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# Management of acute food allergic reactions by general practitioners

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## KEY WORDS

Food allergy, management, general practitioner, anaphylaxis, epinephrine

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## SUMMARY

**Background:** Food is one of the leading causes of anaphylaxis. In the Netherlands, patients visit a general practitioner (GP) as often as an emergency department (ED) in case of an acute food allergic reaction. So far, the management of food allergic reactions by GPs has not been investigated. Therefore, we explored the management of acute food allergic reactions by GPs regarding specific treatment, observation period, prescription of emergency medication to treat new episodes, diet advices and referral to a specialist. **Methods:** A questionnaire containing three hypothetical cases (two anaphylactic and one mild case) with questions about their management was sent to 571 GPs. **Results:** Overall, treatment choice was dependent on the severity of the reaction (mild vs. anaphylaxis,  $P < .001$ ). However, epinephrine was used for treatment of anaphylaxis with mainly respiratory symptoms in only 27% and for anaphylaxis with mainly cardiovascular symptoms in 73%. At discharge, the percentages for prescription of self-injectable epinephrine were 53% and 77%, respectively. A short observation period of <2 hours was advised by 42% of general practitioners in case of anaphylaxis. **Conclusions:** Treatment of food induced anaphylaxis by GPs appears to be suboptimal: a considerable number of patients would not be treated with epinephrine for the acute reaction (especially anaphylactic cases with respiratory symptoms), the observation period chosen by GPs was often too short and self-injectable epinephrine was not always prescribed at discharge to treat possible new episodes. Education programs are needed to increase the awareness of GPs to recognize and treat anaphylactic reactions.

## Background

Food is one of the leading causes of anaphylaxis cases presenting to emergency departments (EDs) (1-4). While mild food allergic reactions can be treated adequately with antihistamines, epinephrine is the first choice treatment for severe reactions (5-7). Although rare, fatal anaphylaxis is related to absent or delayed administration of epinephrine (8). Current guidelines recommend treatment of an acute anaphylactic reaction with epinephrine, prescription

of self-injectable epinephrine at discharge with proper education and referral to an allergy specialist for further evaluation, like identification of and advice on how to avoid exposure to the offending allergen (5-7, 9-11). Studies across EDs that retrospectively analyzed charts of patients presenting with a food allergic reaction showed that concordance with recommended guidelines is low (12-15). Clark et al. found that only 24% of patients presenting to EDs with an anaphylactic reaction to food was treated with epinephrine at the acute moment, whereas at

discharge only 22% was prescribed self-injectable epinephrine to treat possible future reactions (12). In several studies, advice on how to avoid the offending allergen was given in less than 35% of cases and less than 24% of patients that experienced an acute food allergic reaction was referred to an allergy specialist (12-15).

In a previous study, we investigated the management of food allergic reactions from the patient perspective using a questionnaire that was sent to all patients who were referred to our tertiary center with a suspicion of food allergy. We found that epinephrine at discharge was overprescribed to patients with mild food allergic reactions and more importantly, that there was an underprescription to patients with severe reactions (16). We also observed that patients with severe acute food allergic reactions visited a general practitioner (GP) as often as an ED, which implies a very important role for the GP in the management of acute food allergic reactions. This is in line with previous studies on other acute illnesses (such as stroke) showing that a considerable part of patients seek help from GPs in first instance (17,18). The health care system in The Netherlands favors first contacting the GP even in urgent situations (19).

Previous studies have focused on the management of food allergic reactions in EDs, Studies investigating the management of food allergic reactions by GPs have not yet been conducted. One study investigated the knowledge of GPs in Portugal about anaphylaxis in general (20). Only one third of the GPs in that study appeared to know that epinephrine is the first choice treatment for anaphylaxis. However, that study did not address food allergic reactions in particular, nor analyzed whether GPs adequately recognized anaphylactic reactions. The investigators did not ask the GPs about observation periods, referrals or diet advice. The aim of our study was to investigate the management of acute food allergic reactions by GPs with regard to treatment of the acute reaction, observation period, prescription of emergency medication, diet advice and referral to a specialist.

## Methods

### *Study design*

A questionnaire containing three hypothetical food allergic cases experiencing an acute food allergic reaction was sent to 571 GPs in the province of Utrecht and in the cities of Almere and Utrecht, the Netherlands. Before distribution, a

pilot study among 30 GPs was performed and small adjustments to the questionnaire were made. A maximum of two reminders was sent to non-responders at two week intervals.

### *Questionnaire*

The GPs were presented with three hypothetical cases experiencing varying degrees of severity of an acute food allergic reaction to peanuts. One case involved a patient with only mild symptoms (oral allergy symptoms (OAS) and a few urticaria on the abdomen) while the other two cases fulfilled the criteria for anaphylaxis as proposed by Sampson et al. (21). Of these two anaphylactic cases, one expressed respiratory symptoms as the most severe clinical symptom (OAS, generalized urticaria, dyspnea and prolonged expirium) while the other had cardiovascular symptoms as the most severe clinical symptom (OAS, generalized urticaria, dizziness and hypotension of 85/65 mm Hg). In this paper, these cases will be referred to as mild, respiratory and cardiovascular case, respectively. To rule out that answers could be influenced by the sequence of the cases, six different versions of the questionnaire were made with each version having a different sequence of the three cases. The different versions were randomly distributed to the GPs.

The questionnaire included five similar multiple choice questions for all three cases about the following items: treatment of the acute reaction, observation period, prescription of emergency medication to treat possible future reactions, diet advice and referral to a specialist for further evaluation. An additional question was asked as to whether the GP considered asthma, having a peanut allergy and having a severe reaction in the past as risk factors for a more severe course of the reaction. Furthermore, GPs were asked about the incidence of food allergic reactions in their medical practice, how long they were practicing as a GP and whether or not they had used resources to complete the questionnaire.

### *Statistics*

All analyses were performed using SPSS version 15.0 (2007, SPSS Inc., Chicago, IL, USA). Data are presented as proportions. Chi-square tests and where appropriate Fisher's exact tests were used to test the differences between the mild case and the two anaphylactic cases (i.e. mild vs. anaphylaxis) and between the two anaphylactic cases (i.e. respiratory vs. cardiovascular case). A P-value of < .05 was considered significant.

## Results

### *GP characteristics*

254 GPs completed and returned the questionnaire (response rate 46%). The mean working experience of the GPs was 15 years (range 1-38). On average three patients with an acute food allergic reaction visited a GP each year (range 0-30). Ten GPs used a resource to complete the questionnaire.

### *Management of the acute allergic reaction*

All prescribed medication, except for antihistamines, differed significantly ( $P < .05$ ) between the mild case and the two anaphylactic cases (i.e. mild vs. anaphylaxis, Table 1). This indicates that the prescribed medication was related to the severity of symptoms.

Ninety-five percent of the GPs would treat the mild case with at least antihistamines at the acute moment, whereas a small number of GPs chose observation without medication (4.3%) or prescribed epinephrine (2%) (Table 1). The majority of GPs would not add any other medication to antihistamines in the mild case (Figure 1). Prednisone would be given in 16% of cases.

The respiratory and the cardiovascular case would be treated by GPs with at least antihistamines in 95% and

88% ( $P < .01$ ), respectively. Remarkably, antihistamines would be used as the only treatment in 10% of both cases with anaphylaxis (Figure 1). Epinephrine was not used for treatment of both anaphylactic cases in the acute phase in a significant number of cases: only 27% of the GPs would choose to treat the respiratory case with epinephrine and for the cardiovascular case this was 73% ( $P < .001$ ). The subcutaneous route of administration was preferred in the mild and the respiratory case by 80 and 52% of GPs, respectively (Table 1). In the mild case however, only 5 GPs chose to prescribe epinephrine.

### *Prescription of medication to treat possible future reactions*

Antihistamines would be frequently prescribed to treat possible future reactions in the mild, respiratory and cardiovascular case, whereas only a minority of GPs would prescribe prednisone at discharge (Table 2). Epinephrine would be prescribed in 19% of the mild cases at discharge. Remarkably, GPs would prescribe epinephrine at discharge significantly less often in the respiratory case compared to the cardiovascular case (53% vs. 77%,  $P < .001$ ). In anaphylactic cases, GPs that would not have prescribed epinephrine in the acute phase would also have less often prescribed self-injectable epinephrine at discharge (40% in the respiratory case and 42% in the cardiovascular case). Epinephrine would be more often prescribed at discharge to treat possible future re-

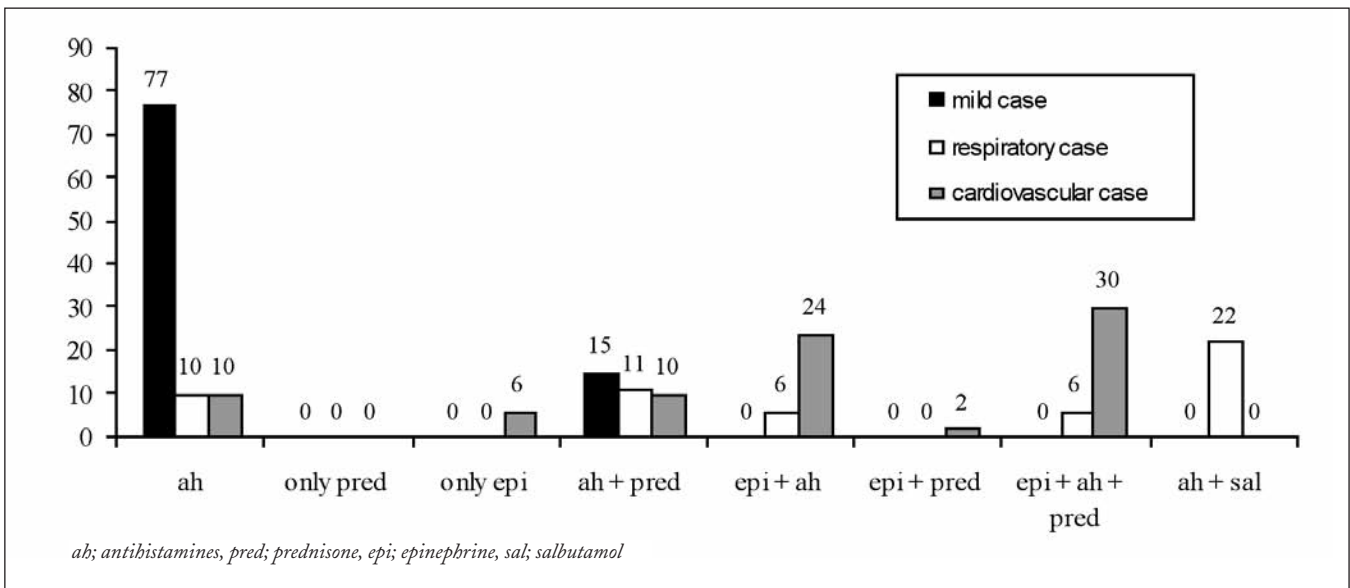
**Table 1** - Treatment of the food allergic reaction in the acute phase (N = 254)

	Mild case (%)	Anaphylactic respiratory case (%)	Anaphylactic cardiovascular case (%)	P value*	
				a	b
Observation only	4.3	0	1.2	<0.001	0.25
Antihistamines	95	95	88	0.07	0.01
-oral	72	26	14	< 0.001	< 0.001
-intramuscular	25	71	75	< 0.001	0.32
Prednisone	16	48	45	< 0.001	0.59
-20mg	12	30	26	< 0.001	0.37
-60mg	3.9	18	19	< 0.001	0.82
Epinephrine	2	27	73	< 0.001	< 0.001
-subcutaneous	1.6	14	37	< 0.001	< 0.001
-intramuscular	0.4	13	37	< 0.001	< 0.001
Salbutamol	0.4	64	5.1	< 0.001	< 0.001
Other**	1.2	6.7	10	< 0.001	0.20

\* mild case vs. both anaphylactic cases;

<sup>a</sup> anaphylactic respiratory vs. anaphylactic cardiovascular case

<sup>b</sup> mainly antihistamines or prednisone in another dose or route of administration

**Figure 1** - Main combinations of medication treatment in the acute phase**Table 2** - Prescription of medication at discharge to treat possible future reactions (N = 254)

	Mild case (%)	Anaphylactic respiratory case (%)	Anaphylactic cardiovascular case (%)	P value*	
				a	b
No medication	4.3	0	0.8	< 0.001	0.50
Antihistamines	88	76	61	< 0.001	< 0.001
Prednisone	5.1	14	13	< 0.001	0.90
Salbutamol	1.2	35	3.5	< 0.001	< 0.001
Epinephrine	19	53	77	< 0.001	< 0.001
Other**	0	1.2	1.2	0.19	1.00

\* mild case vs. both anaphylactic cases

b anaphylactic respiratory vs. anaphylactic cardiovascular case

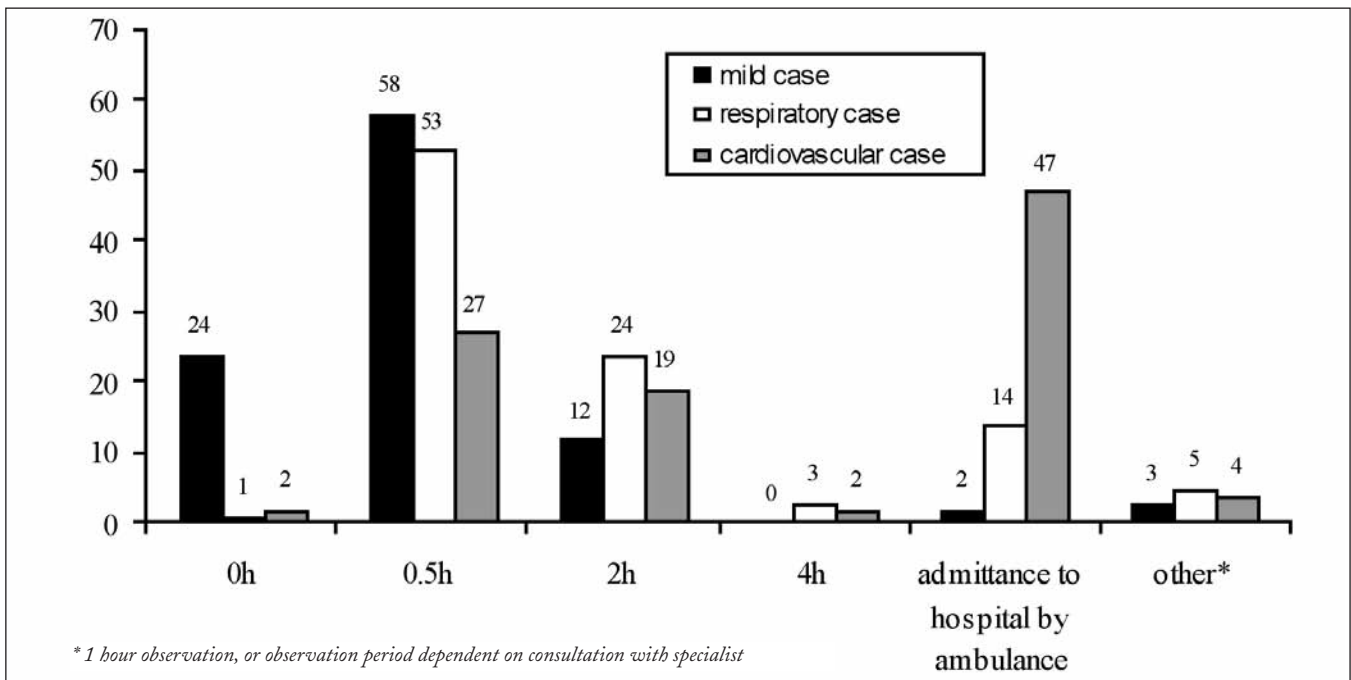
actions than for treatment of the acute reaction in all three cases (mild case: 19% vs. 2%, respiratory case: 53% vs. 27% and cardiovascular case: 77% vs. 75%, respectively).

#### Observation period

Twenty four percent of the GPs chose to send the patient back home immediately in the mild case, while most GPs (58%) chose to observe the patient for half an hour (Figure 2). A minority of GPs decided to observe the patient with a mild reaction for 2 or 4 hours or to send the patient to a hospital by ambulance (Figure 2).

The current guidelines suggest an observation period of at least two hours or admittance to a hospital by ambulance. This was preferred by GPs in 41% of the respiratory cases and 68% of the cardiovascular cases. In a considerable portion of the anaphylactic cases (42%), the observation period was too short or even absent. The patient with respiratory symptoms would be less often admitted to the hospital by ambulance compared to the patient with cardiovascular symptoms (Figure 2).

Treatment with epinephrine in the acute phase, which was suboptimal in the anaphylactic cases, was even worse in the subgroup of patients who would be sent home im-

**Figure 2** - Observation period (N = 254)

mediately or after half an hour (18% (25/136) in the respiratory case and 47% (34/72) in the cardiovascular case).

#### Diet advices

Almost all patients would be advised to avoid eating peanuts in the future (Figure 3). However, still 6% of the GPs in the mild case, 2% in the respiratory case and 1% in the cardiovascular case decided not to advise the patient to avoid peanuts.

Most of the diet advices would be given by the GP (Figure 3). In the mild case, the patient was referred less often to a specialist for diet advice compared to both anaphylactic cases. In all three cases, a minority was referred to a dietician. The decision as to whether a diet advice would be given by the GP, a dietician or a specialist was associated with the severity of the reaction ( $P < .001$ , Figure 3).

#### Further evaluation by allergy tests and referral to a specialist

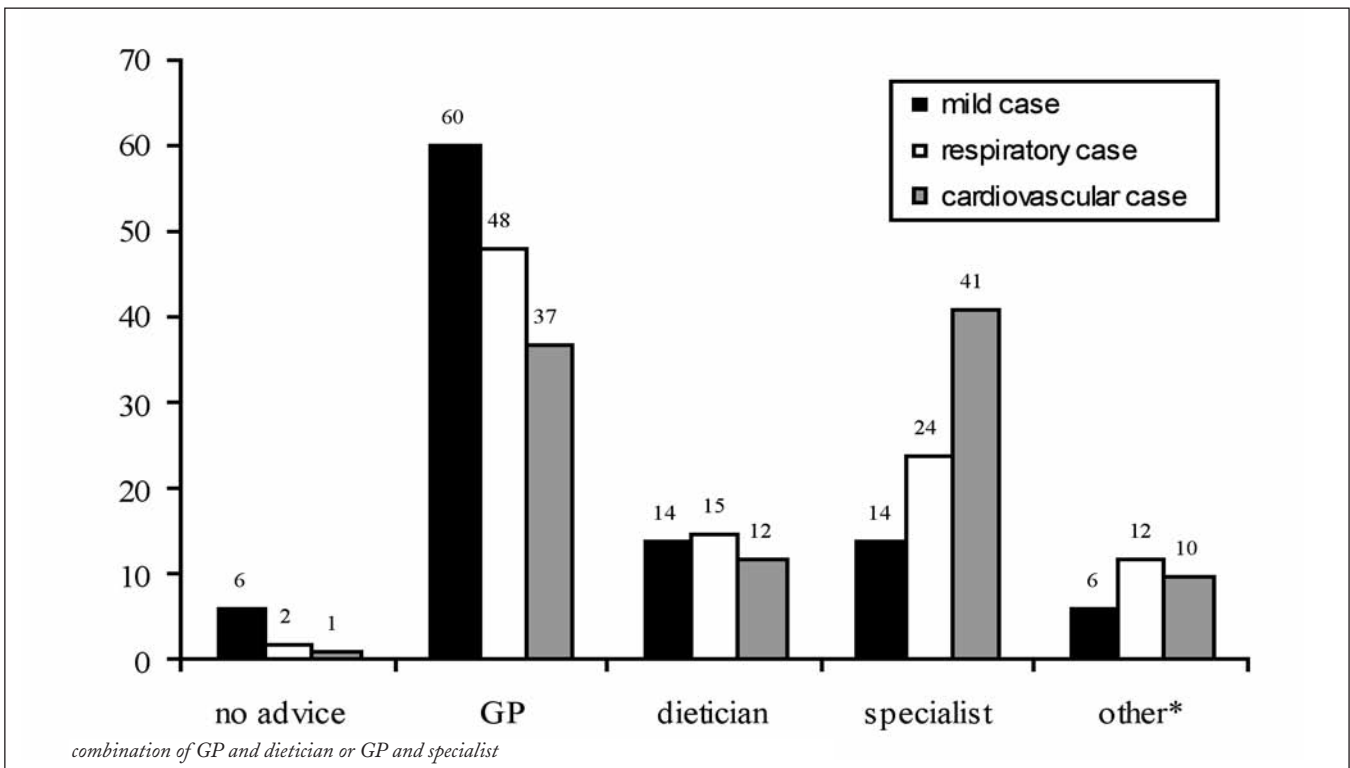
A significant number of patients would not be further evaluated (Figure 4). If further evaluated, allergy tests in patients with a mild reaction would be most frequently done by the GP (38%), whereas patients with respiratory or cardiovascular symptoms were most often referred to a

specialist for further evaluation (61% and 72%, respectively). When further evaluation by allergy tests was done by a specialist, GPs preferred to refer to an allergologist rather than a dermatologist in all three cases, while in the Netherlands both specialists are trained in allergology (Figure 4). The choice for further evaluation by allergy tests and referral was associated with the severity of the reaction ( $P < .001$ ).

It appeared that GPs who would choose to do no further evaluation in the anaphylactic cases or did the evaluation themselves, would less often prescribe epinephrine, either at the acute moment or at discharge compared to the whole group of GPs (data not shown).

#### Risk factors

Almost all GPs (97%) recognized that a severe food allergic reaction in the past is a risk factor for a more severe future course. Seventy-seven percent identified peanut allergy also as a risk factor, while only 37% knew that asthma is a risk factor for a more severe course of a food allergic reaction. No more than 30% of GPs were aware of all these risk factors: asthma, having a peanut allergy and having a severe reaction in the past.

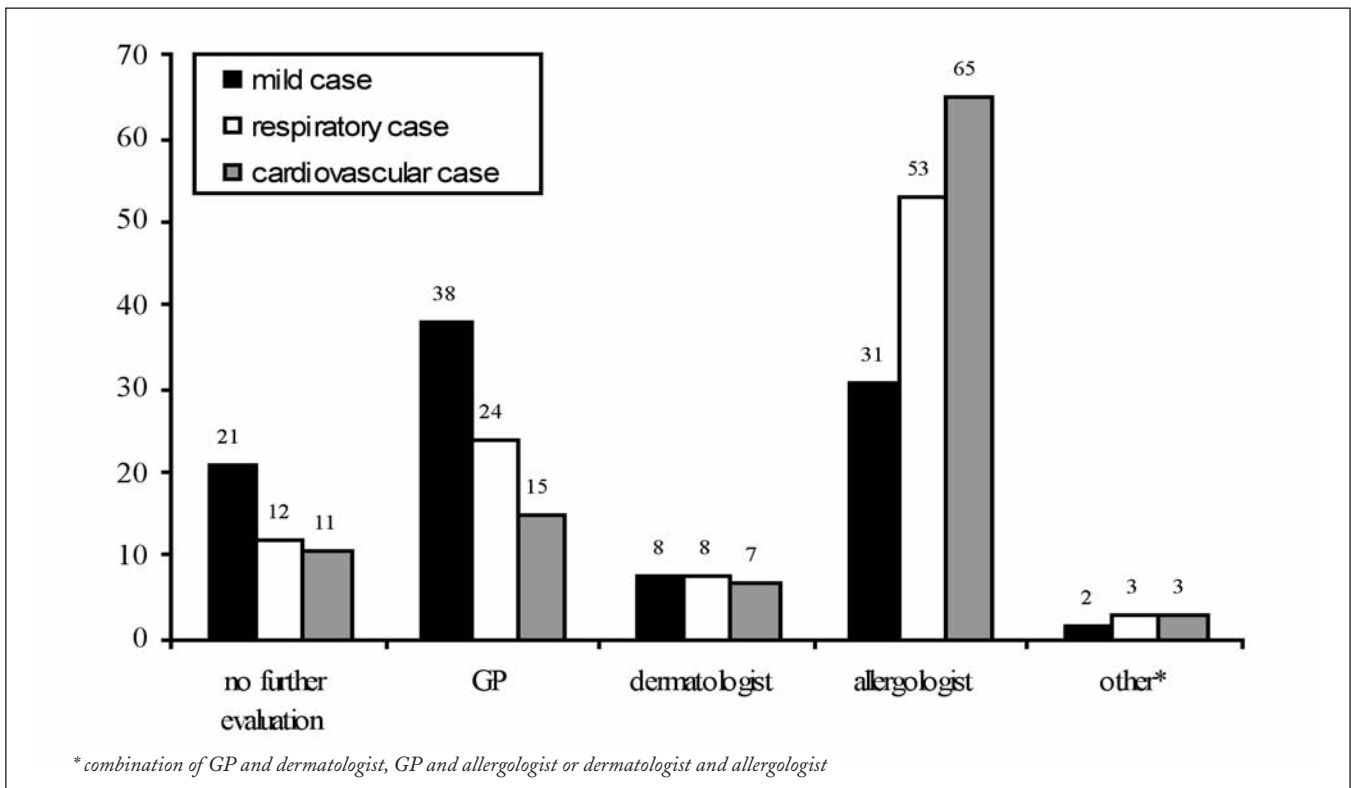
**Figure 3** - Preferred clinician to provide diet advice for avoidance of the offending allergen (N = 254)

## Discussion

This study shows that at present a considerable number of GPs would not treat an anaphylactic patient with epinephrine. Remarkably, anaphylaxis with respiratory symptoms was less often a trigger for GPs to administer epinephrine than anaphylaxis with cardiovascular symptoms. Both the respiratory and the cardiovascular case in our study meet the criteria for an anaphylactic reaction as proposed by Sampson et al (21). This consensus paper recommends, in concordance with several other guidelines and studies, that every anaphylactic reaction should be treated with epinephrine at the acute moment (5-7,9,11). Since both anaphylactic cases in our study meet the criteria for anaphylaxis, treatment with epinephrine would have been the treatment of choice. A possible explanation for the undertreatment with epinephrine might be that GPs are afraid to administer epinephrine because of the assumed narrow therapeutic window (7). However, severe side effects of epinephrine, such as ventricular arrhythmias or myocardial infarction, are rare and occur primarily after an overdose (7). Moreover, it has been shown that fatal

food allergic reactions are associated with absent or delayed administration of epinephrine (8). GPs in our study preferred to administer epinephrine subcutaneously in the majority of cases while the intramuscular route of administration leads to a better and faster absorption (22,23). Self-injectable epinephrine would be more often prescribed at discharge to treat possible future reactions than it would be prescribed at the acute phase. However, it would be underprescribed in the anaphylaxis cases, but overprescribed in the mild case. These findings are in agreement with a previous study performed at our centre (16). In this previous study we found that 26% of patients with only mild symptoms (i.e. OAS) was prescribed self-injectable epinephrine, compared to 26% of patients with severe symptoms (respiratory or cardiovascular). Our finding that some GPs' knowledge regarding the acute treatment of anaphylactic reactions is suboptimal is in line with other studies that have been done among specialists. Wang et al. (24) found that 72% of the respondents of an internal medicine and pediatrics department would treat a hypothetical case of anaphylaxis with epinephrine (compared to 27% and 73% for our respiratory



**Figure 4** - Preferred clinician to perform further evaluation by allergy tests (N = 254)

and cardiovascular anaphylactic cases). In the same study, only half selected the right dose and route of administration of epinephrine. Another study among senior house officers showed that only a minority of respondents knew the preferred route of administration of epinephrine and the right dose (25). From these data we conclude that there is a general problem among medical doctors concerning the correct management of acute food allergic reactions, which is neither restricted to, nor specific for GPs. In fact, GPs seem as capable as specialists when it comes to the treatment of acute allergic reactions, which is important given their prominent role in the management of such patients.

The only other study performed among GPs deals with anaphylaxis treatment in general and demonstrated that only a third of the GPs in Portugal were informed that epinephrine is the first choice treatment for anaphylaxis and only a minority knew about the most appropriate route of administration (20). However, this study did not address food allergic reactions in particular, nor did it evaluate proper diagnosis of an anaphylactic reaction among GPs.

Nearly all GPs in our study chose to prescribe antihistamines to treat the acute reaction in both anaphylactic cases. These drugs relieve itch and hives but doubt has been raised about their efficacy in relieving respiratory or cardiovascular symptoms (7,26). Randomized controlled trials investigating the additive effect of antihistamines to epinephrine in anaphylaxis would face ethical difficulties and have not been done (27). Additional treatment with steroids is based on clinical experience only. They are assumed to help to prevent protracted or biphasic reactions (9). A systematic review comparing several international anaphylaxis guidelines showed that most guidelines recommend treatment with antihistamines and steroids in addition to epinephrine (5). However, these guidelines revealed great differences as concerns dose and route of administration. Furthermore, the level of evidence to support these treatments was low. We can conclude that treatment with antihistamines and prednisone can be recommended in addition to epinephrine in case of anaphylaxis but treatment with these medications in absence of epinephrine can not be justified.

A significant number of GPs decided to observe a patient with an anaphylactic reaction for no longer than half an

hour. This is significantly shorter than the preferred minimal observation period of 2 hours (28). Biphasic anaphylactic reactions were described to occur in 1-20% of cases with an onset of the second phase ranging from 1-72 hours (29-32). No reliable clinical predictors were found to identify patients at increased risk of a biphasic reaction (32). Therefore, guidelines recommend that the observation period has to be individualized on the basis of the severity of the initial reaction, the reliability of the patient to seek further medical care if needed and the access to health care (9,21). A minimum observation of two hours is suggested (28). However, a prolonged observation period of 4-6 hours (11,21) or even 8 hours (28) might be preferred. The patient should be sent home only when the reaction has completely resolved and with a prescription for self-injectable epinephrine (28). When a longer observation period is difficult to achieve in daily practice of a GP, the best option would be referral to the ED of a hospital. Alarming is the fact that epinephrine would be less often prescribed by the GPs who chose an insufficient observation period in both anaphylactic cases, both at the acute moment and at discharge. This means that these patients would be at higher risk of developing a more severe reaction.

In this study 46% of GPs returned our questionnaire. Such a response rate is not unusual when approaching health professionals like GPs by questionnaire and also found in other recent studies done among GPs (33-34). We have no indication that the non-responder group was different from the responder group with regard to years of experience or interest in food allergy. Moreover, the data were analyzed after dividing the GPs into three groups, based on their time of responding (i.e., immediate response, response after 1st reminder and response after 2nd reminder). In this analysis, no difference was seen in the years of experience or percentages of correct answers between these three groups.

In conclusion, this study demonstrates that the management of GPs regarding the treatment of food allergic reactions is suboptimal, especially in anaphylactic cases with respiratory symptoms. This results in undertreatment and underprescription of epinephrine and too short observation periods. Education programs are needed to increase the awareness of GPs, but also other health care workers, to recognize and treat anaphylactic reactions.

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