

Baked Milk- and Egg-Containing Diet in the Management of Milk and Egg Allergy

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Stephanie A. Leonard, MD, Jean-Christoph Caubet, MD, Jennifer S. Kim, MD, Marion Groetch, RN, and Anna Nowak-Węgrzyn, MD

Activity Objectives

1. To discuss the rationale for inclusion of egg- or milk-containing baked goods in the diets of children with milk and egg allergy.
2. To identify indications for oral food challenge (baked milk/egg) in the clinical office setting and counsel patients post-challenge.

Recognition of Commercial Support: This CME has not received external commercial support.

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Cow's milk (CM) and hen's egg allergies are among the most common food allergies in children. With evidence of increasing food allergy prevalence and more persistent disease, it has become vital to improve the management of CM and egg allergies. The ability to tolerate baked milk or egg, such as in a cake or muffin, has been associated with an increased chance of tolerance development. Studies report that about 70% of CM- and egg-allergic children can tolerate baked milk or egg and that

incorporating baked milk or egg into the diet is well tolerated. Being able to add baked milk or egg into the diet can also increase quality of life by expanding the diet, boosting nutrition, and promoting inclusion in social activities. There is some debate over how baked milk and egg should be introduced, at home or in a supervised setting. Anaphylaxis and treatment with epinephrine during baked milk or egg challenges have been reported. Study of potential biomarkers to predict tolerability of

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Abbreviations used

CM- Cow's milk
EoE- Eosinophilic esophagitis
EW- Egg white
GM- Goat's milk
OIT- Oral immunotherapy
OFC- Oral food challenge
OM- Ovomucoid
OVA- Ovalbumin
SM- Sheep's milk
SPT- Skin prick test

baked milk and egg, such as serum specific IgE levels and skin prick test wheal diameters, is ongoing. Many parents can reliably report that their CM- or egg-allergic child is already consuming baked goods without symptoms. However, for those who cannot report such tolerance, the most prudent approach is to perform a supervised oral food challenge to determine the tolerability of baked milk and egg. The purpose of this article was to review the pathophysiology, clinical data, and safety of baked milk and egg and provide a practical guide to managing CM allergy and/or egg allergy. Recipes for baked milk and egg challenges and guidance on how to add baked milk and egg if tolerated to the child's regular diet are provided. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:13-23)

Key words: Cow's milk allergy; hen's egg allergy; baked milk; baked egg; extensively heated milk; extensively heated egg

Cow's milk (CM) and hen's egg allergies are among the most common food allergies in children. The US National Health and Nutrition Examination Survey reported clinical CM and egg allergy at 1.8% in children aged 1 to 5 years.¹ A study performed in Australia that included oral food challenges (OFCs) reported an even higher prevalence of raw egg allergy at 8.9% in 1-year-olds.² Overall, estimates of prevalence in children range from 0.4% to 2.0% for egg allergy and 0.5% to 3.8% for CM allergy.^{3,4} Evidence from multiple studies supports an increasing prevalence of food allergy in childhood.⁵

The prognosis of CM and egg allergy is favorable, with about 80% of children eventually becoming tolerant. Population-based and prospective studies show most of the CM- or egg-allergic children achieving tolerance by school age.⁶⁻¹⁰ However, retrospective studies from tertiary care centers that have populations with more severe phenotypes suggest that for many children CM or egg tolerance may not occur until late childhood or adolescence.¹¹⁻¹⁴ Predictors of CM allergy persistence included higher specific IgE levels, increased binding to casein, larger skin prick test (SPT) wheal, early age of onset, and concurrent atopic diseases.^{11,14-17} Predictors of egg allergy persistence included higher egg white (EW)-specific IgE levels, increased binding to ovomucoid (OM), more severe symptoms during initial reaction, a history of other food allergies, and concurrent atopic diseases.^{12,16,18} In addition, the rate of tolerance development in food allergy appears to slow down with age.^{6,18}

Recent prospective multicenter observational studies from the Consortium of Food Allergy Research examined a population of infants with CM and egg allergy. Diagnosis of CM and egg allergy was determined by having a positive physician-supervised

OFC, or a convincing immediate-type allergic reaction confirmed by positive testing, defined as a specific IgE level of 0.35 kU_A/L or more and/or SPT wheal diameter 3 mm greater than that of the negative control, or moderate-to-severe eczema and positive testing, defined as milk-specific IgE level of more than 5 kU_A/L or egg-specific IgE level of more than 2 kU_A/L, the diagnostic decision points with the 95% positive predictive values for infants. Results indicated that 154 of 293 (52.6%) children in the CM-allergic cohort became tolerant at a median age of 5.3 years (median age of follow-up, 5.5 years).¹⁷ Within the egg-allergic cohort, 105 of 213 (49.3%) children became tolerant at a median age of 6 years (median age of follow-up, 6.2 years).¹⁹ These data are consistent with the average age of resolution among previous studies and may represent a referral population with regular evaluation. In these studies, the ability to tolerate baked milk or egg was associated with an increased chance of tolerance development.^{17,19}

With evidence of increasing food allergy prevalence and more persistent disease, it has become vital to improve the management of CM and egg allergies. Previous standard of care often included advice to avoid all forms of CM or egg, despite historical nonreactivity with such foods, in an effort to prevent unpredictable reactions and clear immunologic memory.²⁰ However, recent studies have reported that about 70% of CM- and egg-allergic children can tolerate baked milk or egg.^{21,22} Data support that incorporating baked milk or egg into the diet is well tolerated and may decrease the time to tolerability of regular milk or egg, thus helping children outgrow their CM or egg allergy sooner.²³⁻²⁶ Being able to add baked milk or egg to the diet can also increase quality of life by expanding the diet, boosting nutrition, and promoting inclusion in social activities, such as birthday celebrations. The purpose of this article was to review the pathophysiology, clinical data, and safety of baked milk and egg and provide a practical guide to managing CM allergy and/or egg allergy. For the purposes of this article, baked milk and egg will pertain to extensively heated foods such as bread, muffins, cakes, cupcakes, cookies, and brownies.

EFFECTS OF HIGH TEMPERATURE ON IgE BINDING AND ALLERGENICITY OF CM AND EW PROTEINS

It is well known that cooking and/or processing can change the protein structure of food, which, in turn, alters recognition by the immune system. Heat can denature conformational epitopes, making them no longer recognizable by the epitope-specific IgE. This process of making proteins less allergenic is known to occur with extensively heating milk or egg.²⁷ Alternatively, heating can strengthen certain protein bonds or create neo-epitopes, such as when amino acids react with aldehyde or ketone groups on sugars (glycation) in enzymatic browning or roasting known as the Maillard reaction. This process of making proteins more allergenic is known to occur when roasting peanuts or cooking shellfish.²⁷ Peanut protein component Ara h2 forms aggregates during this reaction that are harder to digest and more easily recognized by epitope-specific IgE.

The predominant protein in EW, ovalbumin (OVA), is a conformational epitope and heat labile, whereas the other major allergen, OM, is a sequential epitope and heat resistant, making OM potentially more allergenic. The whey proteins in CM, such as alpha-lactalbumin and beta-lactoglobulin, contain conformational epitopes that are heat labile (significantly reduced after 20

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