

Clinical Utilization of Repeated Open Application Test Among American Contact Dermatitis Society Members

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Background: The repeated open application test (ROAT) provides useful information regarding allergens in suspected cases of allergic contact dermatitis; however, standardized methodology has not been established.

Objective: The aim of this study was to assess how ROAT is used in clinical and research settings.

Methods: We distributed a survey regarding ROAT practice to the American Contact Dermatitis Society and conducted a literature review of ROAT utilization in research.

Results: A total of 67 American Contact Dermatitis Society members participated in the survey. Respondents most frequently recommend application of leave-on products twice daily (46.0%) and rinse-off products once daily (43.5%). The most commonly used anatomical sites include the forearm (38.7%) and antecubital fossa (32.3%). Most respondents continue ROAT for 1 (49.2%) or 2 weeks (31.7%). Literature review of 32 studies (26 leave-on, 6 rinse-off) revealed that application frequency is most common at twice daily for both leave-on (96.2%) and rinse-off (50.0%) products. The most common anatomical site is the forearm (62.5%), with an overall study duration of 3 to 4 weeks (65.6%).

Conclusions: When comparing ROAT clinical and research practice, the majority trend was consistent for leave-on product application frequency and anatomical site, but not for rinse-off product application frequency, or overall duration. Further research is needed to determine best practice recommendations.

Allergic contact dermatitis (ACD) is characterized by cutaneous inflammation resulting from a delayed type 4 hypersensitivity reaction against an allergen in a previously sensitized individual. Contact allergy is common among the general population, with an estimated prevalence of 19.5%.¹ Although the history and physical examination often provide enough information to render a probable diagnosis of ACD, it is difficult for even experts to accurately identify the responsible allergen with this limited knowledge.²

The patch test is the criterion standard in the diagnostic approach to identify the allergen source in cases of suspected ACD. The most commonly used testing series include the TRUE (Thin-Layer Rapid Use Epicutaneous) test and the NACDG (North American Contact Dermatitis Group) standard series. Survey studies have shown that community dermatologists most commonly use the TRUE test,³ whereas most American Contact Dermatitis Society

(ACDS) members prefer the NACDG series.⁴ Although the development and refinement of patch testing has undoubtedly contributed to the advancement of the contact dermatitis subspecialty, there are technical factors and individual characteristics that confound patch testing and limit the interpretation and applicability of results. Factors that influence elicitation of a contact allergy include allergen concentration, frequency of exposures, occlusion, combination of allergens and irritants, anatomical site, and allergen oxidation.⁵ The allergen dose applied per unit area is an important factor in inducing and eliciting contact allergy.⁶ Although a patch test may detect a weak allergy, the reaction is not always clinically significant because the concentration of the allergen in the patch test is often much higher than the concentration in a retail product, which may also result in chemical irritation. Conversely, the combination of allergens in a product may result in a synergistic response,⁷ which may not be reflected in the single allergen exposure pattern of patch testing. Patch testing is generally conducted on the back, whereas the offending allergen may be in a product used on a different area of the body, which complicates the interpretation and applicability of a test result. Areas such as the face and axillae are at increased risk for sensitization due to the disrupted barrier as a result of shaving.⁸ Furthermore, substances that are generally innocuous may become relevant sources of ACD when oxidized.⁹

The repeated open application test (ROAT) is a practical adjuvant investigative measure to patch testing. Repeated open application test may identify a clinically relevant allergen by simulating an exposure

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pattern the patient is likely to experience with regular product use. In contrast to the patch test, ROAT evaluates 1 substance at a time without occlusion, which minimizes irritation and false-positive reactions. Repeated open application test may be used to determine whether a patient will react to a product containing an allergen that rendered a positive patch test. Furthermore, ROAT is useful in evaluating sensitization to an ingredient in home products that is not available in commercial patch tests. Although the ROAT provides valuable information in the diagnosis of ACD, the elicitation of a reaction depends on multiple factors that may be impacted by technical aspects of carrying out the test. Furthermore, there is variation in ROAT methodology and utilization within the dermatologic literature, and ROAT practice among experts in contact dermatitis is unknown.

The objective of this study was to assess the utilization of ROAT in clinical and research settings. To investigate the study objective, we surveyed ACDS members regarding ROAT practice and conducted a literature review of ROAT methodology in published clinical studies.

METHODS

We created a survey regarding ROAT using an online electronic poll Web site (www.surveymonkey.com). The survey contained 9 multiple-choice questions and 1 open-ended question that assessed various aspects of ROAT methodology (Table 1). In addition, most questions had a mechanism for participants to provide opinions and experiences regarding the use of testing. Survey responses were anonymous and did not contain any identifying information. The survey was distributed electronically to ACDS members between

TABLE 1. Survey Questions Distributed to ACDS Members

Item Number	Survey Item
1	What volume of patients do you patch test?
2	What volume of patients do you recommend utilize a use test?
3	How frequently do you instruct the patient to apply a leave-on product?
4	Do you recommend occlusion (with gauze and paper tape or a band aid for example) for leave-on products?
5	How frequently do you instruct the patient to apply a rinse-off product?
6	How long do you instruct the patient to apply the rinse-off product before washing off?
7	How long do you instruct the patient to continue the use test (if there is no reaction)?
8	How does the patient provide feedback (check all that apply)?
9	What location of the body do you instruct the patient to apply the product?
10	Please share your personal experience or thoughts regarding the use test.

TABLE 2. Results of Survey Distributed to ACDS Members

Question	Response	Respondents, n (%)
No. patients undergoing patch testing	1–2 per mo	9 (13.6)
	1–2 per wk	19 (28.8)
	3–6 per wk	24 (36.4)
	>6 per wk	11 (16.7)
	Other	3 (4.5)
	Total respondents	66
No. patients undergoing ROAT	1–2 per y	6 (9.2)
	1–2 per mo	29 (44.6)
	1–2 per wk	21 (32.3)
	3–6 per wk	4 (6.2)
	>6 per wk	1 (1.5)
	Other	4 (6.2)
Exposure frequency (leave-on product)	Total respondents	65
	Once daily	22 (34.9)
	Twice daily	29 (46)
	A few times per wk	5 (7.9)
	Once per wk	2 (3.2)
	Other	5 (7.9)
Occlusion recommended (leave-on product)	Total respondents	63
	Yes	10 (15.1)
	No	56 (84.9)
	Total respondents	66
Exposure frequency (rinse-off product)	Once daily	27 (43.5)
	Twice daily	11 (17.7)
	A few times per wk	2 (3.2)
	Once per wk	4 (6.5)
	Other	18 (29)
	Total respondents	62
Length of exposure (rinse-off products)	5 min or less	29 (46.7)
	30 min or less	12 (19.4)
	1–2 h	0 (0)
	2–12 h	3 (4.8)
	Do not wash off	4 (6.5)
	Do not recommend	12 (19.4)
Test length	Other	2 (3.2)
	Total respondents	62
	1 wk	31 (49.2)
	2 wk	20 (31.7)
	3 wk	0 (0)
	4 wk	7 (11.1)
Feedback mechanism	Other	5 (7.9)
	Total respondents	63
	By describing results at next visit	47 (74.6)
	By describing results over the phone	29 (46)
	By describing results via e-mail	16 (25.4)
	By taking photographs	22 (34.9)
	Total respondents	63

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TABLE 2. (Continued)

Question	Response	Respondents, n (%)
Anatomical location	Forearm	24 (38.7)
	Upper inner arm	14 (22.6)
	Antecubital fossa	20 (32.3)
	Other	4 (6.5)
	Total respondents	62

June 2014 and August 2014. To supplement the results of the survey, we conducted a literature review of ROAT methodology on PubMed from January 1986 to December 2014 to identify studies that used ROAT in patients with ACD.

RESULTS

Respondents

We solicited participation from all ACDS members. Of the 816 ACDS members who were contacted to participate in the survey, 67 responded to the survey with 62 respondents completing the survey in its entirety. No demographic or identifying information was collected from survey participants. The results of the survey are represented in Table 2.

Clinical Utilization of Patch Testing and ROAT

American Contact Dermatitis Society members were asked about the volume of patients in which they use patch testing or ROAT in their practice. Over 80% of respondents reported administering patch tests multiple times per week (1–2 per week, 28.8% [19/66]; 3–6 per week, 36.4% [24/66]; >6 per week, 16.7% [11/66]). With regard to ROAT, 40.0% of respondents regularly recommend ROAT to at least 1 to 2 patients per week (1–2 per week, 32.3% [21/65]; 3–6 per week, 6.2% [4/65]; >6 per week, 1.5% [1/65]). A large proportion of participants (44.6%, 29/65) recommend ROAT on an average of 1 to 2 patients per month, with the remainder of respondents indicating less frequent ROAT utilization.

Recommended ROAT Methodology

The survey inquired ACDS members about specific aspects of ROAT procedures. For leave-on products, most patients are instructed to apply the product either once or twice daily (34.9% [22/63] and 46.0% [29/63], respectively). Most respondents do not recommend occlusion with leave-on products (84.9%, 56/66).

With regard to rinse-off products, 43.5% (27/62) of members instruct patients to apply the product once daily. However, many respondents (19.4%, 12/62) never instruct a patient to use ROAT with a rinse-off product. Of the 80.6% (50/62) of the ACDS members who do recommend ROAT for rinse-off products, patients are most often instructed to apply the product for 5 minutes

or less (58.0%, 29/50) or 30 minutes or less (24.0%, 12/50). The remainder of respondents recommends that the rinse-off product either remain on the skin for 2 to 12 hours before washing off (6.0%, 3/50) or for product to not be washed off at all (12.0%, 6/50).

Various anatomical sites on the upper extremity are recommended for ROAT, including the forearm (38.7%, 24/62), antecubital fossa (32.3%, 20/62), and upper inner arm (22.6%, 14/62).

Physicians were asked how long they advise patients to continue the ROAT if there is no cutaneous reaction. Most frequently, ACDS members instruct patients to continue ROAT for 1 or 2 weeks if there is no reaction (49.2% [32/63] and 31.7% [20/63], respectively), and rarely for 4 weeks (11.1%, 7/63). A small percentage of respondents recommended a much shorter overall ROAT duration of less than a week if there is no reaction (4.8%, 3/63).

Mechanisms of Obtaining Patient Feedback

American Contact Dermatitis Society members were asked to indicate how they receive feedback from patients regarding test results. Participants were given the opportunity to select multiple mechanisms if applicable. The most common approaches include describing results at next visit (74.6%, 47/63) and over the phone (46.0%, 29/63), followed by showing photographs (34.9%, 22/63) and e-mail correspondence (25.4%, 16/63).

Literature Review

A total of 32 studies in the literature that used ROAT were included in the literature review. There were 26 studies evaluating leave-on products and 6 studies investigating rinse-off products.

Most studies evaluating leave-on products required subjects to apply product twice daily (96.2%, 25/26), with only 1 study requiring once daily application (3.8%, 1/26). Of the studies evaluating rinse-off products, study participants most often applied product twice daily (50.0%, 3/6), with the remainder of studies applying products less frequently at once daily (33.3%, 2/6) or 3 times weekly (16.7%, 1/6). The duration of exposure for rinse-off products was at 5 minutes or less for all studies with an exception of one that set exposure duration at less than 30 minutes.

The anatomical site most commonly tested was the volar forearm (62.5%, 20/32), followed by the ventral upper arm (12.5%, 4/32) and antecubital fossa (9.4%, 3/32). Less commonly used anatomical sites included the axillae (6.3%, 2/32), dorsal upper arm (3.1%, 1/32), neck (3.1%, 1/32), and scalp (3.1%, 1/32).

For the overall duration of ROAT, most studies continued study procedures for at least 3 or 4 weeks (21.9% [7/32] and 43.8% [14/32], respectively). The remainder of studies continued ROAT for only 1 or 2 weeks (12.5% [4/32] and 18.8% [6/32], respectively). This trend was observed for both leave-on and rinse-off product studies.

DISCUSSION

The results of this study revealed that while a significant proportion of ACDS members regularly recommend ROAT to

TABLE 3. Summary of Majority Trends for ROAT Use Among Experts Compared With the Literature

	Expert Practice	Literature
Exposure frequency (leave-on products)	Twice daily	Twice daily
Exposure frequency (rinse-off products)	Once daily	Twice daily
Anatomical site	Volar forearm	Volar forearm
Overall ROAT duration	1–2 wk	3–4 wk

patients, it is not used as frequently as patch testing in clinical practice. There is variability in ROAT methodology among ACDS members with regard to the frequency of application, duration of exposure to potential allergen, anatomical site, and overall testing period duration. The expert practice majority trend was consistent with the literature for the frequency of application for leave-on products and anatomical site; however, variability existed for rinse-off product application frequency and overall duration of ROAT (Table 3). The majority of the literature supported a duration of 4 weeks, whereas the ACDS members recommended only a single-week duration in most cases. American Contact Dermatitis Society member feedback showed a great interest in learning about the ROAT practice conduct among other clinicians.

The exposure frequency for leave-on products was most common at twice daily both among ACDS members and in the dermatologic literature (Fig. 1). The number of exposures to an allergen has been shown to be one of the most important factors with regard to eliciting an allergic reaction. In a study with paraphenylenediamine (PPD), more frequent exposures to lower concentrations of allergen was found to be more sensitizing than fewer exposures to higher concentrations.¹⁰ Similarly, a study evaluating carbon-14–labeled PPD cutaneous accumulation in a rodent model found that thrice daily 5-minute topical application resulted in greater accumulation compared with a single 5-minute exposure.¹¹

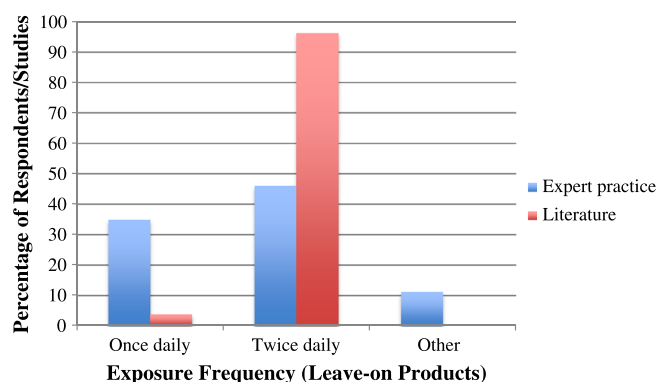


Figure 1. ROAT leave-on product exposure frequency among experts versus the literature. A comparison of ROAT leave-on product exposure frequency recommended by ACDS members (blue bars) and study methodology published in the literature (red bars).

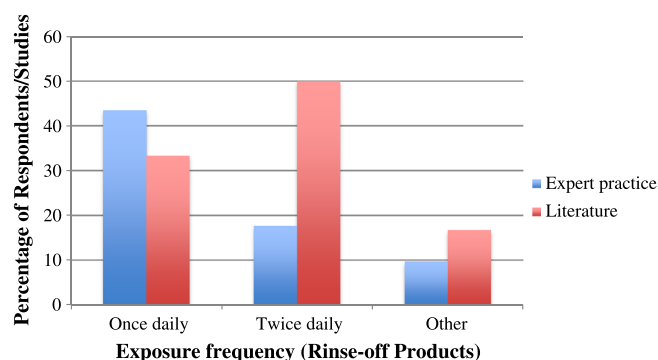


Figure 2. ROAT rinse-off product exposure frequency among experts versus the literature. A comparison of ROAT rinse-off product exposure frequency recommended by ACDS members (blue bars) and study methodology published in the literature (red bars).

With regard to the exposure duration for rinse-off products, there was more variability among ACDS members compared with the literature. Most survey respondents recommend rinse-off product application once daily in contrast to the more frequent twice daily application in the literature (Fig. 2). The length of time that the subject is exposed to the allergen greatly affects the results of the test. In a study of PPD and various exposure times, the response was found to be proportional to the duration of exposure.¹² An increasing proportion of patients exhibited a positive reaction with increasing exposure times (16% at 5 minutes, 38% at 15 minutes, 50% at 30 minutes, and 69% at 120 minutes).¹² This observation is primarily applicable to leave-on products, as the elicitation of ACD from rinse-off products is less common as a result of limited exposure duration during ROAT. Although leave-on methyldibromoglutaronitrile resulted in a positive ROAT in more than 30% to 50% of sensitized patients,¹³ rinse-off methyldibromoglutaronitrile at the same concentration was tolerated in most sensitized patients.¹⁴

Consistent with ROAT methodology reported in the literature, most ACDS members use the forearm as the location of exposure

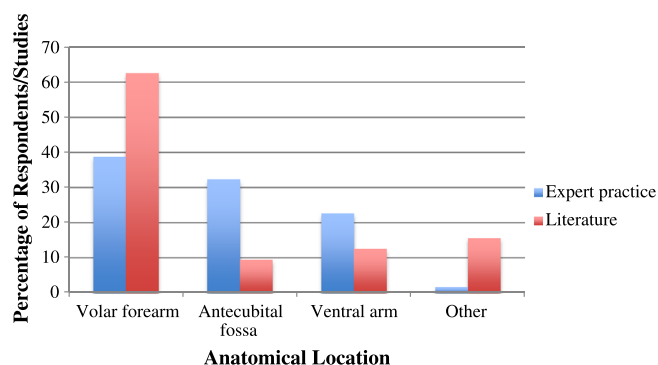


Figure 3. ROAT anatomical location among experts versus the literature. A comparison of anatomical location for ROAT recommended by ACDS members (blue bars) and study methodology published in the literature (red bars).

(Fig. 3). A systematic study with simultaneous patch testing on different anatomical locations found that the upper and lower back reacted more frequently than the arms or legs when exposed to the same allergen at the same concentration.¹⁵ Although a patient may have a clearly positive result on the back, the same method may result in a negative response on the arms or thighs.¹⁵ The higher incidence of positive patch tests compared with ROAT in sensitized individuals may be complicated by the location of testing, in which patch testing is most commonly conducted on the back, which is more reactive than sites used in ROAT.

There was variability with regard to the overall duration of testing both among ACDS members and within the literature (Fig. 4). American Contact Dermatitis Society members tend to perform ROAT for a shorter period compared with published studies. The trend toward longer testing periods was observed in studies in the literature for both leave-on and rinse-off products (Fig. 5). Although the ROAT was originally recommended for twice daily application for 7 days,¹⁶ more recent studies have shown that a ROAT testing period longer than 7 days may be necessary to identify sensitized patients with a delayed response.^{17,18} In a study evaluating linalool, most reactions occurred in the third week,¹⁷ whereas a study with eugenol found most sensitive patients to react in the fourth week.¹⁸ Corticosteroid testing may also require a longer exposure and observation period because the anti-inflammatory properties of steroids result in a tendency to suppress immunologic reactions, even in allergic individuals. However, nickel may elicit a reaction within 1 week.¹⁹ Therefore, the ideal length of ROAT likely depends on the allergen in question.

In contrast to the standardized scoring system used in patch testing, the assessment and interpretation of ROAT varies both in clinical and research settings. Interpretation is complicated by variation in patient compliance to testing procedures and the patients' personal interpretation of the test results. Providing the patient with both written and demonstrational instructions has

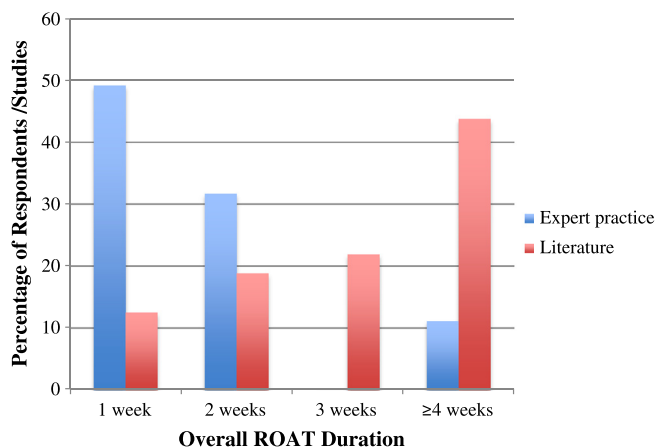


Figure 4. Overall ROAT duration among experts versus the literature. A comparison of overall ROAT duration recommended by ACDS members (blue bars) and study methodology published in the literature (red bars).

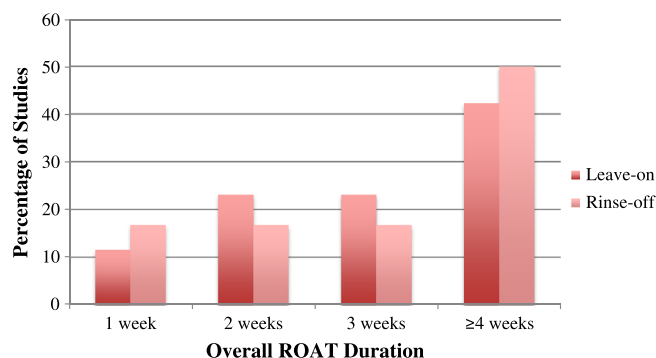


Figure 5. ROAT duration for studies in the literature regarding leave-on versus rinse-off products. The ROAT duration published in the literature for studies on leave-on products (dark red) compared with studies on rinse-off products (light red).

been recommended to effectively educate the patient on properly performing ROAT.²⁰ Furthermore, a negative control is not routinely used in ROAT, which would exclude an irritant reaction to the vehicle. A standardized scale of evaluation for ROAT has been proposed²¹; however, widespread use of a common assessment tool has yet to emerge.

There were several limitations to this study. Because of a low response rate, these results may not fully represent clinical practice of the ACDS. Furthermore, a significant proportion of respondents recommend ROAT once or twice a month or less, and the infrequent use may contribute to variable practice. Studies utilizing ROAT involve patients already known to be allergic to a particular allergen, which may also contribute to a different method of testing. Repeated open application test in clinical studies is focused with application of 1 allergen, whereas ROAT in clinical practice is more nonspecific with the patient's home products used, potentially exposing the patient to multiple allergens.

CONCLUSIONS

This was the first cross-sectional survey study investigating the clinical utilization of ROAT among patch test experts. The results of this survey study reveal that technical practice of ROAT varies among ACDS members. Most trends reported by ACDS members were consistent with the literature for leave-on product application frequency and anatomical site; however, variability existed for overall duration of ROAT and the rinse-off product application frequency. Repeated open application test has great potential to provide clinical relevance to patch testing, but there is a need to standardize testing procedures and assessment criteria. Further research is needed to determine the best approach for ROAT conduct to develop standardized best practice recommendations.

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