

Clinical cross-reactivity among foods of the Rosaceae family

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Background: Foods from the Rosaceae botanical family have been increasingly reported as causes of allergic reaction.

Patients frequently have positive skin tests or radioallergosorbent test results for multiple members of this botanical family.

Objective: Our purpose was to investigate the clinical cross-reactivity assessed by double-blind, placebo-controlled food challenge (DBPCFC) of Rosaceae foods (apricot, almond, plum, strawberry, apple, peach, and pear).

Methods: Thirty-four consecutive adult patients complaining of adverse reactions to Rosaceae were included in the study. Skin prick tests and CAP System (FEIA) were performed with Rosaceae foods in all patients. Clinical reactivity to Rosaceae was systematically evaluated by open food challenges (OFCs), unless there was a convincing history of a recent severe anaphylaxis. Positive reactions on OFCs were subsequently evaluated by DBPCFCs.

Results: Twenty-six and 24 patients had positive skin prick tests and CAP FEIA with Rosaceae, respectively; from these 88% and 100% had positive tests with ≥ 2 . No evidence of clinical reactivity was found in 66% percent of positive skin prick tests and 63% of positive specific IgE determinations to fruits. A total of 226 food challenges (including OFC and DBPCFC) were performed in the 28 patients with positive skin prick tests or CAP System FEIA. Of 182 initial OFCs carried out, 26 (14%) reactions were confirmed by DBPCFCs. Overall, 40 reactions were considered positive in 22 patients with positive skin tests or CAP FEIA. Thirty-eight reactions had been previously reported, the remaining two were detected by systematic challenges. Most reactions were caused by peach (22 patients), apple (6), and apricot (5). Ten patients (46%) were clinically allergic to peach and other Rosaceae.

Conclusion: Positive skin test and CAP System FEIA should not be taken as the only guide for multi-species dietary restrictions. Nevertheless, the potential clinical allergy to other Rosaceae should not be neglected. If the reported reaction is confirmed, current tolerance to other Rosaceae should be precisely established unless there has been ingestion without symptoms after the reaction. (*J Allergy Clin Immunol* 2000;106:183-9.)

Key words: Food hypersensitivity, fruit, Rosaceae, double-blind placebo-controlled food challenge, skin prick test, CAP System FEIA, clinical cross-reactivity, apple, peach, apricot

Fruits from the Rosaceae family are widely consumed in the Mediterranean area and have been increasingly reported as causes of allergic reactions, particularly in adults with pollinosis.¹⁻³ This botanical family includes common foods such as peach, apricot, plum, almond, cherry (Prunoideae subfamily), apple, pear (Pomoideae subfamily), blackberry, and strawberry (Rosoideae subfamily). Patients frequently have positive skin tests or radioallergosorbent test results for multiple members of this botanical family.^{4,5} These are sometimes taken as a basis for broad dietary restrictions, which are rarely necessary. Immunologic cross-reactivity is an in-vitro phenomenon caused by IgE antibodies directed against epitopes expressed in molecular structures from different allergenic sources. In recent years several cross-reactive allergens have been identified and sequenced in fruits of the Rosaceae family. The major allergens in apple (Mal d 1), pear (Pyr c 1), apricot (Pru ar 1), and sweet cherry (Pru av 1) are structural homologs to the birch pollen major allergen Bet v 1, which belongs to class 10 of pathogenesis-related proteins.^{6,7} Other major allergens from apple (Mal d 2) and cherry (Pru av 2) have been identified as thaumatin-like proteins.⁸ More recently, a lipid transfer protein has been reported to be an important allergen in peach (Pru p 3), apricot (Pru ar 3), and apple (Mal d 3).^{9,10} Common epitopes in these allergens could be responsible for the extensive immunologic cross-reactivity interspecies and with pollens. In fact, lipid transfer proteins from apple and peach showed a homology higher than 90%, which clearly explains immunochemical cross-reactivity in patients not allergic to birch pollen.¹¹ In contrast, Bet v 1 homolog structures and profilins could explain frequent cross-reactivity interspecies and with pollen, commonly manifested as the oral allergy syndrome.^{5,12} However, clinically relevant cross-reactivity for most botanical families dramatically contrasts with the extensive immunologic cross-reactivity when it is evaluated by placebo-controlled food challenges.^{13,14} On the basis of these data, our hypothesis was that clinical reactivity to Rosaceae foods could be very specific, with most patients with positive skin prick or in vitro tests lacking clinical responses. Hence the purpose of our study was to investigate the clinical relevance assessed by double-blind, placebo-controlled food challenges

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Abbreviations used

CI:	Confidence interval
DBPCFC:	Double-blind placebo-controlled food challenge
OFC:	Open food challenge

(DBPCFC) of immunologic reactivity to seven commonly consumed foods of the Rosaceae family (apricot, almond, plum, strawberry, apple, peach, and pear).

METHODS

Subjects

Thirty-four consecutive patients referred to the Allergy Division of the Hospital Universitario Doce de Octubre (Madrid, Spain) complaining on adverse reactions to one or more of seven foods from the Rosaceae family (apricot, almond, plum, strawberry, apple, peach, and pear) were included in the study. Ages ranged from 14 to 62 years (median 24.5 years). The patients reported a total of 64 reactions (peach, 31 patients; apple, 9; apricot, 8; plum, 6; almond, 4; pear, 3; and strawberry, 3). Fifteen patients reported adverse reactions to one fruit (12 to peach, 1 to apricot, 1 to almond, and 1 to apple), 14 to two fruits (apricot-peach, 6; apple-peach, 4; plum-peach, 3; and almond-peach, 1), 1 to three fruits (apple-strawberry-peach), 2 to five fruits (apricot-plum-strawberry-apple-peach and almond-plum-apple-peach-pear), and 1 to six fruits (apricot-plum-strawberry-apple-peach-pear).

Diagnostic procedures

The first diagnostic stage consisted of a medical and dietary history and skin prick tests. The medical history included questions on family history, other diseases, offending food, number of episodes, symptoms, time between intake and onset of the symptoms, minimum amount of food to produce symptoms, other causes of the patient's complaints, physical exertion, treatment in the emergency department, and medications used. Antiallergic drug treatment was withdrawn before skin testing as described elsewhere.¹⁵ All patients were off antihistamines throughout the whole study, including all oral challenges. Skin prick tests were performed systematically with almond extract (CBF-LETI laboratories, Madrid, Spain), fresh fruits (apricot, plum, strawberry, apple, peach, and pear provided by the patient) by the prick-prick technique¹⁶ and inhalant allergens (ALK-Abello Laboratories, Copenhagen, Denmark); the study was completed with other offending foods mentioned in the history. Skin testing was not performed with strawberry in three patients, almond in three patients, and plum in one patient. A positive skin prick test result was defined as a mean (average of orthogonal to largest diameter) wheal of 3 mm or greater (after subtracting the diameter of the wheal induced by the diluent control). Negative and positive controls for skin testing were saline solution and histamine dihydrochloride (10 mg/mL), respectively. On the same day blood samples were drawn and stored at -20°C. Serum samples from all patients were analyzed for total and antigen-specific IgE antibodies by use of the CAP System FEIA (Pharmacia, Uppsala, Sweden) as detailed by the manufacturer. Sera from all patients were analyzed for apricot, almond, plum, strawberry, apple, peach, pear, and other offending food mentioned in the history. The cutoff value for a positive result was set at 0.35 kilounits of allergen-specific IgE per liter.

Actual clinical reactivity to apricot, almond, plum, strawberry, apple, peach, pear, and other offending food mentioned in the history was first evaluated by open food challenges (OFC) with the whole fresh fruit. Subjects showing a positive reaction on open

provocation were subsequently challenged in a double-blind fashion. DBPCFCs were performed as described elsewhere.^{17,18} A total of 17 g of dehydrated whole fruit was masked in a mix of orange (200 mL) and pineapple (200 mL) juices, sugar (16 g), wheat meal (13 g), and liquid coloring (McCormick). Randomization and preparation of the challenges were performed in the allergy laboratory. Subjects were challenged first randomly with either food or placebo, and the interval before the second part of the DBPCFC was at least 24 hours. Confirmation by DBPCFC was accepted if the subject had symptoms after provocation with the active substance and no symptoms after the placebo challenge. An open feeding of the whole fresh fruit in identical conditions and quantity as in the initial OFC followed all negative blinded challenges. The time between initial and final OFCs was not more than 10 days. Food challenge was not performed when a patient with positive skin test or food-specific IgE had a convincing history of a recent severe anaphylaxis to the food, defined as objective findings (marked laryngeal edema, significant wheezing, or hypotension), that developed immediately after the isolated ingestion of the suspected food and required emergency management within the last year.

Data analysis

Descriptive statistics were calculated to assess the frequency of positive results of skin prick tests, CAP System FEIA, and clinical reactivity. Confidence intervals of a proportion were calculated with use of the Fleiss quadratic approximation. To obtain insights in the structure of the data a graphic method that displays the relationships between categorical variables was performed.¹⁹ This exploratory technique, called multiple correspondence analysis, was used to identify the pattern of clinical reactivity to the different foods of the Rosaceae botanical family under study.

RESULTS

Table I lists the patients found to have immunologic reactivity (one or more positive results of skin tests or CAP System FEIA) to Rosaceae foods. Two hundred thirty-one skin prick tests (not performed with strawberry in patients No. 12, 17, and 19; with almond in patients No. 16, 18, and 19; and with plum in patient No. 23) and 238 specific IgE determinations for the seven Rosaceae were performed. One hundred twenty-one skin prick tests were positive in 26 patients (24 to peach, 19 to plum, 18 to pear, 18 to apple, 15 to almond, 14 to apricot, and 13 to strawberry). One hundred nine results of the CAP System FEIA (23 to peach, 22 to apple, 18 to apricot, 16 to plum, 14 to strawberry, 10 to pear, and 6 to almond) were positive in 24 patients. There was no significant difference in the frequency of positive results of CAP System FEIA and those of skin prick tests, with the exception of pear and almond ($P = .04$ and $P = .008$, respectively). Most patients reacted to multiple Rosaceae by skin testing (median, 5 foods; 23 patients to two or more foods; 14 patients to five or more foods) and had specific IgE antibodies to several fruits (median, 5 foods; 24 patients to two or more foods; 13 patients to five or more). Overall, 28 of 34 patients reporting adverse reactions had positive skin testing or serum-specific IgE antibodies for the evaluated Rosaceae fruits, most of them (27 patients) having immunologic hypersensitivity to more than one Rosaceae food.

A total of 226 food challenges (including OFC and DBPCFC) were performed in the 28 patients with positive

TABLE I. Clinical and immunologic findings in 28 patients with positive results of skin prick tests or CAP System FEIA to Rosaceae foods, including apricot, almond, plum, strawberry, apple, peach, or pear

Patient No.	Age (y)	Sex	Immunologic and clinical reactivity to Rosaceae fruits				Other food allergies*	Pollinosis
			Positive skin prick tests	Positive CAP System FEIA	Clinical reactivity			
1	28	M	A, Pl, S, Ap, P, Pe	A, Al, Pl, S, Ap, P, Pe	P	H		
2	22	M	Al, Pl, Ap, P†‡	A, Pl, Ap, P	A, P			
3	19	F	A, Al, Pl, S, Ap, P, Pe	A, Pl, Ap, P, Pe	Ap, P	H		
4	36	F	A, Al, Pl, S, Ap, P, Pe	Pl, S, Ap, P, Pe	P			X
5	27	M	P	A, Ap, P, Pe	P	As		X
6	32	M	—	A, Al, Pl, S, Ap, P, Pe	—			
7	39	M	Pl	—	—			
8	16	M	A, Al, Pl, Ap, P, Pe†	A, Pl, S, Ap, P	—	W		X
9	16	F	A, Pl, S, Ap, P, Pe	Pl, S, Ap, P	Pl, Ap, P	Av		X
10	26	F	A, Pl, P, Pe	—	A,§ Pl, P	Me, W, Fi		X
11	29	M	Al, Pl, S, Ap, P	A, Al, S, Ap, P	P	H, W		
12	24	F	A, Al, Pl, S, Ap, P, Pe	A, Pl, S, Ap, Pe	P	Pn, Ss		X
13	25	M	A, Al, Pl, S, Ap, P, Pe	A, Ap, P	P			X
14	51	M	S, Ap, P, Pe‡	A, Pl, S, Ap, P	P			X
15	19	F	Al, Pl, S, Ap, P, Pe	A, Pl, S, Ap, P	A, Pl, Ap, P			
16	22	M	Pl, Ap, P, Pe‡	Ap, P	—			X
17	24	F	A, Al, Pl, S, Ap, P, Pe	A, Pl, Ap, P	P	W		X
18	23	F	A, P	A, Pl, P	P			
19	17	F	Al, Ap, P, Pe	A, Ap, P	Ap, P			
20	62	F	Al, Pe	—	Al, P			
21	24	M	A, P	—	—			X
22	62	F	—	S, Ap, P, Pe	—			
23	14	M	P	A, Pl, Ap, P, Pe	P			X
24	26	M	A, Al, Pl, S, P, Pe	S, Ap, P	P			X
25	25	F	A, Pl, S, Ap, P, Pe	A, Al, Pl, S, Ap, P, Pe	A, Pl, S, Ap, P, Pe			X
26	25	F	Al, Pl, Ap, P, Pe	A, Pl, S, Ap, P	Ap, P			
27	22	F	Al, Pl, Ap, P†	Al, P	P			X
28	18	M	A, Al, Pl, S, Ap, P, Pe	A, Al, Pl, S, Ap, P, Pe	A,§P			X

M, Male; A, apricot; Pl, plum; S, strawberry; Ap, apple; P, peach; Pe, pear; Al, almond; H, hazelnut; F, female; As, asparagus; W, walnut; Av, avocado; Me, melon; Fi, fig; Pn, peanut; Ss, sunflower seed.

*Clinical allergy.

†Strawberry not tested.

‡Almond not tested.

§Not reported as offender in the medical history because has not been ingested after reactions (clinical allergy detected by systematic challenges).

||Plum not tested.

skin prick tests or CAP System FEIA (Fig 1). One hundred forty-seven of 182 initial OFCs were negative. DBPCFCs confirmed 26 (14%) positive initial OFCs. All final open challenges after negative placebo-controlled challenges were also negative. Another 14 reactions considered positive were based on a recent history of a convincing episode of severe anaphylaxis. Overall, 40 reactions were considered positive in 22 of 28 patients with positive skin test or specific IgE antibodies to Rosaceae. The majority of reactions were observed in response to peach (22 patients), followed by apple (6 patients), apricot (5 patients), plum (4 patients), almond (1 patient), pear (1 patient), and strawberry (1 patient). Table II lists the symptoms of the reactions to fruits. No evidence of clinical reactivity was found in 66% of positive skin prick tests and 63% of positive specific IgE determinations to fruits. The rates of clinical reactivity by positive results of skin prick and CAP System FEIA to Rosaceae foods are shown in Fig 2. Results of the CAP System FEIA were

comparable to those of skin prick tests in predicting symptomatic Rosaceae allergy. Clinical reactivity ranged from less than 10% for positive skin tests with pear, almond, or strawberry to more than 90% for positive skin tests with peach. Twelve patients (54%, 95% confidence interval [CI] 33%-75%) of the 22 had positive clinical responses to only one fruit (peach). Six patients (27%, 95% CI 12%-50%) had clinical reactivity to two fruits (3/6 to peach and apple, 2/6 to peach and apricot, and 1/6 to peach and almond). Two patients (9%, 95% CI 2%-31%) had positive clinical responses to three fruits (peach, plum, and apricot; peach, plum, and apple). One patient (5%, 95% CI 0.2%-25%) had clinical reactivity to four fruits (peach, plum, apple, and apricot). One patient (5%, 95% CI 0.2%-25%) had clinical reactivity to six fruits (peach, plum, apple, apricot, pear, and strawberry). The multiple correspondence analysis of clinical responses to Rosaceae foods showed a pattern of simultaneous reactivity to apricot, plum, apple, and peach (Fig 3).

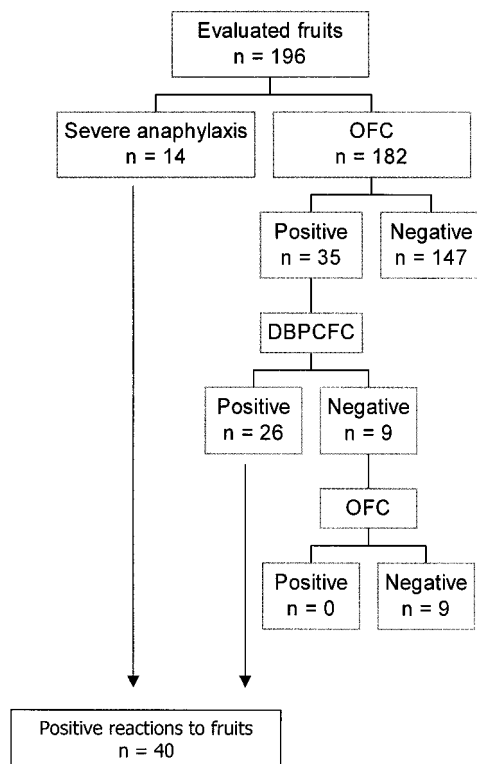


FIG 1. Evaluation of the clinical reactivity to seven foods of the Rosaceae family (apricot, almond, plum, strawberry, apple, peach, and pear) in 28 patients with positive results to skin prick tests or CAP System FEIA. Clinical reactivity to a total number of 196 foods (seven fruits per patient) was first evaluated by OFC unless there was a documented history of recent systemic anaphylaxis. When positive, OFCs were followed by DBPCFC. After a negative DBPCFC, a final OFC was carried out in all cases.

Nine of the 22 patients with clinical reactivity to Rosaceae had other associated food allergies up to 13 foods. Of these, 9 were nut allergies, walnut and hazelnut being the most common. Thirteen of the 22 patients with clinical reactivity to Rosaceae were allergic to pollens.

DISCUSSION

In evaluating patients with hypersensitivity to foods of vegetable origin, many groups of investigators have noted extensive *in vitro* cross-reactivity, which does not correlate with clinical allergy when evaluated by DBPCFCs. Bernhisel-Broadbent and Sampson¹³ were the first to evaluate the relationship between asymptomatic (immunologic) hypersensitivity and symptomatic (clinical) hypersensitivity interspecies of the same botanical family. Sixty-nine children with skin prick tests positive to one or more legumes were evaluated in a DBPCFC study. Clinical reactivity to a legume was confirmed in 41 of the children, but only 2 (5%) were allergic to more than one legume (peanut and soybean). Jones

et al¹⁴ reported that 31 (21%) of 145 patients suspected of having cereal grain hypersensitivity, as determined by history or skin prick test results, had symptomatic reactivity by DBPCFC, and only 6 (20%) of the reactions occurred in response to two or more cereal grains. Bock and Atkins²⁰ studied a group of 32 children with positive DBPCFC to peanut. Each of these patients was also skin tested with pea and soybean. Twenty-two patients had positive skin test results to soybean or pea, but only two (6%) patients had positive double-blind challenges (one to pea and one to soybean). During the same period, 14 different children who tolerated peanut ingestion were evaluated for adverse reactions to tree nuts. Only 2 (15%) patients reacted by DBPCFC to two or more tree nuts.

In this study we evaluated actual clinical allergy to seven commonly consumed foods of the Rosaceae family in adult subjects, including six fresh fruits (apricot, plum, strawberry, apple, peach, and pear) and a tree nut (almond). These foods are an important part of the staple diet in Spain, with a per capita sale of approximately 32.4 kg per year.²¹ Our study also shows extensive immunologic reactivity to foods of the Rosaceae family (median 5 foods). Twenty-six and 24 patients had positive skin prick tests and CAP system FEIA to foods of the Rosaceae family, respectively; from these 23 (88%) and 24 (100%) had immunologic reactivity to two or more evaluated foods. Actual clinical allergy to a food of the Rosaceae family was confirmed in 22 patients. Ten (46%) patients were clinically allergic to more than one evaluated food. Several studies designed to assess the *in vivo* and *in vitro* cross-reactivity between some fruits of the Rosaceae family provided additional information on clinical cross-reactivity. Pastorello et al⁴ evaluated the immunologic cross-reactivity by immunoblot inhibition between fruits of the Prunoideae subfamily (peach, cherry, apricot, and plum). They selected patients on the basis of a clear history of oral allergy syndrome to peach and positive skin prick test responses and radioallergosorbent test results for this fruit and for the other main Prunoideae (cherry, plum, and apricot). Patients underwent OFCs with peach, cherry, apricot, and plum. Sixty-three percent or 12 of 19 patients had positive OFC to more than one Prunoideae fruit. More recently, the same group¹¹ evaluated the IgE reactivity pattern to an apple extract with sera from 43 patients with allergy to apple confirmed by OFC; other Rosaceae causing symptoms were reported to occur in 31 (72%) subjects. These figures of clinical cross-reactivity among Rosaceae are significantly higher than those previously reported for other botanical families (Fig 4).

Peach was the most common cause of Rosaceae clinical allergy, alone (10 patients) or associated with other fruits (12 patients), especially apple, apricot, and plum, in our study. In fact, it can be established that clinical cross-reactivity of peach with other Rosaceae was 46%. Positive results of skin tests and CAP System FEIA with peach were associated with high rates of clinical allergy (92% and 96%, respectively). However, significantly lower rates were found for the remaining Rosaceae foods evaluated (Fig 2).

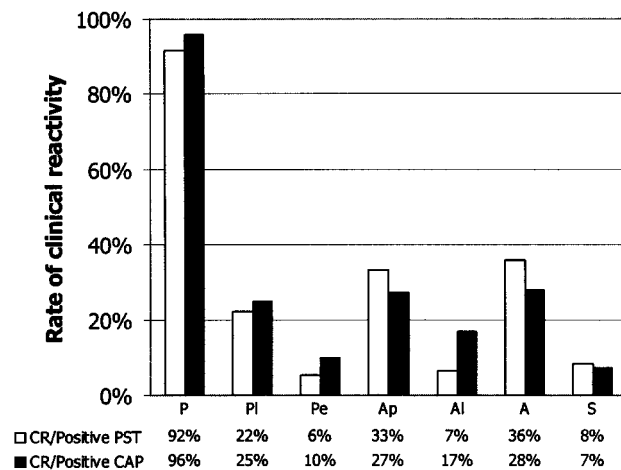


FIG 2. Rates of clinical reactivity (CR) to seven foods of the Rosaceae family in patients with a positive skin prick test (PST) (white columns) and CAP System FEIA (CAP) results (gray columns). P, Peach; Pl, plum; Pe, pear; Ap, apple; Al, almond; A, apricot; S, strawberry. Rate of clinical reactivity = No. of confirmed clinical reactions/No. of positive results of skin prick tests or CAP System FEIA.

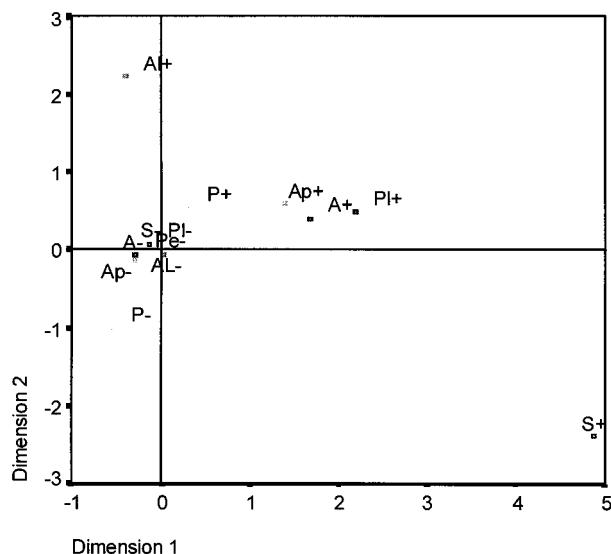


FIG 3. Two-dimensional scatterplot produced by multiple correspondence analysis of the pattern of clinical reactivity to seven foods of the Rosaceae family. It shows a pattern of simultaneous reactivity to apricot (A), plum (Pl), apple (Ap), and peach (P). Pe, Pear; Al, almond; S, strawberry.

TABLE II. Symptoms of 40 reactions to Rosaceae foods in 22 patients

	Peach	Plum	Pear	Apple	Almond	Apricot	Strawberry
Reported reactions	31	6	3	9	4	8	3
Confirmed reactions	22 (71%)	4 (67%)	1 (33%)	6 (67%)	1 (25%)	5 (63%)*	1 (33%)
Symptoms							
Oral	13	2	—	2	1	3	—
Cutaneous	3†	—	—	—	—	—	—
Gastrointestinal	1	1†	—	—	—	—	—
Generalized anaphylaxis‡	5	1	1	4	—	2	1

*Two of them (patients No. 10 and 28) were not reported reactions (detected by systematic challenges).

†A patient also had oral symptoms. No patients had isolated respiratory symptoms.

‡Not challenged.

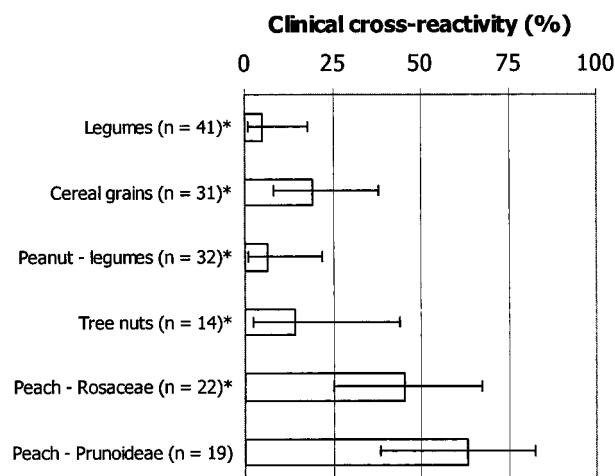


FIG 4. Percentage (95% CI) of clinical cross-reactivity among foods of vegetable origin. Legumes included peanut, soybean, pea, green bean, and lima bean.¹² Cereal grains included wheat, rye, barley, oat, rice, and corn.¹³ Peanut—legumes (pea and soybean).¹⁷ Tree nuts included walnut, cashew, pecan, pistachio, and hazelnut.¹⁷ Peach—Rosaceae (apricot, almond, plum, strawberry, apple, and pear) (current study). Peach—Prunoideae (plum, apricot, and cherry).³ Asterisk, DBPCFC studies.

Finally, actual clinical reactivity to Rosaceae foods was confirmed in 38 of the 64 reported reactions in 22 patients. Nevertheless, the systematic evaluation performed in our patients by means of oral challenges detected two additional unreported reactions (both to apricot in patients No. 10 and 28). These findings have some important implications when patients reporting allergic reactions to a Rosaceae fruit, especially peach, are evaluated. If the reported reaction is confirmed, current tolerance to other Rosaceae fruits, particularly apricot, apple, and plum, should be precisely established by OFC, unless there has been ingestion without symptoms after the reported reaction.

In conclusion, positive skin test and CAP System FEIA results with Rosaceae foods should not be taken as the only guide for probably unnecessary dietary restrictions. Nevertheless, the potential clinical allergy to other Rosaceae foods should not be overlooked. Currently, only challenge testing with these foods should provide a rationale for a comprehensive management plan.

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