

Original article

What safety measures need to be taken in oral food challenges in children?

Background: Food allergens are often accused of causing numerous ailments. This is particularly true for the pediatric population, where the incidence of food allergy is four times as high as in adults. As food challenges may provoke life-threatening reactions, intensive safety measures need to be taken during provocation, and prompt medical intervention may become necessary.

Methods: We retrospectively evaluated 349 oral challenges in 204 children with atopic dermatitis, looking for criteria to help the physician decide which patients need medical intervention.

Results: A total of 178 (51%) oral food challenges with the four allergens (cow's milk [CM], hen's egg [HE], wheat, and soy) showed a positive clinical reaction. Of these, 120 (67%) needed medical intervention. In 42 (35%) cases, intervention was parenteral, and oral medication was given in 78 (65%) cases. There was a strong positive correlation (90%) between the level of specific IgE and the need for medical intervention (≥ 17.50 kU/l for CM, wheat, and soy; ≥ 3.50 kU/l for HE). Patient history of food allergy was an indicator of the need for medical intervention ($P=0.01$). A positive patient history and a high level of specific IgE were significantly ($P=0.003$) associated with parenteral medication in HE.

Conclusions: Patient history of food allergy is a reliable indicator of the need for medical intervention in the cases of CM, wheat, and soy regardless of the level of specific IgE. With HE, a positive patient history plus a high level of specific IgE significantly indicates the need for parenteral medication. On the basis of our results, we recommend establishing intravenous access in children with a level of specific IgE of ≥ 17.50 kU/l (CAP class 4) to CM and wheat, or with specific IgE of ≥ 3.50 kU/l (CAP class 3) to HE.

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Food allergens are often accused of causing numerous ailments. This is particularly true for the pediatric population, where the incidence of food allergy is four times as high as in adults (1–3). Especially, about one-third of children with atopic dermatitis (AD) are found to suffer from food allergy as concomitant, clinically active disease (2–4). Symptoms range from cutaneous, gastrointestinal, or respiratory symptoms to the worsening of the AD. These symptoms occur individually and in combination, the most dramatic presentation being anaphylactic shock (2, 3, 6).

The “gold standard” for diagnosing the clinical relevance of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC) (7). As food challenges carry the risk of provoking life-threatening reactions, intensive safety measures need to be taken during provocation in case prompt medical intervention becomes necessary (8, 9). Although an invasive

procedure, intravenous catheters have the advantage of allowing immediate parenteral drug administration. Children with AD have been shown often to have a permanent colonization by *Staphylococcus aureus*, a fact which represents an added risk of infection of the intravenous catheter (local infection and sepsis).

Several publications offer general advice on the management of allergic reactions (10–14). Since no prediction can be made as to the severity of symptoms, it is generally recommended that any allergic reaction other than a slight cutaneous reaction be treated systemically via the intravenous route (13, 14). To date, there are no guidelines to help in deciding which patients need medical intervention, and no study has specifically addressed the problem of safety measures in DBPCFC. The aim of our study was to investigate the reliability of predictors, such as patient history, specific IgE in serum, or type of allergen, for the outcome of

provocations and, consequently, their reliability in guiding the pediatrician in the decision to establish intravenous access prior to food challenge. We propose criteria which could help to decide for or against intravenous access.

Material and methods

Patients

We retrospectively evaluated 349 oral provocations in 204 children (89 girls, 115 boys), whose ages ranged from 3 months to 19 years (median 33 months). Sixty-one infants were below 1 year of age, 92 children were between 1 and 3 years, 25 children were between 4 and 7 years, and 26 children were older than 7 years. A total of 170 (83%) suffered from AD, as defined by the criteria of Sampson and Seymour modified from Hanifin & Rajka (16–18). Of the entire group, 78 children (38%) had a history of immediate- or late-type clinical reactions, 126 children (62%) had no history but showed atopic disorders (AD), and 162 (79%) children were sensitized (specific IgE of >0.35 kU/l) to at least one of the following allergens: cow's milk (CM), hen's egg (HE), wheat, and soy. The remaining 42 subjects (21%) were not sensitized.

Determination of serum IgE

Blood was drawn prior to food challenge. Patient sera were analyzed for concentrations of total IgE and specific IgE antibody titers to CM, HE, wheat, and soy, as determined by FEIA with the Pharmacia CAP-System (Kabi-Pharmacia, Uppsala, Sweden) (19). The detection limit was 0.35 kU/l IgE; children were regarded as sensitized if specific IgE was above the detection limit.

History and physical examination

A thorough medical history with particular attention to the foods involved, symptoms evoked, timing of symptoms, age of onset of sensitivity, current dietary plan, and the method of treatment was obtained. In the interview, we focused on current symptoms and immediate- or late-type clinical reactions (food-related

worsening eczema and gastrointestinal symptoms) known to the patients or their parents. The children or parents were asked about other atopic disorders in the child or family. A thorough physical examination including the cutaneous, respiratory, and gastrointestinal systems was undertaken.

Oral food challenges

In total, 349 consecutive food challenges were surveyed. The most commonly tested food allergens in children were CM, HE, wheat, and soy. The data analysis presented concentrates on this patient group. Children were advised to avoid antihistamines (72 h) before provocation. Topical glucocorticosteroids were allowed twice a day at a concentration of 1% hydrocortisone or 0.1% betamethasone.

Oral food challenges were performed either in a double-blind, placebo-controlled manner ($n=210$), as previously described, or as open food challenge ($n=139$) (7). Randomization and preparation of the challenges were performed by the clinical dietitian. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100.0 ml) of fresh pasteurized CM containing 3.5% fat and soy milk or placebo (Neocate[®], SHS, Liverpool, UK) were administered. Raw HE (white of egg and yolk) and wheat powder (Kröner, Ibbenbüren, Germany) dissolved in water (total amount of 10 g of wheat protein) were given in a similar regimen (ml) as for CM. The time interval between doses was 20 min.

Provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed for 48 h after each challenge on an inpatient basis. The food challenges were scored as positive by a pediatric allergist if a single symptom or a combination of the following objective clinical reactions was observed: urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, shock, or exacerbation of eczema.

Type and route of medication

Before a food challenge started, the full emergency equipment including drugs (epinephrine, antihistamines, glucocorticosteroids, and β -agonists) was pre-

Table 1. Staging and intervention of allergic reactions (modified from Tryba, Ref. 13)

Stage	Site	Symptoms	Management
0	Local reactions	Clearly defined cutaneous reactions (e.g., swelling of lips)	Oral antihistamine
I	Mild generalized reactions	Disseminated urticaria, flush, pruritus; mucosal reactions (nasal, conjunctival)	i.v. antihistamine, i.v. steroid
II	Definite generalized reactions	Mild dyspnea, tachycardia, mild hypotension	i.v. antihistamine, i.v. steroid, fluid, inhaled β_2 -adrenergics, inhaled epinephrine
III	Severe generalized reactions	Severe hypotension, severe dyspnea, somnolence	i.v. epinephrine, i.v. antihistamine, i.v. steroid, oxygen, fluid, inhaled epinephrine, inhaled β_2 -adrenergics, etc.
IV	Organ failure	Cardiovascular collapse	Resuscitation

Table 2. Reactions to positive food challenges ($n=178$)

Reactions to positive food challenge	CM	HE	Wheat	Soy
Cutaneous ($n=125$)				
Immediate (urticaria, flush, angioedema)	31	39	4	1
Delayed (worsening eczema)	11	5	15	8
Immediate and delayed	4	5	1	1
Gastrointestinal ($n=45$)				
Immediate (emesis, diarrhea)	9	12	1	1
Immediate and skin symptoms	10	10	2	0
Respiratory ($n=8$)				
Immediate (stridor/wheezing)	3	1	0	0
Immediate and skin symptoms	4	0	0	0

pared and was at hand throughout the provocation. Intravenous access was established in 110 (53.9%) children, on either the child's hand or head, and this stayed in place for an average of 3 days. The indication for intravenous access was assessed in each of the children before food challenge. Criteria for the establishment of intravenous access were type of allergen (HE), patient history of systemic reactions, or an unknown type of reaction (i.e., patient had a history of AD or was sensitized without a history of contact, as common in breast-fed infants). The children were observed by the dietitian, nurse, or physician constantly for the first hour. The pediatrician checked the patient every 15 min for around another hour.

According to the criteria of Tryba (13), medication was given as soon as one or more of the following symptoms were noted: nausea, dyspnea or tachycardia together with pruritus, urticaria, flush, angioedema, or beginning centralization. If medication was necessary, oral, topical, parenteral, or inhalative application was decided upon by the pediatric allergist after examining the patient on the basis of the severity and progression of symptoms (Table 1).

Statistical analyses

The statistical analysis was performed by SPSS/PC (Version 8.0.0), SPSS, Inc., USA. Pearson's chi-square test was used to analyze the association of categorical data, and the nonparametric Mann-Whitney U-test or Kruskal-Wallis test for the association of categorical and

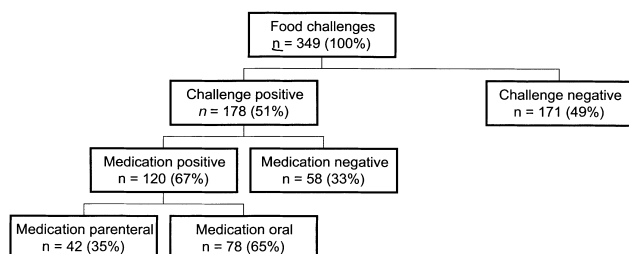


Figure 1. Frequency of positive food challenges and medical intervention (oral/parenteral).

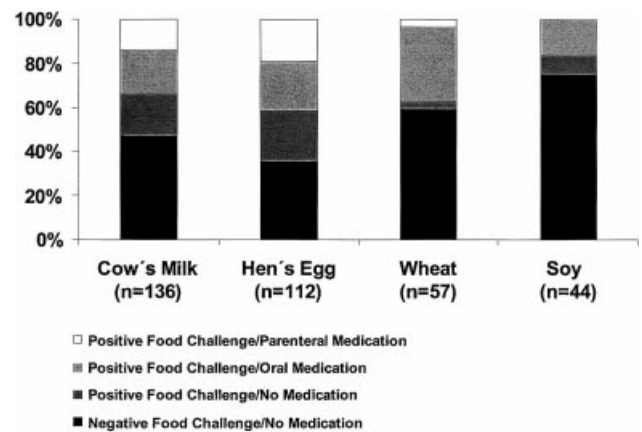


Figure 2. Results of food challenges: reaction and medical intervention for each allergen.

continuous data. Logistic regression analysis was performed with "medication" as the dependent variable. Statistical significance was accepted at $P < 0.05$.

Results

Oral provocations

Of the total number of 349 oral food challenges with the four allergens, 178 (51%) showed positive clinical reactions. Symptoms and frequency of the positive food challenges for each allergen are summarized in Table 2. Cutaneous symptoms were observed in 125 (70%) of positive food challenges and with all types of allergens. Immediate reactions primarily consisted of urticaria, flush, or angioedema, and delayed reactions, such as the worsening of AD, were seen within the first 4–48 hours. Gastrointestinal symptoms (nausea, emesis, and diarrhea) occurred predominantly with CM and HE in 45 (25%) of positive reactions. Respiratory symptoms

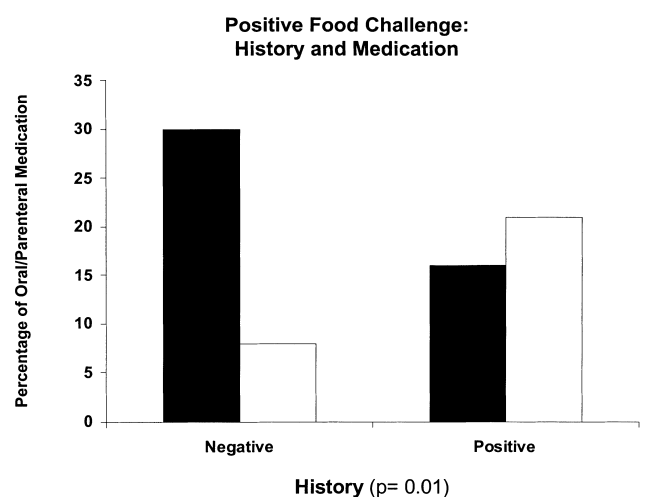


Figure 3. If food challenge was positive, we looked for history and what kind of medication was needed. Black: oral medication; white: parenteral.

were found only in eight (5%) provocations after giving CM and HE; no symptoms appeared with wheat. In soy challenges, few positive reactions were seen: one child with specific IgE of >100 kU/l reacted, and 50% of children with specific IgE of ≥ 17.50 kU/l showed symptoms of food allergy. No severe clinical reactions were observed when challenging with this allergen.

Medication

Of the 178 (51%) positive provocations, 120 (34%) subjects needed medical intervention, and 58 (17%) had a positive challenge but needed no medication. In 42 (35%) food challenges, medical intervention was parenteral, and oral medication was given in 78 (65%) cases (Fig. 1). The results of food challenges for each allergen and type of medical intervention are shown in Fig. 2. Of the 42 parenteral interventions, 19 were for CM, 21 for HE, and two for wheat. No parenteral medication had to be used in the soy challenges. Oral medication was given in 78 (65%) cases (27 CM, 25 HE, 19 wheat, and seven soy).

Level of specific IgE and medication

Positive clinical reactions were strongly correlated with the level of specific IgE: for CM, wheat, and soy, 90% of challenges with a level of specific IgE of ≥ 17.50 kU/l (CAP class 4) were positive, while challenges for HE were positive for a level of specific IgE of ≥ 3.50 kU/l (CAP class 3). CM, wheat, and soy challenges with specific IgE 0–3.50 kU/l were found to be positive in 0–49% of cases. Medical interventions were necessary in 65% of all positive food challenges.

Patient history and medication

Of the 204 children studied, 78 (38%) had a positive history of perceived food allergy to one or more of the tested allergens. Medication was given in both groups (Fig. 3). Multiregression analysis was carried out to identify determinants for medical intervention. Patient history of food allergy was an indicator of the need for medical intervention ($P=0.01$). A positive patient history and a high level of specific IgE (≥ 3.50 kU/l) were significantly associated with parenteral medication in HE ($P=0.003$). No parenteral medication was necessary in the soy challenges.

Complications

A total of four children showed complications related to the intravenous access. The rate of severe complications connected with intravenous catheters was 0.3%. Three children developed local thrombophlebitis of the hand or arm; a girl developed septic arthritis of the hip. *S. aureus* was identified as the causative bacterium in the blood cultures and was also found on the patient's skin.

Discussion

The prevalence of food hypersensitivity in the pediatric population was found to be 4–8% (1), with a much greater prevalence of about 33% in those suffering from AD (2, 3, 5, 20, 21). Patient history, skin prick test, and specific IgE are indicative of food allergy, but the “gold standard” for a diagnosis of food allergy is the DBPCFC (7). Allergic reactions can be found to almost all kinds of foods (22, 23), but a small number of allergens account for the majority of complaints: CM, HE, wheat, and soy (2, 21). The distribution of allergic reactions to foods observed in our studied population reflects this pattern of distribution.

We noted a clear difference in the severity of reactions per allergen and the type and route of subsequent medical intervention: in 78 (65%) food challenges, oral medication was necessary; in 42 (35%) challenges, interventions were parenteral. Medication was given according to the severity of symptoms, but ambiguity existed with regard to the factors leading pediatricians to establish intravenous access (13). Intravenous catheters are vital in the treatment of anaphylactic reactions, as they secure the quick and safe administration of parenteral medication. The disadvantages of using intravenous lines are the invasive nature of the procedure and the threat of infection. Meticulous skin disinfection is obligatory in children with AD, because the chronic bacterial skin colonization with *S. aureus* puts them at increased risk of line infection (23–25). As line infection and bacteremia are a danger with every intravenous catheter, none should be administered without good reason, nor should they remain in place longer than indicated. Hence, a brief period of intravenous access is mandatory. The nature of DBPCFC makes it impossible to determine how long intravenous access will be needed, as many test episodes may be required.

As our data show, patient history of food allergy proved to be a significant indicator of a positive food challenge and the need for medical intervention. Furthermore, the level of specific IgE and patient history were predictors of the need for parenteral medication in HE challenges. The conjunction of a positive history and a level of specific IgE of ≥ 3.50 kU/l correlated with a positive outcome of HE provocations in 90% of challenges with subsequent primarily intravenous intervention. HE is acknowledged to be a very strong allergen. On the basis of current evidence, it has been generally accepted that there is a need to establish intravenous access in every provocation. In our study, we also observed the most dramatic reactions when challenging with HE, but we saw no anaphylactic shock in this series of challenges.

On the basis of our results, we recommend establishing intravenous access in children with specific IgE of ≥ 3.50 kU/l during HE challenges. In CM, a positive reaction was seen in over 90% of provocations with

specific IgE of ≥ 17.50 kU/l. The reactions were again mostly cutaneous, and interventions were mostly topical or oral. When we challenged with wheat protein, the symptoms were mainly gastrointestinal and required oral or parenteral medication. According to our results, the use of intravenous access seems to be advisable for children with suspected allergy to CM or wheat showing a level of specific IgE of ≥ 17.50 kU/l. In soy challenges, no severe clinical reactions were observed. According to our data, regardless of the level of specific IgE, intravenous access does not seem to be compulsory in this group.

In conclusion, patient history of food allergy is a reliable indicator of the need for medical intervention in CM, wheat, and soy regardless of the level of specific IgE. In HE, a positive patient history plus a high level of specific IgE significantly indicates the need for parenteral medication. On the basis of our results, we recommend establishing intravenous access in children with a level of specific IgE of ≥ 17.50 kU/l (CAP class 4) to CM and wheat, and in those with specific IgE of ≥ 3.50 kU/l (CAP class 3) to HE.

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