

OPTIMIZING NUTRITION IN INFANTS AT HIGH RISK OF DEVELOPING ALLERGY

RECENT COURSE UPDATES



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How do you determine whether an elimination diet is necessary in infants with suspected cow's milk allergy (CMA)?

There is increasing evidence that CMA and other forms of allergy are being overdiagnosed in infants.¹ The international Milk Allergy in Primary Care (iMAP) guidelines for the diagnosis of CMA include symptoms such as persistent irritability (colic), vomiting (reflux), food refusal, diarrhea, constipation, bloody or mucousy stools, rash, and erythema.² However, there is evidence that these symptoms are common in otherwise well infants. In a recent analysis of the Enquiring About Tolerance (EAT) randomized controlled trial, which enrolled 1303 exclusively breastfed 3-month-old infants, 3 in 4 infants experienced at least 2 mild or moderate CMA symptoms by 1 year of age. Furthermore, 6-month-old infants who ingested cow's milk experienced 2 or more mild or moderate CMA symptoms at the same rate as those who did not ingest cow's milk (35.3% vs 29.5%).¹ Therefore, clinicians should use their clinical judgement to determine whether CMA is a likely cause of common CMA symptoms, particularly in infants who are exclusively breastfed, where continued breastfeeding should be supported. If CMA is strongly suspected, maternal elimination diets can be trialed in those with exclusively breastfed infants, while hydrolyzed formulas can be trialed in infants receiving formula.²

Should the presence of atopic dermatitis in an infant who presents with other mild or moderate symptoms of food allergy increase your suspicion of CMA?

Infants and children with atopic dermatitis are at higher risk for food allergy; however, the prevalence of food allergy in people with atopic dermatitis is still below 20%, and thus it is not a foregone conclusion that these patients will develop a food allergy. Nonetheless, the misperception that food allergy is a common cause of atopic dermatitis persists among clinicians and parents. As such, infants with atopic dermatitis are sometimes prescribed restrictive elimination diets without any evidence of food allergy.

Diagnosing food allergies in infants can be difficult. Skin prick tests are rarely used prior to age 1 year, and food-specific IgE testing has low specificity and high false-positive rates in patients with atopic dermatitis, complicating food allergy diagnosis in this patient population. As such, the necessity of elimination diets in patients with atopic dermatitis should be confirmed with an oral food challenge, performed by a physician, when a food allergy is suspected. Involving an allergist or immunologist is also reasonable.³

What are the harms of overdiagnosing CMA in infants?

Overdiagnosing CMA in infants has several associated consequences. While symptoms of CMA, such as colic, can be normal in well-appearing infants, it is also possible that another condition with similar symptoms may be misdiagnosed as CMA. Furthermore, breastfeeding mothers may follow needlessly restrictive elimination diets or stop breastfeeding altogether in favor of hypoallergenic formulas. These formulas are costly and can place unnecessary financial burdens on families and healthcare systems. In the UK, prescriptions of hypoallergenic formulas have increased by 500% in the last decade, and healthcare spending on these formulas increased by 700%.⁴ Aside from the financial burden, restrictive diets in infants and children have been linked with hypocalcemia, vitamin D deficiency, and other signs of malnutrition.⁵ Furthermore, there is growing evidence that early exposure to allergenic foods decreases IgE-mediated allergies later in life. Similarly, we can theorize that by avoiding early exposure to dairy, we may be setting up the infant for increased allergies in the future.

Finally, diagnosis of CMA can lead to psychological harm. Parents of children with newly diagnosed CMA have elevated levels of stress, anxiety, and depression.^{6,7} For these reasons, we encourage clinicians to be cautious when diagnosing CMA and to consider the possibility that common infant symptoms such as reflux may not have an underlying cause.

If you are presented with a well-appearing 2-month-old with a history of mild rectal bleeding and reflux, that resolved on introduction of hydrolyzed formula, when would you rechallenge with cow's milk?

Many symptoms of suspected CMA are self-limited and do not require extended use of hydrolyzed formulas and elimination diets.^{1,8} A recent study evaluated time to resolution of rectal bleeding upon elimination of cow's milk in 76 infants younger than 4 months. Cow's milk protein was reintroduced 2 to 8 weeks after resolution of rectal bleeding. Researchers found that more than two-thirds of infants were able to tolerate cow's milk protein at the first rechallenge. Of those infants with recurrent rectal bleeding, on reintroduction to cow's milk, most were tolerant to cow's milk by about 7 months of age.⁸

These data challenge the conventional wisdom that we should be waiting months or even a full year before reintroducing cow's milk protein into the diets of well-appearing infants with suspected CMA, and suggest that earlier reintroduction at 4 to 6 weeks after symptom resolution may be more reasonable. For an infant such as the one described above, CMA could certainly be considered in the differential diagnosis, but their symptoms could be attributable to other causes (eg, infection) or have no underlying cause at all. Therefore, reintroduction of cow's milk can be considered 4 to 6 weeks after symptom resolution. If symptoms return, reintroduction can be attempted in 2-month intervals after symptom resolution.

What is the role for soy formulas for infants with CMA?

We are continuing to find that there are limited applications for plant-based formulas in infants with CMA, despite high soy and plant-based formula use in the United States.⁹ For infants with CMA, both the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend starting with hypoallergenic hydrolyzed or amino acid–based formulas.^{10,11} These recommendations are based on the established effectiveness of hypoallergenic formulas for infants with CMA, the potential for sensitization to soy, and ongoing concerns regarding the phytoestrogen content of soy formulas.^{10,12-14} Based on results of animal studies, it has been suggested that phytoestrogen exposure in infancy may increase the risk for early puberty; results continue to be mixed on this topic, but as of yet the hypothesis has not been conclusively disproven in human studies.¹⁵⁻¹⁷

Nonetheless, NASPGHAN recognizes that hydrolyzed and amino acid–based formulas can be cost prohibitive for many families. In these cases, a trial of soy formula can be considered safe in full-term infants older than 6 months.¹⁰

How should parents who are using prescription formulas be counseled when a formula recall occurs?

If parents are using a brand of infant formula that has been recalled, they should check the lot codes and dates of the formula that they have on hand. If they have products that are included in a recall, they should immediately discontinue use of those products and follow the recommendations of the US Food and Drug Administration (FDA) regarding monitoring for symptoms of disease.¹⁸

If the recalled formula was the only source of nutrition for a child with suspected CMA, parents will need to find alternatives for the recalled formula. As a first step, clinicians should work with parents to determine whether hypoallergenic formula is truly indicated. Given the high rate of overdiagnosis of CMA, it is likely that many children will be able to transition off hypoallergenic formulas. For those infants who are truly intolerant to cow's milk protein, clinicians should work with parents to find alternative solutions, including reverting to exclusive breastfeeding (with a maternal elimination diet, if indicated) or switching to a different hypoallergenic formula that may be a different generic brand. During recalls, lists of temporary replacement options are often made available by NASPGHAN (<https://naspghan.org/recent-news/naspghan-tools-for-hcps-affected-by-formula-recall/>), American Academy of Pediatrics, formula manufacturers, and local governmental organizations.¹⁹ It is never appropriate for parents to attempt to use homemade formula solutions or dilute formula when their access to formula is limited by recalls, due to the risk of serious or even life-threatening adverse effects, including contamination, malnutrition, and other health risks.²⁰

What, if any, is the role for early introduction of cow's milk formula to prevent CMA?

Evidence is emerging that early introduction of cow's milk protein prior to 6 months of age may help to prevent the development of CMA. In a Japanese randomized controlled trial, daily feeding of at least 10 mL of cow's milk formula, between 1 to 2 months of age, resulted in an 88% lower risk of CMA at 6 months compared with infants who did not receive any cow's milk formula (soy formula supplementation was used as needed).²¹ The practicality of this study is still being determined, as many families with fully breastfed infants may be hesitant to offer daily small volumes of cow's milk formula. However, the study does further suggest that early exposure to cow milk protein is beneficial, particularly if an infant is at high risk for CMA. Researchers in this study showed that introduction of cow's milk formula did not compete with breastfeeding. However, this is the first study of this kind, and additional research would be needed before we recommend small-volume formula in breastfed infants. If this approach were to be recommended, clinicians should ensure that parents are aware of the benefits of continued breastfeeding during this time period.²¹

For more context, watch Dr. Hofmekler's recorded CE/CME webcast, *Optimizing Nutrition in Infants at High Risk for Developing Allergy*.

It's part of our extensive collection of educational material, *Understanding Food Allergies in Infants and Children*.

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