

Natural Course and Risk Factors for Persistence of IgE-Mediated Cow's Milk Allergy

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Objective To describe the natural course of IgE-mediated cow's milk allergy (IgE-CMA) and to determine risk factors for its persistence in a population-based cohort.

Study design In a prospective cohort study, 54 infants with IgE-CMA were identified from a population of 13 019 children followed from birth. Diagnosis of IgE-CMA was based on history, skin prick test (SPT), and an oral food challenge (OFC) when indicated. Allergic infants were followed for 48-60 months. Families were contacted by telephone every 6 months and asked about recent exposures to milk. OFC was repeated to evaluate for recovery. Clinical characteristics, SPT, and OFC outcomes were compared between infants with persistent IgE-CMA and infants who recovered.

Results Thirty-one infants (57.4%) recovered from IgE-CMA during the study period. Most infants (70.9%) recovered within the first 2 years. Risk factors for persistence on multivariate analysis included a reaction to <10 mL of milk on OFC (or on first exposure as estimated by the guardian, if OFC was not performed) ($P = .01$), a larger wheal size on SPT ($P = .014$), and age of ≤ 30 days at time of first reaction ($P = .05$).

Conclusions Resolution occurs in most infants with IgE-CMA. Infants reacting to <10 mL of milk or in the first month of life, and those with a larger wheal size on SPT, are at increased risk for persistence. (*J Pediatr* 2012; ■: ■-■).

Cow's milk allergy (CMA) is a common, significant, and potentially fatal food allergy with previously reported incidence of 2%-5%.¹⁻³ The study of CMA is hampered by the use of various definitions and diagnostic criteria leading to diverse and often contradictory findings.

Although IgE-mediated reaction is a risk factor for CMA persistence,⁴⁻⁶ most infants with IgE-CMA recover. Two studies in infants with IgE-CMA demonstrated that a larger wheal size on skin prick test (SPT) and higher IgE levels to cow's milk protein (CMP) pose risk for persistence. However, these studies might have been affected by only 40% catchment of the intention to treat population⁷ and by the use of referred patients from a large clinic.^{8,9} Therefore, prospective population-based studies are required to identify risk factors for persistence of IgE-CMA.¹⁰ The optimal criteria would be those that could be used at the time of diagnosis and applied to clinical practice.

The present study is part of a large population-based study in 13 234 infants with 98.4% recruitment of the target population.¹¹ Infants with IgE-CMA were prospectively followed from birth until the age of 4-6 years. Persistence was defined as IgE-CMA at the end of the study period. Our aim was to describe rates of resolution in this group of patients and to identify risk factors for persistence.

Methods

The research protocol was approved by the Helsinki Review Board of Assaf Harofeh Medical Center. As previously described, 13 234 newborns born over a 2-year period (June 10, 2004-June 30, 2006) at Assaf-Harofeh Hospital (Zerifin, Israel) were enrolled and 13 019 completed the study. Parents were asked to contact the allergy clinic immediately after any adverse reaction (cutaneous, respiratory, gastrointestinal, or systemic) suspected to be related to the initiation of CMP-based feeding or 14-30 days after the initiation of CMP-based feeding. All parents were contacted 3 months after birth and the feeding pattern was recorded. Parents providing full breastfeeding were subsequently contacted bimonthly until the newborn consumed dairy products. Parents noting a possible adverse event related to CMP ($n = 381$) were interviewed by one of the investigators, and their infants were

CMA	Cow's milk allergy
CMP	Cow's milk protein
OFC	Oral food challenge
SPT	Skin prick test

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examined. Of those, 66 infants were presumed to have IgE-CMA based on history and positive SPT to CMP.¹¹ The parents of 12 infants refused oral food challenge (OFC) to secure the diagnosis, and the remaining 54 infants (confirmed IgE-CMA) were used for subsequent analysis.

SPTs

SPTs in infants were done to CMP and soy and in parents to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (5000 Au/mL), sagebrush, mix grasses, pellitory (1:20 wt/vol), dog, cat hair (5000 BAU/mL), cat pelt (10 000 BAU/mL), olive tree (1:20 wt/vol), and *Alternaria* (1:10 wt/vol) by using the volar arm and reading the reaction after 20 minutes. A negative control, and histamine (1 mg/mL; ALK-Abelló, Port Washington, New York) were used. A 3-mm or larger wheal response was considered positive.¹²

Oral Challenge

Challenge to cow's milk formula was performed using Materna (Maabarot Products Ltd, Maabarot, Israel) infant formula unless a history of a life-threatening reaction manifested by either anaphylaxis or severe respiratory distress upon exposure to CMP was described. Increasing doses were given, from a 1:10 diluted formula of 1.0 mL (2.7 mg of CMP) up to 120 mL (3.24 g of CMP) every 30 minutes. The challenge was terminated if a cutaneous, respiratory, gastrointestinal, or systemic response was observed. In case of a negative challenge result, the infant was observed for 3 hours, and a subsequent contact was made 2 weeks later to inquire about his feeding habits.

Follow-Up

All 54 children with confirmed CMA were followed for 48-60 months. Families were contacted by telephone every 6 months and were asked about recent exposures to milk. Children were invited annually for an OFC to examine for potential recovery unless an exposure within the last 3 months, leading to an adverse reaction, was described. In cases in which children were exposed to milk with no adverse events and, subsequently, began consuming milk products with no limitation, an OFC was not performed.

Statistical Analysis

Statistical analyses were performed with SPSS software (v. 16; SPSS Inc, Chicago, Illinois). Abnormally distributed continuous variables were analyzed using the Mann-Whitney non-parametric test. Fisher exact test was used to analyze differences between groups in categorical variables. Log rank test was used to analyze the effect of each of the risk factors on cumulative recovery from milk allergy. Cox regression analysis was performed to determine the effect of multiple risk factors for persistence on the cumulative recovery from CMP allergy and hazard ratios were determined. All analyses were 2-tailed and a *P* value of <.05 was considered significant.

Results

Mode of Diagnosis and Rate of Recovery

Out of the 66 infants presumed to have IgE-CMA based on history of an immediate adverse reaction upon consumption of milk and a positive SPT, the diagnosis was confirmed in 54 infants. In 48 infants (72.8%), confirmation was achieved by a positive OFC, and in 6 additional infants, by a history of a life threatening reaction (**Figure 1**; available at www.jpeds.com). Reaction to CMP occurred at an average of 1.67 ± 1.67 days after initial exposure. Thus, age of initial exposure and age at first reaction to CMP represent similar variables with similar statistical significance. Only the term reaction will be used for simplification. Thirty-one infants (57.4%) recovered from CMA during the study period. Recovery was established by OFC, followed by regular consumption of milk in 17 patients. The other 14 patients were randomly exposed to CMP, had no reaction, and began regular consumption of milk (**Figure 1**). Most infants who recovered (70.9%) did so during the first 2 years of life. Rates of recovery then reached a plateau with an average annual rate of 7.3%. No additional recoveries were noted during the last year of follow-up, when subjects were 4 years or older.

Risk Factors for Persistence of CMP Allergy

Infants who recovered from IgE-CMA and those who did not were comparable in sex, in whether or not they were exposed to CMP at the maternity ward, and in their atopic background (parental and infant SPT positivity and doctor-diagnosed atopic dermatitis) (**Table**). More infants with persistent CMA reacted in the first month of life but statistical significance was not met (*P* = .078). Age range at initial reaction in the group of infants who reacted after the first month of life was 45-360 days.

Although age at time of diagnostic work-up was comparable in the 2 groups, wheal size on diagnostic SPT was larger in infants who subsequently had persistent CMA (*P* = .05) (**Table**). A wheal size cutoff of 6 mm was found to best differentiate between transient and persistent allergy (*P* = .09). Infants in the persistent group responded to a lower amount of milk on OFC (or on first exposure, if OFC was not performed) (*P* = .06), and significantly more patients in this group responded to <10 mL of milk (*P* = .006). Symptoms upon exposure to CMP during the OFC (or first exposure in those not challenged) also differed between the 2 groups. Infants who recovered tended to experience gastrointestinal symptoms (in addition to rash), and infants with persistent CMA tended to experience lower respiratory tract symptoms (in addition to rash), although statistical significance was not met. Of the 3 differentiating factors described above (the amount of milk inducing a reaction, the age at first reaction, and the wheal size on SPT to milk), early age at first reaction was most predictive of persistence as only 30% of infants reacting at ≤ 30 days compared with $\sim 40\%$ of infants who reacted to <10 mL or had a wheal size >6 mm on SPT recovered (**Figure 2**).

Table. Comparison of milk-allergic groups based on recovery

		Patients diagnosed by OFC or life-threatening reaction		P value
Parameter		Recovery n = 31	No recovery n = 23	
Onset of allergy	Male sex	15 (48.4%)	12 (52.2%)	1.0
	Milk in nursery	12/27 (44.4%)	11/22 (50%)	.78
	Age (d)	117.1 ± 64.9	96 ± 77.9	.16
	Age ≤30 d	3 (9.7%)	7 (30.4%)	.08
Atopic tendency	Atopic dermatitis	0	1/23 (4.3%)	.44
	Child SPT (+)	6/30 (20%)	10 (43.5%)	.08
	Maternal SPT (+)	10/28 (35.7%)	11/22 (50%)	.39
	Paternal SPT (+)	14/25 (56%)	10/21 (47.6%)	.77
Diagnostic work-up	Age at SPT (m)	10.2 ± 4.5	11.9 ± 8.9	.8
	Milk wheal size	5.2 ± 2	7.2 ± 3.5	.05
	Wheal >6 mm	8 (25.8%)	12 (52.2%)	.09
	Milk (mL)*	22.1 ± 22.3	14.5 ± 19.9	.06
Symptoms	Milk <10 mL*	8 (25.8%)	15 (65.2%)	.006
	Rash	29 (93.5%)	22 (95.7%)	1.0
	Gastrointestinal	18 (58.1%)	8 (34.8%)	.1
	Wheeze	3 (9.7%)	6 (26.1%)	.15
	Life-threatening	3 (9.7%)	4 (17.4%)	.44

*On OFC or on first exposure in patients who did not perform OFC.

Risk Factors for Delayed Recovery

Cumulative recovery from CMA was significantly delayed in infants reacting in ≤30 days of life ($P = .04$), and in infants reacting to <10 mL of milk ($P = .005$). A larger wheal size on SPT was also a risk factor for delayed recovery ($P = .011$), but significance was borderline for a wheal size cutoff of >6 mm on SPT ($P = .057$). On multivariate analysis using Cox regression analysis for these 3 parameters, reaction to <10 mL of milk remained a significant risk factor for delayed recovery ($HR = 2.93$, $P = .01$) (Figure 3, A). Reaction at ≤30 days of life also conferred risk for delayed recovery, and although the significance was borderline ($HR = 3.31$, $P = .05$), it was still considered to contribute to the model (Figure 3, B). A larger wheal size on SPT to milk also remained a significant predictive factor for delayed recovery ($P = .014$) but the cutoff of 6 mm did not reach statistical significance ($P = 0.1$) (Figure 3, C).

CMP Allergy in Infants Diagnosed by History and Positive SPT Only

Parents of 12 infants refused OFC and so were excluded from the analysis. Only 5 of 12 infants (41.7%), compared with all 6 infants who did not perform OFC because of a history of a life-threatening reaction, reacted to <10 mL of milk on initial exposure ($P = .038$). All 12 patients in this group, compared with 57.4% (31/54) of those who were diagnosed based on either OFC or a life-threatening reaction upon initial exposure, had recovered ($P = .005$). In addition, resolution in the first year occurred in 5 of 12 infants in this group compared with 3 of 31 infants (9.7%) diagnosed by OFC or a life-threatening reaction in whom CMA subsequently resolved ($P = .028$). The high rate and the relative short time to resolution of CMA in infants diagnosed by history and SPT alone suggest that these infants might have been erroneously diagnosed with IgE-CMA. However, all these infants

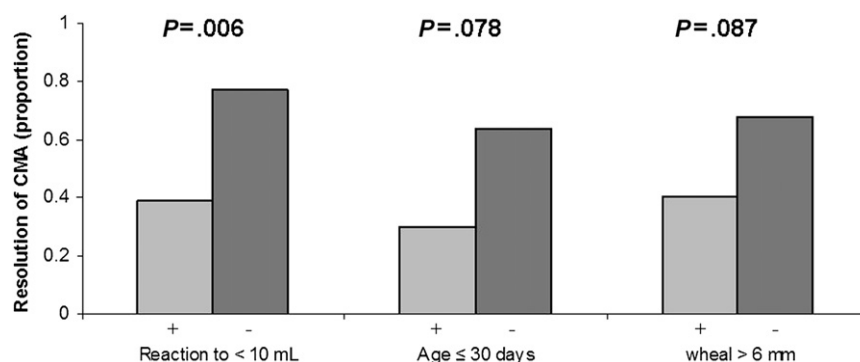


Figure 2. Proportion of infants recovering from IgE-CMA. Patients' recovery from CMA was compared based on the amount of milk evoking a reaction, the age at first reaction, and the wheal size on diagnostic SPT. Fisher exact test was used to analyze differences between groups.

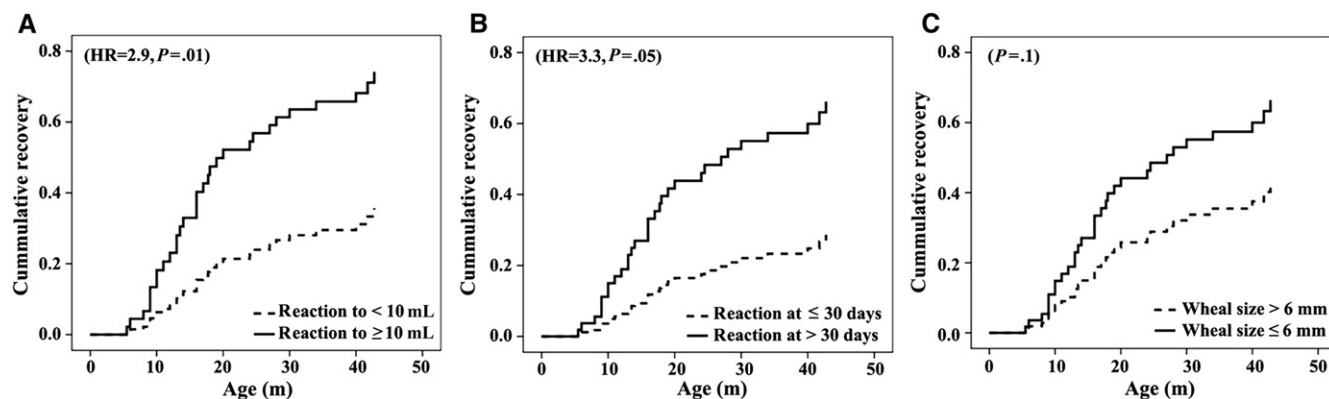


Figure 3. Predicting factors for recovery from IgE-CMA. Cumulative recovery from CMA was compared based on **A**, the amount of milk evoking a reaction, **B**, the age at first reaction, and **C**, the wheal size on diagnostic SPT. Cox regression analysis was performed to analyze cumulative recovery.

had immediate reactions to CMP and on more than one occasion (which may be the reason for the parental refusal for OFC), and are, thus, still likely to have had IgE-CMA. We, therefore, repeated the analysis for all 66 infants with presumptive IgE-CMA. Cumulative recovery from CMP in infants who reacted to < 10 mL of milk ($HR = 2.57$, $P = .003$) and in infants who reacted to milk at ≤ 30 days of life ($HR = 3.67$, $P = .031$) remained significant risk factors for persistence, and milk wheal size > 6 mm did not reach statistical significance ($P = .089$).

Discussion

In this prospective population-based study focusing on infants with IgE-CMA, we found that a reaction in the first 30 days of life, a greater wheal size on SPT, and a lower reaction threshold to milk predicted the persistence of allergy. These factors may reflect a more severe underlying immune reactivity to CMP.

Cow's milk-specific IgE levels were shown in the past to correlate with the persistence of CMA.¹³ Specific IgE levels were also found to predict pass rates of an OFC and to correlate with the eliciting dose of a positive challenge test.¹⁴⁻¹⁶ The concept, therefore, that the eliciting dose on OFC might predict persistence is attractive. However, this has been previously shown by only 1 study.¹⁷ In addition, the time frame of 6 hours that was used in this study to define a positive reaction on food challenge might have led to the inclusion of patients with food protein-induced enterocolitis syndrome.¹⁸ Indeed, the range of SPT-wheal size and of specific IgE levels suggest that patients with non-IgE-CMA were included. Moreover, the significance of the eliciting dose in predicting persistence of CMA was lost on multivariate analysis. A recent National Institute of Allergy and Infectious Diseases-sponsored expert panel¹⁹ did not include the eliciting dose on OFC in the prognostic factors for CMA persistence. Therefore, our finding that a lower eliciting dose on OFC predicts persistence in patients with IgE-CMA on multivariate

analysis is important. A response to an eliciting dose ≥ 10 mL may be used to reassure parents that their infant's CMA is likely to resolve.

Another predictive factor for IgE-CMA persistence in our study, in contrast to other studies, was a reaction to CMP in ≤ 30 days of life.^{17,20} Inclusion of patients with non-IgE-CMA¹⁶ and different definitions for persistence²¹ may account for these differences. Given the short interval between exposure and reaction, an early exposure might be a risk factor for persistence of CMA. This is in contrast to the previously described protective effect of early exposure to CMP.¹¹ Patients who develop IgE-CMA relatively early in life may comprise a subgroup with higher IgE levels to CMP in which tolerance might be more difficult to induce. This theory is supported by studies demonstrating that infants with IgE-CMA, whose disease persists for more than 2-3 years, have higher serum IgE antibodies to specific CMP even from the outset of their disease.^{21,22} Another potential confounder is the effect of repeated accidental exposures, which may reduce the probability of recovery from food allergy.^{23,24} Our study was not designed to record prospectively such exposures and can, therefore, not answer that question. Nevertheless, it is possible that the protective benefit of early exposure to CMP applies only to a subgroup of infants at risk for CMA.

A wheal size on SPT performed 12 months after, but not at the time of, diagnosis was found predictive of persistence in patients with IgE-CMA.⁴ A wheal size > 10 mm correlated with CMA persistence in 2 other studies.^{4,8} However, these were limited by a low catchment rate and the use of a selected group of patients. In our study, a larger wheal size on SPT, performed at the time of diagnosis, was associated with persistence of CMA on multivariate analysis, although no specific cutoff was found. Regardless, this parameter is largely technique-dependent and may, therefore, be too variable to serve as a reliable predictive factor for persistence.

Gastrointestinal symptoms were found more often in infants who eventually recovered from CMA.²⁵ However, these characteristics likely reflect different proportions of infants

with IgE- vs non-IgE-CMA in these sub-groups.^{11,14,26,27} Symptoms on OFC were not found to predict persistence in selected groups (with no recoveries before the age of 2-3 years) of IgE-CMA infants.^{8,12,21} We found that respiratory tract symptoms were associated with persistence of CMA, and gastrointestinal symptoms were associated with recovery. Although statistical significance was not met, these trends raise the possibility that infants with transient and persistent CMA differ in their specific organ responsiveness to milk.

The rate of resolution of IgE-CMA is not completely clear. Although some studies reported a relatively low rate of recovery, ranging from 20%-40%,^{9,21,22} others reported a much more favorable prognosis with 75% resolution until the age of 3 years.⁵ These differences likely reflect the difference between children followed in specialized referral centers vs population-based studies. The high rate of resolution (65% until the age of 4 years) found in our study is in agreement with other population-based studies.⁵

One limitation in our study is that 12 patients with possible IgE-CMA had to be excluded as they did not perform OFC because of parental refusal. However, risk factors for persistence remained similar whether or not these patients were included in the analysis. Another limitation is that our study population had a lower prevalence of IgE-CMA than previous reports.¹⁻³ However, when similar diagnostic criteria to our study were used, similar prevalence rates were found in Spain (0.36%), Norway (0.2%), and Turkey (0.3%).²⁸⁻³⁰

In summary, our study, following infants with IgE-CMA prospectively, demonstrates that a reaction to <10 mL of milk, a reaction in the first month of life, and a larger wheal size on SPT to milk, are risk factors for persistence. Our findings are in agreement with previous studies suggesting that patients with more severe disease recover less frequently. The advantage of the present study is that the parameters identified are based on a relatively large population-based cohort and that they do not require laboratory workup. These factors can be translated into clinical practice, assisting allergists and pediatricians in guiding parents regarding the natural course and prognosis of their infant's allergy. ■

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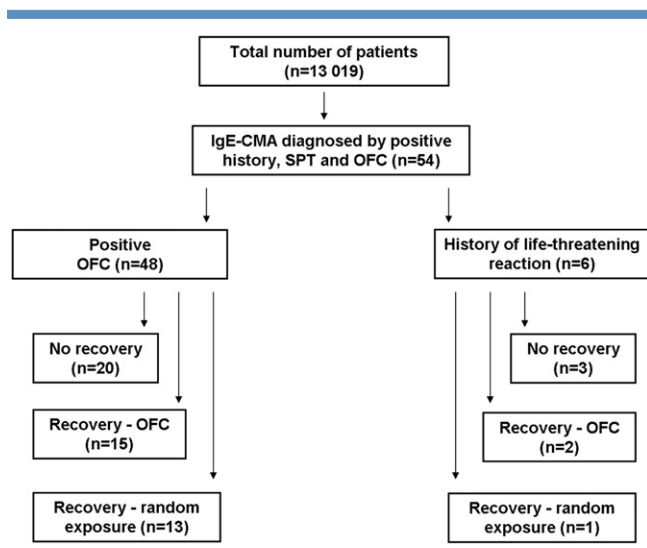


Figure 1. Patients' mode of diagnosis and recovery. An algorithm demonstrating patients' method of diagnosis, follow-up, and rate of recovery.