

Reaction severity to oral food challenge to milk is unpredictable: A caveat for clinical practice

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Abstract. *Background and aim:* Cow's milk allergy (CMA) is common in infancy and early childhood; its work-up also is demanding. Oral food challenge (OFC) represents the gold-standard for diagnosis, but it may be dangerous. The present study aimed to identify possible risk factors predictive of severe reactions in clinical practice. *Methods:* The study retrospectively evaluated data concerning children with positive OFC. The study evaluated detailed clinical history, including comorbidity, reactions' characteristics, specific IgE to milk and its molecular components, and cumulative allergen dose. *Results:* This study included 30 children (9 females and 21 males, mean age 89 months); 22 developed mild clinical reactions, four moderate, and four severe. There was no risk factor predictive for severe reaction. *Conclusions:* This study emphasized the unpredictability of anaphylaxis during the OFC procedure, as no predictive and reasonable risk factors could rule out a severe reaction with absolute certainty. Consequently, OFC should be performed only at third-level pediatric allergy centers. (www.actabiomedica.it)

Key words: cow's milk allergy, oral food challenge, clinical reaction, anaphylaxis

Introduction

Cow's milk allergy (CMA) work-up is a demanding issue in clinical practice. Clinical history and IgE assessment are mandatory steps but are only sometimes conclusive. Namely, only the oral food challenge (OFC) allows documenting CMA. In addition, OFC has two main indications: diagnostic and prognostic. A positive OFC confirms CMA if the subject develops a clinical reaction after suspected food ingestion. A negative OFC usually excludes CMA or documents the acquired milk tolerance in subjects with CMA. However, OFC is a potentially unsafe procedure that requires adequate personnel and setting. In fact, OFC may also cause severe reactions, potentially fatal, as it has been reported that 28% of subjects undergoing OFC developed anaphylactic reactions (1). Therefore,

several attempts were made to identify predictive risk factors for a severe reaction to OFC.

Different risk factors were proposed, including age, comorbidity (mainly asthma), clinical sensitivity, allergy tests (level of specific IgE, wheal diameter), exercise, and concomitant medications (1). However, skin testing and specific IgE levels, even if related to challenging outcomes, were inconsistent as having low positive predicting values.² In this regard, considering clinical data combined with allergy tests, the proposed food challenge score predicted severe reactions to OFC, even if not optimally, for CMA (2). A Japanese study partially demonstrated that high specific IgE levels, total IgE count, and milk avoidance could be risk factors for severe reactions to OFC (3). Another Japanese study explored the likelihood of a predictive formula including IgE levels, milk avoidance, and

asthma (4). Unfortunately, the outcomes showed inconsistent sensitivity and specificity; subjects with low probability still developed severe reactions. A further study, based on many children undergoing double-blind OFC, concluded that the milk-specific IgE level and skin test results poorly predicted severe reactions (5). Consistently, these authors concluded that absolute cut-off values are useless in clinical practice (5). A recent study did not identify any significant predictor for an anaphylactic reaction to OFC in a cohort of 83 children with documented CMA (6). Consistent results were reported by a very recent Finnish study (7).

Based on this background, the present study aimed to identify possible predictive factors for reaction severity to milk OFC, performed in clinical practice of a specialistic setting.

Methods

The study retrospectively evaluated data concerning children with positive OFC. In particular, OFC was defined as positive if a clinical reaction occurred after milk ingestion. The study collected data concerning the OFC performed in 2022. In addition, milk OFC was diagnostic, such as performed to confirm suspected CMA. The procedure was conducted at a third-level pediatric center.

The study evaluated accurate clinical history, including comorbidity, clinical reactions' characteristics, serum-specific IgE to milk and its molecular components (casein, α -lactalbumin, β -lactoglobulin), and cumulative allergen dose.

IgE was measured using ELISA assays provided by Thermofisher (Milan, Italy). The total serum IgE normal level is < 100 kU/L. Sensitization is defined when the value of allergen-specific IgE is > 0.35 kUA/L.

The inclusion criteria were the need to perform OFC for suspected CMA, suggested by symptom occurrence after CM ingestion, sensitization to CM extract and/or milk molecules, and pediatric age. Exclusion criteria were concomitant diseases and medications that could interfere with interpreting results.

The oral food challenge was performed using the following procedure: patients started with doses between 0.05 mL and 1 mL of unheated cow's milk,

progressively incremented, such as by initially doubling the administered dose each time (e.g., 1, 2, 4, 8, and 16 mL) and successively giving 20 and 30 mL. The OFC ended when a clinical manifestation occurred, or a cumulative dose of 81 mL had been reached. The OFC was performed exclusively in the hospital.

The severity of reactions to food challenges was classified according to a validated score (8).

The Ethics Committee of the IRCCS Istituto Giannina Gaslini approved the procedure (10/17; 04/05/2017). Parents signed informed consent.

A univariate logistic regression model was applied to identify which variables best predict response after OFC. A 2-tailed P value of .05 was considered significant. All statistical analyses were performed using SPSS 23.0 (SPSS, Chicago, Illinois).

Results

This study included 30 children (9 females and 21 males, mean age 89 months); 22 developed mild clinical reactions, four moderate, and four severe. Twelve (40%) children presented multi-organ reactions. Clinical reactions were most frequent at the gastrointestinal level (40%) and upper (23.3%) and lower (23.3%) airways.

The cardiovascular symptoms included mild tachycardia; upper respiratory tract complaints were sneezing and rhinorrhea; lower respiratory tract symptoms were dyspnea, wheezing, and cough; skin symptoms were itching, and urticaria; abdominal symptoms included nausea, vomiting, colics, and diarrhea.

As the number of patients with moderate and severe reactions was very few, the children were stratified into two subgroups according to reaction severity (moderate and severe reactions were joined for statistical purposes). The analysis did not reveal any significant difference between subgroups, even if the mean specific IgE levels tended to be higher in children with moderate/severe reactions (Table 1).

There was an impressive inconsistency among the four children with a severe reaction, mainly concerning the specific IgE patterns, as reported in Table 2. Namely, one child had very high IgE to raw milk and

Table 1. Predictive factors for severity of response following OFC.

		Mild Reaction (N = 22)	Moderate/Severe Reaction (N = 8)	p
Sex	Females	7 (31.8%)	2 (25.0%)	0.99
	Males	15 (68.2%)	6 (75.0%)	
Age (months)		90.8 ± 66.15	75.5 ± 54.49	0.48
Age at first reaction (months)		16.5 ± 22.90	32.8 ± 37.03	0.67
Family Allergy	Yes	13 (59.1%)	3 (37.5%)	0.42
Atopic dermatitis	Yes	8 (36.4%)	3 (37.5%)	0.99
Sensitization to other foods	Yes	18 (81.8%)	7 (87.5%)	0.99
Sensitization to inhalants	Yes	17 (77.3%)	7 (87.5%)	0.99
Asthma	Yes	14 (63.6%)	6 (75.0%)	0.68
Allergic rhinitis	Yes	6 (27.3%)	4 (50.0%)	0.38
Chronic Urticaria	Yes	1 (4.5%)	0 (0.0%)	0.99
Previous allergic reaction to milk	Yes	18 (81.8%)	6 (75.0%)	0.65
More than one previous allergic reaction to milk	Yes	9 (50.0%)	5 (83.3%)	0.34
The most severe reaction involving the skin	Yes	13 (72.2%)	5 (83.3%)	0.99
The most severe reaction involving the upper airway	Yes	2 (11.1%)	2 (33.3%)	0.25
The most severe reaction involving the lower airways	Yes	6 (33.3%)	2 (33.3%)	0.99
The most severe reaction involving the gastrointestinal tract	Yes	6 (33.3%)	5 (83.3%)	0.06
The most severe reaction involving the cardiovascular system	Yes	1 (5.6%)	0 (0.0%)	0.99
Total IgE (kU/L)		686.6 ± 1164.69	592.1 ± 644.90	0.53
IgE to casein (kUA/ml)		15.3 ± 23.38	26.2 ± 36.35	0.74
IgE to α-lactoglobulin (kUA/L)		9.8 ± 15.12	14.4 ± 34.73	0.22
IgE to β-lactoalbumin (kUA/mL)		5.1 ± 7.72	10.1 ± 21.27	0.83
IgE to cow milk (kUA/L)		20.7 ± 29.05	28.4 ± 36.81	0.58
Total daily cumulative dose (mL)		30.9 ± 49.52	15.7 ± 12.83	0.73

all its molecular components. Contrarily, one child had very low IgE levels for these allergens.

Discussion

The present study did not identify any risk factor predictive of severe reaction to OFC. However, this finding was not unexpected as the literature provided conflicting outcomes.

Usually, children with CMA and presenting anaphylaxis after milk ingestion have high IgE levels in

milk molecules, mainly concerning casein (8,9). Therefore, high milk-specific IgE levels may suggest a high probability of having a severe reaction to milk ingestion (1). Consistently, a Japanese study reported that milk-specific IgE, casein-specific IgE, and a history of anaphylaxis to cow's milk are risk factors for anaphylaxis (10).

On the other hand, it is quite common in clinical practice to encounter subjects with high IgE levels who actually tolerate the food allergen clinically (11). This concept also applies to inhalant allergens. The basis of this assumption is that one must always differentiate

Table 2. Narrative description of four patients with anaphylactic reaction after milk OFC (N = 4).

Sex	Sensitization to other foods	Sensitization to inhalants	Atopic dermatitis	Asthma	Allergic rhinitis	Chronic Urticaria	Other food allergies	Family history	Previous milk intake without reaction	OFC in the past for milk	Age at first reaction (months)	More than one reaction	Most severe reaction involving the skin	Most severe reaction involving the upper airway	Most severe reaction involving the lower airways	Most severe reaction involving the gastrointestinal tract	The most severe reaction involving the cardiovascular system	Total IgE (kU/L)	IgE to casein (kUAl/l)	IgE to a-lactoglobulin (kUAl/L)	IgE to b-lactalbumin (kUAl/L)	IgE to cow milk (kUAl/L)	Total cumulative dose (mL)
Male	Yes	Si	No	Yes	No	No	No	No	Taken in the form of raw milk	Yes	96	Yes	No	Yes	Yes	Yes	No	537.0	63.2	7.2	7.6	71.0	16.1
Male	Yes	Yes	No	Yes	Yes	No	No	No	Never assumed	No	4	Yes	Yes	No	No	Yes	No	717.0	17.1	.0	1.5	14.8	10.0
Male	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Never assumed	No	.	No	906.0	19.2	6.5	2.8	21.1	20.0
Female	Yes	No	No	No	No	No	No	Yes	Taken in the form of raw milk	No	.	No	24.6	.1	.0	.1	.2	38.0

between sensitization (the mere production of specific IgE) and true allergy (i.e., the appearance of symptoms after exposure to the causative allergen). A paradigmatic example is sensitization to LTP fruits: some subjects with high IgE values to LTP can eat Rosaceae fruit without any problems as they tolerate the sensitizing food. In other words, these subjects clinically tolerate sensitizing food allergens.

In contrast, particularly susceptible subjects may experience severe and fatal anaphylactic reactions after ingesting traces of the allergenic food. Therefore, individual risk factors for severe reactions should not be considered infallible. In this regard, there is a considerable consensus that severe and life-threatening reactions to milk OFC are still challenging to predict, as recently concluded by Turner and colleagues (12). Consequently, the clinical message to emphasize is that OFC cannot yet be considered a completely safe procedure and that potentially lethal anaphylaxis can always occur, regardless of the dose of milk

administered the timing, and any possible risk factors. Therefore, OFC is a procedure that constantly requires attention, care, sufficient time, well-trained staff, and an appropriate environment (with rapid access to the intensive care unit).

The small number of evaluated subjects and the lack of a placebo-controlled challenge were the main limitations of this study. In addition, the highest cumulative dose of OFC was 81 mL (approximately 2500 mg). This is a medium-dose OFC, and some patients may develop a reaction at higher doses. As a result, the findings could not be considered particularly robust. In addition, the sensitization outcomes concerned a selected population of Italian children. In this regard, the present study did not evaluate a cut-off value of specific IgE to cow's milk as a recent study investigated this issue (13). The outcomes suggested that a single cut-off could reasonably identify patients eligible for OFC.

On the other hand, we choose a validated and specific score for establishing the severity of food

challenge reactions (8). We did not consider a previous score as it was a proposal and generically indicated for allergic reactions (14).

Interestingly, Cianferoni and colleagues reported that the score 3–4 had a positive predictive value for anaphylaxis higher for egg (92%) and peanut (86%) compared to milk (62%), while a score of 0–1 had a negative predictive value for multisystem reaction of 95% for milk OFC, 91% for egg, and 93% for peanut (2). However, that study concerned data from about one thousand children undergoing OFC. Unfortunately, the present study included a limited number of children, so no significant associations were reported.

Also, the present findings could only be generalized to some oral food challenge tests for two main reasons. First, significant geographical variations exist concerning food allergy epidemiology. In this regard, a previous study compared food allergy characteristics between children living in Piemonte and Liguria, such as two neighboring regions (15). There were significant differences in the prevalence of different food allergies. Second, each food allergen has peculiar allergenic characteristics that differentiate clinical reactions to them.

Conclusions

This study emphasized the unpredictability of anaphylaxis during the OFC procedure, as no predictive and reasonable risk factors could rule out a severe reaction with absolute certainty. Consequently, OFC should be performed only at third-level pediatric allergy centers where an adequate and appropriate treatment of severe reactions can be provided.

Ethics Committee: The Ethics Committee of the IRCCS Istituto Giannina Gaslini approved the procedure (10/17; 04/05/2017).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MAT designed the study and discussed the paper; MN and CT collected cases; IS analyzed the data, GC wrote the manuscript.

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