

EDITORIAL

Cow's Milk and Vitamin D Supplementation in Infants—Timing Is Everything

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In this issue of *JAMA Pediatrics*, Urashima and colleagues¹ ask whether very early (within 3 days of birth) exposure to cow's milk formula (CMF) (a common practice in Japan) and vitamin D supplementation (uncommon in Japan) lowers or increases the risk of developing food allergy (as determined by cow's milk-specific IgE [CM-IgE] sensitization at 5 months and 2 years of age) in infants at risk of atopy (risk was defined as having ≥ 1 of the father, mother, and/or siblings with current and/or past atopic diseases [eg, asthma]). In recent years, the approach for primary prevention of food allergy has changed dramatically. Earlier recommendations to delay the introduction of allergenic foods to 1 to 3 years of age have now been replaced by newer recommendations to introduce allergenic foods such as peanut and egg at 4 to 6 months of age, after a period of exclusive breastfeeding (EBF).² The World Health Organization and the European Academy of Allergy and Clinical Immunology (EAACI) recommend EBF for a minimum of 6 months and 4 months, respectively.³ However, whether introduction of all typically allergic foods before 4 to 6 months can decrease risk of allergy is unclear. In the case of CM, this issue is of special importance because supplementation or replacement with formula, even in the first days of life, is not infrequent. Partially or extensively hydrolyzed formulas have been developed to reduce the allergenicity of CM. There is currently a lack of consensus among national allergy societies with respect to recommendations for the use of hypoallergenic formula for the prevention of food allergy in infants who are unable to EBF. Although the EAACI³ and American Academy of Allergy, Asthma and Immunology (AAAAI) currently recommend the use of hypoallergenic formulas in infants at high risk of allergy, the Australian Society of Clinical Immunology and Allergy does not. The EAACI and the AAAAI are likely to reconsider their guidelines because results of more recent studies have been contradictory. At the current time, insufficient evidence suggests that hydrolyzed formulas might decrease risk of developing food allergy.⁴



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Timing of introduction of foods plays a role in the development of tolerance and allergy. Microbial composition changes rapidly, soon after birth. During the first few days of life, bacterial composition resembles that found in the mother's breast milk or vaginal swabs, but, by 4 to 6 months, the gut microbiome of the infant is vastly different from that of the mother.⁵ The optimal window during which exposure to common food proteins induces tolerance is unclear. In the study by Urashima et al¹ on the effects of early CM exposure on food allergy incidence, the authors conclude that sensitization to CM is primarily preventable by avoiding CMF supplementation for the first 3 days of life (their primary outcome). Their post hoc analysis found that switching to CMF

after the first 3 days of life showed no difference in food allergy. Furthermore, no difference in food allergy incidence occurred between those fed hydrolyzed CMF vs those fed nonhydrolyzed CMF starting 3 days after birth. This study begins to help our understanding of timing, but further studies and analyses are needed before making broad conclusions or applications to feeding, because this study focused only on the first 3 days of life.

Studies, many of which were observational, have evaluated the role of supplemental formulas soon after birth on the risk of CM allergy (CMA) with contradicting results. Høst et al⁶ found that breastfed infants with early occasional exposure to CM proteins had greater risk of food allergy. In a large prospective randomized study of more than 6000 healthy full-term infants,⁷ those who were supplemented with CMF while in the hospital had higher risk of CMA than those who were supplemented with whey hydrolysate formula or pasteurized breast milk. It should be noted that these earlier studies did not quantitate IgE-CM levels, and many of the symptoms that they used for diagnosis would not be considered to represent milk allergy today. In a single-center cohort study from Israel,⁸ CMF introduction within the first 2 weeks of life was associated with the lowest rate of milk allergy, whereas the highest rate was observed in infants exposed to CMF at 4 to 6 months of age. An observational study (HealthNuts)⁹ showed that introduction of CM protein before 3 months of age is associated with significantly reduced risk for CM sensitization and CMA at 12 months of age. The Enquiring About Tolerance (EAT) study¹⁰ examined the effect of early introduction of several allergenic foods, including CM, after 3 months of EBF, on the development of food allergy. It indicated that early introduction may be effective in reducing the rate of peanut and egg allergies (in the per protocol but not the intention-to-treat analysis) but failed to show statistically significant efficacy for CMA. Further, the EAT results also indicate that milk intake at 3 months was associated with neither a decrease nor an increase in milk allergy. In a recent retrospective study from Ireland,¹¹ the authors found that breastfed infants are at significantly increased risk of CMA by receiving supplemental formula in the first 24 hours of life. However, it is unclear whether CMF supplementation was continued beyond 24 hours. Moreover, infants who were exclusively formula fed were not at increased risk for CMA. These data may suggest that for early (before 3 months of age) introduction of CMF to be potentially protective against CMA, it should be sustained. Intermitent exposure may paradoxically increase the risk of CMA.

Urashima et al¹ also examined the role of vitamin D supplementation, because some studies have suggested an association between vitamin D and food allergy; however, these results have not been conclusive.¹² A study of infants with eczema supplemented with vitamin D found no significant decrease

in the severity of eczema at 3 months; however, food allergy was increased at 2 years.¹³ Another study found that infants with CMA had lower levels of vitamin D.¹⁴ Guidelines for vitamin D supplementation in newborn infants differ. For example, guidelines in the United States and United Kingdom recommend routine vitamin D supplementation in all breastfed infants, whereas guidelines in Australia recommend supplementation only in breastfed infants at high risk of vitamin D deficiency.¹⁵ The American Association of Pediatrics and the Institute of Medicine define vitamin D insufficiency as 25-hydroxyvitamin D concentrations of less than 20 ng/mL in children. Urashima et al¹ performed a subgroup analysis, prespecified by tertiles of serum 25-OH-D levels at 5 months of age, and found that avoiding CMF in the first 3 days of life was effective in decreasing risk of CMA only in the middle tertile of 25-OH-D levels (21-36 ng/mL).

This study by Urashima et al¹ provides valuable data that could assist in determining optimal timing for supplementation and formula type for newborn infants at risk of atopy who cannot receive EBF. However, the evidence provided by the

study needs further validation before changes to infant feeding practice guidelines can be considered. Importantly, the study included infants at risk of atopy, and these results may not be applicable for all newborns. The authors reference the importance of gut microbiota in tolerance and allergy; however, it is not clear why only the first 3 days of life are considered the most critical for gut exposures to dairy. Future studies should evaluate the effect of cofounders such as method of birth, emollient use, and maternal/newborn antibiotic use, because these greatly affect infant gut microbiota and potentially food allergy risk. The question regarding vitamin D and other diverse food supplementation in infants and breastfeeding mothers should be further evaluated by randomized studies.

In summary, Urashima and colleagues¹ address an important question that has not been adequately answered to date. Further studies are needed to validate and build on these findings. However, studies in this area might be limited or of inferior design because of the ethical restraints around randomizing infants away from EBF. Efforts to optimize the initiation and continuation of breastfeeding need to be encouraged.

ARTICLE INFORMATION

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