

# The Prevention of Milk Allergy and the Risks of Stopping Too Soon



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Multiple observational studies suggest that early introduction of cow's milk (CM) may be protective against cow's milk allergy (CMA).<sup>1-3</sup> However, this has not been demonstrated consistently across randomized trials.<sup>4-8</sup> Recent consensus guidelines from the American Academy of Allergy, Asthma, and Immunology, American College of Allergy, Asthma, and Immunology, and Canadian Society for Allergy and Clinical Immunology concluded that whereas there was a trend toward prevention of CMA with early introduction, there was insufficient evidence to provide guidance on the matter.<sup>5</sup> A systematic review published in 2020 by the European Academy of Allergy and Clinical Immunology Food Allergy, Anaphylaxis Guidelines Group came to similar conclusions, adding that exposure to CM in the first week of life may increase the risk for CMA.<sup>4</sup>

The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study, published subsequent to the development of these reviews, was a multisite, open-label, randomized trial of cow's milk formula (CMF) ingestion or avoidance from age 1 to 3 months in a general population of infants in Okinawa, Japan.<sup>7</sup> The difference in CMA was striking: 0.8% of the consumption group and 6.8% of the avoidance group developed CMA by age 6 months.<sup>7</sup> The follow-up analysis presented by Sakihara et al in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* provides potential answers regarding why these differences were so pronounced.<sup>9</sup>

To understand this subsequent analysis, some background is needed on the SPADE trial. An important aspect of the SPADE trial is that nearly all participants had introduced CMF before enrollment; 431 of 462 had CMF in the first 3 days of life.<sup>7</sup> Participants were also allowed to reintroduce CMF after the intervention period and before the conclusion of the trial.<sup>7</sup> Furthermore, all participants, including those in the avoidance arm, underwent oral food challenges at 1, 3, and 6 months of age.<sup>7</sup> This variability in CMF consumption left areas of uncertainty

regarding whether early exposure and subsequent discontinuation or inconsistent exposure to CMF could potentially induce CMA.

The article by Sakihara et al<sup>9</sup> in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* explores the impact of early CMF discontinuation on the development of CMA. The authors found that among those who had introduced CMF in the first 3 days of life, discontinuation of CMF at home before age 6 months was strongly associated with subsequent development of CMA.<sup>9</sup> In these participants, CMF was not discontinued owing to the perception of CMA.<sup>9</sup> Participants who discontinued CMF at home had subsequent exposures to CM through the study oral food challenges at 1 and 3 months of age.<sup>7,9</sup> Thus, early exposure and subsequent limited and inconsistent consumption were associated with increased risk for CMA.

None of the 31 SPADE trial participants who abstained from CMF in the first 3 days of life had CMA at age 6 months.<sup>7</sup> The significance of these results is supported by the previously published Atopy Induced by Breastfeeding or Cow's Milk Formula trial, which found increased risk for CM sensitization and CMA at age 24 months among those exposed to CMF in the first 3 days of life.<sup>8</sup> Together, these studies suggest an increased risk for CMA if introduction of CMF occurs in the neonatal period and consistent consumption is not continued through the first several months of life. Further research is needed to understand mechanistically why neonatal CMF exposure may pose increased risk for CMA development and how long this risk period lasts.

Sakihara et al<sup>9</sup> also show that those who developed CMA in the SPADE trial consumed significantly less CMF than their nonallergic counterparts, with an average of just 6 days and 6.2 mL/d of CMF ingestion. This raises the possibility of a minimum volume and frequency needed to prevent the development of CMA. In the SPADE trial, no participants who consumed 70 mL/wk or greater of CMF during the intervention period developed CMA.<sup>7</sup> An ongoing nonrandomized trial (NCT02785679) comparing exclusive breastfeeding, small volume, large volume, and exclusive CMF consumption in 2500 infants may provide insight into this question.

The potential importance of consistent consumption, or rather the risk for variable consumption, has significant implications for families, many of whom initiate CMF early in infancy. Survey data from the 2018 CDC National Immunization Survey reported that approximately 20% of infants in the United States are introduced to formula in the first 2 days of life, and 30% by 3 months.<sup>10</sup> Families may introduce and switch or discontinue formula products for a variety of reasons, including initial difficulties with or inability to initiate breastfeeding during the neonatal period, other medical concerns, personal preferences, or cost. The potential risk for discontinuing CMF should also be considered in inpatient

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neonatal and pediatric care units in which formulas may be used temporarily or may differ from what is used at home. Guidance is needed to support these families and patients to prevent CMA.

What remains unknown is whether there is a benefit to early introduction for those who do not introduce CMF in the first 3 days of life. If so, when and for whom should this introduction occur? The Enquiring About Tolerance (EAT) study, a randomized controlled trial of early versus standard introduction of multiple allergenic foods, including milk, found no significant difference in the rate of milk allergy.<sup>6</sup> An important difference from the SPADE trial is that EAT participants were required to have been exclusively breastfed up to age 3 months, thus excluding those who had been introduced to CMF in the first 3 days of life. Perhaps 3 months is too late to see a difference, or perhaps the greatest risk is conferred by early introduction and subsequent inconsistent exposure to CMF, as suggested by the study from Sakhira et al.<sup>9</sup>

If there is risk to introducing milk too early and a lack of benefit to introducing it too late, when is the time just right? Several ongoing open-label trials may shed light on this issue, including NCT0278567, as noted earlier, as well as Preventing Atopic Dermatitis and Allergies in Children, a prospective birth cohort with a 2 × 2 randomized trial of skin care and early food introduction (NCT02449850). There has yet to be a randomized placebo-controlled trial of CMF introduction. As shown by the SPADE and EAT studies, early CMF introduction trials can be conducted without impairing continued breastfeeding.<sup>6,7</sup> Furthermore, unlike many other foods for which blinding may be difficult, it might be possible to conduct a double-blind placebo-controlled trial of CM introduction. Such a trial would likely provide much-needed guidance about whether early

introduction is truly protective against CMA, when it should be done, and for whom.

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