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Small percentage of anaphylactic reactions treated with epinephrine during food challenges in Dutch children

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ABSTRACT

Background: Severe allergic reactions, including anaphylaxis, occur during oral food challenges (OFCs) and the first-line treatment of anaphylaxis is epinephrine.

Objective: To evaluate the percentage of anaphylactic reactions treated with epinephrine during OFCs and to identify associated factors for the administration of epinephrine.

Methods: Children who underwent an OFC with peanut, hazelnut, cow's milk, hen's egg, or cashew nut from 2005 through 2015 in the Netherlands were evaluated. Children with reactions meeting the criteria for anaphylaxis according to the European Academy of Allergy and Clinical Immunology guidelines for food allergy and anaphylaxis were included. Children with an anaphylactic reaction treated with vs without epinephrine were compared. Possible factors associated with the administration of epinephrine, such as age, sex, symptoms consistent with asthma, history of an allergic reaction to the tested allergen, and symptom types during the anaphylactic reaction, were evaluated using logistic regression analysis.

Results: Eighty-three children in clinical and research settings (43% boys; median age, 7 years; range, 1–17) who met the criteria for anaphylaxis were included in this study. Thirty-two of 83 children (39%) with anaphylaxis were treated with epinephrine. Respiratory symptoms during the OFC were treated significantly more often with epinephrine than gastrointestinal symptoms ($P = .01$).

Conclusion: Only 39% of children with anaphylaxis, according to the guideline criteria, were treated with epinephrine during the OFC and most of these children had respiratory symptoms. There is need for an easy-to-use international guideline for the treatment of allergic symptoms during OFCs.

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Introduction

Oral food challenges (OFCs) are usually required to confirm the diagnosis of food allergy, to evaluate food allergy over time, or to

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confirm oral tolerance to a tested food. The OFC is considered the reference standard in the diagnosis of food allergy.¹ Literature on the severity of allergic symptoms during OFCs describes prevalence in the range of 20% to 50% for anaphylactic reactions.^{2,3} Currently, anaphylaxis is a clinical diagnosis often based on criteria of the European Academy of Allergy and Clinical Immunology (EAACI) guidelines for food allergy and anaphylaxis⁴ (Table 1). The first-line treatment of anaphylaxis is epinephrine.⁵ However, the actual use of epinephrine for the treatment of anaphylaxis during OFCs is poorly described and numbers are unknown. Furthermore, the guidelines were not specifically developed for the use of epinephrine during OFCs. The primary aim of this study was to evaluate the percentage of anaphylactic reactions treated with epinephrine during OFCs and to identify factors associated with the administration of epinephrine.

Table 1
Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:	
1	Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg, generalized hives; pruritus or flushing; swollen lips, tongue, or uvula) and ≥ 1 of the following:
a	Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, decreased PEF, hypoxemia)
b	Decreased BP and associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2	≥ 2 of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a	Involvement of skin and mucosal tissue (eg, generalized hives, itch or flush, swollen lips, tongue, or uvula)
b	Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, decreased PEF, hypoxemia)
c	Decreased BP with associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d	Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3	Decreased BP after exposure to known allergen for that patient (minutes to several hours)
a	Infants and children: low systolic BP (age specific) or $>30\%$ decrease in systolic BP ^a
b	Adults: systolic BP <90 mm Hg or $>30\%$ decrease from that person's baseline

Abbreviations: BP, blood pressure; PEF, peak expiratory flow.

^aLow systolic BP for children is defined as lower than 70 mm Hg at 1 month to 1 year, lower than 70 mm Hg $+(2 \times \text{age})$ at 1 to 10 years, and lower than 90 mm Hg at 11 to 17 years.

Methods

Study Design and Subject Selection

This retrospective study evaluated open and double-blinded placebo-controlled (DBPC) OFCs with peanut, hazelnut, cow's milk, hen's egg, or cashew nut performed in children 0 to 18 years old from 2005 through 2015 at 3 tertiary care centers in the Netherlands. The OFCs were performed in a clinical setting (C-group; open and DBPC OFCs) and a research setting (R-group; DBPC OFCs; IDEAL cashew nut study, collaboration of 3 tertiary care centers for food allergy, trial number NTR3572).⁶ Children with an anaphylactic reaction during the OFC were included. Criteria of the EAACI guidelines were used to define anaphylaxis⁴ (Table 1). Information on age, sex, skin prick test results of tested allergens, asthma, history of allergic reaction, type and severity of reaction during the OFCs, time from exposure to reaction, and the amount of allergen causing the reaction were collected in a database.

Oral Food Challenge

All children underwent an OFC with peanut, hazelnut, cow's milk, hen's egg, or cashew nut. The tested allergen was administered in increasing amounts at a maximum of 7 doses at 30-minute

intervals. The OFC material was standardized and validated⁷ and the amount of allergen per dose increased semi-logarithmically. The first step consisted of 1 mg of food protein, followed by increasing doses of 3, 10, 30, 100, 300, and 1,000 mg. In the R-group, the children received an extra dose (dose 8) containing 1,736 mg of cashew nut protein. In the present study, a failed OFC was considered a positive result (ie, allergy confirmed) when (1) objective symptoms occurred, (2) when subjective symptoms reoccurred twice after the same dose of OFC material had been administered (ie, symptoms occurring on 3 consecutive administrations of the same dose),⁸ or (3) severe subjective symptoms persisted for longer than 1 hour. Children with an anaphylactic reaction during the OFC received a prescription for an epinephrine auto-injector with extensive instructions for use.

Statistical Analysis

The patient and study characteristics were reported as median, range, and proportion. Children with an anaphylactic reaction treated with epinephrine were compared with children with an anaphylactic reaction not treated with epinephrine. Potential influencing factors associated with the administration of epinephrine during an anaphylactic reaction, such as age, sex, symptoms consistent with asthma, history of an allergic reaction to the tested allergen, symptom types during the anaphylactic reaction, open OFCs vs DBPC OFCs, the individual challenged food, having 1 vs multiple food allergies, eczema, rhinoconjunctivitis, and previous anaphylactic reaction, were investigated with multivariable logistic regression analysis. Characteristics of children from the C-group and R-group were compared using χ^2 test, Mann-Whitney *U* test, and univariate logistic regression. *P* values less than .05 were considered statistically significant. Statistical analyses were done using SPSS Statistics 21 (IBM Corp, Armonk, New York).

Results

Study Population

In total, 312 of 900 (35%) OFC reactions (714 [79%] in the C-group and 186 [21%] in the R-group) with peanut, hazelnut, cow's milk, hen's egg, or cashew nut were assessed as positive (175 of 714 in the C-group [25%]; 137 of 186 in the R-group [74%]). Of the 175 positive OFC reactions in the C-group, 34 children (19%) met the criteria for anaphylaxis; of the 137 positive OFC reactions in the R-group, 49 children (36%) met the criteria for anaphylaxis. Eighty-three children (43% boys; median age, 7 years; range, 1–17 years) were included in this study. For the C-group and R-group combined, 32 of 83 children (39%) with an anaphylactic reaction received epinephrine during the OFC (Table 2). Two children in the R-group and 6 children in the C-group received epinephrine

Table 2
Number of Patients Treated With Epinephrine With and Without Anaphylaxis in the Clinical and Research Groups

	Positive challenge reactions 312	Anaphylaxis		No anaphylaxis	
		83 (27%)		229 (73%)	
		Epinephrine	No epinephrine	Epinephrine	No epinephrine
Clinical group	175	24	10	6	135
Peanut	74	11 (15%)	4 (5%)	3 (4%)	56 (76%)
Hazelnut	26	3 (12%)	1 (4%)	1 (4%)	21 (81%)
Milk	30	4 (13%)	2 (7%)	1 (3%)	23 (77%)
Egg	45	6 (13%)	3 (7%)	1 (2%)	35 (78%)
Research group	137	8	41	2	86
Cashew	137	8 (6%)	41 (30%)	2 (1%)	86 (63%)
Total epinephrine		32 (39%)		8 (3%)	

Table 3

Demographic Clinical Characteristics of Children With Anaphylactic Reactions During Oral Food Challenges in the Clinical and Research Groups (N = 83)

	Clinical group	Research group	Statistically significant difference (<i>P</i> value)
Total, n (%)	34 (19)	49 (37)	
Boys, n (%)	14 (41)	22 (45)	.82
Age (y), median (range)	5.5 (1.1–17.0)	9.0 (3.2–17.5)	.003
History of allergic reaction to tested allergen, n (%)	19 (56)	36 (73)	.10
Self-reported asthma, n (%)	17 (50)	15 (31)	.07

without meeting the criteria for anaphylaxis. These 8 cases were not included in the analysis.

In the R-group, all OFCs were performed in DBPC fashion. In the C-group, 16 of 34 OFCs (47%) were open and the others were DBPC. Reasons to perform an open OFC were age (<4 years) or to ascertain tolerance for egg or milk.

The median ages of children in the C-group and R-group were 5.5 and 9.0 years, respectively, and differed significantly ($P = .003$). Self-reported asthma was more prevalent in the C-group ($P = .07$). The sex of the children and the number of patients with a history of allergy to the tested allergenic food were comparable (Table 3). Children in the C-group were treated significantly more often with epinephrine than those in the R-group ($P < .001$).

Symptoms During OFCs

The most commonly observed anaphylactic reaction type was a combination of skin and gastrointestinal symptoms (50 children; 60%), followed by skin symptoms and respiratory symptoms (20 children; 24%). Gastrointestinal with cardiovascular and gastrointestinal with respiratory symptoms each were observed once. A decrease in blood pressure was reported in 1 child (Table 4). The symptoms of children treated with epinephrine without anaphylaxis ($n = 8$) consisted mainly of severe persistent gastrointestinal symptoms or lower airway symptoms.

The type of anaphylaxis in the C-group and R-group differed significantly ($P < .001$). Respiratory symptoms (with skin symptoms) were most frequently observed in the C-group and gastrointestinal symptoms (with skin symptoms) were most frequently observed in the R-group. Other medications, in addition to or instead of epinephrine, used to treat severe reactions during the OFC were antihistamines (oral or intravenous), corticosteroids, and/or β_2 -agonists (Table 5).

Table 4

Type of Anaphylactic Reactions for Positive Food Challenge Test Results

Anaphylactic symptoms (N = 83)	Clinical group (n = 34)	Research group (n = 49)
Skin and respiratory	17	3
Skin and gastrointestinal	10	40
Skin, respiratory, and gastrointestinal	5	6
Respiratory and gastrointestinal	1	0
Skin and decrease of blood pressure ^a	0	0
Respiratory and decrease of blood pressure ^a	0	0
Gastrointestinal and decrease of blood pressure ^a	1	0
Decrease of systolic blood pressure >30%	0	0

^aOr associated symptoms such as syncope, incontinence, and collapse.**Table 5**

Additional Medication for Treatment of Severe Reactions During Food Challenge Tests

	Epinephrine (n = 32), n (%)	No epinephrine (n = 51), n (%)
Oral H ₁ antihistamine	29 (91)	37 (73)
Intravenous antihistamine	9 (28)	1 (2)
β_2 -agonist	7 (22)	5 (10)
Corticosteroid	25 (78)	2 (4)

Potential Influencing Factors of Epinephrine Treatment During Anaphylaxis

Possible factors, such as age, sex, symptoms consistent with asthma, and history of an allergic reaction to the tested food, were not significantly associated with the administration of epinephrine. Only the combination of symptom types during the anaphylactic reaction was significantly associated with the administration of epinephrine ($P = .01$; Table 6). A smaller number of children were treated with epinephrine for their anaphylactic reaction when the symptoms were of gastrointestinal origin (22%) compared with symptoms of respiratory origin (both in combination with skin symptoms; 70%).

Furthermore, there were no significant differences in epinephrine vs no epinephrine treatment with respect to OFC method (open vs DBPC OFCs; $P = .21$), the individual foods ($P = .51$), having 1 vs multiple food allergies ($P = .99$), eczema ($P = .81$), rhinoconjunctivitis ($P = .28$), or previous anaphylactic reaction ($P = .80$).

Discussion

We performed a retrospective study on the epinephrine treatment of anaphylactic reactions during OFCs in 83 Dutch children. To our knowledge, this is the first study on the rate of epinephrine treatment for anaphylactic reactions during OFCs. Only 33 children (39%) with anaphylaxis were treated with epinephrine in our study. This relatively small percentage could be explained by the fact that most children developed gastrointestinal symptoms (in combination with skin symptoms). These children often were not treated with epinephrine, although this combination of symptoms meets the criteria of anaphylaxis according to the EAACI guidelines.⁴ One could argue epinephrine should be administered in these cases

Table 6

Potential Influencing Factors of Epinephrine Treatment During Anaphylaxis (N = 83)

	Epinephrine (n = 32), n (%)	No epinephrine (n = 51), n (%)	Statistical significance (<i>P</i> value)
Age (y)			.22 ^a
0–3	11 (78)	3 (22)	
4–8	13 (37)	22 (63)	
≥9	8 (23)	26 (77)	
Sex			.36
Boys	12 (33)	24 (67)	
Girls	20 (42)	27 (58)	
Asthma			.29
Yes	15 (46)	17 (54)	
No	17 (33)	34 (77)	
History of reaction			.39
Yes	18 (32)	37 (68)	
No	14 (50)	14 (50)	
Type of anaphylaxis (symptoms)			.01
Skin and respiratory	14 (70)	6 (30)	
Skin and gastrointestinal	11 (22)	39 (78)	
Skin, respiratory, and gastrointestinal	6 (54)	5 (46)	

^aBased on continuous variables.

with relatively mild symptoms without compromised circulation or respiration. Gastrointestinal symptoms are not perceived as potentially life-threatening symptoms in contrast to respiratory symptoms.⁹ Furthermore, decrease in blood pressure, which can be a life-threatening sign, was not common in our group of children with anaphylaxis during the OFCs, which is in agreement with the findings of Caffarelli et al.¹⁰

A study by Noone et al.¹¹ showed comparable results; they also investigated the use of epinephrine during OFCs, performed as a screening test for food allergy therapy trials. OFCs were performed with peanut, milk, cashew nut, sesame seed, salmon, and codfish in children and adults. Of the 74 positive DBPC OFC reactions, only 29 (39.2%) were treated with epinephrine. Lower respiratory tract symptoms and cardiovascular symptoms were significantly associated with epinephrine treatment. The study did not specifically focus on anaphylaxis.

Had other definitions of anaphylaxis or grading systems been applied to the systemic reactions in this study, the percentage of anaphylactic reactions treated with epinephrine would have been larger. A study by Eller et al.¹² emphasized that there appeared to be different scoring systems for anaphylaxis and, hence, the use of epinephrine. They compared 6 existing instruments for scoring anaphylaxis severity and concluded that most scored symptoms are transferable but that the decision for epinephrine administration varies considerably among different scoring systems. As a result of the heterogeneity of severity scoring systems, Niggemann and Beyer¹³ presented a 3-category grading system for allergic reactions, in which they tried to overcome disadvantages of the existing systems and avoid the problem of grading “anaphylaxis” without systemic allergic symptoms.

Criteria that describe whether an allergic reaction can be defined as an anaphylactic reaction have been reported, but there is no universal agreement in the criteria for administering epinephrine in the context of OFCs.¹⁴ Currently, in the absence of clear diagnostic criteria, many physicians rely on personal clinical experiences to provide guidance on the treatment of anaphylaxis. Standard guidelines with clear criteria on epinephrine administration during OFCs are needed. Such a guideline based on the type and severity of symptoms should provide clarity on the precise moment of epinephrine administration during OFCs. The guideline also should provide recommendations on the use of other medications and combinations with epinephrine (eg, antihistamines, β_2 -agonist, and corticosteroids).

A remarkable finding in this study is that the 2 groups showed a female predominance, which is contrary to the male predominance reported in by Grabenhenrich et al.¹⁵ (35% female). This suggests that selection bias favoring female predominance could have been operative in our study, although other forms of bias cannot be excluded.

There are several limitations in this study. First, the duration of the study might have influenced the results, especially during the retrospective analysis of 10 years; certain management and treatment practices might have changed. Second, we could not use the PRACTALL grading system.¹⁶ The PRACTALL guidelines were not yet published and therefore not in use in the clinic or in the study. Thus, symptoms were not graded as mild, moderate, or severe and the severity of symptoms could not be analyzed. Third, the study was restricted to certain allergens and cannot be extrapolated to other allergenic foods.

We found significantly greater use of epinephrine in the C-group than in the R-group, which is apparently caused by differences in

symptoms involved in anaphylaxis between these groups. The C-group showed more respiratory symptoms and these symptoms were significantly associated with epinephrine treatment. Nevertheless, pooling of patients from the research and clinical settings strengthens the study, because the 2 study groups supported the observation that not all children with anaphylaxis were treated with epinephrine and that respiratory symptoms (with skin symptoms) were more frequently treated with epinephrine.

In conclusion, only 39% of children with an anaphylactic reaction during an OFC were treated with epinephrine in this study. Gastrointestinal symptoms (with skin symptoms) were treated significantly less often with epinephrine than respiratory symptoms (with skin symptoms).

Although many authorities recommend giving epinephrine for anaphylaxis, this recommendation requires some further refinement and should be formulated to guide clinical practice. A simple algorithm based on symptoms and key characteristics of a reaction could be developed from the existing evidence and consolidated by consensus among experienced clinicians. Such a guideline would need to be tested in clinical practice to ensure its validity.

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