

RESEARCH LETTER

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Adherence to adrenaline autoinjector prescriptions in patients with severe food allergy

To the Editor,

Adrenaline autoinjectors (AAIs) are first-line treatment of severe out-of-hospital allergic reactions¹ and must be carried by individuals at risk of food-induced anaphylaxis.² However, patients may fail to collect or carry AAIs,^{1,3} and data on fulfilled prescriptions are lacking. This study evaluates adherence to AAI prescriptions among individuals with challenge-verified allergies to peanuts and hazelnuts.

This retrospective study included patients with cumulative thresholds up to 568.5mg peanut protein and 305.1mg hazelnut protein during oral food challenge (OFC) to whom AAIs are always prescribed. Peanut and hazelnut allergies were studied as they are often persistent from childhood to adulthood. The OFCs were performed between 2001 and 2015, following EAACI guidelines.² The dosages were titrated (0.25-2.5-24.6-49.2-172.2-319.8-639.6-1476 mg peanut protein and 0.13-1.3-13.2-26.4-92.4-171.6-343.2-660 mg hazelnut protein). Stopping criteria were confined to objective allergic signs.² The severity of allergic reactions during OFCs was evaluated using Sampson's severity score.⁴ The patients were seen at least yearly after diagnosis.

In Denmark, AAIs require prescriptions. The Odense University Pharmacoepidemiological Database (OPED)⁵ provided data on reimbursed AAI prescriptions between 2001 and 2015 from all Danish pharmacies.

Patients (mainly Caucasians) were evaluated for AAI prescription retrieval from 1 year prior to 1 year after the diagnostic OFC (considered year 1) and annually until the next OFC with the same allergen or until the end of the study period. Adherent patients were defined as patients retrieving AAI all years. However, as the shelf life on an AAI could be more than 12 months, we allowed 1 year without retrieval of an AAI in the study period.

Proportions were compared by the chi-squared (χ^2), while χ^2 trend-tests analysed trends across age and patient groups. Statistical significance was defined as p -value < .05. Data analysis was performed with STATA version 17 (StataCorp, USA).

The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20120203) and the Danish Data Protection Agency (12/26172).

In total, 344 patients (41.3% females) with a median age of 13 years (interquartile range: 9–17 years) with peanut allergy ($n=237$), hazelnut allergy ($n=67$) or both ($n=40$) were included. ED50 were 76.5mg peanut protein ($n=277$) and 59.4mg hazelnut protein ($n=107$). Within the study period, 75.9% (261/344) retrieved ≥ 1 AAI, without differences between peanut (211/277) and hazelnut (85/107) allergic patients.

The overall adherence to AAI retrieving during the study period was 63.7% (219/344) (Table 1). Approximately 70% ($n=53$) of children ≤ 6 years were adherent, being significantly higher ($p=.043$) compared with adolescents (52.2%) (12–17 years, $n=115$). No differences were found between children ≤ 6 years and school-aged children (7–11 years, $n=95$) or adults (≥ 18 years, $n=81$). Furthermore, more females (70.4%) were adherent to retrieve AAI ($p=.029$) compared with males (58.9%). Among children ≤ 6 years, girls (similar proportion of females as the whole population, $p=.125$) had significantly higher adherence compared with boys (93.8% vs. 59.5%, $p=.013$), whereas no gender-specific association was found among school-aged children, adolescents or adults; data not shown. There was no difference in adherence to AAI (χ^2 , $p=.922$) between adults 18 and 28 years ($n=69$) and adults ≥ 29 years ($n=12$), thus being combined into one group. No associations were found when comparing adherence to AAI across the cumulative threshold intervals, being consistent in a subanalysis of patients allergic to peanuts ($n=237$) or hazelnuts ($n=67$) without concomitant allergy to the other (data not shown). We found no associations between adherence and causative allergens or the most severe allergic reaction during OFC.

This study was the first to evaluate adherence to AAI prescription among peanut and hazelnut allergic patients requiring AAIs.

The adherence (63.7%) was similar to other anaphylaxis populations, with elicitors being foods, venom and unknown,^{6–8} and highest among females and youngest children.⁸ However, aged-based comparisons may be confounded by shorter follow-up from OFC to data extraction in children, parental supervision, clinicians' recommendation of multiple AAIs and potential institutional regulations regarding the presence of AAIs. We have no specific explanations for the gender differences, as retrieval is parental-initiated for children/adolescents.

However, the low adherence found in adolescents in this study requires particular focus due to increased risk-taking behaviour and fatal food-induced anaphylaxis.⁹ Some patients may struggle to afford AAI, costing approximately 65 euros/70 USD in Denmark, although a previous study did not identify an association.⁷ Healthcare professionals can improve adherence to AAI by educating patients and relatives, and guiding them on treatment strategies, addressing issues such as lack of disease knowledge, fear of side-effects of adrenaline, overreliance on other medications and spontaneous recovery, hampering the patient's perception of the importance of

Summary box

- Sixty-four per cent of peanut or hazelnut allergic patients who required adrenaline autoinjectors adhered to their prescriptions.
- Adherence to prescriptions was highest among females and young children and significantly lower among adolescents.

TABLE 1 Adherence to adrenaline autoinjector (AAI) among 344 patients with cumulative thresholds ≤ 2311 mg of peanut (568.5 mg peanut protein), hazelnut (305.1 mg hazelnut protein) or both during oral food challenges (OFC) between 2001 and 2015, stratified by age, gender, the severity of the allergic reaction and the cumulative thresholds during oral food challenge at the Department of Dermatology and Allergy Centre, Odense University Hospital.

	Total (n = 344)	AAI adherence ^a		p-value χ^2 trend-test	p-value χ^2 -test
		Yes, % (n)	No, % (n)		
All	344	63.7 (219)	36.3 (125)	-	-
Lowest threshold during OFC, stratified by culprit					
Peanut, ≤ 2311 mg (568.5 mg protein)	237	62 (147)	40 (90)	.598	-
Hazelnut, ≤ 2311 mg (305.1 mg protein)	67	68.7 (46)	31.3 (21)		
Peanut and hazelnut ^b , ≤ 2311 mg	40	65 (26)	35 (14)		
Age at year 2015 ^c					
0–6 years	53	69.8 (37)	30.2 (16)	.010	Reference
7–11 years	95	73.7 (70)	26.3 (25)		.720
12–17 years	115	52.2 (60)	47.8 (55)		.043
≥ 18 years	81	64.2 (52)	35.8 (29)		.576
Sex					
Female	142	70.4 (100)	29.6 (42)	-	.029 ^d
0–6 years	16	93.8 (15)	6.3 (1)		
7–11 years	36	80.6 (29)	19.4 (7)		
12–17 years	47	53.2 (25)	46.8 (22)		
≥ 18 years	43	72.1 (31)	27.9 (12)		
Male	202	58.9 (119)	41.1 (83)		
0–6 years	37	59.5 (22)	40.5 (15)		
7–11 years	59	69.5 (41)	30.5 (18)		
12–17 years	68	51.5 (35)	48.5 (33)		
≥ 18 years	38	55.3 (21)	44.7 (17)		
Most severe allergic reaction during OFC with the lowest threshold					
Sampson's severity score 2–3	277	63.5 (176)	36.5 (101)	-	.922
Sampson's severity score 4–5	67	64.2 (43)	35.8 (24)		
Peanut threshold					
≤ 111 mg (≤ 27.3 mg protein)	52	53.9 (28)	46.2 (24)	.655	
112–311 mg (27.6–76.5 mg protein)	100	63 (63)	37 (37)		
312–1011 mg (76.8–248.7 mg protein)	64	64.1 (41)	35.9 (23)		
1012–2311 mg (249.0–568.5 mg protein)	61	59 (36)	41 (25)		

TABLE 1 (Continued)

	Total (n = 344)	AAI adherence ^a		p-value χ^2 trend-test	p-value χ^2 -test
		Yes, % (n)	No, % (n)		
Hazelnut threshold					
≤111 mg (≤14.7 mg protein)	30	60 (18)	40 (12)	.811	
112–311 mg (14.8–41.1 mg protein)	20	65 (13)	35 (7)		
312–1011 mg (41.2–133.5 mg protein)	35	62.9 (22)	37.1 (13)		
1012–2311 mg (133.6–305.1 mg protein)	22	72.7 (16)	27.3 (6)		

^aAdherence is the retrieval of AAI within 1 year prior and 1 year after the oral food challenge (OFC) with the lowest threshold, and afterwards, yearly retrieval until the next OFC or end of the study in 2015; 1 year without retrieval in this period is accepted.

^b40 patients had a cumulative threshold of ≤2311 mg for peanut and hazelnut.

^cAge at the time of responding to the questionnaire in 2015.

^dp-value chi-squared test comparing all females (n = 142) and males (n = 202).

AAIs. These approaches are used in highly specialized centres like ours; however, patients and parents ultimately decide whether to collect the AAI at the pharmacy. Additionally, factors such as severity and number of previous accidental reactions and daily risk for accidental allergen exposure may affect retrieving an AAI prescription.

The OPED register constitutes a possibility for studying adherence to AAI prescription, for example, if the patient collects the AAI. However, the present study lacks information on actual carriage and the ability to use the AAI correctly. Additionally, both AAI shelf-life extending beyond 1 year and the small number of participants in hazelnut threshold groups may weaken statistical associations. In Denmark, patients have free and equal access to health care, potentially improving adherence estimates compared with areas without such access.

In conclusion, two-thirds of patients adhered to AAI prescriptions, indicating a need for continuous patient education and interventions to improve adherence.

KEYWORDS

adherence, adrenaline autoinjector, anaphylaxis, food allergy, hazelnut allergy, peanut allergy, Sampson's severity score

AUTHOR CONTRIBUTIONS

Sebastian Vigand Svendsen: Writing – Original Draft Preparation, Formal Analysis. **Annemarie Schaeffer Senders:** Writing – Review & Editing. **Athamaica Ruiz Oropeza:** Investigation, Resources, Writing – Review & Editing. **Annmarie Lassen:** Writing – Review & Editing, Conceptualization. **Henrik Fomsgaard Kjaer:** Writing – Review & Editing. **Carsten Bindslev-Jensen:** Writing – Review & Editing, Conceptualization. **Charlotte G. Mortz:** Conceptualization, Supervision, Writing – Review & Editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not available due to restrictions from the Regional Committees on Health Research Ethics for Southern Denmark and the Danish Data Protection Agency.

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