Diagnosis and assessment of food allergy in children and young people in primary care and community settings

Full guideline

November 2010

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

Contents

Introduction

Food allergy is an adverse immune response to a food. It can be classified into IgE-mediated and non-IgE mediated reactions. Many non-IgE reactions, which are poorly defined both clinically and scientifically, are believed to be T-cell mediated. Some reactions involve a mixture of both IgE and non-IgE responses and are classified as mixed IgE and non-IgE allergic reactions. Food allergy may be confused with food intolerance, which is a non-immunological reaction that can be caused by enzyme deficiencies, pharmacological agents and naturally occurring substances. Food intolerance will not be covered in this guideline. The starting point for the guideline is a suspicion of food allergy, and the use of an allergy-focused clinical history will help to determine whether a food allergy is likely.

In its review of allergy services in 2006, the Department of Health concluded that there was considerable variation in current practice for allergy care, with no agreed treatment pathways, referral criteria or service models. Specifically, it was reported that many people with allergies practised self-care, using alternative sources of support rather than NHS services (for example, complementary services with non-validated tests and treatments).

In the NHS, most allergy care takes place in primary care. People with a clear diagnosis, and mild but persistent symptoms, are usually managed in general practice without referral to a specialist service. Some people with allergies, and the parents or carers of children and young people with allergies, also buy over-the-counter medicines from community or high-street pharmacies. However, if there is diagnostic doubt or symptoms of a more severe disease, GPs often consider referral for a specialist opinion.

Patient-centred care

This guideline offers best practice advice on the care of children and young people with suspected food allergies.

Treatment and care should take into account patients' needs and preferences. Children and young people with suspected food allergies and their parents and carers should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If children do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

If the child or young person is under 16, healthcare professionals should follow the guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and children or young people with a suspected food allergy is essential. It should be supported by evidence-based written information tailored to the needs of the child or young person and their family. Treatment and care, and the information children and young people are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

Parents and carers should have the opportunity to be involved in decisions about treatment and care. Where appropriate, for example for older children, this should be with the child's agreement. Parents and carers should also be given the information and support they need. Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

1 Summary

1.1 List of all recommendations

Assessment and allergy-focused clinical history

1.1.1 Consider the possibility of food allergy in children and young people who have one or more of the signs and symptoms in table 1, below. Pay particular attention to persistent symptoms that involve different organ systems.

Table 1 Signs and symptoms of possible food allergy. (This list is not exhaustive. The absence of these symptoms does not exclude food allergy).

IgE- mediated	**Non-IgE-mediated**
The skin	
Pruritus	Pruritus
Erythema	Erythema
Acute urticaria – localised or generalised	Atopic Eczema
Acute angioedema – most commonly lips, face, around eyes	
The gastrointestinal system	
Angioedema of the lips, tongue and palate	Gastroesophageal Reflux Disease
Oral pruritus	Loose or frequent stools
Nausea	Blood and/or mucus in stools
Colicky abdominal pain	Abdominal pain
Vomiting	Infantile Colic
Diarrhoea	Food refusal or aversion
	Constipation
	Perianal redness
	Pallor and tiredness
	Faltering growth-in conjunction with at least one or more GIT symptoms above (with or without significant atopic eczema)

The Respiratory system (usually in combination with one or more of the above symptoms and signs)	
Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea or congestion (with or without conjunctivitis))	
Lower respiratory tract symptoms (cough, chest tightness, wheezing or shortness of breath)	
Other	
Signs or symptoms of anaphylaxis or other systemic allergic reactions	

1.1.2 Consider the possibility of food allergy in children and young people whose symptoms do not respond adequately to treatment for:

- atopic eczema[1]
- gastro-oesophageal reflux disease
- chronic gastrointestinal symptoms including chronic constipation

1.1.3 If food allergy is suspected (by a healthcare professional or the parent, carer, child or young person), a healthcare professional with the appropriate competencies (either a GP or other healthcare professional) should take an allergy-focused clinical history tailored to the presenting symptoms and age of the child or young person. This should include:

- any personal history of atopic disease (such as eczema)
- any individual and family history of atopic disease (such as asthma, eczema, allergic rhinitis or food allergy) in parents or siblings
- details of any foods that are avoided and the reasons why
- an assessment of presenting symptoms and other symptoms that may be associated with food allergy (see recommendation 1.1.1), including questions about:
  - the age of the child or young person when symptoms first started
  - speed of onset of symptoms following food contact
  - duration of symptoms
  - severity of reaction
  - frequency of occurrence
  - setting of reaction (for example, at school or home)
  - reproducibility of symptoms on repeated exposure
  - what food and how much exposure to it causes a reaction
  - cultural and religious factors that affect the foods they eat
- who has raised the concern and suspects the food allergy
- what the suspected allergen is

[1] For information about treatment for atopic eczema see 'Atopic eczema in children' (NICE clinical guideline 57)

- the child or young person's feeding history, including the age at which they were weaned and whether they were breastfed or formula-fed. If the child is currently being breastfed, consider the mother's diet.
- details of any previous treatment, including medication, for the presenting symptoms and the response to this
- any response to the elimination and reintroduction of foods.

1.1.4 Based on the findings of the allergy-focused clinical history, physically examine the child or young person, paying particular attention to:

- growth and physical signs of malnutrition
- signs indicating allergy-related comorbidities (atopic eczema, asthma and allergic rhinitis).

Diagnosis

Food allergy can be classified into IgE-mediated and non-IgE mediated allergy. IgE-mediated reactions are acute and frequently have rapid onset. Non-IgE mediated reactions are generally characterised by delayed and non-acute reactions.

Non-IgE mediated food allergy

1.1.5 Based on the results of the allergy-focused clinical history, if non-IgE mediated food allergy is suspected, trial elimination of the suspected allergen (normally for between 2–6 weeks) and reintroduce after the trial. Seek advice from a dietitian with appropriate competencies, about nutritional adequacies and follow-up.

IgE-mediated food allergy

1.1.6 Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, offer the child or young person a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens.

1.1.7 Tests should only be undertaken by healthcare professionals with the appropriate competencies to select, perform and interpret them.

1.1.8 Skin prick tests should only be undertaken where there are facilities to deal with an anaphylactic reaction.

1.1.9 Choose between a skin prick test and a specific IgE antibody blood test based on:

- the results of the allergy-focused clinical history **and**
- whether the test is suitable for, safe for and acceptable to the child or young person (or their parent or carer) **and**
- the available competencies of the healthcare professional to undertake the test and interpret the results.

1.1.10 Do not carry out allergy testing without first taking an allergy-focused clinical history. Interpret the results of tests in the context of information from the allergy-focused clinical history.

1.1.11 Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated allergy in primary care or community settings.

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

1.1.12 Based on the allergy-focused clinical history, offer the child or young person and their parent or carer, information that is age-appropriate about the:

- type of allergy suspected
- risk of severe allergic reaction
- potential impact of the suspected allergy on other healthcare issues, including vaccination
- diagnostic process, which may include:
  - an elimination diet followed by a possible planned rechallenge or initial food reintroduction procedure
  - skin prick tests and specific IgE antibody testing, including the safety and limitations of these tests
  - referral to secondary or specialist care.

1.1.13 Offer the child or young person and their parent or carer, information that is relevant to the type of allergy (IgE-mediated, non-IgE mediated or mixed) .

1.1.14 If a food elimination diet is advised as part of the diagnostic process (see recommendation 1.1.5), offer the child or young person and their parent or

carer, taking into account socioeconomic status and cultural and religious issues, information on:

- what foods and drinks to avoid
- how to interpret food labels
- alternative sources of nutrition to ensure adequate nutritional intake
- the safety and limitations of an elimination diet
- the proposed duration of the elimination diet
- when, where and how an oral food challenge or food reintroduction procedure may be undertaken
- the safety and limitations of the oral food challenge or food reintroduction procedure.

1.1.15 For babies and young children with suspected allergy to cows' milk protein, offer:

- food avoidance advice to breastfeeding mothers
- information on the most appropriate hypoallergenic formula or milk substitute to mothers of formula-fed babies.

Seek advice from a dietitian with appropriate competencies.

1.1.16 Offer the child or young person, or their parent or carer, information about the support available and details of how to contact support groups.

Referral to secondary or specialist care

1.1.17 Based on the allergy-focused clinical history, consider referral to secondary or specialist care in any of the following circumstances.

- The child or young person has:
  - faltering growth in combination with one or more of the gastrointestinal symptoms described in recommendation 1.1.1
  - not responded to a single-allergen elimination diet
  - had acute systemic reactions
  - had severe delayed reaction
  - confirmed IgE-mediated food allergy and concurrent asthma

- significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer.

- There is:
  - persisting parental suspicion of food allergy (especially in children or young people with difficult or perplexing symptoms) despite a lack of supporting history
  - strong clinical suspicion of IgE-mediated food allergy but allergy test results are negative
  - clinical suspicion of multiple food allergies.

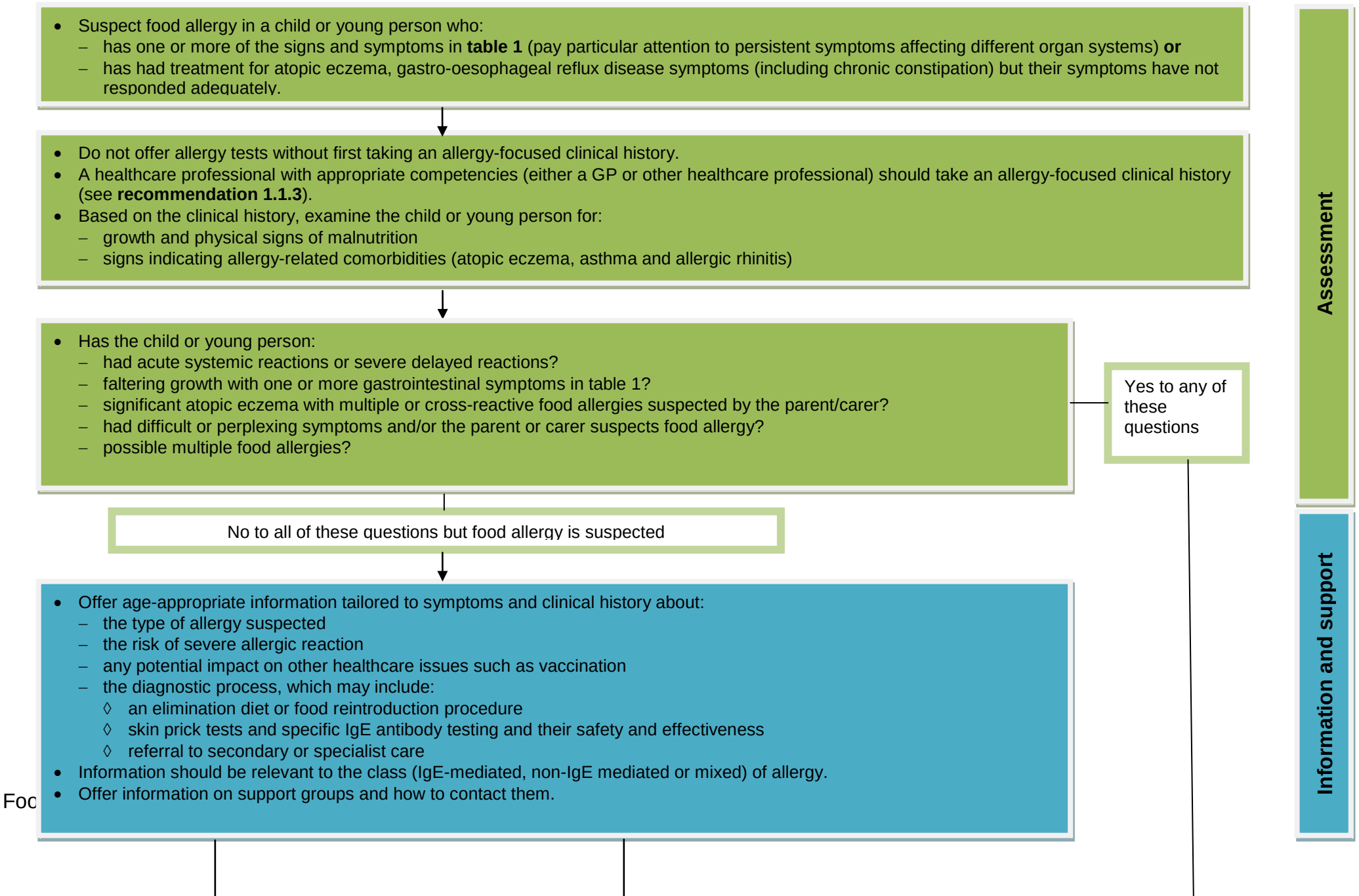
Alternative diagnostic tools

1.1.18 Do not use the following alternative diagnostic tests in the diagnosis of food allergy:

- vega test
- applied kinesiology
- hair analysis.

1.1.19 Do not use serum-specific IgG testing in the diagnosis of food allergy.

1.2 Care Pathway



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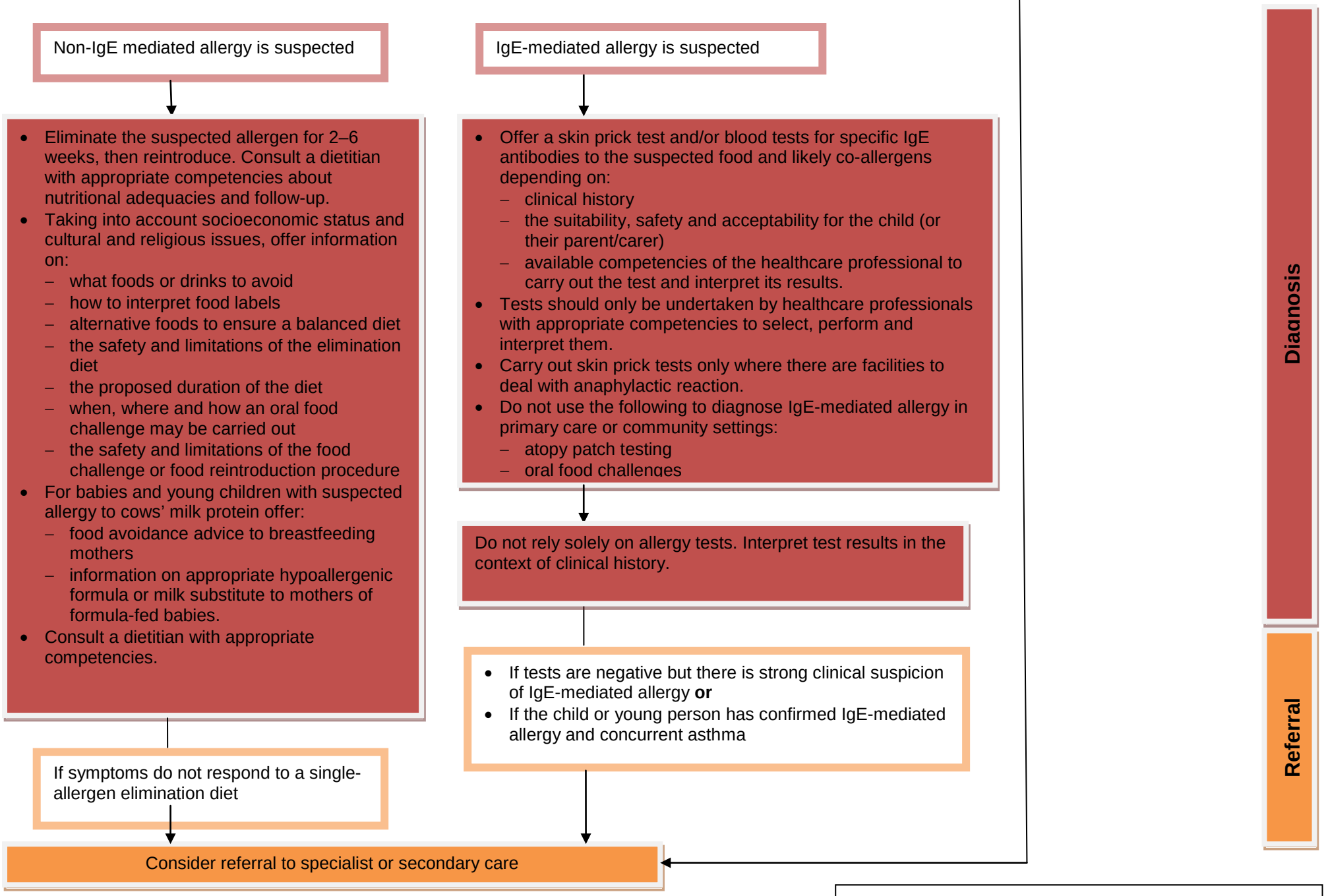

Non-IgE mediated allergy is suspected
IgE-mediated allergy is suspected
Diagnosis
Referral
• Eliminate the suspected allergen for 2–6 weeks, then reintroduce. Consult a dietitian with appropriate competencies about nutritional adequacies and follow-up.
• Taking into account socioeconomic status and cultural and religious issues, offer information on:
– what foods or drinks to avoid
– how to interpret food labels
– alternative foods to ensure a balanced diet
– the safety and limitations of the elimination diet
– the proposed duration of the diet
– when, where and how an oral food challenge may be carried out
– the safety and limitations of the food challenge or food reintroduction procedure
• For babies and young children with suspected allergy to cows' milk protein offer:
– food avoidance advice to breastfeeding mothers
– information on appropriate hypoallergenic formula or milk substitute to mothers of formula-fed babies.
• Consult a dietitian with appropriate competencies.
• Offer a skin prick test and/or blood tests for specific IgE antibodies to the suspected food and likely co-allergens depending on:
– clinical history
– the suitability, safety and acceptability for the child (or their parent/carer)
– available competencies of the healthcare professional to carry out the test and interpret its results.
• Tests should only be undertaken by healthcare professionals with appropriate competencies to select, perform and interpret them.
• Carry out skin prick tests only where there are facilities to deal with anaphylactic reaction.
• Do not use the following to diagnose IgE-mediated allergy in primary care or community settings:
– atopy patch testing
– oral food challenges
Do not rely solely on allergy tests. Interpret test results in the context of clinical history.
• If tests are negative but there is strong clinical suspicion of IgE-mediated allergy **or**
• If the child or young person has confirmed IgE-mediated allergy and concurrent asthma
If symptoms do not respond to a single-allergen elimination diet
Consider referral to specialist or secondary care
• Do not use the following diagnostic tests:
– vega test
– applied kinesiology
– hair analysis
– serum-specific IgG testing

1.3 Overview

1.3.1 Diagnosis of food allergy in children and young people in primary care and community settings

Food allergy is an adverse immune response to food allergens. It can be classified into IgE-mediated, non-IgE mediated and mixed IgE and non-IgE mediated allergy. IgE-mediated reactions are acute and frequently have rapid onset. Non-IgE mediated food allergy is frequently delayed in onset, and may need the opinion of a paediatrician or other specialist. See recommendation 1.1.1 for a detailed list of signs and symptoms.

Food allergy is among the most common of the allergic disorders and has been recognised as a major paediatric health problem in western countries. This is because of the potential severity of reactions and a dramatic increase in prevalence over the past recent decades. The prevalence of food allergy in Europe and North America has been reported to range from 6% to 8% in children up to the age of 3 years.

In the UK, concerns have been expressed about the prevalence of food allergy in the general population, especially by individuals and families affected by food allergy, as well as healthcare staff, schools, food producers and retailers, and government departments.

Correct diagnosis of food allergy, followed by counselling and advice based on accurate tests, is important because it will help to reduce the incidence of adverse reactions resulting from true food allergies, and will also help to reduce the unnecessary dietary exclusion of foods that are safe and should be eaten as part of a normal, healthy diet.

There is currently no evidence-based clinical guideline for use in England, Wales and Northern Ireland that addresses the diagnosis and assessment of food allergies in children and young people. This short clinical guideline aims to improve the care of children and young people with suspected food allergy

by making evidence-based recommendations on the diagnosis and assessment of food allergy.

1.3.2 Who this guideline is for

This document is intended to be relevant to staff in:

- primary care NHS settings
- community settings, including the home environment and health visits, preschools, schools, children's centres and other childcare health settings, community pharmacy, community dietitian and community paediatrician services.

The target population is:

- children and young people up to their 19th birthday with suspected food allergy presenting with symptoms such as atopic eczema, anaphylaxis, urticaria, rhinitis, conjunctivitis, asthma, gastrointestinal symptoms and oral allergy syndrome
- children and young people up to their 19th birthday who are at higher risk of developing food allergy, specifically those with, but not exclusive to:
  - existing atopic diseases, such as asthma, atopic eczema or allergic rhinitis, or
  - a first-degree relative (that is, a parent or sibling) with a food allergy or other atopic disease.

2 How this guideline was developed

2.1 Introduction

‘Diagnosis and assessment of food allergy in children and young people in primary care and community settings’ (NICE clinical guideline [XX]) is a NICE short clinical guideline. The guideline addresses six key clinical questions:

1. What elements should be included in an allergy-focused clinical history?
2. What tests should be used to diagnose non-IgE mediated allergy?

3. What tests should be used to diagnose IgE-mediated food allergy?
4. What information should be provided during the diagnostic process?
5. When should referrals to secondary and/or specialist care be made?
6. What is the value of alternative diagnostic tests?

Wherever possible, grading of recommendations assessment, development and evaluation (GRADE) was used as a method to assess study quality. However, where GRADE tables were not appropriate, quality assessments were based on critical appraisal of the study design and limitations. GRADE is currently only developed for intervention studies and therefore was not appropriate for clinical questions one, four and five, which addressed clinical history taking, the information needs of the child or young person and referral to secondary or specialist care, respectively. Where GRADE was not used, its principles (indirectness, limitations, inconsistency, imprecision and other considerations) formed part of the discussion of the evidence with the GDG. In question one we didn't identify any studies that compared clinical history taking with no clinical history taking. So studies in which clinical history had been taken were evaluated to identify the relevant questions for an allergy-focused clinical history. A review of reviews was done to analyse the risk factors that would be associated with likely development of food allergy. For question four most of the papers identified were qualitative papers, for which it is inappropriate to use a modified GRADE assessment. For question five no studies were identified comparing cohorts of children who had been referred with those who had not. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual

2.2 Assessment and allergy-focused clinical history

What elements should be included in an allergy-focused clinical history taking, physical examination and child/parent food diaries to diagnose and assess food allergy (IgE-mediated, non-IgE mediated or mixed IgE and non-IgE) effectively in children and young people?

2.2.1 Evidence review

Ten studies (Asarnoj et al. 2010; Dean et al. 2007; Hand et al. 2004; Hill and Hosking 2004; Kucukosmanoglu et al. 2008; Orhan et al. 2009; Roehr et al. 2004; Simeone et al. 2008; Skolnick et al. 2001; von et al. 2003) were selected for this question. These studies included papers that had carried out some form of clinical history taking, and the factors they included in the clinical histories described can be seen in evidence statement 2.2.2.2. Due to the lack of evidence a further review of reviews was carried out to identify secondary studies that had reviewed risk factors associated with the prevalence and/or incidence of food allergy. Six studies (see table 1 below) were included in the analysis of risk factors. For identified and excluded studies see appendices 1 and 2.

Table 1. Evidence summary for review of reviews

Evidence was extracted from six reviews which showed that the following risk factors and/or symptoms were important in the development of food allergy.

	Study ID					
Risk factor or symptom	**Lack 2008**	**Schuller 2004**	**Cochrane et al. 2009**	**Koplin et al. 2008**	**Chapman et al. 2006**	**Bahna 2003**
Genetic risk (atopic disease – especially food allergy in parents and/or siblings)	√ e.g. seven-fold increase in peanut allergy if the child has a parent or sibling with peanut allergy	√	√	Not reported	√	Not reported
Other atopic disease (including eczema, asthma and allergic rhinoconjunctivitis)	√ 33–81% of children with infantile eczema have IgE-mediated food allergy. The presence of eczema in the first 6 months of life was associated with an increased risk of peanut allergy, and this risk was higher with more severe eczema.	Not reported	√	Not reported	Not reported	Not reported
Early exposure to food allergens through breastfeeding and/or maternal diet	Lack of evidence	Variable results	Not reported		Variable results	Not reported
Delivery by caesarean section	√ A recent meta-analysis found six studies that confirmed a mild effect of c-section, increasing the risk of food allergy or atopy (OR 1.32; CI 1.12 to 1.55)	Not reported	Still unknown influence on development of food allergy	√ (Eggesbo 2003 OR 1.6; CI 0.5 to 5.1, Renz-Polster 2005 OR 1.34; CI 0.54 to 3.29)	Variable results	Not reported

Maternal smoking up to the end of pregnancy and after birth	Not reported	√	Not reported	Not reported	Not reported	Not reported
Gastrointestinal symptoms (including oral allergy syndrome, vomiting, colic, diarrhoea, gastro-oesophageal reflux, constipation, enterocolitis, eosinophilic gastroenteropathy and protein-losing enteropathy)	Not reported	Not reported	Not reported	Not reported	Not reported	√
Dermatological symptoms (including atopic dermatitis, acute urticaria/angioedema, contact rash, contact dermatitis and vasculitis)	Not reported	Not reported	Not reported	Not reported	Not reported	√
Respiratory symptoms (including rhinitis, laryngeal edema, asthma, chronic otitis media, Heiner syndrome and hypersensitivity pneumonitis)	Not reported	Not reported	Not reported	Not reported	Not reported	√
Systemic anaphylaxis (including food-dependent, exercise-induced anaphylaxis)	Not reported	Not reported	Not reported	Not reported	Not reported	√
OR, odds ratio; CI, confidence interval						

2.2.2 Evidence statements

2.2.2.1 No studies were identified that evaluated the use of a clinical history, or compared different items of a history, for the diagnosis of food allergy.

2.2.2.2 Evidence from ten low-quality studies reported clinical history taking or questionnaires used in the diagnosis of food allergy. The following items were included:

- *gender and current age of the child or young person*
- *family history of atopic disease such as asthma and eczema*
- *age of onset of perceived allergy*
- *adverse reactions within 2 hours of eating specific foods*
- *symptoms experienced, including:*
  - *cutaneous (eruption, itching, rash, swelling)*
  - *nasal (sneezing, itching, secretion, blockage)*
  - *ocular (redness, itching, secretion)*
  - *bronchial (cough, wheezing, shortness of breath)*
  - *gastrointestinal (stomach ache, nausea, vomiting, diarrhoea)*
  - *laryngeal (difficulty swallowing or speaking)*
  - *cardiovascular (palpitations, tachycardia, hypotension)*
- *previous food allergy*
- *resolution or lack of resolution of reactions*
- *duration of exclusive breastfeeding in babies*
- *age of starting certain foods, such as cows' milk, and solid foods when weaning*
- *current dietary habits*
- *smoking habits of children and cohabitants, such as parents.*
- *any previous physician-diagnosed symptoms and current medication*

- *pet ownership*
- *environmental allergen exposure and cross-sensitisation*
- *questionnaire administered by trained allergy nurse/professional.*

2.2.2.3 *Evidence from four low-quality reviews showed that atopic disease or food allergy in parents or siblings is a risk factor for the development of food allergy.*

2.2.2.4 *Evidence from two low-quality reviews showed that children with other atopic disease were more likely to develop food allergy.*

2.2.2.5 *Evidence from one moderate-quality review showed that children with more severe and earlier onset of eczema were more likely to develop food allergy.*

2.2.2.6 *Evidence from two low-quality reviews showed variable evidence that early exposure to food allergens through breastfeeding and maternal diet was a risk factor for food allergy.*

2.2.2.7 *Evidence from three low-quality reviews showed variable results for caesarean section as a risk factor for developing food allergy.*

2.2.2.8 *Evidence from one moderate-quality review showed a marginal increase in food allergy associated with caesarean section.*

2.2.2.9 *Evidence from one low-quality review showed that maternal smoking up to the end of pregnancy may be a risk factor for food allergy.*

2.2.2.10 *Evidence from one low-quality review showed that gastrointestinal, dermatological and respiratory symptoms, and systemic anaphylaxis were signs of food allergy.*

2.2.3 Evidence to recommendations

The GDG considered the evidence within the framework of factors that would prompt investigation of possible food allergy. These would be undertaken in the following sequence: initial assessment, allergy-focused clinical history

taking and further investigations. Following evidence from the review of reviews, the GDG felt that signs and symptoms should be highlighted as a first recommendation because it would be these that the child or young person would present to their GP. The group agreed that assessing for genetic risk and the presence of other atopic disease would form part of the allergy-focused clinical history and would not need to be included with the initial signs and symptoms. It was also felt that smoking was not typically used in clinical practice to assess risk for developing food allergy and the evidence was not strong enough to support a specific recommendation. The GDG agreed that the three main systems most commonly affected by food allergy were the gut, skin and respiratory system. As the evidence base was weak, GDG consensus was used to list the most common symptoms of food allergy, based on GDG members' expertise and clinical experience. The GDG agreed that the initial assessment of signs and symptoms should be split by whether an IgE or non-IgE food allergy is most likely and that particular attention should be given to persistent symptoms that affect different organ systems. The group also agreed that respiratory symptoms in isolation were not likely to be predictive of food allergy but were usually present with other symptoms. As well as the evidence reviewed for clinical history taking, the GDG considered suspicion of an adverse reaction to a food by a healthcare professional or the parent, carer, child, or young person to be an important factor. It was acknowledged that although this may not be predictive of confirmed allergy, it should lead to an allergy-focused clinical history. In addition, the GDG considered feeding history to be an important factor. It was also agreed that the risk attributable to family history of atopy should be restricted to first-degree relatives.

The GDG agreed that the evidence presented was limited and did not include all the important components of an allergy-focused clinical history. As a result, many of the recommendations were made on the basis of consensus. Although the evidence for early exposure to food allergens through breastfeeding and/or maternal diet was shown to be variable, the GDG discussed how some non-IgE mediated symptoms appear during breastfeeding and stop when breastfeeding is stopped. There was consensus

that this should be included in the allergy-focused clinical history. It was also felt that a physical examination should always follow on from an allergy-focused clinical history. Although allergies do not always affect growth, there was a consensus that growth and nutrition were important aspects that should be highlighted. The group also discussed the importance of assessing co morbidities that may be related to food allergy.

2.2.4 Recommendations

Recommendation 1.1.1

Consider the possibility of food allergy in children and young people who have one or more of the following signs and symptoms in table 1, below. Pay particular to persistent symptoms that involve different organ systems:

Table 1 Signs and symptoms of possible food allergy. (This list is not exhaustive. The absence of these symptoms does not exclude food allergy).

IgE- mediated	Non-IgE-mediated
The skin	
Pruritus	Pruritus
Erythema	Erythema
Acute urticaria – localised or generalised	Atopic Eczema
Acute angioedema – most commonly lips, face, around eyes	
The gastrointestinal system	
Angioedema of the lips, tongue and palate	Gastroesophageal Reflux Disease
Oral pruritus	Loose or frequent stools
Nausea	Blood and/or mucus in stools
Colicky abdominal pain	Abdominal pain
Vomiting	Infantile Colic
Diarrhoea	Food refusal or aversion
	Constipation
	Perianal redness
	Pallor and tiredness
	Faltering growth-in conjunction with at least one or more GIT symptoms above (with or without significant atopic eczema)
The Respiratory system (usually in combination with one or more of the above symptoms and signs)	
Upper respiratory tract symptoms (nasal itching, sneezing, rhinorrhoea or congestion (with or without	

conjunctivitis))	
Lower respiratory tract symptoms (cough, chest tightness, wheezing or shortness of breath)	
Other	
Signs or symptoms of anaphylaxis or other systemic allergic reactions	

Recommendation 1.1.2

Consider the possibility of food allergy in children and young people whose symptoms do not respond adequately to treatment for:

- atopic eczema[2]
- gastro-oesophageal reflux disease
- chronic gastrointestinal symptoms including chronic constipation

Recommendation 1.1.3

If food allergy is suspected (by a healthcare professional or the parent, carer, child or young person), a healthcare professional with the appropriate competencies (either a GP or other healthcare professional) should take an allergy-focused clinical history tailored to the presenting symptoms and age of the child or young person. This should include:

- any personal history of atopic disease (such as eczema)
- any individual and family history of atopic disease (such as asthma, eczema, allergic rhinitis or food allergy) in parents or siblings
- details of any foods that are avoided and the reasons why
- an assessment of presenting symptoms and other symptoms that may be associated with food allergy (see recommendation 1.1.1), including questions about:
  - the age of the child or young person when symptoms first started

[2] For information about treatment for atopic eczema see 'Atopic eczema in children' (NICE clinical guideline 57)

  - speed of onset of symptoms following food contact
  - duration of symptoms
  - severity of reaction
  - frequency of occurrence
  - setting of reaction (for example, at school or home)
  - reproducibility of symptoms on repeated exposure
  - what food and how much exposure to it causes a reaction
  - cultural and religious factors that affect the foods they eat
- who has raised the concern and suspects the food allergy
- what the suspected allergen is
- the child or young person's feeding history, including the age at which they were weaned and whether they were breastfed or formula-fed. If the child is currently being breastfed, consider the mother's diet.
- details of any previous treatment, including medication, for the presenting symptoms and the response to this
- any response to the elimination and reintroduction of foods.
-

Recommendation 1.1.4

Based on the findings of the allergy-focused clinical history, physically examine the child or young person, paying particular attention to:

- growth and physical signs of malnutrition
- signs related to allergy-related co morbidities (atopic eczema, asthma and allergic rhinitis).

2.3 Diagnosis of non-IgE mediated food allergy

What diagnostic tools and strategy are most appropriate to diagnose non-IgE mediated and mixed IgE and non-IgE mediated food allergy in children and young people in primary care?

2.3.1 Evidence review

11 papers were included for critical appraisal for this question.

Of these, six studies (Cavataio et al. 1996; Fiocchi et al. 2004; Ford et al. 1983; Kalach et al. 2005; Niggemann et al. 2000; Verini et al. 2007) analysed the differential diagnosis of non-IgE, IgE and mixed IgE and non-IgE mediated food allergy. Three studies (Cavataio et al. 1996; Iacono et al. 1995; Nielsen et al. 2006) assessed the utility of various tools such as biopsy, atopy patch testing, oesophageal endoscopy, 24-hour oesophageal pH monitoring and double-blind placebo-controlled food challenge (DBPCFC) to diagnose various forms of non-IgE mediated food allergy. Four studies (Fogg et al. 2006; Kalach et al. 2005; Nielsen et al. 2004; Niggemann et al. 2000) examined the diagnostic utility of atopy patch testing for the diagnosis of non-IgE mediated food allergy. Three studies (Cavataio et al. 1996; Nielsen et al. 2004; Nielsen et al. 2006) looked at the utility of food elimination and reintroduction in the diagnosis of non-IgE mediated food allergy. The evidence from these summaries is presented in the GRADE profiles below. For identified and excluded studies see appendices 1 and 2.

GRADE profile 1: Differential diagnosis of non-IgE and mixed IgE and non-IgE mediated food allergy

Studies	Design	Diagnostic tests	Comparators	Type of food	Diagnosis	Limitations*	Inconsistency *	Indirectness*	Imprecision*	Other Considerations	Quality
Outcome: differential diagnosis of non-IgE and mixed IgE and non-IgE delayed onset and immediate using combinations of tests											
Six studies (Cavataio et al. 1996; Kalach et al. 2005; Ford et al. 1983; Fiocchi et al. 2004; Niggeman et al. 2000; Verini et al. 2007)	Observational	Specific IgE antibody test, atopy patch test	Endoscopy biopsy and DBPCFC	Cows' milk, soy, hens' eggs, wheat, peanuts	Conflicting results. No clear-cut differential diagnosis. Studies more definite on IgE and very vague on non-IgE	Y	Y	Y	Y	N	Very low

* Please see footnotes 3–6 for criteria for downgrading

GRADE profile 2: The utility of different tools for the correct diagnosis of non-IgE and mixed IgE and non-IgE mediated food allergy

Studies	Outcome: utility of various tools for the correct diagnosis and assessment of non-IgE and mixed IgE and non-IgE mediated food allergy in children in primary care	Limitations*	Inconsistency*	Indirectness*	Imprecision*	Other Considerations	Quality
Three studies (Cavataio et al. 1996); Nielsen et al. 2006; Iacono et al. 1995)	Combination of biopsy, atopy patch test, oesophageal endoscopy, 24-hour oesophageal pH monitoring and DBPCFC to diagnose various forms of non-IgE food allergy. Each endoscopy, biopsy and/or food challenge was done in secondary or specialist care.	Y	Y	Y	Y	N	Very low
Three studies (Cavataio et al. 1996; Nielsen et al. 2006; Iacono et al. 1995)	483 children with suspected gastro-oesophageal reflux disease and/or hypersensitivity to cows' milk protein had to be referred to secondary or specialist care for a differential diagnosis. Upon evaluation it was found that 30 of 72 children with gastro-oesophageal reflux also had hypersensitivity to cows' milk protein. In these children 24-hour oesophageal pH monitoring was needed to identify cases of gastro-oesophageal reflux associated with the cows' milk protein hypersensitivity. The pH monitoring was found to be 90% sensitive and 100% specific. Circulating eosinophil count also had sensitivity of between 33% and 40% and specificity ranging from 57% to 100%.	Y	Y	Y	Y	N	Very low

* Please see footnotes 3–6 for criteria for downgrading

GRADE profile 3: The diagnostic utility of the atopy patch test for diagnosis of non-IgE mediated food allergy

Studies	Outcome: diagnostic utility of the atopy patch test in diagnosing non-IgE mediated food allergy Foods tested: cows' milk, wheat, soy, oats, rice, hens' eggs	Limitations*	Inconsistency*	Indirectness*	Imprecision*	Other considerations	Quality
Sensitivity, specificity and predictive values for the atopy patch test for diagnosis of non-IgE mediated food allergy							
Four studies (Kalach et al. 2005, Fogg et al. 2006, Niggeman et al. 2000, Nielsen 2004)	Positive predictive values ranged from 75% to 95%. Negative predictive values ranged from 51.7% to 100%	Y	Y	Y	Y	N	Very low
	Sensitivities ranged from 44% to 100% Specificities ranged from 71% to 100%	Y	Y	Y	Y	N	Very low

* Please see footnotes 3–6 for criteria for downgrading

GRADE profile 4: The utility of food elimination and other diagnostic tools in the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease

Studies	Outcome: utility of food elimination in combination with other diagnostic tools for the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease	Limitations*	Inconsistency*	Indirectness*	Imprecision*	Other Considerations	Quality
Three studies (Cavataio et al. 1996; Nielsen et al. 2004, 2006)	Evaluation of the studies showed that in 200 children, food elimination was used initially to identify possible food allergy and to differentiate between food allergy and primary gastro-oesophageal reflux disease. A cohort of 140 children was differentially diagnosed with either cows' milk protein allergy or primary gastro-oesophageal reflux disease or both, using a combination of food elimination, food challenge and biopsy.	Y	Y	Y	Y	N	Very low

* Please see footnotes 3–6 for criteria for downgrading

Studies	Outcome: utility of food elimination in combination with other diagnostic tools for the differential diagnosis of non-IgE mediated food allergy and gastro-oesophageal reflux disease	Limitations[3]	Inconsistency[4]	Indirectness[5]	Imprecision[6]	Other Considerations	Quality
Three studies (Cavataio et al. 1996; Nielsen 2004, 2006)	Serum IgG, 24-hour oesophageal pH metric testing, 48-hour testing in combination with food elimination needed for differential diagnosis of non-IgE food allergy.	Y	Y	Y	Y	N	Very low

[3] Limitations: not all cases of food challenge were carried out blind and there was no consistent definition of non-IgE mediated food allergy diagnosis, causing heterogeneity across study population characteristics.
[4] Inconsistencies: differences in diagnostic performance could not be explained by differences in the study population and so has been downgraded.
[5] Indirectness: not all papers compared the same tests with DBCPFC. Endoscopy was needed to confirm diagnosis in some cases.
[6] Imprecision: cannot be assessed in diagnostic studies so it has been assumed that imprecision exists here and has been downgraded.

2.3.2 Evidence statements

2.3.2.1 *Very low-quality evidence from six studies of 618 children showed that there is ambiguity in the differential diagnosis of IgE, non-IgE, and mixed IgE and non-IgE food allergy. The studies used a combination of tests such as specific IgE antibody test, skin prick test, atopy patch test, endoscopy, biopsy, and double-blind placebo-controlled food challenge.*

2.3.2.2 *Very low-quality evidence from three studies of 483 children showed that a combination of diagnostic tests was needed to diagnose various forms of non-IgE mediated food allergy. These tests included biopsy, atopy patch test, 24-hour oesophageal pH monitoring and double-blind placebo-controlled food challenge. The confirmatory tests, such as endoscopy, biopsy (in the case of eosinophilic esophagitis) and food challenge, were undertaken in secondary or specialist care.*

2.3.2.3 *Very low-quality evidence from four studies of 161 children in secondary or specialist care showed that the atopy patch test was a useful diagnostic tool in the diagnosis of non-IgE mediated food allergy to foods such as cows' milk, wheat, soy, oats, rice, and hens' eggs. Sensitivity ranged from 44% to 100% with associated specificities ranging from 71% to 100%.*

2.3.2.4 *Very low-quality evidence from three studies of 340 children showed that food elimination and reintroduction was a useful diagnostic tool for non-IgE mediated food allergy.*

2.3.2.5 *Very low-quality evidence from three studies of 200 children showed that food elimination and rechallenge in combination with other tests was useful in differentiating between food allergy and primary gastro-oesophageal reflux disease.*

2.3.3 Health economic modelling

Approach

The GDG concluded on the basis of the data that the preferred clinical pathway for children and young people with a suspected non-IgE mediated food allergy would be a full allergy-focused clinical history followed by a food elimination diet.

Food elimination represents not only a diagnostic tool for food allergy but also its treatment. If someone has a suspected food allergy they will be put on a food elimination diet. If the allergy is confirmed by their symptoms improving, the diet is continued as treatment. Therefore, the economic question is not immediately apparent.

This guideline is restricted to the diagnosis of food allergy in children and young people, so it is not possible to evaluate how food elimination is used to manage food allergy. This also means that reintroducing the food at a later date cannot be evaluated.

In conclusion, there does not appear to be any economic question to answer, as there is no opportunity cost involved. Work has been done by Sladkevicius et al. in 2010 to examine the resource use of diagnosing and managing allergy to cows' milk protein (the majority of which is non-IgE mediated) in the UK. This paper will be used to see where potential efficiencies could be made in the diagnosis of non-IgE mediated food allergy.

Sladkevicius et al. 2010

Sladkevicius et al. 2010 used data from the Health Improvement Network database, which has data from 300 GP practices and 5 million people. The study selected at random 1000 babies (aged under 1 year) with newly diagnosed cows' milk protein allergy and followed them for 12 months after their first presentation. Data recorded included age, sex, diagnosis, other symptoms and morbidities and duration of symptoms. Several resource uses were recorded; these included appointments with specialists and GP visits.

A health economic model was devised which depicted the treatment received by these babies. This model was based on a previous model (Guest and Nagy et al. 2009). Several pathways were modelled which accounted for comorbidities and symptoms. All resource costs were from 2006/07 using the Personal Social Services Research Unit (PSSRU) and NHS reference costs.

Results

This paper indicated that the key issues are the high number of GP visits (on average 18.2 visits per baby) and, in particular, the high number of GP visits before starting a food elimination diet (4.2 visits) and the time taken to identify an appropriate milk formula (2.9 months). On average, it was 3.6 months until diagnosis, indicating that current practice is to use the food elimination diet as a diagnostic tool. The key to reducing healthcare resource use is faster diagnosis and starting the appropriate formula.

Review

A full review is included in appendix 3. This review indicates that the paper is of good quality and is applicable to the question. The GDG expressed concerns about the GP-centric focus and the possibility that community nurses and other services may have been excluded. This was echoed by examination of the model used in previous analyses, in which all pathways focused on the GP (or equivalent). No model structure was produced in the 2010 paper, which makes it difficult to identify whether the paper includes NHS-specific pathways. However, as it is based on GP data and uses NHS costs it should be applicable. The paper is appropriate to generalise the diagnosis of non-IgE mediated food allergy.

Recommendations made in this guideline on involving a dietitian in diagnosis should reduce the time to diagnosis and appropriate milk formula chosen. This should lead to an economic saving for the NHS brought about by reduced GP visits.

2.3.4 Evidence to recommendations

Although the evidence showed that the atopy patch test may be useful in the diagnosis of non-IgE mediated food allergy, it was recognised that there was

wide variation in the sensitivities and specificities of this test. The GDG discussed the methodology and interpretation of the atopy patch test and felt it was less well-standardised and more variable than other tests. The group also felt that the results may not be directly applicable to a diverse primary care population as the papers reviewed were all conducted in secondary or specialist settings where the test may have performed more effectively. As a result the GDG concluded that the test was of little value in diagnosing non-IgE mediated food allergy in primary care settings.

The GDG discussed the limited evidence on the utility of the various tests for diagnosing non-IgE mediated food allergy. There was a consensus that the chance of misdiagnosis would be reduced by taking an allergy-focused clinical history, despite the lack of evidence of its value. It was felt that the history. would be especially useful in situations where food elimination had resolved symptoms.

Although the evidence evaluating food elimination was of low quality, the GDG felt that a well-managed and supervised food elimination and reintroduction diet in combination with a correctly carried out allergy-focused clinical history was a sensible way to diagnose non-IgE mediated food allergy in primary care. The GDG discussed the duration of food elimination diets and the competencies needed by healthcare professionals to oversee them. It was also agreed that, although a referral would not always be necessary, advice should be sought from a dietitian and this should include follow-up and nutritional issues.

There was also discussion about whether food elimination should include food reintroduction. Evidence was very poor in addressing food elimination for various age groups, but the GDG felt that the principle of food elimination would be applicable to all age groups. The GDG also recognised the potential risks of an immediate allergic reaction on reintroduction following a period of elimination in children who have presented with an apparently non-IgE mediated food allergy (particularly with symptoms of eczema). GDG consensus suggests this is a rare occurrence, and is generally limited to allergies to cows' milk protein and hens' eggs. It did not justify a

recommendation to perform diagnostic tests on all children before reintroduction in suspected non-IgE mediated food allergy.

2.3.5 Recommendations

Recommendation 1.1.5

Based on the results of the allergy-focused clinical history, if non-IgE mediated food allergy is suspected, trial elimination of the suspected allergen (normally for between 2–6 weeks) and reintroduce after the trial. Seek advice from a dietitian with appropriate competencies, about nutritional adequacies and follow-up.

2.4 Diagnosis of IgE-mediated food allergy

What diagnostic tools and strategy are most appropriate to diagnose IgE-mediated food allergy in children and young people in primary care?

2.4.1 Evidence review

Twenty-three studies were included for critical appraisal for this question.

Of these, 16 studies (Caffarelli et al. 1995; Canani et al. 2007; Dieguez et al. 2008; Dieguez et al. 2009; Eigenmann and Sampson 1998; Hansen et al. 2004; Hill et al. 2004; Knight et al. 2006; Mehl et al. 2006; Monti et al. 2002; Niggemann et al. 2002; Osterballe et al. 2004; Roehr et al. 2001; Sampson 1998; Verstege et al. 2005; Vierrucci et al. 1989), eleven studies (Ando et al. 2008; Caffarelli et al. 1995; Canani et al. 2007; Celik-Bilgili et al. 2005; Dieguez et al. 2009; Knight et al. 2006; Mehl et al. 2006; Osterballe et al. 2004; Roehr et al. 2001; Sampson 1998; Vierrucci et al. 1989) and six studies (Canani et al. 2007; Hansen et al. 2004; Mehl et al. 2006; Niggemann et al. 2002; Osterballe et al. 2004; Roehr et al. 2001) looked at the utility of the skin prick test, specific IgE antibody test and atopy patch test respectively in the diagnosis of allergy to hens' eggs.

Twelve studies (Canani et al. 2007; Eigenmann and Sampson 1998; Garcia-Ara et al. 2001; Hill et al. 2004; Mehl et al. 2006; Niggemann et al. 2002; Osterballe et al. 2004; Roehr et al. 2001; Saarinen et al. 2001; Sampson 1998; Verstege et al. 2005; Vierrucci et al. 1989), eight studies (Canani et al. 2007; Celik-Bilgili et al. 2005; Garcia-Ara et al. 2001; Mehl et al. 2006; Osterballe et al. 2004; Roehr et al. 2001; Sampson 1998; Vierrucci et al. 1989) and seven studies (Canani et al. 2007; Cudowska and Kaczmarski 2005; de et al. 2003; Mehl et al. 2006; Niggemann et al. 2002; Osterballe et al. 2004; Roehr et al. 2001) evaluated the utility of the skin prick test, specific IgE antibody test and atopy patch test respectively in the diagnosis of cows' milk protein allergy.

Five studies (Eigenmann and Sampson 1998; Hill et al. 2004; Rancé et al. 2002; Sampson 1998; Vierrucci et al. 1989) and three studies (Rancé et al. 2002; Sampson 1998; Vierrucci et al. 1989) assessed the value of the skin

prick test and specific IgE antibody test respectively in the diagnosis of peanut allergy.

Eight individual studies (Celik-Bilgili et al. 2005; Eigenmann and Sampson 1998; Jarvinen et al. 2003; Mehl et al. 2006; Niggemann et al. 2002; Roehr et al. 2001; Sampson 1998; Verstege et al. 2005) assessed the value of the skin prick test, specific IgE antibody test and atopy patch test in the diagnosis of wheat allergy.

Seven individual studies (Celik-Bilgili et al. 2005; Eigenmann and Sampson 1998; Mehl et al. 2006; Niggemann et al. 2002; Roehr et al. 2001; Sampson 1998; Verstege et al. 2005) assessed the value of the skin prick test, specific IgE antibody test and atopy patch test in the diagnosis of soy allergy.

In addition, three studies (Fiocchi et al. 2002; Sampson 1998; Vierrucci et al. 1989) assessed the use of the skin prick test and/or the specific IgE antibody test in the diagnosis of tomato, fish and beef allergy respectively.

For identified and excluded studies see appendices 1 and 2.

GRADE profile 5: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated allergy to hens' eggs

Studies	Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated allergy to hens' eggs Evaluation of 18 individual studies for allergy to hens' eggs	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Sixteen studies (Vierrucci et al. 1989, Niggemann et al. 2002, Dieguez et al. 2008, Hill et al. 2004, Sampson et al. 1998, Eigenmann & Sampson 1998, Roehr et al. 2001, Dieguez et al. 2009, Verstege et al. 2005, Mehl et al. 2006, Caffarelli et al. 1995, Hansen et al. 2004, Knight 2006, Canani et al. 2007, Osterballe et al.2004, Monti et al. 2002)	Sensitivities ranged from 57.8% to 100% Specificities ranged from 20% to 99% Positive predictive values ranged from 40% to 93%. Negative predictive values ranged from 50% to 100%	Skin prick test	Y	Y	N	Y	Y	Very Low
Eleven studies (Vierrucci et al. 1989, Sampson et al. 1998, Roehr et al. 2001, Celik-Bilgili et al. 2005, Dieguez et al.2009, Mehl et al. 2006, Ando et al. 2008, Caffarelli et al. 1995, Knight et al. 2006, Canani et al. 2007, Osterballe et al. 2004)	Sensitivities ranged from 31.5% to 100% Specificities ranged from 20% to 89% Positive predictive values ranged from 40% to 84%. Negative predictive values ranged from 50% to 100%	IgE	Y	Y	N	Y	Y	Very low

Six studies (Niggemann et al. 2002, Roehr et al. 2001, Mehl et al. 2006, Hansen et al. 2004, Canani et al. 2007, Osterballe et al. 2004)	Sensitivities ranged from 5.26% to 84.2% Specificities ranged from 87% to 100% Positive predictive values ranged from 75% to 100%. Negative predictive values ranged from 43% to 90%	Atopy patch test	Y	Y	N	Y	Y	Very low

***Please see footnotes 7–10 for criteria for downgrading**

GRADE profile 6: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated cows' milk protein allergy

Studies	Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated cows' milk protein allergy Evaluation of 15 individual studies for cows' milk protein allergy	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Twelve studies (Vierrucci et al. 1989, Niggemann et al. 2002, Hill et al. 2004, Sampson 1998, Eigenmann & Sampson 1998, Roehr et al. 2001, Verstege et al.2005, Mehl et al. 2006, Saarinen et al. 2001, Osterballe et al. 2004, Garcia-Ara et al. 2001, Canani et al. 2007)	Sensitivities ranged from 28% to 96% Specificities ranged from 46% to 100% Positive predictive values ranged from 66% to 82%. Negative predictive values ranged from 44% to 93%	Skin prick test	Y	Y	N	Y	Y	Very low
Eight studies (Vierrucci et al. 1989, Sampson et al.1998, Roehr et al.2001, Celik-Bilgili et al.2005, Mehl et al.2006, Osterballe et al.2004, Garcia-Ara et al.2001, Canani et al.2007)	Sensitivities ranged from 22.5% to 100% Specificities ranged from 30% to 98% Positive predictive values ranged from 57% to 71%. Negative predictive values ranged from 50% to 100%	IgE	Y	Y	N	Y	Y	Very low

Seven studies (Niggemann et al.2002 Roehr et al. 2001, Mehl et al.2006, Cudowska et al2005, Osterballe et al.2004, De Boissieu et al.2003, Canani et al.2007)	Sensitivities ranged from 0% to 80% Specificities ranged from 70% to 100% Positive predictive values ranged from 0% to 100%. Negative predictive values ranged from 11% to 73%	Atopy patch test	Y	Y	N	Y	Y	Very low

*Please see footnotes 7–10 for criteria for downgrading

GRADE profile 7: The diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE-mediated peanut allergy

Studies	Outcome: Diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE-mediated peanut allergy Evaluation of five individual studies for peanut allergy	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Five studies (Vierrucci et al.1989, Hill et al.2004, Sampson et al.1998, Eigenmann & Sampson 1998, Rance et al.2002)	Sensitivities ranged from 80% to 100% Specificities ranged from 29% to 72% Positive predictive values ranged from 55% to 94%. Negative predictive values ranged from 50% to 100%	Skin prick test	Y	Y	N	Y	Y	Very low
Three studies (Vierrucci et al.1989, Sampson et al.1998, Rance et al.2002)	Sensitivities ranged from 25% to 97% Specificities ranged from 38% to 100% Positive predictive values ranged from 33% to 78%. Negative predictive values ranged from 25% to 95%	IgE	Y	Y	N	Y	Y	Very low

*Please see footnotes 7–10 for criteria for downgrading

GRADE profile 8: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated wheat allergy

Studies	Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated wheat allergy Evaluation of eight individual studies for wheat allergy	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Seven studies (Niggemann et al.2002, Sampson 1998, Eigenmann & Sampson 1998, Roehr et al.2001, Verstege et al.2005, Mehl et al.2006, Jarvinen et al.2003)	Sensitivities ranged from 23% to 90% Specificities ranged from 51% to 100% Positive predictive values ranged from 35% to 68%. Negative predictive values ranged from 60% to 94%	Skin prick test	Y	Y	N	Y	Y	Very low
Four studies (Sampson et al.1998, Roehr et al.2001, Celik-Bilgili et al.2005, Mehl et al.2006)	Sensitivities ranged from 67% to 96% Specificities ranged from 20% to 47% Positive predictive values ranged from 14% to 57%. Negative predictive values ranged from 57% to 97%	IgE	Y	Y	N	Y	Y	Very low
Four studies (Niggemann et al.2002, Roehr et al.2001, Mehl et al.2006, Jarvinen et al.2003)	Sensitivities ranged from 0% to 100% Specificities ranged from 89% to 100% Positive predictive values ranged from 0% to 94%. Negative predictive values ranged from 69% to 100%	Atopy patch test	Y	Y	N	Y	Y	Very low

*Please see footnotes 7–10 for criteria for downgrading

GRADE profile 9: The diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated soy allergy

Studies	Outcome: diagnostic utility of skin prick test, specific IgE antibody test and atopy patch test in diagnosing IgE-mediated soy allergy Evaluation of seven individual studies for soy allergy	Diagnostic test	Limitations*	Inconsistency*	Indirectness	Imprecision*	Other considerations*	Quality
Six studies (Niggemann et al.2002, Sampson et al1998, Eigenmann & Sampson 1998, Roehr et al.2001, Verstege et al.2005, Mehl et al.2006)	Sensitivities ranged from 21% to 76% Specificities ranged from 47% to 100% Positive predictive values ranged from 29% to 100%. Negative predictive values ranged from 58% to 90%	Skin prick test	Y	Y	N	Y	Y	Very low
Four studies (Sampson et al.1998, Roehr et al.2001, Celik-Bilgili et al.2005, Mehl et al.2006)	Sensitivities ranged from 65% to 94% Specificities ranged from 25% to 52% Positive predictive values ranged from 21% to 23%. Negative predictive values ranged from 86% to 95%	IgE	Y	Y	N	Y	Y	Very low
Three studies (Niggemann et al.2002, Roehr et al.2001, Mehl et al.2006)	Sensitivities ranged from 0% to 100% Specificities ranged from 86% to 100% Positive predictive values ranged from 0% to 100%. Negative predictive values ranged from 82% to 100%	Atopy patch test	Y	Y	N	Y	Y	Very low

*Please see footnotes 7–10 for criteria for downgrading

GRADE profile 10: The diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE-mediated allergy to tomato, fish or beef

Studies	Outcome: diagnostic utility of skin prick test and specific IgE antibody test in diagnosing IgE-mediated allergy to tomato, fish or beef Evaluation of three individual studies for tomato, fish and beef allergy	Food tested	Diagnostic test	Limitations[7]	Inconsistency[8]	Indirectness	Imprecision[9]	Other considerations[10]	Quality
One study (Vierrucci et al.1989)	Sensitivity 100%, Specificity 66% Positive predictive value 40% Negative predictive value 100%	Tomato	Skin prick test	Y	Y	N	Y	Y	Very low
	Sensitivity 14%, Specificity 50% Positive predictive value 33% Negative predictive value 25%	Tomato	IgE	Y	Y	N	Y	Y	Very low
One study (Sampson et al.1998)	Sensitivity 90%, Specificity 57% Positive predictive value 77% Negative predictive value 80%	Fish	Skin prick test	Y	Y	N	-	Y	Very low

[7] Limitations: studies had verification problems. There were problems with how many food challenges were done for each child. In certain cases, challenges were not done for all children. It also appeared that some of the studies did more tests than challenges (for example, one study carried out more skin prick tests for a particular food than they did food challenges). In studies which did tests for multiple foods, challenges were not done for all foods.
[8] Inconsistency: studies did not explicitly group the children by age group.
[9] Imprecision: cannot be assessed in diagnostic studies so it has been assumed that imprecision exists here and has been downgraded.
[10] Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.

	Sensitivity 94%, Specificity 65% Positive predictive value 49% Negative predictive value 97%	Fish	IgE	Y	Y	N	-	Y	Very low
One study (Fiocchi et al.2002)	Sensitivities ranged from 90% to 100% Specificities ranged from 78% to 100% Positive predictive values ranged from 87% to 100%. Negative predictive values ranged from 88% to 100%	Beef	Skin prick test	Y	Y	N	-	Y	Very low

2.4.2 Evidence statements

2.4.2.1 *Very low-quality evidence from 18 studies of 3165 children showed that the sensitivities of the three tests for hens' egg allergy in children ranged from 58% to 100%, 32% to 100% and 5% to 84% for skin prick test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity ranges were 20% to 99%, 20% to 89% and 87% to 100%.*

2.4.2.2 *Very low-quality evidence from 15 studies of 3031 children showed that the sensitivities of the three tests for cows' milk protein allergy in children ranged from 28% to 96%, 23% to 100% and 0% to 80% for skin prick test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity ranges were 46% to 100%, 30% to 98% and 70% to 100%.*

2.4.2.3 *Very low-quality evidence from five studies of 1392 children showed that the sensitivities of the two tests for peanut allergy in children ranged from 80% to 100% and 25% to 97% for skin prick test and specific IgE antibody test respectively. The corresponding specificity ranges were 29% to 72% and 38% to 100%.*

2.4.2.4 *Very low-quality evidence from eight studies of 1991 children showed that the sensitivities of the three tests for wheat allergy in children ranged from 23% to 90%, 67% to 96% and 0% to 100% for skin prick test, specific IgE antibody test and atopy patch test respectively. The corresponding specificity values were 51% to 100%, 20% to 47% and 89% to 100%.*

2.4.2.5 *Very low-quality evidence from seven studies of 1901 children showed that the sensitivities of the three tests for soy allergy in children ranged from 21% to 76%, 65% to 94% and 0 to 100% for skin prick test, specific IgE antibody test and atopy patch test*

respectively. The corresponding specificity values were 47% to 100%, 25% to 52% and 86% to 100%.

2.4.2.6 *Very low-quality evidence from three studies of 346 children showed that the sensitivities of the two tests for tomato, fish and beef allergies in children ranged from 90% to 100%, and 14 to 94% in skin prick test and specific IgE antibody test respectively. The corresponding specificity values were 57% to 100%, and 50% to 65%.*

2.4.3 Health economic modelling

The decision problem for the health economic analysis was to consider the cost effectiveness of skin prick and specific IgE antibody tests for diagnosing food allergy in children and young people. The atopy patch test and other tests were excluded on clinical grounds. It was also considered impractical for all children and young people to be referred to secondary or specialist care, so this option was not considered. The population examined was those suspected of having a food allergy after the clinical history was taken. Only peanut allergies were considered as it was suggested that more information was available on this allergy, especially on long-term outcomes. The GDG agreed that it would be possible to extrapolate the results derived from peanut allergies to other food allergies.

No suitable cost-effectiveness papers were identified from the literature search, so a new economic analysis was constructed. A decision tree model was developed to model the short-term outcomes of testing, and a Markov model was used for long-term outcomes.

The clinical data on sensitivity and specificity for the two chosen tests were obtained from Rance et al.2002. This study was chosen because its population most closely matched that of the decision problem and it was associated with the highest score in the Youden Index.

The information on the natural history of the condition was based on a long-term prospective study (Ewan et al.1996) of children with peanut allergies.

This provides the estimate for the desensitisation from allergies. Various sources were used for the percentage of people having major, minor and fatal allergic reactions. Age-related mortality was not included, given the age group. For more details see appendix 3.

Given the generally low quality of the evidence and the lack of full reviews to support the inputs into this analysis, the results should be considered exploratory.

The model was run with a relatively short time horizon of 4 years. This was chosen to match the time horizon of Ewan et al.1996. It was considered that longer time horizons would be associated with greater uncertainty. Longer time horizons were considered in sensitivity analysis. In addition, full one-to-one and probabilistic sensitivity analysis was carried out and scenario analyses included epinephrine-pens prescription, re-testing, inclusion of parents' or carers' quality of life and the accuracy of the GP history taking. Value-of-information analysis was also carried out to identify whether further research was valuable, and expected value of perfect parameter information (EVPPI) analysis was conducted to identify which variables should be prioritised for research.

The deterministic and probabilistic base-case results are presented in table 2.

Table 2: deterministic and probabilistic base-case results

	Quality-adjusted life year (QALY)	Cost (£)	Incremental QALYs	Incremental costs (£)	Incremental cost-effectiveness ratio (£)
Deterministic					
GP only	3.38	45	-	-	-
Specific IgE antibody test	3.59	464	0.21	419	1,990
Skin prick test	3.60	414	0.22	369	1,657
Probabilistic					
GP only	3.36	45	0.00	0	0.00
Specific IgE antibody test	3.47	579	0.11	534	4,824

Skin prick test	3.47	559	0.11	514	4,563

The difference between the probabilistic costs and deterministic costs is due to the number of uniform distributions applied to the cost inputs.

The probabilities of these tests being cost effective are presented in table 3, and of being the optimum choice in table 4.

Table 3: Cost-effectiveness acceptability curves results

Threshold	IgE antibody test	Skin prick test
£20,000 per QALY	81%	81%
£30,000 per QALY	86%	86%

Table 4: Cost-effectiveness acceptability frontier results

Threshold	GP alone	IgE antibody test	Skin prick test
£20,000 per QALY	16%	41%	43%
£30,000 per QALY	12%	44%	45%

These results indicate that the tests are likely to be cost effective. The cost-effectiveness acceptability frontiers show that the skin prick test is the optimum choice; however, this is not statistically significant. In addition, the choice between the tests depends partly on the numbers of people being tested. This is because the resources needed for skin prick testing are bought in bulk and therefore to prevent wastage a sufficient number of people need to be tested.

It is not possible to estimate a threshold for the numbers needed to treat before the skin prick test becomes more cost effective than IgE testing, because the costs included in the model are based on averages provided by GDG sources and there is likely to be significant local variation in the costs of these tests. Therefore, their transferability across the UK was not considered appropriate.

Sensitivity analysis indicated that issues around re-testing and management of allergies are unlikely to cause the cost-effectiveness estimates to increase

beyond the usual cost-effectiveness thresholds. In addition, if parents' or carers' quality of life was included, the cost-effectiveness estimates improved significantly.

Value-of-information analysis carried out on a £20,000 per QALY threshold (and assuming 1.8% of children of school age have a nut allergy) indicated that research was very valuable in this area, with uncertainty in the model worth £34,697,442 to resolve. Expected value of perfect information analysis indicated that the quality of life of children with allergies, and the specificity of the tests, is priorities for research. For full results and details of analysis see appendix 3.

2.4.4 Evidence to recommendations

The GDG considered the evidence presented and agreed that it was of low quality and that overall the tests had a wide range of specificities and sensitivities. The evidence showed that both the skin prick test and specific IgE antibody test were similar in their diagnostic performance. The evidence also showed that the atopy patch test may be useful in the diagnosis of IgE-mediated food allergy. However, the GDG discussed the methodology and interpretation of the evidence for the atopy patch test and felt it was less well-standardised and more variable than other tests. The mechanism of action of the test was also discussed, and the GDG viewed the atopy patch test as inappropriate for the diagnosis of IgE-mediated food allergy.

The GDG agreed that the decision to conduct a specific IgE antibody test or a skin prick test should also depend on the competencies of the healthcare professional who is carrying out the test, the results of the allergy-focused clinical history and the suitability of the test for the child or young person. The group also discussed the use of food panels (testing a range of common allergens) and felt it was important to recommend that healthcare professionals should test for the specific allergen suspected from the allergy-focused clinical history, while also taking into account possible cross-reactive and co-reactive allergens. The evidence for specific proteins was not

reviewed. The GDG felt that batch testing should not be considered in the recommendations.

The GDG noted that the health economic evidence showed that both the IgE antibody test and the skin prick test were cost effective compared with no test, but that the skin prick test was cheaper per test. It noted that the optimum choice was highly sensitive to the mean values of sensitivity and specificity inputted into the model. However, it noted that the relative cost effectiveness of the two tests depends on the number of people being tested every year. Also, it was not possible to calculate a threshold value; therefore, it was not possible to definitively conclude that one test was more cost effective than the other.

The GDG raised concerns about the competencies that healthcare professionals needed to perform, read and interpret the results of the allergy tests. The safety of conducting the tests in the community was also highlighted as there is a risk of anaphylactic reaction with skin prick tests. The GDG held the view that the tests could be carried out in community settings where the facilities are similar to those available for routine childhood vaccinations. Healthcare professionals undertaking such tests should be competent and aware of the potential risks of such tests. It was emphasised by the GDG that allergy tests should not be carried out without first taking an allergy-focused clinical history. The value of a positive or negative test in the context of a previously taken history was also discussed. The GDG believed that the tests would be useful in confirming allergy status only if a proper history had been taken. The GDG also discussed the importance of communicating to children and young people with a suspected food allergy, and their parents and carers, the results of the tests in the context of their clinical history, and whether further action is needed.

2.4.5 Recommendations

Recommendation 1.1.6

Based on the results of the allergy-focused clinical history, if IgE-mediated allergy is suspected, offer the child or young person either a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens.

Recommendation 1.1.7

Tests should only be undertaken by healthcare professionals with the appropriate competencies to select, perform and interpret them.

Recommendation 1.1.8

Skin prick tests should only be undertaken where there are facilities to deal with an anaphylactic reaction.

Recommendation 1.1.9

Choose between a skin prick test or a specific IgE antibody blood test based on:

- the results of the allergy-focused clinical history **and**
- whether the test is suitable for, safe for and acceptable to the child or young person (or their parent or carer) **and**
- the available competencies of the healthcare professional to undertake the test and interpret the results.

Recommendation 1.1.10

Do not carry out allergy testing without first taking an allergy-focused clinical history. Interpret the results of tests in the context of information from the allergy-focused clinical history.

Recommendation 1.1.11

Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated allergy in primary care or community settings.

2.5 Providing information and support

What information and support should be offered to children and young people with suspected food allergy and their parents or carers during the diagnostic process?

2.5.1 Evidence review

The review considered the information and support needed by children and young people with suspected food allergy, and their parents or carers, during the diagnostic process. It did not include assessing the knowledge or educational needs of healthcare professionals. The search strategy was designed to identify studies that focused specifically on the needs of the child or young person. In total, 976 papers were identified, of which 88 were considered for inclusion. Studies with children who had previously been diagnosed with food allergy were excluded unless the study was related specifically to the initial diagnosis. Studies that were validating questionnaires or surveys were also excluded (see appendix 2 for the full excluded list)**.** Seven papers were included (Arvola et al. 2000; Barnett 2005; Gillespie et al. 2007; Hu et al. 2007; Lever et al. 1998; Mikkelsen et al. 2005; Weber et al. 2007): these consisted of one randomised controlled trial, five qualitative papers and one observational study (see appendix 1 for the detailed evidence table).

The evidence was synthesised and presented as two evidence summaries. The first summary (see table 5) showed the studies that provided particular information or advice and the stage at which this was provided. The stages of the diagnostic process were:

- the first consultation (1)
- during the diagnostic process (2)
- after diagnosis or referral (3).

As the studies were not explicit about the stage in the diagnostic process, this was assumed based on whether the children had suspected or diagnosed food allergy, had received diagnostic testing during the study and whether they were already on an elimination diet or were started on one during the

study. The second evidence summary related specifically to qualitative components and showed specific information or advice that parents or carers of children and young people with suspected food allergy considered important (see table 6).

Table 5: Evidence summary of information needs

Study	Population	Dietary advice	Food label advice	Education by community pharmacist	Findings	Details of advice	Stage in diagnostic process[11]
Lever 1998 (Ref ID: 4987)	Children with atopic eczema with suspected hens' egg allergy	√	√		Dietary advice on elimination diets and food labelling advice was effective in improving eczema	The dietitian advised children to exclude all foods containing egg. Children and their parents were given a list of foods known to contain egg, and egg-free foods. Food label advice was given.	2
Mikkelsen 2005 (Ref ID: 290)	Children with diagnosed or suspected cows' milk protein allergy	√	√		Most parents were satisfied with information received during the 'milk allergy school'	At group sessions, the dietitian provided information, answered questions and corrected misconceptions. This included label reading from packages in a typical household. Children were given written instructions on how to follow a milk-free diet and booklets of recipes.	2 and/or 3
Barnett 2005 (Ref ID:265)	Members of FANN recall about initial diagnosis of food allergy and use of epi-pen			√	The overall attitude to education was between neutral and favourable	Recall of advice from a community pharmacist. The study examined information and training provided from six possible categories: general food allergy information, signs of allergic reaction, training in epi-pen use, avoidance of specific foods, drug information about epinephrine, and day-to-day management of food allergy.	3
Arvola 2000 (Ref ID: 678)	Breastfed babies with atopic eczema and suspected food allergy	√			Majority of parents reported alleviation in children's symptoms and satisfaction with advice	Individual dietary advice was given by a dietitian, advice on skin treatment by a dermatologist when skin prick tests were performed, and practical advice on elimination diets from a paediatric nurse.	1 and/or 2
Weber 2007 (Ref ID: 144)	Children on cows' milk exclusion diet		√		Although not all parents had previously received advice, the study group generally performed better in correctly identifying milk-containing products	All of the study group were instructed to exclude milk-containing food products; 80% received product label reading instructions; and 38% received previous instructions on words associated with cows' milk from physician and/or nutritionist.	2 and/or 3

[11] 1=at first consultation, 2=during the diagnostic process, 3=After diagnosis/ referral

Table 6: Evidence summary for information needs

	Study	
Information need	**Hu et al.2007**	**Gillespie et al.2007**
Information content		
Practical dietary advice	√	
Advice on diagnostic techniques and interpretation	√	
Recognition and management of reactions	√	
Information sources or types		
Written take-home information	√	
Videos (for educating child, extended family and other carers)	√	
Nurse-led education sessions	√	√
Referral to other parents		√
Physician's role		
Expert knowledge		√
Supportive role		√
Provide trustworthy, reliable information	√	√
Amount of information		
More information	√ (at first visit)	√

2.5.2 Evidence statements

2.5.2.1 *Evidence from one moderate-quality randomised controlled trial and one qualitative study showed that, at initial diagnosis or during the diagnostic process, education about reading and interpreting food labels and/or dietary advice about elimination diets was successful in alleviating children's symptoms of eczema, and parents were generally satisfied with the advice they received.*

2.5.2.2 *Evidence from two low-quality qualitative studies and one observational study showed that during the diagnostic process or after diagnosis, education about reading and interpreting food labels, dietary advice about elimination diets and/or education by a community pharmacist were generally favoured by parents of children with suspected or diagnosed food allergy.*

2.5.2.3 Evidence from two low-quality qualitative studies showed that the following were valued by parents of children with suspected food allergy:

- *information content (including advice on diet, diagnostic techniques and interpretation, and recognition and management of reactions)*
- *the type of information received (including written, video, nurse-led sessions and referral to other parents)*
- *the physician's role (including their expert knowledge, their supportive role and the provision of reliable information)*
- *the amount of information received .*

2.5.3 Evidence to recommendations

The GDG agreed that the evidence presented was limited and did not fully address the clinical question. They discussed the evidence relating to suspected cows' milk protein allergy in detail and felt that young children who were being breastfed and were allergic to cows' milk protein would need special attention. The group also decided that applying the evidence would be difficult because some of the studies focused on the impact of information or advice on symptoms. There was only one study that directly compared giving additional specific advice about food elimination with general advice. That study included only 55 children. Most of the other evidence was from qualitative studies and the conclusions were not as robust as the one from the randomised controlled trial. As a result many of the recommendations were made on the basis of consensus.

The group agreed that children and young people with suspected food allergy would fit into three main groups based on the outcome of an allergy-focused clinical history: those with a low chance of having an allergy; those with a high chance of having an allergy; and those in whom there is uncertainty. It was agreed that information would only need to be provided for the groups where an allergy was probable or possible. The recommendations were based

loosely on the diagnostic stages as set out in the review protocol (see appendix 1), although it was noted that these categories were overlapping.

The GDG agreed that, although some general information would be needed, the healthcare professional should tailor most of the information to the specific needs and background of the child or young person. It was agreed that further information would be needed during the diagnostic process when elimination diets and tests were carried out. The group also considered it important to provide information for the child or young person and their parent or carer about what to do while waiting for the results of diagnostic tests and confirmation of food allergy. This was because there may be a delay between a child having tests carried out and receiving the results

Although evidence related to the safety of vaccination in children with food allergy was not reviewed, anecdotally the GDG felt that this was one of the most common queries from parents of children with suspected food allergy and therefore included this as a recommendation.

2.5.4 Recommendations

Recommendation 1.1.12

Based on the allergy-focused clinical history, offer the child or young person and their parent or carer, information that is age-appropriate about the:

- type of allergy suspected
- risk of severe allergic reaction
- potential impact of the suspected allergy on other healthcare issues, including vaccination
- diagnostic process, which may include:
  - an elimination diet followed by a possible planned rechallenge or initial food reintroduction procedure
  - skin prick tests and specific IgE antibody testing, including the safety and limitations of these tests
  - referral to secondary or specialist care.

Recommendation 1.1.13

2.5.5 Offer the child or young person and their parent or carer, information that is relevant to the type of allergy (IgE-mediated, non-IgE mediated or mixed).

Recommendation 1.1.14

If a food elimination diet is advised as part of the diagnostic process (see recommendation 1.1.5), offer the child or young person and their parent or carer, taking into account socioeconomic status and cultural and religious issues, information on:

- what foods and drinks to avoid
- how to interpret food labels
- alternative sources of nutrition to ensure adequate nutritional intake
- the safety and limitations of an elimination diet
- the proposed duration of the elimination diet
- when, where and how an oral food challenge or food

reintroduction procedure may be undertaken

- the safety and limitations of the oral food challenge or food reintroduction procedure.

Recommendation 1.1.15

For babies and young children with suspected allergy to cows' milk protein, offer:

- food avoidance advice to breastfeeding mothers
- information on the most appropriate hypoallergenic formula or milk substitute to mothers of formula-fed babies.

Seek advice from a dietitian with appropriate competencies.

Recommendation 1.1.16

Offer the child or young person, or their parent or carer, information about the support available and details of how to contact support groups.

2.6 Referral to secondary or specialist care

At which stage in the diagnostic process should children and young people with symptoms of IgE, non-IgE or mixed IgE and non-IgE mediated food allergy be referred to secondary or specialist care?

2.6.1 Evidence review

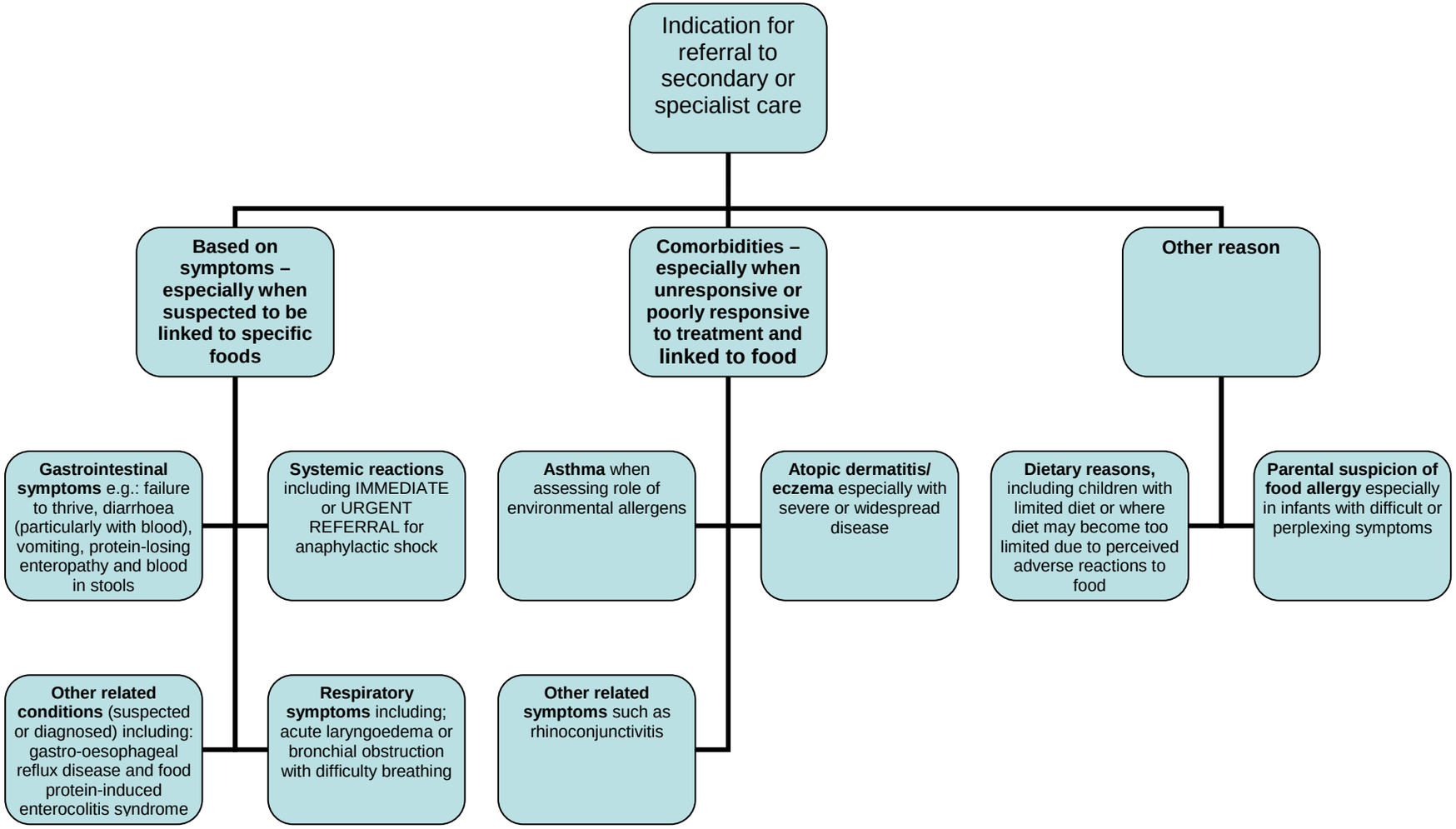
The review considered indications for referring a child or young person with suspected food allergy from primary or community settings to secondary or specialist care. This did not include referrals from secondary or specialist settings, such as dermatology and gastroenterology to specialist allergy clinics. The search strategy was designed to identify studies that focused specifically on referrals to secondary or specialist care. In total, 856 papers were identified, of which 70 were considered for this clinical question. No relevant primary studies were identified and there was no direct evidence explicitly related to referrals from primary or community settings to secondary care (see appendix 2 for a full list of excluded papers). Six papers were included: (Allen 2007; Allen et al. 2009; Kaila 2008; Leung 2006; Robinson

and Smart 2008; Vandenplas et al. 2007) these consisted of three review articles and three guidelines (see appendix 1 for detailed evidence tables). The evidence was synthesised and presented in the form of evidence summaries showing the papers that supported referral based on specific identified indications (see table 7). An illustration of this information was also presented (see figure 1), categorising these indications into three main reasons for referral.

Table 7: Indications for referral to secondary or specialist care

	Study					
Indication for referral	**Allen et al. 2009 (Ref ID: 452)**	**Robinson & Smart 2008 (Ref ID:1034)**	**Allen 2007 (Ref ID: 1037)**	**Vandenplas et al. 2007 (Ref ID: 514)**	**Kalia et al. 2008**	**Leung & Schatz 2006**
Gastrointestinal symptoms and other related conditions (specify)	√		√	√		√
Asthma and other respiratory symptoms		√		√		
Systemic symptoms	√			√		
Atopic dermatitis or eczema, and other related symptoms		√		√	√	
Dietary restrictions					√	√
Parental suspicion					√	

Figure 1: Indications for referral to secondary or specialist care



2.6.2 Evidence statements

2.6.2.1 Evidence from four low-quality studies showed that gastrointestinal symptoms and other related conditions, such as food protein-induced enterocolitis syndrome) and gastro-oesophageal reflux disease, were indications to refer a child to secondary or specialist care.

2.6.2.2 Evidence from two low-quality studies showed that asthma and other respiratory symptoms, such as acute laryngoedema or bronchial obstruction with difficulty breathing, were indications to refer a child to secondary or specialist care.

2.6.2.3 Evidence from two low-quality studies showed that systemic reactions such as anaphylaxis were indications to refer a child to secondary or specialist care.

2.6.2.4 Evidence from three low-quality studies showed that atopic dermatitis and other related symptoms, such as rhinoconjunctivitis, were indications to refer a child to secondary or specialist care.

2.6.2.5 Evidence from two low-quality studies showed that dietary restriction was an indication to refer a child to secondary or specialist allergy care.

2.6.2.6 Evidence from one low-quality study showed that parental suspicion of food allergy, especially in infants with difficult or perplexing symptoms, was an indication to refer a child to secondary or specialist care

2.6.3 Evidence to recommendations

The GDG agreed that the evidence was of low quality but decided it was important to make a recommendation to guide primary healthcare professionals as to when to refer a child with suspected food allergy to secondary or specialist care.

The GDG used the evidence presented as a basis for discussion and considered each indication for referral. There was a consensus that having some symptoms or conditions alone would not warrant referral; it was agreed that symptoms in combination with other factors would be necessary before the healthcare professional should consider a referral.

The GDG agreed that children and young people with anaphylaxis would present directly to secondary care and be managed there, so this group would not need to be considered here. They did feel, however, that acute systemic reactions and severe delayed reactions were important indications for referral that had not been highlighted in the evidence. The group also decided that the following indications should lead to referral:

- a positive clinical history for IgE-mediated allergy with negative allergy tests
- clinical suspicion of multiple food allergies
- failure to respond to a single-allergen elimination diet

2.6.4 Recommendations

Recommendation 1.2.17

Based on the allergy-focused clinical history, consider referral to secondary or specialist care in any of the following circumstances.

- The child or young person has:
  - faltering growth in combination with one or more of the gastrointestinal symptoms described in recommendation 1.1.1
  - not responded to a single-allergen elimination diet
  - had acute systemic reactions
  - had severe delayed reaction
  - confirmed IgE-mediated food allergy and concurrent asthma
  - significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer.
- There is:
  - persisting parental suspicion of food allergy (especially in children or young people with difficult or perplexing symptoms) despite a lack of supporting history
  - strong clinical suspicion of IgE-mediated food allergy but allergy test results are negative
  - clinical suspicion of multiple food allergies.

2.7 Alternative diagnostic tools

What is the value of alternative diagnostic tests in the diagnosis of IgE, non-IgE and mixed IgE and non-IgE food allergy in children and young people in primary care?

2.7.1 Evidence review

Twenty-five papers were identified and considered for inclusion. Studies that did not use a food challenge as a reference standard to confirm food allergy

were excluded (see appendix 2 for the full list of excluded studies). One paper (Moneret-Vautrin et al. 1999) was included which assessed the use of the basophil activation test and the leukotriene C4 (LTC4) release test (see appendix 3 for the detailed evidence table). This study of 21 children concluded that the basophil activation test and the LTC4 release test were reliable for the diagnosis of food allergy; however, this study included some adults. One paper (Osterballe et al. 2004) assessed the use of histamine release from basophils to diagnose allergies to hens' eggs and cows' milk protein in 22 children.

2.7.2 Evidence statements

2.7.2.1 *Low-quality evidence from one paper of 21 children aged up to 15 years showed that the sensitivity of the basophil activation test ranged from 48% to 80% and specificity ranged from 94% to 100%.*

2.7.2.2 *Low-quality evidence from one paper of 21 children aged up to 15 years showed that the sensitivity of the leukotriene C4 release test ranged from 52% to 85% and specificity was 100%.*

2.7.2.3 *Low-quality evidence from one paper of 22 children aged 3 years showed that the sensitivity and specificity of the basophil activation test were 71% and 96% respectively for allergy to hens' eggs.*

2.7.2.4 *Low-quality evidence from one paper of 22 children aged 3 years showed that the sensitivity and specificity of basophil activation test were 67% and 94% respectively for cows' milk protein allergy.*

2.7.2.5 *No evidence on the utilities of vega testing, applied kinesiology, hair analysis or serum specific IgG testing in primary care was identified.*

2.7.3 Evidence to recommendations

The GDG agreed that good-quality evidence for the alternative tests was lacking. Evidence was scarce and of low quality, and the GDG felt that they could not recommend any of the tests for the diagnosis of food allergy.

Although no specific evidence was reviewed, the GDG agreed that serum-specific IgG tests were not appropriate for the diagnosis and assessment of food allergy. They felt this should be highlighted given the science-based marketing of the test. In addition, despite the lack of evidence for vega testing, applied kinesiology and hair analysis and the lack of well-designed studies, the GDG agreed that these tests were not appropriate for diagnosing food allergy.

2.7.4 Recommendations

Recommendation 1.1.18

Do not use the following alternative diagnostic tests in the diagnosis of food allergy:

- vega test
- applied kinesiology
- hair analysis.

Recommendation 1.1.19

Do not use serum specific IgG testing in the diagnosis of food allergy.

3 Research recommendations

We have made the following recommendations for research, based on our review of evidence, to improve NICE guidance and patient care in the future.

The focus of this guideline was the diagnosis and assessment of food allergy in children and young people in primary care and community settings. Therefore, the management of food allergy after a confirmed diagnosis was not reviewed. The research recommendations below focus on assessment and diagnosis.

3.1 Prevalence and natural history of non-IgE mediated food allergy

How common are non-IgE mediated food allergies in children and young people in primary care and community settings and when food allergies may be outgrown?

Why this is important

Food allergy has many presentations. IgE-mediated food allergy manifests itself with a relatively homogenous group of presentations. Along with objective tests, measures of prevalence in the relevant settings and later development of tolerance have yielded useful information on the burden of IgE-mediated food allergy. However, non-IgE mediated food allergy has a more heterogeneous group of presentations and the lack of validated diagnostic tests make it very difficult to assess prevalence without using formal diagnostic food challenges. Until high-quality prevalence studies in primary care and community settings are carried out, the burden of this food allergy will remain unknown. Studies should also evaluate prevalence rates and the resolution of allergies in subgroups, such as by allergies to particular food groups, or by method of infant feeding (exclusive formula, exclusive breastfeeding or mixed).

3.2 Clinical predictors of non-IgE mediated food allergy

Which features in the clinical history best predict the presence of non-IgE mediated food allergy in children and young people in primary care and community settings?

Why this is important

Non-IgE mediated food allergy often presents with non-specific problems that are common in children and are often non-allergy related, such as colic, reflux, diarrhoea, eczema and faltering growth. Failure to recognise food allergy causes unnecessary morbidity, whereas appropriate food elimination can result in rapid improvement in symptoms. In the absence of a simple diagnostic test, it remains for the history to provide the best diagnostic clues as to which child may benefit from a trial of an elimination diet. A validated,

primary care-focused questionnaire, developed by comparison with proven double-blind placebo-controlled food challenge outcomes, would significantly improve the process of diagnosis.

3.3 Information needs for children and young people during their care pathway to diagnosis of food allergy

What do children and young people with IgE-mediated food allergy and their parents or carers want to know during the process of diagnosis and how is this demand best met?

Why this is important

The patient journey to diagnosis, through testing, can last for several months. The needs of children and young people and their parents or carers, and the most effective method of information and support provision during this time of uncertainty, need to be established.

3.4 Values of skin prick testing and specific IgE antibody testing and their predictive value

Can skin prick testing and specific IgE antibody testing cut-off points be established to diagnose IgE-mediated food allergy in children and young people, and to predict the severity of reaction?

Why this is important

It is well described that about 1 in 5 people reporting an adverse reaction to food have a true food allergy. Of these, the majority will have non-IgE mediated allergies. Food challenges are cumbersome and time-consuming and there are some safety risks involved. The availability of skin prick testing and specific IgE testing cut-off points to diagnose food allergy and to predict the severity of reaction would therefore lead to huge cost savings in the NHS and would reduce patient risk. There are published data available from the US, Australia and Europe, but allergists argue that these cut-off points are population-specific and should not be used in the UK.

3.5 Modes of provision of support to healthcare professionals

What would be the impact of dietetic telephone support to healthcare professionals to aid in the diagnosis and assessment of babies showing non-IgE mediated food allergy symptoms in primary care and community settings?

Why this is important

There is currently no evidence to assess the impact of early diagnosis of non-IgE mediated food allergy on the quality of life for babies and their families. The standard method of written referral is not timely (within the first month of presentation), yet there is no evidence whether providing indirect dietary advice via a healthcare professional is acceptable to the family. This system, however, could result in reduced attendances at GP surgeries and health clinics, reduced need for unnecessary medications and treatment, improved health for the whole family and improved skills for the healthcare professionals being supported in the diagnosis. However, it would need increased dietetic support and skills. A community-based randomised controlled trial is needed to compare the standard written dietetic referral method with indirect advice via a healthcare professional following consultation with a dietitian, for families with babies aged under 1 year who present with symptoms of non-IgE mediated food allergy. Primary outcomes should be an assessment of the quality of life and acceptability of this service to the family. Secondary outcome measures could be related to attendance at GP surgeries, and medications and other interventions implemented.

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/guidance/CG[XX]Guidance). **[Note: these details will apply to the published full guideline.]**

Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG[XX]QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG[XX]PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). **[Note: these details will apply when the guideline is published.]**

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about diagnosis and assessment of food allergy in children and young people.

5 Related NICE guidance

Published

- Coeliac disease. NICE clinical guideline 86 (2009). Available from www.nice.org.uk/guidance/CG86
- Diarrhoea and vomiting in children. NICE clinical guideline 84 (2009). Available from www.nice.org.uk/guidance/CG84

- Atopic eczema in children. NICE clinical guideline 57 (2007). Available from www.nice.org.uk/guidance/CG57
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2007). Available from www.nice.org.uk/guidance/TA131

5.1 Guidance under development in parallel with NICE

- The Royal College of Paediatrics and Child Health is currently developing the following related guidance: Food and Gastrointestinal Allergy Care Pathway. The Royal College of Paediatrics and Child Health. Publication expected December 2010.

6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

7 References, glossary and abbreviations

7.1 References

Allen K (2007) The vomiting child: what to do and when to consult. Australian Family Physician 36: 684-8.

Allen KJ, Davidson GP, Day AS et al. (2009) Management of cow's milk protein allergy in infants and young children: An expert panel perspective. Journal of Paediatrics and Child Health 45: 481-6.

Ando H, Moverare R, Kondo Y et al. (2008) Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. Journal of Allergy & Clinical Immunology 122: 583-8.

Arvola T, Tahvanainen A, Isolauri E (2000) Concerns and expectations of parents with atopic infants. Pediatric Allergy & Immunology 11: 183-8.

Asarnoj A, Ostblom E, Ahlstedt S et al. (2010) Reported symptoms to peanut between 4 and 8 years among children sensitized to peanut and birch pollen - results from the BAMSE birth cohort. Allergy 65: 213-9.

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7.2 Glossary

Anaphylaxis

A severe, life-threatening, generalised or systemic hypersensitivity reaction, characterised by rapidly developing life-threatening airway, breathing and/or circulation problems, usually associated with skin and mucosal changes.

Angioedema

Swelling, similar to hives, except that the swelling is beneath the skin rather than on the surface.

Co-allergen

An allergen commonly found to be present in association with another.

Dysphagia

Difficulties with swallowing.

Eosinophilic oesophagitis

An inflammatory condition of the oesophagus, usually presenting with difficulty in swallowing or as gastro-oesophageal reflux in infants.

Food allergy

An adverse immune response to a food.

Gastro-oesophageal reflux disease

A chronic digestive disease that occurs when the contents of the stomach, including acid, flows back (refluxes) into the oesophagus (gullet).

IgE-mediated reaction

An allergic reaction which is acute and frequently has rapid onset.

Laryngeal stridor

A harsh inspiratory noise due to swelling of the larynx, suggestive of upper airway obstruction.

Non-IgE mediated reaction

These reactions are generally characterised by delayed and non-acute reactions.

Pruritus

Itchy skin

Systemic allergic reaction

an allergic reaction involving parts of the body distant to the actual site of allergen contact.

Urticaria

Raised, red, itchy welts (weals or swellings) of various sizes that seem to appear and disappear on the skin.

7.3 Abbreviations

CI	Confidence interval
DBPCFC	Double-blind placebo-controlled food challenge
GDG	Guideline Development Group
GRADE	Grading of recommendations assessment, development and evaluation
ICER	Incremental cost-effectiveness ratio
OR	Odds ratio
QALY	Quality-adjusted life year

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8.2 The short clinical guidelines technical team

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

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8.5 The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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8.6 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

8.7 Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

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