

RESEARCH LETTER

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Oral food challenge management in Japan: A retrospective analysis of health insurance claims data

To the Editor,

Food allergy (FA) is a common adverse health effect in children, which affects their quality of life and may cause severe life-threatening allergic reactions.¹ With the increasing prevalence of FA, the need for an oral food challenge (OFC) is also expected to increase. OFC always accompanies the risk of an anaphylactic reaction and must be conducted by allergy specialists, according to guidelines, to ensure a safe procedure.^{1,2}

In previous studies, the reported proportion of anaphylaxis on OFC was approximately 2%, which is lower than 10%.^{3,4} However, data are lacking on recent practice patterns for allergic reactions and anaphylaxis in a real-world clinical setting. In addition, several studies have been conducted on the safety of OFC in allergy-specialized institutions, but the reported proportions of anaphylaxis during OFC varies in the literature. Therefore, in this study, we used a large health insurance claims database to describe the practice patterns for the treatment of allergic reactions and the proportion of anaphylaxis during OFC in Japan, as well as to examine the factors affecting the occurrence of anaphylaxis during OFC in the various types of medical settings.

We used administrative claims data from the JMDC Claims Database (JMDC Inc.) to conduct our analyses.⁵ The JMDC database includes the data of approximately 100,000 children under 9 years old. This data includes the following patient data: age, sex, dates of hospital or clinic visit, diagnoses recorded under the International Classification of Diseases, Tenth Revision (ICD-10) codes, medical procedures, prescriptions of drugs provided and size and specialty of the medical settings. This retrospective study was approved by the institutional review board of the University of Tokyo, Japan. Informed consent for each patient was not required because of the anonymous nature of the data.

We identified children below 9 years of age who underwent OFC between April 1, 2008, and August 31, 2018. OFC procedures were identified by the Japanese medical procedure code (D291-2), which can only be billed for those aged 9 years or younger. OFC can be conducted in clinics and hospitals where there is at least one skilled physician for paediatric FA, based on the Japanese guidelines.² Patient characteristics that were assessed include age, sex, history of anaphylaxis (ICD-10 codes T780 or T782) and wheezing (J45 or J460) within one year before the OFC, family history of asthma (paternal or maternal) for the past year and medical setting (clinic or hospital).² Age was categorized into the following three groups: 0, 1–2 and ≥ 3 years. Family data were extracted using linked family identity codes. We examined the proportions of treatments for allergic reactions administered on

the day of and the day after OFC, including adrenaline injection, intravenous antihistamine injection, intravenous general corticosteroid injection, β_2 stimulant by a nebulizer, delivery of oxygen supply, fluid transfusion, mechanical ventilation and intensive care unit (ICU) admission. We also examined the number of patients who had died.

Categorical variables are expressed as numbers and percentages. We assessed the differences in the patients' characteristics and treatments by age category using the chi-squared test. We performed a multivariable logistic regression analysis to analyse the risk factors of anaphylaxis by estimating the odds ratio of receiving an adrenaline injection during OFC with adjustment for age, sex, history of anaphylaxis and wheezing, family history of asthma, and medical setting (clinic or hospital). STATA/MP ver16.0 was used for the statistical analysis.

A total of 10,050 OFC procedures involving 6182 patients from 791 hospitals and clinics were identified between 2008 and 2018. Of these, 43.7% were conducted in clinics, and 56.3% in hospitals. Approximately 50% of the patients were aged 0 years, and 80% were younger than 3 years. More than 60% of the patients were male. The proportions of patients with a history of anaphylaxis, history of wheezing and family history of asthma were 13.1%, 41.1% and 10.7%, respectively. The proportions of male patients, patients with a history of anaphylaxis and wheezing, and patients treated in hospitals were highest in the ≥ 3 years group.

Table 1 shows treatments implemented on the day of the OFC procedure, as well as the proportions of each. The proportion of all OFC patients receiving adrenaline injections was 0.8%, and that of patients receiving more than two adrenaline injections was 0.1%. The proportions of OFC patients receiving intravenous antihistamine, intravenous general corticosteroid, β_2 stimulant by nebulizer, oxygen supply and fluid transfusion were 1.0%, 1.1%, 0.7%, 0.2% and 2.4%, respectively. No patient required mechanical ventilation or ICU admission, and no patient died during the study period. There were no differences in characteristics of patients who received a single adrenaline dose versus those who received multiple adrenaline doses (age: 3.9 vs 3.4 years, male: 59% vs. 63%, history of anaphylaxis: 80% vs. 63%, history of wheezing: 77% vs. 88%, family history of asthma: 20% vs. 0%, medical setting (hospital): 69% vs. 75%).

Table 2 shows the multivariable logistic regression analysis results for patients receiving an adrenaline injection following OFC. The proportion of patients receiving an adrenaline injection was significantly higher in patients with a history of anaphylaxis (odds ratio [OR], 20.21; 95% confidence interval [CI], 11.49–35.57) and a history

of wheezing (OR, 1.89; 95% CI, 1.07–3.33). Although not significant, patients aged ≥ 3 years were less likely to receive an adrenaline injection (OR, 0.58; 95% CI, 0.33–1.01). Sex, family history of asthma and medical setting were not associated with receiving adrenaline injections following OFC.

This study used a large health claims database to analyse the practice patterns for allergic reactions during OFCs in young children in Japan, conducted at multiple institutions including general hospitals and clinics. We found that the proportion of patients receiving an adrenaline injection following OFC was 0.8%. There were no cases of life-threatening events that required ICU admission, mechanical ventilation or that resulted in death during OFC. Multivariable logistic regression analysis confirmed the association between a history of anaphylaxis and wheezing with patients receiving an adrenaline injection during OFC; there was no significant difference between hospitals and clinics.

In this study, the proportion of patients receiving adrenaline injections was similar to or less than that in previous studies. Possible reasons for this are as follows. First, the proportion of patients with a history of anaphylaxis in our study (13.1%) was relatively lower than that in previous studies.^{6,7} However, this value might be an underestimate of the true value due to the low sensitivity of the ICD-10 code for anaphylaxis. Second, this study included more general clinics and hospitals. The previous studies were conducted mainly in allergy-specialized hospitals that often carried out high-risk OFC rather than in general hospitals and clinics.

Regarding other treatments, the proportions of patients receiving antihistamines and general corticosteroids were lower than in previous studies.^{3,4,6–8} This may be because our data did not include oral medication data. The proportions of intravenous drug administration in our study could be appropriate because the proportions

Key message

- We analysed treatments given for oral food challenge reactions in children under 9 in Japan.
- Adrenaline was used in 82/10,050 (0.8%) challenges from 2008 to 2018, with no death or ventilation.
- History of anaphylaxis and wheezing were risk factors for needing adrenaline treatment.

were similar to or less than those of adrenaline injections.⁹ The proportions of β_2 stimulant by nebulizer and delivery of oxygen supply were comparable with those in previous studies (0.3%–2.9% and 0.1%–0.7%, respectively). The proportion of fluid transfusion was higher in our study than in previous studies (0.3%–1%). We speculated that a certain number of OFC procedures had been conducted with an intravenous line in advance for safety.

Regression analysis did not show any significant differences between hospitals and clinics, implying that OFC procedures were conducted with a low anaphylaxis rate in both institutions in Japan.

This study has several limitations. First, we were not able to include children over 9 years old who underwent OFC. However, age is a controversial risk factor for OFC.^{6–8} In this study, multivariable logistic regression analysis indicated that age did not have a significant effect on allergic reactions among the patients. Second, we could not obtain detailed data for FA history. If the objective of the OFCs was mainly judgement of tolerance of FA, the anaphylaxis rate would be low. Third, we substituted the adrenaline injection for an anaphylaxis diagnosis because of the data characteristics. Therefore, mild anaphylaxis, which is not treated with adrenaline in practice, was not included. Lastly, because this study used the healthcare coverage

TABLE 1 Treatments implemented on the day of the oral food challenge

	Total (n = 10,050)	0 years (n = 4904)	1–2 years (n = 2347)	≥ 3 years (n = 2799)	p-Value*
Total of each treatment					
Adrenaline	82 (0.8)	39 (0.8)	23 (1)	20 (0.7)	.56
1 injection	74 (0.7)	33 (0.7)	21 (0.9)	20 (0.7)	
≥ 2 injections	8 (0.1)	6 (0.1)	2 (0.1)	0 (0.0)	
Antihistamine injection	98 (1.0)	47 (1.0)	24 (1.0)	27 (1.0)	.96
Corticosteroid injection	113 (1.1)	52 (1.1)	26 (1.1)	35 (1.3)	.75
β_2 stimulant by nebulizer	68 (0.7)	29 (0.6)	16 (0.7)	23 (0.8)	.49
Oxygen supply	18 (0.2)	10 (0.2)	7 (0.3)	1 (0.0)	.07
Fluid transfusion	240 (2.4)	106 (2.2)	66 (2.8)	68 (2.4)	.23
Combination of drugs					
Adrenaline + antihistamine + corticosteroid	23 (0.2)	7 (0.1)	10 (0.4)	6 (0.2)	.06
Adrenaline + antihistamine	30 (0.3)	11 (0.2)	11 (0.5)	8 (0.3)	.2
Adrenaline + corticosteroid	31 (0.3)	13 (0.3)	10 (0.4)	8 (0.3)	.5
Antihistamine + corticosteroid	63 (0.6)	30 (0.6)	16 (0.7)	17 (0.6)	.93

Note: Data are expressed as numbers (percentages).

*Chi-squared test.

TABLE 2 Multivariable logistic regression analysis for adrenaline injection during the oral food challenge

	Odds ratio	95% confidence interval	p-Value
Age (years)			
0	Reference		
1–2	1.20	0.71–2.03	.50
≥3	0.58	0.33–1.01	.05
Sex			
Female	Reference		
Male	0.84	0.53–1.32	.45
Past history of anaphylaxis	20.21	11.49–35.57	<.001
Past history of wheezing	1.89	1.07–3.33	.03
Family history of asthma	1.05	0.59–1.89	.86
Medical setting			
Clinics	Reference		
Hospitals	1.28	0.79–2.07	.32

system in Japan, the findings may not apply to other regions or different healthcare systems.

In conclusion, OFCs are conducted nationwide in general hospitals and clinics, not only in allergy-specialized facilities, as part of daily medical services in Japan. The proportion of anaphylaxis during OFC was relatively low, and there were no life-threatening events in both clinics and hospitals, as exemplified by the low number of adrenaline injections. There were also no life-threatening events during the procedure. However, we should still be very careful when performing OFC in patients with a history of anaphylaxis and wheezing.

AUTHORS' CONTRIBUTION

HO designed this study. HO and HOHbe performed the data collection and statistical analysis. HO, HOHbe and HY edited the manuscript. All the authors participated in the revision of the manuscript and approved the final manuscript.

KEYWORDS

adrenaline, anaphylaxis, food allergy, oral food challenge, safety

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CONFLICT OF INTEREST

Hisako Ogasawara is a contract employee of Janssen Pharmaceutical K.K.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from JMDC Inc. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of JMDC Inc.

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