National Institute for Health and Clinical Excellence

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# Food allergy in children and young people

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

NICE clinical guideline 116
Developed by the Centre for Clinical Practice at NICE

**NICE clinical guideline 116**
**Diagnosis and assessment of food allergy in children and young people in primary care and community settings**

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# 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**

Note: 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 of the lips, face and around the eyes | |
| **The gastrointestinal system** | |
| Angioedema of the lips, tongue and palate | Gastro-oesophageal 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 gastrointestinal 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 (asthma, eczema or allergic rhinitis)
- any individual and family history of atopic disease (such as asthma, eczema or allergic rhinitis) or food allergy in parents or siblings
- details of any foods that are avoided and the reasons why

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

- 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
- 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 a rapid onset.

Non-IgE-mediated reactions are generally characterised by delayed and non-acute reactions.

### IgE-mediated food allergy

1.1.5 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

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

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

1.1.8 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.

1.1.9 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.

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

### Non-IgE-mediated food allergy

1.1.11 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, timings of elimination and reintroduction, and follow-up.

### 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 1.1.11), 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 one or more acute systemic reactions
  - had one or more severe delayed reactions
  - 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*

**Initial recognition**

- Consider food allergy in a child or young person who:
  - has one or more of the signs and symptoms in **table 1** (pay particular attention to persistent symptoms that involve different organ systems) **or**
  - has had treatment for atopic eczema, gastro-oesophageal reflux disease or chronic gastrointestinal symptoms (including chronic constipation) but their symptoms have not responded adequately.

**History and examination**

- Do not offer allergy tests without first taking an allergy-focused clinical history.
- A healthcare professional with the appropriate competencies (a GP or other healthcare professional) should take a clinical history using the questions in **recommendation 1.1.3**.
- Based on the clinical history, physically examine the child or young person, in particular for:
  - growth and physical signs of malnutrition
  - signs indicating allergy-related comorbidities (atopic eczema, asthma and allergic rhinitis).

**When to consider referral (also see referral box below; see recommendation 1.1.17)**

If any of the following apply, consider referral to secondary or specialist care:

- The child or young person has:
  - faltering growth with one or more gastrointestinal symptoms in table 1
  - had one or more acute systemic reactions or severe delayed reactions
  - significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer
  - possible multiple food allergies.
- There is persisting parental suspicion of food allergy (especially where symptoms are difficult or perplexing) despite a lack of supporting history.

**Food allergy is suspected**

- Offer age-appropriate information that is relevant to the type of allergy (IgE-mediated, non-IgE-mediated or mixed). Include:
  - the type of allergy suspected
  - the risk of a severe allergic reaction
  - any impact on other healthcare issues such as vaccination
  - the 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 and their safety and limitations
    - ◊ referral to secondary or specialist care.
- support groups and how to contact them.

**Assessment**

**Information and support**

**IgE-mediated allergy is suspected**

- Offer a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens. Base choice of test on:
  - the clinical history **and**
  - the suitability for, safety for and acceptability to the child (or their parent or carer) **and**
  - the available competencies of the healthcare professional.
- Tests should only be undertaken by healthcare professionals with appropriate competencies.
- Only undertake skin prick tests where there are facilities to deal with an anaphylactic reaction.
- Interpret test results in the context of clinical history.
- Do not use atopy patch testing or oral food challenges to diagnose IgE-mediated allergy in primary care or community settings.

**Non-IgE-mediated allergy is suspected**

- Try eliminating the suspected allergen for 2–6 weeks, then reintroduce. Consult a dietitian with appropriate competencies about nutritional adequacies, timings and follow-up.
- Taking into account socioeconomic, cultural and religious issues, offer information on:
  - what foods and drinks to avoid
  - how to interpret food labels
  - alternative foods to eat to ensure a balanced diet
  - the duration, safety and limitations of an elimination diet
  - oral food challenge or reintroduction procedures, if appropriate, and their safety and limitations.
- If allergy to cows' milk protein is suspected, 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.

**Consider referral to secondary or specialist care if (see recommendation 1.1.17):**

- symptoms do not respond to a single-allergen elimination diet.
- the child or young person has confirmed IgE-mediated food allergy and concurrent asthma.
- tests are negative but there is strong clinical suspicion of IgE-mediated food allergy.

**Alternative diagnostic tools**

- Do not use the following diagnostic tests in the diagnosis of food allergy:
  - vega test
  - applied kinesiology
  - hair analysis
- Do not use serum-specific IgG testing to diagnose food allergy.

## *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 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 list of signs and symptoms of possible food allergy.

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 valid test results, 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 paediatric 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 [116]) 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 IgE-mediated allergy?

3. What tests should be used to diagnose non-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 2 below) were included in the analysis of risk factors. For identified and excluded studies see appendices 1 and 2.

**Table 2 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**

**Note: 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 of the lips, face and around the eyes | |
| **The gastrointestinal system** | |
| Angioedema of the lips, tongue and palate | Gastro-oesophageal 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 gastrointestinal 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 (asthma, eczema or allergic rhinitis)
- any individual and family history of atopic disease (such as asthma, eczema or 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:

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

  - 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
- 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 comorbidities (atopic eczema, asthma and allergic rhinitis).

## *2.3 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?**

### 2.3.1 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 1 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<br><br>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%<br>Specificities ranged from 20% to 99%<br>Positive predictive values ranged from 40% to 93%.<br>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%<br>Specificities ranged from 20% to 89%<br>Positive predictive values ranged from 40% to 84%.<br>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%<br>Specificities ranged from 87% to 100%<br>Positive predictive values ranged from 75% to 100%.<br>Negative predictive values ranged from 43% to 90% | Atopy patch test | Y | Y | N | Y | Y | Very low |

***Please see footnotes 3–6 for criteria for downgrading**

**GRADE profile 2 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<br><br>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%<br>Specificities ranged from 46% to 100%<br>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%<br>Specificities ranged from 30% to 98%<br>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%<br>Specificities ranged from 70% to 100%<br>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 3 – 6 for criteria for downgrading

**GRADE profile 3: 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<br><br>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%<br>Specificities ranged from 29% to 72%<br>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%<br>Specificities ranged from 38% to 100%<br>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 3 –6 for criteria for downgrading

**GRADE profile 4: 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<br><br>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%<br>Specificities ranged from 51% to 100%<br>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%<br>Specificities ranged from 20% to 47%<br>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%<br>Specificities ranged from 89% to 100%<br>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 3 – 6 for criteria for downgrading

**GRADE profile 5 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<br><br>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%<br>Specificities ranged from 47% to 100%<br>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%<br>Specificities ranged from 25% to 52%<br>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%<br>Specificities ranged from 86% to 100%<br>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 3 – 6 for criteria for downgrading

**GRADE profile 6: 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<br><br>Evaluation of three individual studies for tomato, fish and beef allergy | Food tested | Diagnostic test | Limitations[3] | Inconsistency[4] | Indirectness | Imprecision[5] | Other considerations[6] | Quality |
|---|---|---|---|---|---|---|---|---|---|
| One study (Vierrucci et al.1989) | Sensitivity 100%, Specificity 66%<br>Positive predictive value 40%<br>Negative predictive value 100% | Tomato | Skin prick test | Y | Y | N | Y | Y | Very low |
| | Sensitivity 14%, Specificity 50%<br>Positive predictive value 33%<br>Negative predictive value 25% | Tomato | IgE | Y | Y | N | Y | Y | Very low |
| One study (Sampson et al.1998) | Sensitivity 90%, Specificity 57%<br>Positive predictive value 77%<br>Negative predictive value 80% | Fish | Skin prick test | Y | Y | N | - | Y | Very low |

[3] 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.
[4] Inconsistency: studies did not explicitly group the children by age group.
[5] Imprecision: cannot be assessed in diagnostic studies so it has been assumed that imprecision exists here and has been downgraded.
[6] Other considerations: Some studies based their reported outcomes on various thresholds, the validation of which had not been determined.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sensitivity 94%, Specificity 65%<br>Positive predictive value 49%<br>Negative predictive value 97% | Fish | IgE | Y | Y | N | - | Y | Very low |
| One study (Fiocchi et al.2002) | Sensitivities ranged from 90% to 100%<br>Specificities ranged from 78% to 100%<br>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 |

### 2.3.2 Evidence statements

*2.3.2.1* *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%.*

*2.3.2.2* *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%.*

*2.3.2.3* *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%.*

*2.3.2.4* *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%.*

*2.3.2.5* *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%.*

2.3.2.6 *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%.*

### 2.3.3 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 3.

**Table 3: 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** | 3.47 | 559 | 0.11 | 514 | 4,563 |

| | | | | | |
|---|---|---|---|---|---|
| **test** | | | | | |

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 4, and of being the optimum choice in table 5.

**Table 4: 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 5: 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.

### 2.3.4 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.

### 2.3.5 Recommendations

**Recommendation 1.1.5**

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.

**Recommendation 1.1.6**

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

**Recommendation 1.1.7**

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

**Recommendation 1.1.8**

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 1.1.9**

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 1.1.10**

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

## *2.4 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 food allergy in children and young people in primary care?**

### 2.4.1 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 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 7: Differential diagnosis of non-IgE and mixed IgE and non-IgE 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 7 – 10 for criteria for downgrading

**GRADE profile 8: The utility of different tools for the correct diagnosis of non-IgE and mixed IgE and non-IgE food allergy**

| Studies | Outcome: utility of various tools for the correct diagnosis and assessment of non-IgE and mixed IgE and non-IgE 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 7 – 10 for criteria for downgrading

**GRADE profile 9: 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<br>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%<br>Specificities ranged from 71% to 100% | Y | Y | Y | Y | N | Very low |

* Please see footnotes 7 – 10 for criteria for downgrading

**GRADE profile 10: 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 7 – 10 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[7] | Inconsistency[8] | Indirectness[9] | Imprecision[10] | 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 |

[7] 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.
[8] Inconsistencies: differences in diagnostic performance could not be explained by differences in the study population and so has been downgraded.
[9] Indirectness: not all papers compared the same tests with DBCPFC. Endoscopy was needed to confirm diagnosis in some cases.
[10] Imprecision: cannot be assessed in diagnostic studies so it has been assumed that imprecision exists here and has been downgraded.

### 2.4.2 Evidence statements

*2.4.2.1* *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.*

*2.4.2.2* *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.*

*2.4.2.3* *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%.*

*2.4.2.4* *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.*

*2.4.2.5* *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.*

### 2.4.3 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.

### 2.4.4 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.

### 2.4.5 Recommendations

**Recommendation 1.1.11**

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, timings of elimination and reintroduction, and follow-up.

## *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 6) 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 7).

## Table 6: 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 7: 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**

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 1.1.11), 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 food allergy be referred to secondary or specialist care?**

### 2.6.1 Evidence review

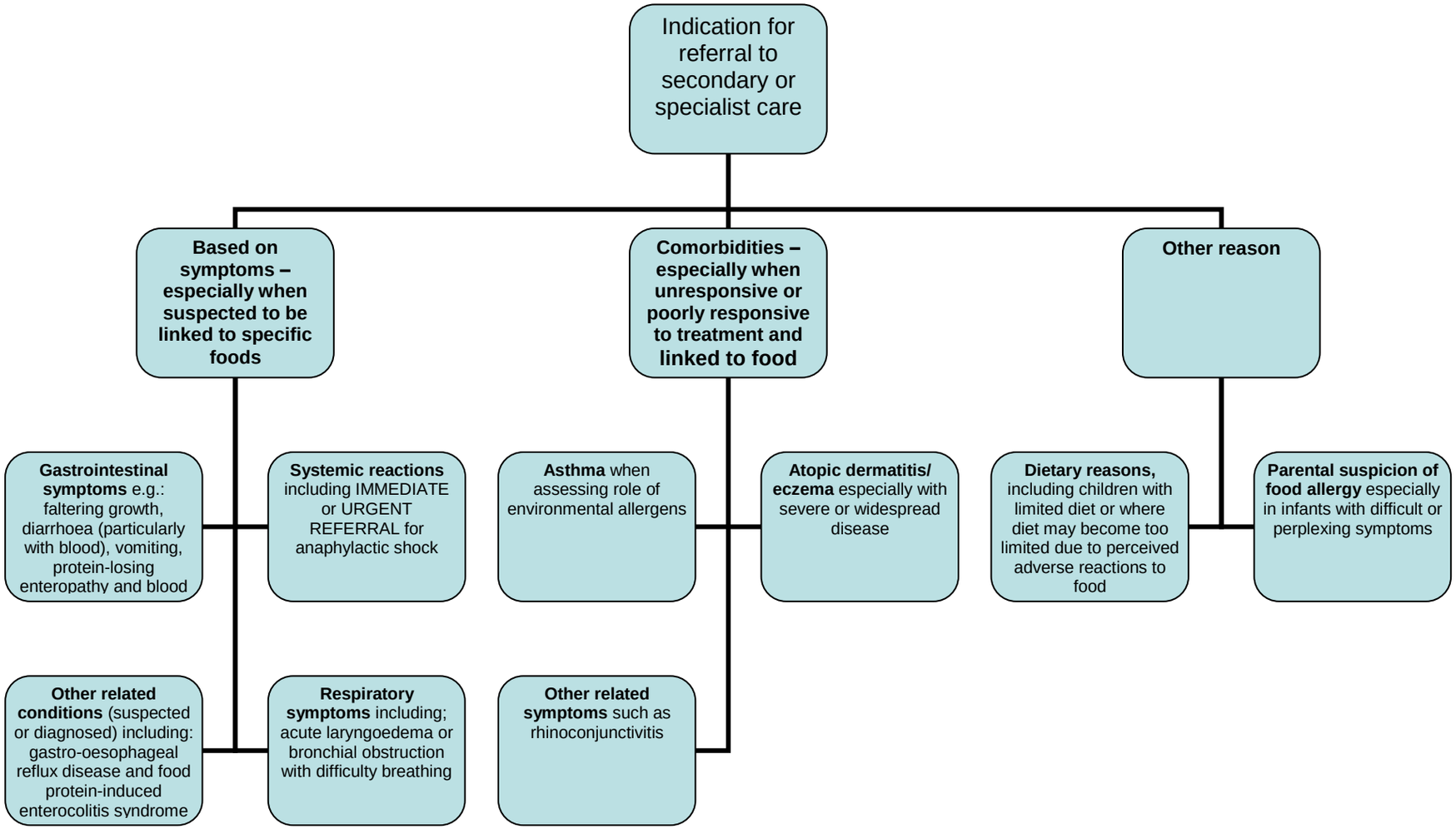
The review considered indications for referring a child or young person with suspected food allergy from primary or community settings to secondary or specialist care. This did not include referrals from secondary or specialist settings, such as dermatology and gastroenterology to specialist allergy 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 8). An illustration of this information was also presented (see figure 1), categorising these indications into three main reasons for referral.

**Table 8: 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 1.1.17**

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 one or more acute systemic reactions
  - had one or more severe delayed reactions
  - 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/CG116Guidance).

**Quick reference guide**

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG116QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2442

**'Understanding NICE guidance'**

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG116PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2443.

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

- Postnatal care: Routine postnatal care of women and their babies. NICE clinical guideline 37 (2006). Available from www.nice.org.uk/guidance/CG37

### *5.1 Guidance under development in parallel with NICE*

- The Royal College of Paediatrics and Child Health are currently developing the following related guidance: The Royal College of Paediatrics and Child Health Care pathway for children with food allergy. Publication expected February 2011.

## 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

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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 |

## 7.4 Appendices

**Appendices 1–4 in separate files**

Appendix 1: scope, literature search, review protocol and evidence

Appendix 2: excluded studies

Appendix 3: health economics

Appendix 4: declarations of interest

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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.

The guideline should be cited as:

National Institute for Health and Clinical Excellence (2011). Diagnosis and assessment of food allergy in children and young people in primary care and community settings. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidance/CG116

# Food Allergy in Children Appendix 1

Appendix 1.0 – Scope

Appendix 1.1 – Review protocol

Appendix 1.2 – Literature search & Search Strategies

Appendix 1.3 – Evidence Tables

- 1.3.1 – Clinical question 1
- 1.3.2 – Clinical question 2
- 1.3.3 – Clinical question 3
- 1.3.4 – JAMA review
- 1.3.5 – Clinical question 4
- 1.3.6 – Clinical question 5
- 1.3.7 – Alternative tests

**Appendix 1.0**

# SCOPE

## 1 Guideline title

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

### *1.1 Short title*

Food allergy in children and young people

## 2 The remit

The Department of Health has asked NICE: ‘To produce a short clinical guideline on the diagnosis and assessment of food allergy in children in primary care and community settings.'

## 3 Clinical need for the guideline

### *3.1 Epidemiology*

a) Food allergy is an adverse immune response to food allergens. It can be classified into IgE-mediated, non-IgE-mediated (including T cell, IgG and eosinophil mediated) and mixed IgE-mediated allergy. The IgE-mediated reactions are acute, frequently have rapid onset and are characterised by:

- anaphylaxis
- angioedema
- asthma or respiratory symptoms, such as wheezing
- conjunctivitis
- oral allergy syndrome
- rhinitis
- urticaria

Non-IgE-mediated food allergy reactions are generally in the form of food intolerance and are characterised by:

- atopic eczema
- chronic pulmonary disease
- constipation
- enterocolitis
- enteropathy
- eosinophilic oesophagitis
- faltering growth
- gastro-oesophageal reflux disease
- proctitis
- proctocolitis

These are frequently delayed onset conditions and may need the opinion of a paediatrician or paediatric gastroenterologist.

b) Sensitisation to food and inhalant allergens increases with increasing eczema disease severity, suggesting a role for the skin barrier in initiating allergic disease.

c) Food allergy in the population is amongst 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 severity of reactions and a dramatic increase in prevalence over the past recent decades.

d) 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.

e) In the UK there have been concerns expressed about the prevalence of food allergy in the general population, especially from individuals and families affected by food allergy, healthcare staff,

schools, food producers and retailers, and government departments.

f) There has also been discrepancy between self -reported food allergy and confirmed correct diagnoses of food allergy. In view of this, there is inconsistency in the reported prevalence of food allergies in children and young people.

g) Only 25–40% of self-reported food allergy is confirmed as true clinical food allergy by an oral food challenge.

h) The following are the most common foods to which children and young people are allergic:

- cows' milk
- hens' eggs
- peanuts
- wheat
- soy
- shellfish
- fish
- sesame
- kiwi fruit
- tree nuts.

Less commonly, there are reported allergies to certain fruits, for instance, banana.

i) Recent evidence suggests that the prevalence of self-reported food allergy differs for individual foods and ranges from 3% to 35%.

j) Correct diagnosis of food allergy, followed by counselling and advice based on reliable criteria, is important because it will help decrease the incidence of adverse food reactions resulting from true food allergies and also help prevent the unnecessary dietary

exclusion of foods which are safe and which should be eaten as part of a normal, healthy diet.

## *3.2 Current practice*

a) In their review of services for allergy (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 allergy 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 within 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 parents and/or carers of children and young people and young people with allergies, also purchase over-the-counter medicines from community pharmacies or high street chains. However, if there is diagnostic doubt or more severe disease the GP may consider referral for a specialist opinion. Depending on the local service provision this may be delivered:

- in an allergy clinic run by an allergist or a paediatric allergist
- in an allergy clinic run by a consultant in another specialty (such as respiratory or immunology)
- within children's services (although many children are seen within adult services).

b) The Department of Health review also suggested, following consensus, that primary care practitioners have limited knowledge or awareness of allergy, are not sufficiently trained in allergy, may overlook multi-system atopy, and lack guidelines for therapy and referral.

c) The Map of Medicine pathway for suspected food allergy shows that on clinical presentation of food allergic symptoms, primary care practitioners should:

- carry out a thorough clinical history, including symptoms, history of episodes, family history of atopy or food allergy, other possible causes, current diet, recent changes in diet and feeding history in young children
- conduct a physical examination to assess factors such as nutritional status and growth patterns, signs of atopy and/or co morbidity
- consider differential diagnoses, such as non-IgE-mediated immune reactions, toxic reactions and asthma
- consider referral to an allergy specialist when, for instance, there is doubt about the diagnosis, a history of anaphylaxis or severe reaction, or the need for several and/or nutritionally important foods to be eliminated.

d) 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.

# 4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

## *4.1 Population*

### 4.1.1 Groups that will be covered

a) Children and young people up to their 19th birthday presenting with suspected food allergy and symptoms such as atopic eczema, anaphylaxis, urticaria, rhinitis, conjunctivitis, asthma, gastrointestinal symptoms and oral allergy syndrome on eating certain foods. Children will be separated into age specific sub-groups (0–6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years and 10–18 years) as appropriate.

b) Children and young people up to their 19th birthday who are at higher risk of developing a food allergy, specifically:

- children with existing atopic diseases such as asthma, atopic eczema and allergic rhinitis
- children with a first degree relative (that is, a parent or sibling) with a food allergy or other atopic disease.

### 4.1.2 Groups that will not be covered

a) Adults aged 19 years and over.

b) Children and young people with non-immunologically mediated (that is, non-allergic) food intolerance such as an intolerance to lactose.

c) Children and young people with a toxic reaction to food, such as protease inhibitors in legumes.

d) Children and young people with a pharmacological reaction to food, such as tyramine in cheese and pickled herrings.

e) Children and young people with a psychological reaction to food, such as food avoidance.

## *4.2 Healthcare setting*

a) Primary care NHS settings.

b) 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.

## *4.3 Clinical diagnosis*

### 4.3.1 Key clinical issues that will be covered

a) Physical examination and assessment, including clinical history for the diagnosis of food allergy.

b) Use of child or parent diaries of episodes of suspected food allergy, including symptoms and food ingested.

c) Evaluation of the following diagnostic tests either alone or in combination, in the diagnosis and assessment of food allergy:

- food elimination
- skin prick test (fresh foods and commercial extracts will be assessed)
- serum specific IgE
- atopy patch test.
- double-blind placebo-controlled food challenge will be included as the comparator for the above tests

d) Determination of a differential diagnosis for IgE, non-IgE and mixed-IgE-mediated food allergy to specific foods.

e) Referral to secondary care or other services, such as allergists, dieticians, respiratory medicine specialists, ENT, immunologists, general paediatricians, as appropriate.

f) The specific information and support needs of children with suspected food allergy and their parent/carers

g) Evaluation of the following alternative diagnostic tools, either alone or in combination, in the diagnosis of food allergy:

- Vega test
- applied kinesiology
- hair analysis
- leucocytotoxic test
- IgG test.

### 4.3.2 Clinical issues that will not be covered

a) Diagnosis of food intolerance.

b) Diagnosis of food allergy in adults aged 19 years and over.

c) Diagnosis of food allergy in children and young people in secondary and tertiary care.

d) Prevention and treatment of food allergy in children and young people in primary care and community settings

## *4.4 Main outcomes*

a) Utility of various tools, history taking and physical examination for the correct diagnosis and assessment of IgE, non-IgE or mixed-IgE-mediated food allergy in children and young people.

b) Rates of referral to secondary or specialist care.

c) Adverse events associated with diagnostic tools.

d) Health-related quality of life associated with diagnosis or misdiagnosis of food allergy.

e) Resource use and costs.

### *4.5 Economic aspects*

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative tests. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

### *4.6 Status*

#### 4.6.1 Scope

This is the final version of the scope.

#### 4.6.2 Timing

The development of the guideline recommendations will begin in March 2010.

## 5 Related NICE guidance

- 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 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual’.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

**Appendix 1.1**

# Review Protocol

| **KEY CLINICAL QUESTION 1** | | |
|---|---|---|
| | Details | Comments |
| REVIEW QUESTION 1 | What elements should allergy focused clinical history taking, physical examination and patient/parent food diaries include in order to effectively diagnose and assess food allergy (IgE, non-IgE-mediated or mixed) in children? | |
| OBJECTIVES | To determine how and when clinical history and physical examinations should be carried out in order to assess food allergy in children effectively.<br>To determine how and when food diaries should be used within the diagnostic process. | |
| CRITERIA FOR CONSIDERING STUDIES | All studies-no restrictions | |
| POPULATION | Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups;<br>Those with existing atopic diseases<br>Those with a first degree relative with a food allergy or other atopic disease<br>Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years) | |
| DIAGNOSTIC TOOL | Key elements of clinical history, physical examination and patient/parent food diary | |
| COMPARATORS | N/A | |
| OUTCOMES | Examining the accuracy of documentation in patient/parent food diaries of episodes of suspected | |

| | | |
|---|---|---|
| | food allergy to specific foods at specific times<br>Utility of history taking and physical examination for the correct diagnosis and assessment of food allergy in children<br>Resource use and cost | |

| **KEY CLINICAL QUESTION 2** | | |
|---|---|---|
| | Details | Comments |
| REVIEW QUESTION 2 | Which diagnostic tools and strategy are most appropriate and accurate to diagnose non-IgE-mediated and mixed IgE-mediated food allergy in children? | |
| OBJECTIVES | To determine whether diagnosis of non-IgE & mixed IgE food allergy can be carried out in primary care<br>To investigate whether there is a clearly focussed and definite diagnosis of non-IgE and mixed IgE food allergy.<br>To determine whether diagnostic tools have differing acceptability within subgroups of the population. | |
| CRITERIA FOR CONSIDERING STUDIES | All studies (no restrictions) | |
| POPULATION | Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups;<br>Those with existing atopic diseases<br>Those with a first degree relative with a food allergy or other atopic disease<br>Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years) | |

| | | |
|---|---|---|
| DIAGNOSTIC TOOL | Endoscopic procedures<br>Skin Prick Test (SPT)<br>Serum Specific IgE tests<br>Elimination diet<br>Atopy Patch Test (APT)<br>Vega test/Applied kinesiology/Hair analysis/ Leucocytotoxic test/IgG test<br>Other diagnostic tests | Most endoscopies carried out in local hospital but some may be offered in larger GP clinics. May be performed by GPwSI in Gastroenterology-not sure if this applies to children? Also may be referred to community endoscopy service provider (CESP). |
| COMPARATORS | Double Blind Placebo Controlled Food Challenge (DBPCFC) | No reference standard as issues of delayed symptoms for non IgE and mixed IgE FA. |
| OUTCOMES | Utility of various tools for the correct diagnosis and assessment of non-IgE and mixed IgE-mediated food allergy in children<br>Acceptability of diagnostic strategies to age-specific subgroups<br>Adverse events associated with diagnostic tools<br>Health related quality of life associated with diagnostic tools in primary care and community settings<br>Resource use and costs | |

| **KEY CLINICAL QUESTION 3** | | |
|---|---|---|
| | Details | Comments |
| **REVIEW QUESTION 3** | Which diagnostic tools and strategy are most appropriate and accurate to diagnose IgE-mediated food allergy in children? | |
| OBJECTIVES | To determine whether test accuracy varies within subgroups of the population.<br>To determine whether threshold values for diagnostic tests differ within subgroups of the population.<br>To determine whether diagnostic tools have differing acceptability within subgroups of the population. | |

| | | |
|---|---|---|
| CRITERIA FOR CONSIDERING STUDIES | All study designs (no restrictions) | |
| POPULATION | Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups;<br>Those with existing atopic diseases<br>Those with a first degree relative with a food allergy or other atopic disease<br>Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years) | |
| DIAGNOSTIC TOOL | Skin Prick Test (SPT) using fresh or commercial extracts<br>Serum Specific IgE tests<br>Elimination diet<br>Atopy Patch Test (APT)<br>Vega test/Applied kinesiology/Hair analysis/ Leucocytotoxic test/IgG test<br>Other diagnostic tests | APT is experimental in diagnosing IgE reactions. |
| COMPARATORS | Double Blind Placebo Controlled Food Challenge (DBPCFC) | NB: Not appropriate for all age groups and may not be used within primary care (need to consider). |
| OUTCOMES | Utility of various tools for the correct diagnosis and assessment of IgE-mediated food allergy in children<br>Diagnostic accuracy of diagnostic tools<br>Threshold values of diagnostic tools for the correct diagnosis of IgE-mediated food allergy in children<br>Acceptability of diagnostic strategies to age-specific subgroups<br>Adverse events associated with diagnostic tools<br>Health related quality of life associated with diagnostic tools in primary care and community settings | |

| | | |
|---|---|---|
| | Resource use and costs | |
| **KEY CLINICAL QUESTION 4** | | |
| | Details | Comments |
| REVIEW QUESTION 4 | At which stage in the diagnostic process should children with symptoms of IgE, non IgE or mixed mediated food allergy be referred to secondary/specialist care? | |
| OBJECTIVES | To determine to what extent GP's are equipped to diagnose IgE and non IgE-mediated food allergy.<br>To determine when children with high risk co morbid states should be referred to secondary/specialist care. | |
| CRITERIA FOR CONSIDERING STUDIES | All studies-no restrictions | |
| POPULATION | Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups;<br>Those with existing atopic diseases<br>Those with a first degree relative with a food allergy or other atopic disease<br>Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years) | |
| DIAGNOSTIC TOOL | Clinical signs and symptoms that lead to a referral to secondary/specialist care | |
| COMPARATORS | N/A | |
| OUTCOMES | Health related quality of life associated with diagnostic tools in primary care and community settings<br>Resource use and costs<br>Appropriate referral to secondary care | |

| **KEY CLINICAL QUESTION 5** | | |
|---|---|---|
| | Details | Comments |
| REVIEW QUESTION 5 | What information should children with suspected food allergy and their parents/carers receive during the diagnostic process? | |
| OBJECTIVES | To determine what information should be provided to children and their parents/carers<br>at first consultation<br>during the diagnostic process<br>following diagnosis/referral | |
| CRITERIA FOR CONSIDERING STUDIES | All studies-no restrictions | |
| POPULATION | Children (under 18 years) presenting with symptoms of food allergy separated in the following sub-groups;<br>Those with existing atopic diseases<br>Those with a first degree relative with a food allergy or other atopic disease<br>Age specific groups (0-6months, 6months-1year, 1-2years, 2-5years, 5-10years and 10-18years) | |
| DIAGNOSTIC TOOL | Information provided to patients and their parents/carers. | |
| COMPARATORS | N/A | |
| OUTCOMES | Health related quality of life associated with diagnostic tools in primary care and community settings<br>The use of food diaries to record patient and parent/carer experiences of adverse reactions to food<br>Appropriate referral to secondary care<br>Patient and parent/carer information and support | |

| | | |
|---|---|---|
| | needs<br>Adverse reactions to diagnostic tests | |

**Appendix 1.2**

# Literature search

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in ‘The guidelines manual' (2009). The purpose of systematically searching the literature is to attempt to comprehensively identify the published evidence to answer the key clinical questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the key clinical questions were developed by the Information Services Team with advice from the Short Clinical Guidelines Technical Team. Structured clinical questions were developed using the PICO (population, intervention, comparison, outcome) model and were translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

To identify economic evaluations the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Search filters to identify economic evaluations and quality of life studies were used to interrogate bibliographic databases. There were no date restrictions imposed on the searches.

In addition to the systematic literature searches, the Guideline Development Group members were asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between January to March 2010.

Scoping searches were undertaken in October 2009 using the following websites and databases (listed in alphabetical order); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

| Guidance/guidelines | Systematic reviews/economic evaluations |
|---|---|
| Allergy UK<br>American Academy of Allergy, Asthma and Immunology<br>The Anaphylaxis Campaign<br>British Dietetic Association<br>British Paediatric Allergy Immunology and Infection Group<br>British Society for Allergy and Clinical Immunology<br>British Society for Gastroenterology<br>Canadian Medical Association Infobase<br>Clinical Knowledge Summaries<br>College of Emergency Medicine<br>Department of Health<br>Food Allergy and Anaphylaxis Network (US)<br>Food Allergy Initiative (US)<br>Food Standards Agency<br>Guidelines International Network (GIN)<br>National Guideline Clearing House (US)<br>National Health and Medical Research Council (Australia)<br>National Institute for Health and Clinical Excellence (NICE) – guidance published & in development<br>National Institute for Health and Clinical Excellence (NICE) – topic selection<br>National Institute of Allergy and Infectious Diseases (US)<br>New Zealand Guidelines Group<br>NHS Evidence<br>Resuscitation Council<br>Royal College of Physicians of London<br>Royal College of Surgeons of Edinburgh<br>Royal College of Surgeons of England<br>Scottish Intercollegiate Guidelines Network (SIGN)<br>Vegetarian Society<br>World Allergy Organization | Clinical Evidence<br>Cochrane Database of Systematic Reviews (CDSR)<br>Database of Abstracts of Reviews of Effects (DARE)<br>Health Economic Evaluations Database (HEED)<br>Health Technology Assessment (HTA) Database<br>NHS Economic Evaluation Database (NHS EED)<br>NHS R&D Service Delivery and Organisation (NHS SDO) Programme<br>National Institute for Health Research (NIHR) Health Technology Assessment Programme<br>TRIP Database |

# Search strategies

The following sources were searched for the topics presented in the sections below.

• Clinical Trials.gov

• Current Controlled Trials

• Cochrane Database of Systematic Reviews – CDSR (Wiley)

• Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)

• Database of Abstracts of Reviews of Effects – DARE (CRD)

• Health Technology Assessment Database – HTA (CRD)

• CINAHL (HDAS via NHS Evidence)

• EMBASE (Ovid)

• MEDLINE (Ovid)

• MEDLINE In-Process (Ovid)

• National Research Register Archive

• UK Clinical Research Network

The searches addressed questions about diagnosis and referral to secondary care as well as patient information needs. A review of reviews was undertaken to attempt to focus in on reviews of the evidence and in this case a systematic review filter was applied, the other searches were not limited by study design.

*The MEDLINE search strategies are presented below. They were translated for use in all of the other databases.*

Diagnosis

Ovid MEDLINE(R) <1950 to January Week 2 2010>

1 exp Food hypersensitivity/ (11458)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6891)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or egg* or peanut* or nut* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana*)).ti,ab. (4518)

4 or/1-3 (15119)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2396979)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1356759)

7 5 or 6 (2774216)

8 Medical history taking/ or Physical examination/ or "Diagnostic Techniques and Procedures"/ or "Sensitivity and Specificity"/ (247715)

9 ((physical or medical) adj3 (examin* or assess*)).ti,ab. (51616)

10 ((medical or parent* or famil* or genetic) adj3 histor*).ti,ab. (51941)

11 ((food* or patient* or parent*) adj3 (diar* or record* or chart*)).ti,ab. (60288)

12 Patch Tests/ or passive cutaneous anaphylaxis/ (10442)

13 ((skin prick or skin-prick or skinprick or patch* or atop* or fresh food* or commercial extract*) adj3 (test* or assess*)).ti,ab. (11515)

14 (SPT or passive cutaneous anaphyla*).ti,ab. (3415)

15 ((serum specific or IgE or immunoglobulin E or radioallergosorbent or allerg*) adj3 (test* or assess*)).ti,ab. (8685)

16 (Microarray* adj3 (food allergen* or diagnos* or assay* or chip based)).ti,ab. (882)

17 (RAST or CAP-RAST or ELISA or ImmunoCAP or Immulite 2000 or Turbo-MP or UniCAP or Fluorescence enzyme immunoassay* or FEIA or Recombinant allergen* or purified native allergen* or Component resolved diagnos* or component-resolved diagnos* or CRD or ISAC).ti,ab. (83864)

18 ((Food* or diet*) adj3 (eliminat* or exclu*)).ti,ab. (1991)

19 (((food* or allergen*) adj3 (challenge* or provoc*)) or DBPCFC).ti,ab. (4000)

20 Endoscopy/ (33344)

21 (endoscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop* or OGD or EGD).ti,ab. (102587)

22 ((Vega or leucocytotoxic* or ALCAT or Neutron or Nutron or IgG or immunoglobulin G or Provocation-neutralisation or pulse) adj3 (test* or assess*)).ti,ab. (4191)

23 (kinesiolog* or hair analys* or Bio-Electronic Regulatory Medicine or BER or Miller technique).ti,ab. (2718)

24 or/8-23 (609302)

25 4 and 7 and 24 (2810)

26 Animals/ not Humans/ (3331323)

27 25 not 26 (2789)

28 limit 27 to english language (2332)

Referral

Ovid MEDLINE(R) <1950 to January Week 5 2010>

1 exp Food hypersensitivity/ (10003)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6449)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (4536)

4 or/1-3 (13017)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (918757)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (983230)

7 5 or 6 (1400615)

8 Pruritus/ (27974)

9 Burning Mouth Syndrome/ (305)

10 ((itch* or burn* or swell* or swollen or pruritis or tight* or inflamm* or irritat*) adj3 (mouth or oral or nose or nasal or nostril* or tongue or lip* or ear* or pharynx or uvula or throat)).ti,ab. (12395)

11 (glossalgia or chelilitis).ti,ab. (11)

12 ((oral or pollen food or pollen-food or exercise-induced food or exercise induced food) adj3 (allerg* or syndrome*)).ti,ab. (1212)

13 Rhinitis/ (7986)

14 rhinitis.ti,ab. (13450)

15 ((inflamm* or runny or irritat* or drip* or congest*) adj3 (nose or nasal or nostril*)).ti,ab. (2640)

16 Conjunctivitis, Allergic/ (1935)

17 (conjunctivitis or rhinoconjunctivitis).ti,ab. (6629)

18 Asthma/ or status asthmaticus/ (85187)

19 (asthma* or wheez* or cough* or (shortness adj1 breath) or (tight* adj3 chest)).ti,ab. (100892)

20 Urticaria/ (13865)

21 Angioedema/ (7054)

22 (urticaria or angioedema or angio-oedema or hives).ti,ab. (9980)

23 Eczema/ (8518)

24 Dermatitis/ (9122)

25 dermatitis herpetiformis/ (1506)

26 (eczema or dermatitis).ti,ab. (33370)

27 ((skin or cutaneous) adj3 (disease* or inflamm* or irritat* or swell* or itch* or condition*)).ti,ab. (23071)

28 exp Diarrhea/ (91819)

29 Vomiting/ (73238)

30 (nause* or diarrhoea or diarrhea or vomit* or sick*).ti,ab. (110879)

31 Abdominal Pain/ (45927)

32 ((abdomin* or stomach or gastrointestin* or GI) adj3 (ache or aching or pain* or cramp* or anaphyla*)).ti,ab. (27074)

33 exp Gastroenteritis/ (7449)

34 eosinophilia/ (12384)

35 (oesophagiti* or esophagiti* or gastroenteriti* or gastriti* or proctiti* or enteropath* or enteriti* or enterocoliti*).ti,ab. (46838)

36 exp Gastroesophageal Reflux/ (20352)

37 ((gastroesophageal or gastroesophageal or gastro-oesophageal or gastro-esophageal or gastro oesophageal or gastro esophageal) adj3 reflux).ti,ab. (12904)

38 (GERD or GORD).ti,ab. (4050)

39 Constipation/ (30152)

40 constipat*.ti,ab. (10361)

41 Celiac Disease/ (9656)

42 ((coeliac or celiac) adj3 (disease or sprue or syndrome*)).ti,ab. (8292)

43 Hemosiderosis/ (1039)

44 ("heiner syndrome" or haemosiderosis* or hemosiderosis* or "chronic pulmonary disease").ti,ab. (1426)

45 "failure to thrive".ti,ab. (2669)

46 or/8-45 (547422)

47 exp primary health care/ (46982)

48 ("primary care" or "primary health care").ti,ab. (44006)

49 Family Practice/ (23938)

50 Physicians, Family/ (32498)

51 Community health nursing/ (214)

52 Patient care team/ (90555)

53 (family practi* or family doctor* or family physician* or gp* or GPwSI or GPSI or PwSI or general practi* or nurs* or health visit*).ti,ab. (181069)

54 ambulatory care facilities/ or outpatient clinics, hospital/ (11524)

55 ((secondary or tertiary or specialist or allerg* or dermatolog* or pediatric or paediatric or immunolog* or hospital* or outpatient* or out-patient* or ambulatory or multidisciplinary or multi-disciplinary or interdisciplinary or inter-disciplinary) adj3 (care or team* or unit* or clinic* or centre* or center* or service*)).ti,ab. (137673)

56 (consultant* or pediatrician* or paediatrician* or immunologist* or allergist* or dermatologist* or specialist respiratory physician* or gastroenterologist*).ti,ab. (37997)

57 "allergy and immunology"/ (11622)

58 "Referral and Consultation"/ (29335)

59 (referral or "second opinion").ti,ab. (34210)

60 Case management/ or Critical pathways/ (2419)

61 ((clinical or critical or care or integrated) adj3 pathway*).ti,ab. (5074)

62 or/47-60 (510282)

63 4 and 7 and 46 and 62 (562)

64 limit 63 to english language (442)

65 Animals/ not Humans/ (19162)

66 64 not 65 (442)

Patient information

Ovid MEDLINE(R) <1950 to February Week 4 2010>

1 exp Food hypersensitivity/ (11545)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6958)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or egg* or peanut* or nut* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana*)).ti,ab. (4557)

4 or/1-3 (15234)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2414071)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1368878)

7 5 or 6 (2795007)

8 4 and 7 (7630)

9 Animals/ not Humans/ (3355096)

10 8 not 9 (7536)

11 Qualitative Research/ (8148)

12 Nursing Methodology Research/ (12981)

13 exp Interviews as topic/ (35673)

14 Questionnaires/ (207131)

15 Narration/ (3114)

16 Health Care Surveys/ (16308)

17 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw. (610023)

18 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj3 analys$) or theoretical sampl$ or purposive sampl$).tw. (23054)

19 (hermeneutic$ or heidegger$ or husserl$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw. (5200)

20 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$).tw. (165)

21 or/11-20 (709017)

22 exp Patients/px (13517)

23 exp Parents/px (22952)

24 exp Family/px (44706)

25 Caregivers/px (8558)

26 Stress, Psychological/ (64917)

27 Adaptation, psychological/ (58654)

28 Emotions/ (30076)

29 Anxiety/ (39754)

30 Fear/ (17426)

31 exp Consumer Satisfaction/ (57355)

32 or/22-31 (283068)

33 21 or 32 (907226)

34 10 and 33 (715)

35 limit 34 to english (631)

Review of reviews

Ovid MEDLINE(R) <1950 to March Week 4 2010>

1 exp Food hypersensitivity/ (11583)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6990)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (5313)

4 or/1-3 (15704)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2422065)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1374417)

7 5 or 6 (2804580)

8 Pruritus/ (6952)

9 Burning Mouth Syndrome/ (561)

10 ((itch* or burn* or swell* or swollen or pruritis or tight* or inflamm* or irritat*) adj3 (mouth or oral or nose or nasal or nostril* or tongue or lip* or ear* or pharynx or uvula or throat)).ti,ab. (13866)

11 (glossalgia or chelilitis).ti,ab. (48)

12 ((oral or pollen food or pollen-food or exercise-induced food or exercise induced food) adj3 (allerg* or syndrome*)).ti,ab. (1395)

13 Rhinitis/ (6614)

14 Rhinitis, Allergic, Seasonal/ (10544)

15 (Hayfever or hay fever or hay-fever or ((season* or allerg*) adj3 rhiniti*) or (pollen* adj2 allerg*) or pollinos*).ti,ab. (14348)

16 rhinitis.ti,ab. (14718)

17 ((inflamm* or runny or irritat* or drip* or congest*) adj3 (nose or nasal or nostril*)).ti,ab. (2719)

18 Conjunctivitis, Allergic/ (2201)

19 (conjunctivitis or rhinoconjunctivitis).ti,ab. (8049)

20 Asthma/ or status asthmaticus/ (88662)

21 (asthma* or wheez* or cough* or (shortness adj1 breath) or (tight* adj3 chest)).ti,ab. (117490)

22 Urticaria/ (8175)

23 Angioedema/ (3595)

24 (urticaria or angioedema or angio-oedema or hives).ti,ab. (10618)

25 Eczema/ (7575)

26 Dermatitis/ (6477)

27 dermatitis herpetiformis/ (2269)

28 (eczema or dermatitis).ti,ab. (37859)

29 ((skin or cutaneous) adj3 (disease* or inflamm* or irritat* or swell* or itch* or condition*)).ti,ab. (25879)

30 exp Diarrhea/ (38235)

31 Vomiting/ (16658)

32 (nause* or diarrhoea or diarrhea or vomit* or sick*).ti,ab. (141890)

33 Abdominal Pain/ (10095)

34 ((abdomin* or stomach or gastrointestin* or GI) adj3 (ache or aching or pain* or cramp* or anaphyla*)).ti,ab. (30039)

35 exp Gastroenteritis/ (128475)

36 eosinophilia/ (10644)

37 (oesophagiti* or esophagiti* or gastroenteriti* or gastriti* or proctiti* or enteropath* or enteriti* or enterocoliti*).ti,ab. (64597)

38 exp Gastroesophageal Reflux/ (17932)

39 ((gastroesophageal or gastroesophageal or gastro-oesophageal or gastro-esophageal or gastro oesophageal or gastro esophageal) adj3 reflux).ti,ab. (13682)

40 (GERD or GORD).ti,ab. (4021)

41 Constipation/ (8418)

42 constipat*.ti,ab. (11079)

43 Celiac Disease/ (12460)

44 ((coeliac or celiac) adj3 (disease or sprue or syndrome*)).ti,ab. (9818)

45 Hemosiderosis/ (2061)

46 ("heiner syndrome" or haemosiderosis* or hemosiderosis* or "chronic pulmonary disease").ti,ab. (2465)

47 "failure to thrive".ti,ab. (3082)

48 or/8-47 (617306)

49 Meta-Analysis.pt. (23594)

50 Meta-Analysis as Topic/ (9973)

51 Review.pt. (1507038)

52 exp Review Literature as Topic/ (4706)

53 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (28357)

54 (review$ or overview$).ti. (198692)

55 (systematic$ adj4 (review$ or overview$)).tw. (23668)

56 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (2268)

57 ((studies or trial$) adj1 (review$ or overview$)).tw. (5084)

58 (integrat$ adj2 (research or review$ or literature)).tw. (2114)

59 (pool$ adj1 (analy$ or data)).tw. (5421)

60 (handsearch$ or (hand adj2 search$)).tw. (3201)

61 (manual$ adj2 search$).tw. (1731)

62 or/49-61 (1621950)

63 4 and 7 and 48 and 62 (755)

64 Animals/ not Humans/ (3363922)

65 63 not 64 (754)

66 limit 65 to english language (576)

Economic search

The following sources were searched to identify economic evaluations and quality of life data featuring the Barrett's Oesophagus patient population.

- Health Economic Evaluations Database – HEED (Wiley)
- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Ovid MEDLINE(R) <1950 to February Week 2 2010>

1 exp Food hypersensitivity/ (11520)

2 (food* adj3 (allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*)).ti,ab. (6935)

3 ((allerg* or hypersensitiv* or reaction* or atop* or hyperallerg* or acute sensitiv* or anaphyla*) adj3 (milk or infant formula or baby formula or egg* or peanut* or nut* or seed* or tree nut* or wheat or soy* or shellfish or fish or seafood* or kiwi fruit* or banana* or corn or strawberr* or celery or rice or red meat or buckwheat or apple* or pear* or peach* or jackfruit or gluten)).ti,ab. (5276)

4 or/1-3 (15604)

5 exp child/ or exp adolescent/ or exp infant/ or exp pediatrics/ (2407842)

6 (child* or adolescen* or infant* or baby or babies or neonat* or paediatric* or pediatric* or kids or teenager* or juvenile* or minor* or youth* or (young adj3 (person* or people))).ti,ab. (1364495)

7 5 or 6 (2787487)

8 Economics/ use mesz (25702)

9 exp "Costs and Cost Analysis"/ (146654)

10 Economics, Dental/ (1787)

11 exp Economics, Hospital/ (16270)

12 exp Economics, Medical/ (12852)

13 Economics, Nursing/ (3800)

14 Economics, Pharmaceutical/ (2077)

15 Budgets/ (8136)

16 exp Models, Economic/ (6944)

17 Markov Chains/ (6065)

18 Monte Carlo Method/ (13281)

19 Decision Trees/ (7024)

20 econom$.tw. (110417)

21 cba.tw. (7733)

22 cea.tw. (12989)

23 cua.tw. (625)

24 markov$.tw. (7099)

25 (monte adj carlo).tw. (13743)

26 (decision adj2 (tree$ or analys$)).tw. (5410)

27 (cost or costs or costing$ or costly or costed).tw. (216095)

28 (price$ or pricing$).tw. (17104)

29 budget$.tw. (13291)

30 expenditure$.tw. (25803)

31 (value adj2 (money or monetary)).tw. (804)

32 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2229)

33 or/8-32 (485568)

34 "Quality of Life"/ use mesz (79428)

35 quality of life.tw. (86740)

36 "Value of Life"/ use mesz (5062)

37 Quality-Adjusted Life Years/ use mesz (4171)

38 quality adjusted life.tw. (3221)

39 (qaly$ or qald$ or qale$ or qtime$).tw. (2670)

40 disability adjusted life.tw. (583)

41 daly$.tw. (634)

42 Health Status Indicators/ use mesz (14451)

43 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (9413)

44 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (788)

45 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1312)

46 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (18)

47 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (289)

48 (euroqol or euro qol or eq5d or eq 5d).tw. (1719)

49 (qol or hql or hqol or hrqol).tw. (13648)

50 (hye or hyes).tw. (49)

51 health$ year$ equivalent$.tw. (36)

52 utilit$.tw. (74099)

53 (hui or hui1 or hui2 or hui3).tw. (552)

54 disutili$.tw. (113)

55 rosser.tw. (63)

56 quality of wellbeing.tw. (2)

57 quality of well-being.tw. (255)

58 qwb.tw. (130)

59 willingness to pay.tw. (1195)

60 standard gamble$.tw. (522)

61 time trade off.tw. (479)

62 time tradeoff.tw. (168)

63 tto.tw. (356)

64 or/34-63 (210965)

65 33 or 64 (667901)

66 4 and 7 and 65 (229)

67 limit 66 to english language (200)

**Appendix 1.3.1**

# Clinical Question 1

What elements should allergy focused clinical history taking, physical examination and patient/parent food diaries include in order to effectively diagnose and assess food allergy (IgE, non-IgE-mediated or mixed) in children?

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Hand et al 2004 (3166) | Case control study | Tree nuts and peanuts | 93 children from the age of 3years with peanut and tree nut sensitivity | Skin prick test and IgE | No oral food challenge | Demographic details, family history of atopy (ingestion of nuts by mothers during pregnancy and lactation) Symptoms graded as follows. Mild: vomiting, abdominal pain, irritability, pruritus urticaria. Moderate: facial oedema (lip and mouth swelling. Severe laryngeal oedema, cyanosis, wheeze, collapse, syncopy anaphylaxis | Not recorded | The authors suggested that the use of DBPCFC raises concerns in clinicians due to possible adverse events and patient resistance to such testing. SPT is an almost painless procedure, was well |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | tolerated in the very young and gave a very good correlation with clinical history. They concluded that the findings emphasize the importance of good clinical history taking in conjunction with confirmatory SPT and/or specific IgE in the diagnosis and |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | management of nut allergy |
| Orhan et al 2009 (4844) | Cross sectional study | Hens egg, beef, cow's milk, fish, tomato, hazelnut, kiwi, black pepper, peanut, corn, walnut, potato, | 3500 children 6 to 9 year old urban schoolchildren | Skin prick test | Double Blind Placebo Controlled Food Challenge | Standard questionnaire. Demographics (age and sex), adverse reaction to food within 2hoursof consumption. Symptoms from a list of 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(swallowing/speaking difficulty) | Not recorded | Authors reported that questionnaire was validated. The most frequently reported clinical manifestations were cutaneous 75.6%, gastrointestinal 56.4%, nasal 37.2%, bronchial 32.0%, and |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | cardiovascular (palpitations/tachycardia, hypotension ) and other(sweating, pallor, fainting, loss of consciousness) symptoms. Specify foods that caused reaction | | ocular 22.4%. 75.6% children reported a reaction that involved more than one organ system. The rate of IgE reported FA was significantly higher than clinically confirmed FA by means of DBPCFC (or 7.46 CI(4.67-12.01) p<0.0001). Although DBPCFC is considered |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | the gold standard for diagnosis of FA its positive predictive value has been suggested to be around 90% in patients with peanut allergy. Therefore a cautionary approach should be adopted particularly in patients with a negative FC but with a consistent history and positive SPT |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Kucukosmanoglu et al 2008 (150) | Observational study | Cow's milk | 1015 infants between 8 and 18months | Skin prick test | Open food challenge | Questionnaire was via face to face interview of parent. Information sort included history of wheezing, atopic dermatitis, breastfeeding, age of initiation of complementary food, CM intake Family history of atopic diseases were also queried | Not recorded | Information in questionnaire helped authors to group infants into whether those with atopic dermatitis and a history of skin rash were more likely to be cow's milk allergic |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Hill D.J. et al 2004 (3155) | Observational study | Cow milk, egg, peanuts | 487 infants from birth | Skin prick test | Open food challenge | Questionnaires administered by trained allergy nurse completed by telephone interview at 4 weekly intervals. Information included infant feeding, the introduction of solid foods, the development of atopic dermatitis and other infant illnesses, contact with health care professionals and medication history. Presence of pets and exposure to environmental allergen exposure, parental smoking and presence of gas heating. Severity of atopic dermatitis was quantified by dividing those subjects into quartiles according to nurse recorded topical steroid use as defined by length of use in days. Gp | Work supported by Victorian Department of Human services, Royal Children's Hospital | In general there was an increase in the proportion of infants with parent reported adverse reactions to specific foods as the severity of atopic dermatitis increased from Gp 0 to4 (19/346 vs 2/36 vs 1/35 vs 3/35 vs 9/35 p= 0.004) Those subjects with IgE-mediated food allergy |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 0 no atopic dermatitis <8 days steroid treatment in the first 12 months (346). Gp1: 8-14 days steroid treatment (36). Gp 2: 15-28 days of steroid treatment (35). Gp 3: 29-73 days steroid treatment in the first 12 months (n=35). Gp 4: 74-232 days of steroid treatment in the first 12 month of life | | were more likely to have reported reactions to ingested foods than those without IgE-mediated food allergy; relative risk 3.2 (95% CI:1.5-6.7) The authors noted that as the severity of atopic dermatitis increased so did the frequency of IgE-mediated food allergy and |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | reported adverse food reactions. |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Roehr et al 2004 (3161) | Observational cross sectional study | Cow's milk, hens egg wheat fish carrot and soy | patients age up to 18 years of age | Skin prick test | Double blind placebo controlled food challenge | Questions about connections between food ingestion and itching, eczema urticaria, angio-oedema, rhinitis, asthma, gastro intestinal symptoms, headache and other symptoms. The degree of clinical reactions, age of onset of reaction, current dietary habits and/or other methods of treatment were elicited. Patients' history, possible risk factors such as smoking, atopic disorders and treatment and the general attitude towards food safety were included. Upon response to the questionnaire, individuals were contacted by telephone and interviewed using a structured questionnaire. Depending on the | German ministry of health supported study and Pharmacia provided kits. | The two stepped approach used in clinical history taking allowed to control for over and under representation secondary to recall errors or ill beliefs of FA/NAFH. Through this screening process, a third of the presumed food reactions were excluded |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | patients history a thorough medical history and physical examination including cutaneous, respiratory, cardiovascular, and GI symptoms was obtained. | | prior to the physical examination and testing on the grounds of lacking reproducibility of symptoms. |
| Dean et al 2007 (323) | Population based cohort study | Peanuts, eggs milk | 543 children from birth to 3years of age | Skin prick test | Double blind placebo food challenge | Clinical history using standardized questionnaire on family structure, family history of atopy, smoking habits, pet ownership, reported symptoms of atopy and physician diagnosed symptoms | Not recorded | There was no significant association between sensitization and sibship (p=0.28) or family history of smoking (p=1.000) There was also no association |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | between sensitization and any reported family history of atopy. However there was a significant association between maternal atopy (considered on its own) and sensitization . |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Skolnick et al 2001(3575) | Observational study | Peanuts | Children 4 years and older | Puncture skin tests, specific IgE tests | Double blind placebo food challenge | Clinical history by way of questionnaire including age of onset of peanut allergy, the characteristics of all prior peanut reactions, and any other food allergies and their resolution or lack of resolution and any history of other atopic diseases. | Not recorded | Patients were determined to have peanut allergy if they had a history of an acute reaction to peanut ingestion and positive results to a skin test or challenge or in some cases positive results to a RAST or a skin test without ever ingesting peanuts |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Asarnoj et al 2009 (4460) | Population-based cohort study | Peanut s allergy | 4089 children born between 1994 and 1996 and followed up at 1,2,4 and 8 years via questionnaires on symptoms of allergic diseases and key exposures. | IgE | No reference test. | Information at 4 years of age: After 2 years of age, Has your child experienced any problems from eating peanuts such as vomiting, diarrhoea, eczema, urticaria/itching rash, swollen lips/eyes itchy, blocked or runny nose or asthma? Information at 8 years of age: Is your child allergic to peanuts? If yes, symptoms options were nose/eye symptoms, 'mouth itching', breathing difficulties', vomiting/diarrhea, eczema, urticaria or excluded because of early symptoms. Peanuts had to be indicated on at least one of these symptoms. They investigated cross sensitization with birch | Work supported by Swedish asthma and allergy foundation | At 4 years of age the proportion of children reporting symptoms from peanut did not differ among peanut sensitized children with or without concomitant sensitization to pollen. At 8 years of age 76% of the children sensitized to peanut but not to birch pollen reported symptoms to peanut, whereas |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | pollen by asking similar question with regard to birch pollen allergy especially in the month of May. | | among children sensitized both to peanut and birch pollen only 46% reported such symptoms p=0.002. They suggested that there is a major risk of misclassifying peanut sensitized individuals as allergic to peanuts |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Von Berg et al 2003 (4933) | Prospective randomized double blind intervention follow up study | Cows milk formula compared with partially hydrolysed and wholly partially formula | 2252 children randomized from weaning | Observation of defined symptoms for such as skin lesions, pruritus, | Not recorded | Mothers were asked to document in weekly diaries the kind of milk the infant was fed for the first six months, time of first introduction and kinds of new solid foods and any health problems. Health problems including symptoms related to AD, allergic urticaria, and food allergy manifestation in the GIT were verified by structured interview and by clinical examination. Information on sociodemographic factors, family and living conditions, and smoking habits were documented. | Not recorded | Authors commented that they could demonstrate that the preventive potential of the different formulas depends on the family history of AD |

| Bibliographic Reference (Ref ID) | Study type | Foods tested | Number of participants /Age Characteristics | Type of Test | Reference Standard | Information retrieved in clinical history and relevant interpretation | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|
| Simeone et al 2008 (158) | Observational prospective study | Cows milk | Study included 69 constipated study subjects and 69 controls. Participants were between the ages of 6months and 6 years | Skin prick test and specific IgE | Not recorded | A detailed questionnaire was completed for each participant. Details included family and personal history of atopic disease, the presence of allergic symptoms, duration of breastfeeding and age at first introduction of cow's milk protein. Presence of symptoms relating to Cows milk allergy such as vomiting, diarrhoea, abdominal pain, painful defecation and the presence of anal fissures or erythema. A detailed dietary history was also recorded. | Not recorded | Participants were asked to go through a period of elimination and events were recorded in a diary. Study shows detailed clinical history taking could be an integral part of food allergy diagnosis |

## Review of reviews

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Lack 2008 (Ref ID:73) | Not systematic review-no mention of how articles were selected & no methodology | **Genetic risk factors**: There is some evidence to support a strong genetic contribution to peanut allergy. In the case of peanut allergy, a child has a 7 fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy.<br>**Other atopic disease**: There is a well-documented link between the presence of early eczema in childhood and the development of food allergy, especially peanut, egg and milk allergies (between 33% and 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 increased with more severe eczema.<br>**Exposure to food allergens**: Although conventional wisdom has always been that early exposure to allergenic food proteins during pregnancy or lactation could lead to food allergies, it is stated that the evidence to support food allergen avoidance is currently lacking and there is no compelling evidence that exclusive breast feeding beyond 4 months of age has any effect on reducing atopic disease<br>**Changes in dietary composition**: There are few data to refute or support the dietary fat hypothesis with respect to food allergy, which argues that reduction in consumption of animal fats and corresponding increases in use of margarine and vegetable oils has led to the increase in allergies. There is no data to support the hypothesis that diets high in antioxidants (from fresh fruits and vegetables) are associated with lower rates of food allergy. There is some evidence to support that increases in vitamin D have led to increased allergies and some to support that inadequate vitamin D have led to an increase in allergies. There is controversy relating to the vitamin D excess and deficiency hypotheses which remains unsolved.<br>**The hygiene hypothesis**: There is limited support for the hygiene hypothesis having a role in the development of food allergies, although evidence is stronger for a role in eczema than in food allergy.<br>**Other factors**: Caesarean sections appear to increase risk for the development of food allergies. A recent meta analysis on the relationship between caesarean delivery and atopic outcome found 6 studies that confirmed a mild effect of caesarean delivery, increasing the risk of food allergy or atopy (OR 1.32, CI 1.12-1.55) | Not reported | In summary the author suggests that antigen exposure through inflamed skin or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. It is also suggested that more interventional trials are needed. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Schuller 2004 (Ref ID:836) | Not systematic review-no mention of how articles were selected & no methodology | **Genetics:** The risk that a particular neonate will develop atopic symptoms during the first two decades of his life is strongly related to the presence of disease in their parents and siblings.<br>**Prenatal:** The interaction of the foetus with the gestation associated environment from the amniotic fluid or nutritional factors at the placental interface may lead to foetal programming and a susceptibility to atopic disease development.<br>**Postnatal:** Elevated umbilical cord IgE was thought to be a specific marker of later atopic disease, but has not been proven to be a sensitive marker of disease development. It has also been documented that IFN-γ at birth is further decreased in infants who are at risk of atopic disease.<br>**Other environmental risk factors**: including increased risk for sensitisation in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. Also lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Endotoxin exposure is a possible element of atopy prevention in early life. Prenatal or perinatal bacterial infections should also be considered risk factors for modulation of atopy.<br>**Feeding:** It has been postulated that maternal secretory IgA may protect against the development of atopic disease in infants. | Not reported | |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Cochrane et al 2009 | Published as part of Europrevall project. No methodology | **Other atopic disease**: Family history of atopy is a strong risk factor for the development of atopic diseases as shown in several studies. Having one atopic disease is a risk factor for developing another atopic disease. The sequential appearance of atopic disease is unlikely to be because one disease causes the other but rather that certain individuals are prone to manifest these atopic disorders under the influence of environmental factors within a particular time-frame.<br>**Genetics:** There are studies that show that the prevalence of allergic disease in first degree relatives of affected individuals was significantly higher than in relatives of unaffected individuals. A literature research indicates a wealth of studies related to asthma but nearly none to food-related allergy disorders.<br>**The gut immune system:** Although no data are available so far on the role of gut-derived dendritic cells in humans, there is some support from a mouse model of food allergy that a reduced production of IL-12 by dendritic cells may play a pivotal role in the development of food allergy in humans as well. Changes to the microflora of the gut may alter the immunological responses in the gut. Other changes to the gut's transport of foods and proteins, such as changes to the M-cells might change susceptibility. Nutritional or pharmacological co-factors may also be important for example broad spectrum antibiotics (changing the bacterial ecosystem) and vitamin D (suppressing normal gut Th1 development).<br>**Allergen exposure**: Whether a person becomes sensitised to an allergen depend on the timing and dose of the allergen as well as the route of exposure.<br>**Acidity of the gut**: It has been speculated that the relatively high pH in the stomach of infants may make them more susceptible to sensitisation by ingested allergens.<br>**Breastfeeding and diet:** The influence of mode of birth (c-section) on the subsequent development of food allergy is still unknown and there are currently no published data on antibiotic use as a risk factor for food allergy. | Funded by the EU through the EuroPrevall project. | The aetiology of food allergy poses specific problems which have been hard to investigate but for which answers are needed. Several hypotheses have been proposed but have little information currently to support them. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Koplin et al 2008 | Systematic review searching MEDLINE and PubMed. 4 papers were included. | Review found evidence that children delivered by caesarean section have an increased rate of sensitisation to food allergens compared with those delivered by vaginal birth (Eggesbo 2003 parent reported food allergy OR 3.2, CI 1.4-7.3 and objectively diagnosed egg allergy OR 1.6, CI 0.5-5.1, Renz-Polster 2005 diagnosis of food allergy OR 1.34, CI 0.54-3.29.) In addition, there is evidence from one study that symptoms of food allergy occur more commonly among children who are born by caesarean section. This study also suggests that this association is stronger in children born to allergic mothers although the evidence for the related findings was modest (OR 4.1, CI 0.9-19, p=0.08). Wide confidence intervals of the relevant estimates including for the interaction term suggest that this is probably related to the inadequate power of the study. Although potential confounding factors may exist that could explain the observed increase in food allergy among children born by caesarean section, three out of four studies included in the analysis controlled for factors that differed between children born by caesarean section compared with children born by vaginal birth. | Not reported | Overall, there is evidence that delivery by caesarean section increases the risk of sensitisation to food allergens but further large studies, ideally using food challenges to establish a diagnosis of food allergy, are needed to confirm whether the same relationship exists between mode of delivery and confirmed food allergy. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Chapman et al 2006 | Food allergy: A practice parameter-guideline developed by the Joint Task Force on Practice Parameters. Each summary statement is supported by graded references. | **Summary statement 31:** The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population.<br>Although currently no genetic tests are available to identify persons at risk of food allergy, a family history of atopy, or food allergy in particular, appears to be the best current screening test. In regard to food allergy, numerous possible environmental risk factors have been investigated with variable and often controversial results. Factors under consideration include maternal diet during pregnancy and breastfeeding, age at solid food exposure, age at introduction to allergenic foods, exposure to indoor and outdoor allergens, birth order, race/ethnicity, caesarean section, maternal age and others. For example soy feeding formula feeding (OR 2 to 6) and complaint of rash consistent with atopic dermatitis (OR 2.6 to 5.2) were independently associated with development of peanut allergy.<br>**Summary statement 32**: Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. The effectiveness of these strategies for safeguarding against the development of food allergies has not been established. | Not reported | |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Bahna 2003 | Data sources include reviews and original articles & classic textbooks. No mention of how articles were selected & no methodology. | **Gastrointestinal manifestation:** The most common GI symptoms are vomiting, colic, and diarrhoea, reflecting hypermotility. However constipation during infancy can be a manifestation of food hypersensitivity. Gastro-esophageal reflux and eosinophilic esophagitis during childhood may be related to food allergy.<br>**Dermatologic manifestation:** Several studies have demonstrated a role of FA in one third to one half of childhood atopic dermatitis. Foods are among the common causes of acute urticaria/angioedema. In chronic urticaria, however, food or food additives are rarely implicated. Food induced erythematous, papular or urticarial contact rashes have been observed in some children. Immediate contact urticaria to food is relatively common and can be localised, generalised or associated with other system involvement. Rare cases of food-induced vasculitis have been reported. Food induced fixed skin eruption has been reported in a few patients.<br>**Respiratory manifestation:** Chronic serious otitis media may develop secondary to chronic rhinitis and Eustachian tube dysfunction. Food induced asthma is more common in young children, particularly in association with atopic dermatitis. Heiner syndrome is a chronic pulmonary disease caused by food hypersensitivity, primarily to cow's milk during infancy. Hypersensitivity pneumonitis to inhaled soybean flour has been reported in one subject.<br>**Systemic anaphylaxis:** When multiple systems are involved in food hypersensitivity the reaction can be life-threatening, particularly when hypotension is combined with respiratory tract obstruction. Asthmatic children are at a particularly high risk, and the reaction may occur by exposure to minute quantities of the offending food that can be hidden in another ingested food or through skin contact or inhalation. In some cases the reaction only occurred when the person exercised within a few hours of eating the food (food dependent, exercise induced anaphylaxis).<br>**Rare miscellaneous manifestations:** Some rare manifestations seem to be reasonably well documented including headache or migraine, irritability or sleepiness in infants, arthropathy, nephropathy and thrombocytopenia. | Not reported. | |

## Review of reviews

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
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| Lack 2008 (Ref ID:73) | Not systematic review-no mention of how articles were selected & no methodology | **Genetic risk factors**: There is some evidence to support a strong genetic contribution to peanut allergy. In the case of peanut allergy, a child has a 7 fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy.<br>**Other atopic disease**: There is a well-documented link between the presence of early eczema in childhood and the development of food allergy, especially peanut, egg and milk allergies (between 33% and 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 increased with more severe eczema.<br>**Exposure to food allergens**: Although conventional wisdom has always been that early exposure to allergenic food proteins during pregnancy or lactation could lead to food allergies, it is stated that the evidence to support food allergen avoidance is currently lacking and there is no compelling evidence that exclusive breast feeding beyond 4 months of age has any effect on reducing atopic disease<br>**Changes in dietary composition**: There are few data to refute or support the dietary fat hypothesis with respect to food allergy, which argues that reduction in consumption of animal fats and corresponding increases in use of margarine and vegetable oils has led to the increase in allergies. There is no data to support the hypothesis that diets high in antioxidants (from fresh fruits and vegetables) are associated with lower rates of food allergy. There is some evidence to support that increases in vitamin D have led to increased allergies and some to support that inadequate vitamin D have led to an increase in allergies. There is controversy relating to the vitamin D excess and deficiency hypotheses which remains unsolved.<br>**The hygiene hypothesis**: There is limited support for the hygiene hypothesis having a role in the development of food allergies, although evidence is stronger for a role in eczema than in food allergy.<br>**Other factors**: Caesarean sections appear to increase risk for the development of food allergies. A recent meta analysis on the relationship between caesarean delivery and atopic outcome found 6 studies that confirmed a mild effect of caesarean delivery, increasing the risk of food allergy or atopy (OR 1.32, CI 1.12-1.55) | Not reported | In summary the author suggests that antigen exposure through inflamed skin or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. It is also suggested that more interventional trials are needed. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
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| Schuller 2004 (Ref ID:836) | Not systematic review-no mention of how articles were selected & no methodology | **Genetics:** The risk that a particular neonate will develop atopic symptoms during the first two decades of his life is strongly related to the presence of disease in their parents and siblings.<br>**Prenatal:** The interaction of the foetus with the gestation associated environment from the amniotic fluid or nutritional factors at the placental interface may lead to foetal programming and a susceptibility to atopic disease development.<br>**Postnatal:** Elevated umbilical cord IgE was thought to be a specific marker of later atopic disease, but has not been proven to be a sensitive marker of disease development. It has also been documented that IFN-γ at birth is further decreased in infants who are at risk of atopic disease.<br>**Other environmental risk factors**: including increased risk for sensitisation in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. Also lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Endotoxin exposure is a possible element of atopy prevention in early life. Prenatal or perinatal bacterial infections should also be considered risk factors for modulation of atopy.<br>**Feeding:** It has been postulated that maternal secretory IgA may protect against the development of atopic disease in infants. | Not reported | |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
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| Cochrane et al 2009 | Published as part of Europrevall project. No methodology | **Other atopic disease**: Family history of atopy is a strong risk factor for the development of atopic diseases as shown in several studies. Having one atopic disease is a risk factor for developing another atopic disease. The sequential appearance of atopic disease is unlikely to be because one disease causes the other but rather that certain individuals are prone to manifest these atopic disorders under the influence of environmental factors within a particular time-frame.<br>**Genetics:** There are studies that show that the prevalence of allergic disease in first degree relatives of affected individuals was significantly higher than in relatives of unaffected individuals. A literature research indicates a wealth of studies related to asthma but nearly none to food-related allergy disorders.<br>**The gut immune system:** Although no data are available so far on the role of gut-derived dendritic cells in humans, there is some support from a mouse model of food allergy that a reduced production of IL-12 by dendritic cells may play a pivotal role in the development of food allergy in humans as well. Changes to the microflora of the gut may alter the immunological responses in the gut. Other changes to the gut's transport of foods and proteins, such as changes to the M-cells might change susceptibility. Nutritional or pharmacological co-factors may also be important for example broad spectrum antibiotics (changing the bacterial ecosystem) and vitamin D (suppressing normal gut Th1 development).<br>**Allergen exposure**: Whether a person becomes sensitised to an allergen depend on the timing and dose of the allergen as well as the route of exposure.<br>**Acidity of the gut**: It has been speculated that the relatively high pH in the stomach of infants may make them more susceptible to sensitisation by ingested allergens.<br>**Breastfeeding and diet:** The influence of mode of birth (c-section) on the subsequent development of food allergy is still unknown and there are currently no published data on antibiotic use as a risk factor for food allergy. | Funded by the EU through the EuroPrevall project. | The aetiology of food allergy poses specific problems which have been hard to investigate but for which answers are needed. Several hypotheses have been proposed but have little information currently to support them. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
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| Koplin et al 2008 | Systematic review searching MEDLINE and PubMed. 4 papers were included. | Review found evidence that children delivered by caesarean section have an increased rate of sensitisation to food allergens compared with those delivered by vaginal birth (Eggesbo 2003 parent reported food allergy OR 3.2, CI 1.4-7.3 and objectively diagnosed egg allergy OR 1.6, CI 0.5-5.1, Renz-Polster 2005 diagnosis of food allergy OR 1.34, CI 0.54-3.29.) In addition, there is evidence from one study that symptoms of food allergy occur more commonly among children who are born by caesarean section. This study also suggests that this association is stronger in children born to allergic mothers although the evidence for the related findings was modest (OR 4.1, CI 0.9-19, p=0.08). Wide confidence intervals of the relevant estimates including for the interaction term suggest that this is probably related to the inadequate power of the study. Although potential confounding factors may exist that could explain the observed increase in food allergy among children born by caesarean section, three out of four studies included in the analysis controlled for factors that differed between children born by caesarean section compared with children born by vaginal birth. | Not reported | Overall, there is evidence that delivery by caesarean section increases the risk of sensitisation to food allergens but further large studies, ideally using food challenges to establish a diagnosis of food allergy, are needed to confirm whether the same relationship exists between mode of delivery and confirmed food allergy. |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
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| Chapman et al 2006 | Food allergy: A practice parameter-guideline developed by the Joint Task Force on Practice Parameters. Each summary statement is supported by graded references. | **Summary statement 31:** The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population.<br>Although currently no genetic tests are available to identify persons at risk of food allergy, a family history of atopy, or food allergy in particular, appears to be the best current screening test. In regard to food allergy, numerous possible environmental risk factors have been investigated with variable and often controversial results. Factors under consideration include maternal diet during pregnancy and breastfeeding, age at solid food exposure, age at introduction to allergenic foods, exposure to indoor and outdoor allergens, birth order, race/ethnicity, caesarean section, maternal age and others. For example soy feeding formula feeding (OR 2 to 6) and complaint of rash consistent with atopic dermatitis (OR 2.6 to 5.2) were independently associated with development of peanut allergy.<br>**Summary statement 32**: Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. The effectiveness of these strategies for safeguarding against the development of food allergies has not been established. | Not reported | |

| Bibliography (Ref ID) | Details of review | Risk factors | Source of funding | Comments |
|---|---|---|---|---|
| Bahna 2003 | Data sources include reviews and original articles & classic textbooks. No mention of how articles were selected & no methodology. | **Gastrointestinal manifestation:** The most common GI symptoms are vomiting, colic, and diarrhoea, reflecting hypermotility. However constipation during infancy can be a manifestation of food hypersensitivity. Gastro-esophageal reflux and eosinophilic esophagitis during childhood may be related to food allergy.<br>**Dermatologic manifestation:** Several studies have demonstrated a role of FA in one third to one half of childhood atopic dermatitis. Foods are among the common causes of acute urticaria/angioedema. In chronic urticaria, however, food or food additives are rarely implicated. Food induced erythematous, papular or urticarial contact rashes have been observed in some children. Immediate contact urticaria to food is relatively common and can be localised, generalised or associated with other system involvement. Rare cases of food-induced vasculitis have been reported. Food induced fixed skin eruption has been reported in a few patients.<br>**Respiratory manifestation:** Chronic serious otitis media may develop secondary to chronic rhinitis and Eustachian tube dysfunction. Food induced asthma is more common in young children, particularly in association with atopic dermatitis. Heiner syndrome is a chronic pulmonary disease caused by food hypersensitivity, primarily to cow's milk during infancy. Hypersensitivity pneumonitis to inhaled soybean flour has been reported in one subject.<br>**Systemic anaphylaxis:** When multiple systems are involved in food hypersensitivity the reaction can be life-threatening, particularly when hypotension is combined with respiratory tract obstruction. Asthmatic children are at a particularly high risk, and the reaction may occur by exposure to minute quantities of the offending food that can be hidden in another ingested food or through skin contact or inhalation. In some cases the reaction only occurred when the person exercised within a few hours of eating the food (food dependent, exercise induced anaphylaxis).<br>**Rare miscellaneous manifestations:** Some rare manifestations seem to be reasonably well documented including headache or migraine, irritability or sleepiness in infants, arthropathy, nephropathy and thrombocytopenia. | Not reported. | |

**Appendix 1.3.2**

# Clinical Question 2

Which diagnostic tools and strategy are most appropriate and accurate to diagnose non-IgE-mediated and mixed IgE-mediated food allergy in children?

| Ref ID | Study aim/ Study type | No of participants/ characteristics | Diagnosis | Type of Test | Reference Standard | Sensitivity and Specificity/ /Modified | PPV or NPV or Modified | Source of Funding | Additional comments | Author's Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|
| Sant'Anna, A.M.G.A., Rolland, S., Founet, J.C., Yazbeck, S., & Drouin, E. (2004)/ Ref ID: 762 | To review the authors experience with eosinophilic esophagitis/ Retrospective chart review. | Review of 12 children with final diagnosis of EE. Each child with EE was matched with 3 controls of same age and same time of exam. Second control group were last 200 pH probe studies from 2001. 9 males, 3 females, median age of presentation=10.8 yrs. Age range: 1-17 years old. | EE: defined histologically as infiltration≥20 eosinophils/HPF. No specific distinctions between IgE and non-IgE reactions. | **Total blood eosinophil count** (peripheral eosinophilia >700 eosinophils/mm³), **total IgE, specific IgE, esophageal pH monitoring** | N/A | Food allergy reported in 8 children (2 cow's milk & dairy, 3 nuts, 3 peanuts). **Peripheral eosinophilia:** documented in 42%, **Total IgE:** elevated 5/7. **Specific IgE:** to casein, lactoglobulin, nuts, soy, peanuts, egg and wheat detected in 6/9. **Symptoms:** Younger children (1-7yrs) presented with abdominal pain, vomiting and failure to thrive while older children (10-17yrs) presented with solid dysphagia and abdominal pain & impaction. **PH probe:** results show none with abnormal acid reflux but did show an alkalinization of the esophagus of variable intensity in all children. | N/A | Not reported. | Food allergy reported in hospital records (challenge not done). | Younger children presented with vomiting and pain, whereas older children presented with solid food dysphagia and impaction. Concomitant atopic disease or FA were reported in 66% of our group. Radiologic evaluation of children with EE usually was normal. The main endoscopic features were white specks on the esophageal mucosa, granula mucosa, eryematous esophagus, esophageal narrowing, esophageal rings & furrowing. Biopsies revealed a median of 65 eos/HPF. |

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| Cavataio, F., Iacono, G., Montalto, G., Soresi, M., Tumminello, M., Campagna, P., Notarbartolo, A., & Carroccio, A. (1996)/ Ref ID: 1611 | To suggest the simplest diagnostic procedure for infants under 1 year old with suspected gastroesophageal reflux (GER) and/or hypersensitivity to cow's milk protein (CMPA) and to confirm the utility of PH-metry analysis in distinguishing between infants with GER only and those with GER & CMPA/ cross sectional | 140 referred to clinic for suspected GER and/or CMPA. Mean age 6 months, age range 1-12 months, 60 males, 80 females. Clinical symptoms of those with GER + CMPA at diagnosis: regurgitation 70%, vomiting 60%, fits of crying 20%, anorexia 16.7%, growth disorder 13.3%, anaemia 10%, dermatitis 10%, rhinitis 3.3%. | GER: 1) those with endoscopic and histological evidence of esophagitis. 2) Those in whom total reflux percentage time (recorded by 24 hour PH) was above normal limits with respect to age. 3) Those with clear link between observation of clinical symptom and an episode of esophageal reflux recorded during PH monitoring. CMPA: Those improved on elimination diet had DBPCFC 6-8 weeks later. Intestinal biopsy performed before and 24 hrs after challenge. **Positive result:** if same symptoms reappeared within 24hrs after challenge or intestinal biopsy normal before challenge and abnormal after. Diagnosis of CMPA based on challenge results. Diagnosed 4 groups: GER alone (42), GER+CMPA (30), CMPA alone (38), no GER or CMPA (30). | Immunological tests: **SPT** (positive result wheal>control & >one fourth the size of histamine wheal), **serum total IgE** (RAST-pos result: >60 KU/liter), **circulating eosinophils**-pos result >400/mm$^3$, **serum IgG** (pos result >36% higher than control standard.) **Esophageal endoscopy & 24 hr PH** | **DBPCFC** with intestinal **biopsy** (clinic) | 30/72 with GER also had CMPA. **GER + CMPA**: Immunological tests were sig more likely to be positive in this group in comparison to GER alone: SPT (43.3%, $\chi^2$=13.5, p<0.0003), total IgE 33.3%, eosinophils 33.3% ($\chi^2$=13.6, p<0.0002), IgG (90%, $\chi^2$=43.0, p<0.0001). Phasic tracing of PH monitoring was sig more likely in those with CMPA in comparison to those without (p<0.0001).**Follow up after 2 & 4 weeks:** 4/30 in GER + CMPA no improvement (but 3 had allergy other than cow's milk & symptoms improved when these foods were eliminated). In 13/30 milk was reintroduced but in 46% symptoms returned & in 54% no negative reaction. | N/A | Not reported. | N/A | The characteristic phasic tracing of PH monitoring is almost 90% sensitive in identifying children with GER + CMPA (26/30) & 100% specific. The 36% IgG cut off we chose as the value with greatest diagnostic accuracy shows sensitivity and specificity of 90% in diagnosis of GER + CMPA. The presence of a 'phasic' pH-metry and an elevated value in the serum IgG are elements sufficient to identify cases of GER associated with CMPA. |

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| Nielsen, R.G., Fenger, C., Bindslev-Jensen, C., & Husby, S. (2006)/ Ref ID: 578 | To assess whether biopsies from the upper GI tract of children with milk sensitive GERD have a specific allergic inflammatory pattern, and to compare two different techniques for measuring inflammatory cells in gastrointestinal biopsies. | 42 children referred to tertiary centre for evaluation of GERD (51 initially). | Severe GERD: criteria included endoscopic oesophagitis and/or reflux index. Those with severe GERD completed 4-6 weeks elimination diet before challenge completed. Positive reactions to challenge continued on elimination diet. No specific distinctions between IgE and non-IgE reactions. | **PH monitor, endoscopy, biopsy, immunohistochemistry** to identify mast cells, eosinophils & T cells, **measurement of inflammatory cells** (cast grid vs. counting cells/HPF) | **Open challenge** in children < 3 yrs & DBPCFC in children > 3yrs. (Tertiary centre). | **Diagnosis:** Severe GERD & CMH (10), severe GERD (7) & control (24). **Other results:** Sig difference (p=0.0001) in thickness of basal zone between endoscopically normal (median 10%) and those with endoscopic oesophagitis (median 40%). Sig higher numbers of mast cells, eosinophils and T cells were found in biopsies from infants with endoscopic oesophagitis. No sig differences were found between clinical groups for mast cell, eosinophil and T cell numbers in all biopsies using the two methods. **Follow up:** biopsies in GERD + CMH showed sig increase in numbers of eosinophils in the biopsies from antrum and duoedenum after elimination diet. | N/A | Not reported. | | No sig differences seen in numbers of eosinophils, mast cells or T-cells in upper GI tract biopsies from children with CMH + GERD compared with primary GERD and controls. Despite sharing an association with FA, CMH & GERD and eosinophilic oesophagitis are 2 distinct entities. |

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| Nielson, R.G., Bindslev-Jensen, C., Kruse-Andersen, S., & Husby, S. (2004)/ Ref ID: 4917 | To examine whether a causal relationship between GERD and CMH could be established in a population of infants and children and to evaluate whether a cow's milk challenge during pH monitoring is useful to identify GERD + CMH sub-group and whether any specific endoscopic or PH findings were characteristic of this group. | 18 children with completed diagnostic work-up & GERD diagnosis (51 invited) 21 excluded children used as controls. Median age 104 months, age range 0-15 years. Follow-up conducted 3-4 months for primary GERD group and after continuous elimination diet for GERD + CMH. | CMH: Challenge performed following 4-6 weeks on diet period. 2 hr observation period. Challenge code not broken until 48 hours after challenge. Primary GERD: negative elimination/ challenge. GERD + CMH: positive elimination/ challenge. No specific distinction between IgE and non-IgE reactions although it is noted in discussion that all but one child showed no evidence of a general IgE-mediated reactivity and that skin patch tests could be a potentially useful diagnostic test in patients with non-IgE-mediated reactions, as the reactivity in the skin patch test presumably depends on T-cell mediated reactions. | **Endoscopy, biopsies, 48 h pH monitoring, RAST, SPT**(prick-prick using fresh foods), | **DBPCFC** (>3 yrs) or open challenge (Paediatric university hospital). | GERD + CMH: 59% (10/17). **SPT-** none were positive in primary GERD group, 1 in GERD + CMH (milk, soy, peanut) & 2 in control group (soy=1, milk & egg=1). **Serum IgE**- No differences between groups. **Patch test-** GERD+CMH (5 at 48hrs & 4 at 72hrs). None in primary GERD. **PH-** Children in GERD+CMH group showed sig increased time of esophageal acid exposure compared to primary GERD (p=0.03). **Follow-up PH**- Sig reduction in total recording time (RI) observed in GERD + CMH group after elimination diet period (primary GERD median RI 15.6, and at follow-up 10.7, p=0.05). 3 children (one from GERD+CMH) showed increased RI at challenge beyond level of day-to-day variability. **Endoscopy-** 7 had esophagitis (primary GERD 4, GERD+CMH 2). | N/A | Ronald McDonald House Charities & The Clinical Institute at University of Southern Denmark, | One child excluded due to anorexia nervosa. | An association of CMH and severe GERD was observed not only in infants but also in preschool/school children. Simultaneous food challenge and pH monitoring did not provide additional diagnostic value. |

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| Kalach, N., Soulaines, P., De Boissieu, D., & Dupont, C. (2005)/ Ref ID: 2996 | To assess the correlation and safety of ready to use APT in comparison with another APT in the evaluation of cow's milk allergy, together with its usefulness in the diagnosis of CMA as determined by open challenge | 41 children with referral to outpatient clinic for FA. Mean age 34.3 months, age range 5-78 months, 18 female, 31 male. Children exhibited min of one symptom of allergy: AD (10.2%), digestive manifestations-loose stools, colic, vomiting, gastroesophageal reflux & failure to thrive (40.8%), and combined manifestations (49%). Exclusions: on exclusion diet, present with skin lesions impeding APT application, Treatment with antihistamines/ steroids for last week. | FA: Open challenge-positive result: disappearance of symptoms on elimination diet & unequivocal adverse reaction to challenge. **Immediate onset reaction:** reaction within 2 hours of challenge. **Delayed onset:** reactions after 2 hrs. Some didn't have challenge and assumed to have FA: history of severe unequivocal adverse reaction to ingestion of CM with positive IgE, SPT or both & having completely recovered with elimination diet. Cite evidence to suggest that in the absence of immediate reactions, delayed onset reactions, most of the time related to non-IgE mechanism. Conclusions state that late onset reactions were non-IgE-mediated. | **Specific IgE:** (RAST)-positive result: ≥ 0.35 KU/L. **SPT**: (fresh milk). Positive result: >3mm than control. **2 x APT:** (Finn Chamber) & ready to use (Diallertest). Occlusion time 48 hrs, read 20 mins and 24 hrs after removal (72hrs). Classified as: negative irritation, significant erythema & erythema with eczema or edema. Positive result: at 72 hrs APT exhibited stronger reaction than negative control. | **Open oral food challenge** (started in hospital for those with risk of anaphylaxis and/or positive IgE and/or SPT or at home in case of delayed symptoms and negative IgE and SPT.) Outpatient basis. | 10.2% positive IgE, 2% positive SPT. **Diallertest:** APT positive in 44.8%, **Finn Chamber**: APT (comparator) positive in 26.5% at 72 hrs. **Food challenge**: Positive challenge in 60.9% (25). Of these 15 carried out at home & 4 in hospital. **Other results**: Overall 56% were delayed reactions, 16% immediate reactions, 28% history of severe reaction at enrolment. 29 children presented with eczema (either isolated or combined with digestive manifestations) and 13 had positive challenge. **Diallertest:** sensitivity 76% (CI 59.2-92.7), specificity 93.8% (81.9-100). **Finn Chamber:** sensitivity 44% (24.5-63.4), specificity 93.8% (81.9-100). Sig diff between sensitivity of two APT types (p=0.02). | **Diallertest:** PPV 95% (85.4-100), NPV 71.4% (52-90.7). Test accuracy: 82.9% (71.3-94.5). **Finn Chamber**: PPV 91.7% (76-100), NPV 51.7% (33.5-69.8). Test accuracy: 63.4% (48.6-78.1). Sig diff between test accuracy of two APT types (p=0.05). | Pharmaceutical firm DBV-Technologies | Funding from makers of Diallertest. | In conclusion, in a population of children with non IgE-mediated late onset reactions (digestive and eczematous) and with reference to open oral food challenge, the ready to use APT exhibited sig higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%) in comparison to Finn Chambers APT, with both techniques exhibiting high spec & PPV and being devoid of any side effects. |

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|---|---|---|---|---|---|---|---|---|---|---|
| Iacono, G., Carroccio, A., Cavataio, F., Montalto, D., Lorello, D., Kazmierska, I., Soresi, M., & Campo, M. (1995)/ Ref ID: 1644 | To report our experience in using a new immunoenzymatic commercial kit for assaying IgG antibetalactoglobulin, in an attempt to indicate the antibody levels useful for a correct diagnosis of CMPA | 301 infants referred to gastroenterology clinic suffering from predominantly GI symptoms & suspected CMPA. Median age 5 months, age range 1 month to 6 years, 180 male, 121 female. IgG also assayed on 218 healthy controls matched for age. Exclusion: breast fed infants. | CMPA: Those who had improved symptoms on elimination diet challenged after 4-6 weeks. Also given intestinal biopsy before and 24hrs after DBPCFC. **Positive result:** if same symptoms reappeared within 24 hrs of DBPCFC, if biopsy normal before and abnormal (partial atrophy & presence of eosinophils) after challenge. No specific distinction between IgE and non-IgE-mediated reactions. | **IgG anti-betalactoglobulin**: (Betalactotest) & other examinations including: **total serum & specific IgE** (RAST), **oesophageal pH-metry**, **oesophago-gastrduodenoscopy & colonoscopy**. | Intestinal **biopsy** & **DBPCFC** (in hospital) | 205 with CMPA & 96 with other GI pathologies. Based on clinical presentation CMPA1 (82 with regurgitation, vomiting, retarded growth), CMPA2 (108 with diarrhoea, retarded growth, anorexia, proctitis) & CMPA3 (41 with constipation, abdominal pain, colic). **IgG test**: IgG values were sig higher in children with CMPA in comparison to those with other GI disease ($p<0.0001$) and healthy controls ($p<0.0001$). Using low cut off of 36% elicited highest diagnostic accuracy in comparison to high cut off of 48% (sensitivity 89%, specificity 85%). **Comparison of CMPA with matched GI controls**: CMPA1 low cut off (sensitivity 90%, specificity 81%) vs high cut off (sens 78%, spec 94%). CMPA2 low cut off (sens 83%, spec 93%) vs high cut off (sens 75%, spec 93%). CMPA3 low cut off (sens 96%, spec 97%) vs high cut off (sens 91%, spec 100%). | N/A | Not reported. | N/A | IgG anti-betalactoglobulin are present in all infants. The higher the cut off value of the IgG, the better the specificity of the test and the lower the sensitivity. In CMPA children, the distribution of IgG values was sig diff to healthy controls and children with other GI disease. Test value> 48% is highly specific in distinguishing between CMPA children and those with other disease with similar clinical symptoms (exception of coeliac disease). |

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| Ford, R.P.K., Hill, D.J., & Hosking, C.S. (1983)/ Ref ID: 2177 | To present data supporting the concept that there are important differences in the clinical patterns of cow's milk hypersensitivity | 72 children with CM hypersensitivity (predominantly GI manifestations). Mean age 18 months, age range 3 months to 10 years 7 months, followed up for periods between 3 months and 4 yrs. Children with cutaneous reactions (angioedema, rash, urticaria, eczema) predominantly immediate onset (46%) (p=0.0001) & those with GI symptoms (vomiting, diarrhoea, colic, abdominal pain) had mainly delayed onset reactions (54%) (p=0.008). | Elimination diet for min of 1 week (usually 4 weeks) prior to challenge. DBPCFC: first single blind in hospital. **Positive result:** severe symptoms on single blind challenge, severe symptoms during DBPCFC, min 2 symptoms over and above those on placebo days. Open challenge: observation for ≥4 hrs. If no or mild symptoms sent home with increasing amounts to be taken at home. Symptoms recorded in diary. Continued for 4 weeks or until symptoms developed. Both definite and probable hypersensitivity considered to have milk hypersensitivity. **Immediate symptoms:** within 1 hr of ingestion, **delayed symptoms**: after 1 hr. Conclude that evidence suggests that immediate onset reactions mediated by IgE as these children had SPT+ & RAST responses indicating specific IgE sensitisation. Delayed onset group did not | **SPT**: (Bencard allergens). Positive result: ≥3mm. | **DBPCFC or open challenge** (both started in hospital) | Those with delayed symptoms less likely to have pos milk SPT (p=0.0001) and pos milk RAST (p=0.017) in comparison to those with immediate reactions. Those with positive SPT (40%) usually had cutaneous symptoms (p=0.002) while negative SPT usually had GI symptoms (p=0.006), less likely to have positive milk RAST (p=0.0001) & raised IgE (p=0.023) in comparison to positive SPT. Positive correlation between time of onset of clinical reaction and result of milk prick test (r=0.28, p=0.011 when controlled for GI symptoms, cutaneous symptoms & atopy). | N/A | National Health and Medical Council (Australia) and Canterbury Medical Research Foundation (New Zealand). | N/A | Found immediate onset reactions and delayed onset reactions. The latter occurring after 1 hr, usually with GI symptoms and negative prick tests. They had correspondingly negative RAST results to milk. |

| Ref ID | Study aim/ Study type | No of participants/ characteristics | Diagnosis | Type of Test | Reference Standard | Sensitivity and Specificity/ /Modified | PPV or NPV or Modified | Source of Funding | Additional comments | Author's Conclusions |
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| Fogg, M.I., Brown-Whitehorn, T.A., Pawlowski, N.A., & Spergel, J.M. (2006)/ Ref ID: 506 | To determine whether the APT is able to predict the results of the OFC in children with suspected food protein-induced enterocolitis syndrome (FPIES) | 19 children with suspected FPIES. Mean age 15.6 months, age range 5-30 months, 10 male, 9 female. 2 children had atopic dermatitis (AD). Exclusion: evidence of IgE-mediated reaction (pos SPT), presence of skin disorders other than AD, severe diffuse AD with no surface area for APT, use of oral immunosuppressant medicines that may affect results, use of oral medicines that may affect interpretation of challenge (e.g. antimotility agents, anti-inflammatory medicines & β-blockers.) | Suspected FPIES based on clinical criteria proposed by Sicherer (2000). FPIES: Confirmed using non-blinded food challenge. Elimination diet of foods positive in APT. Observed 4 hrs-those tolerated in hospital sent home with food reintroduction plan. **Negative result**: If no symptoms on reintroduction. **Positive result:** If GI symptoms with no other cause developed during reintroduction. Telephone follow-up performed to ascertain results of follow-up. Assumption that FPIES is non-IgE-mediated and SPT or in vitro tests for specific IgE not useful as they are negative. Confirmed diagnosis based on challenge results. | **APT**: (Finn Chambers-removed 48 hrs, read 72 hrs). Results: + erythema, ++ erythema & papules, +++ erythema & vesicles. | **Non-blinded oral food challenge** (in allergy clinic). | Sensitivity= 100%, specificity= 71%. | PPV=75%, NPV=100% | Not reported. | APT not standardised test. As FPIES usually outgrown before 36 months, it's likely that several children lost reactivity to suspected food in interval between onset of disease and study. No follow-up. | We will recommend APT for children who have a suggestive clinical history for FPIES. If APT is negative, an oral food challenge will be performed as there is strong possibility that the child is either not sensitive to food or has outgrown sensitivity, this is supported by NPV of 100% in this study. If APT is positive, challenge will be delayed until 1 yr after most recent reaction. |

| Ref ID | Study aim/ Study type | No of participants/ characteristics | Diagnosis | Type of Test | Reference Standard | Sensitivity and Specificity/ /Modified | PPV or NPV or Modified | Source of Funding | Additional comments | Author's Conclusions |
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| Zapatero Remon, L., Alonso Lebrero, E., Martin, Fernandez, E., & Martinez Molero, M.I. (2005)/ Ref ID: 595 | To study 14 infants with FPIES due to fish protein and report the clinical characteristics of these children and their clinical course | 14 children referred for GI symptoms following ingestion of fish. Age range 9-12 months, 6 males, 8 females. | FPIES: based on clinical criteria and in 9 children on oral food challenge. Challenge involved observation for 3 hours. State that FPIES is form of cell-mediated, non-IgE associated food hypersensitivity. | **SPT**-positive result: ≥3mm greater than control. **APT** (Curatest)-occlusion 48 hrs, read 30mins after removal & after 96 hrs. **Serum specific IgE:** (CAP System)-positive result ≥0.35KU/L. | **Open oral food challenge** (referred to allergy clinic). | SPT with commercial extracts to fish and prick-prick with boiled fish negative in all cases. **IgE**: negative in all but one case (positive to hake). **APT**: positive in 3/8. **Oral challenges:** performed in 9 and all positive. Remaining 5 didn't undergo challenge as they referred various evocative episodes of FPIES. **Follow-up:** After elimination diet of 3-4 yrs, undertook follow-up FC. 4 became tolerant, 3 tolerate one single fish, 5 continue elimination diets, 2 had positive rechallenge so continue diet. | N/A | Not reported. | APT not done in all children. | Our report confirms previous observations that measurements of food allergen specific IgE antibodies (SPT or serum levels) are typically negative. |

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| Fiocchi, A., Besana, R., Ryden, A.C., Terracciano, L., Andreotti, M., Arrigoni, S., & Martelli, A. (2004). Ref ID: 737 | To evaluate a blood test, Phadiatop Infant, for differentiating the capability of IgE-mediated disease in young children with recurrent wheezing, eczema, or both/ cross sectional. | 147 children with recurrent wheezing, eczema or both referred for allergy evaluation by primary care physician. Mean age 2 years, 68% male. Results presented by age groups: <2yrs, ≥2yrs & all ages. | Clinical evaluation made by single allergist at each centre. **Preliminary diagnosis:** IgE-mediated symptoms, no such symptoms or inconclusive diagnosis (no clear relationship with allergic reactions). This was based on case history & physical examination. **Final diagnosis:** IgE-mediated, Non-IgE-mediated or inconclusive (discrepancies among case history, SPT and specific IgE). This was based on preliminary diagnosis and additional SPT & specific IgE. Children with positive IgE and final diagnosis of non-IgE-mediated disease were recalled after 2yrs for re-evaluation of allergic status. Diagnoses differentiated between IgE and non-IgE allergies but not clear how these were diagnosed. | **Skin prick test:** (10 food allergen extracts-cow's milk, α-lactalbumin, casein, egg white, egg yolk, peanut, wheat, cod, soy, tomato). Positive result: ≥3mm. **Specific IgE:** (Pharmacia CAP). Positive result: ≥0.35kU/L. | **Final diagnosis** by allergist (2 allergy centres). | **Preliminary diagnosis:** IgE-mediated allergy (31), not IgE-mediated (40), inconclusive (76). **Final diagnosis**: IgE-mediated (61), not IgE-mediated (78), inconclusive (8). **Symptom distribution:** Overall more children with wheezing (58% vs 39.1%), and eczema (50.7% vs 43.5%) in non-IgE than IgE group. **Sensitivity**: 92% (CI 82-97%), **specificity:** 82% (CI 72-90%). Similar results for children <2yrs, 2-4yrs and for children with wheezing and eczema separately. **Follow-up:** 13/14 diagnosed as non-IgE allergy with positive specific IgE re-evaluated after 2 yrs. 12/13 diagnosed as having IgE-mediated disease (specific IgE antibodies to 1 or several allergens). Positive Phadiatop Infant result accurate in predicting IgE allergy in 92%. One persistently evaluated as being non-allergic. | **PPV:** 80% (CI 69-97%), **NPV:** 93% (CI 84-98%) | Pharmacia Diagnostics AB (makers of Phadiatop Infant) | Food challenge not completed & ref used was allergist's final diagnosis. Limited info on how IgE and non-IgE diagnoses were reached. No statistical calculations for symptoms and triggering factors between IgE and non-IgE allergy. | This study supports the use of Phadiatop Infant in a primary care setting to identify candidates most likely to benefit from referral to an allergist. Furthermore, a positive test result could predict the development of IgE-mediated allergic disease. |

| Ref ID | Study aim/ Study type | No of participants/ characteristics | Diagnosis | Type of Test | Reference Standard | Sensitivity and Specificity/ /Modified | PPV or NPV or Modified | Source of Funding | Additional comments | Author's Conclusions |
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| Niggeman, B., Reibel, S., & Wahn, U. (2000)/ Ref ID: 3684 | To evaluate the diagnostic value of the APT with regard to late phase reactions observed in DBPCFC's with cow's milk, hen's egg, wheat and soybean/ | 75 children with suspected FA. 34 female, 41 male, median age 2.1 yrs, age range 4 months to 12.5 years. 69 had AD. Total of 209 oral challenges performed on 75 children (54 CM, 41 HE, 23 wheat, 15 soybean). | AD: Diagnosed according to criteria by Sampson (1990) & Seymor et al (1987). Severity assessed according to SCORAD index. FA: DBPCFC-observed up to 48 hrs. **Positive result:** if objective clinical reaction observed such as urticaria, angioedema, wheezing, vomiting, diarrhoea, abdominal pain or exacerbation of eczema. **Early reaction:** symptoms appeared within 2 hrs of highest dose. **Late reaction:** symptoms occurred >2hrs. Acknowledge that immediate reactions can be easily identified and hypothesize that APT may have high predictive capacity for late phase reactions. In their findings they state that T-cells play an important role in AD & FA and this is supported by findings of study. | **SPT**-reactions read at 15 mins, positive result: ≥3mm & no reaction to control. **APT** (Finn Chambers) occlusion time 48hrs, results read 20min & 24 hrs after removal (72hrs). + erythema and slight infiltration, ++ erythema and papules, +++ erythema and vesicles. **Specific IgE**: (FEIA) positive result: ≥0.35 kU/l. | **DBPCFC** (as inpatient). | 58% (77/133) of challenges and 2.6% (2/76) placebo were positive. Of 77 positive reactions, 66% with HE, 65% with CM, 48% with wheat, 27% with soybean. 51% showed early clinical reactions while 27% showed late reactions. 22% had combined early and late reactions. All late reactions were exacerbation of eczema & combined reactions included eczematous reactions. **Sensitivity for early reactions:** IgE 95%, SPT 95%, APT 33%. **Specificity for early reactions**: IgE 29%, SPT 70%, APT 95%. **Sensitivity for late reactions:** IgE 71%, SPT 58%, APT 76%. **Specificity for late reactions**: IgE 29%, SPT 70%, APT 95%. | **PPV for early reactions**: IgE 62%, SPT 69%, APT 81%. **NPV for early reactions**: IgE 59%, SPT 95%, APT 67%. **PPV for late reactions:** IgE 37%, SPT 41%, APT 81%. **NPV for late reactions**: IgE 72%, SPT 81%, APT 93%. | Not reported. | N/A | APT seems to be a valuable additional tool in the diagnostic work up of FA in children with AD, especially with regard to late phase reactions. At this time, a positive APT does not make challenge superfluous. |

| Ref ID | Study aim/ Study type | No of participants/ characteristics | Diagnosis | Type of Test | Reference Standard | Sensitivity and Specificity/ /Modified | PPV or NPV or Modified | Source of Funding | Additional comments | Author's Conclusions |
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| Verini, M., Di Pillo, S., Spagnuolo, A., Cingolanio, A, Consilvio, N.P., Chiarelli, F. (2007)/ Ref ID: 2585 | To assess the role of APT in evaluating the correlation with age of allergic sensitisation IgE and non IgE-mediated, against main respiratory, food and contact allergens in children with AD/ cross-sectional. | 135 (and 10 controls) outpatients with AD without respiratory symptoms. 79 males, 56 females, mean age 3.7 yrs, age range 1-15 years. Age groups: 1) < 2yrs (50 children). 2) 2-5yrs (40). 3) >5 yrs (45). None of controls showed positive APT. | AD: Diagnosed according to criteria by Hanifin & Rajka. FA: Assessed by SPT, serum specific IgE & APT. **IgE sensitisation**: positive SPT and/or IgE. **Non-IgE sensitisation:** positive APT alone. Differentiate between IgE and non-IgE by test results of SPT, APT and/or serum specific IgE. | **SPT:** (allergen's extract), **specific IgE:** (ImmunoCAP FEIA) positive result: >0.70 KU/L. **APT:** (Curatest) applied for 48 hrs, evaluation after 48 and 72 hrs. | N/A | Overall sensitisation to food allergens 48%. Food allergen sensitisation (SPT, IgE & APT) found in 25.9% for hen's egg protein, 19.9% milk, 18.5% wheat, 14% codfish & 6.8% tomato. **Non-IgE sensitisation:** (APT positive only) found 7.4% for egg, 8.1% milk, 4.4% wheat, 5.2% codfish & 6% tomato. AD improved following elimination diet. **Age specific analyses:** Prevalence of positive food allergen test <2 yrs (64%), 2-5 yrs (50%), >5yrs (26%). Significantly more positive food allergen tests were found in <2's in comparison to 2-5yr age group (p=0.04) and significantly more positive results in 2-5yr group when compared to >5's (p=0.001). Positive APT results found <2 (58%), 2-5yrs (50%), >5yrs (35%). Significantly more positive APTs were found in 2-5yr group compared with >5's (p=0.05). | N/A | Not reported. | No challenge used to confirm FA. | Study showed a higher prevalence of FA in younger groups and of respiratory allergy in older ones. The APT may be helpful in evaluating allergic sensitisation in those children affected with AD with negative SPT and IgE, mainly in children <5 years of age. |

**Appendix 1.3.3**

# Clinical Question 3

Which diagnostic tools and strategy are most appropriate and accurate to diagnose IgE-mediated food allergy in children?

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|
| Vierrucci et al 1989. (Ref ID: 4324) | To report experience in diagnosing food allergy in children with AD/ Italy | Egg, milk, peanut, tomato | 112 children with AD. Age range 0-5 yrs (median age 4.6 yrs). | **SPT:** positive result ≥3mm than control. **Total IgE:** Using PRIST **Specific IgE:** Using RAST | DBPCFC (59 challenges performed in 35 children on the basis of positive SPT and/or suggestive history of food allergy) | **Sensitivity**: SPT (milk=28%, egg= 100%, tomato=100%, peanut=100%). RAST (milk=35%, egg=62%, tomato=14%, peanut=25%). **Specificity**: SPT (milk=80%, egg=25%, tomato=66%, peanut= 50%). RAST (milk=77%, egg=33%, tomato=50%, peanut=100%). | **PPV:** SPT (milk=66%, egg=60%, tomato=40%, peanut= 83%). RAST (milk=71%, egg=71%, tomato=33%, peanut= 33%). **NPV**: SPT (milk=44%, egg=75%, tomato= 100%, peanut= 50%). RAST (milk=50%, egg=50%, tomato=25%, peanut= 25%). | Italian Consiglio Nazionale delle Ricerche. | |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Niggemann et al 2002. (Ref ID: 1009) | To compare the use of smaller chambers for APT in young children/ Germany. | Cow's milk, hen's egg, wheat, soy | 30 children with AD. 17 boys, 13 girls. Age range=3 to 58 months, median=13 months. No other details reported. | **APT:** Using Finn Chambers 12mm and 6mm. **SPT:** Positive reaction ≥3mm without reaction of the negative control. | DBPCFC (55 challenges performed in 30 children) | **Sensitivity:** APT 12mm (CM=60%, HE=71%, soy=100%, wheat=100%). APT 6mm (CM=0, HE=29%, soy=0, wheat=0). SPT (CM=90%, HE=86%, soy=50%, wheat=67%). **Specificity:** APT 12mm (CM=100%, HE=100%, soy= 100%, wheat=89%). APT 6mm (CM=100%, HE= 100%, soy= 100%, wheat=100%). SPT (CM=82%, HE=75%, soy=100%, wheat= 89%). | **PPV:** APT 12mm (CM=100%, HE=100%, soy=100%, wheat=75%). APT 6mm (CM= 0, HE=100%, soy=0, wheat= 0). SPT (CM=82%, HE=86%, soy=100%, wheat=67%). **NPV:** APT 12mm (CM=73%, HE=67%, soy=100%, wheat= 100%). APT 6mm (CM=52%, HE=44%, soy=82%, wheat=75%). SPT (CM=90%, HE=75%, soy=90%, wheat=89%). | Not reported. | Not reported whether all children underwent all testing. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Dieguez et al 2008. (Ref ID: 2629) | To estimate the diagnostic accuracy of the SPT with egg allergens in children with IgE-mediated cow's milk allergy in first known egg exposure/ Spain. | Egg white, OVM | 104 milk allergic children who came to the allergy department at Madrid hospital. Milk allergy included those with anaphylactic reaction, clinical history of recent IgE-mediated reaction to milk, both with positive SPT and/or positive specific IgE, although milk oral food challenge was not performed. 54.8% male. 30.4% had at least one atopic parent, 59.4% with AD, 16.3% with asthma. Children given SPT with egg between age of 12 and 15 months old. | **SPT:** Positive reaction ≥3mm | Egg challenge test (all patients received challenge test regardless of SPT results.) | Values recorded are using SPT cut off 3mm. **Sensitivity:** Egg white =94.6%, OVM=66.7%. **Specificity:** Egg white =40%, OVM=85.3%. Values recorded are using optimal decision point (6mm for egg white & 5mm for OVM). **Sensitivity:** Egg white= 81.1%, OVM =58.3%. **Specificity:** Egg white= 72.5%, OVM =97.1%. Author's also recorded ROC curves, AUC & calculated **optimal cut off points** (calculated as maximum sum of sensitivity and specificity): Egg white (AUC=0.83, optimal decision point (odp)=6mm). Yolk (AUC=0.73, odp= 3mm). OVA (AUC=0.55, odp= 3mm). OVM (AUC=0.82, odp= 5mm). OVT (AUC=0.55). Lisozime (AUC=0.60) | Values recorded are using SPT cut off 3mm. **PPV:** Egg white= 59.3%, OVM =82.7%. **NPV:** Egg white= 88.9%, OVM =70.7%. Values recorded are using SPT cut off optimal decision point (6mm for egg white & 5mm for OVM) . **PPV:** Egg white= 73.2%, OVM =95.4%. **NPV:** Egg white= 80.6%, OVM =69.4%. | Sociedad de Pediatria de Madrid y Castilla La Mancha. | |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Saarinen et al 2001. (Ref ID:4951) | To study the usefulness of the SPT, patch test, IgE and eosinophil cationic protein (ECP) in serum as diagnostic tools for CMA/ Finland. | Cow's milk | 239 full-term newborn infants with suspected CMA. Mean age of those with positive challenge=6.7 months & mean age of 7.1 months in children with negative challenge. | **SPT, Specific IgE:** Using Cap system. Also measured ECP but results not reported in evidence table. **Patch test:** Using Finn Chamber. Occlusion time=48 hrs with results read 48hrs after removal of cups. Positive result involved marked erythema and erythema with induration. | Open challenge (performed at out-patient clinic in all children). | All values based on SPT cut off ≥3mm, 0.35kU/L for IgE and patch test positive for whole CM and/or CM protein fractions. **Sensitivity:** SPT=61%, IgE=72%, patch test=43%. **Specificity:** SPT=76%, IgE=49%, patch test=72%. | All Values based on SPT cut off ≥3mm, 0.35kU/L for IgE and patch test positive for whole CM and/or CM protein fractions. **PPV:** SPT=71%, IgE=58%, patch test=60%. **NPV:** SPT=67%, IgE=64%, patch test=57%. | Research Fund of Helsinki University Central Hospital, the Finnish Society of Allergology and Immunology, the Finnish Foundation for Allergy Research and the Sigrid Juselius Foundation. | Also reported sensitivity, specificity, PPV & NPV values for SPT thresholds 6 & 8mm, IgE cut off values of 0.7 & 3.5 kU/L, Patch test using whole milk and CM protein fractions separately & values based on symptoms. These are not reported in the evidence table. Also provide values for combined accuracy of all 4 tests using different cut-offs but not included as this also includes ECP. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Caffarelli et al 1995. (Ref ID: 1682) | To investigate the relationship between egg specific IgE and positive SPT and/or RAST which had never previously been ingested/ Italy. | Egg | 33 children with food allergy who had never previously ingested egg or egg-containing products. **Patient group:** 21 children (age range 5 months-3yrs 5months) with positive SPT reaction and/or sIgE to egg. **Control group:** 12 patients (age range 11 months-4 yrs 9months) with negative SPT and sIgE reactions to egg. | **SPT:** Positive result ≥3mm after the diameter of the wheal elicited by diluents was subtracted. **Specific IgE (RAST):** Using RAST. Results graded 0 to 4 in accordance with manufacturer's instructions. | DBPCFC (performed in allergy unit and was carried out in all children). | **Sensitivity:** SPT= 92%, RAST=85%, SPT & RAST=92%. **Specificity:** SPT= 57%, RAST=68%, SPT & RAST=57%. There was no significant difference between results of SPT and RAST or SPT plus RAST, in predicting challenge results correctly. | **PPV:** SPT= 61%, RAST=66%, SPT & RAST=61%. **NPV:** SPT= 91%, RAST=86%, SPT & RAST=91%. | Not reported. | Symptoms were separated into immediate and late onset reactions. |
| Fiocchi et al 2002. (Ref ID: 4936) | To present data about the test performance of beef extracts used in SPT among children with AD reporting immediate hypersensitivity to beef/ Italy. | Beef | 34 children with AD and IgE-mediated sensitisation to foods. Age ranged from 1.00-4.41 years (median=2.26 years). | **SPT:** Used commercial (cSPT) and fresh foods (ffSPT). Positive result ≥3.01mm | DBPCFC (all children were tested. 20 children were positive and 14 negative & underwent SPT using commercial and fresh). | **Sensitivity:** cSPT=90%, ffSPT=100%. **Specificity**: cSPT=100%, ffSPT=78.57%. | Authors did not report predictive values. 2 x 2 table calculated: **PPV:** cSPT=100%, ffSPT=87%. **NPV**: cSPT=88%, ffSPT=100%. | Not reported. | Authors did not report predictive values. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Cudowska & Kaczmarski 2005. (Ref ID: 599) | To evaluate the diagnostic accuracy of APT in the detection of food allergy in correlation with SPT, sIgE & positive oral food challenge to milk/ Poland. | Milk | 34 children with AD referred to department of paediatrics for evaluation of atopic eczema dermatitis syndrome (AEDS) suspected of food hypersensitivity. Age ranged from 5 months to 16 years. Children divided into 2 age-groups: A) 20 children < 3 years old & B) 14 children >3 years old. 35 boys and 9 girls. | **SPT:** Positive result ≥3mm without reaction of negative control. **APT:** Using Finn Chambers (8mm for children < 3 years & 12mm for children > 3 years). **Total and specific IgE:** Using UniCAP. Detection limit of CAP system is 0.35 kU/L. Positive sIgE result ≥0.7 kU/L. | Oral food challenge (started in hospital and continued in patient's home. Immediate onset reactions defined as those within 2 hours after last dose. Done in all children. Open challenge used in children < 1 year & blinded in older children). | Values based on SPT and sIgE for immediate onset reactions in group A and APT in patients with delayed onset reactions in group A and B. **Sensitivity:** SPT/sIgE group A=100%, APT (group A=80%, group B=80%). **Specificity:** SPT/sIgE group A=94%, APT (group A=70%, group B=89%). Values based on combined SPT, APT and sIgE. **Sensitivity:** Group A=92%, group B=80%. **Specificity:** Group A=71%, Group B=89%. | Values based on immediate & delayed onset reactions **PPV:** SPT/sIgE group A=75%, APT (group A=73%, group B=80%). **NPV:** SPT/sIgE group A=0%, APT (group A=22%, group B=11%). Values based on combined SPT, APT and sIgE. **PPV:** Group A=85%, group B=80%. **NPV:** Group A=17%, Group B=11%. | Not reported. | Also tested other food allergens but sensitivity/ specificity values only reported for milk. Also reported likelihood ratios but these are not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Hill et al 2004. (Ref ID: 3153) | To present the results of studies on the diagnostic value of SPT and food specific IgE/ Australia. | Cow's milk, egg, peanut | Prospective study of 467 children referred from high risk population for investigation of food allergy. Median age= 3 years. | SPT | Oral food challenge ( 555 challenges performed in 467 children-classified as positive, negative or inconclusive) | Authors present diagnostic accuracy of age specific SPT wheal in children. Data presented are for SPT threshold 3mm. **Sensitivity for children ≥2 years:** CM =79%, egg =87%, & peanut=95%. **Sensitivity for children <2 years:** CM =58%, egg =79%, & peanut=100%. **Specificity for children ≥2 years:** CM =73%, egg =67%, & peanut=72%. **Specificity for children <2 years:** CM =91%, egg =75%, & peanut=67%. Authors also report 100% diagnostic SPT cut off levels (levels representing 100% specificity). **For children ≥2 years:** CM ≥8mm, egg≥7mm, peanut≥8mm. **For children <2 years:** CM ≥6mm, egg≥5mm, peanut≥4mm. | Data presented are for SPT threshold 3mm. **PPV ≥2 years:** CM =75%, egg =93%, & peanut=91% **PPV <2 years:** CM =79%, egg =92%, & peanut=94% . **NPV ≥2 years:** CM =77%, egg =50%, & peanut=81% . **NPV <2 years:** CM =78%, egg =50%, & peanut=100 %. | Not reported. | Also report sensitivity, specificity, PPV & NPV values for SPT wheal diameter 0mm, ≥6mm, ≥8mm (for CM and peanut) and 0mm, ≥6mm, ≥7mm for egg- these are not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Hansen et al 2004. (Ref ID:752) | To determine whether SAFT or APT could increase the diagnostic accuracy in detecting egg allergy/ Denmark | Hen's egg (undiluted fresh whole egg extract used in SPT & SAFT. APT used 100%, 50% & 25% dilution). | **Allergy group**: 10 clinically egg-allergic children (all but 4 tested by challenge) with AD. Age range 10 months-8.4yrs (mean 3.4yrs). **Control group:** 10 egg-tolerant children without AD. Age range 3.6-10.5 yrs (mean 5.8yrs). All tests performed serially in all children (APT, SPT & SAFT). | **SPT:** Positive result ≥3mm than neg control. **SAFT (Skin Application Food Test):** (12mm Finn Chambers). 1=no reaction, 2= erythema, 3=erythema & oedema within chamber, 4=erythema & oedema also outside chamber. Positive result ≥3. **APT:** (12mm Finn Chambers). Positive, doubtful or negative result. Doubtful reaction (mild erythema with no infiltration) regarded as negative. | DBPCFC or OFC (those in allergy group had previous result 2-24 months prior to study). | All values based on SAFT cut-off of ≥3 at 15mins (erythema= negative) and when APT was doubtful it was classified as a negative result. APT used 50% dilutions interpreted after 72 hours. **Sensitivity:** SPT=100%, SAFT =40% & APT=60%. **Specificity**: SPT=85%, SAFT=100% & APT= 95%. **Reproducibility of tests**:1 reacted to negative control in APT, 6 discordant results in duplicate application seen among children concerning SAFT & 4 in APT. | **PPV:** SPT=77%, SAFT=100% & APT=75%. **NPV:** SPT=100%, SAFT=86% & APT=90%. | Not reported. | Results were also reported for SAFT cut-off ≥2 and when a doubtful APT result was classified as a positive result- these are not reported in the evidence table. Results also available for SAFT (30mins) & APT (concentration 25 & 100% at 48 & 72hrs). |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Sampson 1998. (Ref ID:3817) | To evaluate the predictive values of food-specific IgE/ USA | Egg, milk, peanut, soy, wheat & fish. | 200 children with AD and sometimes other symptoms (asthma, allergic rhinitis). No other details reported. | **Skin test (ST):** (positive result ≥ 3mm) & **Specific IgE:** (CAP FEIA). Positive result ≥0.35 kU/l | DBPCFC or convincing history of anaphylaxis. | **Sensitivity:** Skin Test (egg=98%, milk=96%, peanut=90%, soy=76%, wheat=90%, fish=90%). IgE (egg= 98%, milk=100%, peanut= 97%, soy= 94%, wheat=96%, fish= 94%). **Specificity:** Skin Test (egg= 53%, milk=51%, peanut= 29%, soy=47%, wheat= 51%, fish= 57%). IgE (egg= 45%, milk=30%, peanut= 38%, soy= 25%, wheat=20%, fish= 65%). **Cut-off values** (determined by calculating the 95% predictive values):Egg 6 kU/l, milk 32 kU/l, peanut 15 kU/l, fish 20 kU/l, soy 65 kU/l, wheat 100 kU/l. | All values based on prevalence of FA as 100%. **PPV:** ST (egg= 85%, milk= 66%, peanut= 55%, soy= 35%, wheat=35%, fish=77%). IgE (egg= 84%, milk=57%, peanut=78% , soy=21%, wheat=14%, fish=49%). **NPV:** ST (egg=90%, milk=93%, peanut=75% , soy=84%, wheat=94%, fish=80%). IgE (egg= 88%, milk= 100%, peanut=85% , soy=95%, wheat=97%, fish=97%). | Not reported. | Results were also reported for PPV and NPV values based on FA prevalence of 10% which reflect the situation of a normalised population in which only 10% presented with true food allergy- however these figures are not reported in the evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Eigenmann &Sampson 1998. (Ref ID: 3821) | To compare different SPT recording methods with the outcome of the oral food challenge/ | Egg, milk, peanut, soy, wheat | 250 children with AD with suspected IgE-mediated allergies were admitted to the Clinical Research Center for evaluation of food allergy. No details of participants given as characteristics have been previously described. | **SPT:** 2 techniques used to measure wheal size (mean diameter & electronic scanner). | DBPCFC or convincing history of recent anaphylactic reaction (all negative results confirmed by feeding food openly in usual proportion under observation.) | All values reported using ≥3mm as positive SPT result. **Sensitivity:** Egg=100%, milk=94%, peanut= 80%, soy=60%, wheat=81%. **Specificity:** Egg=61%, milk=46%, peanut=47%, soy= 53%, wheat=64%. | **PPV:** Egg=85%, milk=69%, peanut=61% , soy=55%, wheat=68%. **NPV:** Egg= 100%, milk=86%, peanut=69% , soy=58%, wheat=78%. | Swiss National Research Foundation, the Eugenio Litta Foundation, National Institutes of Allergy and Infectious Diseases, the Division of Research Resources, National Institutes of Health. | Reported values for 2 different techniques used to measure SPT wheal but results reported in evidence table relate to wheal by diameter ≥3mm (most commonly used method). |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Rance et al 2002. (Ref ID:4944) | To develop a new strategy combining SPT's and specific IgE for diagnosing peanut allergy, while reducing the need for DBPCFC's/ France | Peanut | 363 children with suspected food hypersensitivity. Median age 4 years (range 0.1-15.9 years) & 67.5% had family history of atopic disease. They were later categorised as allergic (age range=1.0-15yrs, median age=4.4yrs) or non-allergic (age range=0.1-15.9yrs, median=3.7yrs) depending on results of challenge. | **SPT:** using commercial & fresh extracts. Positive result ≥3mm than neg control & at least 50% greater than positive control. **Specific IgE:** using CAP FEIA. Positive result ≥0.35 kU/L. | DBPCFC (performed in all children) | All values reported using SPT cut off ≥3mm & IgE ≥0.35 **Sensitivity:** SPT= 100% (CI 97.9-100), IgE=96.6% (CI 92.7-99.0). **Specificity:** SPT=66.1% (CI 58.8-72.9), IgE=62.4% (CI 55.0-69.3). Authors also present **ROC curve analysis:** IgE threshold ≥57kU/L resulted in 100% specificity and PPV. The SPT thresholds required to exclude false negative and false positive results were 3 and 16mm respectively. **AUC:** Raw extract= 0.90, commercial extract =0.79. | **PPV:** SPT=73.7% (CI 67.7-79.2), IgE=71.0% (CI 64.8-76.6). **NPV:** SPT=100% (CI 97.5-100), IgE=95.1% (CI 89.6-98.2) | Not reported. | Based on ROC curve analysis diagnostic accuracy values were also reported for SPT cut off ≥16mm and specific IgE≥ 57kU/L & combined use (positive diagnosis if at least one of the 2 tests was positive-i.e. SPT≥16mm or specific IgE≥ 57) but these are not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Roehr et al 2001 (Ref ID: 3674) | To evaluate whether a combination of allergologic tests could improve the prognostic value of the individual tests for positive food challenge results/ Germany | Cow's milk (CM), hen's egg (HE), wheat, soy | 98 children with AD with suspected food allergy who were admitted to author's wards. 51 boys, 47 girls with age range 2 months-11.2 years (median age=13 months). 61 had mild AD, 27 moderate AD & 10 with severe AD. | **SPT:** Using fresh foods. Positive reaction ≥3mm without reaction of negative control. **APT:** Using Finn Chambers. Positive result if erythema with infiltration occurred. Results read at 48hrs & 72hrs. **Specific IgE:** Using CAP FEIA. | DBPCFC .All children had DBPCFC, SPT, APT and IgE. (173 challenges were conducted in 98 children). | Values for performance of single tests APT, SPT and specific IgE. **Sensitivity:** IgE (CM=84%, HE=96%, wheat=67%, soy=75%). SPT (CM=78%, HE=89%, wheat=67%, soy=50%). APT (CM=47%, HE=57%, wheat=89%, soy=75%). **Specificity:** IgE (CM=38%, HE=36%, wheat=47%, soy=52%). SPT (CM=69%, HE=57%, wheat=53%, soy=90%). APT (CM=96%, HE=93%, wheat=94%, APT=86%). Authors also reported sensitivity and specificity values for different combinations of tests. A=IgE & SPT, B=APT & IgE, C=APT & SPT, D=APT & SPT & IgE. | **PPV:** IgE (CM=70%, HE=75%, wheat=57%, soy=23%). SPT (CM=81%, HE=81%, wheat=60%, soy=50%). APT (CM=95%, HE=94%, wheat=94%, soy=50%). **NPV:** IgE (CM=59%, HE=83%, wheat=57%, soy=92%). SPT (CM=64%, HE=73%, wheat=60%, soy=90%). APT (CM=51%, HE=52%, wheat=89%, soy=95%). | Not reported. | Also reported sensitivity, specificity, PPV & NPV values for different combinations of tests and late and early phase reactions which are not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Celik-Bilgili et al 2005. (Ref ID: 692) | To evaluate the role of specific IgE in predicting the outcome of oral food challenges and to determine threshold concentrations that could render DBPCFC unnecessary/ Germany | Cow's milk, hen's egg, soy, wheat | 501 children who were admitted to the author's ward with suspicion of food related symptoms. Age range=1 month-16.1 years (median=13 months). 60% boys and 88% with AD. 204 with mild AD, 116 with moderate AD, 56 with severe AD & 64 with no clinical symptoms of AD at time of challenge. | **Specific IgE:** using CAP FEIA. Positive result ≥0.35 kU/L. | Challenge (728 DBPCFC, 264 open challenges in children <1 year and history of immediate type reactions. All children were challenged & given IgE). 992 challenges performed in 501 children. | **Sensitivity of IgE for food challenge:** CM=83%, HE=97%, wheat=79%, soy= 69%. **Specificity of IgE for food challenge:** CM=53%, HE=51%, wheat= 38%, soy=50%. Also used logistic regression model proposed by Sampson to calculate **predicted probabilities** for showing a positive oral food challenge at a given specific IgE value. **For children <1 yr:** CM (90% cut off=25.8kU/L), HE (90%=4.2, 95%=10.9, 99%=88.6kU/L) & no calculated values for wheat or soy. **For children <1 yr:** HE (90%=6.7, 95%=13.2, 99%=58.2kU/L) & no calculated values for CM, wheat or soy. | **PPV:** CM=63%, HE=80%, wheat=41%, soy=22%. **NPV:** CM=76%, HE=89%, wheat=77%, soy=88%. | Not reported. | Authors also presented ROC curves which showed a tendency towards a relationship between specific IgE values and percentages of positive challenges. In the case of CM and HE, challenges were positive from CAP >50.0kU/L. For wheat and soy there was no clear relationship. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Breuer et al 2004. (Ref ID: 803) | To investigate the importance of food for the induction of late eczematous reactions in children with AD and to correlate the clinical outcome to the results of specific IgE determinations and APTs/ Germany. | Cow's milk, hen's egg, wheat, soy | 64 children aged 1-10 years (median 2 yrs) with mild-severe AD who visited the Department of Dermatology as outpatients. APT was performed in 41/64 children-23 had eczematous lesions on their back or refused. | **Total and specific IgE:** Using CAP RAST FEIA. Positive result ≥0.35 kU/L. **APT:** Using 12mm Finn Chambers. Positive result if erythema occurred with infiltration. Erythema without infiltration was considered irritative reaction. | DBPCFC (performed in all children). | Values based on type of reaction: **Sensitivity:** Any reaction (specific IgE=76%, APT=70%). Immediate reactions (IgE=77%, APT= 67%). Eczematous reactions (IgE=68%, APT=67%). **Specificity**: Any reaction (IgE=63%, APT=41%). Immediate reactions (IgE=60%, APT= 38%). Eczematous reactions (IgE=50%, APT =38%. Values based on age: **Sensitivity**: <2 yrs= 86%, ≥2yrs=70%. **Specificity**: <2 yrs= 74%, ≥2yrs=57%. | Values based on type of reaction: **PPV**: Any reaction (IgE=64%, APT=45%). Immediate reactions (IgE=57%, APT= 38%). Eczematous reactions (IgE=33%, APT=24%). **NPV:** Any reaction (IgE=75%, APT=67%). Immediate reactions (IgE=79%, APT= 67%). Eczematous reactions (IgE=81%, APT =79%. Values based on age: **PPV:** <2 yrs= 75%, ≥2yrs=56%. **NPV:** <2 yrs= 95%, ≥2yrs=71%. | Not reported. | Authors don't provide sensitivity, specificity, PPV or NPV values based on foods tested. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Dieguez et al 2009. (Ref ID:2480) | To assess the accuracy of a SPT and specific IgE to egg allergens in order to determine persistent egg allergy in IgE-mediated allergic children/ Spain. | Egg (white, yolk, OVA, lysozyme, OVM, OVT.) | 157 children aged 1-16 years (median age= 2.5yrs). 66.9% of children diagnosed with AD, 19.7% had allergic rhinitis or asthma, 22.9% had non-allergic asthma. 63.6% had other food allergies confirmed by positive SPT, positive IgE & when necessary oral challenge). 61% were male. | **SPT:** Positive reaction ≥3mm. **Total and specific IgE:** Using CAP FEIA. | DBPCFC (performed in all children. Follow-up performed after 1 month-children with negative challenge were in tolerant group while those with positive results were in persistent allergic group). | Tolerant group= 57 children, persistent egg allergy=100 children. All values are based on SPT cut off of 3mm & IgE cut off of 0.35 kU/L. **Sensitivity:** SPT (egg white=86%, OVM=59%). IgE (egg white=86.7%, yolk=55.4%, OVA= 86.7%, OVM=65.5%). **Specificity:** SPT (egg white=42.9%, OVM=74.1%). IgE (egg white=39.6%, yolk=92.3%, OVA= 47.1%, OVM=78.4%). Authors also reported ROC curves of SPT and IgE to egg allergens. **Area under the curve (AUC):** for SPT (egg white=0.79, OVA=0.78, OVM=0.71, yolk=0.64, OVA=0.63, lysozyme=0.56, OVT=0.54) and IgE (egg white=0.77, OVM=0.74, yolk= 0.74). | All values are based on SPT cut off of 3mm & IgE cut off of 0.35 kU/L. **PPV:** SPT (egg white= 72.9%, OVM =80.8%). IgE (egg white =70.9%, yolk=92%, OVA=72.7%, OVM=83.8% ). **NPV:** SPT (egg white= 63.2%, OVM =49.4%). IgE (egg white= 63.6%, yolk =56.5%, OVA=68.6%, OVM=57.1% ). | Fondo para la Investigacion Sanitaria & Premio de Investigacion del Instituto de Estudios del Huevo 2006. | Results also reported values for alternative SPT cut off values (e.g. 5, 7 & 9mm) and IgE cut off values (e.g. 1, 1.5 & 25kU/L) these are not reported in the evidence table. Reported AUC values for SPT-OVA has been reported twice in paper. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Verstege et al 2005. (Ref ID: 4903) | To evaluate the diagnostic capacity of SPT in predicting the outcome of oral food challenges and to determine decision points for wheal size and skin index (SI) that could render DBPCFC unnecessary/ Germany. | Cow's milk, hen's egg, wheat, soy | 385 children referred to Department of Pediatric Pneumology and Immunology at German children's hospital with suspected food-dependent symptoms. Children's ages ranged from 3 months-14.5 years (median 22 months). 58% boys, 42% girls. 335 children had AD: 168 with mild AD, 87 with moderate AD & 41 with severe AD. | **SPT:** Positive test ≥3mm and SI >0.6 (SI is ration of allergen wheal diameter divided by wheal size of histamine). | Oral food challenge (552 DBPCFC & 183 open challenge if children <1 year of age and with history of immediate type reactions. | **Sensitivity:** HE=93%, CM=85%, wheat=65%, soy=21%. **Specificity:** HE=59%, CM=75%, wheat=77%, soy=88%. Authors also reported ROC curves. **AUC** for wheal sizes showed acceptable values for CM (0.82), HE (0.83), wheat (0.75). The values for SI were comparable: CM (0.83), HE (0.85), wheat (0.74). For soy the relationship between sensitivity and specificity in ROC curves was poor and AUC not statistically significant. Logistic regression proposed by Sampson also used to calculate predicted probabilities illustrating the likelihood of patients with a given weal size to generate a positive food challenge. | **PPV:** HE=80%, CM=76%, wheat=52%, soy=29%. **NPV:** HE=83%, CM=83%, wheat=85%, soy=83%. **Predictive probabilities:** All values for 99% cut off. HE (<1 yr=15.4, >1 yr=18.3, all children=17.8) & CM ((<1 yr=13.5, all children=17.3). No values available for wheat and soy. | Not reported. | Also report 90 & 95% predictive probabilities which are not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Mehl et al 2006. (Ref ID:2857) | To study the utility of APT in the diagnostic work up of food allergy/ Germany. | Cow's milk, hen's egg, wheat, soy | 437 children with suspected food allergy referred to author's department. Age ranged from 3 months-14 years (median= 13 months). 60% boys. 391 (90%) had history of AD, 43% of these patients had mild AD, 25% with moderate AD, 12% with severe AD & 20% had no AD at time of challenge. | **SPT, APT:** Using Finn Chambers. Positive result if there was erythema with infiltration or papules. **sIgE:** Positive result ≥0.35kU/L | Oral food challenge (performed based on medical history, and/or pos SPT, and/or pos IgE. 77% were DBPCFC. Open challenges carried out in children <1 year with history of immediate type reactions) Total of 873 challenges analysed in 437 children. | **Sensitivity:** sIgE (CM=87%, HE=96%, wheat=82%, soy=65%). SPT (CM=85%, HE=93%, wheat=75%, soy=29%). APT (CM=31%, HE=41%, wheat=27%, soy=23%). **Specificity:** sIgE (CM=49%, HE=48%, wheat=34%, soy=50%). SPT (CM=70%, HE=54%, wheat=64%, soy=85%). APT (CM=95%, HE=87%, wheat=89%, soy=86%). Author's also calculated decision points for sIgE and SPT. **Decision points:** sIgE (95% HE=15.9, 99% HE=75.5 kU/L). SPT (95% CM= 13.8mm, 99% CM=20mm, 95% HE=14mm, 99% HE=20mm). | **PPV:** sIgE (CM=62%, HE=79%, wheat=41%, soy=22%). SPT (CM=73%, HE=79%, wheat=49%, soy=33%). APT (CM=86%, HE=86%, wheat=58%, soy=30%). **NPV:** sIgE (CM=79%, HE=85%, wheat=77%, soy=86%). SPT (CM=83%, HE=81%, wheat=85%, soy=82%). APT (CM=60%, HE=43%, wheat=69%, soy=82%). | Not reported. | Results also reported sensitivity, specificity, PPV & NPV values based on combination of sIgE, SPT & APT-these results are not reported in evidence table. Also reported decision points for children with positive and negative APT. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Ando et al 2008. (Ref ID: 190) | To evaluate the clinical usefulness and added diagnostic value of IgE antibodies to egg white, ovalbumin & ovomucoid in children with egg allergy/ | Egg white, ovalbumin, ovomucoid | 108 children with suspected egg allergy referred to author's clinic. Children ranged in age from 14 months to 13 years (median=34.5 months) and had mostly AD, asthma and in a few cases GI symptoms and anaphylaxis. Children were divided into 3 groups: A) 38 positive challenge results for heated and raw egg white. B) 29 with positive reactions to raw egg white but negative when heated. C) 41 with negative reactions to both raw & heated egg white. | **Specific and total IgE:** Using ImmunoCAP. | DBPCFC (all children tested). | All values reported are for IgE cut off 0.35kU/L for raw egg white. **Sensitivity:** egg white=97%, ovalbumin=97%, ovomucoid=87%. **Specificity**: egg white=29%, ovalbumin=32%, ovomucoid=41%. All values reported are for IgE cut off 0.35kU/L for heated egg white. **Sensitivity:** egg white=100%, ovalbumin=100%, ovomucoid=97%. **Specificity**: egg white=20%, ovalbumin=21%, ovomucoid=36%. Authors also reported positive and negative decision points based on at least 95% clinical specificity. **95% Negative & positive decision points for raw egg**: Egg white (0.60, 7.38kU/L), ovalbumin (0.79, 9.84kU/L), ovomucoid (positive only=5.21kU/L). | All values reported are for IgE cut off 0.35kU/L for raw egg white. **PPV:** egg white =69%, ovalbumin =70%, ovomucoid= 71%. **NPV**: egg white =86%, ovalbumin =87%, ovomucoid= 65%. All values reported for raw egg white. **PPV:** egg white =40%, ovalbumin =41%, ovomucoid= 45%. **NPV**: egg white =100%, ovalbumin =100%, ovomucoid= 96%. | Health and Labour Science Research Grants from Ministry of Health, Labour and Welfare of Japan. | Also reported sensitivity, specificity, PPV & NPV values for optimal cut off, positive and negative decision points-these are not reported in evidence table. Negative and positive decision points for heated egg also not reported in evidence table. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Sampson & Ho 1997. (Ref ID: 1494) | To determine the efficacy of the CAP system in the diagnosis of IgE-mediated food allergy in a group of children and adolescents referred for evaluation of AD/ USA | Egg, milk, peanut, soy, wheat, fish | 196 children and adolescents with AD (randomly selected from 300). Approx 50% had asthma and allergic rhinitis & 90% with family history of atopic disease. Age ranged from 0.6-17.9 years (mean= 5.2 yrs). 117 boys and 79 girls. | **Total and specific IgE:** Using CAP FEIA. Cut-off of 0.35 kU/L used. **SPT:** Positive result ≥3mm than the negative control. | DBPCFC (all negative results were confirmed using open challenge. DBPCFCs not performed when a patient with evidence of food-specific IgE antibody had a convincing history of a severe allergic reaction to food). 494 DBPCFCs performed in 196 children. | Values for SPT are compared to DBPCFC and for IgE are based on positive DBPCFC results and convincing histories of allergic reactions. **Sensitivity:** SPT (egg=98%, milk=96%, peanut=90%, soy=76%, wheat= 90%, fish=90%). IgE (egg=98%, milk= 100%, peanut=97%, soy=94%, wheat= 96%, fish=94%). **Specificity:** SPT (egg=53%, milk=51%, peanut=29%, soy=47%, wheat= 51%, fish=57%). IgE (egg=45%, milk= 30%, peanut=38%, soy=25%, wheat= 20%, fish=65%). Also report optimal decision points (ODP) selected from ROC curve. Values are based on study population. **ODP when using IgE (CAP):** egg=3.4 kU/L, milk=5.8, peanut= 10.7, soy=5.0, wheat=8.1, fish=1.8. | Values based on study population. **PPV:** SPT (egg=85%, milk=66%, peanut=55% , soy=35%, wheat= 35%, fish=77%). IgE (egg=84%, milk= 57%, peanut=78% , soy=21%, wheat= 14%, fish=49%). **NPV:** SPT (egg=90%, milk=93%, peanut=75% , soy=84%, wheat= 94%, fish=80%). IgE (egg=88%, milk= 100%, peanut=85% , soy=95%, wheat= 97%, fish=97%). | Not reported | Most positive responses to egg, milk, soy & wheat based on challenge but 43% peanut & 33% fish diagnoses based on convincing history. Also reported predictive values based on hypothetical normalised population (10% prevalence of food allergy)- not reported in table. Also report diagnostic accuracy values for ODP (not reported) and additionally report 90% and 95% PPV & NPV values for IgE. 95% PPV (Egg=6, milk=32, peanut=15, fish= 20kU/L). |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Sampson 2001. (Ref ID: 3560) | To determine the utility of 95% predictive decision points in the prospective evaluation of food allergy/ USA. | Egg, milk, peanut, fish, soybean, wheat | 100 children and adolescents referred to paediatric allergy clinic for suspected IgE food hypersensitivity. Age ranged from 3 months-14 years (median=3.8 years). Male/female=62: 38. 61% had AD, approx 50% had asthma & 90% came from atopic families. Validation study of Sampson & Ho 1997 predictive decision points. | **SPT:** Positive result ≥3mm or larger than that produced by negative control. **Specific IgE:** Using CAP FEIA. Considered definitely allergic if IgE ≥95% predictive decision points established in previous study. Considered possibly allergic if IgE<95% predictive decision points. Considered non-allergic if <0.35 kU/L. | Food challenge (single blind or open in children with positive SPT or IgE who were not suspected to have food allergy. Suspected food hypersensitivity confirmed using DBPCFC.) | Values based on 95% predictive decision points established in the retrospective study Sampson & Ho 1997. **Sensitivity:** Egg= 64% (at 6kU/L), milk=34% (at 32kU/L), peanut=57% (at 15kU/L), Fish=25% (at 20kU/L), soybean=24% (at 65kU/L), wheat=13% (at 100kU/L). **Specificity:** Egg= 90% (at 6kU/L), milk=100% (at 32kU/L), peanut=100% (at 15kU/L), Fish=100% (at 20kU/L), soybean=99% (at 65kU/L), wheat=100% (at 100kU/L). | Values based on 95% predictive decision points established in the retrospective study. **PPV:** Egg= 96% (at 6kU/L), milk=100% (at 32kU/L), peanut= 100% (at 15kU/L), Fish=100% (at 20kU/L), soybean= 86% (at 65kU/L), wheat=100% (at 100kU/L). **NPV:** Egg= 39%, milk=44%, peanut= 36%, Fish=89%, soybean= 78%, wheat= 76%. | Pharmacia/ Upjohn Diagnostics, National Institutes of Allergy and Infectious Disease, National Institutes of Health. | Also reported 90% diagnostic decision points (which were generated in retrospective study) but are not reported in evidence table. Also present recommended interpretation of food allergen specific IgE levels in the diagnosis of food allergy (not reported in evidence table). |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Nolan et al 2007. (Ref ID: 2794) | To investigate whether SPT with a commercial extractor fresh food adds additional information to FEIA in discriminating allergic and tolerant children/ Australia. | Peanut | 51 children from pediatric allergy clinics agreed to undergo challenge testing. Median age was 6.3 years (range 3.7-14.8 years). | Previous SPT and FEIA results were obtained from patient file when available. **SPT:** Recorded maximum diameter of wheal and perpendicular maximum diameter. Mean diameter calculated as an average of 2 values. | Open oral food challenge (tolerant if child completed challenge without reacting and remained tolerant at follow-up clinic 2-4 weeks later. There were total of 51 challenges 19 were positive, 27 negative & 5 indeterminate). | **Sensitivity:** 6mm=89%, 7mm=83%. **Specificity:** 6mm=93%, 7mm=97%. Author's also used **ROC curve analysis:** The SPT substrate that best predicted challenge outcome was commercial extract. Using largest diameter (AUC=0.937) was marginally better than mean diameter (AUC=0.930) but not statistically significant. Both raw (AUC=0.887) and roasted peanut extracts (AUC=0.913) correlated strongly with the commercial extract (r=0.85, r=0.83 respectively). Although AUC for fresh foods was lower than commercial extract, this was not statistically significant. | **PPV:** 6mm=89%, 7mm=93%. **NPV:** 6mm=93%. | Not reported. | Values based on cut off of ≥6mm as the largest diameter or 5.5mm as mean diameter for commercial extract and largest diameter of ≥7mm. Authors didn't report NPV for 7mm. |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Heine et al 2006. (Ref ID: 534) | To evaluate the diagnostic properties of single APT skin signs in relation to the outcome of controlled food challenges in order to validate the reading of the APT/ Germany. | Cow's milk, hen's egg, wheat, soy | 87 children with AD and suspected food allergy. Age ranged from 0.5-13.5 years (mean=2.4 years). 57 were male. | **APT:** Using Finn Chambers 12 mm. Skin changes graded for erythema (none, mild, moderate or severe), induration (none, minor within Finn Chamber or extensive beyond Finn Chamber), papule formation (none, 1-3, 4-6, 7+), vesiculation (present, absent) & crescendo (increase in severity of patch test reading at 48 and 72 hours). | DBPCFC (performed in all children) | Values based on crescendo phenomenon, alone and in combination with single APT signs at 72 hours.<br>**Sensitivity:**<br>Crescendo=11%, moderate erythema plus crescendo=5%, induration plus crescendo= 4%, papules (7+) plus crescendo=5%.<br>**Specificity:**<br>Crescendo=93%, moderate erythema plus crescendo=99%, induration plus crescendo= 98%, papules (7+) plus crescendo=98%. | **PPV:**<br>Crescendo= 57%, moderate erythema plus crescendo= 80%, induration plus crescendo= 60%, papules (7+) plus crescendo= 67%.<br>**NPV:**<br>Crescendo= 56%, moderate erythema plus crescendo= 56%, induration plus crescendo= 55%, papules (7+) plus crescendo= 55%. | Not reported. | Also report diagnostic accuracy values of combined APT skin signs which are not reported in evidence table. No analyses based on food tested (focus on APT signs). |

| Bibliography Reference (Ref ID) | Study aim/ Country of participants | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Knight et al 2006. (Ref ID: 2926) | To determine whether the size of SPT to egg white adds diagnostic utility for children with low egg white specific IgE antibody levels/ USA. | Egg | 74 children who were typically selected for oral food challenge based on low egg white specific IgE (≤2.5) and lack of known recent egg associated allergic reactions. Those who passed OFC (age range 1.9-14.6 years, mean age=5.1 yrs, 66% male, 90% other food allergies, 55% asthma, 79% eczema, 55% allergic rhinitis, 3% OAS). Those who failed OFC (age range 2.1-13.6 years, mean age=5.7 yrs, 58% male, 91% other food allergies, 71% asthma, 89% eczema, 82% allergic rhinitis, 4% OAS). | **SPT:** Using commercial extract. **Specific IgE:** Using CAP. Cut-off of 0.35 kU/L used. | Oral food challenge (68/ 78 were DBPCFC). | Authors do not report sensitivity and specificity values. 2 x 2 table for SPT produced using 'passing OFC' as negative result & 'failing OFC' as positive result. Calculated **sensitivity** SPT=93%, **specificity** SPT=31%. | Calculated **PPV**=68%, **NPV**=75%. | National Institutes of Health & American Academy of Allergy, Asthma and Immunology Clinical Fellowship award. | Difficult to interpret what passing and failing an OFC means in terms of positive/ negative results. |

**Appendix 1.3.4**

# JAMA Review

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Canani 2007 (375) | To evaluate the diagnostic accuracy of APT for diagnosing FA related gastrointestinal disease, both alone and with SPT and specific IgE | Cow's milk, hen's egg and wheat | 60 children referred to tertiary clinic for suspected FA-related gastrointestinal symptoms. Children ranged in age from 3 to 48 months, 63% were male and 53% had a positive family history for atopic disorders. | **Specific IgE:** using CAP-RAST positive result ≥0.35kU/L. **SPT**: using fresh foods. **APT:** using Finn chambers and commercial kit (Euromedical) | Open food challenge | **Sensitivity:** cow's milk (IgE=22.5%, SPT=45.1%, APT fresh= 64.5%, APT commercial= 6.45%). Hen's egg (IgE=31.5%, SPT=57.8%, APT fresh= 84.2%, APT commercial= 5.26%). **Specificity:** cow's milk (IgE=73.9%, SPT=69.5%, APT fresh= 95.8%, APT commercial= 95.6%). Hen's egg (IgE=66.6%, SPT=66.6%, APT fresh= 100%, APT commercial= 100%). | **PPV:** Cow's milk (IgE=53.8%, SPT=66.6%, APT fresh= 95.2%, APT commercial= 66.6%). Hen's egg (IgE=66.7%, SPT=78.5%, APT fresh= 100%, APT commercial= 100%). **NPV:** Cow's milk (IgE=41.6%, SPT=51.2%, APT fresh= 67.4%, APT commercial= 43.1%). Hen's egg (IgE=31.5%, SPT=42.8%, APT fresh=75%, APT commercial= 33.3%). | Not reported | Authors concluded that APT is a reliable, safe and useful diagnostic tool with which to evaluate suspected FA-related GI symptoms in childhood and infancy, and that APT with fresh foods has a higher diagnostic accuracy than APT with freeze dried extracts. Also suggest that APT use should be standardised. |

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Osterballe 2004 (763) | To investigate the clinical relevance of APT in predicting hypersensitivity to hen's egg or cow's milk compared to SPT, histamine release (HR) and specific IgE in an unselected population | Cow's milk and hen's egg | Oral challenge was performed in 22 children from a cohort of 495 unselected children aged 3 years. Food hypersensitivity (FHS) was defined as self-reported FHS from questionnaire or positive outcome on one of test procedures. | **Specific IgE:** using Magic Lite positive result ≥1.43SU/ml .**SPT**: using prick-prick. Positive result ≥3mm **APT:** using Finn chambers 8mm cups. **HR:** using glass fiber based histamine assay. Positive result≥10 ng/ml. | Open oral challenge | **Sensitivity:** Hen's egg (APT=40%, SPT=88%, HR=71%, IgE=75%), cow's milk (APT=0%, SPT=67%, HR=67%, IgE=50%). **Specificity:** Hen's egg (APT=99%, SPT=99%, HR=96%, IgE=89%), cow's milk (APT=99%, SPT=100%, HR=94%, IgE=98%). | **PPV:** Hen's egg (APT=39%, SPT=59%, HR=22%, IgE=10%), cow's milk (APT=0%, SPT=45%, HR=6%, IgE=14%). **NPV:** Hen's egg (APT=99%, SPT=99%, HR=99%, IgE=99%), cow's milk (APT=99%, SPT=99%, HR=99%, IgE=99%). | Danish Ministry of Food, Agriculture and Fisheries | Authors concluded that APT could not predict hypersensitivity not predicted by SPT, HR or IgE. Thus APT cannot be recommended in daily practice for the diagnosis of FHS of hen's egg and cow's milk in children aged 3 years old. |

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Garcia-Ara 2001 (3583) | To find the optimal cut-off values for specific IgE antibody levels that discriminate between allergic and tolerant infants by using cow's milk and its principle proteins as allergens | Milk | 161 children consecutively selected over a 4 year period from an allergy service. Age ranged from 1 to 12 months. 50% had a positive family background of atopy and 23% had atopic dermatitis. | **SPT:** using extract. Positive result ≥3mm. **Total and specific IgE:** positive result≥0.35 kU/L. | Open food challenge | **Sensitivity:** SPT=72%, IgE=84% **Specificity:** SPT=62%, IgE=56% | **PPV:** SPT=60%, IgE=61% **NPV:** SPT=73%, IgE=81% | Not reported | Also use specific milk proteins (not reported in evidence table). |
| De Boissieu 2003 (950) | To provide an approach to the accuracy of the APT in the diagnosis of cow's milk allergy in patients with digestive symptoms | Cow's milk | 35 children aged 2 to 57 months referred for diagnosis of nonspecific persistent digestive symptoms. 15 were female and 20 male. | **IgE:** using CAP-RAST. **SPT**: positive result≥ 3mm. **APT:** using Finn Chambers | Open challenge or DBPCFC | **Sensitivity:** APT=79% **Specificity:** APT=91% | N/A | Not reported | Authors reported good sensitivity and specificity values for milk APT in patients with cow's milk allergy but standardisation is needed. |

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Monti 2002 (999) | To compare the outcome of an oral food challenge with never ingested egg and results of SPTs and RASTs | Egg (albumen and yolk) | 107 children referred to atopic dermatitis (AD) service. Their age ranged from 1 to 19 months, 66 males and 41 females. | **SPT:** using commercial extracts. **Specific IgE:** using CAP RAST. Results classified as negative, borderline, positive, highly positive, very highly positive or extremely highly positive. | Food challenge | **Sensitivity:** (at 3mm threshold) SPT albumen =87.5%, SPT yolk=66.6%. **Specificity:** SPT albumen =85.7%, SPT yolk=88.6%. | **PPV:** (at 3mm threshold) SPT albumen =92.6%, SPT yolk=92.3%. **NPV:** SPT albumen =77%, SPT yolk=56.3%. | Not reported | |

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
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| Jarvinen 2003 (3303) | To determine the concurrent occurrence of cereal allergy among children with challenge proven cow's milk allergy who have residual symptoms during elimination diet. | Wheat (using cereal) | 90 children aged between 2.5 to 36 months referred to university hospital due to AD. There were 59 males and 31 females. | **SPT:** using commercial extracts, positive result ≥3mm and at least half size of histamine induced wheal. **APT:** using Finn Chambers | Open food challenge | **Sensitivity:** prick=23%, patch=100%. **Specificity:** prick=67%, patch=79% | **PPV:** prick=100%, patch=32%. **NPV:** prick=90%, patch=46% | Not reported | The authors concluded that patch testing with cereals aids in diagnosing cereal allergy in small children, especially when used together with SPT. |

**Appendix 1.3.5**

# Clinical Question 4

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

| Bibliography (Ref ID) | Study type | Food | Symptoms or risk factors for referral | Source of funding | Comments |
|---|---|---|---|---|---|
| Allen et al 2009 (Ref ID: 452) | Review article (expert panel perspective) | Cow's milk | Recommendations for further referral in difficult-to-manage clinical scenarios of suspected Cow's Milk Protein Allergy (CMPA).<br>• Referral if trial of cow's milk elimination fails (haematemesis, chronic diarrhoea, persistent vomiting, persistent rectal bleeding, iron deficiency anaemia & severe eczema).<br>Urgent referrals for:<br>• anaphylaxis,<br>• Food Protein Induced Enterocolitis Syndrome (FPIES)<br>• severe failure to thrive,<br>• hypoproteinaemia/ protein losing enteropathy | Not reported | Doesn't mention where patients should be referred to or from. |
| Robinson & Smart 2008 (Ref ID: 1034) | Review article | Not specific | Referral to an allergy specialist should be considered in any child with history of:<br>• suspected IgE-mediated food allergy<br>• suspected non-IgE-mediated food allergy<br>• asthma that required a preventer therapy to assess the possible role of environmental allergens<br>• allergic rhinoconjunctivitis that has not responded to maximal therapy<br>• atopic dermatitis where there has been a poor response to topical management or where dietary precipitants are suspected | Not reported | Not specific to food allergy as considers all allergic diseases |

| Bibliography (Ref ID) | Study type | Food | Symptoms or risk factors for referral | Source of funding | Comments |
|---|---|---|---|---|---|
| Allen 2007 (Ref ID: 1037) | Review | Cow's milk | Recommend referral to specialist in a vomiting infant with suspected CMA who has failure to thrive or bloody diarrhoea. Infants with evidence of immediate reactions to CMA suggestive of IgE-mediated food allergy should be urgently referred to pediatric specialist for SPT. | Not reported | Doesn't mention where patients referred from |
| Vandenplas et al 2007 (Ref ID: 514) | Guideline (based on consensus) | Cow's milk | For children who have been exclusively breast fed, refer to paediatrician specialist based on suspicion of severe CMPA and one of more of following symptoms:<br>• Gastrointestinal: failure to thrive because of diarrhoea or regurgitation/ vomiting; refusal to feed, moderate to large amounts of blood in stool with decreased haemoglobin, protein losing enteropathy<br>• Dermatological: failure to thrive and severe atopic dermatitis<br>For children who have been formula fed, refer to paediatrician specialist based on suspicion of severe CMPA and one of more of following symptoms:<br>• Gastrointestinal: failure to thrive because of diarrhoea and/or regurgitation/ vomiting and/or refusal to feed, iron deficient anaemia, protein losing enteropathy, endoscopic /histologically confirmed enteropathy or severe ulcerative colitis<br>• Dermatological: exudative or severe atopic dermatitis with hypoalbuminaemia-anaemia or failure to thrive or iron deficiency anaemia<br>• Respiratory: acute laryngoedema or bronchial obstruction with difficulty breathing<br>• Systemic reactions: (anaphylactic shock needs immediate referral to hospital for management) | SHS/ Nutricia | |

| Bibliography (Ref ID) | Study type | Food | Symptoms or risk factors for referral | Source of funding | Comments |
|---|---|---|---|---|---|
| Kaila et al 2008 | Finnish Guideline by Finnish Medical Society Duodecim | Not specific | Indications for referral to specialist care:<br>• infant with widespread eczema or worsening symptoms<br>• infant with difficult or perplexing symptoms and parents are convinced of food allergy<br>• failure to thrive<br>• diet is limited by parent to dangerously few foods<br>• an older child needs to be referred if the diet threatens to become too limited | Not reported | |
| Leung and Schatz 2006 | Consultation and referral guideline by American Academy of Allergy, Asthma and Immunology | Not specific | Guideline is aimed at patients and healthcare professionals and set out when referral to an allergist-immunologist could be helpful. For food allergy, referrals may be helpful for:<br>• people who have limited their diet on basis of perceived adverse reactions to foods<br>• people with a diagnosed food allergy<br>• atopic families with or expecting a newborn who are interested in identifying risks for and preventing allergy<br>• people who have experience allergic symptoms in association with food exposure<br>• people who experience an itchy mouth from raw fruit and vegetables<br>• Infants with GORD or older individuals with recalcitrant reflux symptoms<br>• Infants with gastrointestinal symptoms including vomiting, diarrhoea (particularly with blood), poor growth etc<br>• people with known eosinophilic inflammation of the gut | Not reported | Most of the disorders affecting infants cannot be identified with simple screening tests. Older individuals might have reflux symptoms and possibly dysphagia caused by eosinophilic esophagitis, a disorder that is also commonly food responsive. |

**Appendix 1.3.6**

# Clinical Question 5

What information should children with suspected food allergy and their parents/carers receive during the diagnostic process?

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| Lever et al 1998 (Ref ID: 4987) | Randomised Control Trial (RCT) to investigate the effect of advice on excluding eggs from the diet of young children with evidence of egg sensitivity and atopic eczema. | 55 (out of 300) children with atopic eczema referred for suspected food allergy. Mean age of presentation 11.3 months in diet group and 17.2 months in control group. All received specific IgE at | (1) Parents of children in the diet group were advised to exclude all foods containing eggs for 4 weeks and were given lists of food known to contain eggs and of egg-free foods. They were also helped with interpreting labels on food.<br><br>(2) Parents of children in the control group were | **Changes in eczema:** Assessed in two ways (1) estimating the area affected by eczema (% of total skin area) and (2) severity score in arbitrary units (0-3) which assessed 6 clinical features at initial presentation, study entry and after the trial. Changes were also analysed correcting for a child's entry value.<br><br>**Results:**<br>**(1) Surface area affected:** During the trial it was found that more children in the diet group showed improvement: 25 (89%) compared to controls 16 (59%). The reduction in mean area affected was significantly greater in the diet group than controls ($t=2.08$, $p=0.04$). In relation to initial entry scores, generally children from diet group improved more than controls and this tended to be greatest in children with the largest affected area at outset. Non-significant linear regression slopes between control and diet group ($p=0.13$) may have been influenced by 2 children; one control whose eczema cleared almost completely during trial and a diet child with marked involvement showing | Not reported | Detailed dietary histories were taken from the parents of 62 children & were randomised by dietitian to diet group or control group. During the 4 week trial treatment continued | Study suggests that children with atopic eczema and sensitivity to eggs benefit from a regime in which parents are advised by a dietitian to exclude eggs and egg |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| | | presentation. All children received DBPCFC after the trial to confirm egg allergy-7 had a negative challenge result. | given no specific advice on avoidance of any particular item of food. | no improvement.<br>**(2) Severity scores:** During the trial similar changes were seen in severity scores and improvement was greater in diet group (t=1.99, p=0.05). In relation to initial entry scores, there were no significant difference in slopes between diet and control groups (p=0.22) although the mean change in severity in the diet group from 33.9 to 24.0 was significantly greater (p=0.04) than that in controls (36.7 to 33.7). | | unchanged in both groups. 7 children had negative challenges. | products from their child's diet. |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
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| Hu et al 2007(Ref ID: 151) | Qualitative study using in-depth semi-structured interviews and focus groups to examine the patient information needs and preferences of parents regarding food allergy | 84 parents of children presenting for evaluation of food allergy recruited from pediatric allergy clinics or a national consumer organisation. Age ranged from 23 to 55 years. | Thematic categories were developed from transcribed interviews and focus groups using the constant comparative method | **Phases in information needs:** parents described 3 distinct phases in information seeking; on initial diagnosis, at follow-up and at milestones. When food allergy was first diagnosed the majority of parents requested that more information be given at the first visit, with only 2 parents stating that they were given too much information.<br><br>**Information content needs:** parents described 2 aspects of information content. The first concerned the reasoning behind the doctor's judgements about their allergy. The second type of information concerned basic medical facts and practical advice related to daily management.<br>**Core areas identified by parents**: What is and what is not anaphylaxis, recognising symptoms of allergic reactions, the timescale of reactions, how accidental exposures occur and how to manage risky situations, what to feed your child (rather than what to avoid), practical allergen avoidance: label reading, shopping, cooking, eating out etc, when and how to give auto injector, how to educate extended family, carers and adults who may give child food, risks and benefits of skin testing and oral challenges, interpretation of results, when follow-up is required and why, where more information can be found, how to educate your child & background information about allergy.<br><br>**Preferences for information delivery:** Information format was one aspect of this theme. Written take home information was strongly preferred as it was difficult to recall details of food ingredients and products but was not a substitute for talking to a healthcare professional. Parents also spoke highly of videos which they found essential for educating their child. They also preferred to receive more trustworthy information from their doctor and found nurse led education sessions valuable. Other aspects included clinic procedures and accessibility & doctor-parent-child relationship. | Australian Allergy Foundation & the National Health and Medical Research Council of Australia | Thematic categories were validated by 6 expert reviewers from allergy and non-allergy specialist, general practice, sociology, consumer and lay background. | Patients prefer information to be delivered in a variety of formats, and in an accessible, ongoing, parent and child-centred manner. These findings may assist development of more effective educational strategies. |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
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| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| Mikkelsen et al 2005 (Ref ID:290) | Questionnaire survey was used to develop a suitable form of group education for families suffering from cow's milk allergy/ intolerance and to evaluate this intervention immediately after participation and 3 years later | 84 families of children diagnosed or suspected to have cow's milk allergy in the primary healthcare system in Sweden who were prescribed a milk free diet. The children's age ranged from 3 months to 5 years. | Milk allergy school: At group sessions participants were encouraged to narrate how the allergy was diagnosed, for how long they had been pursuing a milk free diet and what they experienced as major problems in their new situation. The dietitian provided information, answered questions, corrected eventual misconceptions and kept discussions on track. Sessions also included practical exercises such as reading ingredient labels & parents were also given written instructions on how to follow an elimination diet and booklets of recipes | **Post session evaluation:** 72% of participants indicated at the end of the course that they were satisfied with the content and presentation of information received. 27% felt their need for information had only been partially met. At 3 year follow-up the participant's responses showed more positive attitudes including satisfaction with the information received in most cases (88%) and partial satisfaction in only 9 cases (12%). 56% preferred to get information both individually and in group, 13% considered it sufficient to attend a milk allergy school and 8% would have preferred individual information.<br>**Positive and negative aspects**: Positive aspects of the milk allergy school included qualities of the given information and support (38%), the encounter with other parents in the same situation (35%) or both features (14%). The most common negative aspect was that the composition of the group was heterogeneous according to age and/or symptoms of the children (11%) as well as level of knowledge among participants. Other negative aspects (14%) include the premises and lack of follow-up. | The Swedish Asthma and Allergy Foundation | No control group were used. | The milk allergy school seems to satisfy most families need for information and support to manage the milk-free diet |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
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| Barnett 2005 (Ref ID: 265) | Use an online questionnaire to determine whether community-pharmacist provided food allergy education and auto-injectable epinephrine training is needed. | 1887 recently joined members of the Food Allergy and Anaphylaxis Network (FANN). 4.9% were food allergic individuals & 95.1% were parents or caregivers who answered on behalf of food-allergic individual. Mean age of food-allergic individuals was 5.74 years and had been diagnosed for mean 3.26 years but recall was required | Online questionnaire consisted of 35 items. Demographics and past education and training associated with food allergy and use of auto-injectable epinephrine were explored in 26 questions that used forced choice and open ended responses. | **Education and training provided by prescriber**: 1.4% reported education and training provided by family practitioner. 6 categories of information: general information about food allergy, information about signs of allergic reaction, training in use of epi-pen, information on specific foods to avoid, drug information of epinephrine and day-to-day management information of food allergy. 23% of respondents reported comprehensive information and training, 16.3% reported no information or training, and 60.7% reported incomplete information covering some of the 6 categories.<br>**Initial prescription for auto-injectable epinephrine**: 94% were dispensed in community pharmacy and 0.4% in physician's office. 73.6% received both patient insert and drug information leaflet, 23.8% received only the patient insert, 2% received only drug information leaflet and 0.6% received neither.<br>**Education and training provided by pharmacist**: 86.6% recalled that no oral counselling was offered, 13.4% recalled drug information about epinephrine, 13.3% received training in use of epi-pen, 2.3% received information about signs of allergic reaction, 1.1% about specific foods to avoid, 1% received general information about food allergy and 0.9% had management advice.<br>**Attitudes towards pharmacist provided education:** The mean overall attitude was 3.47 on the 5-point likert scale representing an attitude between neutral and favourable. Stronger attitudes were presented with respect to 4 statements-respondents disagreed with the statements 'A pharmacist that tried to talk with me about food allergies would be wasting my time' (2.32) and 'that only thing that | Not reported | Recall of initial diagnosis may not be accurate. | Community pharmacists should consider working collaboratively with paediatricians and allergists who do not provide education and training at the time of initial prescription order is written for auto-injectable epinephrine. |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
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| | | related to initial diagnosis of food allergy. | | pharmacists should do for the food allergic is fill their prescriptions' (2.23). Respondents agreed with the statements 'When I pick up an epi-pen, the pharmacist should counsel me without asking me or waiting for me to ask' (3.64) and 'I would welcome the chance to update my knowledge and skills about food allergy by talking with a pharmacist' (3.64). | | | |
| Gillespie et al 2007 (Ref ID: 181) | Phenomenological study to develop a narrative description of detailing the central underlying meaning of the mother's lived experience of parenting a child at risk of Food Induced Anaphylaxis (FIA) | 6 mothers of children aged 6 to 12 years old considered at risk of FIA who were required to carry epinephrine. Mother's were recruited from private pediatric allergist's office and from a parent support group. | Semi-structured interviews were used to aid mothers in describing what it was like for them to have a child with a life threatening food allergy. | The essence or meta-theme of the mother's experiences is described as 'living with risk' and is supported by 5 themes including relying on resources.<br>**Relying on resources:** The main resources were identified as personal, help from others and information sources. Within 'help from others' physicians played an important role. Allergists especially were valued for their expert knowledge, as well as some physicians for their supportive manner. How physicians treated the child was important, and mothers praised child-focused encounters. Within 'information resources' all mothers were active in finding information from sources such as the internet. They believed that physicians should clearly indicate not only the seriousness of the allergy at diagnosis but also the fact that it could be managed; in addition physicians should provide reliable information that would help protect the child. They did not all believe that they had received enough information from their physicians and did not know what to ask at first. Some mother's suggested it would be helpful to have a nurse available for teaching, counselling, contact and follow-up after the original appointment. Referral to other parents understanding daily problems was also suggested. | One author supported by Winnipeg Health Sciences Centre Foundation & the other by a Canadian Cancer Society Research Scientist award and a Manitoba Health Research Council | | This study has shown that mothers need support, information and knowledge that people in contact with their child are informed about FIA. Clear information must be given early, with reassurance of the child's prognosis for a healthy life but |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| | | | | | Establishment award. | | acknowledging that challenges will be faced. Printed resources should include what needs to be avoided, the importance and 'how to' of reading labels, how to contact companies and how to deal with problems. |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
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| Arvola et al 2000 (Ref ID: 1218) | Questionnaires used to describe the problems that parents experience in the care of their high risk atopic infant and their expectation of healthcare professional. | 81 breast fed infants with atopic eczema (AE) who were admitted to the Department of Pediatrics at University hospital in Finland. AE had developed during breast feeding at a mean age of 2 months. Mean age at enrolment was 5 months (range 1.5-15 | Intervention team comprised of a pediatric nurse and 2 paediatricians with expertise in food allergy, who consulted regularly with a dietitian and a dermatologist. Foods suspected to cause allergic symptoms (on basis of clinical history, specific IgE and SPT results) were eliminated from the diet and substituted with nutritionally equal foods for 9 months. During study visits patients were clinically examined | The questionnaire before intervention related to: diet of infant and mother at onset of AE symptoms, problems in care before diagnostic and therapeutic intervention, the advice received in primary healthcare and whether this advice was beneficial & expectations from diagnostic and therapeutic evaluation. The questionnaire after the intervention related to: Parent's perception of the care received by intervention team, problems concerning care of the infant during intervention, usefulness of advice received & the realisation of expectations from intervention.<br><br>**Problems in managing infant:** Before intervention 88% found care of atopic infant more demanding than healthy child with severe AE, pruritus, restlessness, sleep loss, difficulties in skin treatment and adherence to strict diet being perceived as most important problems. 53% had consulted a GP and remainder had consulted a nurse for advice. Advice included follow-up (16% of cases) and topical treatment (29%) which parents considered inadequate, whereas elimination of specific food (32%) and diagnostic evaluation (17%) were felt to be necessary. After intervention 92% of parents considered care of atopic infant more demanding than healthy child although | Medical Research Fund of Tampere University Hospital and the Academy of Finland | No control group without intervention | The present data support a comprehensive team approach to the care of atopic infants and their parents. |

| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| | | months). 56% found to have a challenge confirmed allergy during study. | and severity of AE was scored (SCORAD method). Parents also interviewed regarding recent symptoms and were given new list of foods to introduce if no symptoms appeared. Compliance to recommendations were assessed by monitoring growth. Pediatric nurse gave practical advice on elimination diets and was available for enquiries relating to care of infant. Challenge was conducted one month after cessation of breast feeding. | problems in management of infant had significantly diminished.<br><br>**Expectations from intervention:** Parents expected, in order of importance: alleviation of AE symptoms, practical advice on skin treatment and elimination diet, accurate diagnosis of food allergies and follow-up of nutritional state.<br><br>**Perceptions of intervention:** 92% considered help and advice from intervention team to be sufficient in care of their atopic infant. The expectations with regard to alleviation of symptoms were moderately or well fulfilled in 98% of cases, advice on skin treatment and elimination diet in 100%, allergy diagnosis in 94% and follow-up of growth and nutrition in 100% of cases. Parents criticised busy schedule of paediatricians, the dermatologist and the dietitian and hoped for improvement between exchange of information between them. They appreciated the individual doctor-patient relationship, permanence of medical staff, continuous follow-up and the child and family centred care provided by the pediatric nurse. | | | |

<table>
<tr><th>Bibliography (Ref ID)</th><th>Research question/ study design</th><th>Population</th><th>Intervention</th><th>Outcomes</th><th>Source of funding</th><th>Comments</th><th>Authors conclusion</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Weber et al 2007 (Ref ID: 144)</td><td>Questionnaires and interviews used to investigate how well parents of children on cow's milk free diets perform at recognising whether or not expressions describe and foods contain</td><td>24 parents of children on cow's milk free diets and control group of 23 parents of children with no need for any type of exclusion diet. Mean age of study group 30.9 years and 32.7 years in control group.</td><td><u>Dietary guidance:</u><br>In study group 71% had been instructed to exclude cow's milk and by-products and 29% to exclude cow's milk, by-products and soy. Of these 80% had received instruction on how to read product labels and 38% received instructions on words associated with cow's milk.</td><td>Data collected by questionnaire applied in 4 stages: personal details of child's guardian, economic classification, questions about dietary guidance given when elimination diet was prescribed and whether participant was capable of identifying whether 10 commercial foods were free of cow's milk (5 with cow's milk and 5 without).<br><br><u>Results:</u> Table of median products correctly identified for each group<br><table><tr><td>Correct ID</td><td>Study group</td><td>Control group</td><td>p-value</td></tr><tr><td>With milk</td><td>4.0</td><td>3.0</td><td>0.005</td></tr><tr><td>Without milk</td><td>3.0</td><td>2.0</td><td>0.079</td></tr><tr><td>Total</td><td>6.0</td><td>5.0</td><td>0.008</td></tr></table>Table shows median products correctly identified is higher in study group. For popular expressions of whole milk, powdered milk, skimmed milk and semi-skimmed milk there were non-</td><td>Not reported</td><td>Intervention assessed (i.e. dietary guidance) was provided previously and measured using questionnaire. No specific analysis on association between previous dietary</td><td>The capacity of parents to correctly identify products with and without cow's milk and by-products is not completely satisfactory. Strategies should be developed to improve</td></tr>
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| Bibliography (Ref ID) | Research question/ study design | Population | Intervention | Outcomes | Source of funding | Comments | Authors conclusion |
|---|---|---|---|---|---|---|---|
| | cow's milk proteins. | | Those in control group had not received any instruction on elimination diets. | significant differences of correct identification between groups. For technical expressions in study and control group respectively, the following percentages were observed of recognition of dairy products (71% and 45%, p=0.06, cow's milk protein (71% and 9%, p=0.001), traces of milk (54% and 9%, p=0.001) and milk formulation (42% and 13%, p=0.03). Recognition of scientific expressions did not exhibit statistical differences for casein (25% vs. 4%), lactalbumin (17% vs. 4%) or lactoglobulin (8% vs. 4%) but did for caseinate (21% vs. 0%, p=0.03). Only 3 individuals correctly identified all 10 products- all these were from the study group and had received professional instructions on how to identify foods that are and are not permitted in exclusion diet. | | guidance and correct identification of cow's milk containing products. | effectiveness of guidance on implementing elimination diets. |

**Appendix 1.3.7**

# Alternative Tests

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Fundin g | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Funding | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|
| Moneret-Vautrin 1999 (3805) | To assess if flow cytometric analysis of basophil activation could be applied to food allergy diagnosis and if this method paralleled LTC4 release | Several (no specific details given) | **Food allergic group:** 27 individuals with 19 male and 8 female. 21 were <15 years, 5 were 15-40 years and 1 was 40+ years.<br><br>**Control group:** 24 individuals with 10 male and 14 female. 7 were <15 years,10 were 15-40 years and 7 were 40+ years. 10 were atopic. | Basophil Activation Test (BAT) and LTC4 release test (LRT) using direct stimulation and passive sensitisation of basophils taken from blood donors | Food challenge (OFC or DBPCFC) | Values were calculated using extracted 2 X 2 tables.<br>**Sensitivity:** BAT (direct stimulation= 80%, passive sensitisation= 48%) and LRT (direct stimulation= 85%, passive sensitisation= 52%).<br>**Specificity:** BAT (direct stimulation= 100%, passive sensitisation= 94%) and LRT (direct stimulation= 100%, passive sensitisation= 100%). | Not calculated | Not reported | Adults are included in this study however the majority in the food allergic group are children. Authors conclude that the results presented are in favour of the reliability of BAT and LRT for the diagnosis of food allergy. |
| Osterballe et al 2004 | To investigate the clinical | Cow's milk, hen's | 455 children aged 3 years old. 74 had atopic | Histamine release from | Open food challenge | **Sensitivity:** HE=71%, CM=67%. | **PPV:** HE=22%, CM=6%. | Danish Ministry of Food, | Children were also tested with |

| Bibliography Reference (Ref ID) | Study aim | Foods tested for | Number, Age and Characteristics of participants/ | Type of Test | Reference standard | Sensitivity/ Specificity | Positive/ Negative predictive values | Source of Fundin g | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|
| | relevance of APT in predicting hypersensiti vity to cow's milk and hen's egg in unselected children | egg | dermatitis | basophils | | **Specificity:** HE=96%, CM=94%. | **NPV:** HE=99%, CM=99%. | Agricult ure and Fisherie s | APT, IgE and SPT. |

# Food Allergy in Children Appendix 2

## Excluded studies

**REFERENCE LIST OF EXCLUDED PAPERS FOR CLINICAL QUESTION 1 (clinical history) AND REASON FOR EXCLUSION**

Forbes, L.R., Saltzman, R.W., & Spergel, J.M. 2009. Food allergies and atopic dermatitis: differentiating myth from reality. *Pediatric Annals*, 38, (2) 84-90
Ref ID: 100

**EXC: Recommending history taking**

Kim, J.S. 2008. Pediatric atopic dermatitis: the importance of food allergens. [Review] [44 refs]. *Seminars in Cutaneous Medicine & Surgery*, 27, (2) 156-160
Ref ID: 214

**EXC: Recommending history taking**

Gotua, M., Lomidze, N., Dolidze, N., & Gotua, T. 2008. IgE-mediated food hypersensitivity disorders. [Review] [33 refs]. *Georgian Medical News* (157) 39-44
Ref ID: 241

**EXC: Description**

Fiocchi, A., Bouygue, G.R., Terracciano, L., Sarratud, T., & Martelli, A. 2006. Ruling out food allergy in pediatrics and preventing the "march" of the allergic child. [Review] [61 refs]. *Allergy & Asthma Proceedings*, 27, (4) 306-311
Ref ID: 485

**EXC: Recommendation**

Ali, R., Ali, S., Saeed, S.A., Khan, A., Mustafa, M., & Aleem, S. 2005. Latest approaches to the diagnosis and management of food allergies in children. [Review] [35 refs]. *JPMA - Journal of the Pakistan Medical Association*, 55, (10) 458-462
Ref ID: 607

**EXC: Description and Recommendation**

Baral, V.R. & Hourihane, J.O. 2005. Food allergy in children. [Review] [62 refs]. *Postgraduate Medical Journal*, 81, (961) 693-701
Ref ID: 617

**EXC: Description and Recommendation**

Carr, W.W. 2005. Clinical pearls and pitfalls: peanut allergy. [Review] [16 refs]. *Allergy & Asthma Proceedings*, 26, (2) 145-147
Ref ID: 661

**EXC: Description**

Host, A. & Halken, S. 2003. Practical aspects of allergy-testing. *Paediatric Respiratory Reviews*, 4, (4) 312-318
Ref ID: 859

**EXC: Description**

Guarderas, J.C. 131. Is it food allergy? Differentiating the causes of adverse reactions to food. [Review] [17 refs]. *Postgraduate Medicine*, 109, (4) 125-127
Ref ID: 1147

**EXC: Description and Recommendation**

Sicherer, S.H. 2001. Diagnosis and management of childhood food allergy. [Review] [136 refs]. *Current Problems in Pediatrics*, 31, (2) 35-57
Ref ID: 1156

**EXC: Description**

Bengtsson, U., Nilsson-Balknas, U., Hanson, L.A., & Ahlstedt, S. 1996. Double blind, placebo controlled food reactions do not correlate to IgE allergy in the diagnosis of staple food related gastrointestinal symptoms. *Gut*, 39, (1) 130-135
Ref ID: 1581

**EXC: Population includes adults**

Watson, W.T. 1995. Food allergy in children. [Review] [50 refs]. *Clinical Reviews in Allergy & Immunology*, 13, (4) 347-359
Ref ID: 1638

**EXC: Description and Recommendation**

Kueper, T., Martinelli, D., Konetzki, W., Stamerjohn, R.W., & Magill, J.B. 1995. Identification of problem foods using food and symptom diaries. *Otolaryngology - Head & Neck Surgery*, 112, (3) 415-420
Ref ID: 1690

**EXC: Population includes adults**

Parker, S.L., Leznoff, A., Sussman, G.L., Tarlo, S.M., & Krondl, M. 1990. Characteristics of patients with food-related complaints. *Journal of Allergy & Clinical Immunology*, 86, (4:Pt 1) t-11
Ref ID: 1928

**EXC: Population includes adults**

15. Bahna, S.L. & Furukawa, C.T. 1983. Food allergy: diagnosis and treatment. *Annals of Allergy*, 51, (6) 574-580
Ref ID: 2174

**EXC: Description and Recommendation**

Bahna, S.L. & Gandhi, M.D. 1983. Milk hypersensitivity. II. Practical aspects of diagnosis, treatment and prevention. [Review] [53 refs]. *Annals of Allergy*, 50, (5) 295-301
Ref ID: 2194

**EXC: Description and Recommendation**

Kneepkens, C.M.F. & Meijer, Y. 2009. Clinical practice. Diagnosis and treatment of cow's milk allergy. *European Journal of Pediatrics*, 168, (8) 891-896
Ref ID: 2431

**EXC: Review paper**

Ramesh, S. 2008. Food allergy overview in children. *Clinical Reviews in Allergy and Immunology*, 34, (2) 217-230
Ref ID: 2575

**EXC: Description and Recommendation**

Mukoyama, T., Nishima, S., Arita, M., Ito, S., Urisu, A., Ebisawa, M., Ogura, H., Kohno, Y., Kondo, N., Shibata, R., Hurusho, M., Mayumi, M., & Morikawa, A. 2007. Guidelines for diagnosis and management of pediatric food allergy in Japan. *Allergology International*, 56, (4) 349-361
Ref ID: 2684

**EXC: Guidelines description and recommendation**

Bangash, S.A. & Bahna, S.L. 2005. Pediatric food allergy update. *Current Allergy and Asthma Reports*, 5, (6) 437-444
Ref ID: 3003

**EXC: Description and critique**

Sampson, H.A. 2005. Food allergy - Accurately identifying clinical reactivity. *Allergy: European Journal of Allergy and Clinical Immunology, Supplement*, 60, (79) 19-24
Ref ID: 3070

**EXC: Description and Recommendation**

Scurlock, A.M., Lee, L.A., & Burks, A.W. 2005. Food allergy in children. *Immunology and Allergy Clinics of North America*, 25, (2) 369-388
Ref ID: 3078

**EXC: Critique and evaluation**

Kumar, R. 2005. Food allergy in bronchial asthma. *Clinical Pulmonary Medicine*, 12, (3) 139-145
Ref ID: 3079

**EXC: Description and Recommendation**

Bock, S.A. 2003. Diagnostic evaluation. *Pediatrics*, 111, (6 III) 1638-1644
Ref ID: 3334

**EXC: Evaluation**

Sampson, H.A. 2003. 9. Food allergy. *Journal of Allergy and Clinical Immunology*, 111, (2 SUPPL. 2) S540-S547
Ref ID: 3374

**EXC: Recommendation**

James, J.M. 2001. Anaphylactic reactions to foods. *Immunology and Allergy Clinics of North America*, 21, (4) 653-667
Ref ID: 3507

**EXC: Recommendation**

**REFERENCE LIST OF EXCLUDED PAPERS FOR CLINICAL QUESTION 2 (non-IgE) AND REASON FOR EXCLUSION**

Anthoni, S., Savilahti, E., Rautelin, H., & Kolho, K.L. 2009. Milk protein IgG and IgA: the association with milk-induced gastrointestinal symptoms in adults. *World Journal of Gastroenterology*, 15, (39) 4915-4918
Ref ID: 9

**EXC: Adult study**

Allen, K.J., Davidson, G.P., Day, A.S., Hill, D.J., Kemp, A.S., Peake, J.E., Prescott, S.L., Shugg, A., Sinn, J.K., & Heine, R.G. 2009. Management of cow's milk protein allergy in infants and young children: an expert panel perspective. [Review] [36 refs]. *Journal of Paediatrics & Child Health*, 45, (9) 481-486
Ref ID: 12

**EXC: Review**

Benhamou, A.H., Schappi Tempia, M.G., Belli, D.C., & Eigenmann, P.A. 2009. An overview of cow's milk allergy in children. [Review] [52 refs]. *Swiss Medical Weekly*, 139, (21-22) 300-307
Ref ID: 74

**EXC: Review**

Simeone, D., Miele, E., Boccia, G., Marino, A., Troncone, R., & Staiano, A. 2008. Prevalence of atopy in children with chronic constipation. *Archives of Disease in Childhood*, 93, (12) 1044-1047
Ref ID: 158

**EXC: Not focused on diagnosis of food allergy**

Husby, S. 2008. Food allergy as seen by a paediatric gastroenterologist. [Review] [22 refs]. *Journal of Pediatric Gastroenterology & Nutrition*, 47, Suppl-52
Ref ID: 171

**EXC: Review**

Eigenmann, P.A., Beyer, K., Wesley, B.A., Lack, G., Liacouras, C.A., Hourihane, J.O., Sampson, H.A., & Sodergren, E. 2008. New visions for food allergy: an iPAC summary and future trends. [Review] [114 refs]. *Pediatric Allergy & Immunology*, 19, Suppl-39
Ref ID: 212

**EXC: Review**

Ozbek, O.Y., Canan, O., Ozcay, F., & Bilezikci, B. 2007. Cows milk protein enteropathy and granulomatous duodenitis in a newborn. *Journal of Paediatrics & Child Health*, 43, (6) 494-496
Ref ID: 383

**EXC: Case report**

Hirose, R., Yamada, T., & Hayashida, Y. 2006. Massive bloody stools in two neonates caused by cow's milk allergy. *Pediatric Surgery International*, 22, (11) 935-938
Ref ID: 465

**EXC: Case report**

Venter, C., Pereira, B., Grundy, J., Clayton, C.B., Arshad, S.H., & Dean, T. 2006. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatric Allergy & Immunology*, 17, (5) 356-363
Ref ID: 505

**EXC: Focus on prevalence (to be considered for CQ3)**

Hojsak, I., Kljaic-Turkalj, M., Misak, Z., & Kolacek, S. 2006. Rice protein-induced enterocolitis syndrome. *Clinical Nutrition*, 25, (3) 533-536
Ref ID: 515

**EXC: Case series**

De, A.P., Markowitz, J.E., Torroni, F., Caldaro, T., Pane, A., Morino, G., Wietrzykowska, R.S., di Abriola, G.F., Ponticelli, A., & Dall'Oglio, L. 2006. Paediatric eosinophilic oesophagitis: towards early diagnosis and best treatment. *Digestive & Liver Disease*, 38, (4) 245-251
Ref ID: 553

**EXC: Focus on treatment**

Augustin, M.T., Kokkonen, J., Karttunen, R., & Karttunen, T.J. 2005. Serum granzymes and CD30 are increased in children's milk protein sensitive enteropathy and celiac disease. *Journal of Allergy & Clinical Immunology*, 115, (1) 157-162
Ref ID: 709

**EXC: no mention of diagnostic tools**

Arora, A.S. & Yamazaki, K. 2004. Eosinophilic esophagitis: asthma of the esophagus?. [Review] [66 refs]. *Clinical Gastroenterology & Hepatology*, 2, (7) 523-530
Ref ID: 789

**EXC: Review/description**

Chen, M.J., Chu, C.H., Lin, S.C., Shih, S.C., & Wang, T.E. 2003. Eosinophilic gastroenteritis: clinical experience with 15 patients. *World Journal of Gastroenterology*, 9, (12) 2813-2816
Ref ID: 853

**EXC: No mention of diagnostic tools**

Bahna, S.L. 2002. Cow's milk allergy versus cow milk intolerance. [Review] [41 refs]. *Annals of Allergy, Asthma, & Immunology*, 89, (6:Suppl 1) Suppl-60
Ref ID: 974

**EXC: Review**

Turjanmaa, K. 2002. "Atopy patch tests" in the diagnosis of delayed food hypersensitivity. [Review] [10 refs]. *Allergie et Immunologie*, 34, (3) 95-97
Ref ID: 1040

**EXC: Review**

Kino, M., Kojima, T., Yamamoto, A., Sasal, M., Taniuchi, S., & Kobayashi, Y. 2002. Bowel wall thickening in infants with food allergy. *Pediatric Radiology*, 32, (1) 31-33
Ref ID: 1070

**EXC: No confirmed food allergy**

Hoffman, K.M., Ho, D.G., & Sampson, H.A. 1997. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. *Journal of Allergy & Clinical Immunology*, 99, (3) 360-366
Ref ID: 1549

**EXC: Lymphocyte culture not in scope**

Eigenmann, P.A., Belli, D.C., Ludi, F., Kahn, J.M., & Polla, B.S. 1995. In vitro lymphocyte proliferation with milk and a casein-whey protein hydrolyzed formula in children with cow's milk allergy. *Journal of Allergy & Clinical Immunology*, 96, (4) 549-557
Ref ID: 1670

**EXC: Lymphocyte proliferation not in scope**

Barau, E. & Dupont, C. 1994. Allergy to cow's milk proteins in mother's milk or in hydrolyzed cow's milk infant formulas as assessed by intestinal permeability measurements. *Allergy*, 49, (4) 295-298
Ref ID: 1740

**EXC: Case reports**

Taylor, C.J., Hendrickse, R.G., McGaw, J., & Macfarlane, S.B. 1988. Detection of cow's milk protein intolerance by an enzyme-linked immunosorbent assay. *Acta Paediatrica Scandinavica*, 77, (1) 49-54
Ref ID: 2032

**EXC: Food intolerance, test not in scope**

Khoshoo, V., Bhan, M.K., Arora, N.K., Sood, D., Kumar, R., & Stintzing, G. 1986. Leucocyte migration inhibition in cow's milk protein intolerance. *Acta Paediatrica Scandinavica*, 75, (2) 308-312
Ref ID: 2100

**EXC: Food intolerance, test not in scope**

Hindocha, P. & Wood, C.B. 1985. Histamine release from human leucocytes by IgG4 subclass in the sera of allergic children. *Allergy*, 40, (7) 523-528
Ref ID: 2107

**EXC: Not focused on diagnosis of food allergy**

Selbekk, B.H. 1985. A comparison between in vitro jejunal mast cell degranulation and intragastric challenge in patients with suspected food intolerance. *Scandinavian Journal of*

*Gastroenterology*, 20, (3) 299-303
Ref ID: 2125

**EXC: Adult study**

Atherton, D.J. 1984. Diagnosis and management of skin disorders caused by food allergy. [Review] [14 refs]. *Annals of Allergy*, 53, (6:Pt 2) t-8
Ref ID: 2147

**EXC: Review**

Ruokonen, J., Holopainen, E., Palva, T., & Backman, A. 1981. Secretory otitis media and allergy. With special reference to the cytotoxic leucocyte test. *Allergy*, 36, (1) 59-68
Ref ID: 2237

**EXC: Not focused on diagnosis**

Hammar, H. 1977. Provocation with cow's milk and cereals in atopic dermatitis. *Acta Dermato-Venereologica*, 57, (2) 159-163
Ref ID: 2286

**EXC: Challenge procedure unclear**

Shiner, M., Ballard, J., Brook, C.G., & Herman, S. 1975. Intestinal biopsy in the diagnosis of cow's milk protein intolerance without acute symptoms. *Lancet*, 2, (7944) 1060-1063
Ref ID: 2312

**EXC: Case series**

Walsh, W.E. 1975. Food allergy in atopic dermatitis. Diagnosis of food sensitivity using patch tests. *Minnesota Medicine*, 58, (4) 310-312
Ref ID: 2314

**EXC: Case series**

Bone, J., Claver, A., Guallar, I., & Plaza, A.M. 2009. Allergic proctocolitis, food-induced enterocolitis: immune mechanisms, diagnosis and treatment. *Allergologia et Immunopathologia*, 37, (1) 36-42
Ref ID: 2383

**EXC: Review**

Heine, R.G. 2008. Allergic gastrointestinal motility disorders in infancy and early childhood. *Pediatric Allergy and Immunology* , 19, (5) 383-391
Ref ID: 2594

**EXC: Case series**

Stapel, S.O., Asero, R., Ballmer-Weber, B.K., Knol, E.F., Strobel, S., Vieths, S., & Kleine-Tebbe, J. 2008. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy: European Journal of Allergy and Clinical Immunology*, 63, (7) 793-796
Ref ID: 2609

**EXC: Position paper**

Furuta, G.T., Liacouras, C.A., Collins, M.H., Gupta, S.K., Justinich, C., Putnam, P.E., Bonis, P., Hassall, E., Straumann, A., & Rothenberg, M.E. 2007. Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment. Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. *Gastroenterology*, 133, (4) 1342-1363
Ref ID: 2719

**EXC: Review**

Werfel, T., Ballmer-Weber, B., Eigenmann, P.A., Niggemann, B., Rance, F., Turjanmaa, K., & Worm, M. 2007. Eczematous reactions to food in atopic eczema: Position paper of the EAACI and GA<sup>2</sup>LEN. *Allergy: European Journal of Allergy and Clinical Immunology*, 62, (7) 723-728
Ref ID: 2759

**EXC: Position paper**

Grimshaw, E.C. 2006. Symposium on 'Nutrition and health in children and adolescents' Session 5: Risk and management of food allergy in children - Dietary management of food allergy in children. *Proceedings of the Nutrition Society*, 65, (4) 412-417
Ref ID: 2822

**EXC: Review & not focused on diagnosis**

Gray, H.C., Foy, T.M., Becker, B.A., & Knutsen, A.P. 2004. Rice-induced enterocolitis in an infant: T<sub>H</sub>1/T<sub>H</sub>2 cellular hypersensitivity and absent IgE reactivity. *Annals of Allergy, Asthma and Immunology*, 93, (6) 601-605
Ref ID: 3132

**EXC: Case report**

Niggemann, B. 2004. Role of oral food challenges in the diagnostic work-up of food allergy in atopic eczema dermatitis syndrome. *Allergy: European Journal of Allergy and Clinical Immunology, Supplement*, 59, (78) 32-34
Ref ID: 3192

**EXC: Review**

Werfel, T. 2001. Skin manifestations in food allergy. *Allergy: European Journal of Allergy and Clinical Immunology, Supplement*, 56, (67) 98-101
Ref ID: 3542

**EXC: Review**

Justinich, C.J. 2000. Food allergy and eosinophilic gastroenteropathy: A pediatric gastroenterologist's perspective. *Revue Francaise d'Allergologie et d'Immunologie Clinique*, 40, (1) 92-97
Ref ID: 3688

**EXC: Review**

Lucarelli, S., Frediani, T., Corbi, S., Del, G., I, Ranauro, E., Barbato, M., & Cardi, E. 1998. Specific IgG and IgA antibodies and related subclasses in the diagnosis of gastrointestinal disorders or atopic dermatitis due to cow's milk and egg. *International Journal of*

*Immunopathology and Pharmacology*, 11, (2) 77-85
Ref ID: 3848

**EXC: Food intolerance-not in scope**

Taylor, G.A. 1988. Cow's milk protein/soy protein allergy: Gastrointestinal imaging. *Radiology*, 167, (3) 866
Ref ID: 4362

**EXC: Editorial**

Walker-Smith, J.A., Ford, R.P.K., & Phillips, A.D. 1984. The spectrum of gastrointestinal allergies to food. *Annals of Allergy*, 53, (6 II) 629-636
Ref ID: 4411

**EXC: Review**

Basavaraju, K.P. & Wong, T. 2008. Eosinophilic oesophagitis: a common cause of dysphagia in young adults? *International Journal of Clinical Practice*, 62, (7) 1096-1108
Ref ID: 4544

**EXC: Review**

Pentiuk, S.P., Miller, C.K., & Kaul, A. 2007. Eosinophilic esophagitis in infants and toddlers. *Dysphagia (0179051X)*, 22, (1) 44-49
Ref ID: 4587

**EXC: Adult study**

Dauer, E.H., Ponikau, J.U., Smyrk, T.C., Murray, J.A., & Thompson, D.M. 2006. Airway manifestations of pediatric eosinophilic esophagitis: a clinical and histopathologic report of an emerging association. *Annals of Otology, Rhinology & Laryngology*, 115, (7) 507-518
Ref ID: 4619

**EXC: Case series**

Katzka, D.A. 2006. Eosinophilic esophagitis. *Current Opinion in Gastroenterology*, 22, (4) 429-433
Ref ID: 4620

**EXC: Review**

Sicherer, S.H. 2003. Clinical aspects of gastrointestinal food allergy in childhood. *Pediatrics*, 111, (6) 1609-1617
Ref ID: 4718

**EXC: Review**

Semeniuk, J. & Kaczmarski, M. 2006. Gastroesophageal reflux (GER) in children and adolescents with regard to food intolerance. *Advances in Medical Sciences*, 51, 321-326
Ref ID: 440

**EXC: No comparison of tests-uses food challenge to diagnose**

Baxi, S., Gupta, S.K., Swigonski, N., & Fitzgerald, J.F. 2006. Clinical presentation of patients with eosinophilic inflammation of the esophagus. *Gastrointestinal Endoscopy*, 64, (4) 473-478
Ref ID: 474

**EXC: Focus on PH probe and characteristics of EE**

Spergel, J.M., Beausoleil, J.L., Mascarenhas, M., & Liacouras, C.A. 2002. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*, 109, (2) 363-368
Ref ID: 3483

**EXC: No information given on testing as diagnosis of food allergy**

## REFERENCE LIST OF EXCLUDED PAPERS FOR CLINICAL QUESTION 3 (IgE) AND REASON FOR EXCLUSION

Eller, E., Kjaer, H.F., Host, A., Andersen, K.E., & Bindslev-Jensen, C. 2009. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy*, 64, (7) 1023-1029
Ref ID: 23
**EXC-Focus on food sensitisation**

Du, T.G., Santos, A., Roberts, G., Fox, A.T., Smith, P., & Lack, G. 2009. The diagnosis of IgE-mediated food allergy in childhood. *Pediatric Allergy & Immunology*, 20, (4) 309-319
Ref ID: 62
**EXC-Case series**

Patriarca, G., Schiavino, D., Pecora, V., Lombardo, C., Pollastrini, E., Aruanno, A., Sabato, V., Colagiovanni, A., Rizzi, A., De, P.T., Roncallo, C., Decinti, M., Musumeci, S., Gasbarrini, G., Buonomo, A., & Nucera, E. 2009. Food allergy and food intolerance: diagnosis and treatment. [Review] [59 refs]. *Internal & Emergency Medicine*, 4, (1) 11-24
Ref ID: 109
**EXC-Review**

Devillers, A.C., de Waard-van der Spek FB, Mulder, P.G., & Oranje, A.P. 2009. Delayed- and immediate-type reactions in the atopy patch test with food allergens in young children with atopic dermatitis. *Pediatric Allergy & Immunology*, 20, (1) 53-58
Ref ID: 112
**EXC-No sensitivity or specificity**

Jensen, L.B., Pedersen, M.H., Skov, P.S., Poulsen, L.K., Bindslev-Jensen, C., Andersen, S.B., & Torp, A.M. 2008. Peanut cross-reacting allergens in seeds and sprouts of a range of legumes. *Clinical & Experimental Allergy*, 38, (12) 1969-1977
Ref ID: 153
**EXC-Cross reactivity**

Vlieg-Boerstra, B.J., Duiverman, E.J., van der Heide, S., Bijleveld, C.M., Kukler, J., & Dubois, A.E. 2008. Should children with a history of anaphylaxis to foods undergo challenge testing? *Clinical & Experimental Allergy*, 38, (12) 1935-1942
Ref ID: 155
**EXC-Focus on anaphylaxis**

Nowak-Wegrzyn, A., Bloom, K.A., Sicherer, S.H., Shreffler, W.G., Noone, S., Wanich, N., & Sampson, H.A. 347. Tolerance to extensively heated milk in children with cow's milk allergy. *Journal of Allergy & Clinical Immunology*, 122, (2) 342-347

Ref ID: 208
**EXC-Focus on tolerance**

Benhamou, A.H., Zamora, S.A., & Eigenmann, P.A. 2008. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatric Allergy & Immunology*, 19, (2) 173-179
Ref ID: 284
**EXC-Review of past data on oral food challenges**

Contin-Bordes, C., Petersen, A., Chahine, I., Boralevi, F., Chahine, H., Taieb, A., Sarrat, A., Moreau, J.F., & Taupin, J.L. 2007. Comparison of ADVIA Centaur and Pharmacia UniCAP tests in the diagnosis of food allergy in children with atopic dermatitis. *Pediatric Allergy & Immunology*, 18, (7) 614-620
Ref ID: 315
**EXC-Comparison of commercially available IgE tests**

de, L.R., Perez, M.D., Sanchez, L., Lavilla, M., & Calvo, M. 2007. Development of two immunoassay formats to detect beta-lactoglobulin: influence of heat treatment on beta-lactoglobulin immunoreactivity and assay applicability in processed food. *Journal of Food Protection*, 70, (7) 1691-1697
Ref ID: 346
**EXC-Focus on specific milk proteins**

Brand, P.L., Vlieg-Boerstra, B.J., & Dubois, A.E. 2007. Dietary prevention of allergic disease in children: are current recommendations really based on good evidence?. [Review] [42 refs]. *Pediatric Allergy & Immunology*, 18, (6) 475-479
Ref ID: 347
**EXC-Review/critical appraisal**

Niggemann, B. & Beyer, K. 2007. Pitfalls in double-blind, placebo-controlled oral food challenges. [Review] [16 refs]. *Allergy*, 62, (7) 729-732
Ref ID: 376
**EXC-Review**

Wainstein, B.K., Kashef, S., Ziegler, M., Jelley, D., & Ziegler, J.B. 2007. Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children. *Clinical & Experimental Allergy*, 37, (6) 839-845
Ref ID: 386
**EXC-No sensitivity or specificity**

Wainstein, B.K., Yee, A., Jelley, D., Ziegler, M., & Ziegler, J.B. 2007. Combining skin prick, immediate skin application and specific-IgE testing in the diagnosis of peanut allergy in children. *Pediatric Allergy & Immunology*, 18, (3) 231-239
Ref ID: 399
**EXC-Validation study**

Cohen, A., Goldberg, M., Levy, B., Leshno, M., & Katz, Y. 2007. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. *Pediatric Allergy & Immunology*, 18, (3) 217-223
Ref ID: 401
**EXC-Follow-up study , no sensitivity or specificity**

Asero, R., Ballmer-Weber, B.K., Beyer, K., Conti, A., Dubakiene, R., Fernandez-Rivas, M., Hoffmann-Sommergruber, K., Lidholm, J., Mustakov, T., Oude Elberink, J.N., Pumphrey, R.S., Stahl, S.P., van, R.R., Vlieg-Boerstra, B.J., Hiller, R., Hourihane, J.O., Kowalski, M.,

Papadopoulos, N.G., Wal, J.M., Mills, E.N., & Vieths, S. 2007. IgE-mediated food allergy diagnosis: Current status and new perspectives. [Review] [68 refs]. *Molecular Nutrition & Food Research*, 51, (1) 135-147
Ref ID: 432
**EXC-Review**

Moneret-Vautrin, D.A., Morisset, M., Lemerdy, P., Hatahet, R., Frentz, P., & Cuny, J.M. 2006. Are low levels of specific IGE useful in diagnosing clinically relevant food sensitization? *European Annals of Allergy & Clinical Immunology*, 38, (9) 307-309
Ref ID: 446
**EXC-No sensitivity or specificity**

Bischoff, S.C. 2006. Food allergies. [Review] [41 refs]. *Current Gastroenterology Reports*, 8, (5) 374-382
Ref ID: 476
**EXC-Review**

Codreanu, F., Moneret-Vautrin, D.A., Morisset, M., Guenard, L., Rance, F., Kanny, G., & Lemerdy, P. 2006. The risk of systemic reactions to skin prick-tests using food allergens: CICBAA data and literature review. [Review] [25 refs]. *European Annals of Allergy & Clinical Immunology*, 38, (2) 52-54
Ref ID: 522
**EXC-Review**

Heine, R.G., Laske, N., & Hill, D.J. 2006. The diagnosis and management of egg allergy. *Current Allergy & Asthma Reports*, 6, (2) 145-152
Ref ID: 554
**EXC-Review**

Das, A., Chakraborti, P., Chatterjee, U., Monddal, G., & Chatterjee, B.P. 2005. Identification of allergens in Indian fishes: hilsa and pomfret exemplified by ELISA and immunoblotting. *Indian Journal of Experimental Biology*, 43, (12) 1170-1175
Ref ID: 596
**EXC-No sensitivity or specificity**

Kalach, N., Soulaines, P., Guerin, S., de, B.D., & Dupont, C. 2005. Time course of total and food specific IgE antibodies (Rast Fx5) in the developing allergic child. *European Annals of Allergy & Clinical Immunology*, 37, (7) 257-261
Ref ID: 612
**EXC-No sensitivity or specificity & no challenge**

Giusti, F. & Seidenari, S. 2005. Patch testing with egg represents a useful integration to diagnosis of egg allergy in children with atopic dermatitis. *Pediatric Dermatology*, 22, (2) 109-111
Ref ID: 687
**EXC-challenge procedure unclear**

Bohle, B. & Vieths, S. 2004. Improving diagnostic tests for food allergy with recombinant allergens. [Review] [82 refs]. *Methods (Duluth)*, 32, (3) 292-299
Ref ID: 833
**EXC-Review**

Bernard, H., Paty, E., Mondoulet, L., Burks, A.W., Bannon, G.A., Wal, J.M., & Scheinmann, P. 2003. Serological characteristics of peanut allergy in children. *Allergy*, 58, (12) 1285-1292

Ref ID: 864
**EXC-Focus on validation**

Caffarelli, C. & Petroccione, T. 2001. False-negative food challenges in children with suspected food allergy. *Lancet*, 358, (9296) 1871-1872
Ref ID: 1085
**EXC-No sensitivity or specificity**

Sampson, H.A. 2001. Use of food-challenge tests in children. *Lancet*, 358, (9296) 1832-1833
Ref ID: 1086
**EXC-Focus on use of challenge**

Niggemann, B., Reibel, S., Roehr, C.C., Felger, D., Ziegert, M., Sommerfeld, C., & Wahn, U. 2001. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *Journal of Allergy & Clinical Immunology*, 108, (6) 1053-1058
Ref ID: 1087
**EXC-Non-IgE**

Palosuo, K., Varjonen, E., Kekki, O.M., Klemola, T., Kalkkinen, N., Alenius, H., & Reunala, T. 2001. Wheat omega-5 gliadin is a major allergen in children with immediate allergy to ingested wheat. *Journal of Allergy & Clinical Immunology*, 108, (4) 634-638
Ref ID: 1104
**EXC-Focus on specific allergen**

Munoz-Lopez, F. 2001. Diagnosing food allergy: a test of patience. *Allergologia et Immunopathologia*, 29, (2) 45-49
Ref ID: 1120
**EXC-Editorial**

Niggemann, B. 2001. The role of the atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis. [Review] [22 refs]. *Pediatric Allergy & Immunology*, 12, Suppl-40
Ref ID: 1134
**EXC-No sensitivity or specificity**

Somos, S., Schneider, I., & Farkas, B. 2001. Immunoglobulins in tears and sera in patients with atopic dermatitis. *Allergy & Asthma Proceedings*, 22, (2) 81-86
Ref ID: 1145
**EXC-No sensitivity or specificity, focus on testing tears**

Park, J.W., Kang, D.B., Kim, C.W., koh, S.H., Yum, H.Y., Kim, K.E., Hong, C.S., & Lee, K.Y. 2000. Identification and characterization of the major allergens of buckwheat. *Allergy*, 55, (11) 1035-1041
Ref ID: 1195
**EXC-Focus on identifying allergens**

Armstrong, D. & Rylance, G. 2000. Nut allergy in children. *Archives of Disease in Childhood*, 82, (5) 428
Ref ID: 1251
**EXC-Commentary**

Pumphrey, R.S., Wilson, P.B., Faragher, E.B., & Edwards, S.R. 1999. Specific immunoglobulin E to peanut, hazelnut and brazil nut in 731 patients: similar patterns found at all ages. *Clinical & Experimental Allergy*, 29, (9) 1256-1259

Ref ID: 1300
**EXC-Record of food challenge based on clinical history**

Armstrong, D. & Rylance, G. 1999. Definitive diagnosis of nut allergy. *Archives of Disease in Childhood*, 80, (2) 175-177
Ref ID: 1330
**EXC-No sensitivity or specificity**

Rance, F. & Dutau, G. 1999. Peanut hypersensitivity in children. *Pediatric Pulmonology - Supplement*, 18, 165-167
Ref ID: 1344
**EXC-No sensitivity or specificity**

Fiocchi, A., Bouygue, B., Sala, M., & Travaini, M. 1999. The clinical interpretation of skin prick tests (SPT). *Pediatric Allergy & Immunology*, 10, (4) 274-275
Ref ID: 1364
**EXC-Focus on interpretation of SPT**

Yazicioglu, M., Baspinar, I., Ones, U., Pala, O., & Kiziler, U. 1999. Egg and milk allergy in asthmatic children: assessment by immulite allergy food panel, skin prick tests and double-blind placebo-controlled food challenges. *Allergologia et Immunopathologia*, 27, (6) 287-293
Ref ID: 1371
**EXC-No sensitivity or specificity**

de Waard-van der Spek FB, Elst, E.F., Mulder, P.G., Munte, K., Devillers, A.C., & Oranje, A.P. 1998. Diagnostic tests in children with atopic dermatitis and food allergy. *Allergy*, 53, (11) 1087-1091
Ref ID: 1398
**EXC-No sensitivity or specificity**

Bindslev-Jensen, C. & Poulsen, L.K. 1998. Accuracy of in vivo and in vitro tests. *Allergy*, 53, (46:Suppl) Suppl-4
Ref ID: 1406
**EXC-Overview**

Caffarelli, C., Romanini, E., Caruana, P., Street, M.E., & de', A.G. 1998. Clinical food hypersensitivity: the relevance of duodenal immunoglobulin E-positive cells. *Pediatric Research*, 44, (4) 485-490
Ref ID: 1418
**EXC-Focus on duodenal IgE positive cells**

Cantani, A. & Gagliesi, D. 1998. Labial food challenge in children with food allergy.[Erratum appears in Pediatr Allergy Immunol 1998 Aug;9(3):169 Note: Bagliesi D [corrected to Gagliesi D]]. *Pediatric Allergy & Immunology*, 9, (2) 103
Ref ID: 1437
**EXC-Letter**

Lin, H.Y., Shyur, S.D., Fu, J.L., & Lai, Y.C. 1998. Whey and casein specific IgE and the cow's milk challenge test for atopic children. *Chung-Hua Min Kuo Hsiao Erh Ko i Hsueh Hui Tsa Chih*, 39, (2) 99-102
Ref ID: 1447
**EXC-No sensitivity or specificity**

Rance, F. & Dutau, G. 1997. Practical strategy for the diagnosis of food allergies. [Review] [6 refs]. *Pediatric Pulmonology - Supplement*, 16, 228-229

Ref ID: 1479
**EXC-Overview of diagnosis**

Rance, F., Juchet, A., Bremont, F., & Dutau, G. 1997. Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy*, 52, (10) 1031-1035
Ref ID: 1489
**EXC-Labial challenge used**

Rance, F. & Dutau, G. 1997. Labial food challenge in children with food allergy. *Pediatric Allergy & Immunology*, 8, (1) 41-44
Ref ID: 1508
**EXC-No sensitivity or specificity**

Kanny, G., De, H.C., & Moneret-Vautrin, D.A. 1996. Sesame seed and sesame seed oil contain masked allergens of growing importance. [Review] [23 refs]. *Allergy*, 51, (12) 952-957
Ref ID: 1561
**EXC-Adult study**

de, G.H., de Jong, N.W., Vuijk, M.H., & Gerth van, W.R. 1996. Birch pollinosis and atopy caused by apple, peach, and hazelnut; comparison of three extraction procedures with two apple strains. *Allergy*, 51, (10) 712-718
Ref ID: 1575
**EXC-Adult study**

Corey, J.P. & Gungor, A. 1996. In vitro testing for immunoglobulin E-mediated food allergies. *Otolaryngology - Head & Neck Surgery*, 115, (4) 312-318
Ref ID: 1585
**EXC-Age ranged from 4 to 78 years**

Romano, A., Di, F.M., Giuffreda, F., Quaratino, D., Papa, G., Palmieri, V., Zeppilli, P., & Venuti, A. 1995. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy*, 50, (10) 817-824
Ref ID: 1640
**EXC-Mostly adults**

Norgaard, A., Bindslev-Jensen, C., Skov, P.S., & Poulsen, L.K. 1995. Specific serum IgE in the diagnosis of egg and milk allergy in adults. *Allergy*, 50, (8) 636-647
Ref ID: 1654
**EXC-Adult study**

Moneret-Vautrin, D.A., Fremont, S., Kanny, G., Dejardin, G., Hatahet, R., & Nicolas, J.P. 1995. The use of two multitests fx5 and fx10 in the diagnosis of food allergy in children: regarding 42 cases. *Allergie et Immunologie*, 27, (1) 2-6
Ref ID: 1688
**EXC-Focus on multi tests (mixture of several food allergens and give global result)**

Bock, S.A. & Sampson, H.A. 1994. Food allergy in infancy. [Review] [89 refs]. *Pediatric Clinics of North America*, 41, (5) 1047-1067
Ref ID: 1723
**EXC-Review**

Crespo, J.F., Pascual, C., Ferrer, A., Burks, A.W., Diaz Pena, J.M., & Martin, E.M. 1994. Egg white-specific IgE level as a tolerance marker in the follow up of egg allergy. *Allergy Proceedings*, 15, (2) 73-76

Ref ID: 1741
**EXC-Focus on development of tolerance**

Niggemann, B., Wahn, U., & Sampson, H.A. 1994. Proposals for standardization of oral food challenge tests in infants and children. [Review] [17 refs]. *Pediatric Allergy & Immunology*, 5, (1) 11-13
Ref ID: 1758
**EXC-Focus on how to carry out food challenge**

Wahn, U., Niggemann, B., Kleinau, I., & Beyer, K. 2000. Monitoring of inflammation during challenge tests in children. *Allergy*, 48, (17:Suppl) Suppl-9
Ref ID: 1769
**EXC-Focus on monitoring during challenge**

Du Buske, L.M. 1993. Introduction: basophil histamine release and the diagnosis of food allergy. [Review] [41 refs]. *Allergy Proceedings*, 14, (4) 243-249
Ref ID: 1774
**EXC-Review of basophil histamine release test**

Moneret-Vautrin, D.A., Kanny, G., & Halpern, G. 1993. Detection of antifood IgE by in vitro tests and diagnosis of food allergy. [Review] [33 refs]. *Allergie et Immunologie*, 25, (5) 198-204
Ref ID: 1796
**EXC-Review**

Holmes, S. 1993. A positive response to an adverse reaction. Diagnosis and management of food intolerance in children. *Professional Nurse*, 8, (7) 423-428
Ref ID: 1802
**EXC-Overview of food intolerance**

Schwartz, R.H. 660. Allergy, intolerance, and other adverse reactions to foods. [Review] [66 refs]. *Pediatric Annals*, 21, (10) 654-655
Ref ID: 1848
**EXC-Review**

Paganelli, R., Fanales-Belasio, E., & Samolewska, M. 1991. New perspectives on the screening of food allergy. [Review] [5 refs]. *Allergie et Immunologie*, 23, (10) 436-437
Ref ID: 1875
**EXC-Overview of screening for food allergy**

Bahna, S.L. 1991. New aspects of diagnosis of milk allergy in children. [Review] [25 refs]. *Allergy Proceedings*, 12, (4) 217-220
Ref ID: 1891
**EXC-Overview of diagnosis**

Oranje, A.P., Aarsen, R.S., Mulder, P.G., & Liefaard, G. 1991. Immediate contact reactions to cow's milk and egg in atopic children. *Acta Dermato-Venereologica*, 71, (3) 263-266
Ref ID: 1896
**EXC-No sensitivity or specificity**

Volonakis, M.K., Tsaptsinos, N.J., & Kontou-Fili, K. 1991. The diagnostic value of skin-prick tests in dermographic individuals. *Allergy Proceedings*, 12, (2) 103-106
Ref ID: 1903
**EXC-Review**

van Toorenenbergen, A.W., Oranje, A.P., Vermeulen, A.M., & Aarsen, R.S. 1991. IgE antibody screening in children. Evaluation of the Phadiatop Paediatric. *Allergy*, 46, (3) 180-185
Ref ID: 1906
**EXC-Comparison of different IgE tests**

Amat, P.P., Sanosa, V.J., Lluch, P.M., Malet, C.A., & Garcia Calderon, P.A. 1990. Dried fruit hypersensitivity and its correlation with pollen allergy. [Review] [52 refs]. *Allergologia et Immunopathologia*, 18, (1) 27-34
Ref ID: 1941
**EXC-Mean age is 18 years**

Moneret-Vautrin, D.A., Gueant, J.L., Abdel-Ghani, A., Maria, Y., & Nicolas, J.P. 1990. Comparative evaluation between two immunoenzymatic techniques (FAST and Phadezym) and the Phadebas RAST in food allergy. *Allergy*, 45, (2) 104-108
Ref ID: 1951
**EXC-Comparison of different IgE tests**

Malet, A., Sanosa, J., & Garcia-Calderon, P.A. 1988. Diagnosis of allergy to peach. A comparative study of "in vivo" and "in vitro" techniques. *Allergologia et Immunopathologia*, 16, (3) 181-184
Ref ID: 2017
**EXC-Study includes mostly adults**

Leinhas, J.L., McCaskill, C.C., & Sampson, H.A. 1987. Food allergy challenges: guidelines and implications. *Journal of the American Dietetic Association*, 87, (5) 604-608
Ref ID: 2069
**EXC-No sensitivity or specificity, age range 0-24 years**

Clinton, P.M., Kemeny, D.M., Amlot, P., Urbanek, R., & Lessof, M.H. 1986. Histamine release from peripheral blood leucocytes in egg-allergic patients. *Clinical Allergy*, 16, (4) 345-354
Ref ID: 2090
**EXC-Investigating histamine release**

Plebani, A., Avanzini, M.A., Scotta, M.S., Monafo, V., Giunta, A.M., Guandalini, S., Ugazio, A.G., & Burgio, R.G. 1986. Role of IgE in the pathogenesis of milk allergy in infancy: reassessment by a new ELISA technique. *Journal of Clinical & Laboratory Immunology*, 20, (2) 93-96
Ref ID: 2092
**EXC-No food challenge**

Homburger, H.A. 1986. Diagnosis of allergy: in vitro testing. [Review] [201 refs]. *Critical Reviews in Clinical Laboratory Sciences*, 23, (4) 279-314
Ref ID: 2093
**EXC-Biochemistry of test**

Plebani, A., Ugazio, A.G., Avanzini, A.M., Monafo, V., & Burgio, G.R. 1986. An enzyme-linked immunosorbent assay for cow's milk protein-specific IgE using biotinylated antigen. Avoidance of interference by specific IgG. *Journal of Immunological Methods*, 90, (2) 241-246
Ref ID: 2095
**EXC-No sensitivity or specificity**

Stricker, W.E., Anorve-Lopez, E., & Reed, C.E. 1986. Food skin testing in patients with idiopathic anaphylaxis. *Journal of Allergy & Clinical Immunology*, 77, (3) 516-519
Ref ID: 2102
**EXC-No sensitivity or specificity**

Reimann, H.J., Ring, J., Ultsch, B., & Wendt, P. 1985. Intragastral provocation under endoscopic control (IPEC) in food allergy: mast cell and histamine changes in gastric mucosa. *Clinical Allergy*, 15, (2) 195-202
Ref ID: 2127
**EXC-No sensitivity or specificity**

Martin, M.E., Guthrie, L.A., & Bock, S.A. 1984. Serum complement changes during double-blind food challenges in children with a history of food sensitivity. *Pediatrics*, 73, (4) 532-537
Ref ID: 2169
**EXC-No sensitivity or specificity**

Benincori, N., Novarino, D., Cantani, A., Di, C.C., Messina, E., Perlini, R., & Businco, L. 1983. On the reliability of RAST in childhood food allergy. *Allergologia et Immunopathologia*, 11, (4) 255-260
Ref ID: 2178
**EXC-Focus on concordance between tests**

Rottem, M., Shostak, D., & Foldi, S. 2008. The predictive value of specific immunoglobulin E on the outcome of milk agency. *Israel Medical Association Journal*, 10, (12) 862-864
Ref ID: 2384
**EXC-Focus on development of tolerance, no sensitivity or specificity values for foods**

Rance, F., Deschildre, A., Villard-Truc, F., Gomez, S.A., Paty, E., Santos, C., Couderc, L., Fauquert, J.L., De, B.J., Bidat, E., Dupont, C., Eigenmann, P., Lack, G., & Scheinmann, P. 2009. Oral food challenge in children: An expert review. *European Annals of Allergy and Clinical Immunology*, 41, (2) 35-49
Ref ID: 2424
**EXC-Overview of oral food challenges**

Ocmant, A., Mulier, S., Hanssens, L., Goldman, M., Casimir, G., Mascart, F., & Schandene, L. 2009. Basophil activation tests for the diagnosis of food allergy in children. *Clinical and Experimental Allergy*, 39, (8) 1234-1245
Ref ID: 2445
**EXC-Investigating basophil activity**

Ott, H., Baron, J.M., Heise, R., Ocklenburg, C., Stanzel, S., Merk, H.-F., Niggemann, B., & Beyer, K. 2008. Clinical usefulness of microarray-based IgE detection in children with suspected food allergy. *Allergy: European Journal of Allergy and Clinical Immunology*, 63, (11) 1521-1528
Ref ID: 2552
**EXC-Focus on specific proteins**

Canani, R.B., Ruotolo, S., Discepolo, V., & Troncone, R. 2008. The diagnosis of food allergy in children. *Current Opinion in Pediatrics*, 20, (5) 584-589
Ref ID: 2556
**EXC-Mixed IgE and non-IgE**

Werfel, T. 2008. Food allergy. [German, English]. *JDDG - Journal of the German Society of Dermatology*, 6, (7) 573-583
Ref ID: 2614
**EXC-No sensitivity or specificity**

Jacquenet, S. & Moneret-Vautrin, D.-A. 2007. Nut allergies - A review on the prevalence and on current clinical aspects. *European Annals of Allergy and Clinical Immunology*, 39, (9) 300-302

Ref ID: 2673
**EXC-Commentary**

Calvani, M., Alessandri, C., Frediani, T., Lucarelli, S., Miceli, S.S., Panetta, V., Zappala, D., & Zicari, A.M. 2008. Correlation between skin prick test using commercial extract of cow's milk protein and fresh milk and food challenge (Pediatric Allergy and Immunology (2007) 18, (583-588)). *Pediatric Allergy and Immunology*, 19, (1) 97
Ref ID: 2677
**EXC-Focus on specific milk proteins**

Mauro, C., Claudia, A., Tullio, F., Sandra, L., Stefano, M.S., Valentina, P., Daniela, Z., & Maria, Z.A. 2007. Correlation between skin prick test using commercial extract of cow's milk protein and fresh milk and food challenges. *Pediatric Allergy and Immunology*, 18, (7) 583-588
Ref ID: 2708
**EXC-Focus on mixed cow's milk proteins**

Leung, A.K.C. & Robson, W.L.M. 2006. Penile and oral angioedema associated with peanut ingestion. *Journal of the National Medical Association*, 98, (12) 2011-2012
Ref ID: 2829
**EXC-Case series**

Douglass, J.A. & O'Hehir, R.E. 2006. 1. Diagnosis, treatment and prevention of allergic disease: The basics. *Medical Journal of Australia*, 185, (4) 228-233
Ref ID: 2872
**EXC-Case series**

Kalach, N., Soulaines, P., de, B.D., & Dupont, C. 2005. A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children. *Journal of Allergy and Clinical Immunology*, 116, (6) 1321-1326
Ref ID: 2996
**EXC-Non-IgE allergy**

Sinclair, D. & Peters, S.A. 2004. The predictive value of total serum IgE for a positive allergen specific IgE result. *Journal of Clinical Pathology*, 57, (9) 956-959
Ref ID: 3177
**EXC-No food challenge and no sensitivity or specificity**

Perry, T.T., Matsui, E.C., Kay Conover-Walker, M., & Wood, R.A. 2004. The relationship of allergen-specific IgE levels and oral food challenge outcome. *Journal of Allergy and Clinical Immunology*, 114, (1) 144-149
Ref ID: 3195
**EXC-Adult and children study**

Morisset, M., Moneret-Vautrin, D.A., Kanny, G., Guenard, L., Beaudouin, E., Flabbee, J., & Hatahet, R. 2003. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: Evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clinical and Experimental Allergy*, 33, (8) 1046-1051
Ref ID: 3304
**EXC-Not focused on children**

Osterballe, M. & Bindslev-Jensen, C. 2003. Threshold levels in food challenge and specific Ige in patients with egg allergy: Is there a relationship? *Journal of Allergy and Clinical Immunology*, 112, (1) 196-201

Ref ID: 3317
**EXC-Focus on threshold levels**

Cantani, A. & Micera, M. 2003. Epidemiology of atopy in 220 children: Diagnostic reliability of skin prick tests and total and specific IgE levels. [Italian, English]. *Minerva Pediatrica*, 55, (2) 129-142
Ref ID: 3319
**EXC-No sensitivity or specificity**

Di, B.C., Angrisano, A., & Brenna, O.V. 2001. Optimization of cow's milk skin prick test. *Allergy and Clinical Immunology International*, 13, (5) 219-220
Ref ID: 3519
**EXC-Case reports**

Ibanez, S.D., Martinez, S., I, Maranoon, L.F., Fernandez-Caldas, E., Alonso, L.E., & Laso, B.T. 1999. Specific IgE determinations to crude and boiled lentil (Lens culinaris) extracts in lentil-sensitive children and controls. *Allergy: European Journal of Allergy and Clinical Immunology*, 54, (11) 1209-1214
Ref ID: 3717
**EXC-No sensitivity or specificity**

Ortiz, J.C.G., Martin, P.C., & Lopez-Asunsolo, A. 1995. Melon sensitivity shares allergens with Plantago and grass pollens. *Allergy: European Journal of Allergy and Clinical Immunology*, 50, (3) 269-273
Ref ID: 4084
**EXC-Adult study**

Crespo, J.F., Pascual, C., Burks, A.W., Heim, R.M., & Esteban, M.M. 1995. Frequency of food allergy in a pediatric population from Spain. *Pediatric Allergy and Immunology*, 6, (1) 39-43
Ref ID: 4087
**EXC-Focus on frequency of food allergy**

Taieb, A., Debons, M., & Maleville, J. 1992. The predictive value of screening tests for food allergy in infants with atopic dermatitis. *Acta Dermato-Venereologica, Supplement* (176) 141
Ref ID: 4220
**EXC-Comment**

Host, A., Husby, S., Gjesing, B., Larsen, J.N., & Lowenstein, H. 1992. Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. Levels of antibodies to whole milk protein, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy. *Allergy: European Journal of Allergy and Clinical Immunology*, 47, (3) 218-229
Ref ID: 4244
**EXC-Focus on specific proteins and clinical course of allergy**

Pastorello, E., Stocchi, L., Bigi, A., Pravettoni, V., Schilke, M.L., Valente, D., & Zanussi, C. 1989. Value and limits of diagnostic tests in food hypersensitivity. *Allergy: European Journal of Allergy and Clinical Immunology, Supplement*, 44, (9) 151-158
Ref ID: 4322
**EXC-Not exclusively children**

El, R.A., Peters, S.M., Harris, N., & Bellanti, J.A. 1989. Diagnostic value of IgG4 measurements in patients with food allergy. *Annals of Allergy*, 62, (2) 94-99
Ref ID: 4336
**EXC-Focus on IgG test**

Bahna, S.L. 1987. The dilemma of pathogenesis and diagnosis of food allergy. *Immunology and Allergy Clinics of North America*, 7, (2) 299-312
Ref ID: 4368
**EXC-Review**

Hannuksela, M. 1987. Diagnosis of dermatologic food allergy. *Annals of Allergy*, 59, (5 PART II) 153-156
Ref ID: 4373
**EXC-No sensitivity or specificity**

Bahna, S.L. 1987. Milk allergy in infancy. *Annals of Allergy*, 59, (5 PART II) 131-136
Ref ID: 4375
**EXC-Overview**

Dannaeus, A. 1987. Food allergy in infancy and children: State of the art. *Annals of Allergy*, 59, (5 PART II) 124-126
Ref ID: 4376
**EXC-Overview**

Gontzes, P. & Bahna, S.L. 1987. Food allergy for the primary care physician. *Primary Care - Clinics in Office Practice*, 14, (3) 547-558
Ref ID: 4380
**EXC-Review/overview**

Lee, L.A. & Burks, A.W. 2006. Food allergies: prevalence, molecular characterization, and treatment/prevention strategies. *Annual Review of Nutrition*, 26, 539-566
Ref ID: 4609
**EXC-Mixed non-IgE and IgE allergy**

Armentia, A., Arranz, E., Hernandez, N., Garrote, A., Panzani, R., & Blanco, A. 2008. Allergy after inhalation and ingestion of cereals involve different allergens in allergic and celiac disease. *Recent Patents on Inflammation & Allergy Drug Discovery*, 2, (1) 47-57
Ref ID: 4850
**EXC-Adults included**

Longo, G., Barbi, E., Berti, I., Meneghetti, R., Pittalis, A., Ronfani, L., & Ventura, A. 2008. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *The Journal of allergy and clinical immunology*, 121, (2) 343-347
Ref ID: 4861
**EXC-Treatment and management**

Noh, G., Ahn, H.S., Cho, N.Y., Lee, S., & Oh, J.W. 2007. The clinical significance of food specific IgE/IgG4 in food specific atopic dermatitis. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*, 18, (1) 63-70
Ref ID: 4879
**EXC-Mixture of IgE and IgG4**

Sicherer, S.H., Morrow, E.H., & Sampson, H.A. 2000. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. *The Journal of allergy and clinical immunology*, 105, (3) 582-586
Ref ID: 4963
**EXC-No sensitivity or specificity**

Wananukul, S., Chatchatee, P., & Chatproedprai, S. 2005. Food induced urticaria in children. *Asian Pacific Journal of Allergy and Immunology*, 23, (4) 175-179

Ref ID: 2984
**EXC-Included children with and without positive history for food allergy**

Isolauri, E. & Turjanmaa, K. 1996. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *The Journal of allergy and clinical immunology*, 97, (1 Pt 1) 9-15
Ref ID: 5009
**EXC-Alternative SPT threshold used**

Tainio, V.M. & Savilahti, E. 1990. Value of immunologic tests in cow milk allergy. Allergy, 45 (3) 189-196

**EXC- Identified through JAMA review-focus on other tests including IgA and IgM**

**REFERENCE LIST OF EXCLUDED PAPERS FOR CLINICAL QUESTION 4 (patient information needs) AND REASON FOR EXCLUSION**

Williams, N.A., Parra, G.R., & Elkin, T.D. 2009. Parenting children with food allergy: preliminary development of a measure assessing child-rearing behaviors in the context of pediatric food allergy. *Annals of Allergy, Asthma, & Immunology*, 103, (2) 140-145
Ref ID: 20

**EXC-Validation of parenting tool**

Gupta, R.S., Kim, J.S., Springston, E.E., Pongracic, J.A., Wang, X., & Holl, J. 2009. Development of the Chicago Food Allergy Research Surveys: assessing knowledge, attitudes, and beliefs of parents, physicians, and the general public. *BMC Health Services Research*, 9, 142
Ref ID: 21

**EXC-Focus on validating survey**

Noimark, L., Gardner, J., & Warner, J.O. 2009. Parents' attitudes when purchasing products for children with nut allergy: a UK perspective. *Pediatric Allergy & Immunology*, 20, (5) 500-504
Ref ID: 24

**EXC-Children had previous diagnosis of food allergy**

Gupta, R.S., Kim, J.S., Springston, E.E., Smith, B., Pongracic, J.A., Wang, X., & Holl, J. 2009. Food allergy knowledge, attitudes, and beliefs in the United States. *Annals of Allergy, Asthma, & Immunology*, 103, (1) 43-50
Ref ID: 25

**EXC-Focus on knowledge assessment of non-specific population of adults**

Allen, C.W., Kemp, A.S., & Campbell, D.E. 2009. Dietary advice, dietary adherence and the acquisition of tolerance in egg-allergic children: a 5-yr follow-up. *Pediatric Allergy & Immunology*, 20, (3) 213-218
Ref ID: 37

**EXC-Children already diagnosed with food allergy and focus on achieving tolerance**

DunnGalvin, A., Gaffney, A., & Hourihane, J.O. 2009. Developmental pathways in food allergy: a new theoretical framework. *Allergy*, 64, (4) 560-568
Ref ID: 44

**EXC-focus on developmental pathways-not focused on patient information needs**

Gunnarsson, N. & Hyden, L.C. 2009. Organizing allergy and being a 'good' parent: parents' narratives about their children's emerging problems. *Health: an Interdisciplinary Journal for the Social Study of Health, Illness & Medicine*, 13, (2) 157-174
Ref ID: 48

**EXC-Parent perspectives of food allergy, not focused on patient information needs**

Yu, J.E., Kumar, A., Bruhn, C., Teuber, S.S., & Sicherer, S.H. 2008. Development of a food allergy education resource for primary care physicians. *BMC Medical Education*, 8, 45
Ref ID: 75

**EXC-Focus on education needs of primary care practitioners**

Hu, W., Grbich, C., & Kemp, A. 2008. When doctors disagree: a qualitative study of doctors' and parents' views on the risks of childhood food allergy. *Health Expectations*, 11, (3) 208-219
Ref ID: 84

**EXC- Children already diagnosed with food allergy**

Lebovidge, J.S., Timmons, K., Rich, C., Rosenstock, A., Fowler, K., Strauch, H., Kalish, L.A., & Schneider, L.C. 2008. Evaluation of a group intervention for children with food allergy and their parents. *Annals of Allergy, Asthma, & Immunology*, 101, (2) 160-165
Ref ID: 90

**EXC- Children already diagnosed with food allergy with focus on coping and management**

Klinnert, M.D. & Robinson, J.L. 2008. Addressing the psychological needs of families of food-allergic children. [Review] [36 refs]. *Current Allergy & Asthma Reports*, 8, (3) 195-200
Ref ID: 101

**EXC-Review article focusing on management**

Pouessel, G., Deschildre, A., Castelain, C., Sardet, A., Sagot-Bevenot, S., de Sauve-Boeuf, A., Thumerelle, C., & Santos, C. 2006. Parental knowledge and use of epinephrine auto-injector for children with food allergy. *Pediatric Allergy & Immunology*, 17, (3) 221-226
Ref ID: 123

**EXC- Children already diagnosed with food allergy with focus on knowledge of epi pen**

Kalb, C. 2007. Fear and allergies in the lunchroom. *Newsweek*, 150, (19) 42-47
Ref ID: 130

**EXC-Overview of allergies**

Uguz, A., Lack, G., Pumphrey, R., Ewan, P., Warner, J., Dick, J., Briggs, D., Clarke, S., Reading, D., & Hourihane, J. 2005. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clinical & Experimental Allergy*, 35, (6) 746-750
Ref ID: 151

**EXC-Focus on clinical characteristics of food allergy**

Akeson, N., Worth, A., & Sheikh, A. 2007. The psychosocial impact of anaphylaxis on young people and their parents. *Clinical & Experimental Allergy*, 37, (8) 1213-1220
Ref ID: 155

**EXC-Focus on anaphylaxis not food allergy**

Pearce, L. 2007. Allergies in a nutshell. *Nursing Standard*, 21, (40) 18-19
Ref ID: 161

**EXC-Review article focusing on specific nurse**

Weinbaum, H. 2007. Strategies for managing students with food allergies. *School Nurse News*, 24, (3) 10
Ref ID: 167

**EXC-Inaccessible**

Patel, B.M., Bansal, P.J., & Tobin, M.C. 2006. Management of anaphylaxis in child care centers: evaluation 6 and 12 months after an intervention program. *Annals of Allergy, Asthma, & Immunology*, 97, (6) 813-815
Ref ID: 185

**EXC-Focus on education of childcare staff**

Eigenmann, P.A., Caubet, J.C., & Zamora, S.A. 2006. Continuing food-avoidance diets after negative food challenges. *Pediatric Allergy & Immunology*, 17, (8) 601-605
Ref ID: 188

**EXC-Children had previously diagnosed food allergy**

Ko, J., Lee, J.I., Munoz-Furlong, A., Li, X.M., & Sicherer, S.H. 2006. Use of complementary and alternative medicine by food-allergic patients. *Annals of Allergy, Asthma, & Immunology*, 97, (3) 365-369
Ref ID: 195

**EXC-Children already diagnosed with food allergy, focus on prevalence of the use of complementary and alternative medicines**

McDuffie, A.F. 1978. Prevent shock. Learn to recognize severe feeding intolerance early. [Review] [78 refs]. *Advance for Nurse Practitioners*, 10, (4) 61-64
Ref ID: 206

**EXC-Inaccessible**

Sampson, M.A., Munoz-Furlong, A., & Sicherer, S.H. 2006. Risk-taking and coping strategies of adolescents and young adults with food allergy. *Journal of Allergy & Clinical Immunology*, 117, (6) 1440-1445
Ref ID: 216

**EXC-Children already diagnosed with food allergy with focus on coping strategies-management**

Thompson, M.M., Tofte, S.J., Simpson, E.L., & Hanifin, J.M. 2006. Patterns of care and referral in children with atopic dermatitis and concern for food allergy. *Dermatologic Therapy*, 19, (2)

91-96
Ref ID: 221

**EXC-Focus on patterns of care not patient information needs**

Bollinger, M.E., Dahlquist, L.M., Mudd, K., Sonntag, C., Dillinger, L., & McKenna, K. 2006. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma, & Immunology*, 96, (3) 415-421
Ref ID: 227

**EXC-Focus on impact of food allergy on daily activities, outside diagnostic process**

de Vries, T.W., Wierdsma, N., van, E.J., & Heijmans, H.S. 2001. Dieting in children referred to the paediatric outpatient clinic. *European Journal of Pediatrics*, 160, (10) 595-598
Ref ID: 236

**EXC-Not focused on information needs-focus on prevalence of dieting**

Simons, E., Weiss, C.C., Furlong, T.J., & Sicherer, S.H. 2005. Impact of ingredient labeling practices on food allergic consumers. *Annals of Allergy, Asthma, & Immunology*, 95, (5) 426-428
Ref ID: 247

**EXC-Children already diagnosed with food allergy**

Nicol, A.A. 2005. Understanding peanut allergy: an overview of medical and lifestyle concerns. [Review] [34 refs]. *Advance for Nurse Practitioners*, 13, (10) 63-68
Ref ID: 255

**EXC-Inaccessible**

Wahn, U., Staab, D., & Nilsson, L. 1999. Atopic eczema: how to tackle the most common atopic symptom. [Review] [21 refs]. *Pediatric Allergy & Immunology*, 10, (12:Suppl) Suppl-23
Ref ID: 270

**EXC-Management of atopic eczema**

Kim, J.S., Sinacore, J.M., & Pongracic, J.A. 2005. Parental use of EpiPen for children with food allergies. *Journal of Allergy & Clinical Immunology*, 116, (1) 164-168
Ref ID: 272

**EXC-Children had physician diagnosed food allergy**

Bansal, P.J., Marsh, R., Patel, B., & Tobin, M.C. 2005. Recognition, evaluation, and treatment of anaphylaxis in the child care setting. *Annals of Allergy, Asthma, & Immunology*, 94, (1) 55-59
Ref ID: 289

**EXC-Focus on knowledge of childcare staff**

Hiscock, H. & Jordan, B. 2004. 1. Problem crying in infancy. [Review] [32 refs]. *Medical Journal of Australia*, 181, (9) 507-512
Ref ID: 299

**EXC-Not focused on food allergy, focus on crying in general**

Wang, J., Sicherer, S.H., & Nowak-Wegrzyn, A. 2004. Primary care physicians' approach to food-induced anaphylaxis: a survey. *Journal of Allergy & Clinical Immunology*, 114, (3) 689-691
Ref ID: 304

**EXC-Focus on knowledge and education of health care providers**

Aardoom, H.A., Hirasing, R.A., Rona, R.J., Sanavro, F.L., van den Heuvel, E.W., & Leeuwenburg, J. 1997. Food intolerance (food hypersensitivity) and chronic complaints in children: the parents' perception. *European Journal of Pediatrics*, 156, (2) 110-112
Ref ID: 307

**EXC-Focus on prevalence of food intolerance**

Lyons, A.C. & Forde, E.M. 2004. Food allergy in young adults: perceptions and psychological effects. *Journal of Health Psychology*, 9, (4) 497-504
Ref ID: 315

**EXC-Focus on effects of diagnosed food allergy**

Kapoor, S., Roberts, G., Bynoe, Y., Gaughan, M., Habibi, P., & Lack, G. 2004. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy*, 59, (2) 185-191
Ref ID: 330

**EXC-Children already diagnosed with food allergy**

Roesler, T.A., Barry, P.C., & Bock, S.A. 1994. Factitious food allergy and failure to thrive. *Archives of Pediatrics & Adolescent Medicine*, 148, (11) 1150-1155
Ref ID: 332

**EXC-Children were previously assessed for food allergy**

Hughes, J.L. & Stewart, M. 2003. Self-administration of epinephrine in children: a survey of current prescription practice and recommendations for improvement. *Ulster Medical Journal*, 72, (2) 80-85
Ref ID: 337

**EXC-Focus on prescription of epi pen**

Munoz-Furlong, A. 2003. Daily coping strategies for patients and their families. [Review] [24 refs]. *Pediatrics*, 111, (6:Pt 3) t-61
Ref ID: 354

**EXC-Focus on management and coping strategies**

Christie, L., Hine, R.J., Parker, J.G., & Burks, W. 2002. Food allergies in children affect nutrient intake and growth. *Journal of the American Dietetic Association*, 102, (11) 1648-1651
Ref ID: 372

**EXC-Focus on impact of food allergy on growth and nutrition**

Van Asperen, P.P., Lewis, M., Rogers, M., Kemp, A.S., & Thompson, S. 1983. Experience with an elimination diet in children with atopic dermatitis. *Clinical Allergy*, 13, (5) 479-485
Ref ID: 383

**EXC-Focus on elimination diet as diagnostic tool-no focus on patient information needs**

Eigenmann, P.A. & Zamora, S.A. 2002. An internet-based survey on the circumstances of food-induced reactions following the diagnosis of IgE-mediated food allergy. *Allergy*, 57, (5) 449-453
Ref ID: 384

**EXC-Focus on identifying risk situations with children with IgE mediated allergy-not patient info needs**

Watura, J.C. 2002. Nut allergy in schoolchildren: a survey of schools in the Severn NHS Trust. *Archives of Disease in Childhood* , 86, (4) 240-244
Ref ID: 386

**EXC-Focus on training of school staff and management in schools**

Lipscomb, P. 1980. Nursing care study. Food allergy: no milk today. *Nursing Mirror*, 151, (12) 37-38
Ref ID: 387

**EXC-Case report of intolerance**

Blyth, T.P. & Sundrum, R. 2002. Adrenaline autoinjectors and schoolchildren: a community based study. *Archives of Disease in Childhood*, 86, (1) 26-27
Ref ID: 389

**EXC-Focus on use of epi-pen**

Moneret-Vautrin, D.A., Kanny, G., Morisset, M., Flabbee, J., Guenard, L., Beaudouin, E., & Parisot, L. 2001. Food anaphylaxis in schools: evaluation of the management plan and the efficiency of the emergency kit. *Allergy*, 56, (11) 1071-1076
Ref ID: 396

**EXC-Focus on management in schools**

Eggesbo, M., Botten, G., & Stigum, H. 2001. Restricted diets in children with reactions to milk and egg perceived by their parents. *Journal of Pediatrics*, 139, (4) 583-587
Ref ID: 402

**EXC-Focus on risk factors for restricted diet**

Weinberger, M. 2008. Pediatric asthma and related allergic and nonallergic diseases: Patient-oriented evidence-based essentials that mattter. *Pediatric Health*, 2, (5) 631-650
Ref ID: 432

**EXC-Review of asthma in children**

Rance, P. & Bidat, E. 2000. Educational program for children with peanut allergy. *Allergie et Immunologie*, 32, (5) 209-211
Ref ID: 442

**EXC-Review article**

Young, M.C., Munoz-Furlong, A., & Sicherer, S.H. 2009. Management of food allergies in schools: A perspective for allergists. *Journal of Allergy and Clinical Immunology*, 124, (2) 175-

182
Ref ID: 446

**EXC-Management in schools**

De, B.R., Fitzsimons, R., & Brathwaite, N. 2009. Eight myths from the food allergy clinic. *Current Allergy and Clinical Immunology*, 22, (3) 104-108
Ref ID: 456

**EXC-Focus on food allergy myths**

Ebisawa, M. 2009. How to cope with allergic diseases at schools in Japan - From the standpoint of a pediatric allergist. *Japan Medical Association Journal*, 52, (3) 164-167
Ref ID: 457]

**EXC-Management in schools**

Grigg, A., Hanson, C., & Davis, C.M. 2009. Cashew allergy compared to peanut allergy in a us tertiary care center. *Pediatric Asthma, Allergy and Immunology*, 22, (3) 101-104
Ref ID: 464

**EXC-Focus on characteristics of allergy**

Hefle, S.L., Furlong, T.J., Niemann, L., Lemon-Mule, H., Sicherer, S., & Taylor, S.L. 2007. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *Journal of Allergy and Clinical Immunology*, 120, (1) 171-176
Ref ID: 519

**EXC-Focus on accuracy of food labels**

Hon, K.-L., Leung, T.-F., Lam, M.-C., Wong, K.-Y., Chow, C.-M., Ko, W.-S., Fok, T.-F., & Leung, A.K.C. 2007. Eczema exacerbation and food atopy beyond infancy: How should we advise Chinese parents about dietary history, eczema severity, and skin prick testing? *Advances in Therapy*, 24, (2) 223-230
Ref ID: 521

**EXC-Focus on nature of avoidance diets and association with SPT and other foods**

Brydon, M. 1993. The effectiveness of a peripatetic allergy nurse practitioner service in managing atopic allergy in general practice--a pilot study. *Clinical & Experimental Allergy*, 23, (12) 1037-1044
Ref ID: 555

**EXC-Focus on management**

Carroll, P., Caplinger, K.J., & France, G.L. 1992. Guidelines for counseling parents of young children with food sensitivities. *Journal of the American Dietetic Association*, 92, (5) 602-603
Ref ID: 563

**EXC-Review article with limited patient information focus**

Gowland, M.H. 2001. Food allergen avoidance - The patient's viewpoint. *Allergy: European Journal of Allergy and Clinical Immunology, Supplement*, 56, (67) 117-120
Ref ID: 662

**EXC-Review**

Mascarenhas, S. & Aszkenasy, O.M. 2009. EpiPen training provided to parents of children with food allergies
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Archives of Disease in Childhood*, 94, (1) 76
Ref ID: 664

**EXC-Children already diagnosed with food allergy-focus on management (epi pen training)**

Malloy, C. & Yousef, E. 2009. To test or not to test: parent information for discussions of food allergy and autism.
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Delaware medical journal*, 81, (10) 357-359
Ref ID: 701

**EXC-Focus on food allergy and behaviour**

Perry, T.T. 2009. Dietary advice, dietary adherence and the acquisition of tolerance in egg-allergic children: A 5-yr follow-up
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatrics*, 124, (SUPPL. 2) S119-S120
Ref ID: 705

**EXC-Focus on acquisition of tolerance**

Hu, W., Loblay, R., Ziegler, J., & Kemp, A. 2008. Attributes and views of families with food allergic children recruited from allergy clinics and from a consumer organization
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatric Allergy and Immunology*, 19, (3) 264-269
Ref ID: 748

**EXC-Children already diagnosed with food allergy**

Spergel, J.M. & Shuker, M. 2008. Nutritional Management of Eosinophilic Esophagitis
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Gastrointestinal Endoscopy Clinics of North America*, 18, (1) 179-194
Ref ID: 759

**EXC-Review article focusing on management**

Marklund, B., Wilde-Larsson, B., Ahlstedt, S., & Nordstrom, G. 2007. Adolescents' experiences of being food-hypersensitive: A qualitative study
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *BMC Nursing*, 6, 2007. Article Number: 8. Date of Publication: 2007.,
Ref ID: 763

**EXC-Not focused on patient information needs**

Marklund, B., Ahlstedt, S., & Nordstrom, G. 2007. Food hypersensitivity and quality of life
Factors associated with maternal dietary intake, feeding and weaning practices, and the

development of food hypersensitivity in the infant. *Current Opinion in Allergy and Clinical Immunology* , 7, (3) 279-287
Ref ID: 792

**EXC-Focus on diagnosed food hypersensitivity and quality of life**

Davis, K.L. & Mikita, C.P. 2006. Parental use of EpiPen for children with food allergies: Commentary
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatrics*, 118, (SUPPL. 1) S18-S19
Ref ID: 807

**EXC-use of epi pen outside diagnosis**

Nowak-Wegrzyn, A. 2006. Allergic reactions in the community: A questionnaire survey of members of the anaphylaxis campaign: Commentary
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatrics*, 118, (SUPPL. 1) S18
Ref ID: 808

**EXC-Focus on frequency and nature of reactions**

Sone, K.D., Twarog, F.J., Raiselis, S., Bailey, E., & Schneider, L.C. 2004. Parental coping with childhood food allergies [Abstract]. *Journal of Allergy and Clinical Immunology*, 113, (2 Suppl) S149
Ref ID: 833

**EXC-Abstract**

Macdougall, C. & Etuwewe, O. 2005. How dangerous is food allergy?
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Current Paediatrics*, 15, (3) 228-232
Ref ID: 902

**EXC-Review article, not focused on patient information needs**

Baumgart, K., Brown, S., Gold, M., Kemp, A., Loblay, R., Loh, R., Mitrou, D., Mullins, R., Peake, J., Ruhno, J., Said, M., Sinclair, J., Smith, V., Smith, W., Solley, G., Soutter, V., Tang, M., & Ziegler, J. 2004. ASCIA guidelines for prevention of food anaphylactic reactions in schools, preschools and child-care centres
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Journal of Paediatrics and Child Health*, 40, (12) 669-671
Ref ID: 922

**EXC-Management in schools**

Munoz-Furlong, A. 2004. Food allergy in schools: Concerns for allergists, pediatricians, parents, and school staff
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Annals of Allergy, Asthma and Immunology*, 93, (5 SUPPL.) S47-S50
Ref ID: 927

**EXC-Management in schools**

Sicherer, S.H. 2003. How to recognize and manage anaphylaxis: The key points
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Journal of Respiratory Diseases - For Pediatricians*, 5, (5) 191-198
Ref ID: 973

**EXC-Not specific to food allergy, anaphylaxis in general**

Bock, S.A. 2003. Diagnostic evaluation
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Pediatrics*, 111, (6 III) 1638-1644
Ref ID: 986

**EXC-Review not focused on information needs**

Joshi, P., Mofidi, S., & Sicherer, S.H. 2002. Interpretation of commercial food ingredient labels by parents of food-allergic children
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Journal of Allergy and Clinical Immunology*, 109, (6) 1019-1021
Ref ID: 1008

**EXC-Children already diagnosed with food allergy**

Clegg, S.K. & Ritchie, J.M. 2001. 'Epipen' training: A survey of the provision for parents and teachers in West Lothian
Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant. *Ambulatory Child Health*, 7, (3-4) 169-175
Ref ID: 1017

**EXC-Focus on epi pen training with children with previous diagnosis of food allergy**

**REFERENCE LIST OF EXCLUDED PAPERS FOR CLINICAL QUESTION 5 (Referrals to secondary or tertiary care) AND REASON FOR EXCLUSION**

Assa'ad, A. 2009. Eosinophilic gastrointestinal disorders. [Review] [23 refs]. *Allergy & Asthma Proceedings*, 30, (1) 17-22
Ref ID: 23

**EXC-Overview of GI disorders**

Goodwin, H. 2008. Eczema and allergy: how useful is allergy testing? *Paediatric Nursing*, 20, (10) 25-30
Ref ID: 36

**EXC-Focus on value of allergy testing**

Simpson, C.R., Newton, J., Hippisley-Cox, J., & Sheikh, A. 2008. Incidence and prevalence of multiple allergic disorders recorded in a national primary care database. *Journal of the Royal Society of Medicine* , 101, (11) 558-563
Ref ID: 40

**EXC-Prevalence of allergies**

Husby, S. 2008. Food allergy as seen by a paediatric gastroenterologist. [Review] [22 refs]. *Journal of Pediatric Gastroenterology & Nutrition*, 47, Suppl-52
Ref ID: 44

**EXC-Overview of food allergy with no focus on referral**

Lack, G. 2008. Clinical practice. Food allergy. [Review] [55 refs]. *New England Journal of Medicine*, 359, (12) 1252-1260
Ref ID: 48

**EXC-Overview of food allergy with no focus on referral**

Tsang, K. 2008. Anaphylaxis: assessing patients with allergies. [Review] [21 refs]. *Emergency Nurse*, 16, (5) 24-29
Ref ID: 49

**EXC-Case study with focus on anaphylaxis**

Kim, J.S. 2008. Food allergy: diagnosis, treatment, prognosis, and prevention. [Review] [39 refs]. *Pediatric Annals*, 37, (8) 546-551
Ref ID: 53

**EXC-No mention of referrals, focus on standards for allergy clinics**

Wrobel, J.P., O'Hehir, R.E., & Douglass, J.A. 2008. Food allergy in adults. [Review] [19 refs]. *Australian Family Physician*, 37, (4) 222-226
Ref ID: 66

**EXC-Adult review**

Noimark, L. & Cox, H.E. 2008. Nutritional problems related to food allergy in childhood. *Pediatric Allergy & Immunology*, 19, (2) 188-195
Ref ID: 70

**EXC-Case series focusing on effects on nutrition**

Cruz, N.V., Wilson, B.G., Fiocchi, A., Bahna, S.L., & America College of Allergy, A.a.I.A.R.t.F.C. 2007. Survey of physicians' approach to food allergy, Part 1: Prevalence and manifestations. *Annals of Allergy, Asthma, & Immunology*, 99, (4) 325-333
Ref ID: 81

**EXC-Focus on knowledge and attitudes of allergists and non-allergists-no mention of referrals**

Katelaris, C.H. & Peake, J.E. 2006. 5. Allergy and the skin: eczema and chronic urticaria. [Review] [38 refs]. *Medical Journal of Australia*, 185, (9) 517-522
Ref ID: 107

**EXC-Focus on management of eczema**

Fasano, M.B. 2006. Dermatologic food allergy. [Review] [39 refs]. *Pediatric Annals*, 35, (10) 727-731
Ref ID: 112

**EXC-Focus on symptoms of food allergy**

Thompson, M.M., Tofte, S.J., Simpson, E.L., & Hanifin, J.M. 2006. Patterns of care and referral in children with atopic dermatitis and concern for food allergy. *Dermatologic Therapy*, 19, (2) 91-96
Ref ID: 124

**EXC-No mention of when referrals to secondary care should occur**

Ewing, W.M. & Allen, P.J. 2005. The diagnosis and management of cow milk protein intolerance in the primary care setting. [Review] [36 refs]. *Pediatric Nursing*, 31, (6) 486-493
Ref ID: 134

**EXC-Focus on food intolerance**

Hiscock, H. & Jordan, B. 2004. 1. Problem crying in infancy. [Review] [32 refs]. *Medical Journal of Australia*, 181, (9) 507-512
Ref ID: 162

**EXC-Not specific to food allergy**

Leung, D.Y., Nicklas, R.A., Li, J.T., Bernstein, I.L., Blessing-Moore, J., Boguniewicz, M., Chapman, J.A., Khan, D.A., Lang, D., Lee, R.E., Portnoy, J.M., Schuller, D.E., Spector, S.L., & Tilles, S.A. 2004. Disease management of atopic dermatitis: an updated practice parameter. Joint Task Force on Practice Parameters. *Annals of Allergy, Asthma, & Immunology*, 93, (3:Suppl 2) Suppl-21
Ref ID: 166

**EXC-Focus on management of atopic dermatitis**

Bellou, A., Manel, J., Samman-Kaakaji, H., de Korwin, J.D., Moneret-Vautrin, D.A., Bollaert, P.E., & Lambert, H. 2003. Spectrum of acute allergic diseases in an emergency department: an evaluation of one years' experience. *Emergency Medicine (Fremantle, W*, 15, (4) 341-347
Ref ID: 186

**EXC-Patients admitted to ED (secondary care)**

Burks, W. 2003. Skin manifestations of food allergy. [Review] [78 refs]. *Pediatrics*, 111, (6:Pt 3) t-24
Ref ID: 193

**EXC-Overview of skin related symptoms and food allergy**

Sicherer, S.H. 2003. Clinical aspects of gastrointestinal food allergy in childhood. [Review] [81 refs]. *Pediatrics*, 111, (6:Pt 3) t-16
Ref ID: 194

**EXC-Describing GI disorders**

Orchard, D. 2001. Rashes in infants. Pitfalls and masquerades. [Review] [5 refs]. *Australian Family Physician*, 30, (11) 1047-1051
Ref ID: 235

**EXC-Review of rashes-not specific to food allergy**

Leicht, S. & Hanggi, M. 2001. Atopic dermatitis. How to incorporate advances in management. [Review] [12 refs]. *Postgraduate Medicine*, 109, (6) 119-127
Ref ID: 245

**EXC-Management**

Hide, D.W. 1997. Early intervention for the prevention of atopic dermatitis. [Review] [19 refs]. *Pediatric Allergy & Immunology* , 8, (1) 7-10
Ref ID: 299

**EXC-Focus on prevention of atopic dermatitis**

Stewart, A.G. & Ewan, P.W. 1996. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *Qjm*, 89, (11) 859-864
Ref ID: 308

**EXC-Patients in A&E (secondary care)**

1995. Good allergy practice--standards of care for providers and purchasers of allergy services within the National Health Service. Royal College of Physicians and Royal College of Pathologists. *Clinical & Experimental Allergy*, 25, (7) 586-595
Ref ID: 321

**EXC-No mention of referrals, focus on standards for allergy clinics**

Yocum, M.W. & Khan, D.A. 1994. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clinic Proceedings*, 69, (1) 16-23
Ref ID: 337

**EXC-Adult based study**

Kurscheid, T. & Holschneider, A.M. 1993. Necrotizing enterocolitis (NEC)--mortality and long-term results. *European Journal of Pediatric Surgery*, 3, (3) 139-143
Ref ID: 341

**EXC-Focus on necrotizing enterocolitis**

Guillet, G. & Guillet, M.H. 1992. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Archives of Dermatology*, 128, (2) 187-192
Ref ID: 348

**EXC-Focus on natural history of FA in those with atopic dermatitis-no mention of referrals**

Apter, A.J., Rothe, M.J., & Grant-Kels, J.M. 1991. Allergy consultation in the management of atopic dermatitis. *Pediatric Dermatology*, 8, (4) 341-347
Ref ID: 350

**EXC-Secondary care referral**

Gontzes, P. & Bahna, S.L. 1987. Food allergy for the primary care physician. [Review] [33 refs]. *Primary Care; Clinics in Office Practice*, 14, (3) 547-558
Ref ID: 369

**EXC-Overview of food allergies with no mention of referral**

Berman, B.A., Kniker, W.T., & Cohen, G.A. 1986. An allergist's view of atopic dermatitis. [Review] [62 refs]. *Dermatologic Clinics*, 4, (1) 55-66
Ref ID: 374

**EXC-Review of atopic dermatitis with no focus on referrals**

Eastham, E.J. & Walker, W.A. 1977. Effect of cow's milk on the gastrointestinal tract: a persistent dilemma for the pediatrician. *Pediatrics*, 60, (4) 477-481
Ref ID: 394

**EXC-Focus on nature of allergies**

Johnstone, D.E. 1977. The natural history of allergic disease in children. [Review] [48 refs]. *Annals of Allergy*, 38, (6) 387-393
Ref ID: 396

**EXC-Focus on natural history of allergies-not specific to food allergy**

Eade, O.E. & Wright, R. 1976. Dietary hypersensitivity: the gastroenterologist's view. [Review] [50 refs]. *Journal of Human Nutrition*, 30, (3) 157-163
Ref ID: 398

**EXC-Not focused on referral**

Johnstone, D.E. 1972. Office management of food allergy in children. [Review] [35 refs]. *Annals of Allergy*, 30, (4) 173-180
Ref ID: 403

**EXC-Overview of food allergy-no mention of referral**

BOWER, B.D. 1964. Child care in general practice. Diarrhoea, acute and chronic. *British Medical Journal*, 2, (5424) 1577-1579
Ref ID: 409

**EXC-Not specific to food allergy**

Franciosi, J.P., Brown-Whitehorn, T., & Liacouras, C.A. 2008. Pediatric eosinophilic esophagitis: Epidemiology, diagnosis and treatment. *Current Pediatric Reviews*, 4, (4) 266-269
Ref ID: 413

**EXC-Inaccessible**

Tatachar, P. & Kumar, S. 2008. Food-induced anaphylaxis and oral allergy syndrome. *Pediatrics in Review*, 29, (4) e23-e27
Ref ID: 419

**EXC-Inaccessible**

Dietrich, J.J., Quinn, J.M., & England, R.W. 2009. Reasons for outpatient consultation in allergy/immunology. *Allergy and Asthma Proceedings*, 30, (1) 69-74
Ref ID: 421

**EXC-Not specific to food allergy, no focus on when to refer**

Rance, F., Deschildre, A., Villard-Truc, F., Gomez, S.A., Paty, E., Santos, C., Couderc, L., Fauquert, J.L., De, B.J., Bidat, E., Dupont, C., Eigenmann, P., Lack, G., & Scheinmann, P. 2009. Oral food challenge in children: An expert review. *European Annals of Allergy and Clinical Immunology*, 41, (2) 35-49
Ref ID: 435

**EXC-Focus on nature of food challenge**

Liem, J.J., Huq, S., Kozyrskyj, A.L., & Becker, A.B. 2008. Should younger siblings of peanut-allergic children be assessed by an allergist before being fed peanut? *Allergy, Asthma and Clinical Immunology*, 4, (4) 144-149
Ref ID: 440

**EXC-Focus on risk factors for assessment**

Martelli, A., Ghiglioni, D., Sarratud, T., Calcinai, E., Veehof, S., Terracciano, L., & Fiocchi, A. 2008. Anaphylaxis in the emergency department: A paediatric perspective. *Current Opinion in Allergy and Clinical Immunology*, 8, (4) 321-329
Ref ID: 443

**EXC-Inaccessible**

Leung, T.N.H., Au, T.S., Fung, A.Y.P., Ho, K.M., Pei, A.Y.S., Sugunan, V.K., Yeung, C.K., & Young, B.W.Y. 2009. Review and recommendations on clinical management of childhood atopic eczema. *Hong Kong Journal of Dermatology and Venereology*, 17, (3) 136-143
Ref ID: 459

**EXC-Inaccessible**

Levy, M.L., Walker, S., Woods, A., & Sheikh, A. 2009. Service evaluation of a UK primary care-based allergy clinic: Quality improvement report. *Primary Care Respiratory Journal*, 18, (4) 313-319
Ref ID: 465

**EXC-Not specific to food allergy**

Falconer, J. 2009. GOR and GORD in infants. *Community practitioner : the journal of the Community Practitioners' & Health Visitors' Association*, 82, (10) 42-43
Ref ID: 467

**EXC-Overview of management of GOR and GORD**

Tillie-Leblond, I., Magnan, A., Pauli, G., Vervloet, D., Wallaert, B., Didier, A., Ameille, J., Godard, P., & the group of experts 2008. Asthma and allergy: Short texts and recommendations of the expert conference of the French Speaking Pneumology Society (SPLF), in partnership with the French Society of Allergology and Clinical Immunology (SFAIC), the French Society of Occupational Medicine (SFMT) and the "Asthma-Allergy" association. *Respiratory Medicine*, 102, (10) 1483-1493
Ref ID: 480

**EXC-Focus on asthma, no mention of when to refer to secondary care**

Alfaham, M. 2008. The development of an allergy service in secondary care. *Paediatrics and Child Health*, 18, (7) 340-343
Ref ID: 490

**EXC-Focus on secondary care**

Mukoyama, T., Nishima, S., Arita, M., Ito, S., Urisu, A., Ebisawa, M., Ogura, H., Kohno, Y., Kondo, N., Shibata, R., Hurusho, M., Mayumi, M., & Morikawa, A. 2007. Guidelines for diagnosis and management of pediatric food allergy in Japan. *Allergology International*, 56, (4) 349-361
Ref ID: 504

**EXC-Overview of food allergy in Japan- no mention of when to refer to secondary care**

Ferreira, C.T. & Seidman, E. 2007. Food allergy: A practical update from the gastroenterological viewpoint. [Portuguese, English]. *Jornal de Pediatria*, 83, (1) 7-20
Ref ID: 534

**EXC-Not focused on referrals**

Brown, S.G.A., Mullins, R.J., & Gold, M.S. 2006. 2. Anaphylaxis: Diagnosis and management. *Medical Journal of Australia*, 185, (5) 283-289
Ref ID: 544

**EXC-Management of anaphylaxis**

Warner, J.O. 2006. Turf wars in paediatric allergy. *Pediatric Allergy and Immunology*, 17, (6) 393-394
Ref ID: 545

**EXC-Editorial with no mention of when to refer to secondary care**

Akdis, C.A., Akdis, M., Bieber, T., Bindslev-Jensen, C., Boguniewicz, M., Eigenmann, P., Hamid, Q., Kapp, A., Leung, D.Y.M., Lipozencic, J., Luger, T.A., Muraro, A., Novak, N., Platts-Mills, T.A.E., Rosenwasser, L., Scheynius, A., Simons, F.E.R., Spergel, J., Turjanmaa, K., Wahn, U., Weidinger, S., Werfel, T., & Zuberbier, T. 2006. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL consensus report. *Allergy: European Journal of Allergy and Clinical Immunology*, 61, (8) 969-987
Ref ID: 551

**EXC-Focus on diagnosis and treatment of atopic dermatitis**

Pirson, F. 2006. Food allergy: A challenge for the clinician. *Acta Gastro-Enterologica Belgica*, 69, (1) 38-42
Ref ID: 558

**EXC- Overview of food allergy with no focus on referral**

Wang, J., Sicherer, S.H., & Nowak-Wegrzyn, A. 2004. Primary care physicians' approach to food-induced anaphylaxis: A survey [2]. *Journal of Allergy and Clinical Immunology*, 114, (3) 689-691
Ref ID: 598

**EXC-Focus on knowledge of primary care physicians**

Clark, A.T. & Ewan, P.W. 2002. The prevention and management of anaphylaxis in children. *Current Paediatrics*, 12, (5) 370-375
Ref ID: 636

**EXC-Management of anaphylaxis**

Quinn, J.M. 2000. Pediatric inpatient consultation of allergy/immunology. *Pediatric Asthma, Allergy and Immunology*, 14, (4) 293-299
Ref ID: 669

**EXC-Inpatient referrals**

Wanderer, A.A., Bernstein, I.L., Goodman, D.L., Nicklas, R.A., Li, J.T., Berger, W.E., Dykewicz, M.S., Fineman, S.M., Lee, R.E., Portnoy, J.M., Schuller, D.E., & Spector, S.L. 2000. The diagnosis and management of urticaria: A practice parameter. *Annals of Allergy, Asthma and Immunology* , 85, (6 II) viii-544
Ref ID: 670

**EXC-Inaccessible**

Cerio, R. 1997. Therapy of atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology*, 8, (SUPPL. 1) S6-S10
Ref ID: 715

**EXC-Treatment/ management**

Hill, D.J. & Hosking, C.S. 1995. The cow milk allergy complex: Overlapping disease profiles in infancy. *European Journal of Clinical Nutrition*, 49, (SUPPL. 1) S1-S12
Ref ID: 729

**EXC-Overview of milk allergy with no focus on referral**

Dannaeus, A. 1987. Food allergy in infancy and children: State of the art. *Annals of Allergy*, 59, (5 PART II) 124-126
Ref ID: 757

**EXC-Review-no mention of referral**

Vlieg-Boerstra, B.J., Duiverman, E.J., van der Heide, S., Bijleveld, C.M.A., Kukler, J., & Dubois, A.E.J. 2007. DBPCFCs in children with a history of anaphylaxis to foods are they necessary and safe? [Abstract]. *Journal of Allergy and Clinical Immunology*, 119, (1 Suppl) S239
Ref ID: 790

**EXC-Focus on need for DBPCFC**

Hummell, D.S. 2008. Common allergy disorders. *Contemporary Pediatrics*, 25, (8) 40-NaN
Ref ID: 1033

**EXC-Not specific to food allergy**

Meyer, R. 2008. Infant feeding: new guidelines for managing cow's milk allergy in infants. *Journal of Family Health Care*, 18, (1) 27-31
Ref ID: 1036

**EXC-Management**

**REFERENCE LIST OF EXCLUDED PAPERS FOR ALTERNATIVE TESTS AND REASON FOR EXCLUSION**

Worm, M., Vieth, W., Ehlers, I., Sterry, W., & Zuberbier, T. 2001. Increased leukotriene production by food additives in patients with atopic dermatitis and proven food intolerance. *Clinical & Experimental Allergy*, 31, (2) 265-273
Ref ID: 1161
**EXC-not diagnosis**

Schmitt, W.H., Jr. & Leisman, G. 1998. Correlation of applied kinesiology muscle testing findings with serum immunoglobulin levels for food allergies. *International Journal of Neuroscience*, 96, (3-4) 237-244
Ref ID: 1391
**EXC-no reference standard used**

Gilbert, P. 1996. Common feeding problems in babies and children: 2. [Review] [3 refs]. *Professional Care of Mother & Child*, 8, (3) 63-64
Ref ID: 1410
**EXC-not focused on diagnosis of food allergy**

Olszewski, A., Pons, L., Moutete, F., Aimone-Gastin, I., Kanny, G., Moneret-Vautrin, D.A., & Gueant, J.L. 1998. Isolation and characterization of proteic allergens in refined peanut oil. *Clinical & Experimental Allergy*, 28, (7) 850-859
Ref ID: 1428
**EXC-not focused on diagnosis of food allergy**

Moneret-Vautrin, D.A., Kanny, G., & Halpern, G. 1993. Detection of antifood IgE by in vitro tests and diagnosis of food allergy. [Review] [33 refs]. *Allergie et Immunologie*, 25, (5) 198-204
Ref ID: 1796
**EXC-review/descriptive paper**

Hill, D.J., Ball, G., & Hosking, C.S. 1988. Clinical manifestations of cows' milk allergy in childhood. I. Associations with in-vitro cellular immune responses. *Clinical Allergy*, 18, (5) 469-479
Ref ID: 2005
**EXC-not focused on diagnosis**

Clinton, P.M., Kemeny, D.M., Amlot, P., Urbanek, R., & Lessof, M.H. 1986. Histamine release from peripheral blood leucocytes in egg-allergic patients. *Clinical Allergy*, 16, (4) 345-354
Ref ID: 2090
**EXC-no reference test used**

Khoshoo, V., Bhan, M.K., Arora, N.K., Sood, D., Kumar, R., & Stintzing, G. 1986. Leucocyte migration inhibition in cow's milk protein intolerance. *Acta Paediatrica Scandinavica*, 75, (2) 308-312
Ref ID: 2100
**EXC-no reference test used to confirm food allergy**

Hindocha, P. & Wood, C.B. 1985. Histamine release from human leucocytes by IgG4 subclass in the sera of allergic children. *Allergy*, 40, (7) 523-528
Ref ID: 2107
**EXC-no reference test used**

Ruokonen, J., Paganus, A., & Lehti, H. 1982. Elimination diets in the treatment of secretory otitis media. *International Journal of Pediatric Otorhinolaryngology*, 4, (1) 39-46
Ref ID: 2221
**EXC-focus on treatment**

Omura, Y. 1981. New simple early diagnostic methods using Omura's "Bi-Digital O-Ring Dysfunction Localization Method" and acupuncture organ representation points, and their applications to the "drug & food compatibility test" for individual organs and to auricular diagnosis of internal organs--part I. *Acupuncture & Electro-Therapeutics Research*, 6, (4) 239-254
Ref ID: 2225
**EXC-descriptive paper**

Ashkenazi, A., Levin, S., Idar, D., Or, A., Barzilai, N., & Handzel, Z.T. 1981. Effect of gluten-free diet on an immunological assay for coeliac disease. *Lancet*, 1, (8226) 914-916
Ref ID: 2236
**EXC-focus on coeliac disease**

Ruokonen, J., Holopainen, E., Palva, T., & Backman, A. 1981. Secretory otitis media and allergy. With special reference to the cytotoxic leucocyte test. *Allergy*, 36, (1) 59-68
Ref ID: 2237
**EXC-no reference test used to confirm food allergy**

Bock, S.A., Buckley, J., Holst, A., & May, C.D. 1977. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clinical Allergy*, 7, (4) 375-383
Ref ID: 2284
**EXC-focus on skin prick tests**

Zizka, J., Hrdy, J., Lodinova-Zadnikova, R., Kocourkova, I., Novotna, O., Sterzl, I., & Prokesova, L. 2007. Effect of breast milk of healthy and allergic mothers on in vitro stimulation of cord blood lymphocytes. *Pediatric Allergy and Immunology*, 18, (6) 486-494
Ref ID: 2733
**EXC-not focused on diagnosis**

Pramod, S.N., Venkatesh, Y.P., & Mahesh, P.A. 2007. Potato lectin activates basophils and mast cells of atopic subjects by its interaction with core chitobiose of cell-bound non-specific immunoglobulin E. *Clinical and Experimental Immunology*, 148, (3) 391-401
Ref ID: 2782
**EXC-not focused on diagnosis**

Jarvinen, K.-M., Laine, S., & Suomalainen, H. 2000. Defective tumour necrosis factor-alpha production in mother's milk is related to cow's milk allergy in suckling infants. *Clinical and Experimental Allergy*, 30, (5) 637-643
Ref ID: 3669
**EXC-not focused on diagnosis**

Kjeldsen-Kragh, J. 1999. Rheumatoid arthritis treated with vegetarian diets. *American Journal of Clinical Nutrition*, 70, (3 SUPPL.) 594S-600S
Ref ID: 3744
**EXC-focus on rheumatoid arthritis**

Szepfalusi, Z., Todoran, L., Elsasser, S., Jagdt, B., Wank, H., & Urbanek, R. 1999. Cord blood leucocytes/basophils produce and release sulfidoleucotrienes in response to allergen stimulation. *Clinical and Experimental Allergy*, 29, (3) 382-387
Ref ID: 3793
**EXC-not focused on diagnosis**

Terwee, C.B. 2008. Succesful treatment of food allergy with Nambudripad's Allergy Elimination Techniques (NAET) in a 3-year old: A case report. *Cases journal*, 1, (1) 166
Ref ID: 4482
**EXC-treatment**

Ko, J., Lee, J.I., MuÃ±oz-Furlong, A., Li, X., & Sicherer, S.H. 2006. Use of complementary and alternative medicine by food-allergic patients. *Annals of Allergy, Asthma & Immunology*, 97, (3) 365-370
Ref ID: 4604
**EXC-focus on use and attitudes towards tests rather than diagnostic accuracy**

Schmidt, E. 2006. Supplemental perioperative oxygen at 80% FIO2 reduced surgical site infections in elective colorectal surgery. *Evidence-Based Nursing*, 9, (2) 52-53
Ref ID: 4630
**EXC-focus on colorectal resection not food allergy**

Williamson, C.S. 2006. Nutrition in pregnancy. *Nutrition Bulletin*, 31, (1) 28-60
Ref ID: 4634
**EXC-review/descriptive paper**

Pozler, O., Parizek, J., Chylkova, V., Nozicka, Z., Fixa, B., Belobradkova, I., & Kubikova, K. 1989. Immunological aspects of diagnosis of celiac sprue in children.[Erratum appears in Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove 1989;32(3):following 351]. *Sbornik Vedeckych Praci Lekarske Fakulty Karlovy Univerzity V Hradci Kralove*, 32, (2) 169-233
Ref ID: 5210
**EXC-not focused on diagnosis of food allergy**

# Food Allergy in Children Appendix 3

## Health Economics

Appendix 3.0 – Non-IgE-mediated food allergy – Cost effectiveness analysis

Appendix 3.1 – IgE-mediated food allergy – Cost effectiveness analysis

# Review of resource use studies for the diagnosis non-IgE-mediated food allergies in children

| **Sladkevicius E, Nagy E, Lack G et al (2010) Resource implications and budget impact of managing cow milk allergy in the UK. Journal of medical economics 13(1): 119-28** | | |
|---|---|---|
| Guideline topic: Food allergy | | Question no:2 |
| Check list completed by Prashanth Kandaswamy | | |
| | | |
| **Section 1: Applicability** | **Yes/ Partly/ No/ Unclear/ NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Yes | Infants with CMA |
| 1.2 Are the interventions appropriate for the guideline? | Yes | |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Yes | |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | Yes | |
| 1.5 Are all direct health effects on individuals included? | N/A | |
| 1.6 Are both costs and health effects discounted at an annual rate of 3.5%? | No | Not necessary given time horizon |
| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | N/A | |
| 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers? | N/A | |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public? | N/A | |
| 1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable<br>There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Applicable | | |
| Other comments | | |

| **Section 2: Study limitations (the level of methodological quality)**<br>*This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline* | **Yes/Partly/No/ Unclear/NA Comments** | **Comments** |
|---|---|---|
| 2.1<br>Does the model structure adequately reflect the nature of the health condition under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long | Yes | A longer time horizon |

| | | |
|---|---|---|
| to reflect all important differences in costs and outcomes? | | would be preferable, but current time horizon appears acceptable |
| 2.3 Are all important and relevant health outcomes included? | Partly | |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative treatment effects from the best available source? | Yes | |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | NHS specific costs used |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | N/A | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Is there no potential conflict of interest? | Partly | Funded by CMA milk maker, but not directly to authors |
| 2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations<br>Minor Limitations | | |

# Testing for IgE-mediated food allergy – Cost effectiveness analysis

## *Introduction*

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on the diagnosis of food allergy in children. This analysis focuses on IgE-mediated food allergy. What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in coming to recommendations. This analysis has been conducted according to NICE methods outlined in the Guide to the methods of technology appraisals, 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost effectiveness analysis to follow) in the methodology utilised. It is advised that the full guideline should be read as full definitions of terminology will be given there.

Given the paucity of available information GDG opinion was used in the identification and selection of papers and data. In addition, the results presented should be considered exploratory given the significant issues in the quality of data and assumptions made.

## *Contents*

## *Decision Problem*

This guideline is examining two main types of food allergy. Non-IgE-mediated food allergy, examined in appendix 3.0. The other is IgE-mediated food allergy. The decision problem for this type of food allergy is described in Table 1 Decision problem.

**Table 1 Decision problem**

| | **Scope** | **Approach taken** |
|---|---|---|
| **Population** | Children with suspected IgE-mediated food allergy | Children with suspected peanut allergy |
| **Interventions** | Skin prick tests or<br>Serum specific IgE blood test<br>Atopic patch test<br>Double blind placebo-controlled food challenge (DBPCFC) | GP diagnosis plus<br>Skin prick tests or<br>Specific IgE blood test |
| **Comparators** | No test | GP diagnosis alone<br>Refer to secondary care |
| **Outcome(s)** | Costs, QALYs and Cost per QALY | Cost per QALY |

### Population

The scope specifies several potential age groups and several food allergies including egg, nut, soya and so on. However, to construct an analysis for each food allergy would be time consuming and also potentially unnecessary. Therefore, only peanut allergies will be considered. This is because it is the most common IgE-mediated food allergy, therefore data should be available. It is also closely associated with the risk of major reactions.

The GDG concluded that only people with a positive clinical history should be tested. Therefore, the populations are those children whose clinical history suggests they have a food allergy. It is likely that it will be possible to extrapolate the results for this population to other allergic diseases.

As will become clearer the majority of children are initially diagnosed at a very young age. Data is available from Ewan et al 1996 which follows children from 1 year to school age (5 years). Therefore, for the model the population will be assumed to be one year old children.

### Interventions

The GDG concluded on the basis of the clinical evidence that the only viable tests are the skin prick tests and specific IgE blood tests.

### Comparators

The current clinical option is GP diagnosis alone. There is the possibility of referring all children to secondary care however, for implementation reasons this is not possible as the waiting time to see an allergist is already significant. In addition, secondary care diagnosis is beyond the scope of this guideline.

### Outcomes

For non-IgE-mediated allergies a cost consequence approach was considered appropriate. However, in this case the expected treatment is an elimination diet. This will not be associated with significant costs and therefore, the benefits to patients of accurate diagnosis need to be accounted for.

## *Literature reviews*

### Cost effectiveness studies

No cost effectiveness studies for IgE-mediated food allergy were identified by the literature search therefore a De Novo model will be required.

### Treatment pathway

The analysis is examining the value of testing after a GP takes a detailed clinical history. The GDG concluded that testing should be used to confirm a positive diagnosis. If the test is positive treatment should commence, if the test is negative than referral to secondary care is recommended since some other underlying condition may be causing the symptoms. The pathways are summarised in Table 2.

**Table 2 Testing pathways - food allergies**

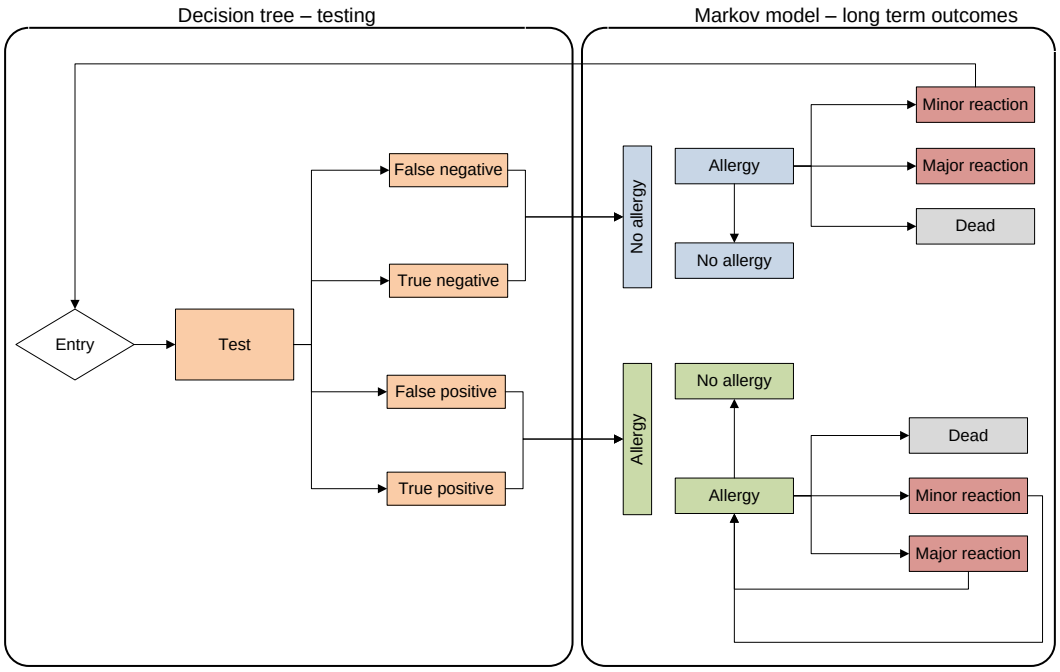
| Clinical history | Test | Result |
|---|---|---|
| Positive | Positive | Initiate treatment |
| | Negative | Refer to secondary care |
| Negative | No test | No action |

Therefore, people enter the analysis after a positive clinical history. As a consequence those with a negative history will not be considered.

## Model structure

A decision tree will be used to model the diagnosis of food allergy in children and a subsequent Markov model will be constructed to explore the long-term outcomes. The model structure is outlined in Figure 1.

**Figure 1 Model structure**




The decision tree section of the model is concerned with the proportion of people who are correctly diagnosed with food allergy. People are divided into standard diagnostic categories: True positive, false positive, true negative and false negative. These affect which diagnostic category they are classified as and any potential future management.

The Markov model follows people from their diagnosis. People diagnosed with a food allergy and have an allergy (true positive) will be assumed to stay on an elimination diet and either have a minor, major or fatal allergic reaction. There is also the possibility that they will become desensitised to the allergen and potentially lose their allergy. The false positives will remain in the allergy diagnostic state unless they are retested at a later date.

True negatives remain in the no allergy state and do not move. False negatives are all assumed to have a minor, major or fatal reaction and re-enter the testing schedule.

As this guideline is only examining the diagnosis of food allergy in children rather than the management we will only examine in detail the diagnosis aspect. However, we will explore the impact of various management issues in sensitivity analysis.

**Assumptions**

- False negatives re-enter testing the next cycle

This assumption is to account for people returning to their GPs if their symptoms have not resolved. It is assumed to happen in the next cycle since the person is not undergoing an active elimination diet. In reality people may take issues into their own hands and initiate elimination diets without the input of a GP or dietician which could have negative effects on the child's health. In addition, they may go straight to secondary care or have the tests done privately. It is not possible to estimate all these potential outcomes therefore, to account for potential NHS resources being used it will be assumed that they re-enter the testing schedule. This will therefore mean that extra resources will be spent on diagnosis.

- False positives have same quality of life as true positives

This is based on the fact that the main impact of allergies on quality of life is from the anxiety of dealing with a major event and also trying to actively avoid events.

- True negatives or false positives do not develop allergies

The majority of allergies develop in the early years of life and therefore, it is unlikely that this is significant factor.

- No age related mortality

For simplicity there will be no other cause mortality. This should not be a major factor given the short time horizon and also the age of the population being tests.

Time horizon

Given the uncertainty over the management of food allergies in this population especially over retesting the base analysis will use a time horizon of 4 years which corresponds with studies that have followed patients with peanut allergies from diagnosis to school age. However, longer time horizons and retesting will be examined in scenario analysis to examine its effect on the cost effectiveness results.

## *Inputs*

### Transitions

The following sections outline the key transitions in the model and their source. It was not possible in the time available to conduct a full review. So papers were identified from the literature search that examined natural history and epidemiological studies. The issue here is that the search was not designed to find these studies and therefore, important information may have been excluded. However, for this analysis which is primarily explorative the papers identified should be sufficient. In addition, all values are validated by the GDG.

### The proportion of allergies detected by clinical history

Evidence from Sampson and Ho 1997 indicated that in a population of people identified with a clinical history plus a skin prick test and/or a blood test that only 49% were confirmed as having a allergy to peanuts after a food challenge. From experience an estimate of 60% was suggested by the GDG. These figures appear to have validity as a history taking is likely to be very sensitive but not very specific. Given the difficultly in accurately estimating this figure, 49% was used in the base case and then varied in sensitivity analysis.

### Sensitivity and specificity of the tests

The estimates for the sensitivity and specificity of the tests were obtained from the clinical review. It should be noted the papers were not of high quality and had several methodological limitations. Therefore, the estimates referred to here should be treated with caution and comparisons between tests should not be undertaken. In addition, this meant that no evidence synthesis could be undertaken such as a meta-analysis. The two methods available would be to use the estimates from the highest quality paper that matches the decision

problem or to use the midpoint from all the studies. For the base case the study which most reflected the population in the decision problem and also using the Youden index as a measure of quality. A sensitivity analysis will be run based on the midpoint from the studies.

### Skin prick tests

Based on the evidence review the sensitivity of skin prick test varied from 80 to 100% and for specificity the values varied from 29 to 72%. The highest quality paper was Rance et al 2002. This paper included testing for peanut allergies and all were confirmed with a DBPCFC. It also had the highest Youden score for the tests look at peanut allergies. The base case estimates are summarized in Table 3 along with the midpoints that will be examined in sensitivity analysis.

**Table 3 Skin prick test - test accuracy**

| | Base value | Midpoint | Lower value | Upper value |
|---|---|---|---|---|
| Sensitivity | 100% | 90% | 80% | 100% |
| Specificity | 66.1% | 50.5% | 29% | 72% |

### IgE Blood tests

Based on the evidence review the sensitivity of IgE blood tests varied from 25 to 97% and for specificity the values varied from 38 to 100%. The highest quality paper was Rance et al 2002. The base case estimates are summarized in Table 4 along with the midpoints that will be examined in sensitivity analysis.

**Table 4 IgE blood test - test accuracy**

| | Base value | Midpoint | Lower value | Upper value |
|---|---|---|---|---|
| Sensitivity | 96.6% | 61% | 25% | 97% |
| Specificity | 62.4% | 69% | 38% | 100% |

### Secondary care – double blind food challenge

The double blind food challenge is often considered the gold standard test for food allergies in children and as such is associated with near 100% sensitivity and specificity. The GDG noted that often secondary care did not always achieve this due to pressure on resources. Therefore, the base case will assume a 98% sensitivity and specificity. These values will be varied in sensitivity analysis.

**Probability of minor reaction**

Fajt and Green 2008 suggested that 75% of patients with a known peanut allergy experience a reaction caused by inadvertent exposure. With an annual incidence estimated at around 14%. In the model the value of 14% is used.

**Probability of major reaction**

Hourihane 2006 reported that 229 children were admitted to hospital between 1998 and 2001. According to Gupta et al 2004 11.8 per 100,000 0-14 year olds were admitted to hospital for allergies. This gives a probability of 0.000118.

**Probability of fatal reaction**

Hourihane 2006 in a review article on the dangers of food allergy estimated that 1 death in every 830,000 is due to food allergies each year. This gives a probability of 0.0000012.

**Desensitisation of allergies**

The estimate for the proportion whose allergy regresses was obtained from Ewan et al 1996. This paper was identified by daisy chaining from the natural history papers which all referred to this paper. Ewan et al 1996 followed a series of children with nut allergies from diagnosis (average age 1 year old) till school age (5 years old). At the end of the study 20% of the children had become desensitised to nuts. This figure of 20% is confirmed by Hourihane et al 1998 and Skolnick et al 2001. To convert these into three monthly transitions to fit the cycle length the following formula will be used where p is the yearly probability (Briggs et al 2003):

$$3\ monthly\ probability = 1 - e^{((\ln 1-P)*(1/4))}$$

The final transition matrix is presented in Table 5

**Table 5 Final transition matrix for long term outcomes up to 5 years of age**

| | Allergy | No Allergy | Confirmed Allergy | Confirmed No Allergy | Minor | Major | Dead |
|---|---|---|---|---|---|---|---|
| Allergy | 0 | 0.01385 | 0 | 0 | 0.986 | 0.00003 | 0.0000012 |
| No Allergy | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Confirmed Allergy | 0 | 0.01385 | 0.949 | 0 | 0.037 | 0.00003 | 0.0000003 |
| Confirmed | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No Allergy | | | | | | | |
| Minor | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Major | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Dead | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

## *Quality of life review*

### Literature

A search for quality of life papers identified 38 papers. The papers can be split into 4 groups. 11 papers were concerned with the development of quality of life measures for people with food allergies. These shall not be considered here. The other 3 groups include 16 papers which review the quality of life of children with food allergies including qualitative studies and narratives. 5 papers examined the affect of food allergies on children and their parents/carers. Only three papers collected quality of life information in people with food allergies with instruments appropriate for the calculation of QALYs (that is an instrument on a 0 to 1 scale with 0 equaling dead and 1 perfect health). Given resource constraints we shall review the papers that collected data suitable for the calculation of QALYs and the papers examining the link between children and their parents/carers.

### Utilities

The three studies identified all used the Health utility index (HUI) 3 for estimating quality of life. This instrument is explicitly mentioned in the NICE methods guide as appropriate for calculating quality of life.

One study however, Mo et al 2004, used the HUI 3 to calculate the odd ratios to determine what factors were linked to quality of life. It unfortunately did not report the absolute figures and as such was not appropriate for the calculation of QALYs. The remaining two studies are summarised in Table 6.

**Table 6 Quality of life papers that collected data suitable for QALYs**

| Study | Country | Population | Age groups considered? | Baseline | Allergy |
|---|---|---|---|---|---|
| Mittmann et al 1999 | Canada | Cross sectional survey of people aged 12 to | 12-19<br>20-29<br>30-39<br>40-49<br>50-59 | 0.94 (0.074)<br>0.94 (0.069)<br>0.94 (0.08)<br>0.93 (0.08)<br>0.92 (0.07) | 0.90 (0.13)<br>0.91 (0.12)<br>0.89 (0.14)<br>0.84 (0.19)<br>0.83 (0.17) |

| | | | | | |
|---|---|---|---|---|---|
| | | 80+ n = 17624 collected 1994 | 60-69<br>70-79<br>80+ | 0.91 (0.079)<br>0.91 (0.1)<br>0.88 (0.1) | 0.78 (0.18)<br>0.78 (0.18)<br>0.64 (0.23) |
| Mittmann et al 2001 | Canada | Cross sectional study of population n = 47534 collected 1996 | No specific age group considered | 0.953 | 0.951 |

Both the Mittmann papers were based on the National population health survey, a prospective national survey of community living Canadians. As can be seen only the Mittmann et al 1999 paper includes stratification by age. The main issues with these papers include the fact that it is a cross sectional survey of a Canadian population and therefore, may not be representative of the UK population. In addition, the 1999 paper is based on the preliminary weights developed for the HUI 3 and therefore, may now be considered inaccurate. Finally while the papers provide some data on the population of interest, it excludes the majority of the population (0 to 12) of interest.

It should be noted that collecting data in very young children is very difficult due to ethical and methodological difficulties. Therefore, the values from Mittmann et al 1999 will be used in the base case and alternative values will be examined in sensitivity analysis.

### The quality of life of parents/carers

An overview of the included studies is provided in Table 7.

**Table 7 Quality of life papers that examined link between parents/carers and child food allergy**

| Studies | Type | Population | Quality of life scales? |
|---|---|---|---|
| King et al 2009 | Cross sectional questionnaire study | 46 families with one child aged 8-12 with an allergy and one older sibling. | World health Organisation Quality of life scale, and a stress and anxiety scale. |
| Marklund et al 2006 | Postal survey | Parents of 134 school children (8-19) (represents a 74% response rate) | CHQ-PF28 and study specific questionnaire |
| Gupta et al 2008 | Focus groups | Parents with children with an allergy (3 groups), physicians (3 groups) and general public (2 groups) | Interviews |
| Bollinger et al 2006 | Questionnaires given to families attending a | 87 families with a child between 0 and 18and spoke English | Food allergy Impact scale (study specific questionnaire) |

| | | | |
|---|---|---|---|
| | university based allergy clinic | | |
| Kilgallen and Gibney et al 1996 | Interview assisted questionnaire in maternity hospital | Parents of 600 children between 0 to 48 months. | Not specifically collected. |

Kilgallen and Gibney et al 1996 specifically examined the perception of food allergy by parents and children rather than quality of life.

None of these papers included data appropriate to calculate QALYs. They were reviewed to see if any of the papers provided an indication of the magnitude difference between the affect of allergies on children and adults. All the papers concluded that the parent's quality of life is adversely affected by a child with an allergy. However, none concluded on the absolute magnitude of the decrement. Therefore, the affect of this additional effect will be explored in sensitivity analysis.

**Minor reactions**

No suitable values were identified for minor reactions however; it is likely that the quality of life associated with allergies takes this into account as almost 75% of people with a peanut allergy have some form of reaction. Therefore, the utility associated with allergy will be extrapolated to minor reactions.

**Major reactions**

For major reactions it is very difficult to collect a utility for this event given its severity and potential impact on the patient. Therefore, other NICE guidance was searched for utility estimates. Omalizumab for uncontrolled asthma in children (appraisal ongoing) reports a value of 0.326 for exacerbations requiring hospitalisation. An asthma exacerbation often requires a long hospital stay and the GDG commented that this was also true for major allergic reactions to foods. The GDG considered that it was appropriate to extrapolate this value to this condition.

## *Costs*

The only appropriate costing paper identified by the search was Sladkevicius et al 2010 which specifically examined cow's milk allergy, a mainly non-IgE-mediated food allergy. Sladkevicius et al 2010 obtained all the costs from

public sources such as the NHS reference costs and the PSSRU. Therefore, these references will be used to identify the key costs in the analysis.

The key costs that will be considered are described in the following sections.

### Diagnostic

GP history taking

All GP appointments are meant to take 10-15 minutes and therefore according to the PSSRU the cost of a GP appointment is £180.

This cost is applied to all diagnostic strategies to represent the initial history taking; this is used particularly when taking into account retesting.

Skin prick tests

There is no appropriate NHS reference cost for skin prick testing and therefore a micro costing approach was taken. Communication with manufacturers and GDG members produced a list of components and prices which are summarised in Table 8.

**Table 8 Cost breakdown for skin prick tests**

| Component | Base case | Lower limit | Upper limit | Source | Distribution |
|---|---|---|---|---|---|
| Cost of vials | £17 | 12 | £34 | GDG | Uniform |
| No of drops per vial | 80 | 60 | 100 | GDG | Uniform |
| Lancet (200) | 12 | 6 | 18 | GDG | Uniform |
| Controls x2 | 12 | 6 | 18 | GDG | Uniform |
| Nurse time minutes | 30 | 20 | 90 | GDG | Uniform |
| Nurse cost per minute | 0.483 | 0.242 | 0.725 | PSSRU 2009 | Uniform |
| GP time minutes | 10 | 5 | 45 | GDG | Uniform |
| GP cost per minute | 3 | 1.5 | 4.5 | PSSRU 2009 | Uniform |
| No of allergies tested for | 8 | 5 | 16 | GDG | Uniform |

For GPs to run a service in their practices they would need to train a nurse to carry out the procedure and to buy the items in bulk. Therefore, setup costs could be considered. However, the way these should be considered is not clear. The usual way to model setup costs is to annualize them and then include them in the costing. It would then be possible to estimate the number

of people required to make the test cost effective. However, in this case there are no capital costs, only consumerables. Therefore, the numbers tested each year should be considered. To do this in a traditional Markov model is not simple unless we include a dynamic population. This level of complexity is not possible in the current analysis and therefore, will not be considered explicitly.

IgE blood tests

Similarly for the Skin prick tests there was no publically available reference cost for carrying out IgE blood tests in primary care. Therefore, again a mixture of communication with pathology labs and GDG members were used to generate the estimates. The values chosen are summarised in Table 9.

**Table 9 IgE blood tests cost breakdown**

| Component | Base case | Lower limit | Upper limit | Source | Distribution |
|---|---|---|---|---|---|
| Cost per allergy tested for | 12 | 6 | 18 | GDG | Uniform |
| No of allergies tested for | 8 | 5 | 16 | GDG | Uniform |
| GP time minutes | 10 | 5 | 45 | PSSRU 2009 | Uniform |
| GP cost per minute | 3 | 1.5 | 4.5 | PSSRU 2009 | Uniform |
| Nurse time minutes | 2 | 1 | 10 | GDG | Uniform |
| HCP cost per minute | 0.483 | 0.242 | 0.725 | PSSRU 2009 | Uniform |

Secondary care diagnosis

The diagnostic test carried out in secondary care is also assumed to be a double blind oral food challenge. According to information from Manchester hospitals two appointments will be required the first to put someone on a food elimination diet the second to actually carry out the oral food challenge. This could take the form of two outpatient appointments. The suitable code appears to be a consultant led appointment for paediatric clinical immunology and allergy (service code 255) with the corresponding cost of £576 (£288 for each appointment).

**Markov model**

Confirmed Allergy (including true and false positives)

For the base case it will be assumed that there apart from a food elimination diet that there are no further costs involved. However, epinephrine-pens are often prescribed as part of management to treat potential anaphylaxis. However, their value is questioned and potentially may be overprescribed given the perceived risk of peanut allergies. So as a sensitivity analysis it will be assumed that each child gets prescribed 4 epinephrine-pens two for home and two for school with an average shelf life of six months. It shall also be assumed 36% of children get epinephrine-pens (Watura 2002). The cost of epinephrine-pens from the British National Formulary number 59 is £28. This produces a yearly cost of £76.16.

Confirmed No allergy (including true and false negatives)

No costs will be assumed for the 'no allergy' diagnostic states.

Minor reaction

It is assumed that minor reactions are associated with no costs impact, but a sensitivity analysis will be carried out where people go to their GP for any treatment advice. Ergo a 10 to 15 minute GP appointment will be examined.

Major reaction

It is assumed that a major reaction is one that requires hospitalisation. It will be assumed to be a inpatient visit since it may require an overnight stay. The appropriate NHS reference cost is likely to be Shock and anaphylaxis without CC (WA16Y) with a corresponding cost of £991.

## *Analyses*

Given the quality of the evidence available and the considerable uncertainties involved, significant sensitivity analyses will be required.

**Deterministic sensitivity analysis**

All variables in the model will be varied by finding using the upper and lower values, where these were not available 50% increase/decreases will be used.

The time horizon will also be explored by extending it to the age of 18. Data on the desensitization of allergies after five years is not available and therefore, it will be assumed that after five years no one becomes desensitized to allergies.

The cost of treatment will be explored via the addition of epinephrine-pens and also minor reactions being associated with a GP visit.

## *Scenario analysis*

### Retesting

Children often grow out of their allergies as they get older and as such will get reviewed regularly. This may involve retesting. Therefore, retesting every year until school age will be explored to see what effect it has on the cost effectiveness results. Re-testing will only look at those previously diagnosed as having an allergy to examine whether they have outgrown it and become desensitized to the allergy. In addition, it will be assumed that the children are being retested with the same diagnostic tool they were diagnosed with originally.

### Parent's quality of life

As mentioned in the quality of life section there is evidence of a link between a child's food allergy and their parent/carer and even their siblings. However, no evidence was identified to suggest what the magnitude of this effect is. Therefore, the magnitude will be explored in sensitivity analysis. This will be done by multiplying the QALY gain by a factor to account for any parental gain.

### Probabilistic sensitivity analysis

Table 10 outlines the variables that are included in the sensitivity analysis along with distributions:

**Table 10 Variables included in probabilistic sensitivity analysis**

| Variable | | Mean | Distribution | Standard error | A | B |
|---|---|---|---|---|---|---|
| Skin prick test sensitivity | | 1 | Uniform | [redacted] | 0.8 | 1 |
| Skin prick test specificity | | 0.661 | Uniform | | 0.29 | 1 |
| IgE blood test sensitivity | | 0.966 | Uniform | | 0.25 | 1 |
| IgE blood test specificity | | 0.624 | Uniform | | 0.38 | 1 |
| Secondary diagnosis sensitivity | | 0.98 | Uniform | | 0.85 | 1 |
| Secondary diagnosis specificity | | 0.98 | Uniform | | 0.85 | 1 |
| Allergy to no allergy | | 0.054258 | Beta | 100* | 5.43 | 94.57 |
| Allergy to minor | | 0.14 | Beta | 100* | 14 | 86 |
| Allergy to major | | 0.000118 | Beta | 100000* | 11.8 | 99988 |
| Allergy to dead | | 0.0000012 | Beta | 830000* | 0.996 | 829999 |
| Confirmed allergy to no allergy | | 0.054258 | Beta | 100* | 5.43 | 94.57 |
| Confirmed allergy to minor | | 0.14 | Beta | 100* | 14 | 86 |
| Confirmed allergy to major | | 0.000118 | Beta | 100000* | 11.8 | 99988.2 |
| Confirmed allergy to dead | | 0.0000012 | Beta | 830000* | 0.996 | 829999 |
| Quality of life | | | | | | |
| No allergy | | 0.235 | Beta | | | |
| Allergy | | 0.225 | Beta | | | |
| Minor | | 0.235 | Beta | | | |
| Major | | 0.0815 | Beta | 0.05 | 2.359 | 26.584 |
| Cost | | | | | | |
| Secondary diagnosis cost | | 516 | Gamma | 386.86 | 1.779 | 290.042 |
| Major reaction | | 991 | Gamma | 188.16 | 27.739 | 35.726 |
| GP history taking | GP appointment time * GP cost per minute = Total | | | | | |
| | GP appointment time | 15 | Uniform | [redacted] | 5 | 15 |
| | GP cost per minute | 3 | Uniform | | 1.5 | 4.5 |
| Skin prick test | Total | (((a/b)+(c/200))*i)+(d/b)+(e*f)+(g*h) | | | | |
| | Cost of vials (a) | 17 | Uniform | | 12 | 34 |
| | No. of drops per vial (b) | 80 | Uniform | | 60 | 100 |
| | Lancet (200) (c) | 12 | Uniform | | 6 | 18 |
| | Controls x2 (d) | 12 | Uniform | | 6 | 18 |
| | Nurse time minutes (e) | 30 | Uniform | | 20 | 90 |
| | HCP cost per minute (f) | 0.483 | Uniform | | 0.242 | 0.725 |
| | GP time minutes (g) | 10 | Uniform | | 5 | 45 |
| | GP cost per minute (h) | 3 | Uniform | | 1.5 | 4.5 |
| | No of allergies tested for (i) | 8 | Uniform | | 5 | 16 |
| IgE blood test | Total | (u*v)+(v*x)+(y*z) | | | | |
| | Cost per allergy tested for (u) | 12 | Uniform | | 6 | 18 |
| | No of allergies tested for (v) | 8 | Uniform | | 5 | 16 |
| | GP time minutes (w) | 10 | Uniform | | 5 | 45 |
| | GP cost per minute (x) | 3 | Uniform | | 1.5 | 4.5 |
| | Nurse time minutes (y) | 2 | Uniform | | 1 | 10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | HCP cost per minute (z) | 0.483 | Uniform | [redacted] | 0.242 | 0.725 |
| Cost of managing allergies | Total | I*II*III | | | | |
| | Proportion receiving epinephrine-pens (I) | 0.34 | Uniform | [redacted] | 0 | 1 |
| | Number of epinephrine-pens (II) | 4 | Uniform | | 1 | 6 |
| | Cost of epinephrine-pens (III) | 28 | Uniform | | 20 | 35 |
| *is the sample size this is then used to calculate A and B, where A is the mean and B is sample size – mean. | | | | | | |

The reason for the number of uniform distributions was an absence of information informing the estimates. Therefore, a uniform distribution accurately represents the current knowledge about the values.

**Quality of life values**

A novel approach will be used for the probabilistic sensitivity analysis for utilities. Since the utilities for the health states decrease with the severity of the condition it will be necessary to ensure that in any probabilistic sensitivity analysis this remains true otherwise counterintuitive results will be produced. Therefore, beta distributions of the differences between the estimates will be used to ensure that the probabilistic results remain consistent. Table 11 outlines the utilities that are varied according to their difference. The standard error of the difference was calculated using the following formula:

$$SE(of\ difference) = \sqrt{(\left(\frac{sd^2}{n_a}\right) + \left(\frac{sd^2}{n_b}\right))}$$

Where sd = the standard deviation of the source population, n = the size of the sample.

**Table 11Quality of life estimates in probabilistic sensitivity analysis**

| State | Mean | Standard deviation | Difference | Standard error of the difference | Distribution | Alpha | Beta |
|---|---|---|---|---|---|---|---|
| **No allergy** | 0.94 | 0.074 | NA | NA | Beta | 8.742 | 0.558 |
| **Allergy** | 0.90 | 0.13 | 0.04 | 0.077 | Beta | 0.251 | 5.646 |

**Value of information analysis**

Value of information analysis is used to identify the parameters which contribute most to decision uncertainty. Decision uncertainty can be defined as the probability that a wrong decision concerning optimal therapy is made

and the consequences of such a wrong decision. Value of information analysis is conducted for all parameters within the model and for different subsets of parameters. Decision uncertainty can be measured in terms of opportunity loss – the probability that a wrong decision is made multiplied by the consequence of these wrong decisions. Value of information analysis can identify the reduction in opportunity loss associated with having perfect information about a parameter or group of parameters. By having perfect information we necessarily will have less uncertainty and thus less opportunity loss.

Expected value of perfect information (EVPI) is the estimate of opportunity loss for all parameters. Expected value of perfect parameter information (EVPPI) is the opportunity loss associated with imperfect information on specific parameters. EVPI and EVPPI will be conducted to identify whether further research is required and in what areas. For EVPI the approximate size of the population is required. Information from Peanut UK indicates that 1.8% of children of school entry age have a peanut allergy. If it is assumed that school entry age is 4 years according to population statistics from the office of national statistics suggests that in 2009 there were 638.8 thousand children of 4 years in England and Wales. Therefore, the potential number of children who could benefit from improved testing is 11,498 children. This value will be used to calculate the population EVPI.

# Results

## *Base case*

### Deterministic and probabilistic

Table 12 summarises the deterministic and probabilistic results from the economic model all compared to GP diagnosis without a test with a time horizon of 4 years and with the best quality studies used for estimates of sensitivity and specificity:

**Table 12 Deterministic and probabilistic cost effectiveness results (per person)**

| | QALY | Cost (£) | Incremental QALYs | Incremental Costs (£) | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic** | | | | | |
| **GP only** | 3.38 | 45 | 0.00 | 0.00 | £0.00 |
| **IgE blood 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 |
| **IgE blood test** | 3.47 | 579 | 0.11 | 534 | £4,824 |
| **Skin Prick Test** | 3.47 | 559 | 0.11 | 514 | £4,563 |

These results indicate that the tests are cost effective compared to not using a test and that overall skin prick testing is more cost effective than IgE blood testing. The difference between the deterministic and probabilistic sensitivity analysis is due to the number of uniform distributions. This particularly evident since the majority of uniform distributions are allocated to costs and the incremental cost appears to be the variable that is significantly different between the deterministic and probabilistic.

## *Sensitivity analysis*

### One-to-one sensitivity analysis

Figure 2 and Figure 3 display the tornado graphs from the deterministic sensitivity analysis for IgE blood and skin prick tests.

**Figure 2 Deterministic sensitivity analysis - IgE blood tests**

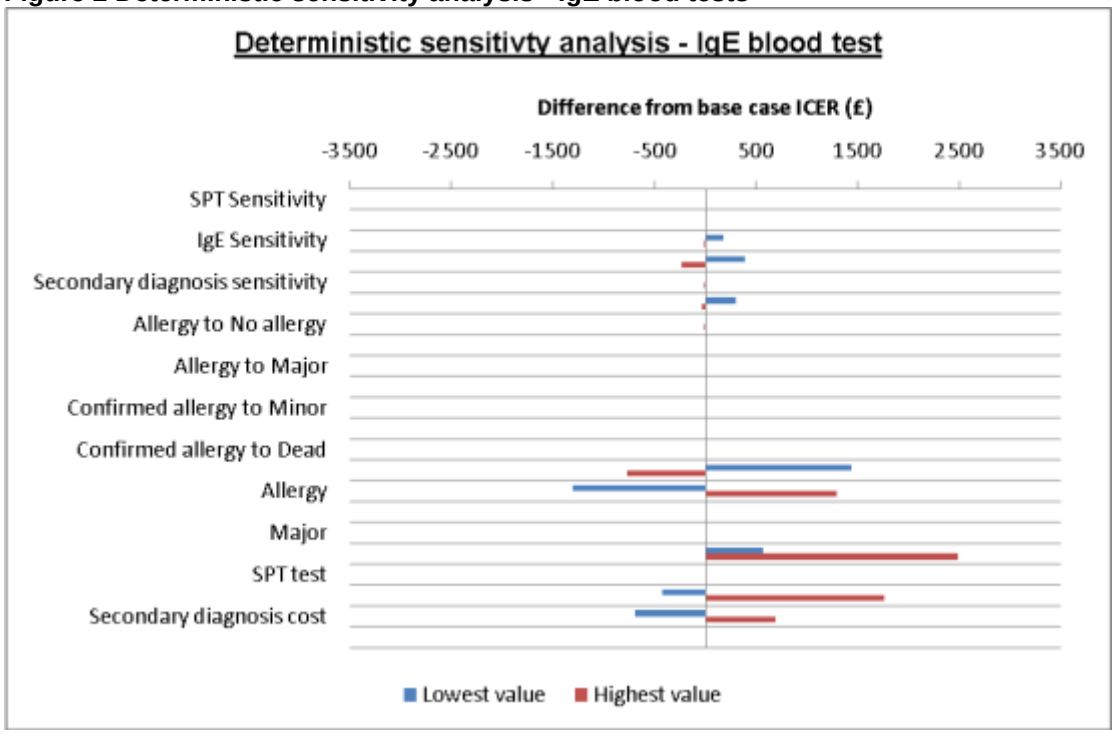
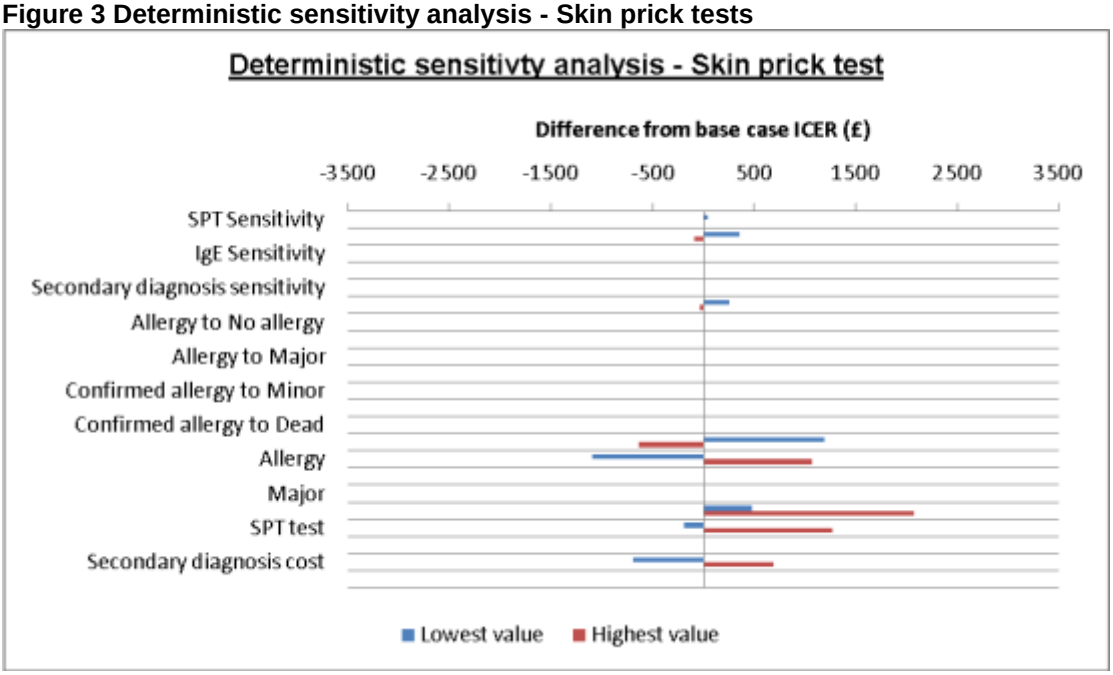


**Figure 3 Deterministic sensitivity analysis - Skin prick tests**




These results indicate that none of the analyses result in the ICERs going over £20,000 per QALY. The biggest drivers are the quality of life difference between having an allergy to no allergy and the cost of the tests. As can be see the long term outcomes do not significantly affect the ICER. This is probably due to the small percentages involved.

### Time horizon

Table 13 presents the ICERs for both tests at different time horizons. These probably represent overestimates since it is assumed that children cannot move diagnostic categories unless they are retested. In reality it is likely that children will discover by accident they no longer have an allergy. So the quality of life loss would be lower ergo the ICERs would be higher.

**Table 13 Cost effectiveness of tests at different time horizons**

| | Time horizon (Age) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Test** | **1** | **2** | **3** | **4** | **5** | **10** | **18** |
| **IgE blood test** | £20,008 | £7,723 | £4214 | £2,685 | £1873 | £585 | £214 |
| **Skin Prick Test** | £14,167 | £5,484 | £2995 | £1,909 | £1331 | £416 | £152 |

## Retesting

Table 14 presents the results of the inclusion of yearly retesting.

**Table 14 Cost effectiveness results of including yearly testing**

| | QALY | Cost (£) | Incremental QALYs | Incremental Costs (£) | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic** | | | | | |
| **GP only** | 3.38 | 210 | 0 | 0 | 0 |
| **IgE blood test** | 3.69 | 503 | 0.31 | 293 | £939 |
| **Skin Prick Test** | 3.70 | 450 | 0.32 | 240 | £757 |
| **Probabilistic** | | | | | |
| **GP only** | 3.39 | 207 | 0 | 0 | 0 |
| **IgE blood test** | 3.56 | 671 | 0.17 | 464.13 | £2,752 |
| **Skin Prick Test** | 3.56 | 649 | 0.17 | 441.96 | £2,600 |

The probability that the skin prick test is cost effective at £20,000 per QALY gained is 98% and for IgE blood tests the probability is 94%. These results indicate that the inclusion of future retesting improves the cost effectiveness probably due to the costs of management increasing. Therefore, the value on an accurate diagnosis becomes more valuable.

## Cost of managing an allergy

To explore the effect of the prescription of epinephrine-pens it was assumed that people will be allocated 4 pens each with each one costing £28 (BNF). These values were varied between plus and minus 50%. It was assumed that the shelf life is approximately 6 months. Table 15 demonstrates the deterministic and probabilistic results of including these costs.

**Table 15 Cost effectiveness results including allergy management**

| | QALY | Cost (£) | Incremental QALYs | Incremental Costs (£) | ICER (£) |
|---|---|---|---|---|---|
| **Deterministic** | | | | | |
| **GP only** | 3.38 | 196 | 0 | 0 | 0 |
| **IgE blood test** | 3.59 | 531 | 0.21 | 335 | £1,594 |
| **Skin Prick Test** | 3.60 | 477 | 0.22 | 281 | £1,262 |
| **Probabilistic** | | | | | |
| **GP only** | 3.37 | 177 | 0 | 0 | 0 |
| **IgE blood test** | 3.49 | 668 | 0.12 | 490 | £4,084 |
| **Skin Prick Test** | 3.49 | 650 | 0.12 | 472 | £3,968 |

The inclusion of these management costs results in the ICERs decreasing. Skin prick tests are have a 99% probability of being cost effective at £20,000

per QALY gained. For IgE blood tests this probability is 96%. These results indicate that the more expensive management becomes the more cost effective accurate diagnosing becomes.

### GP clinical history taking

Table 16 demonstrates the effect of the accuracy of the initial GP history taking on the ICER.

**Table 16 GP history taking accuracy and cost effectiveness results**

| GP clinical history | IgE blood tests | Skin prick tests |
|---|---|---|
| 1 | -£1,008,068 | No QALY difference |
| 0.9 | £7,528 | £3,895 |
| 0.8 | £4,405 | £2,636 |
| 0.7 | £3,368 | £2,217 |
| 0.6 | £2,851 | £2,007 |
| 0.5 | £2,541 | £1,881 |
| 0.4 | £2,334 | £1,797 |
| 0.3 | £2,186 | £1,737 |
| 0.2 | £2,076 | £1,692 |
| 0.1 | £1,990 | £1,657 |

As the GP clinical effectiveness improves the ICER increases, however, it is only when the value gets over 0.9. This suggests that there is always value in carrying out the test.

### Minor reaction cost

Table 17 presents the cost effectiveness results with the addition of an additional GP consultation to those affected by a minor reaction.

**Table 17 Minor reaction cost**

| | **QALY** | **Cost (£)** | **Incremental QALYs** | **Incremental Costs (£)** | **ICER (£)** |
|---|---|---|---|---|---|
| **Deterministic** | | | | | |
| **GP only** | 3.38 | 46 | 0 | 0 | 0 |
| **IgE blood test** | 3.59 | 465 | 0.21 | 419 | £1,990 |
| **Skin Prick Test** | 3.60 | 416 | 0.22 | 369 | £1,657 |
| **Probabilistic** | | | | | |
| **GP only** | 3.36 | 63 | 0 | 0 | 0 |
| **IgE blood test** | 3.48 | 601 | 0.12 | 537 | £4,455 |
| **Skin Prick Test** | 3.48 | 575 | 0.12 | 512 | £4,230 |

The addition of a cost for minor reactions is that the deterministic results stay the same and the probabilistic results improve. This is because the impact of incorrect diagnosis is now greater and therefore, the cost effectiveness is likely to be less uncertain.

### Parent's quality of life

Table 18 demonstrates the effect of including a weight for the parent's quality of life on the ICER.

**Table 18 Inclusion of parent's quality of life**

| Parents weight | IgE blood test | Skin prick test |
|---|---|---|
| **0** | £1,990 | £1,657 |
| **0.1** | £1,809 | £1,507 |
| **0.2** | £1,658 | £1,381 |
| **0.3** | £1,530 | £1,275 |
| **0.4** | £1,421 | £1,184 |
| **0.5** | £1,326 | £1,105 |
| **0.6** | £1,243 | £1,036 |
| **0.7** | £1,170 | £975 |
| **0.8** | £1,105 | £921 |
| **0.9** | £1,047 | £872 |
| **1** | £995 | £829 |

As should be expected as the effect on the parent's quality of life increases the ICER decreases. Therefore, when considering the cost effectiveness estimates the addition of parents quality of life would improve the cost effectiveness of the tests.

### Cost effectiveness acceptability curves

Figure 4 cost effectiveness acceptability curvespresents the cost effectiveness acceptability curves (CEACs) which demonstrate the probability of the intervention being cost effective at different thresholds of cost effectiveness.

**Figure 4 cost effectiveness acceptability curves**

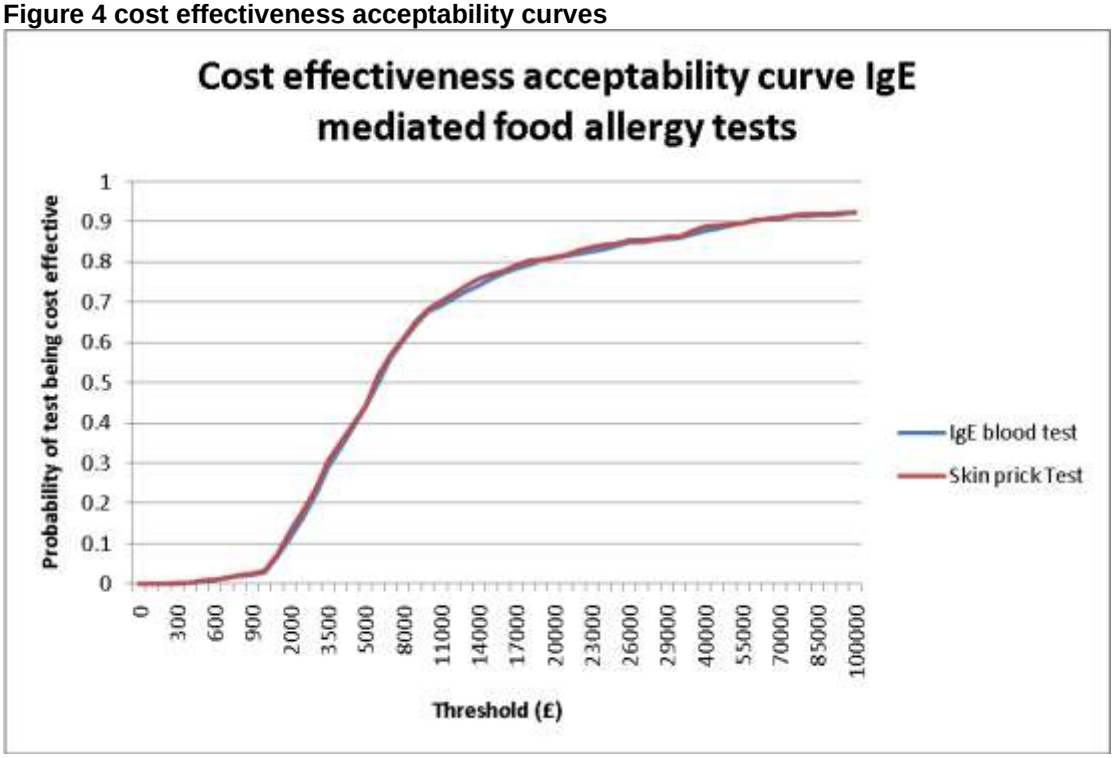



Table 19 gives the probabilities at each threshold.

**Table 19 Probability of tests being cost effective at £20,000 and £30,000 per QALY gained**

| Threshold | IgE blood test | Skin prick test |
|---|---|---|
| £20,000 per QALY | 81% | 81% |
| £30,000 per QALY | 86% | 86% |

These results indicate that the tests have very high probability of being cost effective with probabilities over 85%. These results though are likely to be highly influenced by the simplified structure of the model.

### Cost effectiveness acceptability frontiers

Figure 5 and Table 20 outlines the cost effectiveness acceptability frontier which indicates which option no test, IgE blood test and skin prick test is associated with the greatest gain.

**Figure 5 Cost effectiveness acceptability frontier**

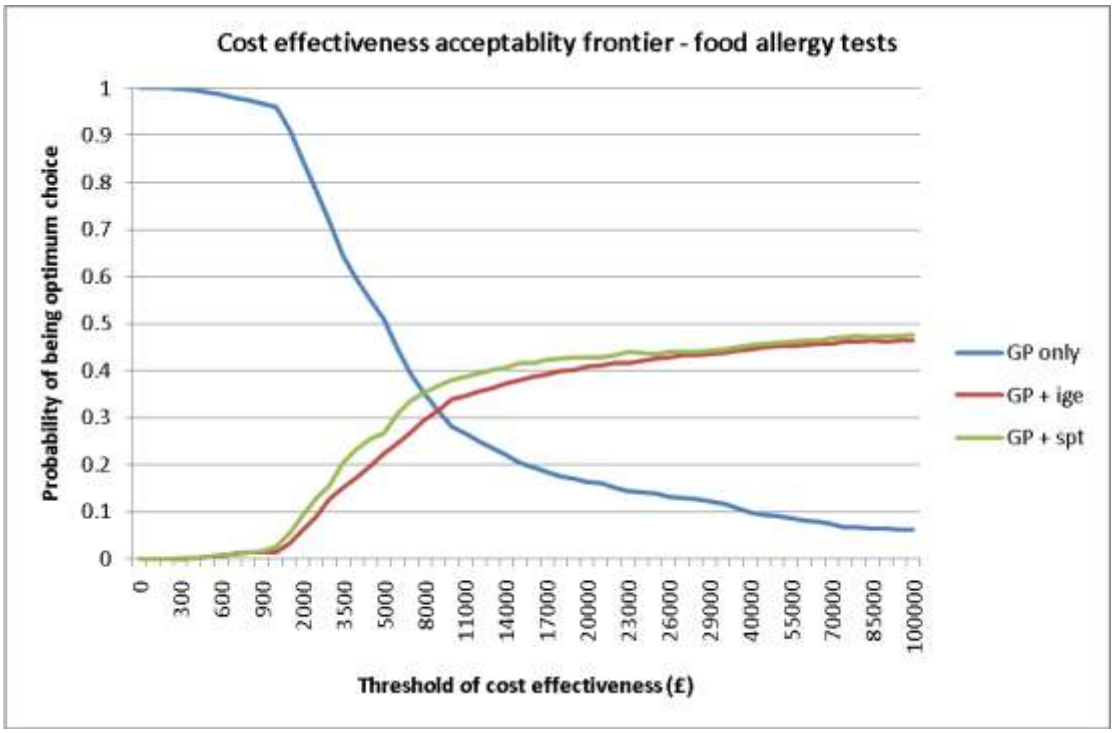



**Table 20 Probability of being optimum choice at £20,000 and £30,000 per QALY gained**

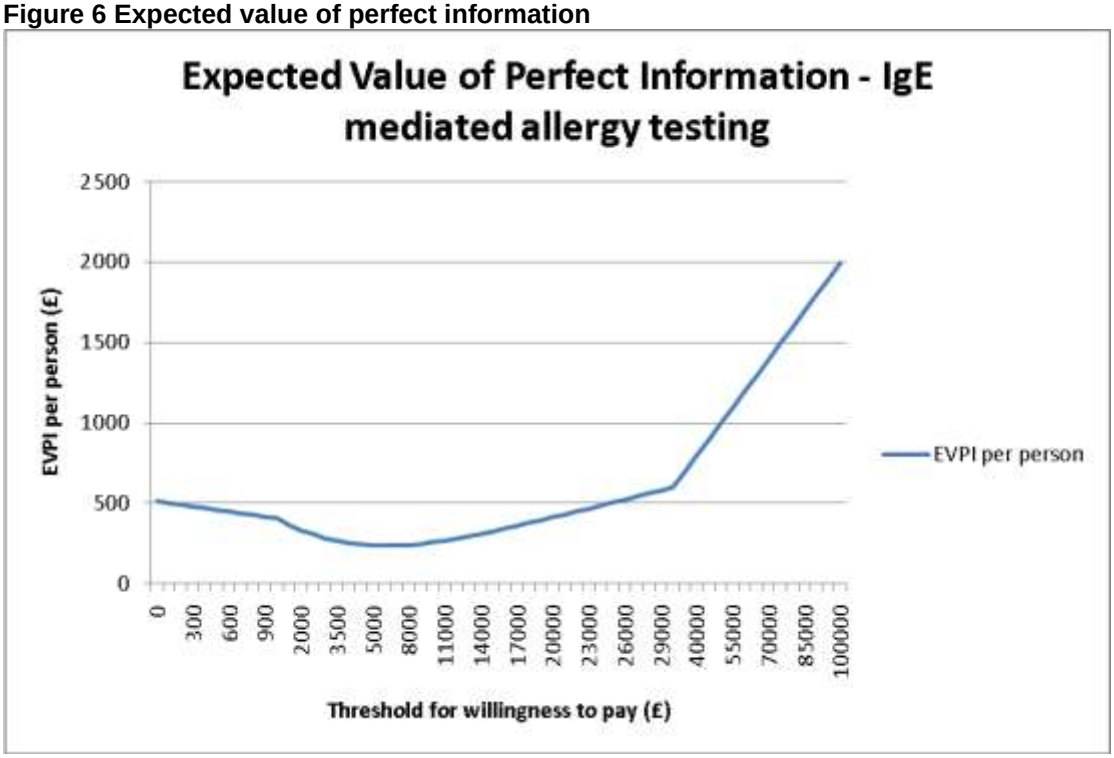
| Threshold | GP alone | IgE blood test | Skin prick test |
|---|---|---|---|
| £20,000 per QALY | 0.164 | 0.409 | 0.427 |
| £30,000 per QALY | 0.117 | 0.438 | 0.445 |

These results indicate that of the options skin prick test is likely to be the optimum choice. However, there is little difference between the skin prick test and IgE blood test. These results are going to depend on the number of patients tested per year due to the skin prick test being associated with significant bulk buying.

### Value of information

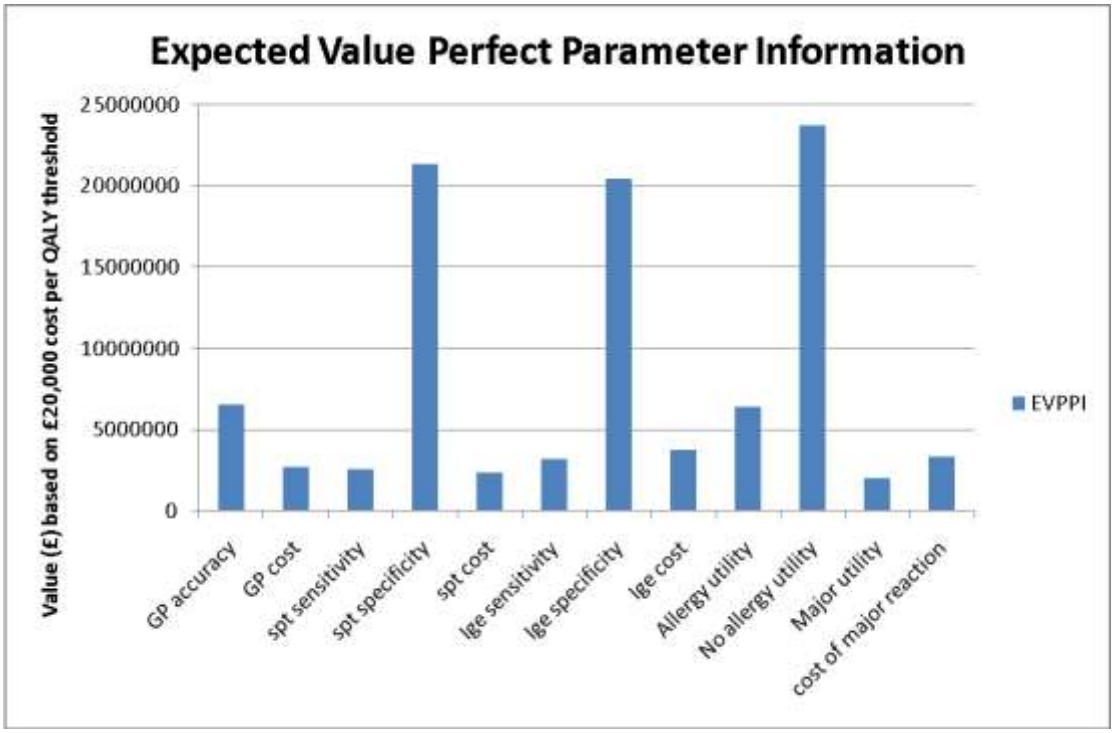
The expected value of perfect information analysis is presented below in Figure 6.

**Figure 6 Expected value of perfect information**




The total population EVPI using the estimates of 11,498 children in England and Wales using a £20,000 per QALY threshold is £34,697,442. This is the value of resolving the uncertainty in the model. Therefore, this indicates that research is valuable in this area. The EVPPI results in Figure 7 indicate where this research should be prioritised.

**Figure 7 Expected value of perfect parameter information for diagnosing food allergies in children**




These results indicate that research is valuable into the majority of the variables in the analyses; however, the specificity of the tests appears to warrant significant investment. This is because the distribution varies significantly from 20% up to 90%. This is consistent with the deterministic sensitivity analysis where these factors made the largest impact. It is also the factor that could decide between the two tests. The quality of life for no allergy is in fact likely to be linked to the difference between allergy and no allergy, with smaller differences resulting in higher ICERs. Therefore, the quality of life of people with allergies compared to no allergies would be a useful area or research.

## *Limitations*

### Poor quality of the clinical information

The model must be viewed as purely exploratory given the very poor information available on the treatment pathway and the natural history. The clinical data underpinning the model was not based on systematic reviews and was therefore, a rather arbitrary selection of available evidence sources.

The diagnostic studies were of low quality and therefore, the estimates of sensitivity and specificity are associated with considerable uncertainty. However, this should have been captured in the probabilistic sensitivity analysis.

The modeling of long term outcomes was based on the little information available and resource constraints. Therefore, important factors that could affect the cost effectiveness could have been excluded.

The quality of life values are relatively robust given the difficulty of collecting quality of life data in this population. However, the data was collected in a older population (12 year olds) than the tested population.

**Population**

The model only considered one population rather than the range of IgE-mediated allergies. Therefore, there are issues with transferability to other populations that need to be considered. In this case it should be transferable the main sources of uncertainty are the initial age of diagnosis, rate of desensitization, sensitivity and specificity of the tests. However, these are unlikely to affect the cost effectiveness of the tests, but the way the tests are used and possibly the downstream management of the condition. Therefore, the cost effectiveness results should be transferable to other allergies.

**Treatment of allergies**

The management of allergies in the model is a very simplified version of what happens in reality. Therefore, the reassessments and treatments such as sensitization of allergies and the proper modeling of epinephrine-pens are not included. The impact of these issues on the cost effectiveness of testing is unclear since if it is more expensive than currently modeled then the value of more accurate diagnosis could be more value. Alternatively if it increases the rate of desensitization than the value of testing may be less than modeled. However, it appears that the more expensive management is then the mode cost effective testing becomes.

## Discussion and conclusion

The results from this analysis appear to suggest that skin prick and IgE blood testing to confirm a diagnosis of food allergy in children is associated with ICERs below a threshold of £20,000 per QALY gained. The difference in quality of life between those with allergies and those without appears to be the main driver behind the cost effectiveness. Sensitivity analyses indicate that this decision is robust with very high probabilities of being cost effective. The skin prick test appears to be the most cost effective option; however this is likely to depend on the number of people tested per year to make sure that wastage does not occur.

The analysis is very simplistic in terms of the model structure and the data inputted into the model. Therefore, these results should be approached with caution. The full impact of allergies on individuals and the health service are not captured fully by the analysis. Nutritional well being of the child and the impact of repeat appointments from concerned parents are not comprehensively captured by the analysis. It is unclear in which way these factors would affect the cost effectiveness estimates.

Future work should concentrate on a more sophisticated representation of the management of food allergies after diagnosis including management techniques and retesting. In addition, it should be based on a full review of the available data.

Another area that would warrant further work is to examine the effect of diagnosing allergies in a realistic population, where there are a number of different allergies present. This could then determine whether there is one test that can be used for diagnosing all allergies or if both are required.

In conclusion, testing for food allergies appears to be a cost effective use of resources. However, further work is required to fully capture the potential benefits and costs of testing.

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## Declarations of interest: Food Allergy in Children

| GDG Member | Interest Declared | Type of Interest | Decisions Taken |
|---|---|---|---|
| Trevor Brown | Occasional paid lecture fee from: Danone (Nutricia), GSK, MSD-UK, Mead Johnson. Currently no paid consultancy work. | Personal Pecuniary specific | Declare and can participate in discussions on all topics. |
| | Financial support with Shering-Plough (now MSU-UK) Re: Respiratory Allergy Research Project. | Non-Personal Pecuniary | Declare and can participate in discussions on all topics. |
| Sue Clarke | The Anaphylaxis Campaign has received an educational grant from Lincoln medical (manufacturer of the Ana pen) for a project I am currently involved in.<br><br>Education for Health have received a fee for a project which I was involved in recently from Merck Sharp & Dohme Ltd. (MSD) (manufacturers of Singular, used for some kinds of allergic disease, but not food allergy). | Non-Personal Pecuniary, non-specific | Declare and can participate in discussions on all topics. |
| | Member of Medical Advisory Board for ALK-Abello (manufacturer of EpiPen) | Personal Non-Pecuniary, non specific | Declare and can participate in discussions on all topics. |
| Mandy East | The National Strategy Group for whom I am contracted to work on a consultancy basis is funded by industry donations [ Phadia, Allergy Therapeutics, Danone/Nutricia] | Non-Personal Pecuniary, specific | Declare and can participate in discussions on all topics. |
| Adam Fox | Consultancy work with SHS Nutricia, Lactofree, Mead Johnson, Annabel Karrel, Dorling Kindersley, ALK-abello, Allergy & Gluten Free show. Lecture fees from mead Johnson, shering-plough, MSD, Glaxo Smith-Kline. | Personal Pecuniary Specific. | Declare and can participate in discussions on all topics. |
| | Director of King's College London, Allergy Academy which receives annual sponsorship from SHS Nutritia, Danone, ALK-abello, Phadia, Novartis.<br><br>BSACI education leads including | Personal Non-Pecuniary, specific | Declare and can participate in discussions on all topics. |

| | | | |
|---|---|---|---|
| | programmes sponsored by Mead Johnson.<br>Advisory board of Allergy UK & Anaphylaxis Campaign. Trustee of Allergy UK.<br><br>Executive committee member of BSACI & BPAIIG.<br><br>Member of EAACI<br><br>Commissioning editor for Educational Clinical Case series on Food Allergy, Paediatric Allergy & immunology.<br><br>Chair of RCPCH Pathway: Food Allergy in Childhood. | | |
| Carina Venter | Member of the Infant and Toddler Forum (www.infantandtoddlerforum.org) which is supported by and Educational Grant from Danone Baby.<br><br>Provided paid lectures and consultancy to Mead Johnson, Danone baby and GlaxoSmithKline. | Personal Pecuniary, specific | Declare and can participate in discussions on all topics. |
| | Vice-chair of the International Network for Diet and Nutrition in Allergy supported by Mead Johnson, Danone Baby and Nestle Nutrition Institute.<br><br>Member of AAAAI, EAACI and BSACI<br><br>Member of Eczema Care Pathway of RCPCH<br><br>My research and publications covers all aspects of diagnosis and management of food hypersensitivity. | Personal Non-Pecuniary, specific | Declare and can participate in discussions on all topics. |
| Joanne Walsh | Member of BSACI and work with NASG. | Personal Non-Pecuniary, specific | Declare and can participate in discussions on all topics. |