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Organ-specific symptom patterns during oral food challenge in children with peanut and tree nut allergy

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Abstract

Background: Peanut and tree nut allergies are common in childhood and often severe in nature. The clinical picture shows a wide variety of symptoms.

Objective: To analyze the distribution of clinical symptoms and severity during oral food challenges (OFC) in children.

Methods: Analysis of 1.013 prospectively recorded, positive OFCs with peanut (n = 607), hazelnut (n = 266), walnut (n = 97), and cashew (n = 43). Symptoms were categorized as immediate-type skin, gastrointestinal, upper and lower respiratory, cardiovascular symptoms, and eczema exacerbation. Symptom severity and treatment were recorded.

Results: Skin symptoms presented in 78%, followed by gastrointestinal (47%), upper (42%), and lower respiratory symptoms (32%). Cardiovascular symptoms presented in 6%. In three-quarter of the reactions, more than one organ was involved. Importantly, severe reactions occurred at every dose level. Peanut- and cashew-allergic patients had a higher relative risk of gastrointestinal symptoms compared with hazelnut- and

Abbreviations: DBPCFC, Double-blind, placebo-controlled food challenge; ED, Eliciting dose; GI, Gastrointestinal; IgE, Immunoglobulin E; OFC, Oral food challenge.

walnut-allergic patients. Patients without vomiting had a 1.7 times higher risk developing immediate-type skin and/or lower respiratory symptoms. Three-quarter of the patients ever had eczema but worsening presented in only 10.5% of the OFCs. In patients with multiple food allergies, organs involved, eliciting dose and severity differed between allergens.

Conclusion: Although comparisons between allergen groups with different clinical history, severity, comorbidities and laboratory data are difficult and might contain bias, our data confirm the high allergenic potential of peanut and tree nuts. The rare occurrence of eczema worsening emphasizes that avoidance diets of peanuts and tree nuts to cure eczema seem to be unnecessary and may hamper tolerance maintenance.

KEYWORDS

food allergy, organ-specific symptom, peanut, severity, tree nut

1 | INTRODUCTION

Peanut and tree nuts are common elicitors of food allergy often resulting in anaphylactic reactions.[1] While cow's milk and hen's egg allergy are often outgrown,[2,3] peanut and tree nut allergy show persistence in around 80% of the patients.[4,5] Food allergy is known to cause a heterogeneous pattern of clinical symptoms,[6] which may change in characteristics and severity during life.[7] Little is known about possible differences in peanut and tree nut allergic reactions regarding specific organ systems.

Oral food challenges (OFC) are the gold standard in the diagnostics of suspected food allergy. Even though clinical staff is well-prepared and full emergency equipment and drugs are at hand, OFCs are a risk for the patient. Knowing which symptom pattern to expect challenging a specific food allergen would be helpful. Moreover, if certain allergens tend to affect specific organ systems more commonly than others, unraveling the mechanisms behind it would be of interest.

Peanut and tree nut allergy seem to affect the respiratory system more often compared with other food allergens such as hen's egg or cow's milk.[6–8] Allergic reactions are therefore often severe in nature. Furthermore, it has been shown that patients with severe symptoms seem to have lower threshold doses compared to patients with mild symptoms.[9] In contrast, a recent retrospective survey of 525 positive peanut challenges in children from the United Kingdom, Ireland, and Australia[10] showed that 38% reacted after consuming 1 g or more of whole peanut and severity increased if more peanut was consumed during OFC. The level of food-specific serum IgE correlates with the likelihood of a positive food challenge and risk of anaphylaxis during OFC.[7,11–13]

The aim of this study was to investigate the distribution of clinical symptoms during OFC in peanut and tree nut allergy and to investigate whether individual patients with multiple allergies to peanut and tree nut present a similar allergic reaction profile to the different allergens in terms of organ system involvement, eliciting dose (ED) and severity.

Key Message

In a large dataset of peanut and tree nut challenges, we were able to accurately describe organ-specific symptoms and show that immediate-type skin reactions are the most common reaction regardless of the allergen but worsening of eczema rarely represented in children with eczema and "nut" allergy. Patients without vomiting had a higher risk of immediate-type skin and/or lower airway reactions. Due to the high potential of peanut and tree nut to cause severe allergic reactions good education on anaphylaxis including training of the correct use of adrenaline-auto-injectors by patients and families is of great importance and necessity. Finally, it is of great clinical importance that even in children with multiple food allergies toward peanut and tree nut, the organ system involvement, eliciting dose and severity of the reaction may differ between the different allergens.

The hereby-gained knowledge in peanut and tree nut allergy may provide a better understanding of the disease and may help clinical staff as well as patients and their families to better recognize and treat allergic reactions.

2 | METHODS

In a multicenter study, clinical and laboratory data of infants and children with suspected food allergy, who underwent an OFC for clinical purpose, were recorded prospectively. The study was approved by the local ethical committee of each individual study site and written informed consent was obtained before participation. Only patients presenting a positive outcome during their initial OFC for peanut, hazelnut, walnut, or cashew and a complete dataset regarding sex,

age and food challenge protocol, were included. Additional information on the study population, OFC procedure, allergic reaction assessment, and statistical analysis is described in the electronic repository.

3 | RESULTS

We report on 916 patients with a total of 1.013 positive OFCs for the respective allergen with peanut (n = 607), hazelnut (n = 266), walnut (n = 97), or cashew (n = 43). Ninety-four patients (10%) were multi-allergic to more than one of respective allergens. To avoid paired-sample analysis, multi-allergic patients were considered for one allergen group only, in favor of the OFC with the most severe clinical reaction. Therefore, our core group comprises 916 OFCs from 916 patients (peanut n = 575; hazelnut n = 219; walnut n = 84; and cashew n = 38). The allergen groups differ in terms of patient age and atopic diseases (Table 1).

3.1 | Organ-specific symptoms

Immediate-type skin symptoms were the most common symptom for each allergen followed by gastrointestinal symptoms, upper, and lower respiratory symptoms (Figure 1). Cardiovascular symptoms appeared in 6% of the OFCs (63.5% (33/52) with drop in blood pressure and 36.5% (19/52) with tachycardia). Overall, multi-organ reactions occurred commonly in more than two-thirds of the patients (Figure 1). Eczema exacerbation occurred in 10.5% of all OFCs only, although 69% of the patients ever had eczema (Figure 2). None of the patients presented with worsening of eczema only. In comparison with our core group, the entire set of OFCs (n = 1.013; 94 patients appear in several groups) were considered within Figure S1 showing similar results. Interestingly, patients without vomiting had a 1.7 times higher risk to develop either immediate-type skin symptoms (p = <.001; 95% CI: 1.472–1858) and/or lower respiratory symptoms (p = <.001; 95% CI: 1.332–2.185; Figure S2). No significant differences were found on the presence versus the absence of vomiting on other immediate-type reactions (further details regarding organ systems involved are shown in Table S1–S4).

In a subpopulation of patients with multiple allergies, more than 60% of the patients experienced immediate-type skin symptoms to all allergens tested, followed by gastrointestinal, upper, and lower respiratory symptoms (Figure 3). A total of 69% of these patients showed allergic reactions at higher dose levels (titration step 4 up to cumulative dose) and about 58% presented with similar severity grades, either mild or moderate to severe, to the respective allergens (Figure 3). Excluding the "cumulative dose" did not change the results.

TABLE 1 Characteristics of study population

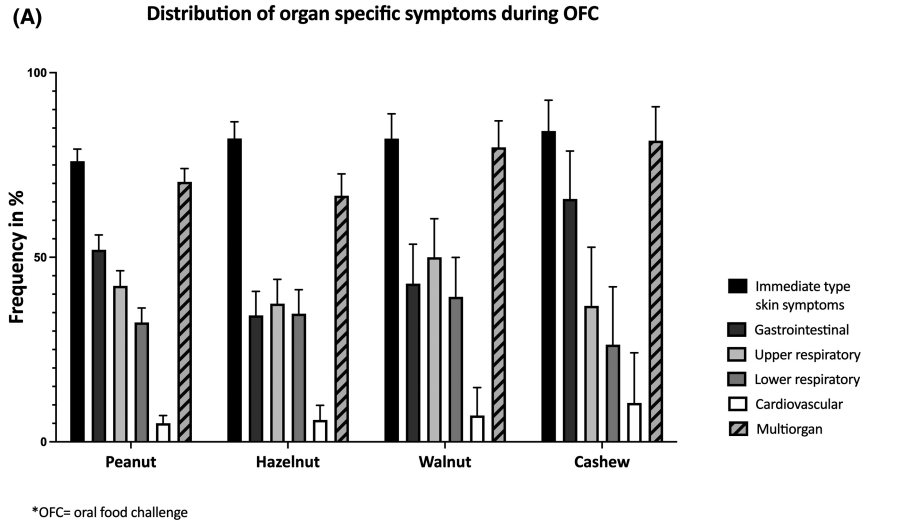
	Peanut (n = 575)	Hazelnut (n = 219)	Walnut (n = 84)	Cashew (n = 38)
Sex, male, no. (%)	361 (63%)	138 (63%)	53 (63%)	21 (55%)
		* p=.02		
Age (median, range)	4.6 (0.7–17.9)	4.2 (1.0–17.8)	6.0 (1.3–16.5)	5.8 (1.4–14.6)
Total IgE*[1] (median, range) in Ku/l	236.5 (9–9832)	257.0(4–7618)	319.5 (6–7043)	*247.0 (3–5000)*
Specific IgE*[2] (median, range) in Ku/l	13.5 (<0.35- >100)	13.40 (<0.35- >100)	4.74 (<0.35–100)	*1.91* (<0.35–*59*)
Comorbidities ever (most frequent only)				
None	92 (16%)	35 (16%)	16 (19%)	7 (18%)
	* p=.004			
Eczema	370 (64%)	173 (79%)	56 (67%)	28 (74%)
Asthma	181 (32%)	56 (26%)	23 (28%)	8 (21%)
Rhino- conjunctivitis	35 (6%)	11 (5%)	3 (4%)	1 (3%)
Gastrointestinal*[3]	1 (0.2%)	–	–	–
Double-blind, placebo-controlled	197 (34%)	83 (38%)	27 (32%)	15 (40%)
Open (not blinded)	378 (66%)	136 (62%)	57 (68%)	23 (61%)

Note: Data on study population were based on the individual patient. The respective allergen groups differ in terms of patient age and atopic diseases. Hazelnut allergic patients had a significantly higher incidence of eczema ever (79%) than walnut allergic children (67%) (p = .004). Moreover, patients within the hazelnut group were significantly younger (median age 4.9 years) than patients within the walnut group (median age 6.4 years) (p = .02). p-Values were adjusted using the Bonferroni adjustment.

*[1]Missing data on total IgE in 8/38 patients in the cashew, 63/219 patients in the hazelnut, 165/575 patients in the peanut and 30/82 patients in the walnut group.

*[2]Missing data on specific IgE in 8/38 patients in the cashew, 50/219 patients in the hazelnut, 100/575 patients in the peanut and 14/84 patients in the walnut group.

*[3]E.g., eosinophilic gastroenteritis, eosinophilic proctocolitis, FPIES



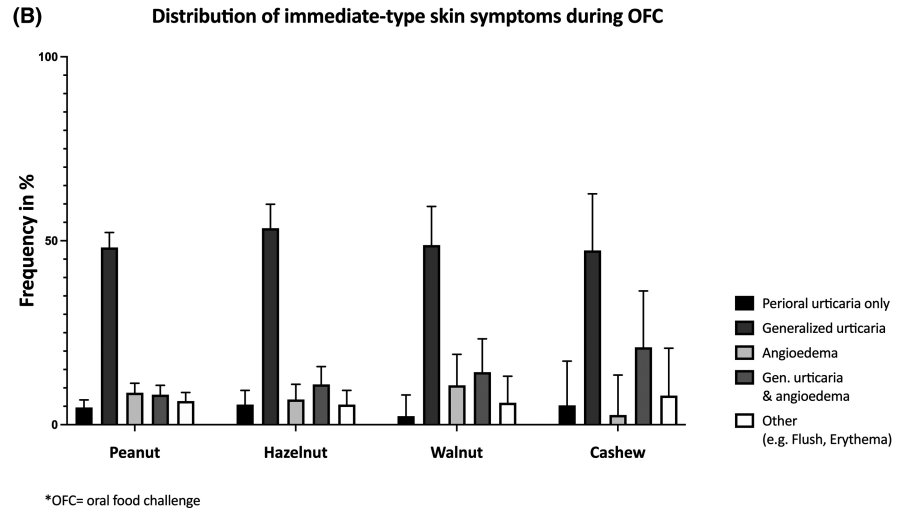


FIGURE 1 Organ-specific symptoms (A) and immediate-type skin symptoms during oral food challenge (B). All patients within the core group (included with a total number of $n = 575$ for peanut, $n = 219$ for hazelnut, $n = 84$ for walnut and $n = 38$ for cashew oral food challenges. Organ-specific symptoms were categorized as immediate-type skin symptoms (e.g., generalized urticaria, and angioedema), gastrointestinal (e.g., vomiting and diarrhea), upper respiratory (rhino-/conjunctivitis), lower respiratory (e.g., repetitive coughing and wheezing) and cardiovascular (e.g., drop in blood pressure, tachycardia). Missing data for cardiovascular symptoms for peanut ($n = 1$) and gastrointestinal symptoms for peanut ($n = 1$) according to total collective. Bonferroni-corrected 95% confidence intervals were applied

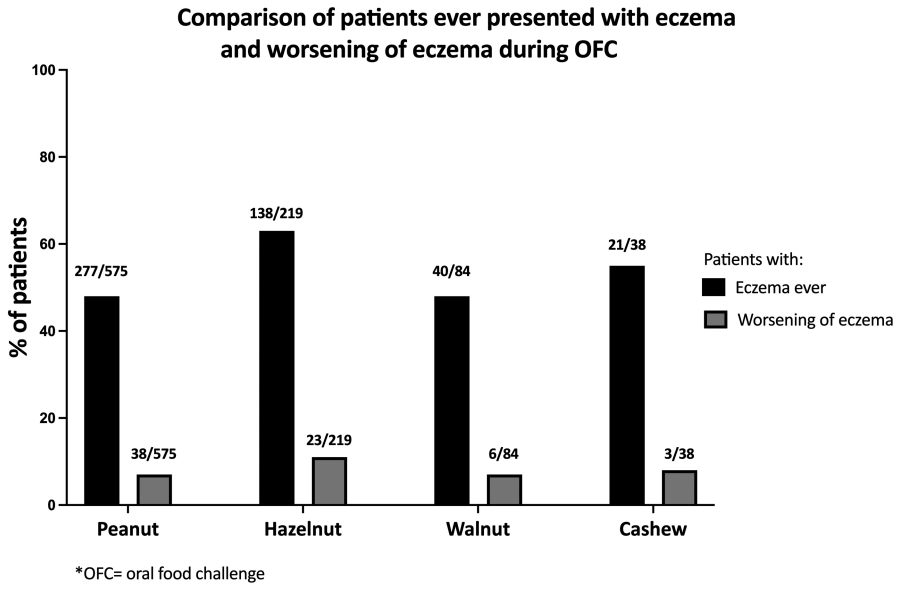


FIGURE 2 Comparison of patients ever presented with eczema and worsening of eczema during OFC. All patients within the core group ($n = 916$) included with a total number of $n = 575$ for peanut, $n = 219$ for hazelnut, $n = 84$ for walnut, and $n = 38$ for cashew oral food challenges

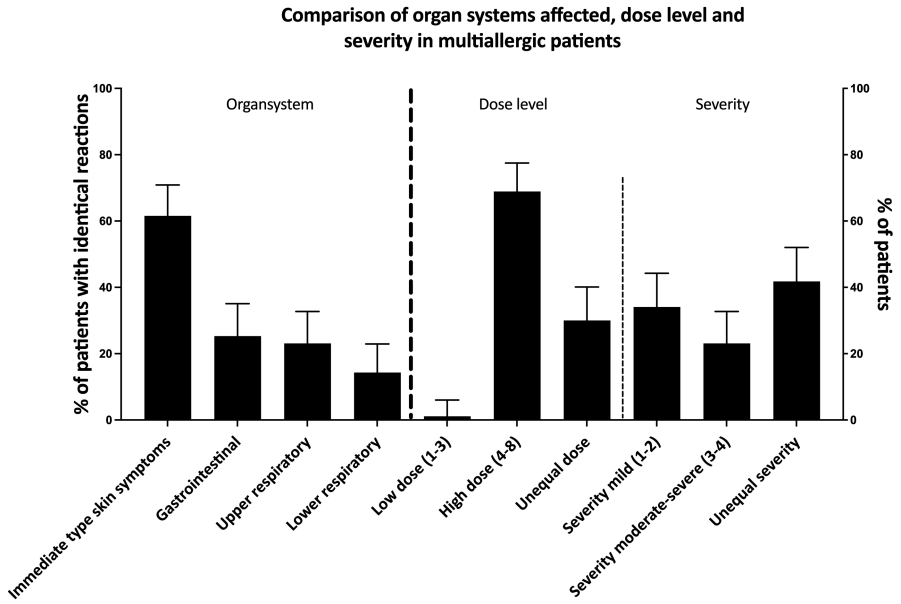


FIGURE 3 Comparison of organ systems affected, dose level, and severity in patients with multiple allergies toward peanut and tree nut. Ninety-one patients presented allergic to two of the investigated allergens comprising the following combination: 59 of 91 (63%) patients were allergic to peanut and hazelnut, 14 of 91 (14.9%) to hazelnut and walnut, 10 of 91 (10.6%) to peanut and walnut, 3 of 91 (3.2%) patients each were allergic to either walnut and cashew or hazelnut and cashew, and 2 of 91 (2.1%) to peanut and cashew. Patients compared in terms of presenting with identical organ-specific symptoms as well as similar severity grade and reaction eliciting dose steps. Dose levels divided into low dose including titration step 1 to 3 and high dose including titration step 4 to cumulative dose. Severity grades divided into mild grade summarizing grade I and II and moderate summarizing grade III and IV. Bonferroni-corrected 95% confidence intervals were applied

3.2 | Eliciting dose, severity, and administration of rescue medication

The whole spectrum of severity, with the exception of fatal or near-fatal symptoms (Grade V), was seen at every given dose during OFC for all allergens (Figure 4). The majority of the patients developed allergic symptoms upon higher dose levels ranging from 0.1 g to 4 g protein in all groups, respectively (Figure 4). About one-third of the patients either allergic to peanut (36%), hazelnut (33%), or cashew (32%) and 45% of the patients allergic to walnut presented with symptoms according to severity grade IV at the aforementioned dose steps (dose step 4 to cumulative dose) compared with either 5% of the peanut or cashew, 6% of the hazelnut, and 4% of the walnut allergic patients with severity grade IV at lower dose steps.(1–3) Thus, showing that one-third of all patients reacting at higher dose levels presented with more severe allergic reactions. Rescue medication was administered at every dose step, with an increased use of adrenaline at higher dose steps (Figure 4). Using the entire set of OFCs ($n = 1.013$), no substantial differences were found (see supplementary and Figure S3).

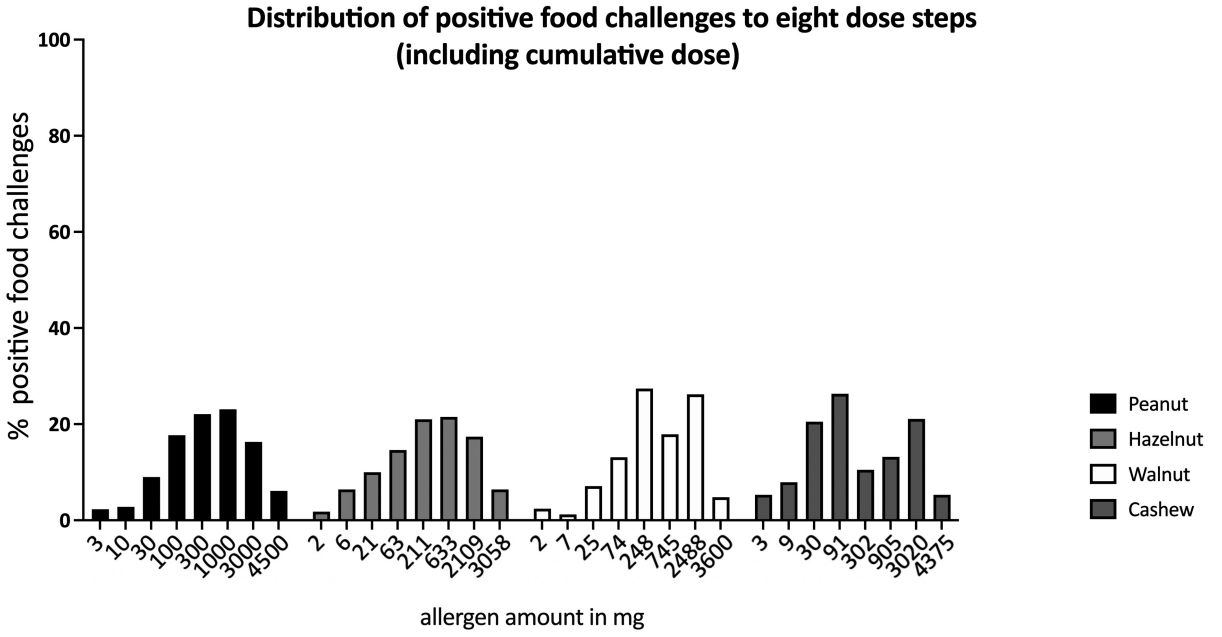
3.3 | Age and gender influence the occurrence of allergic symptoms

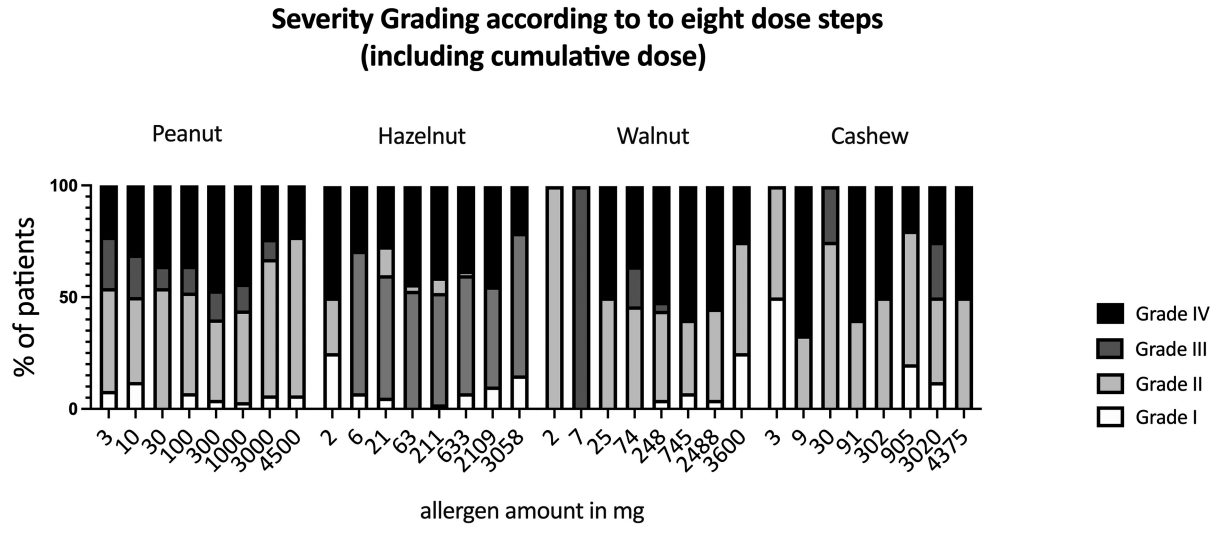
The older a patient the more likely the occurrence of gastrointestinal (OR = 1.212; 95% CI: 1.134–1.296; $p = <.001$), upper respiratory (OR = 1.139; 95% CI: 1.075–1.208; $p = .000$), and multi-organ symptoms (OR = 1.204; 95% CI: 1.115–1.299; $p = <.001$) and the less likely the development of immediate-type skin symptoms (OR = .918; 95% CI: 0.861–0.979; $p = .009$) or worsening of eczema (OR = .843; 95% CI: 0.723–0.984; $p = .030$). Moreover, women presented with a lower probability of multi-organ reactions (OR = .556; 95% CI: 0.368–0.839; $p = .005$) than men.

4 | DISCUSSION

To our knowledge, this is the first detailed report on characterization and comparison of organ-specific symptoms in a larger dataset of more than one thousand OFCs with peanut and tree nut allowing for the investigation of reaction patterns, eliciting doses, and severity grading in a smaller subpopulation with multiple allergies to peanut and tree nut.

This study shows that immediate-type skin symptoms represent the most common allergic reaction within all allergen groups. Therefore, a close evaluation of the patient is important, for example, examination of the skin under clothes before proceeding to the next titration step. In this study, one of three patients presented with symptoms of the lower respiratory tract thus indicating signs of anaphylaxis. It has been shown previously in the European anaphylaxis registry that the involvement of the lower respiratory tract occurs typically in childhood.[14] The high incidence of lower respiratory tract symptoms is comparable with previous findings confirming the high allergic reactivity potential of peanut and tree nuts.[6,7,15,16] The





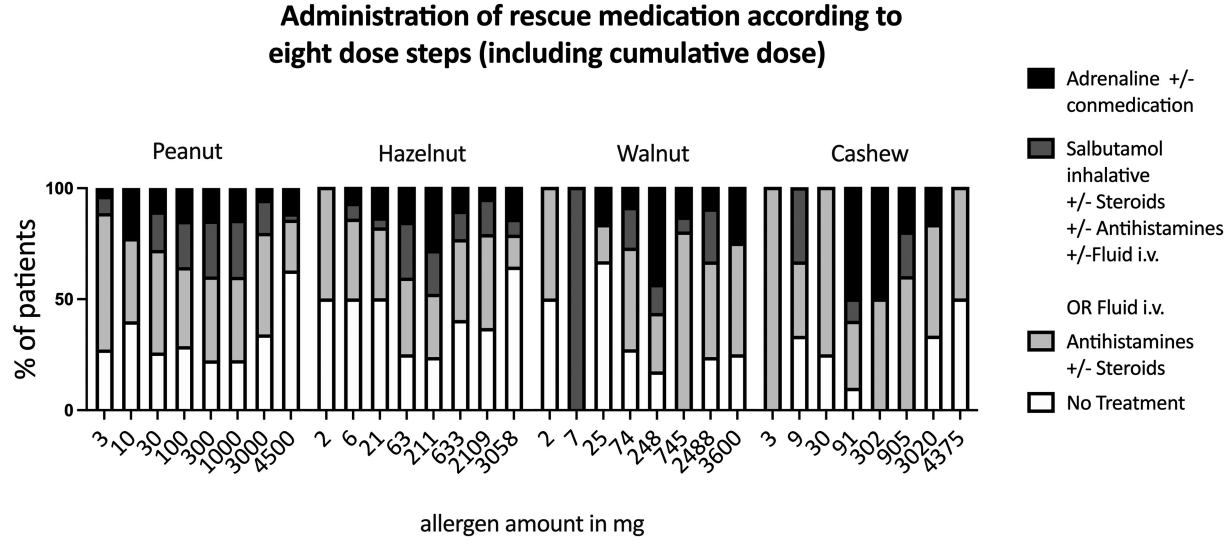


FIGURE 4 Distribution of positive food challenges to seven allergen dose steps, severity of clinical reactions and administration of rescue medication. All patients within the core group ($n = 916$) included with a total number of $n = 575$ for peanut, $n = 219$ for hazelnut, $n = 84$ for walnut, and $n = 38$ for cashew oral food challenges. Missing data on rescue medication for hazelnut ($n = 1$), walnut ($n = 1$), and cashew ($n = 1$); missing data on titration step for peanut ($n = 3$) and hazelnut ($n = 2$) according to total collective

development of GI symptoms was not distributed homogeneously in-between allergens and was more common after challenges with peanut and cashew as has been described earlier by Elizur et al.[17] It has been shown previously that vomiting was a prevalent symptom in the first decade of life, and nausea, as a subjective symptom, was prevalent later in life.[14] As the age range of our children was similar, it seems that not only the age but also the consumed allergen contributes to the elicited symptoms confirming earlier findings. Interestingly, vomiting as the most common GI symptom, was associated with fewer lower respiratory symptoms. To our knowledge, this has not been shown previously and it could be hypothesized that vomiting could reduce the allergen amount in the body, which could alleviate the severity of the reaction.

Our study showed different characteristics of an allergic reaction from one allergen to another in a small subset of children with concurrent food allergy to peanut and/or different tree nuts. This should be kept in mind regarding the management in patients with food allergy to multiple nuts and/or peanut. It should be highlighted to the patients and caregivers that symptom patterns, severity, and threshold doses may differ between allergenic foods intra-individually.

About one-third of children with moderate-to-severe eczema suffer from IgE-mediated food allergy.[18] In many cases, independently or upon on their physician's advice, parents eliminate suspected foods solely on the presence of sensitization with the aim of alleviating eczema symptoms. Although food avoidance may improve eczema in selected cases, avoidance diets rarely cure it, may even have detrimental effects such as progression to immediate-type allergy.[19] Despite the fact that 2/3 of the patients in this study ever had eczema, only few children showed an exacerbation of their disease upon exposure. These results are in contrast to other food allergens such as soy or wheat where worsening of eczema seems more common.[6] This is supported by another study investigating cow's milk, hen's egg, wheat, and soy allergy, showing that in 94% of late reactions and in 83% of combined reactions, eczema exacerbation was present.[20] Regarding peanut and hazelnut, data by Ahrens et al. confirmed our findings in a smaller patient population, pointing out that there are less patients presenting with worsening of eczema during peanut OFC.[6] This indicates that peanuts and tree nuts might be overestimated in the pathophysiology of eczema exacerbation. However, the administration of cortisone in case of allergic reactions might also improve the skin status in case of eczema ever and may prevent eczema exacerbation during OFC. Therefore, the evaluation of delayed worsening of eczema after OFC in case of rescue medication administration is limited.

As underlined by our data, most patients reacted to higher dose amounts with the majority of reactions observed between 0.1 g and 4 g food protein, respectively. One-third of all patients developed symptoms at higher dose levels with more severe allergic reactions according to severity grade IV. This is in accordance with the aforementioned retrospective survey by Arkwright et al. and findings by Elizur et al.[10,17] It could be debated whether the current protocol for OFCs, following seven titration steps, should be revised regarding the starting dose or time intervals. As most patients did not show any symptoms at lower dose levels, starting at higher dose levels (100–300 mg allergenic protein) might offer a valuable time saving. On the other hand, the severity of the reactions was about equally distributed between the different titration steps. Even if severe reactions were common at higher doses, 5% of the patients still presented with allergic reactions according to severity grade IV upon lower doses. Therefore, the benefit of possible time saving by starting on higher dose amounts might be overshadowed by the higher risk of more severe allergic reactions as had been addressed in the PRACTALL consensus report before.[21]

Knowledge in the individual threshold has a diagnostic importance, for example, for identifying suitable patients for therapy but also improvement for patients and family's quality of life.[22] All OFCs were conducted based on PRACTALL international guidelines for oral food challenges using semi logarithmic increases every 30 min. Previously, it has been shown that, for example, the median time to onset of the first objective immediate-type reaction in peanut allergic patients was 55 min using a modified challenge procedure with does intervals of 120 min.[23] Thus, it is unknown if a patient may have presented with an allergic reaction upon a single or cumulative dose and the presented eliciting doses might be lower than anticipated. Although lower eliciting doses correlated with biological markers of sensitization, no correlation between ED and response severity could be found.[22,23] Nevertheless, clinical practice is dependent on the—very often young—patients, when it comes to food allergy diagnostics, so that prolonged challenge durations per allergen may not very feasible in routine practice.

The analysis of our dataset is limited by the fact that the study population is not completely homogenous and differs in size. Different indications for OFC were accepted such as positive medical history hinting at the allergen or elevated food-specific IgE prior to first consumption. In addition, not all children underwent an OFC for all allergens analyzed but only for which an allergy was suspected. No data on occurrence, severity, or time point of prior food reactions have been collected. Also, it has to be taken into consideration that our allergen groups are not equally represented in age and allergic comorbidities. We would like to highlight that comparisons between each allergen groups with different "clinical history," "severity of food allergy," "comorbidities," and "laboratory data" are extremely difficult, and these would contain bias and confounding factors.

A total of 65% of the OFCs were not conducted in a double-blind, placebo-controlled manner. However, all patients presented with objective allergic symptoms, including anaphylaxis. Therefore, it is unlikely that the lack of placebo-control and blinding had a meaningful effect on our conclusions. Additionally, our original dataset of 1.013 OFCs included 94 patients with multiple allergies to peanut and tree nut. The reduction in the dataset in favor of the OFC with the most severe allergic reaction to avoid paired-sample analysis may have biased the results. However, analysis of all 1.013 food challenges gave similar outcomes.

In summary, in a large dataset of peanut- and tree nut-allergic patients, we were able to accurately describe organ-specific symptoms and show that immediate-type skin reactions are the most common reaction regardless of the allergen. On the contrary, worsening of eczema rarely represented in children with eczema ever and peanut or tree nut allergy. Patients without vomiting had a higher risk of immediate-type reactions of the skin and/or lower airways. Our data emphasize the high potential of peanut and tree nut to cause severe allergic reactions yet again. Therefore, as done in most countries already, good education on anaphylaxis including training of the correct use of adrenaline-auto-injectors by patients and families is of great importance and necessity. Possible predictors for specific reaction patterns should be taken into account when it comes to management and education of patients and families. Finally, it is of great clinical importance that in children with multiple food allergies toward peanut and tree nut, the organ system involvement, ED and severity of the reaction may differ between the different allergens.

AUTHOR CONTRIBUTION

Josefine Dobbertin-Welsch: Data curation (lead); Formal analysis (lead); Investigation (equal); Project administration (lead); Validation (equal); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Olga Staudacher:** Formal analysis (supporting); Investigation (equal); Writing – review & editing (equal). **Songül Yürek:** Investigation (equal); Writing – review & editing (equal). **Valérie Trendelenburg:** Formal analysis (supporting); Investigation (equal); Writing – review & editing (equal). **Sebastian Tschirner:** Investigation (equal); Writing – review & editing (equal). **Mandy Ziegert:** Investigation (equal); Writing – review & editing (equal). **Frank Ahrens:** Investigation (equal); Writing – review & editing (equal). **Martina Millner-Uhlemann:** Investigation (equal); Writing – review & editing (equal). **Susanne Büsing:** Investigation (equal); Writing – review & editing (equal). **Anne Striegel:** Investigation (equal); Writing – review & editing (equal). **H. Ott:** Investigation (equal); Writing – review & editing (equal). **Alisa Arens:** Investigation (equal); Writing – review & editing (equal). **Monika Gappa:** Investigation (equal); Writing – review & editing (equal). **Lars Lange:** Investigation (equal); Writing – review & editing (equal). **Sunhild Gernert:** Investigation (equal); Writing – review & editing (equal). **Bodo Niggemann:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing – review & editing (equal). **Kirsten BEYER:** Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing – review & editing (equal).

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CONFLICT OF INTEREST

Kirsten Beyer reports grants and personal fees from Aimmune, personal fees from Bencard Allergie, grants and personal fees from Danone - Nutricia, grants from DBV, personal fees from Hycor, grants and personal fees from InfectoPharm, personal fees from Jenapharm GmbH, grants from Hipp, personal fees from Mylan -Meda, personal fees from Nestle, outside the submitted work; Valérie Trendelenburg reports personal fees from Danone, outside the submitted work. All other authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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