Mammalian milk allergy: avoidance strategies and oral desensitization

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Purpose of review

To address what is currently the most significant, fundamental question in the management of milk-allergic patients: is the best pathway to developing tolerance to milk via complete avoidance or by regular intentional exposure to the offending agent?

Recent findings

The current standard of care for the management of milk-allergic patients, and food-allergic patients in general, remains avoidance of suspected allergens. However, there is growing evidence that regular oral exposure to gradually increasing amounts of an allergenic food can lead to a desensitized state in most food-allergic children. A limited number of studies have attempted to demonstrate permanent tolerance induction. In those cases, a minority of participants has achieved this. Mechanisms of action have not been extensively evaluated, but when serologic studies have been reported, changes have been similar to those seen with standard subcutaneous immunotherapy. That is, food-specific IgE is typically unchanged or slightly decreased, whereas food-specific IgG4 increases substantially.

Summary

Consumption of extensively heated cow's milk and treatment with orally or sublingually administered milk immunotherapy are promising therapeutic approaches. It remains to be determined whether or not the majority of milk-allergic patients can be permanently tolerized through these methods and what the mechanisms of action are for both desensitization and tolerization.

Keywords

avoidance, cow's milk allergy, desensitization, food allergy, oral immunotherapy

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Introduction

The importance of mammalian milk in the human diet cannot be understated. During the first several months of life, breast milk or various types of cow's milk-based formulas are the sole source of nutrition. Throughout the rest of life, the typical human diet often includes concentrated forms of cow's milk and almost universally includes cow's milk as an ingredient in many foods. Therefore, as we face young children with cow's milk allergy (CMA), with many cases persisting later into life, strategies for how to best manage the issue become increasingly relevant. The standard of care for management has been, and remains, patient education on avoiding allergens and developing a plan for recognizing and treating allergic reactions.

However, it is now more than 20 years since early reports of orally desensitizing patients first began to appear [1]. Although much remains to be determined with this type of treatment, there are a rapidly expanding number of studies utilizing variations of the basic approach. In this review, we discuss the data supporting avoidance as a strategy and the progress that has been made with oral desensitization. Table 1 [2,3•,4,5•,6••,7,8] summarizes the recent studies involving desensitization.

Avoidance

The complete avoidance of even minute exposures to known allergens has been the long-standing cornerstone principle in the management of food allergy. This has been thought to serve two purposes: reduction in the number of allergic reactions a patient experiences over time and the best pathway to both primary prevention of food allergy and the resolution of established food allergy. Some recent data have challenged this idea, instead attempting to incorporate small, extensively heated food proteins into the diets of allergic individuals. This new approach is discussed within the context of avoidance, as it still involves continued avoidance of exposure to concentrated, unaltered forms of the protein. However, this is clearly in a 'gray area' between an alternative avoidance strategy and an oral immunotherapy (OIT) strategy.

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Table 1 Recent oral and sublingual immunotherapy trials

Author, year	Food(s)	Maintenance dose	Duration of therapy (months)	Control group	Desensitization success rate	Tolerance success rate	Dropouts
Oral immunotherapy							
Buchanan *et al.* [2]	Egg	400 mg	24	No	7/7	2/7	0
Longo *et al.* [3•]	Milk	165–5000 mg	12	Untreated	27/30	Not tested	3
Patriarca *et al.* [4]	Milk	4290 mg	6–8	No	12/18	Not tested	6
	Egg	One egg	5–8		10/14		3
	Codfish	100 g	5–10		9/9		1
Skripak *et al.* [5•]	Milk	500 mg	5–8	Placebo	12/13 treated; 0/7 placebo	Not tested	1
Staden *et al.* [6••]	Milk	3300–8250 mg	18–24	Untreated	16/25	9/25 treated (7/20 untreated)	9
	Egg	1600–2800 mg					
Zapatero *et al.* [7]	Milk	1320–8250 mg	8–12	No	16/18		2
Sublingual immunotherapy							
Enrique *et al.* [8]	Hazelnut extract	66.25 mg	2	Placebo	9/11 treated; 2/11 placebo	Not tested	0

Complete avoidance

Unfortunately, investigation of both maternal and infant avoidance of allergens has yielded varying results. It is clear that in a substantial number of women, various dietary proteins, including cow's milk proteins, are excreted in breast milk [9•,10,11]. It has also been demonstrated that exclusively breast-fed infants can develop symptoms as a direct result of certain foods in the maternal diet [12]. However, even maternal avoidance of allergen does not ensure the absence of that protein in breast milk [13]. Lastly, it is unclear whether maternal avoidance of specific allergens during pregnancy, lactation, or both has any benefit in preventing or treating atopic disease [14]. Therefore, there essentially is no consistent or highly convincing evidence as to whether maternal food avoidance has a potential benefit to infants at high risk of atopy.

Infants prone to atopy who are formula-fed from birth do appear to benefit from certain dietary strategies. Infants fed hydrolyzed formulas have a reduced risk of developing CMA than those fed cow's milk formula [15]. However, the same does not appear to be true when comparing soy formula with cow's milk formula [16]. As diets exclusive for either hydrolyzed or soy formula should both constitute avoidance of whole cow's milk protein, it is unclear why one should provide protection against CMA but not the other.

Another less common avoidance strategy is the use of milk from nonbovine, nonhuman mammalian milk. Goat's milk [17–19], deer's milk [20,21], and buffalo's milk [19,21] have all shown significant cross-reactivity with cow's milk by various measurements, including skin prick test (SPT), inhibition assays, and oral food challenges in cow's milk-allergic children. On the contrary, donkey's milk [18,22], mare's milk [23], pig's milk [21], and camel's milk [19,21] have exhibited low cross-reactivity potential either immunologically, clinically, or both. No study has evaluated these noncross-reactive mammalian milks for the prevention of CMA. Therefore, there are several mammalian sources of milk with no, or low, potential for cross-reactivity with cow's milk that could represent viable approaches to avoid cow's milk. Overall though, it certainly seems that availability and cost factors weigh heavily in favor of hydrolyzed formulas in developed countries.

Partial avoidance: consuming extensively heated protein

IgE repertoires for sequential versus conformational epitopes vary among cow's milk-allergic individuals [24]. Therefore, some milk-allergic individuals (especially those who predominately recognize cow's milk protein 'conformational' epitopes) may be more likely to tolerate extensively heated milk protein. This hypothesis was recently tested by Nowak-Wegrzyn *et al.* [25••] in a prospective clinical trial. Milk-allergic participants who reacted during oral food challenges to unheated milk, but not to extensively heated (baked) milk, were continued on foods containing baked milk for 3 months. Smaller baseline milk SPT wheal diameter and lower milk-specific IgE levels were predictive of tolerating baked milk. However, there were individuals with large milk SPT wheals and very high milk-specific IgEs who tolerated the baked milk. After 3 months, there was a small but statistically significant decrease in the median milk SPT wheal diameter and increase in casein-specific IgG4. There were no serious acute reactions reported. Only one individual reported oral pruritis with homemade milk-containing baked goods, which resolved when more extensive baking was undertaken.

These findings are interesting and significant for three reasons. First, this change from a milk-avoidance diet to a milk-limited diet could provide a substantial improvement

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in the quality of life of milk-allergic individuals. Second, the frequency of prolonged or permanent milk allergy may be reduced if this type of diet can augment the development of tolerance. Third, these children receiving limited, extensively heated milk essentially reported no acute milk-induced allergic reactions as a result of this diet. Taking these factors together, it is reasonable to believe that at least a subset of individuals allergic to certain heat-labile foods may benefit from this vastly altered approach to food allergy management.

It has been demonstrated that some egg proteins can exhibit reduced allergenicity after heating [26], and a majority of individuals who react to egg may be able to tolerate baked egg [27]. A recent study by Lemon-Mule *et al.* [28••] found that three-fourths of children with probable egg allergies were able to tolerate extensively heated egg (muffins and waffles). Although smaller egg SPT wheal diameter and lower egg-specific IgE at baseline predicted higher likelihood of tolerating heated egg, even some individuals with very high egg-specific IgE tolerated heated egg. Those who tolerated the heated egg challenge were continued on heated egg in their diets for 1 year, with no reports of acute reactions during that time. There was only one dropout for parental concerns of egg-related symptoms (subjectively increased eczema). Immunologic markers followed over the study period showed a statistically significant decrease in egg SPT wheal diameter and ovalbumin-specific IgE levels and increased ovalbumin-specific and ovomucoid-specific IgG4 levels. These are changes typically seen with successful immunotherapy, so this may indicate that the immunologic changes may be ones of progression toward tolerance to egg.

The findings in this study seem to confirm those of Nowak-Wegrzyn *et al.* [25••] in that there is a subset of egg-allergic patients who can consume limited amounts of extensively heated egg protein on a regular basis with a very low likelihood of experiencing a serious acute allergic reaction. More data are needed though, to determine the long-term safety and efficacy of this approach.

Oral desensitization

The natural history of milk allergy has typically been described as one with a good prognosis for the natural development of tolerance [29,30]. However, no birth or early life cohort studies have followed those with persistent milk allergy beyond the first few years of life. Studies that have followed milk-allergic children beyond the first few years of life demonstrate that a significant percentage of them fail to develop tolerance [31,32]. It is this group who appears to be in need of a therapeutic intervention that can promote the development of tolerance to cow's milk.

The initial attempts to treat food-allergic individuals with a subcutaneously injected dose of the allergen exhibited some efficacy in desensitizing but resulted in numerous severe adverse reactions [33,34]. Since then, desensitization via the oral or sublingual route has become preferred. There have been variations on how best to approach this.

Oral desensitization

Although there are many variations in the approaches to oral desensitization, the unifying feature is the delivery of a gradually increasing amount of a known allergenic food via the gastrointestinal route. In the last few years, experience with food-specific OIT [2,3•,4,5•,6••,7,35–38,39•, 40–42,43•] and sublingual immunotherapy (SLIT) [8,41,44,45] has increased significantly. Many of these trials have included treatment for CMA [3•,4,5•,6••,7,38, 39•,40,41,43•,44].

Although both are orally administered, OIT and SLIT should still be considered separately. No studies have compared the two from a mechanistic standpoint. Only one study involving grass pollen treatment has compared them from a clinical standpoint [46].

Oral immunotherapy

Prior to multiple publications in the past 2 years, studies of OIT periodically appeared over the past two-plus decades [1,37,42,47–51]. These studies established that the process of desensitization to several major food allergens is possible and generally well tolerated in multiple patients over several trials, and it often results in a decrease in food-specific IgE, SPT wheal size, or both, along with an increase in food-specific IgG4, over time. However, these previous studies usually lacked controls for comparison, and none attempted to remove the food from the diet temporarily after treatment.

Staden *et al.* [6••] published a controlled trial of OIT in 2007. This was one of the first trials to include a period of avoidance 'after' treatment. This study included 45 children allergic to milk or egg, with 25 randomized to the treatment group and 20 to the untreated control group. They underwent a dose escalation up to a maintenance dose of 3–8 g of milk protein or 1.5–3 g of egg protein for 18–24 months. Treatment was generally well tolerated, although adverse effects occurred during the dose-escalation phase and the maintenance phase. These reactions were considered mild (e.g. single hives, oral tingling, nausea, or worsening eczema) in most (84%) of the participants, whereas the other four experienced moderate reactions requiring treatment with antihistamines and steroids but not with epinephrine. Various factors such as exercise, development of respiratory tract infections, or significant pollen exposure were associated

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with increased adverse reactions. Overall, 16 participants (64%) were able to tolerate some maintenance dose. After completion of OIT, a 2-month period of allergen avoidance was undertaken, and nine of 25 (36%) children remained nonreactive (tolerant) to egg or milk as confirmed by oral food challenges. Interestingly, 35% of the untreated control group also became tolerant, as determined by oral food challenge, over the same time period. The fact that about one-third of treated 'and' untreated patients were tolerant at the end of the study places the potential for this type of treatment to induce permanent tolerance at question.

The first blinded, placebo-controlled trial also demonstrated that most milk-allergic children could be desensitized with this type of treatment [5•]. In this study, 12 of 13 milk-treated patients were able to tolerate the 500 mg maintenance dose for 3–4 months. Only one patient could not tolerate the build-up because of persistent eczema. This was a higher frequency reaching maintenance when compared with the study by Staden *et al.* [6••], but the maintenance dose was much lower in this study (500 compared with 3300 mg). The change in threshold for reactivity to milk was substantial, increasing from a median of 40 mg before treatment to 5140 mg after treatment. The placebo group exhibited no change, with a 40 mg threshold before and after treatment. One significant difference in safety from the study by Staden *et al.* [6••] was the need for epinephrine to treat four dose-related allergic reactions. There was no period of milk avoidance after treatment to assess these children for long-term tolerance.

Once children in desensitization protocols complete treatment, those who tolerated the treatment presumably continue to ingest milk-containing products in the majority of cases. One prior milk desensitization study [48] resulted in 18 of 21 participants tolerating large amounts ($n = 15$) or at least small amounts ($n = 3$) of milk. A long-term follow-up of these patients revealed that 14 of 20 still completely ($n = 13$) or partially ($n = 1$) tolerated cow's milk [39•]. One was lost to follow-up. None of those who continued to consume dairy products had experienced any acute allergic reaction. (However, in a follow-up of the Skripak *et al.* [5•] study by Narisety *et al.* [52], all participants experienced at least some allergic reactions, and some were even severe.) Reasons for discontinuing milk consumption in the others who had previously tolerated it ranged from clear milk-induced reactions such as acute urticaria (on milk reintroduction after a period of avoidance) to likely unrelated problems such as chronic rhinitis. No severe reactions were reported in this group who discontinued dairy either.

The last recent study to highlight is that of a different approach to the dose-increase phase [43•]. In this study, six of nine milk-allergic children were able to tolerate a rapid escalation of milk doses to a maximum of 120 ml in 3–7 days. They were all continued at home on 100 ml of milk daily. The other three participants were discharged to home after 1 week with some substantially lower amount of milk to be consumed daily (3–40 ml). No epinephrine was required for the treatment of side effects.

Sublingual immunotherapy

Despite extensive study of sublingual pollen immunotherapy in Europe, data for milk SLIT, or for any foods in general, are extremely limited. Enrique *et al.* [8] reported a placebo-controlled trial of treatment with a hazelnut extract in 2005 that was effective in increasing the average hazelnut dose-eliciting symptoms. The safety profile was quite good. Only 0.2% of SLIT doses resulted in systemic reactions, with all of these controlled by treatment with an antihistamine.

The only study [43•] on treating milk-allergic patients sublingually involved eight patients aged 6 years or older with IgE-mediated CMA. All eight reacted at a baseline oral milk challenge, with a mean eliciting dose for objective symptoms of 39 ml (range 4–106 ml). The children were treated with 0.1 ml SLIT daily initially, building up to 1 ml daily and continued for 6 months. One dropped out because of oral symptoms, whereas the remaining seven completed the treatment course and underwent posttreatment milk challenges. The mean eliciting dose after treatment was 143 ml (range 44 to >200 ml), with three of these children experiencing no reaction.

Although SLIT has had limited study in food-allergic children, these few reports seem to warrant further investigation. If in fact this route achieves efficacy outcomes comparable to those seen with OIT, it may be a much better option because of the likely lower rate of systemic reactions occurring with the significantly lower doses.

Conclusion

Although there has clearly been building interest and excitement with oral desensitization in recent years, much remains to be done. At the current time, multiple questions and concerns remain regarding food-specific immunotherapy. Although the pursuit for answers to these questions continues, it is clearly in the best interest of milk-allergic patients to continue the routine clinical approach of avoidance counseling. The possibility that a subset of milk-allergic patients can practice partial avoidance while consuming extensively heated milk-containing foods appears likely. Future directions in the study of food-specific immunotherapy must further emphasize the issues of tolerance versus desensitization, identifying characteristics predictive of 'susceptibility' to tolerance

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induction, optimal route and dose for delivery, and finally, whether adjunctive treatments can increase the safety and efficacy of this approach.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1 Patriarca C, Romano A, Venuti A, *et al.* Oral specific hyposensitization in the management of patients allergic to food. Allergol Immunopathol (Madr) 1984; 12:275–281.

2 Buchanan AD, Green TD, Jones SM, *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol 2007; 119:199–205.
In this study, all seven participants were desensitized to egg, with four of the seven showing no reaction during egg oral food challenge. However, when these four restricted egg again for 3–4 months, two of them reacted again at subsequent egg challenges.

3 • Longo G, Barbi E, Berti I, *et al.* Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008; 121:343–347.
This study showed that milk desensitization could be used successfully in many milk-allergic individuals with very high milk-specific IgE levels.

4 Patriarca G, Nucera E, Pollastrini E, *et al.* Oral specific desensitization in food-allergic children. Dig Dis Sci 2007; 52:1662–1672.

5 • Skripak JM, Nash SD, Rowley H, *et al.* A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008; 122:1154–1160.
This study demonstrated that when compared with placebo, milk OIT was capable of desensitizing all participants to varying degrees.

6 •• Staden U, Rolinck-Werninghaus C, Brewe F, *et al.* Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy 2007; 62:1261–1269.
This studied confirmed the findings of Burks and Jones [35] that despite successful desensitization, many patients redeveloped allergic reactions to milk or egg after a period of avoidance.

7 Zapatero L, Alonso E, Fuentes V, *et al.* Oral desensitization in children with cow's milk allergy. J Investig Allergol Clin Immunol 2008; 18:389–396.

8 Enrique E, Pineda F, Malek T, *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 2005; 116:1073–1079.

9 • Palmer DJ, Gold MS, Makrides M. Effect of maternal egg consumption on breast milk ovalbumin concentration. Clin Exp Allergy 2008; 38:1186–1191.
Ovalbumin was detected in the breast milk of only three-fourths of mothers who regularly consumed egg-containing muffins.

10 Sorva R, Makinen-Kiljunen S, Juntunen-Backman K. Beta-lactoglobulin secretion in human milk varies widely after cow's milk ingestion in mothers of infants with cow's milk allergy. J Allergy Clin Immunol 1994; 93:787–792.

11 Vadas P, Wai Y, Burks W, *et al.* Detection of peanut allergens in breast milk of lactating women. JAMA 2001; 285:1746–1748.

12 Jarvinen KM, Makinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. J Pediatr 1999; 135:506–512.

13 Vance GH, Lewis SA, Grimshaw KE, *et al.* Exposure of the fetus and infant to hens' egg ovalbumin via the placenta and breast milk in relation to maternal intake of dietary egg. Clin Exp Allergy 2005; 35:1318–1326.

14 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 2006:CD000133.

15 Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006:CD003664.

16 Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006:CD003741.

17 Bellioni-Businco B, Paganelli R, Lucenti P, *et al.* Allergenicity of goat's milk in children with cow's milk allergy. J Allergy Clin Immunol 1999; 103:1191–1194.

18 Vita D, Passalacqua G, Di Pasquale G, *et al.* Ass's milk in children with atopic dermatitis and cow's milk allergy: crossover comparison with goat's milk. Pediatr Allergy Immunol 2007; 18:594–598.

19 Restani P, Gaiaschi A, Plebani A, *et al.* Cross-reactivity between milk proteins from different animal species. Clin Exp Allergy 1999; 29:997–1004.

20 Suutari TJ, Valkonen KH, Karttunen TJ, *et al.* IgE cross reactivity between reindeer and bovine milk beta-lactoglobulins in cow's milk allergic patients. J Investig Allergol Clin Immunol 2006; 16:296–302.

21 Katz Y, Goldberg MR, Zadik-Mnuhin G, *et al.* Cross-sensitization between milk proteins: reactivity to a 'kosher' epitope? Isr Med Assoc J 2008; 10:85–88.

22 Monti G, Bertino E, Muratore MC, *et al.* Efficacy of donkey's milk in treating highly problematic cow's milk allergic children: an in vivo and in vitro study. Pediatr Allergy Immunol 2007; 18:258–264.

23 Businco L, Giampietro PG, Lucenti P, *et al.* Allergenicity of mare's milk in children with cow's milk allergy. J Allergy Clin Immunol 2000; 105:1031–1034.

24 Vila L, Beyer K, Jarvinen KM, *et al.* Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. Clin Exp Allergy 2001; 31:1599–1606.

25 •• Nowak-Wegrzyn A, Bloom KA, Sicherer SH, *et al.* Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol 2008; 122:342–347; 347.e1–347.e2.
This study found that a substantial proportion of children with milk allergy could tolerate extensively heated milk. With continued heated milk ingestion for 3 months, small decreases in milk SPT wheal diameter and increases in casein-specific IgG4 were seen.

26 Joo K, Kato Y. Assessment of allergenic activity of a heat-coagulated ovalbumin after in vivo digestion. Biosci Biotechnol Biochem 2006; 70:591–597.

27 Des Roches A, Nguyen M, Paradis L, *et al.* Tolerance to cooked egg in an egg allergic population. Allergy 2006; 61:900–901.

28 •• Lemon-Mule H, Sampson HA, Sicherer SH, *et al.* Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol 2008; 122:977–983.e1.
This study's findings showed that a substantial proportion of children with egg allergy could tolerate extensively heated forms of egg. With continued heated egg ingestion for 3 months, small decreases in egg SPT diameter and ovalbumin-specific IgE and increases in ovalbumin-specific and ovomucoid-specific IgG4 were seen.

29 Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. Pediatrics 1987; 79:683–688.

30 Host A, Jacobsen HP, Halken S, *et al.* The natural history of cow's milk protein allergy/intolerance. Eur J Clin Nutr 1995; 49 (Suppl 1):S13–S18.

31 Saarinen KM, Pelkonen AS, Makela MJ, *et al.* Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol 2005; 116:869–875.

32 Skripak JM, Matsui EC, Mudd K, *et al.* The natural history of IgE-mediated cow's milk allergy. J Allergy Clin Immunol 2007; 120:1172–1177.

33 Nelson HS, Lahr J, Rule R, *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997; 99:744–751.

34 Oppenheimer JJ, Nelson HS, Bock SA, *et al.* Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992; 90:256–262.

35 Burks AW, Jones SM. Egg oral immunotherapy in nonanaphylactic children with egg allergy: follow-up. J Allergy Clin Immunol 2008; 121:270–271.

36 Calvani M, Sopo SM. Exercise-induced anaphylaxis caused by wheat during specific oral tolerance induction. Ann Allergy Asthma Immunol 2007; 98:98–99.

37 Mansfield L. Successful oral desensitization for systemic peanut allergy. Ann Allergy Asthma Immunol 2006; 97:266–267.

38 Martorell Aragones A, Felix Toledo R, Cerda Mir JC, *et al.* Oral rush desensitization to cow milk: following of desensitized patients during three years. Allergol Immunopathol (Madr) 2007; 35:174–176.

39 • Meglio P, Giampietro PG, Gianni S, *et al.* Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy: follow-up at 4 yr and 8 months. Pediatr Allergy Immunol 2008; 19:412–419.
Children who were previously treated with an oral milk desensitization protocol were followed up 4–5 years later. The majority of those who were successfully desensitized initially continued to tolerate cow's milk at follow-up. Compared with baseline measurements, there were more participants with negative milk SPT, and on average, casein and alpha-lactalbumin IgE levels were decreased.

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40 Morisset M, Moneret-Vautrin DA, Guenard L, *et al.* Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases: a randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol 2007; 39:12–19.

41 Nucera E, Schiavino D, Buonomo A, *et al.* Sublingual-oral rush desensitization to mixed cow and sheep milk: a case report. J Investig Allergol Clin Immunol 2008; 18:219–222.

42 Patriarca G, Nucera E, Pollastrini E, *et al.* Oral rush desensitization in peanut allergy: a case report. Dig Dis Sci 2006; 51:471–473.

43 Staden U, Blumchen K, Blankenstein N, *et al.* Rush oral immunotherapy in • children with persistent cow's milk allergy. J Allergy Clin Immunol 2008; 122:418–419.
In this study, an alternative approach to increasing the milk OIT treatment doses was studied. Children were given multiple dose increases per day over the course of 1 week, with six of nine reaching the minimal goal or more.

44 de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy 2006; 61:1238–1239.

45 Enrique E, Malek T, Pineda F, *et al.* Sublingual immunotherapy for hazelnut food allergy: a follow-up study. Ann Allergy Asthma Immunol 2008; 100:283–284.

46 Panzner P, Petras M, Sykora T, Lesná I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. Respir Med 2008; 102:1296–1304.

47 Bauer A, Ekanayake Mudiyanselage S, Wigger-Alberti W, *et al.* Oral rush desensitization to milk. Allergy 1999; 54:894–895.

48 Meglio P, Bartone E, Plantamura M, *et al.* A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy 2004; 59:980–987.

49 Nucera E, Schiavino D, D'Ambrosio C, *et al.* Immunological aspects of oral desensitization in food allergy. Dig Dis Sci 2000; 45:637–641.

50 Patriarca G, Nucera E, Roncallo C, *et al.* Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther 2003; 17:459–465.

51 Patriarca G, Schiavino D, Nucera E, *et al.* Food allergy in children: results of a standardized protocol for oral desensitization. Hepatogastroenterology 1998; 45:52–58.

52 Narisety SD, Skripak JM, Nash SD, *et al.* Open label maintenance following milk oral immunotherapy (MOIT) for IgE mediated cow's milk allergy [abstract]. J Allergy Clin Immunol 2009; 123:S174.

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