Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy

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Background: The diversity in the perceived prevalence, recovery, and risk factors for cow's milk allergy (CMA) necessitated a large-scale, population-based prospective study.

Objective: We sought to determine the prevalence, cross-reactivity with soy allergy, and risk factors for the development of CMA.

Methods: In a prospective study the feeding history of 13,019 infants was obtained by means of telephone interview (95.8%) or questionnaire (4.2%). Infants with probable adverse reactions to milk were examined, skin prick tested, and challenged orally.

Results: Ninety-eight percent of the cohort participated in the study. The cumulative incidence for IgE-mediated CMA was 0.5% (66/13,019 patients). The mean age of cow's milk protein (CMP) introduction was significantly different ($P < .001$) between the healthy infants (61.6 ± 92.5 days) and those with IgE-mediated CMA (116.1 ± 64.9 days). Only 0.05% of the infants who were started on regular CMP formula within the first 14 days versus 1.75% who were started on formula between the ages of 105 and 194 days had IgE-mediated CMA ($P < .001$). The odds ratio was 19.3 (95% CI, 6.0-62.1) for development of IgE-mediated CMA among infants with exposure to CMP at the age of 15 days or more ($P < .001$). Sixty-four patients with IgE-mediated CMA tolerated soy, and none had a proved allergy to soy.

Conclusions: IgE-mediated CMA is much less common than generally reported. Early exposure to CMP as a supplement to breast-feeding might promote tolerance. Finally, soy is a reasonable feeding alternative in patients with IgE-mediated CMA. (J Allergy Clin Immunol 2010;126:77-82.)

Key words: *IgE-mediated cow's milk allergy, soy allergy, breast-feeding, skin prick test, oral challenge*

Cow's milk protein (CMP) allergy is one of the most common food allergies and is potentially fatal.[1] The reported incidence of CMP allergy is in the range of 2% to 5%, of which only 60% are IgE mediated.[2,3] The rate of reported growing out of the allergy and the ability to tolerate milk also varies considerably and ranges between 29% and 76% for IgE-mediated cow's milk allergy (IgE-CMA).[4] Two major sources of confusion regarding the prevalence of CMP allergy are data collected by self-reporting and the lack of standardized criteria in diagnosing this illness.

The latter source of confusion has been recognized as early as 1957.[5] It is now well accepted that in patients with IgE-CMA the response to exposure to milk is immediate, usually within 15 to 30 minutes, the recommended and practiced time interval in food challenges.[6-9] Other well-accepted criteria of IgE-CMA are a positive skin prick test (SPT) response and, in most cases, a cutaneous reaction.[3,10] Other immunologically non–IgE-mediated reactions to food are cell mediated, such as food protein–induced enterocolitis syndrome (FPIES) or a mixed IgE-associated and cell-mediated reaction, such as atopic dermatitis and eosinophilic esophagitis.[10] Other clinical entities, including infantile colic, isolated failure to thrive, or chronic rhinitis and recurrent wheezing, are no longer considered to be in the spectrum of CMA.[10]

A broad classification for CMA necessitates following a truly large cohort to obtain meaningful data. Armed with the knowledge of the differing diagnostic criteria used in previous studies, we conducted a large-scale prospective study analyzing CMA that was exclusively IgE mediated. All newborns (13,234) born over a 2-year period in a single medical center were enrolled in the study. Our recruitment of greater than 98% of the cohort allowed for definitive answers regarding the incidence of IgE-CMA, the potential for cross-reactivity of IgE-CMA to soy allergy, and novel conclusions regarding risk factors for the development of IgE-CMA.

METHODS

Study population

The research protocol was approved by the Helsinki Review Board of the Assaf Harofeh Medical Center. All newborns (13,234) born from June 10, 2004, to June 30, 2006, at the Assaf-Harofeh Hospital (Zerifin, Israel) were enrolled. Contact details were verified after the routine anticipatory guidance session in which breast-feeding was encouraged but other alternative CMP-based feeding regimens were also discussed. The purpose of the project was explained, and the mothers were asked to fill out a questionnaire or, alternatively, to contact the allergy clinic immediately after any adverse reaction suspected to be related to the initiation of CMP-based feeding or, in

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Abbreviations used
CMA: Cow's milk allergy
CMP: Cow's milk protein
FPIRES: Food protein–induced enterocolitis syndrome
IgE-CMA: IgE-mediated cow's milk allergy
OFC: Oral food challenge
SPT: Skin prick test

the lack of any unusual event, 14 to 30 days after the initiation of CMP-based feeding. The mothers were supplied with a kit containing an explanatory letter about the project, a prestamped envelope, and a card with contact details. An explanatory letter about the project was distributed to all health care providers in the region.

If the parents did not contact the clinic by the age of 3 months, a telephone or mail contact was established, and the questionnaire was provided. The questionnaire requested demographic details; the length of exclusive breast-feeding, almost exclusive (including ingestion of water and juice) breast-feeding, and partial breast-feeding; the age of introduction of CMP-based formula on a regular basis (at least once daily); and whether any adverse responses to CMP were noted. If the infant was still breast-fed at the time of the contact, the mother was encouraged to continue breast-feeding, and contacts were maintained at 2-month intervals until the infant started to consume CMP. Any parent noting a possible adverse event related to CMP (n = 381) was interviewed by one of the investigators (N.R.), and their infants were invited for an examination. Fifty-two patients refused to have a full examination. These 52 had a second interview by another investigator (Y.K.) during which another attempt to recruit the infant for examination was done and a presumed diagnosis was made. Each final diagnosis was made independently by 2 investigators (Y.K. and A.C.). Cases of disagreement (2 cases) were resolved in a conjoint discussion. In the clinic, the patient was examined and an SPT and an open challenge[6] were offered, unless clinically contraindicated.

SPTs

SPTs were done to CMP, soy, a negative control, and histamine (1 mg/mL; ALK-Abelló, Port Washington, NY) by using the volar arm and reading the reaction after 20 minutes. A reaction of a 3-mm or larger wheal was considered positive.[11]

Challenge to cow's milk formula was carried out with Materna (Maabarot Products Ltd, Maabarot, Israel) infant formula by using increasing doses 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 infants were observed for 3 hours, and a subsequent contact was made 2 weeks later inquiring about their infants' status.

Statistical analysis

Statistical analyses were performed with SPSS software (version 16; SPSS, Inc, Chicago, Ill) and MATLAB (Mathworks, Inc, Natick, Mass). The risk factors that were extracted from the maternity files were entered into the hospital database, NAMER, an SAP-based system. The data were then transferred to Microsoft Access and Excel for analysis. Comparisons of risk factor between-group data for continuous variables were assessed with the use of a *t* test for independent variables or a Mann-Whitney *U* test, as appropriate (Table I). A χ^2 test was used to evaluate categorical variables. A stepwise logistic regression model was used to analyze all potential risk factors for IgE-CMA (Table II). The entry probability for stepwise analysis was 20%, and the removal probability for stepwise analysis was 25%. The *P* value of the Hosmer and Lemeshow test for goodness of fit was .52, supporting the goodness of fit of the model. To study the dependence of IgE-CMA risk on CMP exposure age, we classified the cohort into 4 groups according to their age at the first regular CMP exposure. The fraction of infants with IgE-CMA in the 4 groups was compared, and significance was assessed by using the Bonferroni-corrected Fisher exact test for 2 × 2 contingency tables. The relevant raw data of the cohort are available on request.

RESULTS

Study population

Recruitment into the study reached 98.4% (13,019) of our cohort (Fig 1). Initial contact was made by means of telephone interview in 12,473 (95.8%) infants and by means of questionnaire for the remaining 546 (4.2%) infants. The initial information regarding CMP-related adverse effects was obtained within 1 week of the event in most of the cases (58%) and in only 25% of cases in 30 days or longer. In 381 (2.9% of the sample) cases the parents either complained about adverse effects that they considered CMP related, or alternatively, these parents avoided CMP exposure despite having discontinued exclusive or almost exclusive breast-feeding. A causal relationship between the complaint and CMP was ruled out in 244 cases among these infants. In 71 (0.5%) cases, which will be described separately, a diagnosis of non–IgE-mediated adverse reaction to CMP was established (Fig 1). In this latter group 36 patients were given diagnoses of FPIES and 21 were given diagnoses of proctocolitis; 14 had other symptoms in which a causative relationship to CMP could not be excluded.

IgE-mediated CMA

Sixty-six infants (0.5% of those studied) were given diagnoses of IgE-CMA (Fig 1). Forty-eight (72.7%) patients fulfilled all criteria, including a suggestive history of an immediate response, a positive SPT response, and a positive challenge result to CMP. Seventeen patients did not perform an oral challenge. In 6 (9.1%) of these infants, an oral challenge was not offered because of life-threatening responses to CMP exposure. In 11 infants an oral challenge was not performed because of parental refusal. In a single case the diagnosis was made by a private allergist, and by the time the infant was available for examination at the age of 9 months, the challenge result was negative. The most common symptoms of IgE-CMA were cutaneous reactions (95.5%), including urticaria, angioedema, and pruritus, followed by gastrointestinal (54.6%) and respiratory (27.3%) symptoms (see Fig E1 in this article's Online Repository at www.jacionline.org).

The distribution of the age of onset of IgE-CMA in this cohort is presented in Fig 2. In 8 patients the onset of IgE-CMA was greater than 240 days. These 8 patients were classified as having secondary IgE-CMA. They were initially given diagnoses of FPIES because of the delayed clinical response of vomiting and lethargy, the lack of cutaneous symptoms, and a negative SPT response in all but one. However, on a subsequent examination at the age of 8 to 14 months, after a period of withdrawal of CMP, their SPT responses converted to positive, and in 7 of these cases, an immediate response of 10 minutes or less to small amounts of CMP was demonstrated. In a single case the IgE-type reaction appeared after 30 minutes. For these 8 patients, it is uncertain whether the age of onset is the age of the FPIES reaction or when they had an IgE-CMA reaction. We therefore excluded them from any analysis in which the age of onset or age of CMP introduction was involved, unless otherwise specified.

TABLE I. Characteristics and risk factors of infants with IgE-CMA and healthy infants

	Infants with IgE-CMA (n = 66)	Healthy infants (n = 12,638)	*P* value
Male sex	41/66 (62.1%)	6,409/12,638 (50.7%)	.064
Female sex	25/66 (37.9%)	6,229/12,638 (49.3)	
Gestational age (wk)	39.2 ± 1.7	39.15 ± 1.9	.909
Birth weight (kg)	3,255 ± 0.42	3,196 ± 0.55	.394
Maternal age (y)	29.58 ± 4.76	29.69 ± 5.23	.858
Type of delivery, PS	52/66 (78.8%)	10,696/12,638 (84.6%)	.189
Type of delivery, CS	14/66 (21.2%)	1,942/12,638 (15.4%)	
No. of siblings	2.26 ± 1.53	2.35 ± 1.53	.424
Dairy product consumption by mother	66/66 (100%)	12,531/12,638 (99.15%)	
Religion*: Jewish	63/66 (95.5%)	9,789/12,267 (78.9%)	.002
Religion: non-Jewish	3/66 (4.5%)	2,478/12,267 (20.2%)	
Age of CMP introduction (d)	116.12 ± 64.88 (for 58 patients) 110.09 ± 68.82 (for 66 patients†) 156.14 ± 133.02 (for 66 patients‡)	61.63 ± 92.45	<.001

For the age of CMP introduction, the 58 patients with primary IgE-CMA are first presented. Similar results were obtained when the 8 patients with secondary IgE-CMA were determined as being exposed to CMP on the day of the onset of FPIES *(†)* or the day of the diagnosis of IgE-CMA *(‡)*.
CS, Cesarean section; *PS*, Partus spontaneous.
*In Israel a person's religion is written down in the national identity card unless the citizen specifies "no religion." The non-Jewish population consists mostly of Arab-Muslim mothers (62.6%) and Arab-Christian mothers (5.5%), and for the rest, no religion was specified. Those for whom no data were recorded (n = 371) were excluded.

Excluding these patients, the mean age of onset of IgE-CMA was 3.9 ± 2.2 months.

The onset of symptoms started on the first day of consumption of CMP in 82.8% (48/58) of patients and within 7 days for the rest. The time from exposure to CMP to the presentation of a clinical response was measured during the challenge when feasible or obtained from the parents through history. It was less than 10 minutes in 55 (83%) infants, 10 to 20 minutes in 7 (11%) infants, and up to 30 minutes in 4 infants.

Risk factors for the development of IgE-CMA

Healthy infants from the cohort (n = 12,638) were compared with those given diagnoses of IgE-CMA (n = 66) to determine the risk factors leading to the development of IgE-CMA. All infants whose parents raised concern about adverse effects but were not proved to have IgE-CMA were excluded from this analysis (n = 315). Table I presents the risk factors that were extracted from the medical chart and from the primary questionnaire obtained from the parent during the first interview or the first visit. The age of CMP introduction was significantly different between the healthy infants and those with IgE-CMA ($P < .001$, Table I). A second statistically significant difference was noted between the Jewish and non-Jewish infants ($P < .002$, Table I). In a multivariate logistic regression analysis the odds ratio of having IgE-CMA among infants with exposure to CMP in the age range of 15 to 194 days was 19.3 (95% CI, 6.0-62.1) compared with that seen in infants with exposure to CMP before the age of 14 days (Table II). The odds ratio was similarly high when only infants for whom a diagnosis was established with an oral food challenge (OFC) were evaluated (13.13; $P < .001$). The odds ratio of sex was 1.80 (95% CI, 1.03-3.17).

We next analyzed the risk of IgE-CMA as a function of the age of regular exposure to CMP (Fig 3). We used the time the mother discontinued exclusive or almost exclusive breast-feeding and converted to CMP-containing formula alone or along with breast-feeding as the age of CMP introduction. One hundred four infants who were not exposed to CMP during the first year were not included. There are 3 well-defined periods. IgE-CMA risk was very low (0.05% [3/6502], group I) in infants introduced to CMP during the first 14 days, increased with CMP introduction age, peaked at ages 105 to 194 days (1.75% [28/1600], group III), and then decreased again (0.5%, group IV). The role of other confounders, such as social class, pets, smoking habits, and atopic background, as risk factors was not studied in the whole cohort. However, in a subanalysis these confounders were not found to be significantly different between the control and IgE-CMA groups. Specifically, parents of the infants with IgE-CMA were not more atopic, whether evaluated based on self-reporting or objectively based on SPT positivity to common allergens. Furthermore, in only 4 of the 66 IgE-CMA cases did parents mention family atopy as a reason for breast-feeding, and this was not significantly different from a randomly chosen control group from the cohort (data not shown).

Breast-feeding and exposure to CMP

In Table III the feeding patterns of Jewish and Muslim mothers during the first week of life is depicted. There were clear attitudinal differences between them toward exclusive or almost exclusive breast-feeding. Although Arab-Muslim mothers breast-feed in more than 80% of cases, only 28.3% exclusively breast-fed. In contrast, Jewish mothers exclusively or almost exclusively breast-fed 57.5% of the time. These differences result in a higher exposure to CMP during the first week of life in the offspring of Arab-Muslim mothers compared with Jewish mothers (71.7% vs 42.5%; $P < .001$, Fisher exact test), even though Arab-Muslim offspring were more likely to be breast-fed compared with Jewish infants (80.6% vs 75.0%, $P < .001$). Strikingly, only a single newborn of 1,806 born to an Arab-Muslim mother had IgE-CMA, whereas 55 of 10,135 infants born to Jewish mothers had IgE-CMA ($P < .001$, Fisher exact test). These data indicate that breast-feeding by itself was not a risk factor but rather that exposure to CMP is protective.

Cosensitization and allergy to soy among patients with IgE-CMA

None of the 66 patients with IgE-CMA had a positive SPT response to soy. Fifty-nine (89%) patients were on a soy diet on

TABLE II. Stepwise multivariate logistic regression analysis of risk factors for IgE-CMA

	OR	95% CI	*P* value
Sex (male)	1.806	1.027-3.175	.0406
No. of siblings	0.855	0.671-1.091	.208
Jewish	2.55	0.789-8.244	.118
Late exposure (15-194 d vs ≤14 d)	19.30	6.00-62.09	.000

Late exposure was defined as age greater 14 days. Other definitions of late exposure revealed similar results. For example, when the definition of late exposure was 30 days, the odds ratio for late exposure was 12.2 (95% CI, 5.2-28.6). The odds ratio remains increased (13.13, $P < .001$), even when the 11 patients who did not perform an oral challenge are excluded.
OR, Odds ratio.

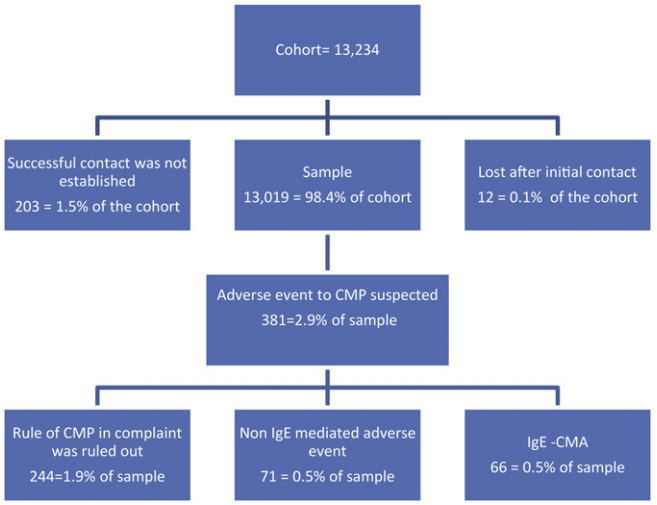

FIG 1. Cohort description. All 381 parents of infants in whom an adverse reaction to CMP was suspected were interviewed by one of the investigators (N.R.), and their infants were invited for an examination. Additional contacts were made as appropriate in these patients, and at the final contact at the ages of 3 to 5 years, 21 infants were lost to follow-up.

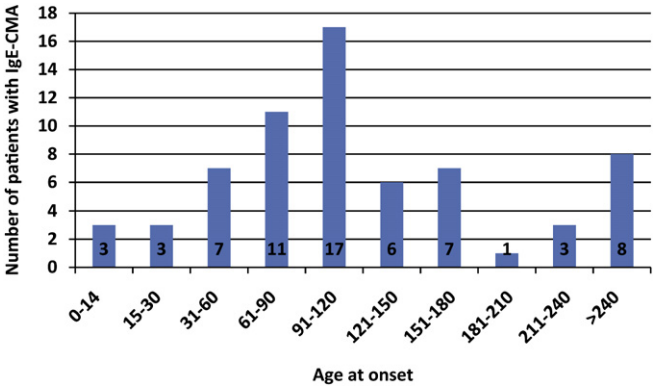

FIG 2. Number of patients with IgE-CMA according to their age of onset (in days). The 8 patients with onset of IgE-CMA at an age of 240 days or greater were initially given diagnoses of FPIES.

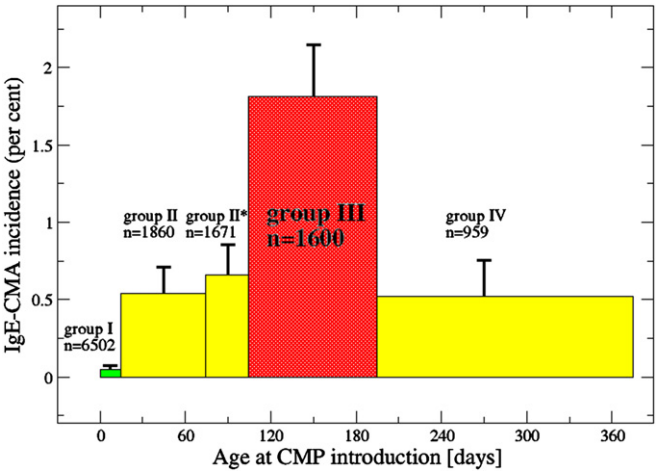

FIG 3. IgE-CMA occurrence as a function of the age of CMP introduction. The different groups are defined as follows: group I (*green*), age of CMP exposure of 0 to 14 days; group II (II+II*) (*yellow*), age of CMP exposure of 15 to 104 days; group III (*red*), age of CMP exposure of 105 to 194 days; and group IV (*yellow*), age of CMP exposure of 195 to 374 days. For statistical analysis, the second and third bins were combined into one group (group II, group II*). The *error bar* represents the statistical error caused by the finite group size (1 SD). A fraction of infants with IgE-CMA are significantly ($P < .001$) different for all pairwise comparisons among the 4 groups, except for group II versus group IV.

the first examination for a period ranging from 16 to 120 days, 6 were fed with extensively hydrolyzed milk (Nutramigen; Mead Johnson, Glenview, Ill), and 1 consumed an amino acid–based formula (Neocate; SHS, Liverpool, United Kingdom). After evaluation, 5 added soy to the diet, and only 1 with a negative challenge result to soy continued to consume Nutramigen because of parental preference. In the 1 patient who consumed Neocate, the diagnosis of IgE-CMA was made by a private allergist, and at the time of evaluation, the challenge result to CMP was negative. None of the infants had soy allergy during their soy diets. Thus none in this cohort had a protein allergy to soy, but it could not be excluded in that last case.

DISCUSSION

This article presents a large, prospective noninterventional study in which several fundamental questions regarding milk allergy were evaluated. To minimize bias, we aimed to reach the highest possible percentage of the target population. We therefore used the least invasive methods for diagnosis, including SPT, rather than measuring specific IgE cow's milk antibodies, and a less demanding open OFC rather than a double-blind placebo-controlled challenge. Importantly, the SPT is considered a reliable and sensitive method in this age group,[10] as is an open OFC.[6] Furthermore, our end point to rule out IgE-CMA was regular consumption of CMP, and therefore not even a single case of clinically relevant milk allergy was missed. In a previous study designed to examine milk allergy in a similar patient population, only 41% of the target population was recruited.[12] Our recruitment of 98.4% of the cohort allowed for definitive answers regarding the prevalence of IgE-CMA, the potential for cross-reactivity of IgE-CMA to soy allergy, and novel conclusions regarding risk factors for IgE-CMA.

The cumulative incidence of IgE-CMA was 0.5%, a percentage that includes a small fraction of patients with FPIES who later converted to IgE-CMA, as previously noted,[13] and 11 patients who did not have an OFC. The incidence rate we observed is similar to that in an independent cross-sectional study of 9,070

TABLE III. Feeding pattern during the first week

	No.	Exclusively or almost exclusively breast-fed (%)	Partial breast-feeding (%)	No breast-feeding (%)	Total (%) breast-fed	Total (%) CMP fed
Whole population	13,019	6,920 (53.2)	2,925 (22.5)	3,174 (24.4)	9,845 (75.6)	6,099 (46.8)
Jewish	10,135	5,826 (57.5)	1,772 (17.5)	2,537 (25)	7,598 (75)	4,303 (42.5)
Muslim	1,806	511 (28.3)	944 (52.3)	351 (19.4)	1,455 (80.6)	1,295 (71.7)
Other*	1,078	583 (54.1)	209 (19.4)	286 (26.5)	792 (73.5)	495 (45.9)

*Christian, atheists, and not known.

infants, in Israel in which the prevalence of IgE-CMA was estimated to be between 0.3% to 0.4%,[14] but is significantly lower than the most widely cited figure of 1.5% for IgE-CMA,[3] which is based on observations in other countries. We doubt this low prevalence reflects genetic or geographic variation because other prospective population-based studies from Spain[15] and Norway[16] found a similar cumulative incidence of IgE-CMA. The most obvious explanation for the difference is that other studies included patients who have had milk-related adverse events[5] that would not fulfill the criteria for the diagnosis of IgE-CMA, as defined in this study. For example, in our study 95% of the patients with IgE-CMA had immediate cutaneous symptoms, as previously described.[17-19] In many other studies,[12,20] however, only a fraction of the patients had immediate cutaneous symptoms, such as urticaria or angioedema, and thus only a subset truly had IgE-CMA.

The second major finding from this study relates to the question of cross-reactivity of patients with IgE-CMA to soy. In contrast to the recent position statement of the American Academy of Pediatrics,[21] in which soy milk was not recommended for patients with IgE-CMA because of a 10% to 14% reported incidence of cross-reactivity to soy, none of our patients with IgE-CMA had soy allergy. The American Academy of Pediatrics statement was mainly based on 2 prospective randomized trials by Zeiger et al[22] and Klemola et al.[23] In the first study[22] there were 13 children with soy allergy, 12 of whom were recruited from a single center, a multiple-food allergy clinic, whereas the last one had eosinophilic esophagitis, another condition in which multiple food allergies is likely. In the second study[23] only a single patient had documented IgE antibodies directed against soy protein. It seems reasonable to conclude that soy allergy is uncommon in patients with IgE-CMA unless the patient has multiple food allergies.

The third and perhaps most important finding is the fact that development of IgE-CMA is influenced by the timing of exposure to CMP. Infants whose regular exposure to CMP was withheld until the age of 4 to 6 months were at the highest risk for IgE-CMA. Although the parents did not keep a daily record of feeding, close telephone contact was maintained with the parents, and all parents were interviewed in detail on the visit, allowing for an accurate reported onset of the disease. The average age of onset of IgE-CMA in this cohort (3.9 months) is in the range of numerous other reports.[12,18,19,24] Finally, in the vast majority of patients of our cohort, the symptoms started on either the first day of exposure to CMP or during the first 3 days of repeated exposure. Similar patterns were noted by other investigators.[15,17-19] In our study almost half of the newborns were exposed to CMP in the first 2 weeks. The incidence of IgE-CMA among these infants was extremely low. Thus it is likely that infants exposed regularly to CMP starting from the neonatal period rarely have IgE-CMA. We do not have data to substantiate an explanation as to why the risk for IgE-CMA decreased for those exposed in the oldest age group (group IV) compared with the prior period (group III).

Three lines of evidence argue against the role of atopy as a risk factor in our cohort, influencing the choice of feeding, or both. First, whether evaluated based on self-reporting or objectively based on SPT response positivity to common allergens, parents of infants with IgE-CMA were not more atopic. Second, parents of infants with IgE-CMA did not mention atopy as a reason for breast-feeding with any significant difference from a randomly chosen control group from the cohort. Finally, parental atopy was never shown based on objective criteria to be a significant risk factor for IgE-CMA. Thus although we cannot completely exclude reverse causality as an explanation for our findings, we have no evidence that atopy predisposition in parents or infants influenced parental feeding decisions.

Our data are likely to be supported by an analysis of the feeding regimens that are actually practiced globally. The rate of compliance with prolonged and exclusive breast-feeding is low, even in high-risk infants.[25] In the Netherlands, for example, only 63% of mothers expressed intention to breast-feed.[26] Because an allergic reaction to CMP develops within days[15,17-19] yet few infants have IgE-CMA in the first 2 weeks of life,[2] one must conclude that there is a protective role for early CMP exposure.

Regular early exposure to CMP might also explain the interesting finding that the risk of IgE-CMA among infants born to Muslim-Arab women was much lower when compared with the risk of those born to Jewish women. Despite a higher rate of intention to breast-feed among Arab women compared with Jewish women,[27] the rate of exclusive or almost exclusive breast-feeding is lower,[28] resulting in a much earlier exposure to CMP in Arab versus Jewish infants. Because of the way our data were collected, we cannot exclude neonatal exposure to small quantities of CMP formula in the newborn nursery either forgotten by the mother or done without her knowledge. However, the role of a brief intermittent early exposure to milk in the neonatal unit is controversial[12,29] and might have a low effect, if any, on the development of atopy. Accordingly, we found it appropriate not to consider such intermittent exposures to CMP in this study.

The role of early oral exposure to dietary proteins in rendering tolerance is gaining recognition.[30] The exact timing and mechanism by which this tolerance occurs is still poorly understood.[31,32] It is possible that different proteins have varying patterns of tolerance versus sensitization and allergenic timing.[33] Introduction of peanuts at the age of 6 to 8 months, for example, appears to induce tolerance,[34] whereas in our study milk tolerance appears to be induced by its introduction at an earlier age. A similar idea was reported previously,[35] but those findings were not integrated into common practice. The idea of the protective effect of early oral introduction of protein was suggested more than 25 years ago by Jarret.[36] Our study provides large-scale, prospective clinical evidence to support this hypothesis. Therefore we cannot rule

out that some infants with very mild clinical reactions were continued to be fed CMP and developed tolerance who otherwise would have eventually had clinically significant IgE-CMA. Finally, a limitation of this study is the lack of information on the amount of CMP that has to be introduced to prevent IgE-CMA.

The data should not be interpreted as discouraging breast-feeding. The great advantages of breast-feeding in providing essential nutrients and immunomodulatory effects are well appreciated. Therefore it seems reasonable to consider early complementary feeding of CMP along with breast-feeding to promote oral tolerance, especially in high-risk infants.

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Clinical implications: Supplementation at birth with CMP should be recommended to promote its tolerance. For those patients with IgE-mediated CMP allergy, soy is a reasonable feeding alternative.

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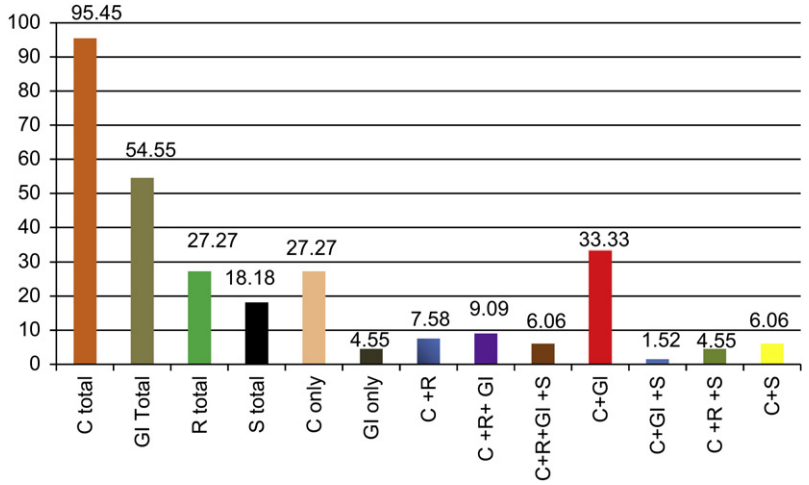

FIG E1. Systems affected in patients during IgE-mediated reactions. *C*, Cutaneous reaction (urticaria, angioedema, and pruritus); *GI*, gastrointestinal reactions (vomiting and diarrhea); *R*, respiratory system (sneezing, shortness of breath, coughing, and choking); *S*, systemic reaction (shock, crying, fainting, and restlessness). Although we rated pruritis, crying, restlessness, and choking, more objective findings, such as urticaria, vomiting, shortness of breath, and anaphylaxis, were used to establish the diagnosis.