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BSACI 2021 guideline for the management of egg allergy

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Abstract

This guideline advises on the management of patients with egg allergy. Most commonly egg allergy presents in infancy, with a prevalence of approximately 2% in children and 0.1% in adults. A clear clinical history will confirm the diagnosis in most cases. Investigation by measuring egg-specific IgE (by skin prick testing or specific IgE assay) is useful in moderate-severe cases or where there is diagnostic uncertainty. Following an acute allergic reaction, egg avoidance advice should be provided. Egg allergy usually resolves, and reintroduction can be achieved at home if reactions have been mild and there is no asthma. Patients with a history of severe reactions or asthma should have reintroduction guided by a specialist. All children with egg allergy should receive the MMR vaccine. Most adults and children with egg allergy can receive the influenza vaccine in primary care, unless they have had anaphylaxis to egg requiring intensive care support. Yellow Fever vaccines should only be considered in egg-allergic patients under the guidance of an allergy specialist. This guideline was prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) and is intended for allergists and others with a special interest in allergy. The recommendations are evidence based. Where evidence was lacking, consensus was reached by the panel of specialists on the committee. The document encompasses epidemiology, risk factors, diagnosis, treatment, prognosis and co-morbid associations.

KEYWORDS

adrenaline, aetiology, allergy, anaphylaxis, BSACI, diagnosis, egg, epinephrine, food, management, SOCC

1 | INTRODUCTION

One in 50 children present with egg allergy. This is an update of the BSACI guideline for the management of egg allergy.¹ It was prepared by an expert group of the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) and addresses the diagnosis and treatment of patients with egg allergy, for healthcare professionals working in secondary care. It includes guidance for families with egg-allergic children and adult egg-allergic

patients. The guideline working group included paediatric and adult allergists, paediatric and adult allergy specialist dietitians and clinical psychologists working with egg-allergic patients. During development of this guideline, representatives from patient organizations (Allergy UK and Anaphylaxis Campaign) were part of the guideline writing group and involved in selection of topics, evidence, recommendations and draft reviews. Declarations of interest of the guideline lead and the writing group members are held at BSACI office and are available on request. None jeopardized unbiased guideline

Key Message

Grades of recommendation, A-E are based on evidence graded using SIGN criteria (appendix VI)

- Egg allergy is an adverse immunological reaction induced by egg protein. This guideline focuses on type-1 IgE-mediated allergy to egg.
- The prevalence of egg allergy is estimated at approximately 2% in children and 0.1% in adults in the United Kingdom (Grade of recommendation = B).
- Allergic sensitization to egg, without a history of reacting, is common in infancy and should not prevent the introduction of egg into the diet, because this carries a risk of unnecessary dietary exclusion (Grade of recommendation = D).
- Egg allergy presents most commonly in infancy, usually after the first apparent ingestion, with rapid onset of erythema, urticaria, angio-oedema and/or vomiting (Grade of recommendation = B).
- Severe reactions involving respiratory or cardiovascular symptoms, presenting with cough, wheeze, breathing difficulty or pallor and floppiness are uncommon (Grade of recommendation = B).
- The clinical diagnosis is made by the rapid onset of typical symptoms (usually within minutes) after ingestion of egg (Grade of recommendation = B).
- Reaction severity is related to the amount of egg ingested and the degree of cooking, with raw egg white being the most allergenic (Grade of recommendation = D).
- The presence of egg-specific immunoglobulin E (IgE) or positive egg skin prick test (SPT) is useful in the management of moderate-severe cases or where there is diagnostic uncertainty (Grade of recommendation = B).
- The reported level of egg-specific IgE required to support a diagnosis varies between studies. It is not possible to identify a single cut-off value for egg-specific IgE which is 'diagnostic' for egg allergy at all ages (Grade of recommendation = B).
- An egg SPT weal of 3 mm or more in combination with a clinical history is considered adequate to confirm a diagnosis of egg allergy in most cases (Grade of recommendation = B).
- Clinical severity cannot be judged on basis of SPT weal size or serum-specific IgE alone (Grade of recommendation = C).
- In the absence of having a suspected reaction to egg, patients should not routinely be tested for egg allergy (Grade of recommendation = D).
- A food challenge may be necessary to confirm or refute conflicting history and test results but is rarely required in practice to confirm the diagnosis of egg allergy (Grade of recommendation = D).
- Following an acute allergic reaction to egg, egg avoidance advice is the cornerstone of management (Grade of recommendation = D).
- Most infants with egg allergy should continue to breastfeed, with their mother on an unrestricted diet (Grade of recommendation = D).
- Mothers breastfeeding egg-allergic infants may wish to try egg exclusion if their infants have persistent eczema and egg is a trigger, or if the infant is suspected of reacting to maternal egg ingestion (Grade of recommendation = C).
- Referral to a dietician is required if there are multiple food allergies, nutritional concerns or help needed following the reintroduction ladder (Grade of recommendation = D).
- Referral to a dietician is needed for children with severe egg allergy for advice about strict egg avoidance (Grade of recommendation = D).
- Mild egg allergy usually resolves. Attempts to introduce baked egg as an ingredient (e.g. in cake) may be made from the age of 12 months, or 6 months from the last reaction (Grade of recommendation = B).
- Regular ingestion of baked egg may promote tolerance (Grade of recommendation = C).
- Once loosely cooked egg is tolerated, egg allergy is outgrown and egg should be eaten as part of the normal diet (Grade of recommendation = D).
- Resolution occurs gradually over time. Assessment for reintroduction of baked egg in all infants/young children presenting with egg allergy is advised as prolonged total exclusion may lead to more persistent allergy and increases dietary and social exclusion (Grade of recommendation = B).
- Children with mild-moderate symptoms can reintroduce egg at home, starting with baked egg in small amounts (Grade of recommendation = D).
- Children with a history of a severe egg reaction or severe eczema and faltering growth are more likely to have persistent disease and avoidance and reintroduction should be guided by a specialist allergy service (Grade of recommendation = D).

- Early introduction of well-cooked or baked egg into the diet of infants with eczema reduces the incidence of egg allergy (Grade of recommendation = A).
- Egg allergy in infancy is associated with an increased risk of developing peanut allergy. This may be prevented by the early introduction of peanut into the diet (Grade of recommendation = B).
- New onset egg allergy in adults is rare; it is usually more severe and persists (Grade of recommendation = D).
- All children with egg allergy should receive the MMR immunization in primary care (Grade of recommendation = B).
- Children with egg allergy can receive the nasal live attenuated influenza vaccine (LAIV) and most children and adults can receive the intramuscular influenza vaccine in primary care, unless they have had anaphylaxis to egg requiring admission to intensive care (Grade of recommendation = B).
- Yellow Fever vaccines contain detectable, but not quantified amounts of egg protein. If these vaccines are required, the egg-allergic patient should be referred to an allergy specialist with access to a designated yellow fever vaccination centre for assessment and immunization (Grade of recommendation = B).

BOX 1 Which patients with egg allergy should be referred to an allergy clinic

- History of moderate to severe reaction (See Box 4)
- Where there is diagnostic uncertainty
- Egg allergy in association with other IgE mediated food allergies
- Severe eczema in children on an egg-containing diet
- Allergy to baked egg which persists beyond the common age of resolution (6-7 years).
- Adult-onset egg allergy
- Egg allergy with requirement for yellow fever immunisation
- Any child wishing to reintroduce egg but unable due to high anxiety.
- Egg allergic patients on biologics and immunosuppressants

development. Evidence for the recommendations was obtained from electronic literature searches of Medline/PubMed, NICE and the Cochrane library to 07/12/19 using the following strategy and keywords—(allergy OR skin prick test OR anaphylaxis OR contraindications OR immediate adverse reactions) AND (egg OR lecithin OR ovalbumin). The strategy and search results are outlined in Appendix S5. The expert knowledge of the specialist literature and hand searches were used in addition. Evidence was assessed using SIGN criteria (Appendix S6). Where evidence was lacking, consensus was reached amongst the experts on the committee.

All BSACI members were consulted on the guideline, using a web-based system, prior to submission for publication, and their comments and suggestions were carefully considered by the Standards of Care Committee and responses are available on request.

2 | DEFINITION AND MECHANISM

Egg allergy is an adverse immunological reaction, most often induced by the proteins in egg white, usually ovalbumin (Gal d 2) and/or ovomucoid (Gal d 1) mediated by egg-specific IgE. Ovomuroid is heat stable and immunodominant.^{2,3} Late-phase and delayed hypersensitivity reactions also occur, typically in eczema.

The production of egg-specific IgE is a pre-requisite for developing type-1 hypersensitivity to egg. The route, timing and dose of

egg protein exposure, resulting in sensitization and clinical allergy, are unknown.

3 | PREVALENCE

The EuroPrevall birth cohort reports that challenge confirmed hen's egg allergy, in children at 2 years of age, is about 1% across Europe and 2% in the UK.^{4,5} Egg allergy is much less common in adults. The prevalence of egg allergy in the adult population has been estimated at 0.1%.⁶ Newly diagnosed egg allergy in adults is rare.

4 | RISK FACTORS

Egg allergy in children is associated with eczema and rhinitis.⁷ Eczema is a significant risk factor for egg allergy.⁸ The onset of eczema predates egg allergy by an average of 3.5 months and the likelihood of egg allergy increases with the severity of eczema.⁷ Boys with early-life eczema have the highest prevalence of egg sensitization.⁹ Egg allergy is not associated with age of introduction of egg into the diet.⁷ Children who received antibiotics in the first week of life are more likely to develop egg allergy.⁷ Egg allergy may occur in association with other food allergies, such as cow's milk protein or peanut.

BOX 2 Making a diagnosis of egg allergy

- Most children should receive a clinical diagnosis without resorting to food challenge.
- If the history is unclear, a negative skin prick test can exclude egg allergy.
- Skin prick test weal size or level of specific IgE does not predict the severity of allergic reactions to egg²⁹.
- The severity of a reaction depends on the amount of allergen ingested, the matrix, how well it is cooked and concomitant asthma, exercise or illness.

5 | CLINICAL PRESENTATION AND SEVERITY

The onset of egg allergy is usually observed early in life, in children with eczema and atopy. Egg allergy most commonly presents after the first apparent ingestion.^{8,10,11} Most reactions occur to lightly cooked egg, with reactions to baked egg and raw egg being less common.¹⁰ Clinical reactions include urticaria and/or angio-oedema in 80–90% (within minutes) and gastrointestinal symptoms in 10–44% (within 2 h).^{10,12–14}

Most reactions occurring in the community are mild, with facial erythema and/or urticaria. In children, a mild reaction is characterized by cutaneous symptoms on significant exposure (e.g. a mouthful of cooked egg) sometimes associated with a single vomit. A hoarse cry, change in voice pitch, cough, stridor or wheeze indicates involvement of the respiratory tract and a more severe reaction. Occasionally young children develop pallor and floppiness. Moderate to severe reactions with respiratory symptoms are less common; 5–10% in challenge studies, but less in the community, where the initial triggering dose is usually lower.^{10,12,13} Prior to presentation to allergy services, anaphylaxis occurs in 7%.¹⁰

The severity of allergic reactions correlates with the amount of egg protein exposure¹⁵; as determined by the amount of egg protein ingested and the degree of processing (baked in wheat, cooked or raw, cooking duration and temperature). Baked egg as an ingredient in sponge cake would mostly cause a mild cutaneous reaction. Skin contact to raw egg may induce local cutaneous reactions. Systemic reactions have been reported when egg white has been applied to skin for the treatment of nappy rash.¹⁶ Ingestion of raw or undercooked egg triggers more severe clinical reactions than well-cooked egg. One death due to egg allergy has been reported in an adult patient in the UK since 1992.^{17,18} In children with eczema who are allergic to egg protein, dietary exclusion of egg results in improvement of their eczema.¹⁹ Clinical case examples of egg allergy presenting with varying degrees of severity are described in Appendix S1. Egg allergic patients requiring referral to an allergy clinic are defined in Box 1.

Note: Early referral is beneficial as a delay in baked egg introduction may limit the development of tolerance.

6 | DIAGNOSIS

Acute clinical signs have usually resolved by the time the patient reaches medical attention. The clinical diagnosis is, therefore, made

by a typical history of erythema, urticaria, angio-oedema and/or vomiting with rapid onset (usually within minutes) after ingestion of egg. Children with a clear history of a mild reaction to egg can be diagnosed and managed in a primary care setting without further testing. Only children with moderate-severe reactions, or where the history remains unclear, require further investigation to confirm and manage egg allergy.

7 | INVESTIGATIONS**7.1 | Skin prick test**

Skin prick testing (SPT) has a poor positive predictive value as a screening tool in the absence of a suspected allergic reaction to egg. SPT using commercially available standardized whole egg reagent should only be carried out if there is clinical suspicion of egg allergy. SPT weal size does not correlate with clinical severity. Traditionally, cut-off levels for egg white SPT weal size of ≥ 3 mm^{8,20} have been used to support a clinical diagnosis of egg allergy. Higher cut-off levels are associated with higher specificity and positive predictive values, e.g., a SPT weal size of 5 mm to egg white is 100% diagnostic in a child under 2 years of age.²¹ Cut-off values for prick to prick testing with raw egg are reported as ≥ 13 mm.²² Skin testing with raw egg does not predict tolerance to baked egg in egg-allergic children²³. It is not standardized and there is a risk of severe reactions, so is not routinely recommended outside research settings. Skin prick testing using a slurry of baked egg had a high negative predictive value for a negative baked egg challenge in one study.²⁴ It is not routinely used in clinical practice.

7.2 | Egg-specific IgE

When skin prick testing is not available, measurement of egg-specific IgE may be carried out in patients with a history of moderate/severe reactions to egg containing food, to confirm a clinical suspicion of egg allergy. It is not possible to identify a cut-off for serum-specific IgE because of a lack of consistency between studies. Although there is a demonstrable relationship between serum IgE levels and challenge outcome within studies, there is poor agreement between centres. This is because of differences in

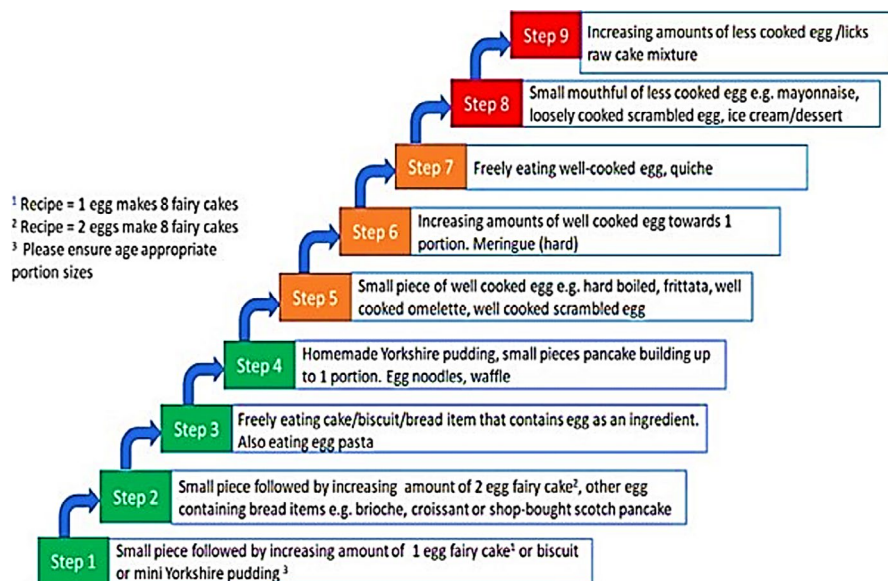


FIGURE 1 BSACI Egg Ladder—a practical guide to reintroduction. To be used in conjunction with BSACI egg-allergic patient information leaflet (Appendix S3) and Food classification stages (Figure 2)

inclusion criteria, significance levels, challenge method, outcome criteria, patient age and eczema prevalence between studies. With so many interfering variables, these cut-off levels are not applicable to a general population. Low levels of egg-specific IgE may be found in children without clinical egg allergy.¹³ The measurement of egg-specific IgE in the absence of a history of egg ingestion is discouraged as, in this circumstance, the test has poor specificity and low negative predictive value; cautious home introduction or oral challenge will subsequently be required if the egg-specific IgE level is positive but low.⁸ Measurement of peanut-specific IgE should be included in infants with moderate/severe egg allergy to guide peanut allergy prevention advice.²⁵

7.3 | Egg component testing

The egg white components are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4) and livetin (Gal d 5). Ovomucoid (Gal d 1) is heat stable and immunodominant.^{2,3} The role of component allergens in predicting tolerance to baked egg white, or resolution of egg allergy in routine clinical practice has yet to be established.²⁴ Persisting egg allergy is associated with a positive Gal d 1, and a level ≥ 11 kU/L indicates a high risk of reacting to cooked and raw egg.³ Gal d 1 is also a good indicator of whether the child is allergic only to raw egg, or to both cooked and raw egg.²⁶ The acquisition of tolerance to egg is associated with a decrease in IgE to egg white and Gal d 1.²⁷ When using test results to identify children at a high risk of anaphylaxis, although egg white sIgE levels are more sensitive, Gal d 1 has better positive predictive value and specificity.²⁸ The current evidence suggests that egg components are rarely needed for the routine diagnosis and management of egg allergy in children but can be a useful adjunct for the assessment of egg allergy resolution in adults (Box 2).

8 | MANAGEMENT

8.1 | Avoidance diets

Eggs served in a recognizable form are relatively easy to avoid. They are used as an ingredient of many manufactured foods; therefore, food labels must be consistently checked. Uncommon sources of egg include quorn, confectionary and egg hidden in a food, usually 'egg free', e.g., pizza dough. Extra care needs to be taken with foods sold loose (non-pre-packed) as there may be risk of cross-contamination. Individuals with severe egg allergy will need to completely avoid food sold loose/on buffets. All species of egg (e.g. quail/duck) are given the generic name 'egg' on a label. Verbal and written advice on avoidance of egg products should be provided (see Appendices S2 and S3).

8.2 | Allergen labelling

Egg is one of the 14 allergens required by EU legislation³⁰ to be declared on the labels of all packaged foods manufactured and sold within the EU, however, small the amount. Egg must be emphasized in bold in the ingredient list. Other terms for egg include albumin, ovalbumin, globulin, ovoglobulin, livetin, ovomucin, vitellin, ovovitellin, lysozyme and alpha-livetin. These are not allowed to be substituted for the term 'egg'. Knowledge of these terms may be useful for detecting egg protein in non-EU products.

8.3 | Breastfeeding and egg allergy

Most breastfeeding mothers with egg-allergic children should continue to breastfeed on an unrestricted diet. Egg protein from the maternal diet is detectable in breast milk and may cause reactions in

a very small number of infants.^{31,32} A trial of maternal egg-free diet may be helpful in the following circumstances:

1. Infants with persistent eczema poorly responsive to treatment, where egg is a known or suspected trigger.
2. Infants suspected to be reacting to maternal ingestion of egg.

Strict maternal egg exclusion should be recommended for 4–6 weeks, followed by reintroduction to ensure unnecessary egg exclusion does not continue.

8.4 | Cross-reactivity between eggs from hens and other bird species

Skin test reactivity to other avian eggs (especially quail and duck) is common in children with hen's egg allergy.³³ It is generally accepted that those avoiding hen's egg should also avoid eggs from other avian species, such as duck, goose and quail. There are case reports of reactions to quail, duck and goose egg in those who are not allergic to hen's eggs.^{34,35}

8.5 | When to refer to a dietician

Eggs are a good source of energy, protein, B vitamins and vitamin D, which is important in calcium homeostasis and bone health. Those who are not regularly exposed to sunlight benefit from having rich sources of vitamin D in the diet.³⁶ Although it may appear easy to take supplements or substitute other foods, many composite foods may contain eggs; adherence may be difficult without adversely affecting nutritional intake or quality of life. Therefore, whilst the exclusion of eggs does not necessarily lead to nutritional deficiency, a registered dietician should be involved if the diet is also compromised by the exclusion of other foods due to multiple food allergies, lifestyle or religious reasons.³⁷

Patients/families often wish to discuss avoidance in more detail, for example, with regard to specialist replacement products, recipes, eating out or management of children's parties. Egg-allergic children have a two-fold increased risk of accidental reactions to egg, where there is no dietetic involvement in counselling the family.³⁸ Dieticians provide valuable advice following hospital-based food challenges. They play an important role in reintroduction plans, especially in advising on home-baked egg ladder progression (Figure 1) and alternative ideas when common baked egg food (such as cake) is disliked (Classification of egg containing foods, Figure 2). Contact with a dietician, 6 months after starting home introduction using the egg ladder, to assess progress is beneficial.

8.6 | Provision of emergency medication and treatment plans

All families with egg-allergic children should have an appropriate oral antihistamine available, preferably a second generation, non-drowsy

antihistamine, to treat allergic reactions due to accidental ingestion. In practice, adrenaline autoinjectors are rarely required for children with egg allergy.¹⁰ The minority of children, who have had severe reactions with evidence of airway narrowing (e.g. wheeze, voice change, choking) or hypotension, should be provided with injectable adrenaline^{39–41} and their families reviewed annually by an allergy specialist. Children with egg allergy and asthma, requiring regular preventative treatment with inhaled corticosteroids, should also be considered for an adrenaline autoinjector. Families should receive training in how to use their emergency medication, including demonstration with a trainer device and provision of a management plan.⁴¹

Adults and young people with persisting egg allergy should be re-assessed, especially prior to a move away from home, for example, to attend university, join the armed forces or travel overseas. They should be provided with updated information about dietary management and the need for an adrenaline autoinjector reviewed.

9 | RESOLUTION OF EGG ALLERGY

9.1 | Prediction of resolution

At 1 year of age, complete resolution of egg allergy is more likely in children who can tolerate baked egg than those who continue to react.⁴² The phenotyping of egg allergy (baked egg tolerant vs. allergic) has prognostic implications and eases dietary restrictions.⁴² Children with mild/moderate egg allergy or with cutaneous reactions only are more likely to resolve.⁴³

Persistence of egg allergy is associated with respiratory or multisystem symptoms, high egg specific IgE, presence of other food allergies or atopic co-morbidities.^{43–46} Sensitization to multiple egg allergen components, Gal d 1, Gal d 2, Gal d 3 or Gal d 5, may identify children at risk of persistent egg allergy.⁴⁷

9.2 | Natural history of resolution

Egg allergy resolves spontaneously in many affected children over several years, whereas in adults it tends to persist. Allergy to well-cooked egg resolves in about one third of children by 3 years of age, and two-thirds by 6 years (Figure 3).¹⁰ The rate of resolution varies between studies^{42,43,48,49} and egg allergy may continue until the teens.¹⁰ Systematic reviews suggest that the median age of resolution is 6–9 years, with 68% of egg-allergic individuals experiencing resolution by the age of 16 years.⁵⁰

Tolerance to well-processed (baked or lightly cooked) egg occurs long before tolerance to uncooked egg (Figure 3). Children who can tolerate baked egg may continue to react to lightly cooked egg. Children outgrow allergy to well-cooked egg approximately twice as quickly as they outgrow allergy to uncooked egg. Establishing the former is important to allow relaxation of dietary restrictions and may help establish tolerance.

		Stage 3. Raw egg products
	Stage 2. Well cooked egg dishes and loosely cooked egg	Mayonnaise and mayonnaise-based sauces, e.g., Horseradish sauce, tartar sauce, ranch dressing
Stage 1. Baked/well cooked egg, (low egg / with matrix)	Early-stage introduction: *Home-made Pancakes, crepes, and waffles Batter, *Homemade Yorkshire pudding Egg noodles	Salad cream, coleslaw Dippy/uncooked boiled/fried/poached egg. Sorbet, Cold / hot Souffle
Early-stage introduction: Cake (1egg/8 cake recipe) Hard Biscuits TUC crackers Mini Frozen Yorkshire pudding Pastry containing egg (sausage roll, pie, Choux) Trifle sponge/Jaffa cake Breadcrumb coating e.g. fishfinger, nugget Wheat free bread/bread sticks Later stage introduction: Bread containing egg e.g., Brioche, Croissants, Buns, Panettone, Naan, Focaccia, *Cake (standard recipe), *Muffins, madeleines Scotch pancakes, *blinis, Welsh cakes Soft cookies Toasting waffles, waffle cones Egg pasta and dishes with pasta, Cooked egg glaze, Prawn crackers,	Scrambled egg (firm) Hard Boiled /fried/poached egg. Scotch egg Omelette/ frittata Egg fried rice. Quiche and flans *Duchess potato Heated sauces e.g., Hollandaise sauce Egg custard, Crème caramel Crème Brulée Nougat and Nougat confectionary e.g., mars *Hard Meringue/pavlova Later stage introduction: *Loosely cooked scrambled egg or omelette *Carbonara Sauce *French toast *Welsh rarebit	Luxury and fresh ice cream e.g., BenJerry, Haagan Daaz Soft meringue (lemon meringue, pavlova) Fresh Mousse and other uncooked desserts Sushi Tartare steak Confit Egg, Florentine pizza, eggs benedict Soft Mallow e.g., snowball, teacake Royal and fondant icing /decorations Raw cake mixture Homemade marzipan Fondant confectionary e.g., crème egg Uncooked egg white powder Cocktails / drinks e.g., Advocaat
	*Egg as binder e.g., burger, meatball -well cooked Quorn	Pasteurised egg

- Each stage to be tried in small amounts first. Reduce to lower stage/smaller amount if symptoms.
- * these foods may cause allergic reaction depending on degree of cooking (fully cooked = less allergen)

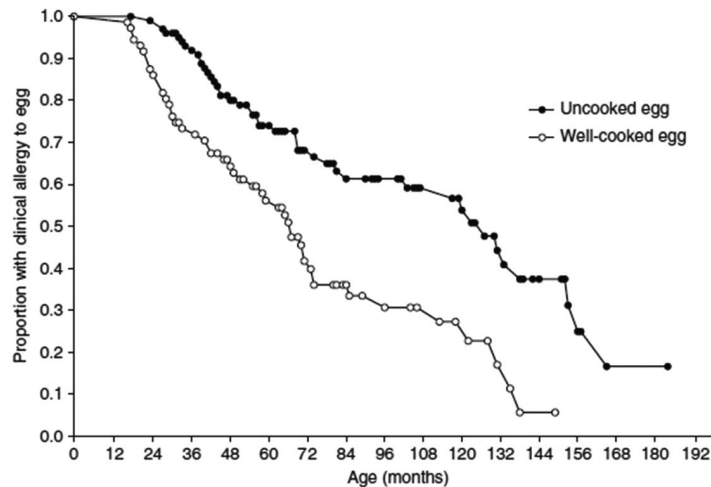
FIGURE 2 Classification of egg-containing foods. Each stage to be tried in small amounts first. Reduce to lower stage/smaller amount if symptoms. * these foods may cause allergic reaction depending on degree of cooking (fully cooked = less allergen)

9.3 | Reintroduction of egg into the diet

Most children with mild egg allergy tolerate gradual staged home introduction according to an egg ladder (Figure 1). Baked egg introduction improves quality of life for egg-allergic children, enhances the natural development of tolerance and de-restricts the diet. The speed with which egg allergy resolves varies between individuals, and therefore the timing and appropriateness of egg reintroduction

should be individually assessed.⁴⁶ Egg-allergic children who can tolerate baked egg at diagnosis and continue to consume baked egg achieve tolerance earlier than those who continue to avoid all forms of egg.⁵¹ In children with previous mild reactions and no asthma, the introduction of baked egg into the diet at home from 12 months of age is safe and may support the development of tolerance.⁵²⁻⁵⁵ Reintroduction should not be attempted within 6 months of a significant reaction to egg.

FIGURE 3 Cumulative persistence (survival) of allergy to well-cooked and uncooked egg expressed using Kaplan-Meier survival curves. Log-rank test for difference between curves: $p < 0.0001$. Median age at acquisition of tolerance is 67 months (5.6 years) for well-cooked and 127 months (10.3 years) for uncooked egg



Ref: ¹

BOX 3 Potential benefits of home introduction of egg in egg-allergic children

- Promotion of natural resolution of egg allergy⁵²
- Reduction of food-related anxiety
- Expansion and normalization of the diet
- Improved nutritional outcomes.
- Avoidance of hospital-related anxiety (e.g. in children with communication disorders)

BOX 4 Hospital based egg challenge should be considered in the following groups of patients after an interval of >1 year from the last reaction

- Patients with severe symptoms following egg ingestion, affecting breathing (cough, wheeze or swelling of the throat, choking), circulation (floppiness or shock) or gastrointestinal tract (severe vomiting or diarrhoea)
- Patients with egg allergy and severe/poorly controlled asthma
- Patients with severe multisystem allergic disease

Relative indications for hospital-based egg challenge:

- Patients with mild-moderate reactions following trace exposure of egg.
- Patients with egg allergy and asthma controlled by a regular asthma preventer.
- Patients with co-existing multiple/complex food allergies
- Patients and families unable to comprehend or adhere to a protocol.
- Patients and families with anxiety precluding home introduction.
- Patients on immune suppressants or biologics
- Older patients with persistent egg allergy

9.4 | Home introduction of egg

Home introduction is not the same as a food challenge. It aims to gradually introduce a food, to which a child previously reacted, back into the patient's diet. Egg is gradually introduced using a ladder (Figure 1), in a form less likely to cause an allergic reaction, at low amounts. The quantity and allergenicity are gradually increased as the child is able to tolerate it. This approach helps ensure safety with a view to promoting tolerance to more allergenic forms of the food.

Children without asthma, or with well-controlled mild asthma, and who have had only mild cutaneous symptoms on significant exposure (e.g. a mouthful of lightly cooked egg) may try a small amount of baked egg (e.g. pea-sized piece of sponge cake) from the age of about 12 months at home (Appendix S3). If this is tolerated regularly, in good amounts, then gradual staged reintroduction of lightly cooked egg according to the egg ladder (Figure 1 and patient information leaflet Appendix S3) may be considered. Once baked egg is fully tolerated, it should be included 2–3 times per week. Once

loosely cooked egg is tolerated, patients should be reassured that egg allergy is outgrown and egg can be included as part of the normal diet. If there is a reaction, then the previously tolerated diet should be followed, and further reintroduction considered after 3–6 months (Box 3).

Reintroduction at home should not be attempted when there have been severe gastrointestinal, respiratory or cardiovascular symptoms during previous reactions, when only a trace amount has ever been ingested, in the presence of severe eczema (covering >40% of the body), severe multisystem allergic disease or there is ongoing asthma (Box 4). In these patients, hospital egg challenge should be considered. A more cautious approach should be taken with older children who have been on an exclusion diet for a long time.

Children who tolerate cooked egg may still react to raw or undercooked egg. There are case reports of children who, following a negative cooked egg challenge, later have severe reactions to raw egg.⁵⁶ Egg introduction or challenge should not be deferred for concern of increasing sensitization.⁴³

Children undergoing hospital-based baked egg challenges rarely experience anaphylaxis requiring treatment with adrenaline; 2% in one study of 236 children.⁵⁷ Adrenaline was not required in 181 hospital-based egg challenges.¹⁰

A recent study of 678 children undergoing hospital-based egg challenges identified two patients who satisfied BSACI criteria for home reintroduction, and experienced airway symptoms (personal communication – Aljneibi Shaikha). These hospital challenges employed higher starting doses of egg protein (estimated 200-mg egg protein) and rapid dose escalation compared to gradual low-dose home introduction (estimated starting dose 20-mg egg protein).

Patients selected for hospital-based food challenges differ from those selected for home introduction (where those with asthma or a history of severe reactions are excluded). The dose escalation occurs over a shorter period (a dose every few minutes compared to once-a-day increments) and the starting dose of egg for hospital-based challenges is considerably higher than that proposed for home introduction.

The risk of anaphylaxis in young children being given clear guidance on low-dose baked egg being gradually built up according to a ladder is minimal. In 211 children undergoing home-baked egg introduction, there were no reports of anaphylaxis (H. Ball – personal communication).

We emphasize that home introduction regimes should employ a gradual, staged, low dose approach, according to the egg ladder, rather than rapid escalation as used in hospital-based challenges. As the starting dose for home introduction (estimated 20-mg egg protein) is extremely low, if a reaction were to occur, the symptoms would be mild.

We do not advocate testing for egg allergy in children who have no documented reactions to egg; however, children who are allergically sensitized to egg, in the absence of having a documented reaction to egg, should introduce baked egg into their diet at home. If they react, they should be managed as egg allergic.

9.5 | Children with severe egg allergy

Children with severe egg allergy, severe multisystem allergic disease, faltering growth (Box 4) or egg allergy persisting beyond the time of usual resolution (6–7 years) should be followed up periodically to assess the likelihood of resolution and to refresh avoidance advice and emergency medication training. A history of any accidental exposure should be sought and SPTs or specific IgE repeated. There are no prospective studies based on specific IgE levels, to advise when to challenge these children. It is reasonable to attempt reintroduction if there has been no significant recent clinical reaction, accompanied by a reduction in SPT wheal size or serum-specific IgE over time.⁵⁸

These children should have a supervised challenge in hospital and not at home. Supervised baked egg challenge should be using a one egg per eight fairy cake recipes in the first instance. There may be exceptions, for example, if a child has had a subsequent mild reaction after significant accidental exposure. Children on biologics for asthma should be considered for food challenge once their asthma control has improved.

9.6 | Oral immunotherapy

Egg immunotherapy is a deliberate attempt, using regular ingestion of egg, usually with increasing amounts, to generate tolerance to egg in a patient with established egg allergy (usually over 5 years of age). Several studies have demonstrated the safety and efficacy of egg oral immunotherapy (OIT).^{22,59–62} It is time consuming for clinicians and requires significant commitment for families. Desensitization occurs, although tolerance may not be maintained after withdrawal of treatment. A Cochrane review in 2018 commented that studies were small, and the quality of evidence is low.^{63,64} There are no standardized protocols and a high incidence of adverse events.^{63,65} In one study, adrenaline was required in 26% of children.⁶⁵ Early discontinuation is associated with underlying asthma, higher specific IgE and lower threshold during double-blind, placebo-controlled food challenge.⁶⁵ Ovomucoid IgE >8.85 kU/L indicated a 95% probability of early discontinuation or ongoing reactions over time.⁶⁵

More recent protocols achieve tolerance in 50% of patients.^{60,66} The benefits are sustained for up to 5 years after treatment.⁶⁶ Daily dosing is more effective than weekly dosing.⁶⁷ Low pre-treatment levels of egg white and ovomucoid IgE predict sustained unresponsiveness following egg immunotherapy.⁶⁸ Decrease in size of SPT and increase in egg-specific IgG4 over time predicts tolerance in children being treated with egg OIT.⁶¹ Ovalbumin IgG4 and Ovalbumin IgE/IgG4 ratio may be useful to predict the development of tolerance to egg in oral immunotherapy.⁶⁵

EAACI does not currently recommend egg OIT as a treatment to achieve long-term tolerance in children with persistent egg allergy.⁶⁹ Egg oral immunotherapy should only be undertaken in highly specialized allergy centres.⁶⁹

10 | EGG ALLERGY IN ADULTS

In contrast to egg allergy in children, egg allergy in adults is likely to be severe and long lasting. It is due to either persistent childhood egg allergy or to true adult-onset egg allergy, which is rare. Adults with persistence of childhood egg allergy have more sequential than conformational IgE epitopes of ovomucoid.⁷⁰

Adult-onset egg allergy may be:

1. New onset adult egg allergy after eggs have been tolerated for years.⁷¹
2. Part of the bird-egg syndrome (a combination of bird-feather sensitization and egg allergy) with an allergy to egg yolk. 'Bird egg syndrome' was originally described in subjects, mainly women, who were sensitized to egg yolk and bird (budgerigar and hen) feathers.⁷² This syndrome is seen in subjects who are exposed to caged birds or pigeons.⁷³ The allergen responsible is alpha livetin (chicken serum albumin, Gal d 5), found in large amounts in egg yolk.⁷⁴ Typically, patients develop upper and lower respiratory symptoms on exposure to birds and gastrointestinal symptoms with chicken meat or lightly cooked eggs. Patients should receive egg avoidance advice, emergency medication and be trained in its use.
3. Occupational, for example, in workers from the baking industry, who develop sensitization by inhalation.⁷⁵

There is little information on the prognosis of adult egg allergy and patients should be seen periodically to repeat specific IgE and to update training in the use of emergency medication. Older children or adults with a pre-existing egg allergy, presenting to the adult clinic for the first time, should be assessed for the likely resolution of egg allergy. Component testing can be useful in determining whether an OFC is feasible, with a negative test to Gal d 1 (ovomucoid), suggesting that a baked egg challenge might be tolerated. Although systematic review data suggest that 30% of egg-allergic children will continue to have persisting egg allergy after the age of 16 years, there are no data on continued resolution in young adults. Clinical experience shows that although it persists in some and may be life-long, many others may have partly or wholly resolving egg allergy, even in their late 20's. It is extremely important to establish the likelihood of tolerance with oral food challenges, as reactions can be severe and fatal anaphylaxis to egg has been reported in an adult patient.⁷⁶

11 | OTHER EGG-RELATED CONDITIONS

11.1 | Egg allergy and asthma

Children with egg allergy are at increased risk of other allergic diseases especially asthma (odds ratio 5.0).⁷⁷ A careful history should, therefore, be taken to enquire about respiratory symptoms. The presence of asthma may increase the potential severity

of accidental egg reactions and excellent asthma control should be a priority.

11.2 | Egg allergy as a risk factor for peanut allergy

Infants with egg allergy are at risk of developing peanut allergy. The introduction of regular high-dose peanut into the diet of egg-allergic children under 11 months of age reduces the incidence of peanut allergy at 5 years of age.²⁵ Introduction of peanut in children with egg allergy is discussed in the BSACI Early weaning guidance.⁷⁸ Infants undergoing SPT or measurement of specific IgE to egg proteins should also be tested for peanut sensitization, and peanut containing food introduced alongside other solid foods from around 6 months of age.

11.3 | Egg allergy and Eosinophilic oesophagitis

Children and adults with eosinophilic oesophagitis (EoE) respond to elimination of common food allergens, including egg.⁷⁹ Cow's milk and wheat are the most likely triggers of EoE, but a large multi-centre study of both children and adults reported that 15% of the subjects had reactions to egg.⁷⁹ Egg may be a relevant trigger in 35% of children and 26–36% of adults.^{80–82} Egg avoidance is usually included as part of an empiric four or six food elimination diet.⁷⁹ Egg SPT is a poor predictor of egg as a trigger for EoE.⁸³

EoE has been reported as a complication of egg immunotherapy. This is usually reversible after early diagnosis and stopping the immunotherapy product.⁸⁴ There is no evidence that home introduction of egg will cause EoE.

11.4 | Use of Propofol in egg-allergic patients

A commonly used formulation of Propofol contains egg lecithin, derived from egg yolk. Propofol administration is safe in adult patients with egg allergy, or who are sensitized to egg.^{80,85} In a study of propofol administration in egg-allergic children, one child with anaphylaxis to egg developed urticaria and erythema on two occasions after the administration of propofol.⁸⁶ Propofol is safe to use in children with egg allergy.^{87,88}

11.5 | FPIES to egg

Food Protein-Induced Enterocolitis syndrome (FPIES) is a rare form of severe delayed type food allergy, thought to be non-IgE mediated, that leads to recurrent vomiting, fluid loss, dehydration, and shock, normally within 4 h of ingestion.⁸⁹ Egg is a common food trigger for FPIES both in the UK and elsewhere,⁹⁰ 30% of infants with milk or soya FPIES also react to egg protein.⁹¹ The diagnosis is made on clinical history. Tests for specific IgE are usually negative but become

positive in up to a fifth of cases during follow-up.⁸⁹ The natural history is to resolve during childhood, slightly later than milk/soy FPIES, at around 42 months.⁸⁹ Resolution is confirmed by food challenge. This should be in a centre with experience in food challenges, facilities for rapid intravenous fluid resuscitation and prolonged observation.⁸⁹ Tolerance to baked egg seems to occur before raw egg, with one case series showing cake tolerance at 30 months compared to 43 months for raw egg.⁹² FPIES normally occurs in infancy during the introduction of solids but has been reported following reintroduction of egg after resolution of IgE-mediated egg allergy.⁹³

12 | IMMUNIZATION OF EGG-ALLERGIC CHILDREN AND ADULTS

Hen's egg proteins are found in low amounts in most Influenza vaccines and the Yellow Fever vaccine. The measles, mumps and rubella (MMR) vaccine is cultured in chick embryo fibroblast cell culture and not from hen eggs themselves.⁹⁴ It does not contain hen egg allergens in clinically relevant quantities.^{95,96} Chapter 6 of the UK Department of Health Green Book, Immunization Against Infectious Disease⁹⁷ gives advice on immunizing egg-allergic patients.

Most adults and children with egg allergy can be safely immunized in primary care. The exceptions that require referral for specialist supervision are those who require:

1. Influenza vaccine in patients who have experienced *life-threatening* anaphylaxis to egg (requiring admission to intensive care).
2. Yellow Fever Vaccine for travel.

12.1 | Influenza vaccine

Most Influenza vaccines are derived from the extra-embryonic fluid of chicken embryos inoculated with specific types of influenza virus. The vaccines contain measurable quantities of ovalbumin (egg white protein) which vary between batches and manufacturers.^{98,99} As vaccine manufacture has improved, reports of egg-related allergic reactions to influenza vaccines are now largely historical.⁸⁸

Most current influenza vaccines contain very low amounts of ovalbumin (<0.12 mcg/ml or <0.06 mcg in a 0.5 ml dose) and can be administered safely in primary care by the intramuscular route, even in those with a previous history of anaphylaxis to egg.^{100,101} Egg ovalbumin content of current influenza vaccine can be found in the Summary of Product Characteristic (SPC) for the vaccine, or from the May issue of the current year of Vaccine¹⁰² preceding the immunization season. The ovalbumin content of influenza vaccines for the forthcoming influenza season is published annually by Public Health England.¹⁰³

The intranasal live attenuated influenza vaccine (LAIV) is also grown in hen's egg, and therefore, contains egg protein. It is safe to administer in children with egg allergy.⁷⁶ The ovalbumin content

of LAIV¹⁰⁴ is very low (<0.12 mcg/ml). It is safe to use and is recommended to be given to children with egg allergy in any setting, including primary care and schools⁷⁶ (Department of health, 2017). There are no safety data on children who have experienced anaphylaxis to egg, requiring intensive care admission and therefore, these children should be referred to a specialist for supervised immunization or, where available, consider an egg-free influenza vaccine in primary care for children over 9 (Lamb Drugs 2019).

12.2 | Yellow fever vaccine

Yellow Fever is a mosquito-borne viral haemorrhagic fever endemic to central Africa and South and Central America. Infection of non-immune travellers can lead to severe symptoms in up to half of infected persons (Department of Health, 2018). There is no specific cure. Yellow Fever vaccine is administered through a network of Yellow Fever Vaccination Centres¹⁰⁵ who issue certificates of immunization ahead of travel.

The Yellow Fever Vaccine (YFV) is a live vaccine cultured in hen's eggs and contains residual egg proteins.¹⁰⁶ Immunization is relatively contraindicated in egg allergy as most allergic reactions to the vaccine are thought to be related to egg allergy, although other allergens such as gelatine are theoretically possible.¹⁰⁷ The rate of anaphylaxis is 1 in 238 000 doses of YFV alone and 1 in 131 000 when YFV is co-administered with other vaccines.

The potential fatal sequelae from yellow fever means that vaccination should at least be considered. Adults and children with egg allergy who require YFV should be assessed in a specialist allergy centre, ideally at least 2 months prior to travel. Specialist allergy centres should work in collaboration with their local Yellow Fever Vaccination Centre to source the vaccine and provide certification for their patients. Allergy centres with high throughput may wish to train and register as a Yellow Fever Vaccination Centre, in collaboration with other stakeholders within the hospital, such as infectious diseases and occupational health specialists. Further details on registration as a YFVC can be obtained from the National Travel Health Network and Centre (NATHNAC).¹⁰⁸

There are several approaches to YFV immunization of an egg-allergic individual, directed by local practice and risk assessment. A proposed travel history should be taken with confirmation of requirement for YFV immunization by the YFVC, who will also be responsible for issuing a certificate of immunization. Initial investigations may include skin prick testing to egg reagent and undiluted YFV, progressing to intradermal testing should initial skin tests be negative.^{88,109,110} Negative intradermal tests (at 1:10 or 1:100 dilution) predict tolerance of the vaccine.^{109,110} A two dose schedule can be used depending upon risk assessment.¹¹⁰

Positive skin or intradermal testing to the vaccine suggests allergic reactivity and requires a more cautious approach. If no further immunization is preferred, a certificate of exemption can be issued by the YFVC. However, in the face of a positive IDT to YFV, the individual may still seroconvert without further immunization, and the

exemption certificate should be withheld until serological confirmation 2–4 weeks after testing.^{111,112} If intradermal testing is not performed, due to strongly positive SPT, or where there is no evidence of seroconversion at 4 weeks, or if the individual is unable to wait to travel and would prefer the protection of YFV, then a seven-step desensitization regime has been shown to be safe and effective in a small number of egg-allergic people.¹¹⁰

12.3 | MMR vaccine

All children with egg allergy should receive their normal childhood immunizations, including the MMR, as a routine procedure in primary care. No extra precautions are required. Case series of large numbers of egg-allergic children show that there is no increased risk of severe allergic reactions to the MMR vaccine.^{96,113,114}

12.4 | Rabies vaccine

Rabies is a serious viral infection with a high case fatality rate. Rabies vaccines are used as protection before travel to rabies endemic areas, and for post-exposure prophylaxis following the bite of an infected animal. There are two vaccines available, a human diploid cell vaccine that does not contain egg and Purified Chick Embryo Cell (PCEC) vaccine that contains traces of egg protein, including ovalbumin.¹¹⁵ There have been reports of allergic reaction and anaphylaxis to PCEC, some of which may have been related to egg allergy.¹¹⁶ PCEC (Rabipur, GlaxoSmithKline) is relatively contra-indicated in individuals with a history of previous egg anaphylaxis. The contra-indication is relative, as rabies is almost universally fatal and immunization for post-exposure prophylaxis outweighs the risk of allergic reaction to the vaccine (Chapter 27, Green Book 2019). Human Rabies Immunoglobulin (HRIG), a passive immunization used for treatment, does not contain egg protein.

13 | MANAGEMENT OF EGG ALLERGY IN NURSERIES AND SCHOOLS

Nurseries and schools should have a local policy that covers the management of any food allergy, including egg allergy.^{117,118} This includes training in allergen avoidance, food labelling regulations³⁰ and knowledge of which foods might contain egg allergens. Training should also include early recognition of symptoms, knowledge of what medication is needed, where it is stored and how it is administered.

Children with an egg allergy should have a tailored care plan in place, with adaptations made to the school/nursery meals to enable the child to eat a similar meal or packed lunch sitting alongside their peers.¹¹⁹ School trips may require a separate risk assessment. Additional consideration should be given to factors, such as food sharing, food contamination and the provision of 'treat' foods,

such as birthday cake. Where children have a severe egg allergy it may be necessary for a whole class to avoid craft projects with egg boxes or shells (such as cress growing) and lessons/activities using raw egg (e.g. baking). Food technology teachers should be aware of egg-allergic students to allow them to use egg-free recipes and thus avoid reactions.¹¹⁹

14 | PSYCHOLOGICAL AND SOCIAL IMPLICATIONS OF EGG ALLERGY

Any food allergy may adversely affect quality of life, resulting in anxiety and depression.^{120–122} The constant vigilance needed to avoid egg impacts all aspects of the child's life and that of their family.^{123,124} The patient may experience anxiety in relation to eating a restricted diet, food avoidance and having allergic reactions.^{125,126} Children with disabilities, communication disorders and hospital-related anxiety may find home introduction, with dietetic guidance and support, less stressful. Children can experience post-traumatic stress following severe allergic reactions. This may become a particular problem where egg allergy persists into adolescence.¹²⁷ Parental coping is critical in the child's risk perception of allergy, anxiety and coping over time.^{128,129}

Psychological help and intervention is effective^{130–132} in addressing anxiety, phobias and promoting adaptive coping strategies. This can be accessed via paediatric psychology services or CAMHS for children and Improving Access to Psychological Therapies (IAPT) for adults. Patients with mild-moderate egg allergy do not usually require additional psychological support.

15 | PRIMARY PREVENTION; INTRODUCTION OF EGG INTO THE DIET OF INFANTS FROM ATOPIC FAMILIES

Delayed introduction of allergenic foods to the weaning diet increases the risk of food allergy. Conversely, an earlier and focused allergen introduction schedule can be protective.

There is some indication that the early introduction of egg into the infant diet reduces the incidence of egg allergy. Intervention studies show mixed results.^{133–136} In a meta-analysis,¹³⁷ the introduction of egg between 4 and 6 months of age reduced the risk of developing egg allergy.

Current UK guidance on the introduction of complementary foods is underpinned by WHO advice and recommends exclusive breastfeeding until around 6 months of age with solids started around this age.⁶ The current UK weaning guidance states that withholding allergenic foods may increase the risk of allergy and that complementary feeding, including egg and peanut, should be introduced, in an age-appropriate form, from around 6 months of age. The BSACI recommends earlier introduction of egg into the diet of children with eczema, to reduce the risk of developing allergy.⁷⁸ Infants with eczema are at higher risk of developing egg allergy and

should be encouraged to start weaning between 4 and 6 months once they show signs of readiness. Egg should be introduced as an early weaning food, after initially establishing an intake of more traditional early weaning foods.^{8,78} Well-cooked egg starting with a small amount (1 teaspoon) initially, moving upwards towards a full dose. Families should be encouraged not to delay egg introduction in the hope of preventing an allergy.¹³⁸

Studies on early egg introduction have noted that a high proportion of infants are already sensitized to egg protein (positive skin prick test or specific IgE) before weaning and some have clinical egg allergy.^{133,134,139} Infants with moderate-severe or early onset eczema or existing food allergy are at highest risk of reacting on initial egg introduction, so the first couple of ingestions of baked egg in these groups should be in tiny (pea-sized) amounts. The risk of severe reactions in these higher risk babies is low but present.⁷⁸ Egg-specific IgE has a poor predictive value for the development of egg allergy in high-risk infants in the absence of a history of egg ingestion and should not be used in this context.¹⁴⁰

16 | FUTURE RESEARCH

- Prevalence of egg allergy in adults
- Prevalence of allergy to eggs other than hen's egg.
- Allergy to egg yolk
- The use of antibiotics in the first week of life as a risk factor for developing egg allergy.
- Development of more robust diagnostic cut-offs relevant to unselected clinic patients especially for serum-specific IgE and component egg allergens.
- Investigate predictive clinical and laboratory markers for the resolution or persistence of egg allergy.
- The utility of home egg introduction.
- Further investigation of oral immunotherapy for the treatment of egg allergy.

AUTHOR CONTRIBUTIONS

Susan Leech, Pamela Ewan and Andrew Clark wrote the initial draft. Isabel Skypala wrote sections on component testing, egg allergy in adults, and egg allergy case examples (appendix S1), Nicola Brathwaite wrote sections on skin prick testing and use of specific IgE, Mich Erlewyn-LaJeunesse wrote sections on FPIES and immunisations, Sarah Heath wrote sections on avoidance diet, allergen labelling, breastfeeding, management of egg allergy in nurseries and schools, primary prevention, when to refer to a dietician and patient information leaflets (appendices S2, S3 and S4), Heidi Ball Created Figures 1 and 2, wrote the case examples (appendix S1) and patient information leaflets (appendices S2, S3 and S4). Polly James and Karen Murphy wrote the section on psychological implications of egg allergy.

All authors commented on subsequent drafts and Susan Leech edited the final draft.

ACKNOWLEDGEMENTS

The preparation of this document has benefited from extensive discussions within the Standards of Care Committee of the BSACI and we would like to acknowledge the members of this committee for their valuable contribution, namely, Richard Powell, Steve Till, Rita Mirakian, Deb Marriage, Lavanya Diwakar, Deepa Choudhury, Helen Brough, Liz Angier, and David Luyt. These guidelines inform the management of egg allergy. Adherence to these guidelines does not constitute an automatic defence for negligence and conversely, non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed every 5–7 years.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Leech SC, Ewan PW, Skypala JJ, et al. BSACI 2021 guideline for the management of egg allergy. *Clin Exp Allergy*. 2021;51:1262–1278. <https://doi.org/10.1111/cea.14009>