Diagnosis and Management of Infants with Suspected Cow’s Milk Protein Allergy.

A guide for healthcare professionals working in primary care.

This document aims to provide healthcare professionals in primary care with an awareness and understanding of the diagnosis and management of cow’s milk protein allergy. It also provides guidance on formula choice and when a referral to secondary care (Dietitian or Paediatrician) is indicated.

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Care pathway for infants with suspected cow’s milk protein allergy


Disclaimer: This is a guide to assist in the appropriate management of suspected cow’s milk protein allergy, including the appropriate prescribing of formula milk when there are medical reasons to do so. Breast feeding provides the optimum nutrition for healthy infants and this chart is intended when either there are medical reasons for changing a breast fed infant (this will usually entail referral to secondary care) or if the infant is already on a formula milk. These are the products recommended for community prescribing in NHS Fife.
Taking an allergy focused clinical history²

A thorough clinical history and physical examination is required to identify the most likely mechanism of the reaction and suspected food or foods. The vast majority of food allergies are diagnosed via a good clinical history as opposed to conducting laboratory tests. The history should capture the following important factors:

- **Individual/ family history of allergic disease**
- **Presenting symptoms**
- **Age/ situation at onset of symptoms** – consider when symptoms start in relation to change in diet e.g. introduction of infant formula from breast milk
- **Suspected food**
- **Time from ingestion to onset of symptoms and quantity of food required**
- **Number of reactions** – reproducibility of symptoms on repeated exposure
- **Response to previous treatment** e.g. medication such as anti-reflux medication, laxatives or topical treatment for eczema.
- **Response to elimination and reintroduction of suspected food**

Food allergy should be considered in a child who has one or more of the signs and symptoms in Table 2 or who has had treatment for atopic eczema, gastro-oesophageal reflux disease or chronic gastro-intestinal symptoms (including refractory constipation) but their symptoms have not responded adequately.

**Table 2 Common signs and symptoms of cow’s milk protein allergy**

<table>
<thead>
<tr>
<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/ Flushing/ Urticaria</td>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Diarrhoea/Constipation</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Severe colic</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Food refusal</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Faltering growth and one or more of above symptoms</td>
</tr>
</tbody>
</table>

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NHS Fife Formulary hypoallergenic formulas

<table>
<thead>
<tr>
<th>Nutramigen Lipil 1 (Mead Johnson)</th>
<th>Birth to 6 months of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutramigen Lipil 2 (Mead Johnson)</td>
<td>Six months of age onwards</td>
</tr>
</tbody>
</table>

Nutramigen Lipil 1 and 2 are listed in the Fife Formulary and are the preferred choice of hypoallergenic formulas for the management of cow’s milk protein allergy (CMPA). The protein has been extensively broken down (hydrolysed). They are tolerated by at least 90% of infants with diagnosed CMPA\(^3\). Due to their special formulation Nutramigen formulas smell and taste differently to standard infant formulas. Gradual introduction of the formula aids palatability e.g. 2 fl oz Nutramigen with 2 fl oz previous formula, mixed in the same bottle. Increase by 1 fl oz Nutramigen per bottle per day as tolerated. If the baby will not take the formula, parents may flavour the Nutramigen with milk free flavoured syrup/ powder or vanilla essence in the short term. Following the introduction of Nutramigen, infants may initially have an increased appetite and produce frequent, loose stools of a greenish colour. This is quite normal. If parents experience difficulties establishing their baby on Nutramigen, despite gradual introduction and flavouring or there is no symptomatic relief in symptoms within 2 weeks, a referral to secondary care is indicated.

In 2004, the Chief Medical Officer recommended that soya formula should not be used as the first line treatment in the management of infants with CMPA or lactose intolerance under 6 months of age, due to the potential risks of phytoestrogens and possible soya sensitisation\(^4\). The prevalence of soya allergy in infants with CMPA varies between IgE and non-IgE-mediated disease. In non-IgE-mediated allergy it may be up to 50%\(^5\), however in Fife the prevalence is significantly lower.

Hypoallergenic formula may be used until 2 years of age. After that, if growth is adequate and CMPA is unresolved, calcium enriched soya, oat and coconut milk may be offered. Goat and sheep milk are not suitable. Children who react to cow’s milk are at high risk of reacting to other mammalian milks. Rice milk is not advised before the age of 4½ years as recommended by the Food Standards Agency. Healthy Start Vitamins are recommended for all babies consuming less than 600 ml formula until 5 years of age.

**Re-challenging standard infant formula in infants with non-IgE-mediated CMPA after 4 weeks:** Replace 1 fl oz Nutramigen with 1 fl oz of standard infant formula in each bottle and increase by 1 fl oz increments each day as tolerated, whilst monitoring symptoms.
Monthly prescription guide

It is helpful to provide a monthly prescription for these formulas. They are not stocked by chemists. It may take 48 hours to obtain supplies from pharmacy wholesalers. Prescribing 2-3 cans at a time leads to multiple prescription requests each month, multiple trips to the surgery and increased parental anxiety when there is a perceived danger of running out of formula. The recommended month’s prescription is as follows:

<table>
<thead>
<tr>
<th>Age of infant</th>
<th>Approx number of tins per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9 months</td>
<td>12 x 400g</td>
</tr>
<tr>
<td>9-12 months</td>
<td>10 x 400g</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>8 x 400g</td>
</tr>
</tbody>
</table>

References

2. Allergy-focused patient history. http://www.allergyeducation.co.uk

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Appendix 1: Incidence and diagnosis of cows milk protein allergy.

In 2007 the World Health Organisation acknowledged that allergy has become the No.1 environmental epidemic disease facing children of the developed world\textsuperscript{6}. Cow’s milk is the most common food allergen in infants. A review paper by the World Allergy Organisation estimated that up to 4.9\% of children suffer from cow’s milk protein allergy (CMPA)\textsuperscript{7}. UK data from 2008 suggests the prevalence is 2.3\%\textsuperscript{8} yet perceived food allergy may be up to 10 times higher that that confirmed by appropriate tests\textsuperscript{9}. CMPA has major nutritional implications as standard infant formulas are based on cow’s milk protein and are a major source of nutrition in the first year of life.

It is estimated that fifty to sixty per cent of affected children have skin symptoms and/ or gastrointestinal symptoms and 20-30\% have respiratory symptoms\textsuperscript{10}. CMPA may be the underlying cause of gastro-oesophageal reflux disease (GORD) in up to 40\% of infants and young children \textsuperscript{11}. CMPA will resolve in 40-50\% of infants by 1 year, 60-75\% by 2 years and 85-90\% by 3 years\textsuperscript{12}, however the natural history is actively changing, showing a definite trend to persist longer, especially the IgE-mediated clinical expression of CMPA. For example, Skripak et al in 2007 found significantly slower remission in children with IgE-mediated CMPA with only 5\% only resolving by 4 years of age, 21\% by 8 years of age, 37\% by 12 years of age and 55\% by 16 years of age\textsuperscript{13}.
Food intolerance or non-allergic food hypersensitivity may be caused by pharmacological agents, e.g. histamine in foods, naturally occurring substances in foods, e.g. salicylates and enzyme deficiencies such as lactose intolerance. Most infants in Fife suffer secondary lactose intolerance as a result of damage to the gut following gastroenteritis. It is usually a temporary condition resulting in colic, diarrhoea and vomiting, which lasts between 4-6 weeks.

Food allergy or allergic food hypersensitivity can be driven by two distinct immune mechanisms, referred to as IgE-mediated allergy and non-IgE-mediated allergy. IgE-mediated reactions are immediate, requiring only a small quantity of food to be ingested, enabling rapid identification of the allergenic foods. They involve the production of specific IgE antibody protein molecules directed against the food protein. It is a well defined mechanism, which is relatively easy to diagnose using a combination of clinical history and validated tests such as skin prick tests and specific IgE’s. Non-IgE-mediated reactions are delayed by up to 48 hours and larger volumes of food are required, therefore the identification of suspect foods is often difficult. The mechanism is unclear, it is harder to diagnose and there are no validated tests to confirm such an allergic reaction. The cornerstone of all food allergy diagnosis is the relief of symptoms on elimination of the suspected food and return of symptoms on reintroduction.

It is important to note that some children may have a combination of both IgE and non-IgE-mediated reactions. Children with a history suggestive of IgE-mediated allergy should not be re-challenged at home unless advised to do so following assessment in secondary care.