

Clinical Communications

Multiple shifting phenotypes with cow's milk: From eosinophilic esophagitis to immediate hypersensitivity and back again

Stephanie C. Erdle, MD, FRCPC^a, Lianne Soller, PhD^a, Vishal Avinashi, MD, MPH, FRCPC^b, Hannah Roberts, MD, FRCPC^c, Elaine Hsu, MPH^a, and Edmond S. Chan, MD, FRCPC^a

Clinical Implications

- This case suggests that oral immunotherapy may be considered in patients who develop IgE-mediated allergy following an elimination diet if the patient/parent prefers the outcome of worsened eosinophilic esophagitis over the risk of possible anaphylaxis.

TO THE EDITOR:

Cow's milk allergy (CMA) is one of the most common food allergies among children.¹ Although this allergy is outgrown in 75% of children by teenage years,¹ oral immunotherapy (OIT) has been studied in the subset of patients who are unlikely to outgrow it. OIT involves administering incremental doses of cow's milk (CM) protein to a maintenance dose, with the goal of developing tolerance to CM protein.²

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease that has emerged over the last 2 decades.³ Management of EoE involves either medication (proton pump inhibitor or swallowed topical corticosteroid) or dietary elimination of possible food triggers, the most common of which is CM.³ CM elimination can induce histologic remission in up to 64% of patients with EoE.⁴ Although successful, one of the theoretical risks is development of IgE-mediated allergy secondary to CM avoidance. Recently, cases have been reported of IgE-mediated allergy to CM after elimination for EoE treatment.^{5,6}

Although OIT is a promising treatment for food allergy, an association between OIT and the development of EoE has been suggested, estimated at 2.7% (range: 0.99% to 5.33%).⁷ EoE is therefore considered an absolute contraindication to the continuation or initiation of OIT.⁷

We describe a 4-year-old girl with a history of multiple food allergies (peanut, tree nut, sunflower seed, fish), atopic dermatitis, and seasonal allergic rhinitis. She was tolerating regular CM ingestion without adverse reaction. She presented atypically with hematochezia and anemia, and was diagnosed with EoE at age 3 by endoscopy, with 145 eosinophils/hpf proximally, 90 mid and 110 distally. The family opted for CM elimination as initial treatment for her EoE. Although not routinely recommended, at the mother's request, a CM skin prick test (SPT) was performed before elimination, which was negative.

Six months after initiation of CM elimination, repeat endoscopy showed some improvement with 85 eosinophils/hpf proximally, 67 mid and 20 distally, with improvement in her hematochezia and anemia. She was still consuming baked CM,

so the family was advised to eliminate baked products. Nine months after strict elimination of all CM products, repeat endoscopy was performed showing additional improvement with 45 eosinophils/hpf proximally, 30 mid and 20 distally.

Shortly after, she ingested 1 teaspoon of homogenized milk accidentally. Within minutes, she developed isolated perioral urticaria and oral pruritus, which resolved within 30 minutes. After this, her mother began to give her small amounts of CM products (small cube of cheese, 2-3 tbsp yogurt) 2 to 3 times weekly, with each episode resulting in mild perioral urticaria and oral pruritus that self-resolved. Six months later, they returned to clinic, and CM SPT was positive at 10 × 4 mm, with milk-specific IgE (ssIgE) of 2.62 kU/L. The family was advised to continue to give the same quantities of CM regularly, as they were most concerned that her CM allergy could progress to anaphylaxis, and an oral food challenge (OFC) was arranged. The parents decided to give her 1 to 2 tbsp of homogenized milk, 3 to 4 times weekly, with the development of isolated, self-resolving, perioral urticaria and oral pruritus. At the OFC 3 months later, her SPT increased to 20 × 6 mm, with an ssIgE of 1.49 kU/L. She successfully tolerated the CM OFC to a target of 120 mL, with only mild, self-resolving oral pruritus.

We hypothesized that this patient would be desensitized to CM through regular ingestion at home over several months, similar to what would be done in OIT. Although her reaction at OFC was mild, she was advised to continue to ingest small amounts of CM daily (small cube of cheese, 2-3 tbsp of yogurt) to maintain tolerance and prevent the potential development of more severe reactions, such as anaphylaxis, while reducing the risk of EoE exacerbation by not having full servings. She remained asymptomatic from an EoE perspective, and although repeat endoscopy 6 months after the OFC was macroscopically normal, microscopically there was evidence of worsening EoE, with >100 eosinophils/hpf in all areas of the esophagus. The family preferred to keep CM in her diet to avoid the risk of developing anaphylaxis. Although swallowed topical corticosteroids were recommended, the parents declined medical treatment, and wished to monitor clinically given her lack of symptoms. She is currently asymptomatic and awaiting another repeat endoscopy. The family will only agree to topical corticosteroid if her counts continue to worsen even further.

Although cases of IgE-mediated allergy to CM after elimination for the treatment of EoE have been reported,^{5,6} this is the first case in which the patient was subsequently successfully desensitized to milk through intentional milk exposure. We propose a continuum of immune responses to CM (Figure 1), with shifting phenotypes from anaphylactic IgE-mediated allergy (when strictly avoiding CM) to EoE (when regularly ingesting CM), with the ideal of finding a balance where patients can ingest small amounts of CM to prevent anaphylaxis, while maintaining histologic remission and preventing complications from EoE. Although our patient remained asymptomatic from an EoE perspective, she developed histologic worsening of her EoE while ingesting minimal CM.

Previously, EoE development while on OIT has been an absolute contraindication for continuation of OIT.⁷ When CM allergy develops as a consequence of CM elimination for EoE, we

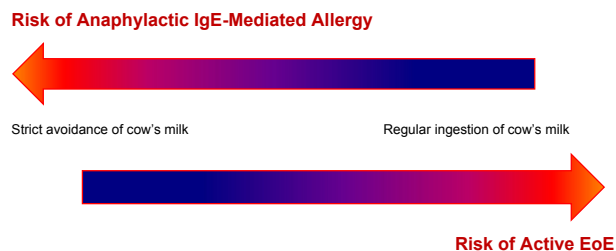


FIGURE 1. Proposed continuum of immune responses to cow's milk with shifting phenotypes from potentially anaphylactic IgE-mediated allergy (when strictly avoiding milk) to EoE (when regularly ingesting milk). *EoE*, Eosinophilic esophagitis.

propose that OIT may be considered, if the patient/parent prefers the outcome of worsened EoE (and possible need for alternative EoE treatment) over the risk of anaphylaxis. It has been reported that liberalized CM elimination, where patients continue to eat “may-contain milk” and baked milk goods, results in histologic remission in 29% of children versus 67% ($P = .099$) of children through strict elimination.⁸ Our patient had a significant decrease in esophageal eosinophilia using the liberalized approach, but achieved further improvement with strict elimination. It is unclear whether maintaining baked CM in the diet could have prevented the development of IgE-mediated milk allergy. It has recently been reported that 38.2% of patients with CM allergy had evidence of esophageal eosinophilia, the majority of which were asymptomatic, further outlining the overlap between EoE and IgE-mediated CM allergy.⁹

In summary, we report a unique case of IgE-mediated CMA in a 4-year-old after CM elimination for EoE, with successful desensitization through intentional milk exposure. This case highlights the importance of weighing potential risks and benefits of elimination diets, particularly in atopic children at higher risk of developing IgE-mediated food allergy. This case suggests that perhaps OIT could be indicated in patients who develop IgE-mediated allergy after an elimination diet if the patient/parent prefers the outcome of worsened EoE (and possible need for alternative treatment with swallowed topical corticosteroids) over the risk of anaphylactic allergy. Other benefits and risks of consuming milk in this setting should be thoroughly discussed with families, including the benefit of improved growth, the risk of topical corticosteroids being ineffective, and the risk of stricture. Further research is needed to evaluate whether it is possible to find an optimal amount of ingestion that can prevent the development of anaphylactic IgE-mediated allergy, while maintaining control of EoE.

Informed consent was obtained from the patient's mother for this publication.

^aDivision of Allergy and Immunology, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada

^bDivision of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada

^cDivision of Allergy and Immunology, Department of Internal Medicine, University of Western Ontario, London, ON, Canada

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Conflicts of interest: E. S. Chan is a member of the committee for the American Gastroenterological Institute and American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Joint Task Force guidelines on the management of eosinophilic esophagitis. He has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Padiapharm, Leo Pharma, and Kaleo; is a member of the scientific advisory board for Food Allergy Canada; and was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention. V. Avinashi has been a member of an advisory board for Avir Pharma Inc. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Stephanie C. Erdle, MD, FRCPC, Division of Allergy and Immunology, Department of Pediatrics, The University of British Columbia, BC Children's Hospital, 4480 Oak St, Vancouver, BC V6H 3V4, Canada. E-mail: Stephanie.erdle@cw.bc.ca.

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