For esomeprazole, SPT results were positive in 1 of the 53 and IDT results in 4 of the 53 patients; for omeprazole and pantoprazole, 1 of the 53 patients had a positive result to SPTs and 5 of the 53 patients had a positive result to IDTs (Table I). SPT result with lansoprazole was positive in 4 and with rabeprazole in 1. Accuracy analysis was performed in patients with previous grade I and II reactions. Of the 44 patients with reactions of grades I and II, 40 underwent OPT. Of the 40 patients tested, 3 of 3 with skin test positivity and 3 of 37 patients with skin test negativity reacted to OPT. Therefore, among this population, unadjusted sensitivity was 50% and specificity was 100%. Adjusted sensitivity was 61.3% (CI 25.0%-87.5%), and adjusted specificity was 100.0% (CI 97.2%-100.0%). LR+ calculated by using adjusted sensitivity and specificity was 61.3 (assuming a specificity of 99.0%) while LR− was 0.39. Positive predictive value was 100%, and negative predictive value was 91.9%.

The diagnostic use of skin tests in patients with immediate PPI reactions has been sporadically described. For omeprazole, Lobera et al[4] reported a skin test positivity in 8 of 9 patients and Sobrevia et al[5] in 5 of 5 patients. In this study, we analyzed 53 patients with immediate reactions to PPIs and estimated the diagnostic performance of SPT and IDT versus OPT. In our population, skin test results were positive in 12 of the 53 patients; 4 of these patients underwent OPT with the suspected drug and the results were positive in all cases. In the 41 patients with a negative result, 3 had a positive OPT result with the suspected drug. We obtained good results with skin tests in terms of specificity (100%), positive predictive value (100%), and negative predictive value (91.9%), whereas the sensitivity was lower. These results were confirmed by a high LR+. In addition, we observed a higher frequency of skin test positivity in patients with more severe reactions.

Concerning the cross-reactivity, we observed that patients with hypersensitivity to pantoprazole, confirmed by skin tests, also had positive skin test results to omeprazole (4 of 5 patients) and, more rarely, to esomeprazole. This result confirms previous reports[10,11] and is probably due to the similar chemical structure of these PPIs. On the contrary, patients monosensitized to lansoprazole and rabeprazole, which have a different side chain, had negative test results with omeprazole, pantoprazole, and esomeprazole. This observation may have important clinical implications, as patients monosensitized to lansoprazole or rabeprazole would more likely tolerate other PPIs. Indeed, the small number of patients does not allow us to make final conclusions about cross-reactive patterns and requires further studies. In conclusion, this multicenter study suggests the usefulness of skin tests in patients with immediate hypersensitivity reactions to PPIs, because a positive skin test result allows one to avoid an oral provocation.

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Organ-specific symptoms during oral food challenge in children with food allergy

To the Editor:

Food-allergic patients have been known to develop a heterogeneous pattern of clinical symptoms on food intake. Symptoms might be expressed via the skin, the gastrointestinal (GI) tract, the respiratory system, and/or the cardiovascular system.[1] However, why and in which constellation these different organ systems are affected is not clear. Cow's milk, hen's egg, peanut, tree nuts, wheat, and soy are responsible for the majority of food-induced allergic reactions in young children[2] with a rate of 2% to 6% in children in the first year of life.[3] Oral food challenges (OFCs) are the gold standard in the diagnostic workup in patients with suspected food allergy.[4] Based on this, our study aimed to analyze the distribution of clinical signs and symptoms on OFCs and to test whether this distribution is dependent on the tested food allergen.

Here we report on a retrospective analysis of 1843 consecutive OFCs, which were performed for clinical purposes on children with 1 or more suspected food allergies based on their clinical history (Table I). For 880 OFCs a positive test outcome occurred. Clinical reactivity to pasteurized, whisked hen's egg, pasteurized cow's milk (3.5% fat content), wheat (gluten powder), soy milk, roasted peanut, and/or raw hazelnut was investigated by OFCs as described in detail previously.[4] In brief, patients received allergen or placebo on 2 different days. A dietician performed randomization and preparation of the challenges. By plan, the

TABLE I. Baseline data of study participants

	Median age (range)	OFC positive	OFC negative
Cow's milk	13 mo (3 mo-16 y)	330	322
Hen's egg	19 mo (4 mo-15 y)	333	141
Wheat	13 mo (4 mo-16 y)	98	173
Soy	13 mo (4 mo-16 y)	56	257
Peanut	40 mo (15 mo-18 y)	46	43
Hazelnut	39 mo (8 mo-18 y)	17	27
OFCs		880	963
Total OFCs		1843	

provocation began in the morning and the child's stomach was empty. In case of a delay, infants and small children were allowed to have a light, nonallergic breakfast. A maximum of 7 gradually increasing titration steps (half-logarithmic) were given at intervals of 30 minutes. In the case of a negative outcome on the first day, a cumulative dose (adding the 7 doses from the first day to a single challenge meal) was given on another day.

Provocation was stopped if objective clinical symptoms such as urticaria, exacerbation of eczema (at least 10-point increase in Scoring Atopic Dermatitis [SCORAD]), angioedema, wheezing, allergic rhinitis or conjunctivitis, vomiting, and/or diarrhea were observed or the highest dose was reached. Clinical symptoms that developed after positive specific food-challenge tests were categorized into 3 groups according to the organ system involved: GI symptoms (vomiting, diarrhea, stomach pain), respiratory symptoms (wheeze, cough, stridor, rhinoconjunctivitis), or skin symptoms (urticaria, redness, itching, worsening of atopic dermatitis, angioedema).

In Fig 1 the proportion of appearance of respiratory, GI, and skin symptoms is depicted for all allergen provocations with a positive test outcome. Within 1 allergen group, the proportions do not add up to 100% as several symptoms can be diagnosed in parallel. GI and respiratory symptoms were not distributed homogenously over the tested food allergens ($P < .001$), whereas skin symptoms showed a homogenous distribution with an overall percentage of 89.9%.

We observed respiratory symptoms in children after specific OFCs at a rate of 3.6% (soy), 17.3% (cow's milk), 11.8% (hazelnut), 19.5% (hen's egg), 13.3% (wheat), and even 41.3% after peanut challenges. It is known that peanut allergy is characterized by more severe reactions and that peanut—because of its high allergenic potential—is the main cause of death due to food-allergic reactions.[5] This supports our observation that pronounced reactions ($P < .05$) such as airway reactions were observed more often in peanut-allergic children upon challenge.

GI symptoms occurred in a range of 17.6% (hazelnut), 21.4% (soy), 24.5% (wheat), and 25.8% (cow's milk) of the cases, while up to 44.4% and 45.7% of the children developed GI symptoms after hen's egg and peanut provocation. We herewith show a dominant occurrence ($P < .05$) of GI symptoms after hen's egg and peanut challenge, compared with cow's milk, soy, or wheat in allergic patients.

The reason for the individual allergen tendency to GI symptoms in hen's egg and peanut-positive OFCs remains unclear and herewith is to our best knowledge described for the first time. One may speculate that there are allergen-specific properties of foods in terms of the development of IgE-mediated clinical symptoms. This may be compared with the different potency of foods to induce allergic symptoms at all or to the food-specific grade of severity (such as more severe symptoms in peanut allergy). Moreover, the particular allergenicity of a food allergen is determined not only by its source but also relies on the condition and the state of processing (cooked, boiled, roasted, etc).[6] In our study, we used all foods in the most allergenic form known, for example, pasteurized hen's egg and cow's milk, roasted peanut, and wheat as gluten powder. In this way, we hoped to be able to compare the organ-specific symptoms in the most appropriate way. From our results we cannot conclude whether a processed form would change our results.

Furthermore, immunologic differences, for example, the expression of intestinal homing markers, might play a role. Different chemokines and chemokine receptors have been correlated with allergic inflammation in different organs: for instance, CCR6 is discussed as having a proallergic role in the GI tract[7] and CCR9 as being required for the induction of oral immune tolerance[8]; a role of CXCL13, CCL21, and CCL19 is described in allergic airway inflammation,[9] and elevated serum levels of TARC/CCL17 (ligand for CCR4) correlate with the intensity of atopic dermatitis.[9] Moreover, it has been shown that individual allergens/allergen extracts are able to induce allergic inflammation responses as well as individual chemokine releases *in vivo* and *in vitro*.[10] Further studies are warranted in this interesting field of an intricate network of circulating and organ-resident cells, for their resulting clinical implications.

In our study population, nearly all patients with a positive food challenge developed skin symptoms such as urticaria, redness, itching, worsening of atopic dermatitis, or angioedema (86.7%-94.1% dependent on allergen) (Fig 1, lower part). To further analyze the proportion of the different skin symptoms in patients with overall positive skin reactions, see the conditional proportions presented in Fig 1. Interestingly, more children developed urticaria after a challenge with hen's egg (78%), peanut (85%), and hazelnut (69%), whereas a worsening of atopic dermatitis, as a late reaction, was observed more often after challenges with soy (69%) and wheat (52%) (Fig 1). In the literature, urticaria and atopic dermatitis are described as 2 forms of IgE-mediated skin reactions.[11] Urticaria represents a classic type I hypersensitivity reaction with allergen-induced cross-linkage of IgE on mast cells, whereas for worsening of eczema in patients with atopic dermatitis, an involvement of other cell types including T cells and Langerhans cells has been discussed.[11]

The distribution of children having developed at least respiratory plus GI symptoms (not excluding additional skin symptoms) was found to be 8.4% after hen's egg challenge and 15.2% after peanut challenge (data not shown). For cow's milk, hazelnut, wheat, and soy challenge, the values were 3%, 5.9%, 2%, and 0%, respectively.

Skin, GI, and respiratory symptoms in parallel developed in 7.2% of the children after hen's-egg challenge and in 13% after peanut challenge (data not shown). Interestingly, after cow's-milk challenge, just 2% (7 of 330) of the children developed this symptom combination (data not shown).

In a study by Spergel et al,[12] the authors performed a retrospective review of food-sensitive children who underwent open food challenges (n = 998 challenges). Similar to our results, they found that the most common presentation of food allergy was cutaneous. However, as they included multiple organ system reactions (defined as symptoms in more than 1 category without life-threatening reaction) in their categorization, and we presented reactions not as "multiorgan" but singularly, the results of the 2 studies are not directly comparable.

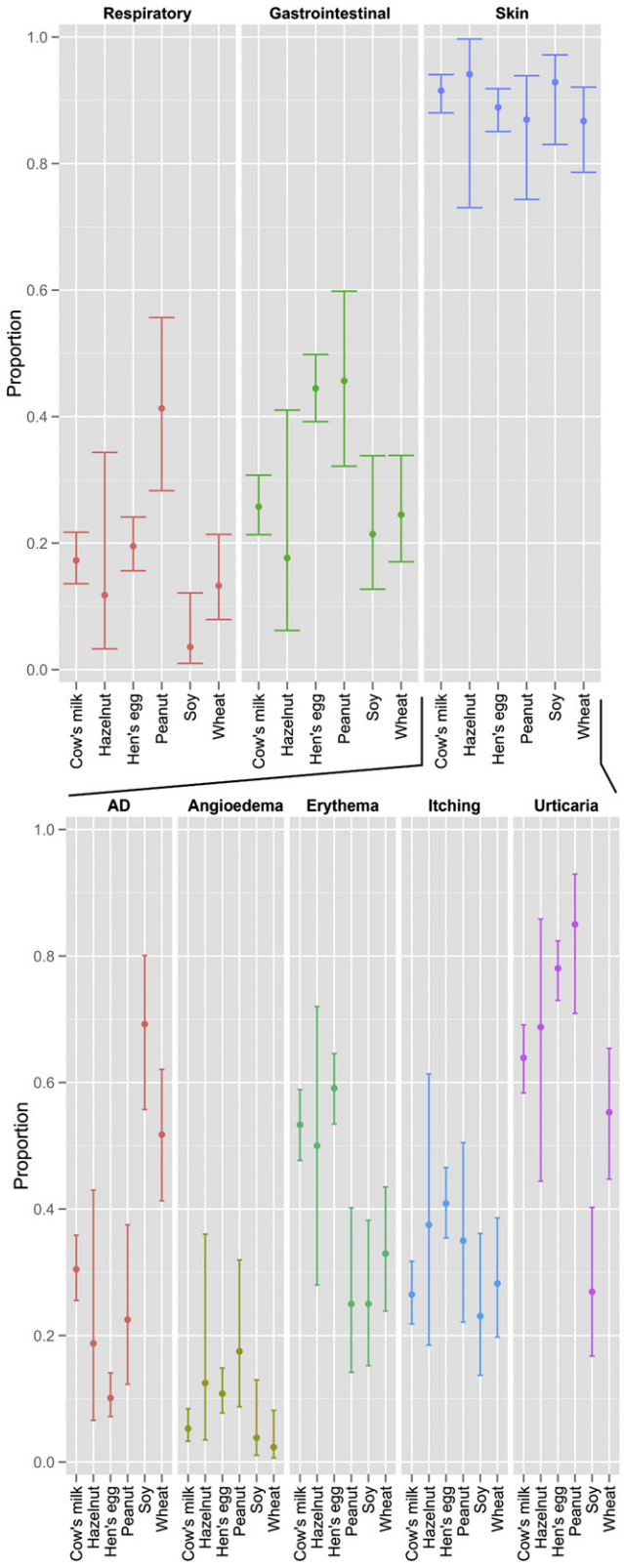

FIG 1. Proportion of clinical symptoms to cow's milk, hazelnut, hen's egg, peanut, soy, and wheat. Also shown is the Bonferroni-adjusted 95% confidence interval (Wilson). Occurrence of respiratory symptoms is significantly higher for peanut than for cow's milk ($P = .0076$), hen's egg ($P = .022$), soy ($P = 3.7 \times 10^{-5}$), and wheat ($P = .0058$). GI Symptoms occurred significantly more often after positive hen's egg challenge compared with cow's milk ($P = 9.4 \times 10^{-6}$), soy ($P = .0149$), and wheat ($P = .0056$). Proportion of skin symptoms (worsening of atopic dermatitis, angioedema, itching, erythema, urticaria) for children who showed allergic skin reactions after OFCs against cow's milk, hazelnut, hen's egg, peanut, soy, or wheat. Comparisons were made by all pairwise Fisher exact test (Holm corrected).

Our analysis revealed that the development of respiratory and GI symptoms after specific allergen challenges is not distributed homogeneously. The development of GI symptoms is more likely after challenges with hen's egg and peanut compared with challenges with cow's milk, soy, and wheat. In addition, the development of respiratory symptoms is more likely after peanut challenges compared with challenges with cow's milk, hen's egg, soy, and wheat. Nearly all positive challenges showed skin symptoms.

In summary, our data indicate that certain foods show a preference for organ-specific symptoms during OFCs.

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