LETTER TO THE EDITOR

Patient selection for milk and egg ladders using a food ladder safety checklist

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Abstract

A food ladder is a form of home-based dietary advancement therapy that gradually increases exposure to an allergenic food through the gradual introduction of egg or milk containing food with increasing quantity and allergenicity from extensively heated forms, such as baked goods, to less processed products. While widely considered safe, the food ladder is not risk-free and most of the egg and milk ladder studies only included preschoolers with mild egg and milk allergies, and with no or well-controlled asthma. We propose a Food Ladder Safety Checklist to assist with patient selection using “4 A’s” based on available evidence for food ladders, including Age, active or poorly controlled Asthma, history of Anaphylaxis, and Adherence.

Keywords: Food ladders, Milk allergy, Egg allergy, Safety

To the Editor,

In May 2021, a young girl in Ontario, Canada, with a history of milk allergy and long-standing asthma, passed away while undergoing a therapy that some have described as a milk ladder, although media reports suggest she did not increase beyond tiny amounts of milk-containing muffin [1, 2]. This tragic incident deeply saddens the allergy community, and underscores the need for careful patient selection and close monitoring of patients undergoing all forms of dietary advancement therapy. This article discusses the benefits, risks, and precautions of food ladders as a form of dietary advancement therapy, as well as how to help our patients and families decide whether ladders are an appropriate treatment option through a shared decision-making process. We propose a Food Ladder Safety Checklist to assist with patient selection.

What is a food ladder?

A food ladder is a form of home-based dietary advancement therapy that gradually increases exposure to an allergenic food. Egg and milk ladders are the two typical forms of food ladders used clinically. The goal of the food ladder is to facilitate the development of natural tolerance through the gradual introduction of egg or milk containing food with increasing quantity and allergenicity through different cooking processes, typically with gradual progression from baked products (e.g., biscuits, muffin), to well-cooked forms (e.g., pancakes, waffles, hard-boiled eggs) and finally to less processed products (e.g., fresh mousse, fresh ice cream) [3]. It has been widely used in Europe and was initially designed to manage non-IgE-mediated food allergies [4, 5]. Subsequently, application of the food ladder has been extrapolated to management of IgE-mediated milk and egg allergy, which has been generally safe and effective [6–8].
What are the benefits and risks of the food ladder?
The primary benefits of home-based treatments such as milk and egg ladders include the demedicalization of food (by providing a structured approach which still allows flexibility in options and pace at which individuals proceed), and reduction in health care utilization. For example, they allow practitioners the ability to allocate limited in-person appointments for oral food challenges and oral immunotherapy to other patients who are too high-risk for home-based treatments. While some practitioners offer a starting dose in the office, home-based therapies typically involve fewer in-office visits. Studies have shown that even home-based oral immunotherapy for IgE-mediated food allergy can be feasible and safe with very carefully selected patients [9, 10], which offers hope for facilitating early commencement of dietary advancement therapy where resources are limited with long waiting times, especially during the COVID-19 pandemic when there were limited non-emergency elective services and lack of regular in-office visits [11, 12].

Ball et al. retrospectively studied 86 children with mild milk allergies who started home-based milk introduction between 8 to 33 months of age; 68 of 86 subjects (79.1%) reached the top of the milk ladder at the two-year mark and two additional subjects tolerated all dairy products at the fourth review. None developed anaphylaxis or required epinephrine autoinjector [6]. Gotesdyner et al. studied 39 children under two years old with mild egg allergy and treated them using a structured graduated exposure protocol, and compared with a matched group of 80 children who were advised to strictly avoid egg at least until two years old or earlier natural resolution and followed to a median age of 69 months. The age of egg allergy resolution in the treatment group was significantly younger than the control group (median age 24 months vs. 78 months, \( p < 0.001 \)), and 82% of children in the treatment group were able to tolerate lightly cooked eggs, versus 54% in the control group (\( p = 0.001 \)) [8].

Thomas et al. retrospectively reviewed 98 children with a median age of 40 months with mild egg allergy and were managed with egg ladder. 43% were managed with an egg ladder over an average of 15.5 months. Only two children had severe reactions, and one required adrenaline; those with severe reactions resumed the ladder and progressed to the last two steps (lightly cooked whole egg or raw egg) successfully. A high proportion (78.7%) of the parents felt satisfied or very satisfied with the egg ladder [7] (Table 1).

Pre-requisites for administering food ladders safely
The food ladder should be administered by well-trained and experienced healthcare professionals with the necessary expertise and experience in food allergy and anaphylaxis management, performance of oral food challenges, and careful selection of patients for food immunotherapy [2]. Patient informed consent should be obtained, and patients should be aware of cofactors that could lower reaction threshold while on any dietary advancement therapy, including febrile illnesses, exercise, hot baths, dosing on an empty stomach, and an increase in total allergen exposure such as dust mite and pollen [23, 24]. Allergists should be readily available to address patient concerns and reactions, and to ensure families are confident and competent at treating anaphylaxis before offering ladders. Allergists should also be aware of conditions where using food ladders as a dietary advancement therapy could be risky and less effective. On-going close follow-up with the allergist administering the food ladders is essential to ensure the safety, ongoing
Table 1  Summary of studies using egg and milk ladders to treat IgE-mediated egg and milk allergy

| Author/Year/Study Type/Ladder | Inclusion criteria | Exclusion criteria | No of subjects in active treatment group | Age | Main outcomes | % of any adverse reactions | Anaphylaxis | Risk factors for anaphylaxis |
|-------------------------------|--------------------|--------------------|-----------------------------------------|-----|---------------|---------------------------|-------------|-----------------------------|
| Ball et al./2019 [6] Retrospective chart review/Milk Ladder | IgE-mediated cow’s milk allergy based on clinical history and positive SPT | - Cow’s milk allergic reactions occurring with trace baked milk ingestion  
- Allergic reactions involving the respiratory or cardiovascular systems  
- History of recurrent wheeze  
- SPT > 8 mm | 86 | Median 13 months (range 8—33 months) | - 68 subjects (79.1%) reached the top of the milk ladder by the two-year mark  
- 2 subjects tolerated all dairy products at the fourth review | 80% | None | N/A |
| Gotesdyner et al./2019 [8] Case Control Study/Egg Ladder | -Children < 2 years old  
-IgE-mediated egg allergy diagnosed by OFC or by positive SPT and/or positive IgE along with a clinical history of an immediate allergic reaction after exposure to cooked or fried eggs in the past year | Children with a history of allergic reaction to baked egg were excluded from the control group | 39 | Median 16 months (IQR: 14—19 months) | - Significantly younger age of allergen resolution in the treatment group than the control group (median age 24 months vs. 78 months, p<0.001)  
- 82% of children in the treatment group were able to tolerate lightly cooked eggs, versus 54% in the control group (p=0.001) | 23% | One patient developed anaphylaxis (rash and vomiting) and EpiPen was given. The protocol was stopped and the child continued with egg avoidance | Not mentioned |
| Thomas et al./2021 [7] Retrospective study/Egg Ladder | - Single food allergy  
- History convincing of IgE-mediated egg allergy  
- Mild or no eczema  
- No or well-controlled asthma  
Written action plan for food allergy management and education provided | History of anaphylaxis to any food containing egg or a non-IgE-mediated egg allergy | 47 | Mean age 40 months (IQR: 12—60 months) | 43% were able to complete the egg ladder over an average of 15.5 months | 59.60% | Two patients had severe reaction (by parent report). One was treated with adrenaline | Not mentioned |

IgE Immunoglobulin E, IQR interquartile range, OFC oral food challenge, SPT skin prick testing
understanding of the procedures and to ensure new unexpected risk factors (e.g. loss of asthma control) have arisen. We propose a Food Ladder Safety Checklist to assist with patient selection using “4 A’s” based on available evidence for food ladders, including Age, active or poorly controlled Asthma, history of Anaphylaxis, and Adherence (Additional file 1). Allergists may decline or delay offering food ladders while optimizing any modifiable factors, such as asthma, or opt for an alternative dietary advancement therapy such as oral immunotherapy (OIT).

**A shared decision-making process to making the most suitable choice**

Shared decision-making (SDM) refers to the process by which patients play an active role in managing their health [25]. It is also a bidirectional conversation that incorporates pros and cons of approaches and integrates patient preferences into decision making. This is different from informed consent, in which patients only agree or disagree with a treatment option. SDM involves three steps: (i) creating choice awareness but providing an unbiased list of options, (ii) discussing options based on clinical relevance and current medical evidence, and (iii) discussing patient preferences, i.e., “what matters most” to the patient. It is essential to clarify goals and expectations of treatment, experience with previous management strategies, and possible fears. In the context of food allergy, it is important that the allergist provides different options to patients and families [25]. For example, if a patient has multiple food allergies, an option of milk or egg OIT instead of ladders could be incorporated as part of a multiple food OIT protocol, which has also been shown to be safe and effective [26]. Ultimately, for patients with identified contraindications such as uncontrolled asthma, or where dose adherence would be unlikely, strict avoidance while carrying an epinephrine autoinjector and future reassessment for spontaneous resolution might be a better option [27].

**Conclusion**

Milk and egg ladders are safe and effective dietary advancement therapies, in patients who have a high likelihood of outgrowing their milk and egg allergies. Nevertheless, any form of dietary advancement therapy carries a risk of allergic reaction, including anaphylaxis, as these patients are still allergic to milk and egg at baseline. Careful attention needs to be paid to proper patient selection and managing allergic comorbidities such as asthma, prior to initiating a milk or egg ladder, and a food ladder safety checklist can assist with patient selection. Despite recent media reports, the risk of death with milk/egg ladders or food immunotherapy in carefully selected patients is extremely remote, and does not exceed the risk of death from avoidance or other forms of allergen immunotherapy such as subcutaneous immunotherapy with Aeroallergens [2].

**Abbreviations**

IgE: Immunoglobulin E; IQR: Interquartile range; OFC: Oral food challenge; OIT: Oral immunotherapy; SDM: Shared decision-making; SPT: Skin prick testing.

**Supplementary Information**

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**Additional file 1.** The food ladder safety checklist.

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**Author contributions**

GTC and ESC drafted the manuscript. JY, SCB, AC, TVL, contributed substantially to the conception of the study. LS, BW, EA, RM critically revised the manuscript. TW supervised and led the study. All authors read and approved the final manuscript and agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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**Ethics approval and consent to participate**

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**Consent for publication**

Not applicable.

**Competing interests**

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