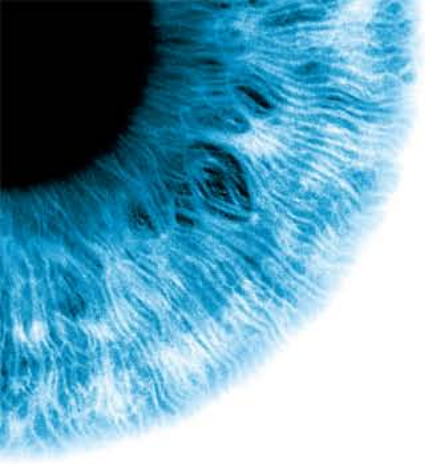

Food allergy in children and young people: Evidence Update May 2012

A summary of selected new evidence relevant to NICE clinical guideline 116 'Diagnosis and assessment of food allergy in children and young people in primary care and community settings' (2011)

Evidence Update 15

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/allergies). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

 [1]**Food allergy in children and young people. NICE clinical guideline 116 (2011). Available from www.nice.org.uk/guidance/CG116**

A search was conducted for new evidence published between 1 January 2010 and 23 December 2011. Over 2600 pieces of evidence were identified and assessed, of which 11 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

 [1]Atopic eczema in children. NICE clinical guideline 57 (2007). Available from www.nice.org.uk/guidance/CG57

Other relevant information

- NICE pathway of care for food allergy in children and young people. Available from www.nice.org.uk/pathways/food-allergy-in-children-and-young-people
- Royal College of Paediatrics and Child Health care pathway for food allergy in children. Available from www.rcpch.ac.uk/allergy/foodallergy

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark 

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

	Effect on guidance	
Key message	**Potential change**	**No change**
Assessment and allergy-focused clinical history		
• Evidence supports current guidance to pay particular attention to growth and physical signs of malnutrition.		✓
Diagnosis		
• As noted in current guidance, there is considerable variation in diagnostic criteria used for food allergy.		✓
IgE-mediated food allergy		
• Current recommendations to use skin prick or specific IgE antibody tests in suspected food allergy are supported by recent evidence showing the methods are equally effective.		✓
• Evidence in relevant patient populations is not yet available to support the primary care or community use of microarray technology assays for IgEs to allergen components.		✓
• Evidence suggests that there is value in combining information from different tests.	✓	
• Current recommendations to test for likely co-allergens is supported by evidence showing that this approach can yield useful information to minimise the number of foods that children need to avoid.		✓
• Evidence supports the current recommendation that atopy patch testing should not be used to diagnose IgE-mediated food allergy in primary care or community settings.		✓

Key message	Effect on guidance	
	Potential change	No change
Non-IgE-mediated food allergy • Evidence indicates that children with non-IgE-mediated allergy may convert to IgE-mediated allergy after an elimination diet. This suggests that conducting IgE-mediated allergy tests may be useful before reintroduction of excluded foods. • Current guidance does not mention atopy patch testing for diagnosis of non-IgE-mediated food allergy, and evidence suggests that it is not an appropriate method to use.	✓	✓
Providing information and support to the child or young person and their parent or carer • Evidence supports current recommendations to seek advice from a dietitian with appropriate competencies to provide information on hypoallergenic formulas and milk substitutes.		✓
Referral to secondary or specialist care • Current recommendations to refer children with one or more acute systemic reaction, severe delayed reaction or multiple food allergies to secondary or specialist care are unaltered by recent evidence.		✓
Alternative diagnostic tools • Evidence supports current recommendations that serum-specific IgG tests should not be used to diagnose food allergy.		✓

Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided. Section headings are taken from the guidance.

1.1 Assessment and allergy-focused clinical history

Based on the findings of an allergy-focused clinical history, NICE CG116 recommends physical examination of the child or young person, with particular attention paid to growth and physical signs of malnutrition. Recent publications by **Cho et al. (2011)**, **Flammarion et al. (2011)** and Meyer et al. (2012) reported the impact on growth in babies and infants with food allergies.

In the study by Flammarion et al. (2011), the weight and height of 96 children (age 6 months to 15 years, mean age 4.7 ± 2.5 years) with food allergies were compared with 95 paired controls (mean age 4.7 ± 2.7 years) without food allergies. Diagnoses of food allergy (peanut 59%, egg 50%, cow's milk 29%, soybean 15%, fish 10%; one food allergy 34%, two food allergies 23%, three or more food allergies 43%) were based on clinical symptoms (65% experienced more than one symptom) and either a positive skin prick test, food-specific IgE levels or positive oral challenge. All children in the allergy group underwent elimination diets for at least 4 months. Most children in this group (88%) received nutrition counselling by a trained dietitian, with the remaining children counselled by their paediatrician.

Children with food allergies had significantly lower Z scores for weight-for-age (0.1 vs 0.6, $p < 0.05$) and height-for-age (0.2 vs 0.8, $p < 0.05$) than the control group. Significantly more children with three or more food allergies were smaller (Z score < −2) than those with one or two food allergies (14.5% vs 1.8%, $p < 0.05$). Analysis of diet records (completed by 62 children with food allergies and 52 in the control group) showed that mean (standard deviation) energy intake in the allergy and non-allergy groups met recommended levels (1230.6 [351] kcal and 1195 [284] kcal respectively). Energy, protein and calcium intakes were similar between groups, leading the authors to conclude that children with food allergies are smaller than their peers even when they receive similar nutritional intake, possibly because of malabsorption.

Similar findings were reported in the study conducted in Korea by Cho et al. (2011), which included 165 children (age 5 to 47 months) with atopic dermatitis and food allergies (most commonly, egg white, cow's milk and wheat). Weight and height were compared with normal values for the local population. After adjusting for birth weight, the number of food allergies was significantly correlated with the Z scores for weight-for-age (partial correlation coefficient [r] = −0.358, $p < 0.001$), height-for-age (r = −0.278, $p = 0.001$) and weight-for-height (r = −0.224, $p = 0.006$). The authors did not give details of the duration of food avoidance, gastrointestinal symptoms or nutritional counselling given to the carers.

A narrative review by Meyer et al. (2012) focused on infants and young children with IgE-mediated and non-IgE-mediated allergy to cow's milk protein. Although protein malnutrition in these children is described as a common problem, the authors found few published studies on prevalence but numerous case study reports. The authors noted that delays in diagnosis place children with allergy to cow's milk protein at risk of protein energy malnutrition and growth retardation, with potentially long-lasting impact.

This evidence demonstrates that adequate dietary intake may not necessarily result in adequate growth in children with multiple food allergies. The evidence supports the recommendations of NICE CG116 for assessment of growth and signs of malnutrition, and

suggests that adequate growth assessment requires measurement of both height/length and weight, and calculation of height-for-age, weight-for-age and weight-for-height.

Key references

Cho HN, Hong S, Lee SH et al. (2011) Nutritional status according to sensitized food allergens in children with atopic dermatitis. Allergy, Asthma & Immunology Research 3: 53–7
Full text: www.e-aair.org/Synapse/Data/PDFData/9999AAIR/aair-3-53.pdf

Flammarion S, Santos C, Guimber D et al. (2011) Diet and nutritional status of children with food allergies. Pediatric Allergy and Immunology 22: 161–5
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1399-3038.2010.01028.x/abstract

Supporting reference

Meyer R, Venter C, Fox AT et al. (2012) Practical dietary management of protein energy malnutrition in young children with cow's milk protein allergy. Pediatric Allergy and Immunology doi: 10.1111/j.1399-3038.2012.01265.x
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1399-3038.2012.01265.x/abstract

1.2 Diagnosis

A systematic review by **Schneider Chafen et al. (2010)** aimed to assess the available evidence on the prevalence, management and prevention of food allergies. From assessment of 85 reviews on food allergy (number of patients not reported), the authors noted that food allergy has no consistently accepted definition. The lack of uniform diagnostic criteria limits determination of best practices for management and prevention. This evidence agrees with the Department of Health review of allergy services in 2006, referred to in the introduction to NICE CG116, which notes the considerable variation in current practices for allergy care. The findings from this review may have relevance to NICE CG57 on atopic eczema (available from www.nice.org.uk/guidance/CG57), because prevention of this condition was also considered.

Key reference

Schneider Chafen JJ, Newberry SJ, Riedl MA et al. (2010) Diagnosing and managing common food allergies. A systematic review. Journal of the American Medical Association 303: 1848–56
Full text: www.jama.ama-assn.org/content/303/18/1848.full.pdf

1.3 IgE-mediated food allergy

Choice of test

In the systematic review by **Schneider Chafen et al. (2010)** (see section 1.2 for details), 18 studies were included on the diagnosis of food allergies to cow's milk, hen's egg, peanut, tree nut, fish and shellfish, involving more than 2800 infants and children (13 studied skin prick testing, 11 studied serum food-specific IgE and 8 evaluated atopy patch testing). Summary receiver operating characteristic curves found no significant difference between skin prick testing (area under the curve [AUC] = 0.87, 95% confidence interval [CI] 0.81 to 0.93) and serum food-specific IgE (AUC = 0.84, 95% CI 0.78 to 0.91, mean difference = 0.03, 95% CI −0.05 to 0.11). This evidence supports NICE CG116, which recognises the equivalence of the two testing approaches by advising a skin prick test and/or blood tests for specific IgE antibodies for suspected IgE-mediated food allergy.

There is an increasing body of literature relating to diagnostic tests that may have potential value in the future. Such studies include microarray technology assessing specific IgE antibodies to individual allergen components (for example, Bublin et al. 2011; Caubet et al. 2011; Codreanu et al. 2011; Nicolaou et al. 2010). Currently, these methods have not been validated in populations relevant to UK primary care or community settings, so have limited relevance to NICE CG116, and further research is needed. Another approach of potential interest for specialist centres is the use of grey-scale and colour Doppler ultrasound to assess

inflammation and gut thickening in infants with suspected cow's milk allergy. A small study evaluating this approach in a case-control study of 34 infants was reported by Epifanio et al. (2011), but further work is needed.

Supporting references

Bublin M, Dennstedt S, Buchegger M et al. (2011) The performance of a component-based allergen microarray for the diagnosis of kiwifruit allergy. Clinical & Experimental Allergy 41: 129–36
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2010.03619.x/abstract

Caubet JC, Kondo Y, Urisu A et al. (2011) Molecular diagnosis of egg allergy. Current Opinion in Allergy and Clinical Immunology 11: 210–5
Abstract: www.journals.lww.com/co-allergy/Abstract/2011/06000

Codreanu F, Collignon O, Roitel O et al. (2011) A novel immunoassay using recombinant allergens simplifies peanut allergy diagnosis. International Archives of Allergy & Immunology 154: 216–26
Abstract: www.karger.com/Abstract224161

Epifanio M, Spolidoro JV, Soder RB et al. (2011) Gray-scale and color Doppler ultrasound findings in children with cow's milk allergy. American Journal of Roentgenology 196: W817–22
Abstract: www.ajronline.org/content/196/6/W817.abstract

Nicolaou N, Poorafshar M, Murray C et al. (2010) Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. Journal of Allergy and Clinical Immunology 125: 191–7
Full text: www.journals.elsevierhealth.com/pdfs/journals/0091-6749/PIIS0091674909015346.pdf

Combining information from multiple tests

If there is diagnostic uncertainty, it may be useful to conduct both skin prick and specific IgE antibody blood testing. This was demonstrated in a study by **Johannsen et al. (2011)**, of 49 children (aged under 5 years) with peanut sensitisation identified during investigation of other allergic conditions, but with no known exposure to peanuts; these children are routinely advised to avoid all nuts. Graded open peanut challenge showed that the children were almost equally distributed between those showing no clinical response (n = 25, 51%) and those with a positive result to the challenge (n =24, 49%).

A skin prick test resulting in wheal diameter greater than 7 mm on the day of the challenge moderately predicted a positive challenge (sensitivity of 83%, negative predictive value of 84%). Fluorescent-enzyme immunoassay testing for specific IgE resulting in values above 2.0 kU/litre also moderately predicted a positive challenge (sensitivity of 79%, negative predictive value of 80%). However, using a combination of both skin prick testing (> 7 mm considered positive) and IgE testing (> 2.0 kU/litre considered positive) increased the predictive ability (sensitivity of 96%, negative predictive value of 95%).

If the outcome of food challenges could be accurately predicted using routinely available clinical data, this could reduce the need to conduct food challenge and be a useful practical aid to primary care and community healthcare professionals caring for children and young people with food allergies. In the first phase (exploration/feasibility) of a study by **DunnGalvin et al. (2011)**, clinical factors associated with a diagnosis of food allergy were identified retrospectively from data from 429 children.

In the second phase (development and evaluation of a predictive model), the predictive ability of six factors (size of skin prick test response, level of serum-specific IgE, total IgE minus serum-specific IgE, symptoms, sex and age) was assessed using data from 289 children from another centre. In the third phase (validation), the model was prospectively evaluated in 70 children undergoing food challenge for peanut, milk or egg allergy; 97% of cases were accurately predicted as positive and 94% as negative. Clinical prediction with the model was superior to serum-specific IgE only (92% accuracy), skin prick test only (57% accuracy) and serum-specific IgE and skin prick test (81% accuracy).

Although further validation is needed in other paediatric centres and it is not an approach recommended in other guidelines on food allergy (Boyce et al. 2010; Fiocchi et al. 2010), there may be value in combining information from a number of sources, which may be a consideration for future guidance reviews.

Key references

DunnGalvin A, Daly D, Cullinane C et al. (2011) Highly accurate prediction of food challenge outcome using routinely available clinical data. Journal of Allergy and Clinical Immunology 127: 633–9
Abstract: www.jacionline.org/article/S0091-6749(10)01883-X/abstract

Johannsen H, Nolan R, Pascoe EM et al. (2011) Skin prick testing and peanut-specific IgE can predict peanut challenge outcomes in preschool children with peanut sensitization. Clinical & Experimental Allergy 41: 994–1000
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2011.03717.x/abstract

Supporting references

Boyce JA, Assa'ad A, Burks AW et al. (2010) Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. Journal of Allergy and Clinical Immunology 126: S1–S58
Full text: www.elsevierhealth.com/pdfs/0091-6749/PIIS0091674910015666.pdf

Fiocchi A, Brozek J, Schünemann H et al. (2010) World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. Pediatric Allergy and Immunology 21: S1–S125
Full text: www.onlinelibrary.wiley.com/doi/10.1111/j.1399-3038.2010.01068.x/pdf

Testing for co-allergens

Children with an IgE-mediated food allergy may also show sensitivity to other related foods. A retrospective audit by **Ball et al. (2011)** reported the results of open nut challenges in 145 children (aged between 28 and 204 months; median 98.5 months) with peanut or tree nut allergy. Challenges were with homemade biscuits containing 8 g of peanut or each tree nut investigated. Among 94 children with peanut allergy subjected to a skin prick test to tree nuts, none of the 72 children with a negative skin prick result and a minority (7 of 22; 31.2%) of children with a positive skin prick result reacted to a mixed tree nut food challenge. Among 51 children with a tree nut allergy subjected to a skin prick test to peanuts and/or other tree nuts, 3 of 38 children (7.9%) with a negative skin prick result and 5 of 13 children (38.4%) with a positive skin prick result reacted to food challenge with peanuts and/or other tree nuts.

The study shows that detailed diagnosis of possible co-allergens can yield useful information to minimise the numbers of foods that a child needs to avoid, and has particular relevance for children with peanut allergy who may otherwise be advised to avoid all nuts. However, care should be taken to ensure that sufficient tree nut protein is included in the challenge to ensure that a negative result indicates lack of reactivity. The value of this approach is limited by current food labelling which often fails to distinguish peanuts and specific tree nuts.

This evidence demonstrates the value of negative skin prick tests and supports the recommendation of NICE CG116 to offer testing for likely co-allergens to children and young people with IgE-mediated food allergy.

Key reference

Ball H, Luyt D, Bravin K et al. (2011) Single nut or total nut avoidance in nut allergic children: outcome of nut challenges to guide exclusion diets. Pediatric Allergy and Immunology 22: 808–12
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1399-3038.2011.01191.x/abstract

Atopy patch testing

A case-control study by **Costa et al. (2011)** included 192 children (age 1–5 years; median age 2 years) who underwent atopy patch testing, in addition to assessment by skin prick testing, serum-specific IgE measurements and oral food challenge to suspected allergens. The accuracy of diagnosis was assessed only for the 44 children with allergy to cow's milk protein, most of whom had non-IgE-mediated allergy. Atopy patch testing showed low sensitivity (25.0%), low positive predictive value (45.8%) and low negative predictive value (64.1%), and although specificity was higher (81.9%), the authors concluded that the method was of little value for the diagnosis of food allergy.

This evidence supports the recommendation of NICE CG116 that atopy patch testing should not be used for the diagnosis of IgE-mediated food allergy in primary care or community settings.

Key reference

Costa AJF, Sarinho ESC, Almeida MEF et al. (2011) Allergy to cow's milk proteins: what contribution does hypersensitivity in skin tests have to this diagnosis? Pediatric Allergy and Immunology 22: e133–8
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1399-3038.2010.00988.x/abstract

1.4 Non-IgE-mediated food allergy

A prospective study of food protein-induced enterocolitis syndrome (FPIES) to cow's milk, a predominantly non-IgE-mediated food allergy with a currently uncharacterised immune basis, was reported by **Katz et al. (2011)**. The study assessed 13,019 newborn babies (98.4% of the 13,234 babies born during 2004–2006 in a single hospital in Israel). The cumulative prevalence of FPIES to cow's milk was 0.34% (44 infants). After a prolonged period of excluding milk protein from the diet, eight of these infants converted from a negative to a positive skin prick test to cow's milk protein (that is, IgE-mediated allergy). FPIES is a potentially life-threatening condition, which should be referred to a specialist centre.

NICE CG116 recommends the use of trial elimination of the suspected allergen for children and young people with suspected non-IgE-mediated food allergy. The risk of conversion to IgE-mediated allergy on reintroduction of cow's milk in some children with FPIES demonstrates the importance of the NICE CG116 recommendation for primary and community healthcare professionals to seek advice from a dietitian with appropriate competencies when commencing an elimination diet. The evidence from Katz et al. (2011) also suggests that conducting allergy tests for IgE-mediated allergy after long-term food exclusion in non-IgE-mediated reactions, to minimise the risk of subsequent IgE-mediated reactions, may be a consideration for future guidance reviews.

Atopy patch testing for non-IgE-mediated food allergy is not mentioned in current guidance and evidence from Costa et al. (2011) (see 'Atopy patch testing' in section 1.3 for details) that atopy patch testing is not an appropriate method for diagnosis is consistent with this.

Key reference

Katz Y, Goldberg MR, Rajuan N et al. (2011) The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large scale, prospective population-based study. Journal of Allergy and Clinical Immunology 127: 647–53
Full text: www.journals.elsevierhealth.com/pdfs/journals/0091-6749/PIIS0091674911000108.pdf

1.5 Providing information and support to the child or young person and their parent or carer

Parents and carers of children or young people with an allergy to one food need information on the likelihood of a response to other foods and, as noted in NICE CG116, what foods and drinks to avoid. Testing for likely co-allergens can yield useful information to minimise the number of foods that a child or young person needs to avoid (see 'Testing for co-allergens' in section 1.3).

Reports by **Cho et al. (2011)**, **Flammarion et al. (2011)** and Meyer et al. (2012) demonstrated the impact of food allergies on growth in children (see section 1.1 for details). Evidence from the narrative review by Meyer et al. (2012) also supports the recommendations of NICE CG116 that, for babies and young children with a suspected allergy to cow's milk protein, advice should be obtained from a dietitian with appropriate competencies. Information should be given on the most appropriate hypoallergenic formula or milk substitute for formula-fed babies. The review by Meyer et al. (2012) noted that although most current hypoallergenic milk formulas provide the recommended levels of protein, infants with cow's milk protein allergy have additional energy requirements to achieve catch-up growth. The authors provided practical suggestions for the choice of hypoallergenic formula, need for feed fortification and feeding strategies to address protein energy malnutrition in these children.

Also supporting the need for specialist dietary advice was evidence from a study by Sladkevicius et al. (2010), considered to be outside the scope of NICE CG116 as it focused on the costs of managing cow's milk allergy. However, the analysis of a database of 5 million patient records in the UK (estimated 1% incidence of cow's milk allergy) noted a mean delay of 2.2 months from the initial GP visit with suspected cow's milk allergy to the start of an exclusion diet. Although contrary to advice to use the most appropriate hypoallergenic formula, 60% of infants were treated initially with a soy-based formula; 9% of these infants were also intolerant to this formula. This evidence highlights the need for prompt diagnosis and specialist advice on the choice of formulas when assessing infants with cow's milk allergy.

Supporting reference

Sladkevicius E, Nagy E, Lack G et al. (2010) Resource implications and budget impact of managing cow milk allergy in the UK. Journal of Medical Economics 13: 119–28
Abstract: www.informahealthcare.com/doi/abs/10.3111/13696990903543242

1.6 Referral to secondary or specialist care

In the study by Katz et al. (2011) (see section 1.4 for details), none of the 44 children with FPIES to cow's milk in this study population showed soy allergy, though the authors noted that soy-induced FPIES can develop. However, the severity of delayed reactions to milk, and the risk of conversion to IgE-mediated allergy on reintroduction of milk, provides evidence to support the recommendation of NICE CG116 for children or young people with one or more acute systemic reaction, or severe delayed reaction, or multiple food allergies to be referred to secondary or specialist care.

1.7 Alternative diagnostic tools

NICE CG116 recommends that diagnosis of food allergy is not made using vega tests, applied kinesiology, hair analysis or serum-specific IgG testing. Recent evidence, supports the recommendation of NICE CG116 not to use serum-specific IgG testing in the diagnosis of food allergy.

A study by **Ahrens et al. (2010)** of diagnosis of allergy to hen's egg in 150 children (aged 5 months to 14 years) demonstrated that the serum level of hen's egg-specific IgE correlated with clinical response; levels were significantly higher in sensitised and allergic patients than sensitised but tolerant children ($p < 0.0001$), with no detectable levels in children who were non-sensitised and tolerant. All children with allergy had hen's egg-specific IgE levels above the proposed cut-off level of 12 kU/L. In contrast, there was no significant difference in levels of hen's egg-specific IgG or IgG4 between the three groups of children. In support of NICE CG116, the authors concluded that specific IgG or IgG4 should not be used for diagnosis.

A case-control, single-blind, observational pilot study by **Neilan et al. (2010)** assessed the levels of serum-specific IgG and IgG4 for a variety of potential food allergens (alpha-lactalbumin, casein, egg white, soy, corn, peanut, wheat). There was no significant difference ($p \geq 0.1$) in levels found in 22 children with functional dyspepsia (with lack of clinical response to acid-reduction therapy) and 19 matched patients with no history of gastrointestinal or allergic disorders. The authors noted that receiver operating characteristics showed IgG and IgG4 tests performed poorly or no better than chance for predicting assignment of children between groups.

Hochwallner et al. (2011) assessed levels of serum-specific IgG subclasses and IgA in 25 patients with IgE-mediated cow's milk allergy (including 18 children aged 4 months to 18 years), 19 adults with non-IgE-mediated intolerance to cow's milk, 15 adults with gastrointestinal problems unrelated to consumption of cow's milk, and a control group of 18 adults without gastrointestinal symptoms or IgE-mediated allergies. Only patients with cow's milk allergy showed elevated levels of cow's milk-specific IgE (1.3 to ≥ 200 kUA/litre vs <0.35 kUA/litre in other groups). These patients also showed generally higher median levels of IgG1 to purified recombinant cow's milk antigens (0.37–1.17 kUA/litre) than patients with non-IgE-mediated intolerance (0.11–0.27 kUA/litre), other gastrointestinal problems (0.10–0.20 kUA/litre) and controls (0.11–0.20 kUA/litre). The adults with non-IgE-mediated cow's milk gastrointestinal symptoms did not show elevated levels of IgG or IgA to purified cow's milk allergens. This evidence supports the view that IgG testing has no value in diagnosis of food allergy.

Key references

Ahrens B, Lopes de Oliveira LC, Schulz G et al. (2010) The role of hen's egg-specific IgE, IgG and IgG4 in the diagnostic procedure of hen's egg allergy. Allergy 65: 1554–7
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2010.02429.x/abstract

Hochwallner H, Schulmeister U, Swoboda I et al. (2011) Patients suffering from non-Ig-E mediated cow's milk protein intolerance cannot be diagnosed based on IgG subclass or IgA responses to milk allergens. Allergy 66: 1201–7
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2011.02635.x/abstract

Neilan NA, Dowling PJ, Taylor DL et al. (2010) Useful biomarkers in pediatric eosinophilic duodenitis and their existence: a case-control, single-blind, observational pilot study. Journal of Pediatric Gastroenterology and Nutrition 50: 377–84
Full text: www.jpgn/Fulltext/2010/04000/Useful_Biomarkers_in_Pediatric_Eosinophilic.6.pdf

2 New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process. However current uncertainties on the diagnosis and assessment of food allergy in children and young people can be found in the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs) at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Food allergy in children and young people. NICE clinical guideline 116 (2011). Available from www.nice.org.uk/guidance/CG116

Searches

The literature was searched to identify RCTs and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 January 2010 (the end of the search period of NICE clinical guideline 116) to 23 December 2011:

- CINAHL
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews – Cochrane Library
- Database of Abstracts of Reviews of Effects
- Embase
- MEDLINE
- NHS Health Economic Evaluation Database

Table 1 provides details of the MEDLINE search strategy used for the population, which was adapted to search the other databases listed above. Search filters were applied to capture studies on diagnosis, referral, patient information and economics (available on request).

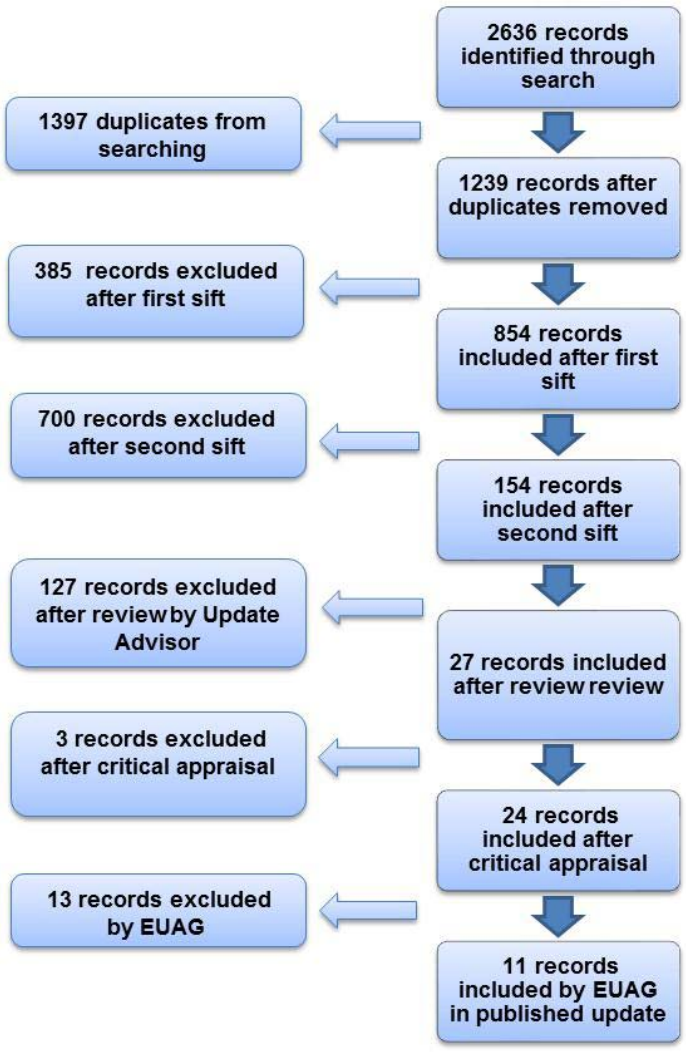
The search strategies were used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews and non-interventional studies (www.sign.ac.uk/methodology/filters.html).

Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies including all filters, are available on request from contactus@evidence.nhs.uk

Table 1 MEDLINE population search strategy (adapted for individual databases)

1	exp Food hypersensitivity/
2	(food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab.
3	((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or egg* or peanut* or nut* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana*)).ti,ab.
4	or/1-3
5	exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2396979)
6	(child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab.
7	5 or 6
8	4 and 7

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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