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Cow's Milk Allergy Prevention

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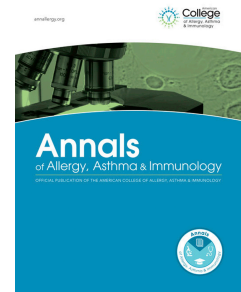
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Title Page

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Abbreviations: Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC); Breastfeeding (BF); Cow's Milk Formula (CMF); Enquiring About Tolerance (EAT); Immunoglobulin-E (IgE); Odds Ratio (OR); Oral food challenge (OFC); Randomized controlled trial (RCT); Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE)

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Objective: Scoping review on IgE-mediated cow's milk allergy prevention

Data Sources: Literature search of PubMed, and gray literature

Study Selections: Peer-reviewed relevant observational and randomized controlled studies in the pediatric population in English language were selected and reviewed. Results: There is increasing literature supporting the role of early, and ongoing cow's milk ingestion in the prevention of cow's milk allergy. The studies supporting a preventative role with early cow's milk ingestion have had a very early age of cow's milk introduction (the majority within the first month of life), suggesting the possibility of a different mechanism of sensitization than other common allergens. It is possible that gut colonization and the diversity and intensity of microbial exposure may play a role in inducing cow's milk tolerance. It is also possible that vitamin D may have a role in modulating those immune functions.

Conclusion: Further research regarding the role early cow's milk ingestion plays in the prevention of cow's milk allergy is required, and questions remain. The absolute amount required for tolerance is unclear. Studies in higher risk populations are required. However, there is an intriguing and increasingly more pervasive association between early ongoing cow's milk ingestion and cow's milk allergy prevention.

Cow's Milk Allergy Prevention

Introduction

Food allergy is one of the most common chronic diseases of childhood, with an increasing prevalence noted over the past few decades.¹⁻³ Cow's milk allergy is one of the most common types of food allergy in North America, affecting approximately 2.6% of young children.⁴ While some studies suggest high rates of resolution of cow's milk allergy, more recent literature suggests a more cautious prognosis and heterogeneity in resolution rates, with a 42-57% rate of resolution by school age.⁵⁻⁸ In a recent US cross-sectional survey, 1.9% of adults reported cow's milk allergy, of which 77.3% noted persistence of this allergy from childhood.⁹ Cow's milk allergy, especially if persistent, has impacts on childhood growth and nutrition and is the most common cause of food-induced anaphylaxis.⁸ As there are little to date to modify the natural course of cow's milk allergy, a focus has shifted from management and treatment to prevention. While there is extensive literature on the prevention of other common food allergies of childhood, such as peanut and egg, less is known about cow's milk allergy prevention. The goal of this Review is to discuss what is known, and what is controversial, regarding cow's milk allergy prevention.

The role of early cow's milk ingestion in cow's milk allergy prevention

There have been three observational studies that document an association between early cow's milk ingestion and a lower incidence of cow's milk allergy among general population infants (Table 1). A prospective feeding study by Katz et al in 2010 of 13,019 newborn infants in Israel found a significant difference between age of cow's

milk protein introduction between infants with Immunoglobulin (Ig)-E mediated cow's milk allergy (116.1 $\pm$ 64.9 days) and those without cow's milk allergy (61.6 $\pm$ 92.5 days; $P < .001$).¹⁰ The odds ratio (OR) was 19.3 (95%CI: 6.0, 62.1) for development of cow's milk allergy among infants first ingesting cow's milk formula on, or after, 15 days of life compared with before ($P < .001$). Only 0.05% of infants started on regular cow's milk protein in the first 14 days of life (versus 1.75% who were started between 105-194 days of life) had cow's milk allergy. A retrospective case-control study by Onizawa et al of 51 children with IgE-mediated cow's milk allergy compared to 102 age-matched controls and 32 unmatched children with IgE-mediated egg allergy (to minimize the effect of confounders) found an association between delayed cow's milk protein introduction (more than one month after birth) and higher prevalence of cow's milk allergy ($P < .001$).¹¹ A retrospective population-based cross-sectional study out of Australia by Peters et al of 5,276 infants noted that early exposure to cow's milk protein in the first three months of life was associated with a reduced risk of cow's milk sensitization (aOR [adjusted odds ratio] 0.44; 95%CI: 0.23-0.83), parent-reported cow's milk reactions (aOR 0.44, 95%CI: .029-0.67) and cow's milk allergy (aOR 0.31, 95%CI: 0.10-0.91) at a year of age.¹² Limitations of these studies include variable definitions of cow's milk allergy (only Katz et al required an oral food challenge [OFC] for diagnosis), predominantly retrospective study designs (increasing the possibility of recall bias), and the inherent limitation of all observational data, which can show an association but not document causation.

The observational literature is now further supported by a recent randomized controlled trial (RCT) examining the benefit of early cow's milk ingestion on the

prevention of cow's milk allergy. The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study randomized 504 general population infants in Japan to daily cow's milk formula supplementation with ongoing breastfeeding between one and two months of age, or cow's milk formula avoidance (supplementation with soy formula if required).¹³ This study involved two OFCs – one at 3 months and one at 6 months of age, with the primary outcome the proportion of infants with confirmed cow's milk allergy based on the 6 month OFC. There was a significant reduction in cow's milk allergy (diagnosed by OFC) in the cow's milk ingestion group compared with the cow's milk avoidance group (0.8% vs 6.8%; risk difference 6.0%; 95% CI: 2.7,9.3). A dose-response relationship was observed, with none of the infants who consumed at least 70 mL of cow's milk formula per week between one and two months of age developing cow's milk allergy. The study authors comment on the high incidence of cow's milk allergy detected in the study, hypothesizing it is related to restricted ongoing cow's milk formula avoidance. It is also interesting in this study that there was a more than doubling of reaction rates between the 3 month and 6-month OFC. The reasons for this are unclear but it is possible that either the window of sensitization remains open between 3-6 months of age, or conversely that the 3-month OFC was sensitizing.

Although literature is mounting about the role of early cow's milk ingestion in cow's milk allergy prevention, a 2016 meta-analysis of two RCTs did not find any significant preventative effect (RR 0.76; 95%CI: 0.32,1.78).¹⁴ This was prior to the SPADE study, and both RCTs included had low adherence rates (63% and 42.8%).^{15,16} One of the two RCTs included in this meta-analysis, the Enquiring About Tolerance

(EAT) study, defined cow's milk avoidance as ingestion of less than 300 mL per day, raising the possibility that the avoidance group had sufficient ongoing exposure.^{13,16} In addition, in the EAT study cow's milk ingestion did not begin until 3 months of age, and it is possible that the preventative interval was already missed by that time. The other RCT, by Lowe et al, randomized 620 infants with a family history of allergic disease to receive either cow's milk formula, partially hydrolyzed formula or soy formula on cessation of exclusive breastfeeding.¹⁵ However, only approximately 50% were transitioned to formula by 4 months of age, once again raising the possibility that the preventative interval was missed.

Further research regarding the role early cow's milk ingestion plays in the prevention of cow's milk allergy is required, and questions remain. The absolute amount required for tolerance is unclear, although SPADE suggests at least 10 mL per day is required. There is variability in the definition of early ingestion including first 14 days of life,¹⁰ first month of life,¹¹ first three months of life,¹² and the interval between one and two months of life.¹³ All the studies are of general population infants, and thus it is unclear whether this strategy has an incremental benefit in those infants at higher risk.

The role of consistent cow's milk ingestion in the prevention of cow's milk allergy

There have been two prospective observational studies and one RCT that support a protective role of ongoing cow's milk ingestion in the prevention of cow's milk allergy. A prospective study of 6209 infants documented a significant association between OFC-proven cow's milk allergy and exposure to cow's milk formula at the hospital ($P < .001$), as well as infrequent exposure to small amounts of cow's milk once

home ($P < .001$).¹⁷ A prospective cohort of 114 infants with atopic dermatitis, belonging to the same cohort as the Prevention of Egg allergy with Tiny amount InTake (PETIT) study, found a borderline lower prevalence of cow's milk allergy (based on questionnaire) among infants with continuous cow's milk ingestion (from birth to 18 months of age) compared to infants with discontinuous ingestion (no longer than one month from birth until 18 months; $P = .069$).¹⁸

The Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC) study randomized 330 newborns at risk of atopy (due to a first degree relative with atopic disease) to breastfeeding with or without amino acid-based elemental formula (BF/EF) for at least the first three days of life or breastfeeding supplemented with cow's milk formula (BF/CMF) from the first day of life to five months of age.¹⁹ Results revealed neonates receiving breastmilk and elemental formula had significantly lower cow's milk sensitization (relative risk [RR] 0.52, 95%CI, 0.34-0.81), and had a significantly lower risk of immediate (RR 0.20, 95%CI, 0.07-0.57) and anaphylactic (RR 0.08, 95%CI, 0.01-0.58) cow's milk allergy at 2 years of age.¹⁹ This study suggests that infants who are fed cow's milk formula for a very brief, and not ongoing, period of time after birth may have an increased risk of cow's milk allergy compared to use of elemental formula. Subgroup analysis with prespecified serum 25 (OH)D (25-hydroxyvitamin D) levels was performed, noting a significant interaction with the intervention for the middle tertile of the 25 (OH)D subgroup, with cow's milk formula avoidance only effective in this subgroup. The study authors conclude this suggests a bimodal function of vitamin D on immune function, though noting "vitamin D hypotheses in food allergy are still far from conclusions."

Studies have also shown that elimination of cow's milk for a period of time from the diet increases the risk of cow's milk allergy, suggesting that ongoing ingestion of cow's milk, once introduced, may play a role in cow's milk allergy prevention.^{20,21} In a recent prospective observational study of infants with food protein-induced allergic proctocolitis (FPIAP), there was a significant association between FPIAP and development of IgE-mediated cow's milk allergy (OR 5.4; 95%CI: 1.4-20.8) further supporting ongoing ingestion as a means of cow's milk allergy prevention.²²

It is important to note that several of the studies supporting a role of early cow's milk ingestion in the prevention of cow's milk allergy have also included, as part of the study design, ongoing regular cow's milk ingestion, raising the possibility that it is the *consistent ingestion* in these studies, *instead of early exposure*, that may be protective. Katz et al defined age of introduction of cow's milk based on regularity of exposure (at least once a day).¹⁰ The role of regularity of ingestion as a preventative mechanism was also supported in the Katz study by the finding that cow's milk allergy was much lower among Muslim-Arab women than Jewish women. The key difference among these populations was that Jewish women were more likely to exclusively or almost exclusively breastfeed, resulting in more ongoing cow's milk exposure in the Muslim-Arab infants. Onizawa et al also noted irregularity of ingestion (less than once daily) to be associated with cow's milk allergy ($P < .001$).¹¹ In fact, the percentage of infants who started cow's milk in the first month of life was not significantly different between the cow's milk allergy and egg allergy subgroups, whereas the number of infants with regular ingestion of cow's milk formula was significantly less in the cow's milk allergy group, "suggest[ing] that sufficient amounts and the continuous intake of cow's milk are

important for the prevention of cow's milk allergy."¹¹ The SPADE study also had ongoing ingestion (at least 10 mL every day) as part of inclusion criteria in the early ingestion group.¹³

There are gaps in the literature to date, and certainly more research is required. However, an increasing body of evidence raises the possibility that it is ongoing ingestion, instead of or in addition to early cow's milk ingestion, that may play a role in cow's milk allergy prevention.

Time Interval of Cow's Milk Introduction and Mechanism of Sensitization

The studies supporting a preventative role with early cow's milk ingestion have had a very early age of cow's milk introduction (the majority within the first month of life; all within the first three months of life), in the form of cow's milk formula.¹⁰⁻¹² This age interval is much younger than the suspected protective age interval for early ingestion of other allergens, such as egg and peanut, which are introduced with transition to solid food. A recent meta-analysis and systematic review noted moderate certainty evidence that egg introduction between 4-6 months of age, and peanut introduction between 4-11 months of age, has a role in egg and peanut allergy prevention respectively.¹⁴ Peters et al, in their study, conclude by suggesting that "the window of opportunity for cow's milk protein exposure to induce tolerance may be earlier than for other allergens."¹²

The dual allergen exposure hypothesis – the concept of transcutaneous sensitization to foods – is the leading hypothesis regarding sensitization to egg and peanut.²³⁻²⁵ With respect to peanut allergy, peanut exposure in the environment increases the risk of peanut allergy, and this risk is augmented with higher environmental exposure or more

severe eczema.²⁶ There is evidence that eczema precedes the development of egg and peanut allergy in keeping with a causal relationship.^{27,28} However, this very early interval of cow's milk ingestion, within the first few months of life, would largely be prior to eczema development and suggests the possibility of a different mechanism of sensitization. The average age of presentation of cow's milk allergy tends to be much younger than for peanut or egg, further supporting the possibility of a different causal mechanism.²⁹ It is interesting that the majority of cow's milk prevention studies are in general population infants, in contrast to the peanut and egg literature which is more focused on infants at risk (largely due to eczema).³⁰⁻³³

As noted by Katz et al, "the exact timing and mechanism by which this tolerance occurs is still poorly understood. It is possible that different proteins have varying patterns of tolerance versus sensitization and allergenic timing."¹⁰ One intriguing hypothesis is the role the microbiome may play in the development of cow's milk allergy.^{34,35} It is possible that gut colonization and the diversity and intensity of microbial exposure may play a role in inducing cow's milk tolerance.³⁶ It has also been suggested that there may be a role of a healthy gut microbiome in preventing enterocolitis early in life, thus reducing gut absorption of allergens.¹⁹ It is also possible that vitamin D may have a role in modulating those immune functions. Finally, it is possible, as discussed above, that sensitization is less related to timing of ingestion but ongoing exposure, which promotes allergen tolerance (Figure 1).

Conclusion

Currently the American Academy of Pediatrics states no evidence that delaying cow's milk protein introduction beyond 4-6 months of age prevents cow's milk allergy but does not provide guidance regarding cow's milk protein introduction prior to four months of age.² The Consensus Guideline on primary prevention of food allergy by the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Canadian Society of Allergy and Clinical Immunology has specific guidance about peanut and egg but less strong recommendations about other allergens including cow's milk (Figure 2), stating there is no evidence to deliberately delay cow's milk protein introduction beyond around 6 months, but not before 4 months of age, rather than a recommendation to "introduce" in that time frame, and does not provide guidance around earlier cow's milk protein supplementation.³⁷ Once introduced, regular cow's milk ingestion is recommended.³⁷

Early ingestion of cow's milk formula in the first few months of life would directly contradict multiple international guidelines including World Health Organization and American Academy of Pediatrics recommendations to exclusively breastfeed for approximately 6 months of life.^{38,39} There is a paucity of literature at present that has examined the impact that early cow's milk formula ingestion would have on ongoing breastfeeding. Peters et al found that the majority of infants who received cow's milk formula in the first three months of life were also breastfed, and no greater protective effect for ongoing breastfeeding was noted among those who were exclusively formula fed compared with those who received a combination of cow's milk formula and breastmilk.¹² The SPADE study also found that early cow's milk formula did not compete with ongoing breastfeeding – approximately 70% of infants in both groups

207 were still breastfed to some degree at six months of age.¹³ Further studies examining
208 the impact of cow's milk formula supplementation on breastfeeding duration are
209 required, as well as the acceptability of this intervention by caregivers and healthcare
210 providers.

211 While much remains unknown at this time, there is increasing evidence that
212 either very early cow's milk ingestion, or regularity of exposure once introduced,
213 reduces the risk of cow's milk allergy. This intriguing finding suggests at possible
214 differences in the mechanism of sensitization of cow's milk allergy, and opens up many
215 avenues of research needs moving forward.

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Table 1: Key Studies Examining the Role of Early, and Ongoing Cow's Milk Ingestion in the Prevention of Cow's Milk Allergy

Author	Study Design	Outcome	Results/Implications	Limitations
Katz et al ¹⁰	Prospective observational feeding study of 13,019 general population infants from birth to starting of CMP	CMA (based on OFC)	Early (within the first 14 days of life) and ongoing (at least once a day) CMP ingestion associated with a lower incidence of CMA ($P<.001$). Only 0.05% of infants started on CMP in first 14 days of life (compared with 1.75% who started CMP on 105-194 days of life) had CMA.	Observational
Onizawa et al ¹¹	Retrospective case control study of 51 children with CMA compared to 102 matched controls and 32 children with egg allergy	CMA (defined as immediate reaction after CMP intake, positive CM-specific IgE, and diagnosis by allergist)	Early (within first month of life) and ongoing (at least once a day) CMP ingestion is associated with reduced risk of CMA ($P<.001$)	Observational, small sample size, retrospective, did not require OFC for diagnosis
Peters et al ¹²	Longitudinal population-based cross-sectional study of 5,276 general population infants	CMA at a year of age (based on parent-reported reaction and evidence of CM sensitization)	Early (within first 3 months of life) CM ingestion is associated with reduced risk of CMA	Observational, retrospective, did not require OFC for diagnosis, did not comment on frequency of ingestion
Sakihara et al ¹³	RCT of 504 general population infants to ingestion (at least 10 mL of CMP daily from 1-2 months of age) or avoidance (avoid CMP between 1-2 months of age)	CMA at 6 months of age (based on OFC)	Early (one month of age) and ongoing (every day) ingestion of at least 10 mL of CM associated with significant reduction in CMA at 2 months of age	Lack of blinding; high incidence of CMA detected
Lowe et al ¹⁵	RCT of 620 infants with family history of atopy to CMP, pHF or soy formula at cessation of breastfeeding	Allergic manifestations including CMA (based on consistent history and SPT) in the first two years of life	No reduction in allergic manifestations in children assigned to pHW or soy formula compared to CMP formula	Only approximately 50% transitioned to formula by 4 months of age, lack of blinding, poor adherence, did not require OFC for diagnosis
Perkin et al ¹⁶	RCT of 1303 general population infants assigned to early introduction (3 months) group of 6 common allergens (peanut, egg, CMP, sesame, whitefish, wheat) or standard introduction (6 months)	Food allergy to one or more of the 6 allergens between 1-3 years of age (based on OFC)	Ongoing ingestion of CM between 3 and 6 months of age in general population infants does not reduce risk of CMA	Poor adherence, CM avoidance defined as <300 mL per day raising possibility of ongoing ingestion in avoidance group
Saarinén et al ¹⁷	Prospective birth cohort of 6209 general population infants from birth to a year of age	CMA (based on OFC)	Risk factors for CMA include early and infrequent exposure to CMP ($P<.001$)	Observational

Natsume et al ¹⁸	Prospective cohort study of 118 infants with atopic dermatitis from birth to 18 months of age	CMA by 18 months of age (diagnosed by allergist based on history)	Continuous (CMP from birth to 18 months of age) associated with trend to reduction in CMA compared to discontinuous (did not consume CMP for longer than one month until 18 months of age) (P=.069)	High risk group, observational, lack of OFC for diagnosis
Urashima et al ¹⁹	RCT of 330 newborns with family history of atopy randomized 1:1 to BF with or without EF for at least the first 3 days of life (BF/EF) or BF supplemented with CMP from the first day of life to 5 months of age (BF/CMP). Subgroup analysis by 24-hydroxyvitamin D levels.	Sensitization to CM and CMA (diagnosed by OFC) by 2 years of age	Significant reduction in CMA in the BF/EF compared to the BF/CMP group (relative risk 0.52). Significant interaction of middle tertile of the 25-hydroxyvitamin D group with the intervention.	Lack of blinding; feasibility of 3 day interval of ingestion in reducing risk of allergic disease; impact of Vitamin D

BF: breastfeeding; CMP: Cow's milk protein; CMA: IgE-mediated cow's milk allergy; CMP: Cow's milk protein; EF: elemental formula; OFC: Oral food challenge; pHF: partially hydrolyzed formula; RCT: Randomized controlled trial; SPT: Skin prick test

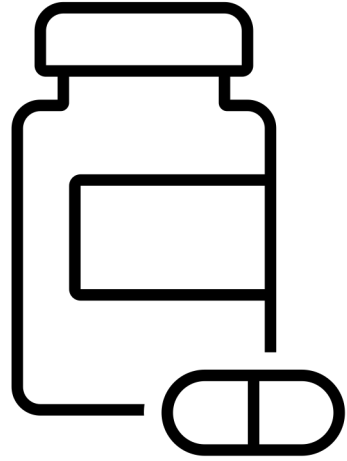
Table 1: Key Studies Examining the Role of Early, and Ongoing Cow's Milk Ingestion in the Prevention of Cow's Milk Allergy

Author	Study Design	Outcome	Results/Implications	Limitations
Katz et al ¹⁰	Prospective observational feeding study of 13,019 general population infants from birth to starting of CMP	CMA (based on OFC)	Early (within the first 14 days of life) and ongoing (at least once a day) CMP ingestion associated with a lower incidence of CMA ($P<.001$). Only 0.05% of infants started on CMP in first 14 days of life (compared with 1.75% who started CMP on 105-194 days of life) had CMA.	Observational
Onizawa et al ¹¹	Retrospective case control study of 51 children with CMA compared to 102 matched controls and 32 children with egg allergy	CMA (defined as immediate reaction after CMP intake, positive CM-specific IgE, and diagnosis by allergist)	Early (within first month of life) and ongoing (at least once a day) CMP ingestion is associated with reduced risk of CMA ($P<.001$)	Observational, small sample size, retrospective, did not require OFC for diagnosis
Peters et al ¹²	Longitudinal population-based cross-sectional study of 5,276 general population infants	CMA at a year of age (based on parent-reported reaction and evidence of CM sensitization)	Early (within first 3 months of life) CM ingestion is associated with reduced risk of CMA	Observational, retrospective, did not require OFC for diagnosis, did not comment on frequency of ingestion
Sakihara et al ¹³	RCT of 504 general population infants to ingestion (at least 10 mL of CMP daily from 1-2 months of age) or avoidance (avoid CMP between 1-2 months of age)	CMA at 6 months of age (based on OFC)	Early (one month of age) and ongoing (every day) ingestion of at least 10 mL of CM associated with significant reduction in CMA at 2 months of age	Lack of blinding; high incidence of CMA detected
Lowe et al ¹⁵	RCT of 620 infants with family history of atopy to CMP, pHF or soy formula at cessation of breastfeeding	Allergic manifestations including CMA (based on consistent history and SPT) in the first two years of life	No reduction in allergic manifestations in children assigned to pHW or soy formula compared to CMP formula	Only approximately 50% transitioned to formula by 4 months of age, lack of blinding, poor adherence, did not require OFC for diagnosis
Perkin et al ¹⁶	RCT of 1303 general population infants assigned to early introduction (3 months) group of 6 common allergens (peanut, egg, CMP, sesame, whitefish, wheat) or standard introduction (6 months)	Food allergy to one or more of the 6 allergens between 1-3 years of age (based on OFC)	Ongoing ingestion of CM between 3 and 6 months of age in general population infants does not reduce risk of CMA	Poor adherence, CM avoidance defined as <300 mL per day raising possibility of ongoing ingestion in avoidance group
Saarinén et al ¹⁷	Prospective birth cohort of 6209 general population infants from birth to a year of age	CMA (based on OFC)	Risk factors for CMA include early and infrequent exposure to CMP ($P<.001$)	Observational

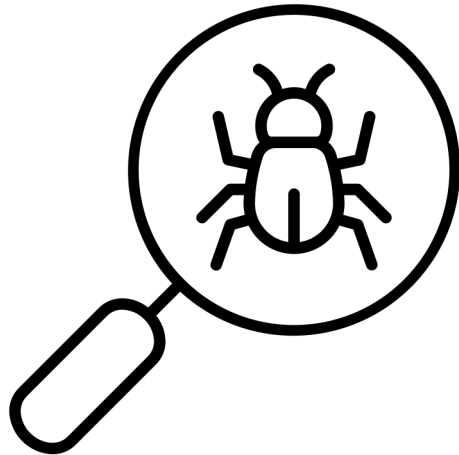
Natsume et al ¹⁸	Prospective cohort study of 118 infants with atopic dermatitis from birth to 18 months of age	CMA by 18 months of age (diagnosed by allergist based on history)	Continuous (CMP from birth to 18 months of age) associated with trend to reduction in CMA compared to discontinuous (did not consume CMP for longer than one month until 18 months of age) (P=.069)	High risk group, observational, lack of OFC for diagnosis
Urashima et al ¹⁹	RCT of 330 newborns with family history of atopy randomized 1:1 to BF with or without EF for at least the first 3 days of life (BF/EF) or BF supplemented with CMP from the first day of life to 5 months of age (BF/CMP). Subgroup analysis by 24-hydroxyvitamin D levels.	Sensitization to CM and CMA (diagnosed by OFC) by 2 years of age	Significant reduction in CMA in the BF/EF compared to the BF/CMP group (relative risk 0.52). Significant interaction of middle tertile of the 25-hydroxyvitamin D group with the intervention.	Lack of blinding; feasibility of 3 day interval of ingestion in reducing risk of allergic disease; impact of Vitamin D

BF: breastfeeding; CMP: Cow's milk protein; CMA: IgE-mediated cow's milk allergy; CMP: Cow's milk protein; EF: elemental formula; OFC: Oral food challenge; pHF: partially hydrolyzed formula; RCT: Randomized controlled trial; SPT: Skin prick test

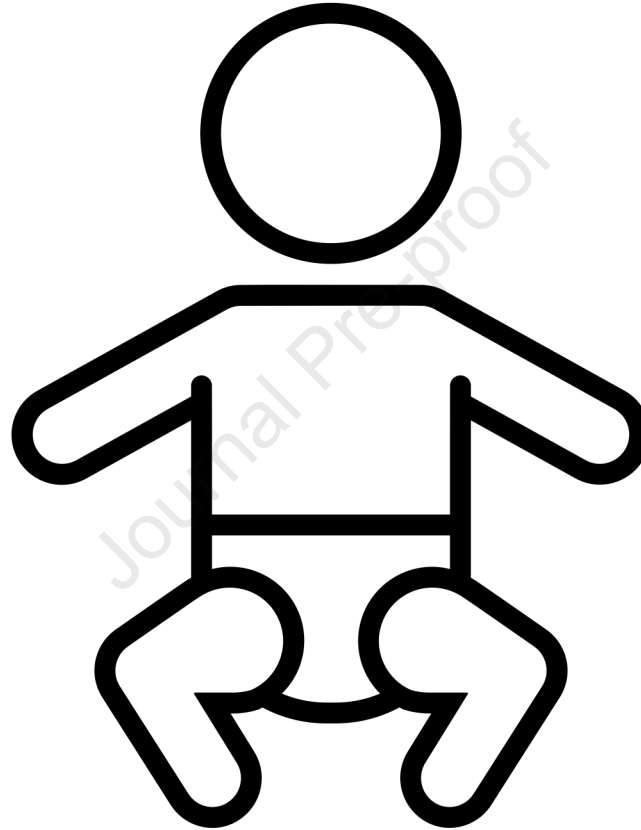
Figure 1: Possible factors involved in the pathogenesis of Cow's Milk Allergy



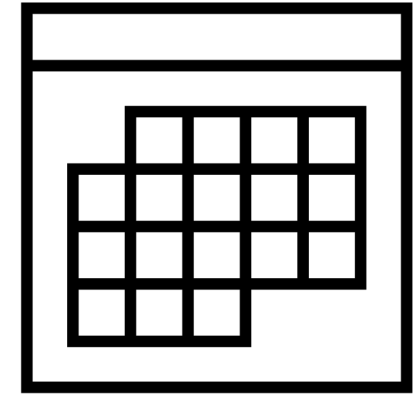
VITAMIN D



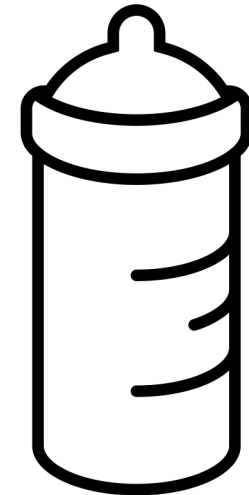
MICROBIOME



COWS MILK ALLERGY PREVENTION



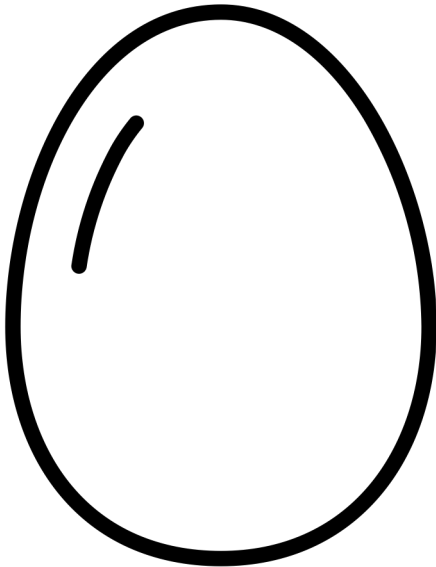
ONGOING INGESTION



EARLY INTRODUCTION

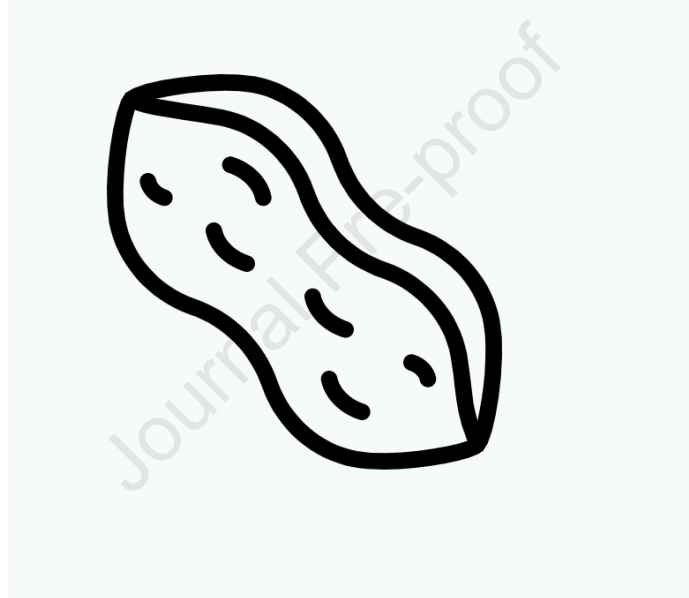
Figure 2: Recommendations of the Consensus Guideline on primary prevention of food allergy by the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Canadian Society of Allergy and Clinical Immunology

EGG



Introduce egg or egg-containing products to all infants, irrespective of their relative risk of developing egg allergy, starting around 6 months of life, though not before 4 months of life. Recommendation: Strong; Strength of Recommendation: A.

PEANUT



Introduce peanut-containing products to all infants, irrespective of their relative risk of developing peanut allergy, starting around 6 months of life, though not before 4 months of life. Recommendation: Strong; Strength of Recommendation: A.

COW'S MILK



Do not deliberately delay the introduction of other potentially allergenic complementary foods (e.g., cow's milk protein), once introduction of complementary foods has commenced at around 6 months though not before 4 months of life. Recommendation: Moderate; Strength of Recommendation: A/B

Key Messages

- There have been several studies supporting an association between early cow's milk ingestion and a lower incidence of cow's milk allergy among predominantly general population infants
- There is also literature supporting a protective role of ongoing cow's milk ingestion in the prevention of cow's milk allergy
- The studies supporting a preventative role with early cow's milk ingestion have had a very early age of cow's milk introduction
- Further research into the role of the microbiome, the modifying effect of vitamin D exposure, and the impact of early cow's milk ingestion on breastfeeding is required

Cow's Milk Allergy Prevention

Introduction

Food allergy is one of the most common chronic diseases of childhood, with an increasing prevalence noted over the past few decades.¹⁻³ Cow's milk allergy is one of the most common types of food allergy in North America, affecting approximately 2.6% of young children.⁴ While some studies suggest high rates of resolution of cow's milk allergy, more recent literature suggests a more cautious prognosis and heterogeneity in resolution rates, with a 42-57% rate of resolution by school age.⁵⁻⁸ In a recent US cross-sectional survey, 1.9% of adults reported cow's milk allergy, of which 77.3% noted persistence of this allergy from childhood.⁹ Cow's milk allergy, especially if persistent, has impacts on childhood growth and nutrition and is the most common cause of food-induced anaphylaxis.⁸ As there are little to date to modify the natural course of cow's milk allergy, a focus has shifted from management and treatment to prevention. While there is extensive literature on the prevention of other common food allergies of childhood, such as peanut and egg, less is known about cow's milk allergy prevention. The goal of this Review is to discuss what is known, and what is controversial, regarding cow's milk allergy prevention.

The role of early cow's milk ingestion in cow's milk allergy prevention

There have been three observational studies that document an association between early cow's milk ingestion and a lower incidence of cow's milk allergy among general population infants (Table 1). A prospective feeding study by Katz et al in 2010 of 13,019 newborn infants in Israel found a significant difference between age of cow's

milk protein introduction between infants with Immunoglobulin (Ig)-E mediated cow's milk allergy (116.1 $\pm$ 64.9 days) and those without cow's milk allergy (61.6 $\pm$ 92.5 days; $P < .001$).¹⁰ The odds ratio (OR) was 19.3 (95%CI: 6.0, 62.1) for development of cow's milk allergy among infants first ingesting cow's milk formula on, or after, 15 days of life compared with before ($P < .001$). Only 0.05% of infants started on regular cow's milk protein in the first 14 days of life (versus 1.75% who were started between 105-194 days of life) had cow's milk allergy. A retrospective case-control study by Onizawa et al of 51 children with IgE-mediated cow's milk allergy compared to 102 age-matched controls and 32 unmatched children with IgE-mediated egg allergy (to minimize the effect of confounders) found an association between delayed cow's milk protein introduction (more than one month after birth) and higher prevalence of cow's milk allergy ($P < .001$).¹¹ A retrospective population-based cross-sectional study out of Australia by Peters et al of 5,276 infants noted that early exposure to cow's milk protein in the first three months of life was associated with a reduced risk of cow's milk sensitization (aOR [adjusted odds ratio] 0.44; 95%CI: 0.23-0.83), parent-reported cow's milk reactions (aOR 0.44, 95%CI: .029-0.67) and cow's milk allergy (aOR 0.31, 95%CI: 0.10-0.91) at a year of age.¹² Limitations of these studies include variable definitions of cow's milk allergy (only Katz et al required an oral food challenge [OFC] for diagnosis), predominantly retrospective study designs (increasing the possibility of recall bias), and the inherent limitation of all observational data, which can show an association but not document causation.

The observational literature is now further supported by a recent randomized controlled trial (RCT) examining the benefit of early cow's milk ingestion on the

prevention of cow's milk allergy. The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study randomized 504 general population infants in Japan to daily cow's milk formula supplementation with ongoing breastfeeding between one and two months of age, or cow's milk formula avoidance (supplementation with soy formula if required).¹³ This study involved two OFCs – one at 3 months and one at 6 months of age, with the primary outcome the proportion of infants with confirmed cow's milk allergy based on the 6 month OFC. There was a significant reduction in cow's milk allergy (diagnosed by OFC) in the cow's milk ingestion group compared with the cow's milk avoidance group (0.8% vs 6.8%; risk difference 6.0%; 95% CI: 2.7,9.3). A dose-response relationship was observed, with none of the infants who consumed at least 70 mL of cow's milk formula per week between one and two months of age developing cow's milk allergy. The study authors comment on the high incidence of cow's milk allergy detected in the study, hypothesizing it is related to restricted ongoing cow's milk formula avoidance. It is also interesting in this study that there was a more than doubling of reaction rates between the 3 month and 6-month OFC. The reasons for this are unclear but it is possible that either the window of sensitization remains open between 3-6 months of age, or conversely that the 3-month OFC was sensitizing.

Although literature is mounting about the role of early cow's milk ingestion in cow's milk allergy prevention, a 2016 meta-analysis of two RCTs did not find any significant preventative effect (RR 0.76; 95%CI: 0.32,1.78).¹⁴ This was prior to the SPADE study, and both RCTs included had low adherence rates (63% and 42.8%).^{15,16} One of the two RCTs included in this meta-analysis, the Enquiring About Tolerance

(EAT) study, defined cow's milk avoidance as ingestion of less than 300 mL per day, raising the possibility that the avoidance group had sufficient ongoing exposure.^{13,16} In addition, in the EAT study cow's milk ingestion did not begin until 3 months of age, and it is possible that the preventative interval was already missed by that time. The other RCT, by Lowe et al, randomized 620 infants with a family history of allergic disease to receive either cow's milk formula, partially hydrolyzed formula or soy formula on cessation of exclusive breastfeeding.¹⁵ However, only approximately 50% were transitioned to formula by 4 months of age, once again raising the possibility that the preventative interval was missed.

Further research regarding the role early cow's milk ingestion plays in the prevention of cow's milk allergy is required, and questions remain. The absolute amount required for tolerance is unclear, although SPADE suggests at least 10 mL per day is required. There is variability in the definition of early ingestion including first 14 days of life,¹⁰ first month of life,¹¹ first three months of life,¹² and the interval between one and two months of life.¹³ All the studies are of general population infants, and thus it is unclear whether this strategy has an incremental benefit in those infants at higher risk.

The role of consistent cow's milk ingestion in the prevention of cow's milk allergy

There have been two prospective observational studies and one RCT that support a protective role of ongoing cow's milk ingestion in the prevention of cow's milk allergy. A prospective study of 6209 infants documented a significant association between OFC-proven cow's milk allergy and exposure to cow's milk formula at the hospital ($P < .001$), as well as infrequent exposure to small amounts of cow's milk once

home ($P < .001$).¹⁷ A prospective cohort of 114 infants with atopic dermatitis, belonging to the same cohort as the Prevention of Egg allergy with Tiny amount InTake (PETIT) study, found a borderline lower prevalence of cow's milk allergy (based on questionnaire) among infants with continuous cow's milk ingestion (from birth to 18 months of age) compared to infants with discontinuous ingestion (no longer than one month from birth until 18 months; $P = .069$).¹⁸

The Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC) study randomized 330 newborns at risk of atopy (due to a first degree relative with atopic disease) to breastfeeding with or without amino acid-based elemental formula (BF/EF) for at least the first three days of life or breastfeeding supplemented with cow's milk formula (BF/CMF) from the first day of life to five months of age.¹⁹ Results revealed neonates receiving breastmilk and elemental formula had significantly lower cow's milk sensitization (relative risk [RR] 0.52, 95%CI, 0.34-0.81), and had a significantly lower risk of immediate (RR 0.20, 95%CI, 0.07-0.57) and anaphylactic (RR 0.08, 95%CI, 0.01-0.58) cow's milk allergy at 2 years of age.¹⁹ This study suggests that infants who are fed cow's milk formula for a very brief, and not ongoing, period of time after birth may have an increased risk of cow's milk allergy compared to use of elemental formula. Subgroup analysis with prespecified serum 25 (OH)D (25-hydroxyvitamin D) levels was performed, noting a significant interaction with the intervention for the middle tertile of the 25 (OH)D subgroup, with cow's milk formula avoidance only effective in this subgroup. The study authors conclude this suggests a bimodal function of vitamin D on immune function, though noting "vitamin D hypotheses in food allergy are still far from conclusions."

Studies have also shown that elimination of cow's milk for a period of time from the diet increases the risk of cow's milk allergy, suggesting that ongoing ingestion of cow's milk, once introduced, may play a role in cow's milk allergy prevention.^{20,21} In a recent prospective observational study of infants with food protein-induced allergic proctocolitis (FPIAP), there was a significant association between FPIAP and development of IgE-mediated cow's milk allergy (OR 5.4; 95%CI: 1.4-20.8) further supporting ongoing ingestion as a means of cow's milk allergy prevention.²²

It is important to note that several of the studies supporting a role of early cow's milk ingestion in the prevention of cow's milk allergy have also included, as part of the study design, ongoing regular cow's milk ingestion, raising the possibility that it is the *consistent ingestion* in these studies, *instead of early exposure*, that may be protective. Katz et al defined age of introduction of cow's milk based on regularity of exposure (at least once a day).¹⁰ The role of regularity of ingestion as a preventative mechanism was also supported in the Katz study by the finding that cow's milk allergy was much lower among Muslim-Arab women than Jewish women. The key difference among these populations was that Jewish women were more likely to exclusively or almost exclusively breastfeed, resulting in more ongoing cow's milk exposure in the Muslim-Arab infants. Onizawa et al also noted irregularity of ingestion (less than once daily) to be associated with cow's milk allergy ($P < .001$).¹¹ In fact, the percentage of infants who started cow's milk in the first month of life was not significantly different between the cow's milk allergy and egg allergy subgroups, whereas the number of infants with regular ingestion of cow's milk formula was significantly less in the cow's milk allergy group, "suggest[ing] that sufficient amounts and the continuous intake of cow's milk are

important for the prevention of cow's milk allergy."¹¹ The SPADE study also had ongoing ingestion (at least 10 mL every day) as part of inclusion criteria in the early ingestion group.¹³

There are gaps in the literature to date, and certainly more research is required. However, an increasing body of evidence raises the possibility that it is ongoing ingestion, instead of or in addition to early cow's milk ingestion, that may play a role in cow's milk allergy prevention.

Time Interval of Cow's Milk Introduction and Mechanism of Sensitization

The studies supporting a preventative role with early cow's milk ingestion have had a very early age of cow's milk introduction (the majority within the first month of life; all within the first three months of life), in the form of cow's milk formula.¹⁰⁻¹² This age interval is much younger than the suspected protective age interval for early ingestion of other allergens, such as egg and peanut, which are introduced with transition to solid food. A recent meta-analysis and systematic review noted moderate certainty evidence that egg introduction between 4-6 months of age, and peanut introduction between 4-11 months of age, has a role in egg and peanut allergy prevention respectively.¹⁴ Peters et al, in their study, conclude by suggesting that "the window of opportunity for cow's milk protein exposure to induce tolerance may be earlier than for other allergens."¹²

The dual allergen exposure hypothesis – the concept of transcutaneous sensitization to foods – is the leading hypothesis regarding sensitization to egg and peanut.²³⁻²⁵ With respect to peanut allergy, peanut exposure in the environment increases the risk of peanut allergy, and this risk is augmented with higher environmental exposure or more

severe eczema.²⁶ There is evidence that eczema precedes the development of egg and peanut allergy in keeping with a causal relationship.^{27,28} However, this very early interval of cow's milk ingestion, within the first few months of life, would largely be prior to eczema development and suggests the possibility of a different mechanism of sensitization. The average age of presentation of cow's milk allergy tends to be much younger than for peanut or egg, further supporting the possibility of a different causal mechanism.²⁹ It is interesting that the majority of cow's milk prevention studies are in general population infants, in contrast to the peanut and egg literature which is more focused on infants at risk (largely due to eczema).³⁰⁻³³

As noted by Katz et al, "the exact timing and mechanism by which this tolerance occurs is still poorly understood. It is possible that different proteins have varying patterns of tolerance versus sensitization and allergenic timing."¹⁰ One intriguing hypothesis is the role the microbiome may play in the development of cow's milk allergy.^{34,35} It is possible that gut colonization and the diversity and intensity of microbial exposure may play a role in inducing cow's milk tolerance.³⁶ It has also been suggested that there may be a role of a healthy gut microbiome in preventing enterocolitis early in life, thus reducing gut absorption of allergens.¹⁹ It is also possible that vitamin D may have a role in modulating those immune functions. Finally, it is possible, as discussed above, that sensitization is less related to timing of ingestion but ongoing exposure, which promotes allergen tolerance (Figure 1).

Conclusion

Currently the American Academy of Pediatrics states no evidence that delaying cow's milk protein introduction beyond 4-6 months of age prevents cow's milk allergy but does not provide guidance regarding cow's milk protein introduction prior to four months of age.² The Consensus Guideline on primary prevention of food allergy by the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Canadian Society of Allergy and Clinical Immunology has specific guidance about peanut and egg but less strong recommendations about other allergens including cow's milk (Figure 2), stating there is no evidence to deliberately delay cow's milk protein introduction beyond around 6 months, but not before 4 months of age, rather than a recommendation to "introduce" in that time frame, and does not provide guidance around earlier cow's milk protein supplementation.³⁷ Once introduced, regular cow's milk ingestion is recommended.³⁷

Early ingestion of cow's milk formula in the first few months of life would directly contradict multiple international guidelines including World Health Organization and American Academy of Pediatrics recommendations to exclusively breastfeed for approximately 6 months of life.^{38,39} There is a paucity of literature at present that has examined the impact that early cow's milk formula ingestion would have on ongoing breastfeeding. Peters et al found that the majority of infants who received cow's milk formula in the first three months of life were also breastfed, and no greater protective effect for ongoing breastfeeding was noted among those who were exclusively formula fed compared with those who received a combination of cow's milk formula and breastmilk.¹² The SPADE study also found that early cow's milk formula did not compete with ongoing breastfeeding – approximately 70% of infants in both groups

were still breastfed to some degree at six months of age.¹³ Further studies examining the impact of cow's milk formula supplementation on breastfeeding duration are required, as well as the acceptability of this intervention by caregivers and healthcare providers.

While much remains unknown at this time, there is increasing evidence that either very early cow's milk ingestion, or regularity of exposure once introduced, reduces the risk of cow's milk allergy. This intriguing finding suggests at possible differences in the mechanism of sensitization of cow's milk allergy, and opens up many avenues of research needs moving forward.