Primary Prevention of Cow's Milk Sensitization and Food Allergy by Avoiding Supplementation With Cow's Milk Formula at Birth

A Randomized Clinical Trial

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Disclosures

- I have no financial disclosures

Introduction

- Prevalence and severity of food allergy is increasing
- To overcome this, exclusive breastfeeding (BF) with or without supplementation with hypoallergenic formulas for infants at risk of atopic disease has been recommended
  - Controversial supporting evidence
  - Breastfeeding previously supplemented with sugar water
- **Hypothesis**: Early exposure to cow's milk formula (CMF) at birth is, at least in part, associated with the recent increase in children with food allergy
- **Study purpose**: Investigate whether the risk of cow's milk sensitization and food allergy is decreased by avoiding supplementation with CMF at birth

Methods

- Single center RCT in Tokyo, Japan
- Newborn Randomization
  - Breastfeeding (BF) / Amino-acid based elemental formula (EF)
  - Breastfeeding (BF) plus cow's milk formula (CMF)
- Inclusion Criteria
  - ≥1 father, mother, or sibling with atopic disease
- Exclusion Criteria
  - Parents intended exclusive BF or CMF
  - Infants born at <36 weeks
  - Birth weight < 2000g
  - Serious congenital anomalies

Methods

Intervention

- BF/EF
  - Exclusive BF for 5 months
  - Supplement with EF prn
  - Switch to CMF if
    - >150mL/day of EF for 3 days
    - Or maternal preference after day 3
- BF plus CMF
  - CMF ≥5mL/d within the first 24hrs of birth until 1 month
  - CMF ≥40mL/d from 1 month until 5 months

Outcomes

- Primary
  - Cow's milk sensitization (CM-IgE ≥ 35 U_A)
- Secondary
  - Clinical food allergies
  - Other atopic diseases
- Safety
  - Any admission or ED visit
  - Growth retardation

Follow-up

- Regular examinations
- Antigen specific IgE to cow's milk and other foods at 5 and 24 months
- OFC ~1 year of age
  - Performed by blinded physicians

Participant Characteristics

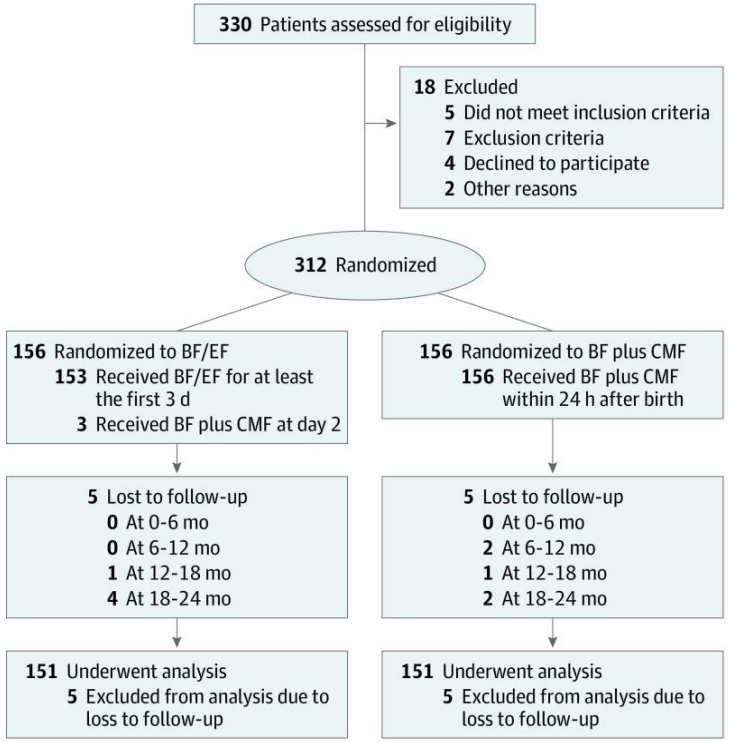


Figure 1. Patient Flow Through the Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC) Trial. BF indicates breastfeeding; CMF, cow's milk formula; and EF, elemental formula.

Characteristic	Study Group	
	BF/EF (n = 156)	BF Plus CMF (n = 156)
Gestational age, median (IQR), wk	39 (38-39)	39 (38-39)
Nonvaginal delivery, No. (%)		
Planned cesarean delivery	16 (10.3)	17 (10.9)
Emergency cesarean delivery	21 (13.5)	20 (12.8)
Female, No. (%)	82 (52.6)	78 (50.0)
Apgar score at 5 min, No. (%)[a]		
8 points	4 (2.7)	10 (6.5)
9 points	131 (84.0)	128 (83.7)
10 points	15 (9.6)	15 (9.8)
Placental weight, mean (SD), g	585 (103)	563 (97)
pH of cord blood, mean (SD)	7.28 (0.06)	7.29 (0.08)
Anthropometry at birth, mean (SD)		
Body weight, g	2994 (313)	2994 (314)
Body height, cm	48.7 (1.7)	48.8 (1.8)
Chest circumference, cm	31.5(1.3)	31.6 (1.4)
Head circumference, cm	34.0 (1.3)	34.1 (1.2)

Characteristic	Study Group	
	BF/EF (n = 156)	BF Plus CMF (n = 156)
Familial Background		
Age, mean (SD), y		
Paternal	37.0 (6.1)	37.7 (6.8)
Maternal	35.0 (4.5)	35.3 (4.3)
Current/previous atopic disease of mother, No. (%)		
Bronchial asthma	9 (5.8)/24 (15.4)	6 (3.8)/20 (12.8)
Atopic dermatitis	18 (11.5)/32 (20.5)	13 (8.3)/32 (20.5)
Food allergy	28 (17.9)/18 (11.5)	15 (9.6)/15 (9.6)
Allergic rhinitis	36 (23.1)/17 (10.9)	40 (25.6)/13 (8.3)
Pollen allergy	85 (54.5)/12 (7.7)	89 (57.1)/11 (7.1)
Current/previous atopic disease of father, No. (%)		
Bronchial asthma	4 (2.6)/22 (14.1)	11 (7.1)/24 (15.4)
Atopic dermatitis	7 (4.5)/14 (9.0)	13 (8.3)/25 (16.0)
Food allergy	20 (12.8)/4 (2.6)	17 (10.9)/9 (5.8)
Allergic rhinitis	37 (23.7)/11 (7.1)	41 (26.3)/17 (10.9)
Pollen allergy	80 (51.3)/11 (7.1)	79 (50.6)/3 (1.9)
Current/previous atopic disease of siblings, No. (%)[a]		
Bronchial asthma	2 (66.7)/1 (33.6)	2 (22.2)/1 (11.1)
Atopic dermatitis	0/0	3 (33.3)/0
Food allergy	1 (33.3)/2 (66.7)	5 (55.6)/1 (11.1)
Allergic rhinitis	2 (66.7)/0	3 (33.3)/0
Pollen allergy	1 (33.3)/0	1 (11.1)/0

Table 1. Participant characteristics. Original table divided to fit the screen

Results

- Significantly fewer infants had cow's milk sensitization in the BF/EF group than the BF plus CMF group
- No difference in sensitization to egg white or other food antigens
- When stratified by Vitamin D level, only middle tertile was significantly different

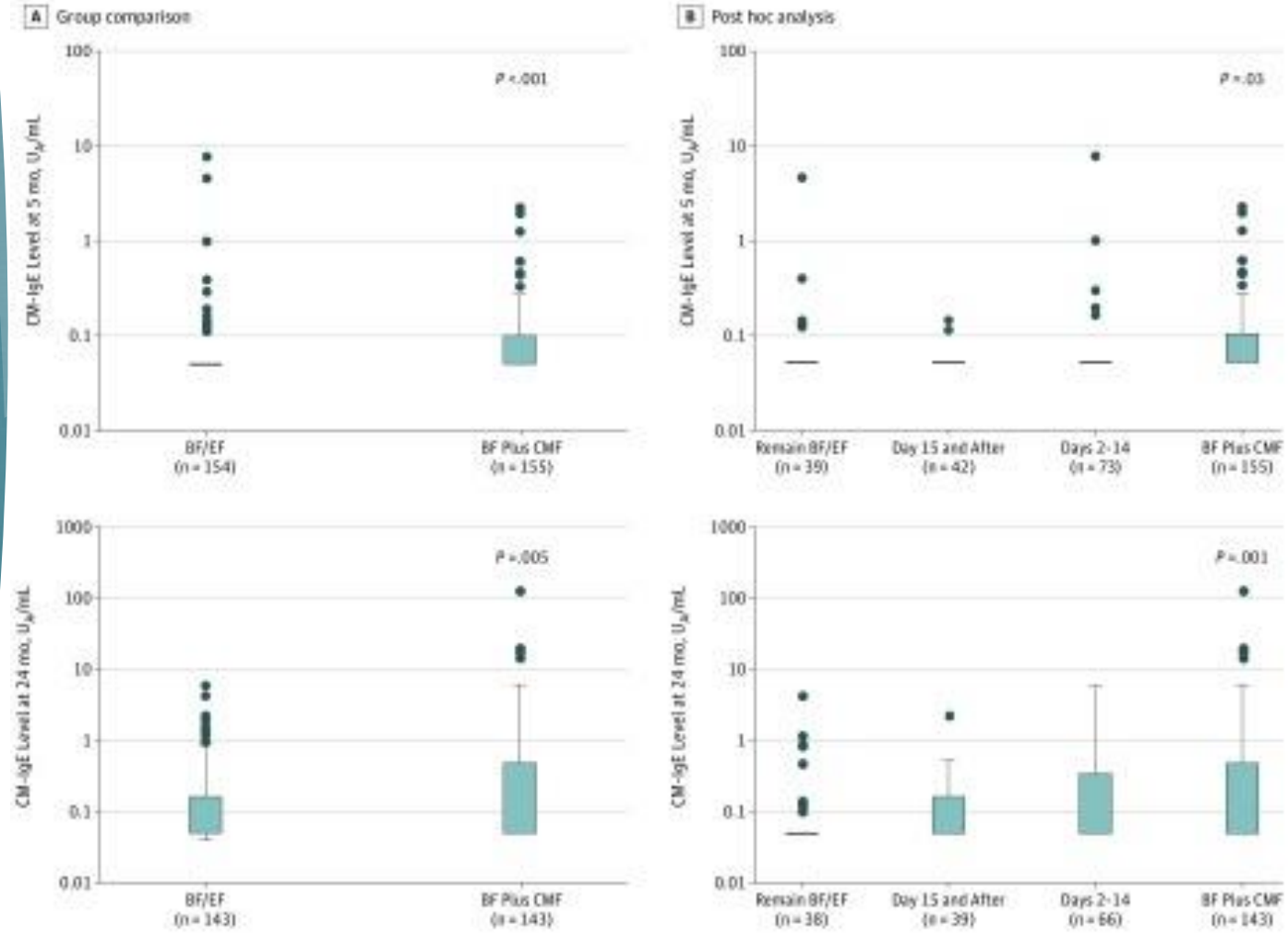
Table 2. Effects of Avoiding CMF at Birth on Antigen-Specific IgE Levels

Subgroups	Study Group, No. (%) of Infants			RR (95% CI)[b]	P Value for Interaction
	Total	BF/EF	BF Plus CMF		
Cow's Milk–Specific IgE Level ≥0.35 UA/mL					
Overall (n = 286)[d]	70 (24.5)	24 (16.8)	46 (32.2)	0.52 (0.34-0.81)	NA
Subgroups stratified by 25(OH)D levels[e]					
Lower tertile (n = 94)	17 (18.1)	8 (17.0)	9 (19.1)	0.89 (0.38-2.11)	
Middle tertile (n = 89)	26 (29.2)	4 (9.1)	22 (49.0)	0.19 (0.07-0.50)	.02
Higher tertile (n = 96)	26 (27.1)	12 (25.0)	14 (29.2)	0.86 (0.44-1.66)	
Egg White–Specific IgE ≥0.35 UA/mL					
Overall (n = 286)[d]	107 (37.4)	53 (37.1)	54 (37.8)	0.98 (0.73-1.32)	NA
Subgroups stratified by 25(OH)D levels[e]					
Lower tertile (n = 94)	32 (34.0)	16 (34.0)	16 (34.0)	1.00 (0.57-1.78)	
Middle tertile (n = 89)	33 (37.1)	11 (25.0)	22 (49.0)	0.51 (0.28-0.92)	.02
Higher tertile (n = 96)	38 (39.6)	23 (47.9)	15 (31.3)	1.53 (0.92-2.56)	

Results

- A: Group Comparison
  - CMF supplementation associated with greater CMF-IgE levels
- B: Post Hoc Analysis
  - 115 infants switched from EF to CMF supplementation during the study
    - 73 within 14 days, 42 after 14 days, 39 remained BF/EF
  - Earlier CMF associated with increased CMF-IgE at 24 months
  - No difference in clinical food allergy

Figure 2. Cow's Milk Specific IgE (CM-IgE) Levels Among Study Groups



Results

- The immediate type of food allergy, anaphylaxis, cow's milk allergy, and egg allergy occurred less in the BF/EF group compared to the BF plus CMF group
- More infants in the BF/EF group outgrew the food allergy by age 2 compared to the BF plus CMF group
- No differences in safety outcomes

Table 3. Effects of Avoiding CMF at Birth on Immediate and Anaphylactic Types of Food Allergy

Effects	Study Group, No. (%) of Infants			RR (95% CI)[b]	P Value for Interaction[c]
	Total (n = 302)	BF/EF (n = 151)	BF Plus CMF (n = 151)		
Immediate Type of Food Allergy					
Cumulative incidence by the second birthday	67 (22.2)	22 (14.6)	45 (29.8)	0.49 (0.31-0.77)	NA
Prevalence at the second birthday	24 (7.9)	4 (2.6)	20 (13.2)	0.20 (0.07-0.57)	NA
Anaphylactic Type of Food Allergy					
Cumulative incidence by second birthday	14 (4.6)	1 (0.7)	13 (8.6)	0.08 (0.01-0.58)	NA
Prevalence at second birthday	14 (4.6)	1 (0.7)	13 (8.6)	0.08 (0.01-0.58)	NA
OFC-Positive Immediate Type of Food Allergy					
Cumulative incidence by second birthday	12 (4.0)	1 (0.7)	11 (7.3)	0.09 (0.01-0.70)	NA
Prevalence at second birthday	9 (3.0)	0	9 (6.0)	0 (NA)	NA
Cow's Milk Allergy					
Cumulative incidence by second birthday	11 (3.6)	1 (0.7)	10 (6.6)	0.10 (0.01-0.77)	NA
Prevalence at second birthday	4 (1.3)	0	4 (2.6)	0 (NA)	NA
Egg Allergy					
Cumulative incidence by second birthday	47 (15.6)	17 (11.3)	30 (19.9)	0.57 (0.33-0.98)	NA
Prevalence at second birthday	9 (3.0)	1 (0.7)	8 (5.3)	0.13 (0.02-0.99)	NA
Wheat Allergy					
Cumulative incidence by second birthday	8 (2.6)	1 (0.7)	7 (4.6)	0.14 (0.02-1.15)	NA
Prevalence at second birthday	5 (1.7)	0	5 (3.3)	0 (NA)	NA

Discussion

- How does this compare with other studies?
- Why did CMF affect prevalence of other food allergies?
  - Early CMF exposure with scarce growth of gut microbiome → enterocolitis → increased gut permeability → increased absorption of food allergens → food allergy
- Role of Vitamin D in food allergy?
  - Still unclear, possible bimodal function
- Limitations
  - Not double-blinded, OFC test not universal, short follow-up, different prevalence of food allergies by country, variable amounts of CMF or EF used, differential misclassification, cows milk sensitization as primary outcome
- Conclusion
  - Authors: sensitization of cow's milk and clinical food allergies may be preventable by avoiding supplementation of cow's milk formula at birth
  - Professional Organizations: inconsistent evidence for a protective benefit of hypoallergenic formulas