin alcohol (30% in petrolatum) when comparing the standard series with the supplemental series. Three (1.05%) of 286 patients had positive reactions to lanolin alcohol (30% in petrolatum) and Amerchol L101 (50% in petrolatum) (both agents manufactured by Chemotechnique), but none of these patients had a positive reaction to lanolin alcohol (30% in petrolatum) in the supplemental series (manufactured by Estée Lauder). Furthermore, none of the 6 patients with positive reactions to lanolin alcohol (30% in petrolatum) in the supplemental series was positive to the analogous agent in the standard series.

Diagnostic Yield and Risk Factors for Lanolin Allergy

Overall, 18 patients (6.29%) had positive reactions with at least 1 of 3 patch test series. Of these, 2 patients had positive reactions to 3 lanolin compounds, 5 had positive reactions to 2 compounds, and 11 had a positive reaction to 1 compound. Eleven (61.11%) of 18 patients reacted to the lanolin derivative in either the standard or cosmetic series. However, 7 patients reacted only to lanolin derivatives in the supplemental series, meaning that 38.89% of patients with lanolin allergy would not have been identified if they had undergone patch testing only with the standard and cosmetic series. The possible risk factors considered were age, asthma, race, and sex. From the univariate analysis, sex was the only significant variable and was considered in the multivariate model. The final model included type of test and sex. After adjusting for the type of patch test series, females were more likely than males to have a positive reaction (OR, 4.98; 95% CI, 1.41–17.61; $P = 0.01$). When controlling for sex, patch testing with Amerchol L101 (50% in petrolatum) was associated with increased reaction rates compared with either the standard series (lanolin alcohol [30% in petrolatum]; OR, 3.81; 95% CI, 1.43–10.11; $P = 0.007$) or the supplemental series (OR, 8.85; 95% CI, 4.38–17.88; $P < 0.001$). The difference in reaction rates between the standard series and the supplemental series was not significant ($P = 0.78$).

DISCUSSION

Prevalence of Lanolin Allergy

According to the fourth lanolin paradox, patch testing with a single lanolin compound (lanolin alcohol [30% in petrolatum]) may be inadequate to reliably detect lanolin allergy. In our cohort, the prevalence of positive reactions to lanolin alcohol (30% in petrolatum) using the Mayo Clinic standard series was consistent with previously reported reaction rates.^{17,18} Interestingly, our results showed that lanolin reaction rates increased (from 1.05% to 6.29%) when multiple lanolin derivatives were tested. The supplemental series had a higher positive reaction rate than the standard series, but the difference was not significant ($P = 0.78$). However, Amerchol L101 (50% in petrolatum) in the Mayo Clinic

TABLE 1. Patient Characteristics (N = 286)

Characteristic	Value
Race, no. (%)	
White	258 (90.21)
Other	28 (9.79)
Male, no. (%)	105 (36.71)
History of asthma, no. (%)	50 (17.48)
Age, y	
Mean (SD)	60.51 (15.84)
Median	62.79
Range	20.60–91.39
Interquartile range	50.94–72.58
Age ≥ 40 y, no. (%)	251 (87.76)

TABLE 2. Reaction Rates for Lanolin Derivatives (N = 286)

Lanolin Derivative*	Reaction Rate†	
	No. (%)	95% CI
Lanolin alcohol (30% in petrolatum), standard series	3 (1.05)	0%–2.23%
Amerchol L101 (50% in petrolatum), cosmetic series	11 (3.85)	1.62%–6.07%
Supplemental series	11 (3.85)	1.62%–6.07%
Lanolin alcohol (30% in petrolatum)	6 (2.10)	—
Lanolin wax glyceride (30% in petrolatum)	3 (1.05)	—
Lanolin acid (5% in petrolatum)	2 (0.70)	—
Lanolin oil (30% in petrolatum)	1 (0.35)	—
Cetyl acetate and acetylated lanolin alcohol (30% in petrolatum)	1 (0.35)	—
Acetylated lanolin alcohol and cetyl acetate (30% in petrolatum)	0 (0)	—
Hydrogenated lanolin (30% in petrolatum)	0 (0)	—
Hydroxylated lanolin (30% in petrolatum)	0 (0)	—
Lanolin wax (30% in mineral oil)	0 (0)	—
Lanolin (pure)	0 (0)	—

*Agents in the standard and cosmetic series were obtained from Chemotechnique. Agents in the supplemental series were obtained from Estée Lauder.

†Overall, 18 patients (6.29%) had positive patch test reactions to lanolin derivatives (standard + cosmetic + supplemental series).

cosmetic series was more likely to show positivity compared with either the supplemental series or the lanolin alcohol (30% in petrolatum) from the standard series, suggesting that this specific lanolin derivative markedly affected our ability to detect lanolin allergy. The utility of testing to Amerchol L101 (50% in petrolatum) has been reported previously²⁹ and is gaining acceptance in the dermatology community, as evidenced by the 2011 modification of the British Contact Dermatitis Society baseline series to include Amerchol L101 (50% in petrolatum). Although the

prevalence of lanolin allergy remains relatively low with the current standard allergen, we predict that as patch testing to Amerchol L101 (50% in petrolatum) becomes more common, the prevalence of lanolin allergy will increase as a consequence of improved testing sensitivity.

Allergens in Lanolin

Consistent with past studies,^{9–15} the highest reaction rates in our study occurred with lanolin alcohol derivatives, which suggests that the alcoholic fraction may be the component causing the allergic reaction. In addition, our results indicate that lanolin allergy is dependent on not only the derivative of lanolin but also the manufacturer. In our study, lanolin alcohol (30% in petrolatum) in the supplemental series was obtained from Estée Lauder and had been stored in our clinic for several years, whereas the lanolin alcohol used in the standard series was obtained from Chemotechnique and had been purchased more recently. The lanolin alcohol in the supplemental series had twice the reaction rate compared with that in the standard series, and patients with positive reactions to lanolin alcohol in one series did not react to the lanolin alcohol in the other. A previous report suggested that oxidative products in aged lanolin may have a role in allergic response,³⁰ and this would be consistent with the increased reaction rates we observed with the older product used in the supplemental series.

These results highlight the complexity of lanolin as an allergen and motivate additional studies to better elucidate the contributions of the multiple components present in lanolin-containing products. Furthermore, our findings suggest that the age and source of lanolin-containing product may affect allergenicity, highlighting the potential benefit of patch testing to the patient's own products.

Lanolin in Consumer Products

Our institution has developed a contact allergen database that now has information on more than 5000 topical skin care

TABLE 3. Strength and Relevance of Positive Patch Test Reactions

Lanolin Derivative	Strength of Patch Test Reaction*			Relevance of Patch Test Reaction				
	Macular Erythema	Weak Reaction	Strong Reaction	I	N	Q	P	R
Lanolin alcohol (30% in petrolatum), standard series	3	—	—	0	0	0	2	1
Amerchol L101 (50% in petrolatum), cosmetic series	8	3	—	0	1	0	7	3
Supplemental series								
Lanolin oil (30% in petrolatum)	—	1	—	0	0	1	0	0
Lanolin wax glyceride (30% in petrolatum)	2	—	1	0	1	0	0	2
Cetyl acetate/acetylated lanolin alcohol (30% in petrolatum)	1	—	—	0	0	0	0	1
Lanolin alcohol (30% in petrolatum)	3	3	—	0	0	2	2	2
Lanolin acid (5% in petrolatum)	2	—	—	0	0	0	1	1

*No extreme reactions were observed.

I indicates irritant; N, not allergic; P, allergic, formerly relevant; Q, allergic, questionable relevance; R, allergic, currently relevant.

products and their ingredients.^{31–33} As of the spring of 2012, this database included 618 lanolin-containing products; of these, only 169 (27.3%) declared lanolin alcohol in the list of ingredients. Thus, the majority of consumer products do not contain the lanolin derivative that is currently used in the patch-testing standard of care for suspected lanolin allergy. This would seem to support the potential importance of using the patient's personal products during patch testing.

The prevalence of lanolin in complex commercial formulations allows for the possibility that other common allergens in these products are leading to overrepresentation of lanolin as a clinically significant contact allergen. However, less than 5% of the lanolin-containing products in the contact allergen database contain fragrance or formaldehyde-related allergens. This supports lanolin's role as an offending contact allergen in the products included in the contact allergen database.

CONCLUSIONS

We report an increased reaction rate to lanolin when multiple lanolin derivatives were used for patch testing. Importantly, we observed that Amerchol L101 (50% in petrolatum) was more likely to demonstrate lanolin allergy than an expanded supplemental series of lanolin derivatives or the current standard, lanolin alcohol (30% in petrolatum). We propose that using 2 forms of lanolin (lanolin alcohol [30% in petrolatum] and Amerchol L101 [50% in petrolatum]) in a standard allergen series will improve identification of lanolin-allergic patients. However, because many consumer products with lanolin contain a derivative other than lanolin alcohol, patch testing using the patient's own products may be necessary to better identify patients with true lanolin allergy.

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