

RESEARCH LETTER

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Duration of skin prick test refractory period following food-induced allergic reactions

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To the Editor,

The skin prick test (SPT) is the main confirmatory test used to establish the diagnosis of food allergies as it is non-invasive, inexpensive and rapidly produces results.¹ Common practice is to postpone SPTs 4–6 weeks after an initial reaction due to a potential refractory period during which a false negative result may be more common.² However, this recommendation is backed up by limited evidence. Two studies assessing venom and drug allergy revealed that only a minority of cases will be false negative when conducted 1–2 weeks following an allergic reaction.^{3,4} The standard practice of delaying SPTs has not been evaluated for non-anaphylactic allergic reactions to food, as well as food-induced anaphylaxis. Therefore, we sought to assess skin tests for the culprit allergen as a function of time after food-induced allergic reaction/anaphylaxis.

We carried out a prospective study on SPTs to various food allergens at several time points including: prior to allergic reaction (baseline), 1–2 h post-symptom initiation, 1–2 weeks later and 30–40 days post-allergic reaction. Ethical approval was obtained from the McGill University Ethics Committee, and informed consent was obtained from all patients/legal guardians for children younger than 18 years old. Patients with a history of food allergy to milk, egg, peanut or hazelnut were recruited at the Montreal Children's Hospital. All patients underwent a baseline SPT. Allergic status was determined

by history and established by conducting a single blind placebo-controlled food challenge.

Incremental doses of the patient's respective allergen were administered at 30-min intervals, starting with an initial dose of 2–5 mg, to a total cumulative dose of up to 1200 mg. Increasing doses of protein were administered until patients developed objective signs of an allergic reaction/anaphylaxis. An allergic reaction was defined as symptoms consistent with an IgE-mediated reaction (including hives, vomiting and respiratory distress) within 2 h after allergen exposure.⁵ Anaphylaxis was defined based on the NIAID definition as an allergic reaction involving two or more physiological systems, or resulting in hypotension.⁶ Patients were permitted to leave the clinic 3 h following symptom resolution.

SPTs were repeated 1–2 h, 1–2 weeks and 30–40 days following the onset of allergic reaction. SPTs performed 1–2 h post-reaction were conducted prior to antihistamine administration and were performed on the opposite arm used for the baseline test. SPTs were performed on the volar forearm, at least 3 cm from the wrist and antecubital fossae. Lincoln Diagnostic's Duotip-Test II® was used, which consists of a tray of wells with extracts and controls. Within each well, a sterile, disposable, plastic bifurcated needle was immersed in test solution, which picks up test doses via capillary attraction. For each extract/control tested, the needle was

simultaneously pricked into the skin at a 45° angle and lifted. The patient's respective allergen extract, a negative control of saline solution and a positive control of histamine solution were pricked at a distance of ≥ 2 cm from one another on the same arm. ALK® allergen extracts were used, which included milk, egg, peanut and hazelnut. Test results were measured 20 min following application using a ruler on the skin. The largest wheal diameter was measured, as it has been reported to have greater reproducibility compared to measuring the erythema.²

The skin prick test results were represented as the wheal diameter of the tested extract minus the wheal diameter of saline solution according to North American and European guidelines.^{2,7} A positive test was defined as a wheal diameter ≥ 3 mm.² Demographic data were presented as percentages and continuous data were presented as a median with an interquartile range (IQR). Given the relatively small sample size and non-normal distribution, a non-parametric test (Wilcoxon signed-rank test) was used to compare changes in wheal size at baseline, 1–2 h, 1–2 weeks and 30–40 days after allergic reaction/anaphylaxis. $p < .05$ was defined as statistically significant. SPT sensitivity was calculated at each time point. Wheal sizes for each time interval were presented as a box plot using JASP software.

Thirty-four patients between the ages of 5 and 34 years old (median age 15) were included in the study (Table 1). Food triggers observed in this cohort included peanut (35%), hazelnut (6%), milk (18%) and egg (41%). All patients were reactive and developed objective allergic symptoms during the food challenge. Of these reactions, 27 (79%) met the criteria for anaphylaxis. SPTs were performed on all patients at baseline and at 1–2 h post-reaction. SPTs were performed on 19 and nine patients at 1–2 weeks and 30–40 days post-reaction, respectively (Table 1). The median (IQR) wheal diameters at baseline, 1–2 h, 1–2 weeks and 30–40 days post-reaction were 7 (3) mm, 3 (3) mm, 5 (4) mm and 7 (8) mm respectively (Figure 1). SPT wheal size significantly decreased from baseline to 1–2 h post-reaction ($p < .01$). However, wheal size significantly increased from 1–2 h to 1–2 weeks post-reaction ($p = .014$). No significant difference in wheal size was measured when comparing 1–2 weeks to 30–40 days ($p = .440$), baseline to 1–2 weeks ($p = .075$) and baseline to 30–40 days ($p = .482$). Using a 3 mm cut-off, SPT sensitivities at 1–2 h, 1–2 weeks and 30–40 days were 71%, 95% and 100% respectively.

TABLE 1 Patient characteristics.

Time point	1–2h	1–2 weeks	30–40 days
N patients (% of total cohort)	34 (100)	19 (56)	9 (26)
Age (mean $\pm$ SD)	15 $\pm$ 7.2	16 $\pm$ 8.0	15 $\pm$ 4.2
Male (%)	19 (56)	11 (58)	6 (67)
Peanut (%)	12 (35)	6 (32)	1 (11)
Hazelnut (%)	2 (6)	1 (5)	0 (0)
Milk (%)	6 (18)	4 (21)	2 (22)
Egg (%)	14 (41)	8 (42)	6 (67)
Anaphylactic patients	27 (79)	14 (74)	7 (78)

Key messages

- A 4–6-week refractory period for skin prick testing following allergic reaction is commonly assumed.
- We assessed the refractory period in 34 children and adults with food-induced allergic reactions.
- Skin prick tests performed 1–2 weeks following allergic reaction were highly sensitive.

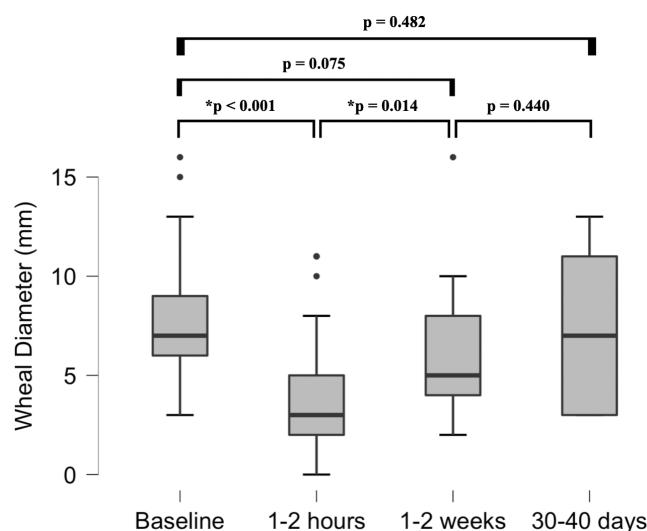


FIGURE 1 Allergen wheal diameter with respect to onset of allergic reaction/anaphylaxis.

SPTs are often postponed 4–6 weeks after an initial reaction due to an assumed refractory period during which a false negative result may be more common.² This recommendation is largely extrapolated from data on skin tests in venom and drug allergies.^{3,4} In one study assessing the diagnosis of drug allergy in the perioperative setting, 60% of patients with an IgE-mediated reaction had a positive skin test 4 days post-reaction while 88% had a positive test 4–8 weeks post-reaction.⁴ In another study of SPT and sIgE tests for venom allergy, 79% of either SPT or sIgE tests were positive 1 week after systemic allergic reaction, whereas a second evaluation was required in 21% of patients 4–6 weeks post-reaction to make the correct diagnosis.³ These studies recommend early skin testing following a systemic reaction, followed by a later skin test if at first negative.^{3,4} Despite the evidence in venom and perioperative drug allergies, the recommendation to postpone SPTs for food allergies exists in the absence of supporting evidence. Therefore, we aimed to assess the temporal trends of SPTs following food-induced allergic reaction/anaphylaxis. To do this, we conducted a prospective study in which SPTs were performed at baseline (prior to allergic reaction) as well as 1–2 h, 1–2 weeks and 30–40 days post-reaction.

The cohort consisted of 34 children and adults, in which the majority (79%) had an anaphylactic reaction. Wheal size significantly decreased 1–2 h post-reaction compared to baseline. No significant

difference was found when comparing wheal size at 1–2 weeks to those at baseline and 30–40 days. The increase in wheal size from 1–2 h to 1–2 weeks was associated with an increase in test sensitivity from 71% at 1–2 h to 95% at 1–2 weeks. These results suggest that the hyposensitivity observed 1–2 h post-reaction is transient, and returns to normal levels 1–2 weeks following allergic reaction to food protein.

The observed changes in sensitivity following allergic reaction may have been due to altered mast cell function. An in vitro study by Zhao et al. reports impaired skin mast cell degranulation and histamine release following exposure to incremental doses of allergen.⁸ Thus, skin mast cells may have been less reactive following the food challenge, resulting in a decreased clinical response 1–2 h post reaction. Additionally, it has been reported that antihistamines diminish skin test sensitivity, which would impact test results at 1–2 h and 1–2 weeks post-reaction.² However, SPTs at the 1–2-hour time point were conducted prior to antihistamine administration. Moreover, studies suggest that the positive histamine control returns to normal levels within 3 days following antihistamine intake.⁹ Therefore, antihistamine administration for allergic reactions during the food challenge unlikely act as an effect modifier in our study.

Our results suggest that SPTs for food-induced reactions (namely milk, egg, peanut and hazelnut) attain high sensitivity 1–2 weeks following an allergic reaction. When comparing our results to previous reports, a test sensitivity of 95% at 1–2 weeks post-reaction was higher than reports for both drug and venom allergy.^{3,4} Similar to the results on venom and drug allergy, we found that while the majority of skin tests may be accurate soon after allergic reaction, there are cases in which skin tests will take longer than 1–2 weeks to become a valid measure. The main limitation of this study is the high attrition rate, which was primarily attributed patients' reluctance to return for additional assessments and repeat skin tests at relatively short time intervals following a positive food challenge. Additionally, results may vary depending on severity of reaction, patient age, allergen type and testing procedure used. Therefore, our results are preliminary and future studies with more robust sample sizes will allow for definitive conclusions on these temporal trends.

AUTHOR CONTRIBUTIONS

Participated in conception/design, data acquisition/analysis and article drafting.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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