

Multiyear Group and Medical Center Patch Test Frequency Data: Confounding Variables

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Patch test frequency data have been extensively published by research groups, such as the International Contact Dermatitis Research Group, North American Contact Dermatitis Group, Dermato-Allergology Study and Research Group, and European Environmental Contact Dermatitis Research Group. As this knowledge accumulation is widely applied in clinical and public health settings, we describe confounding factors to consider when using such data for medical policy considerations. These concepts can also be used in individual reports of new allergens or series of cases. Some of these confounders may have been reported in current literature (until October 2020), whereas others have not been mentioned/considered in most group publications.

We are indebted to an occupational physician, the late Paul Bonnevie,¹ for his medical thesis on using the baseline/standard series for allergic contact dermatitis. Published in German during World War II, this method was adopted by the International Contact Dermatitis Research Group (ICDRG) in the early 1960s. Their first publication of group data forms the basis of much of the subsequent epidemiologic patch test frequency in group publications.²

Subsequently, other study groups, such as the North American Contact Dermatitis Group (NACDG), Dermato-Allergology Study and Research Group, and European Environmental Contact Dermatitis Research Group, as well as individual medical centers, have published such data.³ We also previously described long-term trends in the NACDG data.^{4,5}

This journal and *Contact Dermatitis* extensively publish group data for updating baseline series and probably aided public health judgments in Europe on acceptable exposure levels to certain preservatives. Here, we describe confounding variables worthy of consideration when deciding policy (banning or limiting the use of certain chemicals) and baseline series adjustments. Whereas some of them are reported in current literature (until October 2020), others have not been mentioned/considered in most group publications.

These thoughts will encourage discussion on maximizing the value of the extensive work involved in collaborative studies.

Current literature is aided but not sufficient to diagnose clinical allergic contact dermatitis. In 1985, Benezra et al⁶ detailed the role of additional steps in ascertaining likely clinical relevance. Since then, others have elaborated additional criteria required for a scientific diagnosis of allergic contact dermatitis, such as ruling out excited skin syndrome (angry back) and the product use test/repeat open application test (ROAT).⁷ Documenting actual chemical exposure (in mass per square centimeter) and percutaneous penetration of chemicals in a product, such as fragrances, remains difficult and time-consuming and hence are not always accomplished. Thus, clinical relevance in group publications is often proximate. Some confounding variables may be practical to consider in future studies.

CONFOUNDING VARIABLES

Table 1 summarizes some confounding variables, which will be further elaborated.

The MOAHL Index

The MOAHL index, which stands for Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, and Leg dermatitis, was introduced by Freger et al.² The updated MOAHLFAP index, which includes face dermatitis, age older than 40 years, and positivity rate, is recommended for individual institutions or clinic data reports per the original MOAHL.^{8,53} Patients with occupation-related leg ulcers have different chemical exposures. This confounding factor has been documented.^{8,9}

This index includes the confounders most mentioned by most group publications.³ These confounders are addressed early on in these publications and found to have minimal (<5%) difference between the last reporting cycle.

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TABLE 1. Confounding Variables in Interpreting Group Patch Test Publications

Confounding Variables	References
MOAHL index	Fregert et al, ² Schnuch et al, ⁸ Akasya-Hillenbrand and Ozkaya-Bayazit ⁹
Excited skin syndrome	Mitchell, ¹⁰ Mitchell and Maibach, ¹¹ Fung and Maibach, ¹² Cockayne and Gawkrödger, ¹³ Duarte et al ¹⁴
Environment	Alikhan et al, ¹⁵ DeKoven et al, ¹⁶ Uter et al ¹⁷
Eccrine sweating, sunlight, and exercise	Law et al, ¹⁸ Doooms-Goossens et al, ¹⁹ Edman ²⁰
Circadian rhythms	Matsui et al, ²¹ Pershing et al, ²² Yosipovitch et al ²³
Clinical follow-up	Marrakchi and Maibach, ²⁴ Ale and Maibach, ²⁵ Isaksson et al, ²⁶ Lachapelle ²⁷
Allergen placement	Magnusson and Hersle, ²⁸ Bruynzeel et al, ²⁹ Brasch et al, ³⁰ Hamami and Marks, ³¹ Fisher ³²
Undeclared allergens	MSDSonline, ³³ National Research Council (US) Committee on Toxicology, ³⁴ Ham et al ³⁵
Exposure data	Api and Vey, ³⁶ European Commission ³⁷
Percutaneous penetration	Ngo and Maibach ³⁸
Petrolatum sources	Bao et al ^{39,40}
Dosing	Selvick et al, ⁴¹ Frick-Engfeldt et al, ⁴² FDA ⁴³
Personal care/occupational allergens	Schnuch et al, ⁸ Akasya-Hillenbrand and Ozkaya-Bayazit ⁹
Stability data	Joy et al, ⁴⁴ Mowitz et al ⁴⁵
Actual allergens	Lee and Warshaw, ⁴⁶ Walgrave et al, ⁴⁷ Hausen, ⁴⁸ Uter ⁴⁹
Effect of cross-reactions/coreactions	Uter et al ⁵⁰
Metabolism	Do and Maibach ⁵¹
Clinical/anatomic differences	Law et al ¹⁸
Analytic laboratory	NIOSH ⁵²

FDA, Food and Drug Administration; NIOSH, National Institute for Occupational Safety and Health.

The Excited Skin Syndrome (The Angry Back Syndrome)

Mitchell¹⁰ diagnosed allergic contact dermatitis to a preservative not previously identified as an allergen. However, when retesting the patient, he found a negative result and then wrote the classical article “The Angry Back Syndrome.”¹⁰ This syndrome is due to the hyperreactive state “status eczematicus,” in which regional eczema can induce hyperreactivity of another region. Mitchell and Maibach¹¹ (1997) suggested that because hyperirritability is caused by both irritant and allergic contact dermatitis, a chemical that produces both types of reaction could induce the angry back syndrome.¹¹ Other authors suggested explanations for this widespread phenomenon, including that marginal irritants could become irritants on hyperreactive skin or that chemicals in patch tests get carried to distal sites by lymphatics or bloodstream.¹² Cockayne and Gawkrödger,¹³ in their study with 17 angry back patients over a 4-year period, found that the reactions are not always reproducible, therefore not helpful in the further management of the patients.¹³ Duarte et al¹⁴ found similar results when retesting 39 patients with excited skin syndrome.

Another variable of the excited skin syndrome is a patch test position relative to the other patches, which will be discussed in the allergen placement section hereinafter.

Patch Test Graders

Over the years, study groups have had more than 1 set of physicians reading and interpreting their patch tests. Hence, we consider the variance of these graders and the time available for their clinical evaluation. Attempts to standardize grading by the European Environmental Contact Dermatitis Group, NACDG, and Swedish group reveal considerable variance in grading one individual compared

with another (from senior author's conversations from meetings of the European Environmental Contact Dermatitis Research Group, NACDG, and ICDRG).

In theory, the more experienced the individual physicians, the more likely they would develop consistency in grading and clinical interpretation. Hence, graders' experience and the amount of time and support that they have in their evaluation will influence the interpretation. The popular author Gladwell⁵⁴ suggested that the Beatles would probably not have developed their music sensation if they had not played 10,000 hours in a small Copenhagen nightclub. We suspect that years of graders' experience is another confounding variable.

Environment

Group data often include an extensive geographic diversity, such as the ICDRG and NACDG,^{15,16} and hence, there will be seasonal, temperature, and humidity change.¹⁷ In 2003, Uter et al⁵⁵ found that doubtful reactions against nickel sulfate were associated with colder weather. In 2008, when using results from 12 allergens included in the German Standard Series, Uter et al¹⁷ found, in low temperature or humidity, more irritant or doubtful, weak positive reactions and recommended retesting in warmer conditions or using ROAT to address these false-positive test results. Although available in current literature, this impact of meteorological data has not been considered/mentioned in most group publications.

Eccrine Sweating, Sunlight, and Exercise

As group data are performed in various climates, we have little information about the effect of eccrine sweating and exercise on patch

test reactivity to irritants and allergens.¹⁸ Sunlight influences patch test reactivity; therefore, such exposure could be standardized in future reports.^{19,20}

Circadian Rhythms

Skin response to circadian rhythms could occur depending on testing hours.²¹ Some patch tests would be applied in the morning and others in the afternoon. Using a chroma meter, Pershing et al²² reported that application of topical 0.05% betamethasone dipropionate at 16 hours produced more intense and prolonged changes in skin color over 24 hours than a 9-hour application. Yosipovitch et al²³ found that the skin blood flow shows a circadian variation with a rhythm in 24 hours, which may affect the absorption of topical drugs. This possible confounder has not yet been accounted for in such group reports.

Clinical Follow-up

Using the same rationale as Uter and colleagues^{17,55} study mentioned previously in the Environment section, clinical follow-up should be recommended when there are doubtful/weak positive results. At the final patch test reading, an allergen's clinical relevance is often appreciated, but with many exceptions. Marrakchi and Maibach,²⁴ Ale and Maibach,²⁵ and Isaksson et al²⁶ and Lachapelle²⁷ summarized additional follow-up steps, using single repatch testing, which can minimize the likelihood of the excited skin syndrome (angry back), the provocative use test/ROAT. Marrakchi and Maibach²⁴ mentioned the use of weaker dilutions to help distinguish an irritant reaction and an allergic one. An irritant reaction tends to vanish abruptly, whereas an allergic reaction gradually diminishes with lower concentrations. No group publication separates evaluations performed at the last reading versus those established after long-term clinical follow-up and additional testing. This variable could be dealt with in future group studies.

Allergen Placement

In their publication in the early 1960s, Magnusson and Hersle²⁸ demonstrated that allergens and irritants had as much as a 2-fold difference in response between the upper and lower back. Regarding the excited skin syndrome, the location of a patch test also plays an important role. Bruynzeel et al²⁹ and Brasch et al³⁰ reported that spillover was seen in eczema patients. Hamami and Marks³¹ also found a zone of hyperirritability around a positive patch test reaction, which could explain the angry back syndrome. Fisher³² placed nickel or dichromate patches away from the other patches on a patient with a history that suggested allergy to common allergens and therefore avoided the angry back syndrome.³² Although well established in current literature, group publications have not addressed this confounder.

Undeclared Allergens

The safety data sheet, formerly known as Material Safety Data Sheet (MSDS), provides some chemical exposure data.³³ As chemistry becomes

more sophisticated, more laboratories can verify the correctness/incorrectness of the safety data sheet or the label and identify the presence of undeclared allergens. Recent examples include undeclared allergens in consumer products, such as formalin and methylisothiazolinone.^{34,35} Group publications could document such exposures, especially for those allergens with commercially available spot tests.

Industry Cooperation

The Scandinavian countries and Belgium have a high degree of cooperation between manufacturers and clinicians regarding exposure levels and providing nonstandard allergens for additional patch testing. The United States has less industry cooperation, which needs to be addressed by future studies. Such information may vary between study groups and still constitutes another confounder.

Exposure Data

Concentrations of topical antibiotics and other drugs are provided in readily available data sources. However, we generally do not know about the number of applications, exposure days, exposure areas, and likely percutaneous penetration—still another confounding variable in interpreting group data.

Several dozen fragrance components might present at a small percentage. Fortunately, these data are now available through the International Fragrance Research Association, Brussels, Belgium.³⁶ Such information could aid clinical interpretation of patients who are patch test positive to screening allergens, such as fragrance mixes 1 and 2, and the 26 fragrance allergens mandated for labeling by the European Commission.³⁷

Percutaneous Penetration

There is inadequate percutaneous penetration data for common allergens or the actual product that the individual was exposed to. Ngo and Maibach³⁸ described 15 factors that affect the penetration of chemicals to the skin including the following: physicochemical properties, vehicles, dose, duration, surface areas, frequency, subanatomical pathways, regional variability, population variability, surface conditions, health and integrity, substantivity, binding, distribution, exfoliation, wash effect, metabolic and photochemical transformation, excretion kinetics, and method of determination. These data should be considered in the limitation sections in group and medical center patch test data.

Petrolatum Sources

Petrolatum is widely used in patch testing for most substances as a vehicle because of its stability, nonirritation, and nonsensitization. However, there is limited literature on comparing skin patch test preparations using different sources of petrolatum. Recent data in ophthalmology may explain white petrolatum's various consistencies in common substances. Studies on ophthalmic ointments demonstrated that the sources of white petrolatum and the manufacturing process significantly affected the final products.^{39,40} Because these studies' only variable was petrolatum source, there must be physicochemical

differences in the pure white petrolatum from different sources. Therefore, future group testing could benefit by using 1 highly standardized petrolatum source.

Dosing

Selvick et al⁴¹ found great disparity when using the manual dispensing technique with a 1-mL syringe: the amount of petrolatum dispensed widely ranged from 16 to 85 μ L. Frick-Engfeldt et al⁴² had similar findings when comparing 3 techniques for applying water solutions to Finn Chambers: micropipetting, dripping the solutions, and dripping the solutions, followed by removing excess solution with a soft tissue. Therefore, it is difficult to reproduce patch test results if there is a disparity in dose/area applied. Dosing could be standardized by the universal application of a convenient and reliable dose system. One solution is using commercial allergen patch test kits, which contain uniformly dispersed allergens in standardized concentrations mounted on an adhesive tape.⁴³ Despite their convenience, these commercial tests provide a low number of allergens and may miss reactions toward fragrances, rubber accelerators/pesticides (carbamates and thiurams), formaldehyde, and methylchloroisothiazolinone/methylisothiazolinone.^{56–58}

Personal Care/Occupational Allergens

In group series data, there are often data of those exposed to personal care products compared with occupational allergens (MOAHLFAP index).^{8,53} However, patients with occupational contact dermatitis also use personal care products, hence another confounding variable.

Strength of Data Needed for Regulatory, Marketing, Legal, and Compensation Purposes

Different data strengths are required for regulatory decisions, in addition to workers' compensation and other legal issues. It is beyond the scope of this commentary to delve into these subtleties further. The journal, *Dermatosen*, offers some German viewpoints on these matters.

Ale and Maibach^{25,59} and Marrakchi and Maibach²⁴ offered details on verifying or denying the clinical relevance of a patch test. These include a discussion of excited skin syndrome, individual retesting after the baseline series, and user testing (provocative use testing or ROAT).^{24,60}

Stability Data

Joy et al⁴⁴ provided an in-depth review about allergens and their stability when stored in certain conditions. For example, eugenol is stable in Van der Bend transport chambers at room temperature or refrigerator (4°C) but remains less than 80% initial concentration when stored in Inert Quadrate chambers at room temperature by 24 hours or refrigerator by 72 hours. Most fragrance compounds are volatile and decrease by 20% or more within 8 hours stored in Finn Chambers at room temperature.⁴⁵ Therefore, we believe that group patch test data should include stability information in their results.

Natural Substances

Several widely used natural substances include lanolin, propolis, balsam of Peru, and fragrances.^{46–49} With currently available high-level, highly efficient chemistry, we can refine our knowledge of content and appropriately standardized allergen content and interpret patch test responses.

Effect of Cross-reactions/Coreactions

Much literature on cross-reactions and coreactions is confounded as the data are developed in men, in which we often do not know all previous clinical exposures.⁵⁰ In those countries where guinea pig sensitization testing is used, it may be possible to refine this information and include this in clinical interpretation.

Metabolism

Pharmacology and toxicology have aided our knowledge on metabolism and oral, parenteral, and topical absorption of chemicals. Another area of possible refinement in future studies is noting the metabolic profile of those patients tested. This type of personalized medicine for allergic contact dermatitis remains distant.⁵¹

Clinical/Anatomic Differences

Some group studies provide anatomic dermatitis. Some anatomic areas have greater absorption than others.¹⁸ However, the scalp, the vulva, and, to a lesser extent, the face often hide inflammation, hence another confounder.

Analytic Laboratory

For decades, the fragrance industry has provided much quality analytical data that have advanced our understanding of allergic contact dermatitis. Recently, the National Institute for Occupational Safety and Health has also added high-quality analytical chemistry.⁵²

Although costly and time-consuming, these chemical investigations vastly increase not only our basic but also our clinical understanding. For example, Ham et al³⁵ provide formaldehyde spot tests' relevance in identifying undeclared formaldehyde in consumer products.

CONCLUSIONS

Group data offer guidance of approximate frequency, requiring judgment as to variables involved in their interpretation in public health decisions (eg, possible removal from the market). Statistical trends over years of increase or decrease in patch test frequency seem necessary to decide whether the change is likely real or due to confounding factors—before baseline series or regulatory discussions. These concepts can be used in individual reports of new allergens or series of cases.

Even inclusion/exclusion in the baseline series, an approximate estimate of 1% relevant positives—as suggested by the ICDRG—remains a soft judgment. For instance, for occult exposure allergens of wide-scale usage, a lower positive percentage may be appropriate. The authors welcome criticism and suggestions on all of the above.

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