

Adverse Events in Oral Immunotherapy for the Desensitization of Cow's Milk Allergy in Children: A Randomized Controlled Trial



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What is already known about this topic? Allergic reactions (ARs) are an intrinsic risk during oral immunotherapy (OIT). Data on safety are however usually limited, and there is significant heterogeneity in classification systems used to describe ARs and severity across studies.

What does this article add to our knowledge? Our study is unique as it is the first study to focus on the side effects of OIT using consensus definitions and severity grading specific for anaphylaxis in children.

How does this study impact current management guidelines? The use of consistent definitions will contribute to a better understanding of the risks associated with OIT and will improve the management of anaphylactic ARs and the safety of treatment with OIT.

BACKGROUND: This study focuses on the side effects of cow's milk oral immunotherapy (CM-OIT) using consensus definitions of food-induced anaphylaxis.

OBJECTIVE: To evaluate the risk of allergic reactions (ARs) and to identify risk factors associated with higher risk of anaphylactic ARs (AARs) during CM-OIT in children.

METHODS: Clinical charts of children receiving CM-OIT were carefully reviewed. ARs were defined as single-organ ARs, and AARs were defined as involvement of 2 organ systems and/or hypotension in response to CM protein. Descriptive statistics were used to represent demographics, occurrence, reaction characteristics, and comorbidities. Poisson analysis was performed to evaluate risk factors associated with AARs.

RESULTS: Among 41 children undergoing CM-OIT, 11 discontinued the treatment (N = 26.8%). The mean age at challenge was 12.1 years (standard deviation [SD], 3.6) and half were male (56.1%). The mean number of AARs per patient was 6.0 (SD, 3.5) versus a mean of 17.4 (SD, 11.9) non-AARs per patient. Among withdrawals from OIT, the mean number of AARs per patient was 8.3 versus 5.1 in nonwithdrawals. AARs were more frequent in children with higher specific IgE (sIgE) for α -lactalbumine and casein at baseline (1.11 [95% confidence interval (CI): 1.01, 1.22] and 1.01 [1.0, 1.03], respectively). Children with resolved eczema and higher sIgE for β -lactoglobuline at baseline (0.13 [95% CI: 0.04, 0.46] and 0.96 [95% CI: 0.94, 0.99], respectively) were less likely to develop AARs.

CONCLUSIONS: Although the majority of ARs during OIT are nonanaphylactic, AARs occur frequently. Children with higher sIgE for α -lactalbumine and casein at baseline seem to be at higher risk for AARs during OIT. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1912-9)

Key words: Anaphylaxis; Children; Cow's milk allergy; Oral immunotherapy; Safety

IgE-mediated food allergy currently affects 6% of children,^{1,2} and the prevalence has likely increased in the past few decades.³ Cow's milk allergy (CMA) affects 0.2% to 0.6% of children and is a frequent cause of severe allergic reactions (ARs) and anaphylaxis.¹⁻³

The majority of children outgrow CMA by the age of 3 to 5 years, but recent studies demonstrate an increasing prevalence of persisting CMA.^{4,5}

Current best practice management relies on strict avoidance of CM, with the possible exception of baked milk.⁶

Oral immunotherapy (OIT) to milk and other foods is emerging as an effective strategy to reduce the risk of accidental

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Abbreviations used

AAR- Anaphylactic allergic reaction
ALA- α -Lactalbumine
AR- Allergic reaction
BLG- β -Lactoglobuline
CMA- Cow's milk allergy
EoE- Eosinophilic oesophagitis
MCH- Montreal Children's Hospital
OIT- Oral immunotherapy
sIgE- Specific IgE
SPT- Skin prick test

reactions and achieve desensitization.^{7,8} Safety, however, remains the most important concern given that ARs are an intrinsic risk during OIT.⁹ Data on safety are usually limited, and there is significant heterogeneity in classification systems used to describe ARs and severity across studies.

Up to this point little is known about risk factors associated with ARs in the course of OIT. This study aims to evaluate the risk of AR during CM-OIT in children and to identify possible factors associated with higher risk of anaphylactic allergic reactions (AARs) during CM-OIT. In this study, we have applied a more rigorous definition for AARs to be consistent with studies on anaphylaxis caused by food allergies in children.

METHODS

This is a prospective, randomized-controlled study with a cross-over design performed at the Pediatric Allergy and Clinical Immunology Department of the Montreal Children's Hospital (MCH) in Montreal, Quebec, Canada, between April 2013 and March 2017.

This study received approval from the Research Ethics Board of the McGill University Health Center and written informed consent was obtained from every participant.

Children with IgE-mediated CMA, 6 to 18 years old, were recruited at the allergy clinic of the MCH. Eligible children had a suggestive clinical history of IgE-mediated CMA and the presence of at least one of the following confirmatory tests: positive skin prick test (SPT) defined by a wheal diameter ≥ 3 mm than that of normal saline and/or sIgE >0.35 kU/L to CM protein.

CMA was confirmed in all children, by a placebo-controlled, single-blinded oral challenge to CM. We excluded children with uncontrolled asthma, malignancies, autoimmune diseases and/or severe primary and/or secondary immune deficiencies, treatment with β blockers, and the presence of cardiovascular disease or severe hypertension.

Participants were randomly assigned 1:1, matched for age and sex, through the use of opaque envelopes, to receive treatment with CM-OIT or the control intervention, CM avoidance. All children in the control group were followed for 1 year after which the CM challenge was repeated, and if it was positive, they were offered OIT. Children in the control group were asked to report any AR during their year of observation. In addition, 1 year after the study entry, they had a follow-up visit and were queried on any AR that occurred during their observation year.

All children who either completed the maintenance phase or who withdrew from the protocol were included in the analysis.

All participants had a single-blinded milk challenge at the study entry (total cumulative dose of 200 mL or 8800 mg of CM protein).

Children who were able to tolerate a cumulative dose of 200 mL were not eligible for the study. The protocol was adapted from the protocol published by Martorell Aragones et al.¹⁰

Treatment started at the research unit of the MCH with a 2-day rush desensitization: on the first day, participants received hourly 1-2-4-8 mL of CM diluted 1/100 with water, followed by a last dose of 1.6 mL of CM diluted 1/10 with water. On the second day, they received hourly 1.6-3.2-6.4-12 mL of CM diluted 1/10 with water followed by a last dose of 2.5 mL of undiluted cow's milk. Once the children reached a dose of 2.5 mL, they were instructed to repeat this dose at home daily during 2 weeks. This was subsequently followed by an escalation phase of 16 weeks, during which incremental increases were given on a weekly basis at the research unit of the MCH with the following schedule: 4-6-8-10-12-15-20-25-30-40-50-75-100-125-150-200 mL. Once children had reached a maintenance dose of 200 mL, they were instructed to continue and consume 200 mL of CM daily for 1 month, followed by an open oral challenge with the maximum dose of 300 mL of CM. If well tolerated, they were recommended to consume dairy products without restriction with a minimum of 200 mL of milk twice a week. Children and their families attended regular follow-up visits at our research unit for 12 months.

The primary outcome was to determine the safety of CM-OIT by evaluating the risk of ARs and AARs according to consensus classification systems used to define ARs to foods,^{11,12} and to identify possible risk factors associated with higher risk of AARs during CM-OIT.

The secondary outcome was to determine the efficacy of CM-OIT defined by the proportion of desensitized participants in all participants. Desensitization was defined as no reaction during an open challenge with 300 mL of CM.

Participants were informed on potential side effects and management of possible ARs. They were provided self-administered epinephrine autoinjectors, along with instructions and indications for administration. Participants completed daily home diaries to document the dose intake and to report on ARs occurring after dose intake. Families could contact the research team, by telephone or study email.

If ARs occurred, CM doses were reduced to the previous tolerated dose or the dose would be split into two, depending on the discretion of the supervising allergist. ARs were registered in the medical chart including timing and dose at which the reaction occurred, symptoms, and treatment given.

Cofactors suggested to increase the risk of ARs such as viral illness, exercise, asthma flare, nonsteroidal anti-inflammatory drug (NSAID) usage, and menstruation were documented. Regular exercise was defined as a vigorous physical activity at least 3 times a week (more than 2 hours daily) such as basketball, hockey, or swimming. Eczema severity and asthma control were assessed by the supervising allergist according to previously published guidelines.^{13,14}

Anaphylaxis was defined as involvement of 2 organ systems and/or hypotension in response to a CM protein exposure.¹¹ ARs were categorized into anaphylactic/multiorgan reactions (AARs) versus nonanaphylactic or single-organ ARs. Anaphylaxis severity was classified according to a modified grading system published by Muraro et al.¹²

Mild AARs were characterized by the presence of skin and subcutaneous tissue symptoms such as urticaria, erythema, and angioedema as well as gastrointestinal involvement such as oral pruritus, nausea, mild abdominal pain, or respiratory involvement with nasal congestion and/or sneezing, rhinorrhea or throat tightness, or cardiovascular signs (tachycardia) as well as neurological symptoms such as change in activity level plus anxiety.

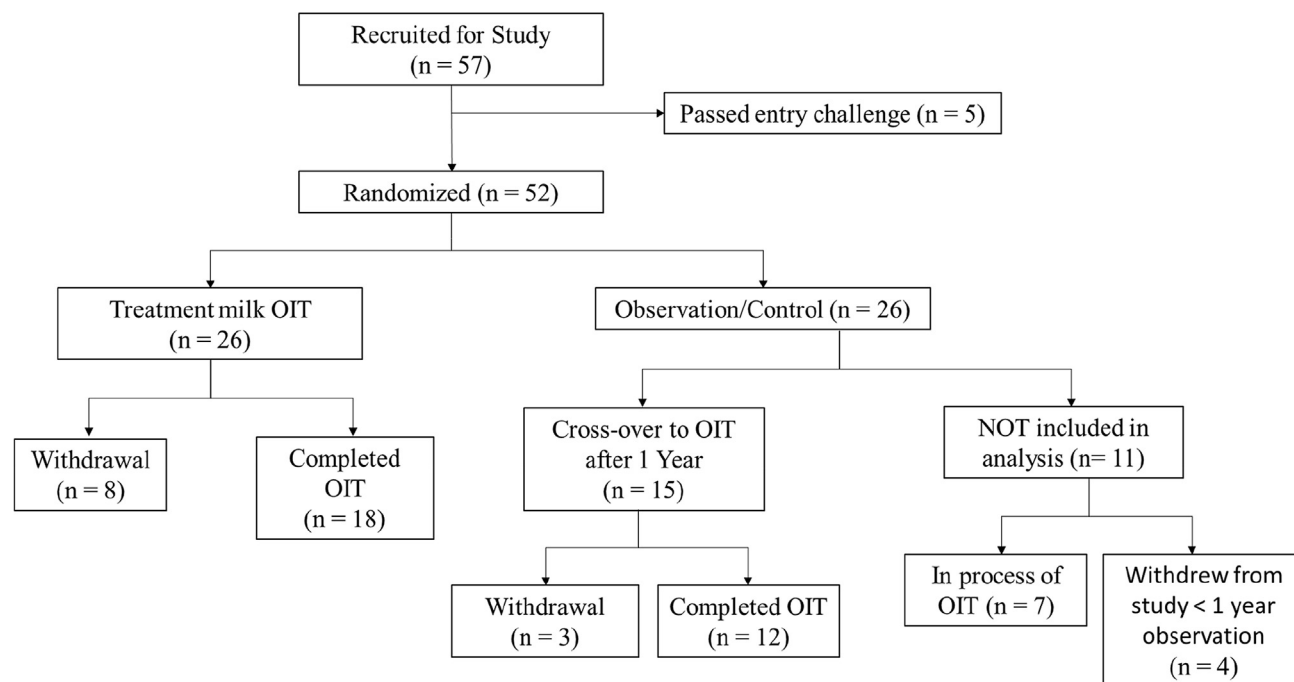


FIGURE 1. Consort diagram of study population. A total of 57 children were recruited for this study. Among them, 5 children passed the entry milk challenge and were not eligible for the study. The remaining 52 children were eligible and randomized to either milk OIT ($n = 26$) or observation ($n = 26$). Among the children in the observation group, 15 children crossed over to the treatment group after 1 year of observation. Among the remaining 11 children in the control group who were not included in the analysis, 7 children are still undergoing OIT but did not complete and 4 were lost to follow-up during the observation year. This analysis focuses on the side effects of milk OIT in 41 children with challenge established CMA ($N = 26$ in the OIT group; $N = 15$ in the control group and cross-over to OIT). Among 41 children, 11 withdrew from the protocol. Among those, a third withdrew ($N = 8$ of 26) from the treatment group versus a fifth of children in the observation group ($N = 3$ of 15) after cross-over to the treatment group. CMA, Cow's milk allergy; OIT, oral immunotherapy.

Moderate AARs were characterized by the presence of any of the previous symptoms as well as crampy abdominal pain, diarrhea or recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light headedness."

Severe AARs were characterized by the presence of any of the previous symptoms as well as loss of bowel control, cyanosis, hypoxia (saturation $< 92\%$), respiratory arrest, hypotension, dysrhythmia, severe bradycardia, and/or cardiac arrest as well as confusion or loss of consciousness.

The severity score was based on the organ system most affected.

Non-AARs were defined when only 1 organ system was affected within 2 hours of exposure, as previously published.^{15,16}

Mild ARs were characterized as pruritus, urticaria, flushing, and rhinoconjunctivitis.

Moderate ARs included the presence of one of the following symptoms: angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties other than wheeze.

Severe ARs were defined as wheeze or cyanosis.

Statistics

Given that previous studies have attributed at least 50% improvement in the ability to tolerate milk with an α of 0.05 and a power ($1 - \beta$) of 0.80, we aimed to recruit at least 18 cases and 18 controls.¹⁷

Descriptive statistics were used to represent demographics, clinical characteristics, and comorbidities. Statistical methods were used to compare groups for primary and secondary outcomes. Poisson

regression was performed to evaluate risk factors associated with AARs.

All statistical analysis was performed using STATA version 15.1 (StataCorp LLC, College Station, Texas) or R version 2.12.0 (R Foundation, Vienna, Austria; 2010).

RESULTS

Figure 1 shows the trial design. A total of 52 children were eligible and randomized for milk OIT. This analysis focuses on side effects in 41 children with challenge established CMA ($N = 26$ in the OIT group; $N = 15$ in the control group and cross-over to OIT). Among the remaining 11 patients in the control group not included in this study, 7 are still undergoing OIT and 4 withdrew from the study during their observation period.

The mean age at the study entry was 12.1 years (SD, 3.6), and almost half of the children were male (56.1%). During treatment, almost half of the children (41.5%) performed regular exercise. The majority had other allergic diseases including pollen allergy (68.3%), well-controlled asthma (85.4%), and eczema (36.6%). At the study entry, the mean cow's milk SPT was 7.7 mm (SD, 3.5) and the mean cow's milk sIgE 21.1 kU/L (SD, 33). Demographics and clinical characteristics are outlined in Table I.

Efficacy

Among all participants, the majority successfully reached maintenance phase ($N = 30$ of 41; 73.2%). A quarter withdrew from OIT ($N = 11$ of 41 = 26.8%) after a mean time of 26

TABLE I. Demographics and clinical characteristics of children undergoing milk OIT

Characteristics	Mean % (SD) (N = 41)*
Age at challenge (y)	12.1 (3.6)
Current age (y)	13.3 (3.6)
Sex: male	56.1
Active asthma	85.4
Resolved asthma	4.9
Active eczema	36.6
Resolved eczema	14.6
Pollen allergy	68.3
Regular antihistamines	17.1
Regular exercise	41.5
sIgE α -lactalbumine (kU/L) [†]	15.7 (30.2)
sIgE β -lactoglobuline (kU/L) [†]	75.8 (154.6)
sIgE casein (kU/L) [†]	143.0 (207.7)
sIgE cow's milk protein (kU/L) [†]	21.1 (33.0)
Skin prick test (mm) [†]	7.7 (3.5)
Mean cumulative reactive dose at baseline challenge (mL)	25 (34.0)

OIT, Oral immunotherapy; sIgE, specific IgE.

*Estimates for all variables are presented in percentage, unless otherwise indicated.

[†]Baseline values.

weeks (SD, 17). Among the 26 children randomized to OIT, 18 were defined as desensitized to milk. Among all control patients (N = 26), 22 children had a repeat single-blinded CM challenge and all were defined as CM allergic 1 year after allocation. The remaining 4 control patients withdrew from the study during their observation period. Hence, the difference in percentage of milk-desensitized children between the groups attributed to the OIT is 69.2% (95% CI: 47.6%, 90.8%).

Demographics and clinical characteristics in withdrawals (N = 11)

A total of 11 children withdrew from the protocol. Among those, a third withdrew (N = 8 of 26; 30.8%) from the treatment group versus a fifth of children in the observation group after cross-over to the treatment group (N = 3 of 15; 20%) (Figure 1). The majority were male (N = 8 of 11; 72.7%) and the mean age was 10.3 years (SD, 3.6). The main reasons for withdrawal included recurrent AARs (N = 7 of 11; 63.6%) and intermittent gastrointestinal complaints (N = 5 of 11; 45.5%). One boy was diagnosed with eosinophilic oesophagitis (EoE) confirmed by biopsy because of persistent vomiting, nausea, and dyspepsia after reaching a dose of 75 mL (N = 1 of 11; 9.1%). His symptoms resolved after discontinuing the treatment. Other reasons for withdrawal were anxiety, poor compliance, and lack of familial support. Demographics and clinical characteristics of children who discontinued the milk OIT are outlined in Table II.

Safety

Allergic reactions during OIT. A total of 1548 ARs were registered. Among all ARs, the majority were nonanaphylactic (N = 1303 of 1548; 84.2%). Of those, the majority occurred during escalation phase (N = 1167 of 1303; 89.6%) and were categorized as mild (N = 804 of 1303; 61.7%), with the majority being oral pruritus (N = 589 of 804; 73.3%).

Among all ARs, 15.8% were AARs (N = 245 of 1548), with the majority being mild to moderate (N = 144 of 245; 58.8% and N = 99 of 245; 40.4%, respectively).

The mean number of AARs per patient was 6.0 (SD, 3.5) versus a mean of 17.4 (SD, 11.9) non-AARs per patient. The number of AARs per patient ranged from 0 to 21 with a median of 4 AARs per patient (interquartile range: 1-10).

Among the AARs, the mean number of mild and moderate AARs per patient was 3.5 (SD, 3.8) and 2.4 (SD, 2.70), respectively. Among withdrawals from OIT, the mean number of AARs per patient was 8.3 (SD, 6.8) versus 5.1 (SD, 4.8) in non-withdrawals. The mean numbers of all ARs per patient are outlined in Table III. Among all AARs, 2 cases were severe (N = 2 of 245; 0.8%) and both occurred at home during the escalation phase.

One reaction occurred in a 14-year-old girl after taking a dose of 125 mL. The reaction was characterized by hypotension (palpitations, sweaty pallor, presyncope, and lump in throat) and was treated with epinephrine at home. She completely recovered, continued the treatment with OIT, and was successfully desensitized. The other reaction included an 8-year-old boy who reacted at a dose of 8 mL. The reaction was characterized by respiratory difficulties including wheezing and cyanosis and treated with intramuscular epinephrine, inhaled salbutamol, and oral prednisone at the emergency department. He recovered completely but withdrew from treatment because of recurrent AARs.

Use of epinephrine. Among all AARs, the mean number of AARs treated with intramuscular epinephrine was 0.6 (SD, 1.2). None of the mild AARs were treated with epinephrine, whereas a fifth of moderate AARs and all severe AARs were treated with epinephrine (mean number of moderate and severe AARs treated with epinephrine 0.5 [SD, 1.2] and 0.05 [SD, 0.2], respectively) (Table III).

Location of reaction. Among all reactions, the majority occurred at home (N = 1072 of 1548; 69.3%) versus in hospital (N = 476 of 1548; 30.7%). Two thirds of AARs (N = 163 of 245; 66.5%) occurred at home versus a third occurring in hospital (N = 82 of 245; 33.5%).

Factors associated with increased risk for AARs (Table IV). A higher sIgE for α -lactalbumine (ALA) (1.11 [95% CI: 1.01, 1.22]) and for casein (1.01 [1.0, 1.03]) at baseline—adjusted for age, sex, atopy, and regular exercise—was associated with a higher risk of AARs during OIT. Children with resolved eczema and higher sIgE for β -lactoglobuline (BLG) at baseline were less likely to develop anaphylaxis (0.13 [95% CI: 0.04, 0.46]; 0.96 [95% CI 0.94, 0.99], respectively).

Adverse events in children who withdrew from OIT (N = 11). Among the children who discontinued the treatment with OIT, the mean number of AARs per patient was 8.3 (SD, 6.8) versus 5.1 (SD, 4.8) in nonwithdrawals.

Among withdrawals, the mean number of AARs treated with epinephrine was 0.4 (SD, 0.9) versus 0.7 (SD, 1.3) in nonwithdrawals.

Comparison of AARs in the randomly assigned treatment versus control group

Among 26 children in the observation group, 4 children withdrew from the study during their observation period and were not included in the analysis.

TABLE II. Demographics and clinical characteristics in withdrawals (N = 11)

N	Age challenge	Active eczema	Pollen allergy	Exercise	SPT baseline (mm)	Dose withdrawal (mL)	Reason withdrawal
1	12	Not documented	Not documented	No	5	6	Anxiety
2	14	Yes	Yes	Yes (basketball competition)	5	20	Recurrent moderate AAR requiring epinephrine
3	13	No	No	Yes (soccer competition)	4	75	EoE
4	7	Yes	No	No	15	1	Recurrent GI symptoms and worsening of eczema
5*	6	No	No	No	9.5	8	Recurrent moderate-to-severe AAR and recurrent GI complaints
6	15	Yes	No	Yes (soccer)	10	6	Recurrent moderate AAR, anxiety, poor compliance
7*	11	No	Yes	Yes (ping pong competition)	11	25	Recurrent GI symptoms and 1 episode of moderate AAR
8	6	Yes	Yes	No	4	8	Recurrent mild-to-moderate AAR
9*	9	No	Yes	No	17	22.5	Anorexia, multiple comorbidities
10	6	Yes	Yes	No	8	8	Recurrent mild-to-moderate AAR and recurrent GI complaints
11	14	Yes	No	Yes (swimming and basketball)	12	8	Recurrent mild-to-moderate AAR and lack of familial support

AAR, Anaphylactic allergic reaction; EoE, eosinophilic oesophagitis; GI, gastrointestinal; SPT, skin prick test.

*All patients indicated in bold are from the control group.

TABLE III. Mean number of ARs and AARs per patient by severity and mean number of AARs treated with epinephrine

Mean number per patient (SD)						
All ARs	Mild	Moderate	Severe	Total	Withdrawals	Nonwithdrawals
AARs	3.5 (3.8)	2.4 (2.7)	0.05 (0.2)	6.0 (5.5)	8.3 (6.8)	5.1 (4.8)
AARs treated with epinephrine	0 (0)	0.5 (1.2)	0.05 (0.2)	0.6 (1.2)	0.4 (0.9)	0.7 (1.3)
ARs	5.2 (5.6)	11.6 (9.8)	0.5 (1.0)	17.4 (11.9)	16.7 (10.4)	17.7 (12.6)

AAR, Anaphylactic allergic reaction; AR, allergic reaction; SD, standard deviation.

During the observation year, overall 2 moderate AARs were documented because of accidental exposure among 22 children in the control group. One reaction occurred in a girl who was in her 11th month of observation. She developed nausea, difficulty swallowing, abdominal pain, and angioedema for which she was treated with 1 dose of epinephrine. The second reaction occurred in a boy during the fourth month of observation. He developed cough, had difficulty breathing, and had vomiting for which he was treated with 1 dose of epinephrine. They both fully recovered and continued with OIT after cross-over. The girl was successfully desensitized, whereas the boy withdrew because of recurrent AARs.

Among the 26 children in the treatment group, a mean 5.5 AARs (SD, 4.7) per patient was documented during the first year of the study and the mean number of reactions treated with epinephrine was 0.5 (SD, 0.9).

DISCUSSION

To the best of our knowledge, we have conducted the first randomized-controlled trial in Canada to assess the safety of a CM-OIT protocol in children with CM allergy. To date, studies report

on safety inconsistently, using different classification systems to describe reaction severity across studies.

Our safety outcomes are in line with previous reports;¹⁸⁻²¹ however, the unique nature of this study is that we have applied the consensus definition for anaphylactic reactions and severity grading specific for children.^{11,12}

For example, studies have defined adverse events as severe, that is, symptoms that prevent daily activities and might require therapeutic intervention, and serious—defined by life-threatening events or death.²¹ However, milder reactions that still meet the consensus definition of anaphylaxis¹³ are often not described as anaphylaxis in these studies but rather as mild reactions.^{21,22} The combination of cough and urticaria—that meets the criteria of moderate anaphylaxis in our study—is not reported as anaphylaxis in other studies although up to 60% of participants may present with these symptoms.²¹

We demonstrate that the majority of ARs (84.2%) occurring during milk OIT are mild, nonanaphylactic reactions, occurring mostly during the escalation phase of our protocol. Among all mild reactions, local oral pruritus is the most common side effect (73.3%). However, our results also show that AARs still occur in 15.8% of children and that a quarter of children (N = 11 of

TABLE IV. Risk factors associated with anaphylaxis in all patients

Risk factors for anaphylaxis (N = 41)	OR (95% CI)
Male	1.01 (0.61, 1.67)
Age at challenge	1.04 (0.97, 1.12)
Regular exercise	0.97 (0.56, 1.66)
Active asthma	1.16 (0.46, 2.94)
Resolved asthma	3.29 (0.54, 20.11)
Active eczema	1.35 (0.85, 2.14)
Resolved eczema	0.13 (0.04, 0.46)
Seasonal allergy	0.8 (0.49, 1.3)
SPT at baseline	1 (0.93, 1.09)
sIgE α -lactalbumine*	1.11 (1.01, 1.22)
sIgE β -lactoglobuline	0.96 (0.94, 0.99)
sIgE casein*	1.01 (1, 1.02)
sIgE cow's milk	1.12 (0.99, 1.27)

CI, Confidence interval; OR, odds ratio; sIgE, specific IgE; SPT, skin prick test.

*Values in bold are associated with higher risk of anaphylaxis.

41 = 26.8%) withdraw because of recurrent anaphylactic reactions (N = 7 of 11; 63.6%) or persistent gastrointestinal symptoms (N = 5 of 11; 45.5%). Importantly, our results demonstrate a high rate of AARs during OIT (mean number of AARs per patient = 5.5 [SD, 4.7]), whereas only 2 AARs occurred among 22 patients of the control group during the 1-year observation. This finding highlights the inherent risk of undergoing OIT versus strict avoidance.

Our findings on the relatively common development of gastrointestinal (GI) symptoms are in line with other studies reporting that in almost 20% of children who discontinued OIT, chronic late onset GI symptoms were the main reason for withdrawal (46.1%).¹⁹

Several reports suggest that OIT can induce EoE; however, not all of children with symptoms consistent with possible EoE undergo an esophageal endoscopy. In our study, we report 1 child diagnosed with EoE by biopsy after repetitive gastrointestinal symptoms suggestive of EoE. His EoE resolved (no clinical symptoms and normal biopsy) within 1 month after he withdrew from the study.

Our results demonstrate that a significant proportion of ARs are AARs (15.8%). The first-line treatment for anaphylaxis is intramuscular epinephrine.¹⁴ Nevertheless, the mean number of AARs treated with epinephrine was overall low. None of the mild AARs were treated with epinephrine, whereas a fifth of moderate AARs and all severe AAs were treated with epinephrine. Given that the majority of AARs (N = 163 of 245; 66.5%) occur at home, this might be explained by fear of using the epinephrine autoinjector at home.²³ This finding is in line with other studies observing an underuse in epinephrine for the treatment of anaphylaxis in children.^{24,25}

These results highlight the need and importance of educating families and caregivers undertaking the commitment of OIT in recognizing anaphylaxis and indications for treatment with epinephrine.

In our series, we describe 2 cases of severe anaphylaxis and we report no fatalities. The rare occurrence of severe anaphylaxis is in line with previous reports.^{9,18-20,26,27}

Our study reveals that children with higher sIgE for ALA and casein at baseline are at increased risk for developing anaphylaxis during OIT, whereas children with higher sIgE for BLG are less likely to develop anaphylactic reactions.

Previous studies have shown a correlation between sIgE to casein and the reaction severity; however, a possible protective effect of BLG has not been described.²⁸ This could possibly be explained by different chemical structures between BLG and casein that may affect the risk of desensitizing mechanisms, for example, different abilities to induce blocking IgG antibodies that may have a protective effect. Indeed studies in rats suggest that BLG induces higher levels of IgG compared with ALA and β -casein (BLG > ALA > β -casein).²⁹

Furthermore, our results reveal that children with resolved eczema are less likely to develop AAR during milk OIT.

Previous studies have reported worsening of eczema during OIT treatment, and uncontrolled eczema is considered as a relative contraindication to starting OIT for food allergy.⁷ It is possible that resolution of eczema reflects a higher probability of resolution of other atopic conditions including milk allergy.³⁰

Our results highlight the importance of optimal control of eczema, before the start of treatment with OIT. The presence of active asthma could not be identified as a risk factor for AAR. We hypothesize that this is due to the fact that only children with well-controlled asthma were included in this study.

Other studies have reported risk factors associated with food OIT that were not identified in our study. Vazquez-Ortiz et al²⁰ found that higher SPT at baseline was associated with an increased risk of anaphylaxis. They further identified 3 variables as independent risk factors of persistent ARs in children undergoing milk OIT: CM-sIgE >50 kU/L, CM-SPT $\geq$ 9 mm, and Sampson's severity grades 2, 3, and 4 at the baseline challenge. They suggest that a combination of 2 or 3 factors could help to identify highly reactive patients before CM-OIT.²⁰

A recent study by Virkud et al³¹ revealed that during peanut OIT, higher baseline SPT and concomitant allergic rhinitis were associated with intolerable gastrointestinal adverse events and increased systemic reactions, respectively.

Even though more than a third of children performed regular exercise (41.5%), this was not identified as a significant risk factor for the increased risk of AAR, which could be explained by the fact that patients were well informed about the risk of systemic reactions in the setting of exercise before the start of OIT and have diligently avoided exercise within 2 hours of administration of their daily milk dose.

Other cofactors have been previously described to increase the risk of anaphylaxis in the context of OIT including medication use (NSAIDs), menses, and viral infections.³² These factors could not be identified as significant cofactors in this study.

Treatment with OIT is safe in the majority of patients, but ARs occur frequently and are often unpredictable. Despite the observation that the majority are mild, nonanaphylactic reactions, severe AARs, do occur and some patients drop out in most studies. The risk of AARs is the main limitation for the routine use of OIT. On the basis of our results, we would recommend vigilant monitoring for all patients for both non-AARs and AARs particularly during the build-up phase, education of children, and their families regarding possible eliciting cofactors and continuous availability of an epinephrine autoinjector.

In patients with higher risk of anaphylactic reactions, we would recommend individualized schedules with a slower and adapted build-up protocol if needed. Alternatively, to reduce the risk of AARs, premedication with antihistamines, omalizumab, or other new biologics could be considered; however, further research is needed.^{33,34}

Strengths and limitations

The unique nature of this study is that we have applied a more rigorous definition for anaphylactic reactions that is consistent with the formal definition of anaphylaxis as previously defined and severity grading specifically addressing anaphylaxis in children.^{11,12} It is crucial to use consistent definitions when assessing reactions to food to convey appropriate information to families and to manage these reactions efficiently.

Given the nature of treatment with OIT, our research was performed as a nonblinded, open study. There was no placebo; however, our results demonstrate that in the absence of treatment with OIT, none of the controls achieved tolerance after 1 year of observation. In addition, our sample includes an older age group compared with other studies. It is possible that a younger age group would have less ARs and that controls would have had a higher likelihood of outgrowing CMA. In addition, none of the children were consuming baked milk at the study entry. Given that studies have suggested that children tolerant to baked milk are more likely to outgrow their allergy, this might affect our results. Finally, the relatively small number of patients might have affected the ability to identify other risk factors such as SPT size, pollen allergy, and NSAID use.

CONCLUSION

This is the first study to focus on the side effects of OIT using consensus definitions and severity grading specific for anaphylaxis in children. Our results reveal that adverse events occur frequently and that the majority are mild, non-life-threatening events. Nevertheless, almost a fifth of children develop AARs during milk OIT.

The use of consistent definitions will contribute to a better understanding of the risks associated with OIT and will improve the management of AARs and the safety of treatment with OIT.

Caregivers should be vigilant regarding the risks associated with CM-OIT, especially in children with higher sIgE for ALA and casein at baseline. In contrast, children with higher sIgE for BLG seem to have a decreased risk for AARs. Although not established at this point, large studies assessing the concomitant use of biologics with OIT are required to assess if better control of eczema will contribute to safer OIT.

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